3.3.2 ***Number of research papers per teachers in the Journals notified on UGC website during the last five years***

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List of UGC Scopus approved journals

S.No.	Title of paper	Name of the author/s	Name of the journal	Year of publication
1	Advances in nanomaterials -based carrier system for the treatment of breast cancer	Sandhya rani mandadi, VVS Rajendra prasad	Journal of pharmaceutical research international	2020-2021
2	Pharmaceutical cocrystals of eprosartan mesylate- Formulation, characterization and evaluation	Dr. S. Dinesh Mohan, Dr. D. Santhosha, Dr. SVVNSM Lakshmi	International Journal of Pharmaceutical Research	2020-2021
3	Nanotechnology based approaches applied to nutraceuticals	Dr. K. Vanitha	Drug Delivery and Translational Research	2020-2021
4	Design, synthesis, anticancer evaluation and binding mode studies of benzimidazole/ benzoxazole linked β-carboline derivatives	Surender Singh Jadav	Journal of Molecular Structure	2020-2021
5	An animal study for antidiabetic action for polyherbal drug	S. Vijay Kumar	Global Journal for Research Analysis	2020-2021
6	Synthesis, docliing and biological activities of novel chromone linked {1,2,3]- triazole derivatives	K.Ramanjaneyulu	Chemical Data Collections	2020-2021
7	A prognostic study on the effect of post-traumatic stress disorder on cerebral ischaemia reperfusion induced stroke	Subramanyam Polopalli	World Journal of Biological Psychiatry	2020-2021
8	3D Printing Technology in Pharmaceutical Dosage forms : Advantages and challenges	K.Vanitha	Current drug Targets	2020-2021
9	Design, synthesis, anticancer evaluation and molecular docking studies of chalcone linked pyrido[4,3-	Surender Singh Jadav	Journal of Molecular Structure	2020-2021

	transport in human and its cardiovascular related dysregulation			
18	Mathematical model of the nfk beta activity interleukin-1 beta through caspase-1 enzyme	T. Sandhya	European Journal of Molecular and Clinical Medicine	2020-2021
19	Synthesis and biological Potentials of 5- aryl-N-[4- (trifluoromethy l) phenyl]- 1,3,4- oxadiazol-2- amines	Surender Singh Jadav	Letters in Organic Chemistry	2020-2021
20	Structure based discovery of small molecule APC-Asef interaction inhibitors: In silico approaches and molecular dynamics simulation	Surender Singh Jadav, Dr. A. Ramesh	Journal of Molecular Modeling	2020-2021
21	Development and validation of UV-Spectroscopic methods for simultaneous estimation of hydrocortisone and iodoquinol in tablet dosage forms	S. Vijay Kumar	Research Journal of Pharmacy and Technology	2019-2020
22	Synthesis, Characterization, And Anticancer Activity Of Some Novel Acridine Derivatives	VVS Rajendra Prasad	Asian Journal of Pharmaceutical and Clinical Research	2019-2020
23	Nutritional impact of foods made from Spirulina on children of slected anganwadisof siddipet district in telangana state in India	A. Ramesh, K. Vanitha	International Journal of Pharmaceutical Sciences and Nanotechnology	2019-2020
24	Design, synthesis and characterization of novel paracetamol derivatives to target breast cancer	K.Ramanjaneyulu, J. Hima bindhu, VVS Rajendra Prasad, T. Umema Naaz	Indian Journal of Chemistry	2019-2020
25	Synthesis, antiproliferative, and Antioxidant Activities of Substituted N- [(1,3,4- Oxadiazol-2- yl) Methyl] Benzamines	Surender Singh Jadav	Letters in Drug Design & Discovery	2019-2020
26	2-Mercapto benzthiazole coupled	Surender Singh Jadav	Chemistry select	2019-2020

	Sofosbuvir and Ledipasvir by RP-HPLC			
35	Development and Optimization of Lovastatin- loaded Transdermal Proniosomal Gel using Box- Behnken Design	C.Soujanya	International Journal of Pharmaceutical Sciences and Nanotechnology	2018-2019
36	Phytochemical screening and In-Vitro antioxidant activity of Senna occidentalis	K. Ramanjaneyulu, J. Himabindhu	Research Journal of Pharmacy and Technology	2018-2019
37	Formulation and evaluation of proniosomal gel based transdermal delivery of atorvastatin calcium by box-behnken design	C. Soujanya	Asian Journal of Pharmaceutical and Clinical Research	2018-2019
38	3-triazol4-yl)-1,4-dihydropyridine derivatives as novel 11-β hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibitors	Vishwanadham Y	Bioorganic Chemistry	2018-2019
39	"Design and synthesis of imidazolo-1, 2,3-triazoles hybrid compounds by microwaveassisted method: Evaluation as an antioxidant and antimicrobial agents and molecular docking studies".	vishwanadh.y	Journal of Molecular Structure	2018-2019
40	Evaluation of in vitro antiurolithiatic activity of vigna radiata	K.Ramanjaneyulu	Research Journal of Pharmacy and Technology	2018-2019
41	New stability- indicating Ultra Performance Liquid Chromatography method development and validation of lenvatinib mesylate in bulk drug and pharmaceutical dosage forms	Jahnavi Bandla	Asian Journal of Pharmaceutical and Clinical Research	2018-2019
42	Evaluation of in vitro anthelmintic activity of spirulina powder	K.Ramanjaneyulu, J. Hima bindhu	Research Journal of Pharmacy and Technology	2017-2018
43	Stability Indicating UPLC Method	Jahnavi Bandla	International Journal of	2017-2018

	cataractogenesis			
53	Formulation and In Vitro Evaluation of Floating Microspheres of Misoprostol	Dr. A. Ramesh	International Journal of Pharmaceutical Sciences and Nanotechnology	2016-2017
54	Evaluation of Phytochemical Screening and In vitro Anthelmintic Activity of Malvastrum coromandalianum	J. Hima bindhu	International Journal of Pharmaceutical Sciences Review and Research	2016-2017
55	Synthesis, Antioxidant, Antibacterial and Cytotoxic Activity of Novel Chromone Derivatives	Ramanjaneyulu K, Hima Bindhu J, Umema Naaz T, Rajendra Prasad VVS, Satya BL	Der Pharma Chemica	2016-2017
56	Nimbolide upregulates RECK by targeting miR-21 and HIF-1α in cell lines and in a hamster oral carcinogenesis model	Deepak Reddy	Scientific Reports	2016-2017
57	Pueraria tuberosa potentially attenuates Arsenic induced oxidative stress mediated cardiotoxicity, blood toxicity and dyslipidemia in rats.	Dr. A. Ramesh	Int J Adv Pharmacy Med Bioallied Sci.	2016-2017

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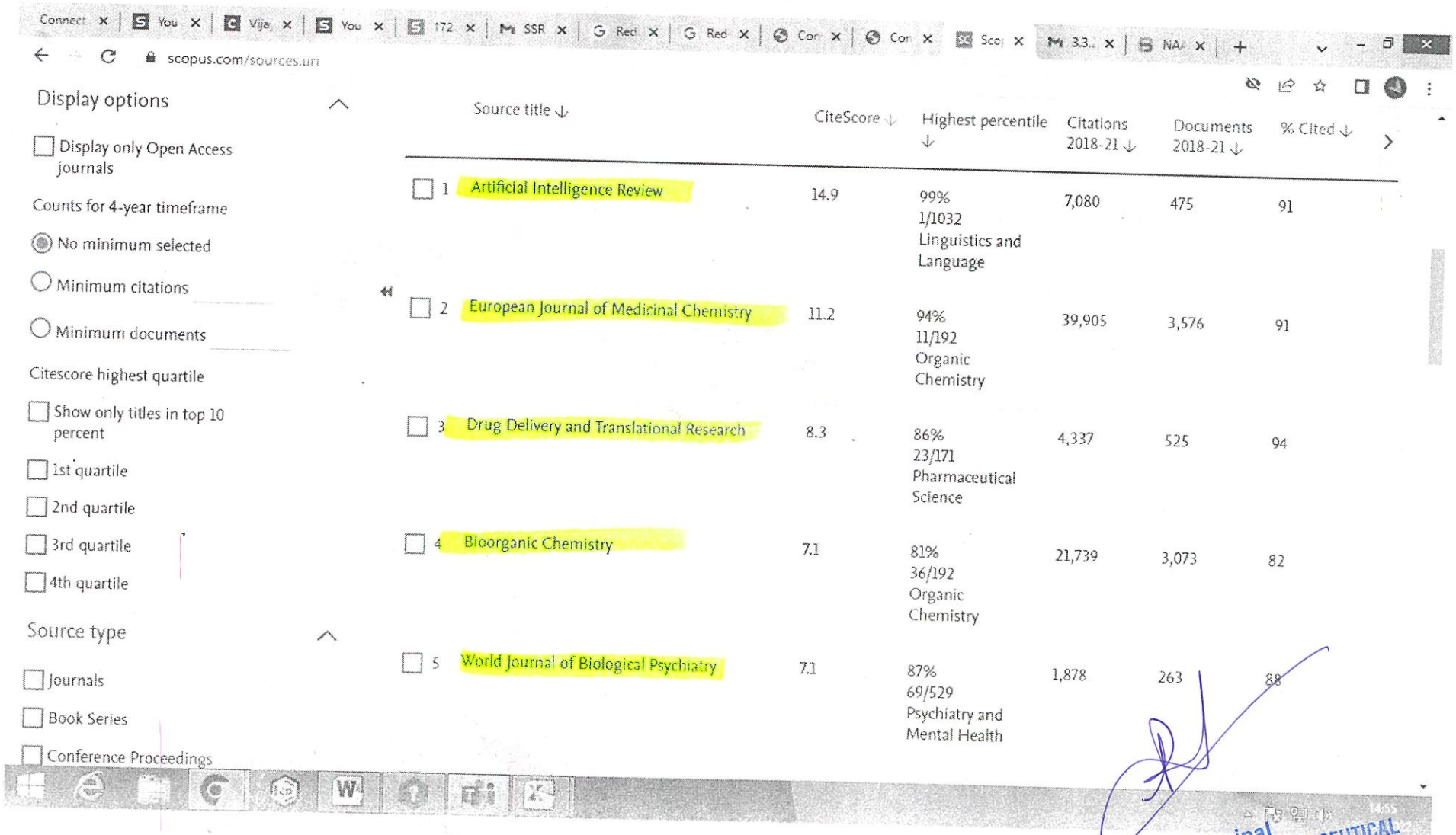

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3	Drug Delivery and Translational Research	8.3	86% 23/171 Pharmaceutical Science	4,337	525	94
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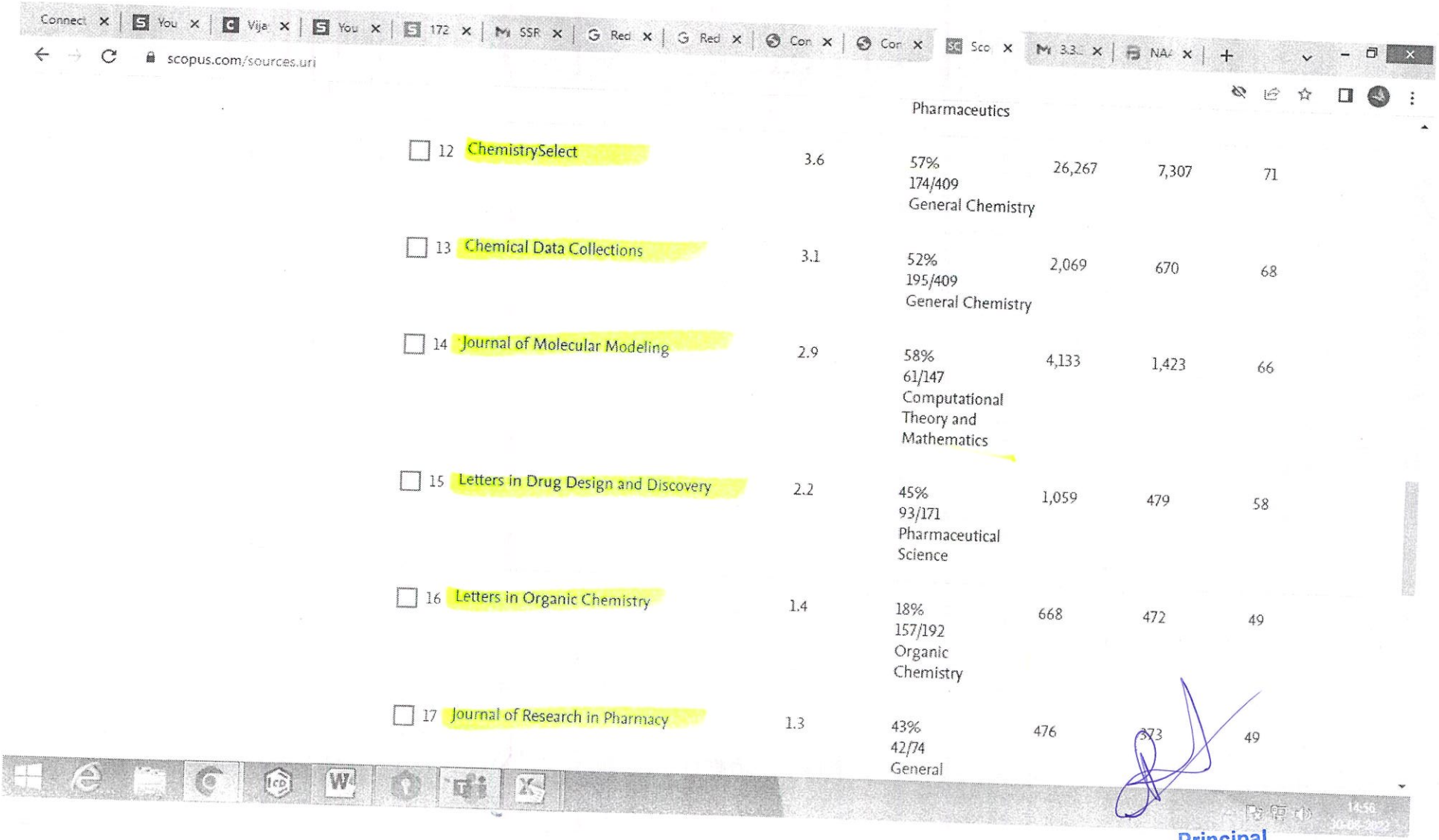

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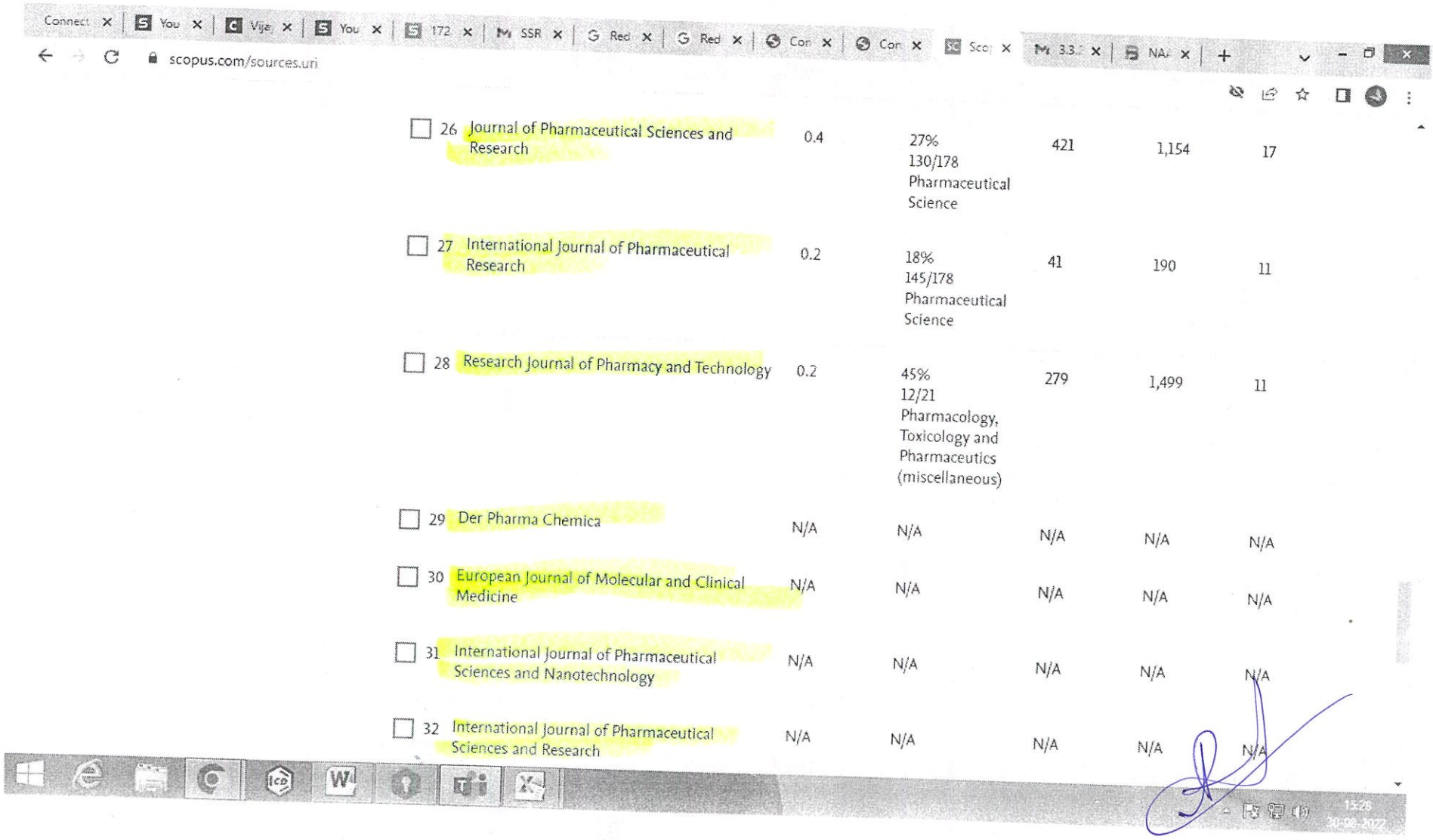

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30	European Journal of Molecular and Clinical Medicine	N/A	N/A	N/A	N/A	N/A
31	International Journal of Pharmaceutical Sciences and Nanotechnology	N/A	N/A	N/A	N/A	N/A
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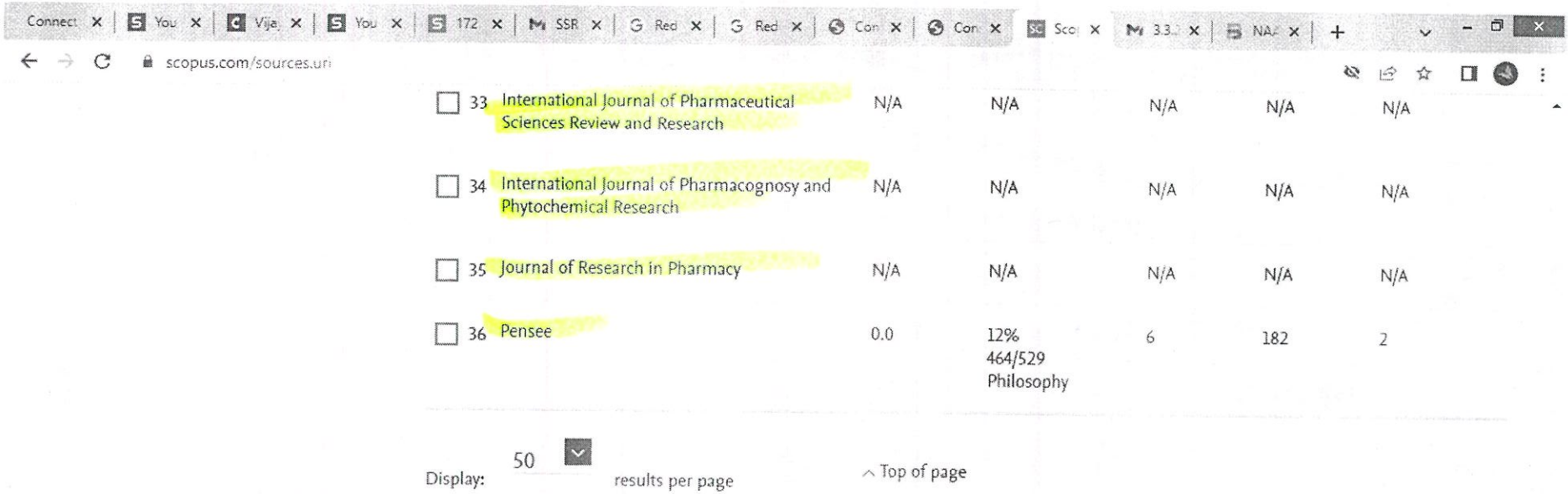

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Advances in Nanomaterials-Based Carrier System for the Treatment of Breast Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. 'All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Nanotherapeutics for the cure of breast cancer remains unswervingly succeeding and being practiced to eradicate innumerable restrictions of conventional practice obtainable for the supervision of breast cancer. Nanoparticles offer an interdisciplinary extent for exploration in imaging, diagnosis and targeting of breast cancer. Through a progressive physicochemical features and improved bioavailability, they spectacle persistent blood circulation through effective tumor targeting. Nanoparticles remain capable to diminish cytotoxic consequence of the active anticancer medications through amassed cancer cell targeting in contrast to conventional preparations. Several nanoparticles-based preparations remain in the preclinical and clinical phases of progress; amongst them, polymeric drug micelles, liposomes, and dendrimer, remain the utmost common. In this review, we have conferred the role of nanoparticles through detail to oncology, by predominantly aiming on the breast cancer and several nanodelivery systems practiced for targeting action and signaling forces through further intracellular pathways in breast cancer.

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Research Article

Pharmaceutical Co-Crystals Of Eprosartan Mesylate:Formulation, Characterization And Evaluation

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ABSTRACT

The purpose of this study was to increase the solubility and dissolution rate of the drug Eprosartan mesylate, which belongs to the Biopharmaceutical Classification System-II. To improve the solubility and dissolution rate of eprosartan mesylate, the co-crystallization process was opted. The drug cocrystals were formulated by solvent drop grinding method using malic acid as coformer (1:1 ratio). The formulated co-crystals were characterized through various methods, namely differential scanning calorimetry, Fourier transform infrared spectroscopy, light microscopy, and powder X-ray diffraction. The solubility tests of prepared co-crystal were conducted in water, and the in vitro dissolution tests were done in phosphate buffer solution of pH 7.4. The co-crystals displayed new crystalline peaks at 2θ values of 7.20, 12.56, 13.98, 14.40, 16.73, 17.76, 18.40, 19.00, 20.1621.07, 22.30, and 24.28 indicated the development of a new crystalline phase. The obtained co-crystals showed the melting point at 98.17°C, which was distinct from that of the pure drug and coformer. The IR spectra of the co-crystals indicated the shifting of absorption peaks of groups of pure components, which reflected the formation of new crystals through hydrogen bond interactions. The solubility and dissolution rate of co-crystals were found to be considerably higher than those of pure drug. The results suggest that co-crystallization process can be the best alternative process for enhancing solubility of poorly soluble drugs.

Keywords: Co-crystal; eprosartan mesylate; solvent-drop grinding; solubility; dissolution rate

INTRODUCTION

Several active pharmaceutical ingredients (APIs) produced by the pharmaceutical industry belong to the "poorly water-soluble" category [1]. According to the Biopharmaceutical Classification System (BCS), Class-II drugs have low solubility and high permeability, resulting in limited absorption and bioavailability [2]. Eprosartan mesylate (ESM) is a BCS Class-II antihypertensive drug [3]. ESM is poorly absorbed in the gastrointestinal tract after oral dosing because to its limited solubility and bioavailability (approximately 13 %) [4]. Poorly water-soluble compounds provide various challenges in creating pharmaceutical dose forms for oral delivery systems due to their low bioavailability. [5]. Thus, a high dose (800 mg) is commonly prescribed for the management of hypertension, often leading to adverse or side effects. Improving the solubility and dissolution of ESM is considered to be an essential part in enhancing its bioavailability and therapeutic effectiveness. Researchers have been attempting to boost the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs by using various methods, such as nanomaterialization [6], salt formation [7], hydrotropy [8], liposome formation [9], liquisolid compaction [10], solid dispersion [11], and self-microemulsifying drug delivery system [12]; several other techniques have been reported to improve the bioavailability of BCS Class-II and Class-IV drugs that are poorly water soluble.

Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-021-00960-3

REVIEW ARTICLE

Nanotechnology-based approaches applied to nutraceuticals

Akanksha R. Singh[1] · Prasanna Kumar Desu[2] · Ramya Krishna Nakkala[3] · Vanitha Kondi[4] · Sushma Devi[5] · Mohammad Sarwar Alam[6] · Hinna Hamid[6] · Rajani B. Athawale[1] · Prashant Kesharwani[7]

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Abstract

Nutraceuticals and food industries are opening to a tremendously upcoming technology in the field of "Nano science". A new prospect has been defined by nanotechnology by conferring modified properties of nanomaterials and its application in the development of nanoformulations, nutritional supplements and food industry. Nanomaterials reveal exclusive properties because of their small size and high surface/volume ratio; thus, they have a complete application in nutraceuticals and food sector. In the existent review article, we obligate to present a comprehensive outline of the application of nanomaterials in development of advanced nano-based nutraceuticals with enhanced bioavailability, solubility, improved encapsulation efficiency, increased stability, sustained and targeted drug delivery, protection against degradation and microbial contamination and with improved pharmacological activity. It also highlights the importance of nanomaterials as nanosensors/nano-bio sensors for encapsulating peptides, antibodies, enzymes, etc. and in the food packaging industry and its future application. Thus, the review aims to focus on the benefits and new dimensions provided by nanomaterials and nanotechnology in health sectors by improving treatment strategies and quality of life.

Keywords Nutraceuticals · Nanomaterials · Nanosensor · Food industries · Nanotechnology · Solubility enhancement

Introduction

Nanotechnology, in a nutshell, is a technology for the development, synthesis and application of nanometer-sized products. Since 1959, it has been presumed that specific material and substance features can be regulated and manipulated by reducing their particle size to very tiny scales [1–3]. Nanotechnology deals with investigating, modifying and controlling the object's atomic/molecular structures extending after 1 to 100 nm in size [4–6]. More specifically, nanoparticle engineering is the study of the synthesis and growth of artificial or designed nanoparticles for technological advances and applications that would otherwise be downright impossible. The term nanoparticles (NPs) and nanostructured materials (NSMs) have been coined with the unprecedented growth of the research over the past few decades [7, 8].

Nanomaterials or materials of nanostructure have distinct sizes intended for their essential components, constellations, crystallites or molecules. Dimensions similar to zero (nanoclusters, nanoparticles and quantum dots), one (nanotubes or nanorods), two (nano-thin films) and three-dimensional (nanomaterials) ranging from 1 to 100 nm [9, 10]. The combination of nanostructure components with other polymers, biomolecules and other elements of the nanostructure or existing in the aggregate shape may lead to the creation of a more extensive particle size material (> 100 nm) [11–13]. These high surface-volume nanomaterials have unimaginable physicochemical properties, similar to strength, solubility, magnetism, toxicity,

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Design, synthesis, anti-cancer evaluation and binding mode studies of benzimidazole/benzoxazole linked β-carboline derivatives

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ABSTRACT

A new series of benzimidazole/benzoxazole linked β-carbolines (**9a-j**) were rationally designed and synthesized by combining two different anti-cancer fragments. The new hybrid β-carbolines are subjected to anti-cancer screening against four different human cancer cell lines such as MCF-7 (breast), A549 (lung), Colo-205 (colon) and A2780 (ovarian) by using standard MTT assay. These hybrid β-carbolines exhibited significant and high fold anti-cancer activity against MCF-7 cell lines than reference standard. They are also proved to be effective against A549 and Colo-205 cell lines. Further, compound **9b, 9c** from benzimidazole and **9i** from benzoxazole series have exhibited maximum anti-cancer activity among these hybrid β-carbolines. Later, all of the hybrid β-carbolines were subjected to molecular interaction analysis against a few selected kinase targets such as cdc-like kinase (CLK-1 to CLK-4), epidermal growth factor reductase (EGFR) kinase, protein (ATR) kinase along with APC-Asef interface. The violin plot of binding energies of 9a-9j have suggested them as good kinase binders. Result interpretation suggested hybrid β-carbolines as promising CLK binders. The anti-cancer data of new hybrid β-carbolines against MCF-7 cell lines are in agreement with parent β-carboline skeleton.

1. Introduction

Nitrogen containing hetero-aromatic skeletons are very crucial intermediates in the synthesis of promising anticancer candidates [1–25]. β-carbolines are a unique class of fused indole-pyrdine based tricyclic heterocyclic moieties and are distributed in various plant kingdoms [26–28]. Previously, compounds containing β-carbolines are reported to exhibit large spectrum of biological functions such as antitumoral [29], DNA intercalate [30], DNA topoisomerase-I and II [31], CDK inhibitor [32], sedative [33], antimicrobial [34], antithrombin [35], anti-inflammatory [36], antiviral [37], anti-convulsant [38], anti-leismanial [39], anti-HIV [40], anti-malarial [41], and antifungal [42]. Harmine (**1**, Fig. 1) is a naturally occurring compound containing β-carboline structural skeleton which was isolated in 1847 and is used as anticancer agent [43,44]. The β-carboline analogues such as 1-Acetyl- β-carboline, Hydroxyethyl- β-carboline, Methoxycarbonyl-β-carboline, Sphecolines, Harmine, Benzoyl-β-carboline and aminoacid derived β-carbolines are investigated as potential anti-cancer agents [45–47] were shown in Fig. 1. Among the afore mentioned analogues, benzoyl and aminoacid derived β-carbolines are examined as protein kinase and tumor migration inhibitors.

On the other hand, benzimidazole is one of the finest fused heterocyclic scaffold which was first synthesized in 1870s [48]. It is associated with a variety of pharmaceutical applications including anti-hypertensive [49], anticancer [50], antiallergic [51], antifungal [52], antibacterial [53], anthelmintic [54], anti-HIV [55], antiviral [56], H3 antagonistic [57], antitubercular [58], and DNA topoisomerase-I inhibition [59]. Among all, nocodazole (**2**) is an potent anti-cancer agent which exerts effects on the tubulin polymerization [60,61]. Similarly, benzoxazoles are fused heterocyclic systems which are reported to exhibit different types of biological properties like human DNA topoisomerase-I and II [62], anticonvulsants [63], antiviral [64], metabolic disorders [65], antineoplastic [66], anti-inflammatory [67], herbicidal [68], antifungal [69], and

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Original Research Paper

Diabetology

AN ANIMAL STUDY FOR ANTI DIABETIC ACTION OF POLY- HERBAL DRUG

Dr. Canchi Bhoopal Dhanraj	MD (AY)(OSM) MPH (ENGLAND) (Ph.D)(UHS), Professor, Bharat Ay, Medical College, Muzaffar Nagar –UP.
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Dr. S. Renuka Rani	MBBS. MD., DCP.UHS), Dy,civil Surgeon (Rtd), S.R.R.I.T.C.D, Hyderabad.
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ABSTRACT *Aim:* To compare the efficacy of the selected poly herbal medicine for anti-diabetic activity. *Methods and Materials:* Healthy thirty six Albino wistar rats are selected and divided into six groups of six each. named as ABCDEF. A group animals as control group without administering the research drug. B group as Standard group animals and were administrated Glibenclamide 10 mg/kg BW. Screening methods for anti diabetic activity are:a)Acute toxicity studies :. The animals of group C,D,E,F are given research drug in different doses and are observed for 48 hours for toxicity effects. b) Normoglycemia—Blood samples were collected through retro-orbital puncture at 0h, 2h, 4h, and 6h after dosing, for determination of blood glucose levels and the blood insulin levels.c) Euglycemic studies: The animals were induced diabetes with Intra peritoneal injection of Streptozotocin 60 mg/per kg body weight and after 48 hours the animals are given the research drug in different dose to Diabetic induced rats. the blood sugar and the blood insulin levels are measured. the study is divided into two phases. A) Short term study , for this group of overnight fasting animals the research drug was given on day one only and samples of blood collected from retro-orbital veins on zero hour at frequent intervals up to 24 hours. B)Long term study.The drug is administered for 14 days, samples are drawn on daily basis and compared with the standard drug group blood samples. After the study one animal from control group, standard group, and F group was selected and sacrificed and pancreas and liver have been taken for histopathological examination. Results: There was no mortality of animals in toxicity studies. Statistical analysis was done with one way ANNOVA and found the drug was effective to reduce the blood sugar level with ($P<0.001$) and increase in Blood insulin level with ($P<0.001$) compared to the standard drug.

KEYWORDS : Glibenclamide, Intra peritoneal, Streptozotocin, retro-orbital.

INTRODUCTION

The first physicians to identify the disease was Charka (1000BC) and Sushrutha 6th Century BC as Madhumeha. The Diabetes word was coined by Apollonius, medical text written around 1425, in 1675 Thomas Willis added Mellitus to Diabetes[1].

The metabolic disease or Diabetes Mellitus or Madhumeha is a condition caused due to body"s infective use of or lack of insulin. 422 million people world wide have Diabetes[2]. The Global prevalence of Diabetes Mellitus for global population over age of 18yrs was 4.7% in 1980 and increased to 8.5% in 2014[3]. India has nearly 33 million diabetic subjects today, which is briefly contributed by the urban population. Diabetes mellitus is a major endocrine disorder affecting nearly 10% of the population worldwide[4]and a key issue of concern.

The disease in its severe state affects major systems of the body, leading to multi-organ complications. The other predisposing causes could be due to excessive body weight or lack of physical activity. The types of diabetes are :1.Type I Diabetes, 2.Type II Diabetes Mellitus, 3.Gestational Diabetes.

Oxidative stress in Diabetes mellitus plays a major role in pathogenesis of the diseases, the same established in Ayurveda as vitiation of Dathus by vata is the cause for conversion of Pramehas to Madhumeha /Diabetes Mellitus[5]. Diabetes increases oxidative stress in many organs, especially in the liver[5,7].Liver is one of the most important organs that maintains blood glucose levels within normal limits thus enhancement of blood sugar yield to imbalance of oxidation-reduction reactions in hepatocytes, so that, hyperglycemia through increasing in AGEs (advanced glycation end products) facilitates free radicals production via disturbance in ROS (reactive oxygen species) production . Early stages of diabetes, tissues injuries are induced via hyperglycemia but its progress in latter stages is not related to hyperglycemia. Therefore, monitoring of blood glucose levels solely is not sufficient in retarding diabetes complications. Thus, a suitable drug must have both antioxidant and blood glucose decreasing properties, with the same principle this drug combination has been chosen[8 to 13]. An ancient physician Vagbhatta of 3 rd century says that all conditions where urine resembles honey in all aspects and even the body becomes sweetish, should be regarded as Madhumeha[14,15]. Madhava kara in his treatise Madhvanidhana describes that Prakarasena Prabhutam Prachuram varam varam karothi Ethi Prameha[16,17]. It means a disease in which large amount, turbid , urine is frequently excreted such an disease is called as Prameha/ Diabetes mellitus. Same was told by

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Data Article

Synthesis, docking and biological activities of novel chromone linked [1,2,3]-triazole derivatives

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ABSTRACT

Estrogen receptor-positive breast cancer is one of the commonly diagnosed cancers today. A series of chromone linked [1,2,3]-triazoles were designed based on literature followed by in silico studies. The in silico studies indicated good docking score for (2E)-(1R-1,2,3-triazol-4-yl)methyl 3-(6-methyl-4-oxo-4H-chromen-3-yl)acrylate derivatives when docked into the Human Estrogen Receptor Alpha Ligand-Binding Domain (PDB ID: 1XP6). So a new series of ten compounds have been synthesized, characterized and evaluated for cytotoxicity, antibacterial and antioxidant activities. The compounds 9f and 9a showed promising cytotoxicity with IC50 value of 18.61 and 20.39 μg/mL respectively. The Compounds 9b, 9c, 9f, 9 g and 9j showed encouraging antioxidant activity with IC50 value of < 30 μM i.e. DPPH scavenging activity levels more than that of positive control, whereas Compounds 9a, 9c, 9e, 9f, 9 h and 9j exhibited moderate antibacterial activities with the MIC value of <240 μM.

Specifications Table

Subject area	*Organic Chemistry*
Compounds	*Chromone linked [1,2,3]-triazole derivatives*
Data category	*Spectral, synthesized, computational simulations, antibreast cancer, antioxidant, and antibacterial studies*
Data acquisition format	*IR, 1H & 13C NMR, Mass spectra analysed*
Data type	*Analyzed, simulated*
Procedure	*A novel series of Chromone linked [1,2,3]-triazole derivatives synthesized, characterized, docked and screened their antibreast cancer, antioxidant, antibacterial activities*
Data accessibility	*Data is within this article*

1. Rationale

Breast cancer is the most commonly occurring cancer in women, comprising almost one third of all malignancies. It is second only to lung cancer as a cause of cancer mortality [1]. Around 60% of breast cancers in premenopausal women, and 70–80% in postmenopausal women, are hormone-dependent (estrogen receptor-positive [ER+]). In ER+ breast cancer, the level of Estrogen is a key factor for the initiation and progression of breast cancer [2-5]. To exert its functions in different

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Original Investigation

A prognostic study on the effect of post-traumatic stress disorder on cerebral ischaemia reperfusion-induced stroke

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Ravi Chandra Sekhara Reddy Danduga & Phani Kumar Kola

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Abstract

Objectives

Previous studies have been established that persons who experienced a stroke are soon likely to develop several anxiety disorders. In which one of the major anxiety disorders is Post-traumatic Stress Disorder (PTSD). Yet, the likelihood of PTSD in conjunction with cerebral stroke has not been well described. Hence, we evaluated

the impact of PTSD on cerebral stroke in rodents subjected to single prolonged stress (SPS) and bilateral common carotid artery occlusion (BCCAo), respectively.

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Design, synthesis, anticancer evaluation and molecular docking studies of chalcone linked pyrido[4,3-b]pyrazin-5(6*H*)-one derivatives

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ABSTRACT

A series of novel chalcone derivatives pyrido[4,3-b]pyrazin-5(6H)-one (**10a-j**) were designed, synthesized and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and mass spectral data. Further, all derivatives were tested for their anticancer activities against five human cancer cell lines such as MCF-7 (breast cancer), A-549 (lung cancer), Colo-205 (colon cancer), A2780 (ovarian cancer) and DU-145 (prostate cancer) by employing MTT assay. The clinically used drug etoposide was used as standard reference and the anticancer activity was expressed as the IC_{50} in μM. Among the ten compounds examined compounds, **10b, 10c, 10d, 10h**, and **10i** possessed more promising anticancer activity. A molecular docking study implying ATR kinase was carried out to observe the binding mode of chalcone derivatives pyrido[4,3-*b*]pyrazin-5(6*H*)-one (**10a-j**) on the active site of ATR kinase. The most promising compound, **10h** showed $\pi-\pi$ stacking interaction of trimethoxy phenyl and pyridone moiety with the residue Trp850, while the carbonyl (α,β-unsaturated carbonyl) and methoxy functions showed H-bond interaction with the residue Ser773 and Thr856 respectively.

1. Introduction

Nitrogen atoms contained hetero-aromatic skeletons are very crucial intermediates in medicinal chemistry because of their numerous biological applications [1–3] including anticancer activities [4–28]. Among the nitrogen heterocyclic, 2-pyridones are most significant class of nitrogen having six-membered heterocyclic compound and possessed wide range of therapeutic applications including antitumor [29], anti-tuberculosis [30], antibacterial [31], anti-hepatitis B virus [32], cardiotonic [33], and also inhibitors of CDK4, EGFR, P38 [34–37]. They are present as active pharmacophores in several natural compounds with biological activity [38–41]. 2-Pyridone nucleus contained chemotherapeutic drug candidate such as Topotecan (**A**) (Fig. 1), is an FDA approved DNA topoisomerase-I inhibitor used for treatment of cancers [42]. Similarly chalcones are excellent compounds having α,β-unsaturated ketone functionality. They are used as precursors of flavonoids, isoflavonoids and have been widely explored as important structural units in the drug development [43]. Chalcones demonstrated a variety of biological activities like antioxidant [44], cytotoxic [45], antituberclosis [46], anticancer [47], antibacterial [48], induceapoptosis [49], antimitotic [50], antimalarial [51], antifungal [52], antioncogenic [53], anti-inflammatory [54], cardiovascular [55], antileishmanial [56], hyperglycaemic [57] and antiviral [58]. Licochalcone (**B**), a human DNA topoisomerase-I inhibitor contains chalcone as a structural unit (Fig. 1) [59]. On the other hand pyrazine is also an important class of heterocycle present in anticancer drugs bortezomib (**C**) [60], and 8DY (**D**) [61]. Some of the pyrazines like 8DY (**D**), compounds; **E, F**, and **G** are also reported as ATR kinase inhibitors [61–64]. Ataxia Telangiectasia and Rad3-related (ATR) kinase is an important target for many anticancer drugs [65].

We are inspired by the above biological information of both skeletons such as pyrazine pyridine, chalcone and in continuance efforts, we have design and synthesized a library of chalcone derivatives of pyrido[4,3-*b*]pyrazin-5(6*H*)-one (**10a-j**) and evaluated their anticancer activity against five human cancer cell lines, such

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Research Article

Design, Development And Evaluation Of Antidiabetc Matrix Tablets Using Natural And Synthetic Polymers

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ABSTRACT

This research was conducted to create anti-diabetic tablets from chemicals that have been compressed using a mechanized direct compression process. The tablets were chemically tested and their release in-vitro experiments were also performed. Different batches of hydrophilic polymer content and Karaya Gum formed tablets with uniform hardness (3-4mm) and thickness (2-3mm). The friability (0.29-0.51%), weight variance (1.18-2.54%), and Substance quality (95.40-98.86%) of multiple tablets was identified inside the limits prescribed. The swelling degree was associated with polymer standard irrespective of whether it was a diluent or polymer. The release profile showed that increasing the concentration of the copolymer had retarded the release of Gliclazide irrespective of the kind of polymer used. Both drug release from all matrix tablets is caused by polymer swelling and relaxation with ratio lies 0.45 to 0.89. Therefore, the FTIR study showed no chemical reactions between medication and polymers used. According to the samples, the sample was found to be hard and the overall substance concentration was over 98 percent at the end of the study. Among the formulations in which F2 HPMCK100M hydrochloride tablets have the best continuous release of glipizide. Using triggered epilepsy rats to evaluate the time course of the drug.

Key words: Matrix tablets; Sustained release; Gliclazide;Direct compression; In- vitro release.

INTRODUCTION

Over the past couple of years, new drug entities have been more expensive and complicated to produce. Thus, focus has changed from old fashioned treatment to extended- or controlled-release drugs [1]. That is the safest way to prescribe drugs through the mouth. Tablets are unit solid dosage types that have medicinal in them. Tablets are reasonably versatile in formulation and can vary from basic immediate release dosage type to prolonged or modified release [3].

Controlled drug delivery system includes the drug being delivered at a predetermined rate, for a specific period of time, or local or systemically throughout the body. In order to maintain the secure effective drug concentration in the body for a long time, fervour design is required for controlled drug release. A continuous prescription system which provides high plasma concentrations of drugs are important for a psychiatric healthcare system [4]. An on-going or controlled delivery system aims to minimise the dosage frequency and make the delivery of medicine more stable at the right site. The aim of drug therapy is to keep your blood or tissue healthy for a long time [5].

Diabetes mellitus is a metabolic disorder characterized by polyuria, polyphagia, polydipsia, unexpected weight loss, fatigue, and blurred vision. It is not a disease, but a disorder that requires continuous administration of drugs for its maintenance [6]. But continuous oral administration of drugs causes patient discomfort. Gliclazide is suitable for controlled oral release because of its limited biological half-life (about 12 hrs) and frequency of administration [7]. Creation of continuous release of an antidiabetic drug will retain the steady plasma volume of drug, lowering the amount of daily dosage, minimizing the local and systemic toxicity. Hence by formulating a sustained controlled release dosage form will offer advantages over convenient tablets and improves patient compliance.

MATERIALS AND METHODS

Gliclazide, hydroxypropylmethylcelluloseK4M, hydroxypropylmethylcellulose

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COMPARATIVE STUDY OF ANTI-INFLAMMATORY ACTIVITY OF GYMNEMA SYLVESTRE LEAVES AND STEM EXTRACT IN RATS

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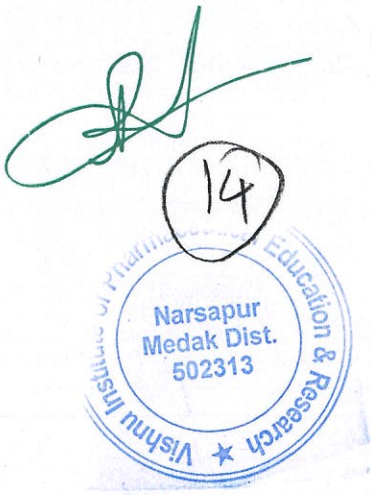

Machine Learning in Drug Discovery: A Review

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Abstract

This review provides the feasible literature on drug discovery through ML tools and techniques that are enforced in every phase of drug development to accelerate the research process and deduce the risk and expenditure in clinical trials. Machine learning techniques improve the decision-making in pharmaceutical data across various applications like QSAR analysis, hit discoveries, de novo drug architectures to retrieve accurate outcomes. Target validation, prognostic biomarkers, digital pathology are considered under problem statements in this review. ML challenges must be applicable for the main cause of inadequacy in interpretability outcomes that may restrict the applications in drug discovery. In clinical trials, absolute and methodological data must be generated to tackle many puzzles in validating ML techniques, improving decision-making, promoting awareness in ML approaches, and deducing risk failures in drug discovery.

Keywords Artificial intelligence · Drug discovery · Machine learning · Target validation · Prognostic biomarkers · Digital pathology

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Original article:

CORIANDRUM SATIVUM ATTENUATES MICROGLIA MEDIATED NEUROINFLAMMATION AND MPTP-INDUCED BEHAVIORAL AND OXIDATIVE CHANGES IN PARKINSON'S DISEASE MOUSE MODEL

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ABSTRACT

Coriandrum sativum Linn. (family: Umbelliferae; *C. sativum*), is a potential herb widely used as a spice and traditional medicine. In the present work, the effects of *C. sativum* fruit extract (CSE), against lipopolysaccharide (LPS)-stimulated BV-2 microglia-mediated neuroinflammation *in vitro* and 1-methyl-4 phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) animal model *in vivo* was investigated. LPS-stimulated increase in nitric oxide (NO), inducible NO synthase, cyclooxygenase-2, interleukin-6 and tumor necrosis factor-alpha were significantly ($p < 0.05 \sim p < 0.001$) inhibited by CSE (25, 50 and 100 µg/mL) in BV-2 microglial cells. Further, CSE inhibited the LPS-induced nuclear factor of kappa-beta activation and IκB-α phosphorylation in BV-2 microglia. *In vivo* studies, CSE (100, 200 and 300 mg/kg) ameliorated the MPTP (25 mg/kg, i.p.)-induced changes in locomotor, cognitive and behavior functions evaluated by rotarod, passive avoidance and open field test significantly ($p < 0.05 \sim p < 0.001$). The MPTP-induced changes in brain oxidative enzyme levels such as superoxide dismutase, catalase, and lipid peroxidation were significantly ($p < 0.01$ and $p < 0.001$ at 200 and 300 mg/kg, respectively) restored with CSE treatment. High-performance thin-layer chromatography fingerprinting analysis of CSE exhibited several distinctive peaks with quercetin and kaempferol-3O-glucoside as identifiable compounds. In conclusion, our study indicated that CSE attenuated neuroinflammatory processes in LPS-stimulated microglia *in vitro* and restored the MPTP-induced behavioral deficits and brain oxidative enzyme status *in vivo* proving its therapeutic potential in the treatment of neuroinflammatory and oxidative stress-mediated neurodegeneration seen in PD.

Keywords: *Coriandrum sativum*, microglia, lipopolysaccharide, interleukin, oxidative stress, MPTP, Parkinson's disease

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Design, synthesis and biological evaluation of selective hybrid coumarin-thiazolidinedione aldose reductase-II inhibitors as potential antidiabetics

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ABSTRACT

Thiazolidinediones (TZD), benzopyrans are the proven scaffolds for inhibiting Aldose reductase (ALR2) activity and their structural confluence with the retention of necessary fragments helped in designing a series of hybrid compounds 2-(5-cycloalkylidene-2,4-dioxothiazolidin-3-yl)-N-(2-oxo-2H-chromen-3-yl)acetamide **(10a-n)** for better ALR2 inhibition. The compounds were synthesized by treating substituted 3-(*N*-bromoacetyl amino) coumarins **(9a-d)** with potassium salt of 5-cyclo alkylidene-1,3-thiazolidine-2,4-diones **(4a-d)**. The inhibition activity against ALR2 with IC_{50} values range from 0.012 ± 0.001 to 0.056 ± 0.007 μM. N-[(6-Bromo-3-coumarinyl)-2-(5-cyclopentylidene-2,4-dioxothiazolidin-3-yl)] acetamide **(10c)** with cyclopentylidene group on one end and the 6-bromo group on the other end showed better inhibitory property (IC_{50} = 0.012 μM) and selectivity index (324.166) against the ALR2, a forty fold superiority over sorbinil, a better molecule over epalrestat and rest of the analogues exhibited a far superior response over sorbinil and slightly better as compared with epalrestat. It was further confirmed by the *insilico* studies that compound **10c** showed best inhibition activity among the synthesized compounds with a high selectivity index against the ALR2. In *invivo* experiments, supplementation of compound **10c** to STZ induced rats delayed the progression of cataract in a dose-dependent manner warranting its further development as a potential agent to treat the diabetic secondary complications especially cataract.

1. Introduction

Diabetes mellitus (DM) is one of the leading metabolic disorders with an estimated 200 million casualities of morbidity and mortality. Under hyperglycemic conditions more than 30% of the blood glucose is converted by the aldose reductase (AR) [1] to the sorbitol causing diabetes and secondary complications such as retinopathy, neuropathy, nephropathy and cataracts [2–5]. Then sorbitol is converted to fructose by sorbitol dehydrogenase in the polyol pathway. Hence, a better strategy to treat the long term complications of diabetes is to inhibit the first step of polyol pathway (AR) with molecules like sorbinil, epalrestat, fidarestat but these too suffer from serious side effects [6–9].

AR is a member of the AKR (Aldo Keto Reductase) super family, composed of approximately 315–330 residues, generally form monomeric proteins with a molecular weight of 36 kDa [10,11] adopting an α/β-TIM barrel structure [12–14] located in the cytosol of most of the cells but not equally distributed. The major physiological role of AR appears to be the removal of potentially toxic aldehydes generated during lipid peroxidation, such as 4-hydroxy-*trans*-2-nonenal (HNE) and their glutathione adducts (GS-HNE), which are reduced more efficiently than glucose by AR [14–16]. The pathogenesis of diabetic complications in polyol pathway can be due to various reasons like sorbitol-osmotic effects, depletion of myoinositol [17], subsequent perturbations in Na+/K + ATPase activity [18], disturbances in cellular redox and free radical defense, increased oxidative and glycation stress [19], activation of PKC [20], nitric oxide (NO) mediated vascular tone [21] and

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Implications of superporous hydrogel composites-based gastroretentive drug delivery systems with improved biopharmaceutical performance of fluvastatin

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ABSTRACT

The present research work describes the systematic development and characterization of novel gastroretentive drug delivery system containing superporous hydrogel composites for improving the bioavailability and anti-hyperlipidemic activity. The superporous hydrogels of fluvastatin exhibited swelling property in presence of the gastric fluid and retains inside the stomach to provide controlled drug release action. These hydrogels were systematically developed and optimized using Box-Behnken design, which includes the concentration of glutaraldehyde (X_1), Span 80 (X_2) and polyvinyl alcohol (X_3) as the independent variables, while swelling ratio (Y_1) and *in vitro* drug release (Y_2) were taken as the dependent variables. The prepared hydrogel formulations were also evaluated for density, porosity and void fraction as their physical properties. DSC and FT-IR study was performed to analyze the drug-excipient interactions. SEM imaging was performed for the morphological characterization of the prepared superporous hydrogels. *In vivo* pharmacokinetic study was conducted for evaluating the drug absorption and elimination parameters, while the pharmacodynamic study was performed for evaluating the antihyperlipidemic activity of the superporous hydrogel formulation. Overall, the studies indicated that optimized superporous hydrogel formulation with improved biopharmaceutical performance.

1. Introduction

Superporous hydrogels (SPHs) are 3D-assemblies of the hydrophilic polymers, which are formed by interaction with the nonorganic solvents. It can suit a lot of liquid rapidly because of the nearness of interconnected minute pores [1]. In contrast the regular hydrogels like acrylamides and cellulosic subordinates, the SPHs exceptionally possess higher surface area and inter/intra-particle void space. This characteristic allows SPHs to hold a lot of liquid and undergoes swelling for multifold augmentation in the surface area. Moreover, these hydrogels being highly biocompatible and biodegradable, thus possess high value in fields like pharmaceutical, biological and material science research [2]. Medications required to be delivered to the duodenum or a lower portion of the gastrointestinal tract has a maximal absorption window of the drug in this region only. Thus, the use of a gastroretentive drug delivery system works very well for such drugs owing to their excellent ability to expand for maximal gastric retention time [3].

Superporous hydrogels are gaining high popularity over the conventional hydrogels for their applicability in designing the gastro-retentive drug delivery systems. Administration of the superporous hydrogels through the oral route can leads to the swelling of the hydrogel inside the stomach due to water permeability and adsorption capacity [4]. Higher mechanical strength, swelling capacity, and acidic resistance nature are the unique properties of the SPHs. Swollen hydrogels are sufficiently able to withstand the weight, scraped area and shear forces in the stomach by gastric liquids. A list of variables tends to influence the performance of the SPHs which include the concentration of the hydrophilic polymer, pore structure, network strength, swelling index, durability and tensile strength of the polymeric network, and gastric acid stability [5].

Fluvastatin is an antihyperlipidemic agent that intensely represses the hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase enzyme

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Original article:

PHOSPHOINOSITIDE 3-KINASE INHIBITOR AS605240 AMELIORATES STREPTOZOTOCIN-INDUCED ALZHEIMER'S DISEASE LIKE SPORADIC DEMENTIA IN EXPERIMENTAL RATS

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ABSTRACT

The quest for chemical entities able to curb the action of the phosphoinositide 3-kinase, (PI3K)/protein kinase B (AKT) signaling pathways is evolving as a potential therapeutic strategy for the treatment and/or prevention of neurodegenerative disorders including Alzheimer's disease (AD). In this study, the effects of a PI3K inhibitor, AS605240 on cognitive dysfunction and antioxidative defense parameters against intra-cerebroventricular-streptozotocin (ICV-STZ)-induced rat model of sporadic AD was evaluated. ICV administration of a single dose of STZ (3 mg/kg) was performed to induce behavioral and biochemical changes in rats using the stereotaxic technique. Animals were administered with varying doses of AS605240 (5, 10 and 15 mg/kg) orally, 1 h before ICV-STZ on day 1 and continued once daily for four weeks. The behavioral parameters (passive avoidance and Morris water maze), antioxidative defense parameters, amyloid-beta (Aβ) protein expression by Western blotting and immunostaining technique were estimated in brain tissue. AS605240 dose-dependently and significantly ($p < 0.05$ and $p < 0.01$ and $p < 0.001$) improved ICV-STZ-induced cognitive impairment and attenuated the altered antioxidative related parameters including superoxide dismutase, lipid peroxidation, glutathione and nitrite levels. Further, the increased Aβ protein expression levels in brain tissue were markedly restored with AS605240 treatment. In conclusion, our study demonstrated that AS605240 exhibited immense potential in attenuating STZ-induced sporadic AD features in rats and may be developed as a therapeutic agent in the treatment and management of sporadic AD.

Keywords: Alzheimer's disease, AS605240, PI3K inhibitor, streptozotocin, intra-cerebroventricular injection, oxidative stress, cognition

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Research Article

Mathematical Three - Compartment Model Analysis of Cholesterol Transport in Human and its Cardiovascular Related Dysregulation

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ABSTRACT

Background: Cholesterol is a crucial basic and utilitarian substance in the human body which is just marginally soluble in water and in this way doesn't effectively flow in the circulation system. Besides, to control the circulatory transporting system of cholesterol in lipoproteins, a measure of cholesterol present relies upon and is constrained by cholesterol dietary intake content, internally de novo synthesis, utilization, and elimination; anomalous as well as uneven cholesterol levels have been appeared to prompt serious results, e.g., cardiovascular infections.

Results: To estimate high risk for the threat of cardiovascular disease and events due to imbalance cholesterol homeostasis leading to cause atheromatous plaque accumulation in the cardiovascular system. We have designed and developed a customized three-compartment model where it describes the first compartment defined as total cholesterol concentration present in the liver, consequently the second compartment defined as total cholesterol concentration present in the circulatory blood (bloodstream), and lastly the third compartment defined as total lipid concentration in the cardiovascular system. As per our study belief was to estimate the amount, rate, and concentration of cholesterol in the third compartment for which we have done a detailed review of physiological model parameters systemic blood flow circulation from the liver to the heart. The varying C_3 were estimated to be predictable i.e. lowers and raises blood cholesterol concentration levels in the third compartment for k_{32}= 0.8 min^{-1} and k_{32}= 1.2 min^{-1}. Further on, C_3 increases followed by intake of a dietary meal rich in cholesterol content for a time interval of up to 3 h. Other conditions to cause an extreme rise in levels of bad cholesterol i.e. LDL levels (by postulating the value of m_{tis} as 0 mg/min) which can be opposed by hindering endogenous cholesterol synthesis thus held by sinking the values of k=500mg^2/min. Brisk of cholesterol flow between compartment II and III has been concurrently adjusted to monitor C_3 fluctuations by decreasing k_{23}=0.1 mg/min or escalating k_{32}= 1.3 mg/min.

Conclusion: Dyslipidemia is a significant reason for cardiovascular syndrome, which is the most profound cause of death over the globe. Mathematical modeling of cholesterol homeostasis representing in a three-compartment model can help in aid choice of ideal precautionary measures and therapeutic strategies for cardiovascular-related diseases.

Keywords: high blood cholesterol, LDL, HDL, mathematical modeling, cardiovascular system, cardiovascular disease.

BACKGROUND

Physiological process of cholesterol synthesis

Cholesterol is a very crucial organic molecule of the human body that has roles in various cellular functioning and also responsible in synthesizing the steroid hormones, the bile acids, and nutrients like vitamin D. Cholesterol obtained from the nutritional diet and de novo synthesis is arranged in the form of protein-lipid complex particles which is carried through the systemic blood circulation in the human body [7, 8, 14, 23].

The stepwise division of cholesterol synthesis accordingly as [3, 9]:

1. Mevalonate synthesis
2. Isopentenyl phosphate synthesis
3. Squalene formation
4. Lanosterol synthesis
5. Cholesterol formation.

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Mathematical Model Of Thenfkβ Activating Interleukin-1β Through Caspase-1 Enzyme

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ABSTRACT:
The Caspase-1 enzyme is one of the crucial elements in activating the protein synthesis of interleukin-1β and leading its corresponding signaling transduction. On the contrary, intense signaling through IL-1β contributes to acting as an inflammatory mediator and further responsible to align various inflammatory-related diseases. We designed and developed an optimistic non-linear ordinary differential equation model of NFkβ activating IL-1β through the Caspase-1in the genetic regulatory path in macrophage cells. A representation of genetic transcription and translation of IL-1β is included in the mathematical compartment model, which is subsequently enabled by the Caspase-1 enzyme, which is a prime regulator of the transduction of IL-1β signals.In the case of body normal physiology, intense signal transduction due to IL-1β subsequently causes the regulation reduction of Caspase-1 activation through genetic control of NFKβ. The calculated parameter values from various literature held to understand the compartment model involve the rate of gene transcription and translation of IL-1β and its control effect through cellular Caspase-1transcribed enzyme level. The genetic process represented in the form of a compartment model of IL-1β signal transduction and its analysis spectacles that the positive state of the signal transduction capable of producing oscillatory convergence signal with consequent increase and decrease in parameter condition. We aimed to find how inflammatory mediator (IL-1β) is maintained within the immune cellular system and the harnessing benefit of our compartment model design and development are elaborated concerning other models of genetic control within the reviewed literature.
Keywords: Interleukin-1β, Caspase-1, NFkβ, Transcription, Translation, Oscillatory convergence.

1. INTRODUCTION

As an essential inflammatory mediator through immune cells, IL-1β is considered for the regulation of the signaling pathway of inflammation and consequently builds immune stability. However, intense signaling of inflammatory mediators IL-1β causes severe inflammation related to cellular stress and trauma, whereas an inadequate level of IL-1β causes immunocompromised cellular destruction [2]. Furthermore, Caspase-1 synthesis and NLRP1 activation is a prime modulator of IL-1β with the management of inflammation induces cellular stress and immune imbalance, thus at the cornerstone of managing inflammatory-related disorders [4]. It is therefore essential to strictly regulate the genetic

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RESEARCH ARTICLE

Synthesis and Biological Potentials of 5-aryl-*N*-[4-(trifluoromethyl) phenyl]-1,3,4-oxadiazol-2-amines

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Abstract: Oxadiazoles are an important class of heterocyclic compounds, having broad-spectrum activity. They were also reported as anticancer, and antioxidant agents, hence it is of significant importance to explore new oxadiazoles. A series of eleven (5-aryl-*N*-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2-amines (**6a-k**) was synthesized based on the structures of reported compounds, SU-101, IMC38525, and FTAB. All these oxadiazoles were synthesized, characterized by spectral data, and further tested against melanoma, leukemia, colon, lung, CNS, ovarian, renal, breast and prostate cancer cell lines' panels at a single dose of 10 µM drug concentrations. *N*-(4-(Trifluoromethyl)phenyl)-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-amine (**6h**) showed significant anticancer activity, and the most sensitive five cell lines were NCI-H522 (% GI = 53.24), K-562 (% GI = 47.22), MOLT-4 (% GI = 43.87), LOX-IMVI (% GI = 43.62), and HL-60(TB) (% GI = 40.30). The compound, **6h** revealed better %GIs than imatinib, against 36 cell lines, taking 54 cell lines in common. The maximum sensitivity was recorded against cancer cell line CCRF-CEM (% GI = 68.89) by 2-(5-(4-(trifluoromethyl) phenylamino)-1,3,4-oxadiazol-2-yl)phenol (**6f**). The antioxidant activity of 4-(5-(4-(trifluoromethyl) phenylamino)-1,3,4-oxadiazol-2-yl)-2-methoxyphenol (**6i**) was promising with an IC_{50} of 15.14 µM. It was observed that the oxadiazoles reported herein showed significant anticancer and antioxidant activities.

Keywords: Anticancer, antioxidants, DPPH assay, oxadiazoles, one dose assay, heterocyclic compounds.

1. INTRODUCTION

In spite of drops in mortality by 1.7%, cancer is still a second leading cause of bereavement, and nearly 8.8 million death tolls were recorded in 2015 [1, 2]. The condition would become more excruciating over the next two decades with an estimated 70% increase in the new cancer cases. Cancers can be prevented between 30-50% by avoiding risk factors, and implementation of preventive strategies based on evidence [3]. Chemotherapy, surgery, radiation, immunotherapy, hormone therapy, *etc.*, are different types of cancer treatments. The chemotherapy is a major approach of cancer treatment, however, it is always associated with an acrid experience of toxicity, genotoxicity, and drug-resistance [4]. Medicinal Chemistry being based on drug discovery programme, may, able to fight against cancer by providing new avenues to synthesize new compounds of medicinal im-

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ORIGINAL PAPER

Structure-based discovery of small molecule APC-Asef interaction inhibitors: In silico approaches and molecular dynamics simulations

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Abstract

Colorectal cancer, which is considered one of the leading causes of mortality worldwide, develops through the formation of benign polyps on the inner colon or rectum wall. Truncations in adenomatous polyposis coli (APC) gene lead to the spread of the disease in the entire colon region when combined with the guanine nucleotide exchange factor (GEF) Asef. A series of peptidomimetic agents were previously discovered as protein-protein interaction inhibitors that can target the APC-Asef interface. Structure-based virtual screening (SBVS), using a set of docking methods combined with molecular dynamics simulations, was carried out to identify new small drug-like agents. After the initial screening process, compounds with diverse chemical scaffolds and direct interaction with Arg549 and other active site residues were chosen and subjected to induce fit. The amide functional group found in the ligand hit structures showed strong interactions with Arg549, leading to observable conformational changes that allow suitable positioning within the peptide binding site. Furthermore, the pH-specific MD simulations of the top hit 838 within the APC-Asef binding site depicted significant interactions required for biochemical recognition in changing microenvironment. Predicted inhibitory constant (Ki) values and binding free energies of hits further described the significance of the amide group over the other chemical scaffolds. This combination of in silico approaches provides key insights for colorectal drug discovery programs targeting the APC-Asef interaction.

Keywords Adenomatous polyposis · Colon cancer · Migration · HTVS · MD simulations · Mechanisms

Highlights
- Colorectal cancer is second leading cause of cancer death worldwide
- APC-Asef complex causes cancer cell migration in the intestine
- SBVS and MD simulations yielded 16 small molecules as APC-Asefinhibitors
- Ligand amide bonds are required for effective binding
- Arg549 can act as an amide bond detector to open the binding site

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00894-020-04467-5) contains supplementary material, which is available to authorized users.

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Introduction

Cancer is the second major cause of mortality across the globe, with over 9 million deaths reported last 2018 [1]. According to the World Health Organization (WHO), cancer causes approximately 1 in 6 deaths and is a principal threat to low- and middle-income countries. Colorectal cancer is the third most common type of cancer, accounting for 1.8 million cases, and is the second leading cause of cancer death worldwide [1]. The development of colorectal cancer requires years and mostly involves the formation of benign polyps. These polyps evolve into aggressive colorectal adenocarcinoma and spread across the colon and rectum [2]. Depending on the stage (I–IV) of the colorectal cancer, treatment options include surgical procedures, chemotherapy, targeted therapy, and radiation therapy [3]. Targeted therapy is an established alternative in combating colorectal cancer using small molecule inhibitors and is known to have less side effects than chemotherapy drugs and other cancer treatment regimens [3].Current chemotherapy or targeted drugs can inhibit or prevent the growth of cancer cells but not their migration. The exploration

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RJPT

RESEARCH ARTICLE

Development and Validation of UV-Spectroscopic methods for simultaneous Estimation of Hydrocortisone and Iodoquinol in Tablet Dosage Forms

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ABSTRACT:

A simple, precise, accurate and economical UV-Spectrophotometric method has been developed and validated for the simultaneous estimation of Hydrocortisone and Iodoquinol in combined pharmaceutical dosage form using simultaneous equation method. Hydrocortisone has absorbance maxima at 245nm and Iodoquinol has absorbance maxima at 250nm in Methanol. The drugs obeyed beer's law in the concentration range of 10-60µg/ml for Hydrocortisone and 5-30µg/ml for Iodoquinol. The correlation coefficient of Hydrocortisone and Iodoquinol was found to be 0.999 and 0.999 respectively. The method was statistically validated as per the ICH guidelines. The low RSD values indicate good precision and high recovery values indicate accuracy of the proposed method. The developed method was simple, precise, accurate, reproducible and economical which can be efficiently and easily applied to pharmaceutical dosage form.

KEYWORDS: Hydrocortisone, Iodoquinol, UV-Spectroscopic method.

INTRODUCTION:

Hydrocortisone (Hydro) is chemically (1S,2R10S,11S,14R,15S,17S)- 14,17- dihyroxy-14 -(2-hydroxyacetyl)- 2,15-dimethyl tetracyclo [8.7.0.0^{2,7} heptadec- 6- en-5- one. HYDRO belongs to Anti-inflammatory Agents. Structure of Hydro was shown in figure 1[1].

Diiodohydroxy quinoline also known as Iodoquinol, is a quinoline derivative that can be used in the treatment of Amoebiasis. Iodoquinol (Iodo) is chemically 5,7-diiodoquinolin-8-ol. Structure of Iodo was shown in Figure 2[2].

Literature studies revealed that there is no method till date developed for the estimation of these two drugs in

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Research Article

SYNTHESIS, CHARACTERIZATION, AND ANTICANCER ACTIVITY OF SOME NOVEL ACRIDINE DERIVATIVES

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ABSTRACT

Objective: The objective of the study was to synthesize and evaluate the anticancer activity of some novel acridine derivatives.

Methods: The present works involve condensation of acridine and various 2, 4-Thiazolidine-2,4-dione derivatives (2a–2h) with chloroacetyl chloride to give a novel acridine derivatives (5a–5l), respectively.

Results: All the newly synthesized molecules (5a–5l) were characterized by FTIR, H^1-NMR, and mass spectral analysis along with physical data. The biological potentials of the new synthesized compounds are evaluated for their *in vitro* anticancer activity by MTT assay.

Conclusion: The synthesized compounds 5a, 5f, and 5h exhibited good anticancer activity against MCF-7 and SKVO3 cancer cell lines at a concentration of 0.5 mg/mL^{-1}.

Keywords: Acridine, 2, 4-Thiazolidinedione, Substituted aldehydes, Chloroacetyl chloride, Anticancer activity, MCF-7, SKVO3 cells.

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INTRODUCTION

Acridine was first isolated by Carl Grabe and Heinrich Caro in Germany in 1870 from high boiling fraction of coal tar [1]. The antimicrobial property [2] of acridine was discovered Ehrlich and Benda in 1917. Bernthsen reported the primary synthesis of acridine, in which diphenylamine was reacted with benzoic acid using zinc chloride and high temperatures. The synthesis of acridine and its derivatives has attracted considerable attention from untreated and medicinal chemists for many natural life, as a number of natural source have been report to have this heterocyclic nucleus. Chemically, acridine is also known by the names of dibenzopyridine, 2,3,5,6-dibenzopyridine, and 10-azaanthracene. It has an irritating odor and crystallizes in colorless to light yellow needles with melting point of 110°C and boiling point of 346°C.

Acridine is a class of heterocyclic compounds which merit special attention because it belongs to a group of substances with activity in medicinal chemistry. This try cyclic nucleus derivatives are associated with anti-inflammatory [3,4], anticancer [5], antimicrobial [6], antitubercular [7,8], antiparasitic [9], antimalarial [10,11], antiviral [12,13], and fungicidal activities [14]. The basic in nature of pyridine, quinoline, and acridine is more or less similar compounds which possess no benzene ring, one benzene ring, and two benzene rings, respectively. Acridone is the one of the heterocyclic compounds with a tricyclic ring having nitrogen at 10^{th} positions and keto group at 9^{th} positions with the formula $C_{13}H_9N$. Acridines are substituted derivative of the parent ring. It is a planar molecule so as to be structurally related to anthracene by means of one of the central CH groups replaced by nitrogen.

In view of the facts mentioned above and the wide applications of acridine molecule and its derivatives in medicinal chemistry, an attempt has been made to synthesize novel 3-(2-(9-oxoacridin-10(9H)-yl) acetyl)-5-(benzylidene) thiazolidine-2,4-dione moiety as new anticancer agents.

METHODS

The synthesized compound was screened for sterile and anticancer activities. Fourier transform IR spectrometer (model Shimadzu 8700) in the range of 400–4000 cm^{-1} using KBr pellets and values are report in cm^{-1} and the spectra were interpreted. ^{1}H-NMR spectra were recorded on DPX-200 MHz NMR spectrometer using DMSO-d_6 and chemical shift (δ) is reported in parts per million downfield from internal reference tetramethylsilane and the spectra were interpreted. Mass spectra were record on mass spectrophotometer (model Shimadzu) by LC–MS and the spectra were interpreted. Pre-coated silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compound: n-Hexane: ethyl acetate (7:3) [15-17].

General procedures

Step 1: Preparation of N-phenyl anthracitic acid

In a 500 ml round-bottomed flask are placed a combination of o-Chlorobenzoic acid (20 g, 0.128 mol), Aniline (11.8 ml, 0.128 mol) and Copper metallic (0.5 g). To this solution 100 ml of amyl alcohol is delivered with constant stirring. To this mixture, dry potassium carbonate (20 g) was slowly added with stirring and the reaction mixture was allowed to reflux for 6 h in a light liquid paraffin oil bath at 135–140°C. Then the amyl alcohol was removed by using steam distillation and combination poured into two 2 L of hot water and acidified with targeted hydrochloric acid. The bluish-black precipitate formed was filtered, washed with hot water, and collected. The crude acid was dissolved in aqueous 10% sodium hydroxide solution, boiled in the presence of activated charcoal, and filtered. On acidification of the filtrates with concentrated hydrochloric acid, light yellowish precipitate was obtained, which was washed with hot water. The crude acid was recrystallized from aqueous methanol to give a light yellow solid.

Step 2: Preparation of acridin-9-one

N-Phenyl anthranilic acid (18 g, 0.084 mol) was taken in a 500 ml of round bottom flask to which polyphosphoric acid (180 g, 0.5327 mol) was added, shaken well, and refluxed on a water bath at 100°C for 3 h. Appearance of yellow color indicated the completion of reaction. Then, it was poured into 2 L of hot water and made alkaline by 25% ammonia solution. The yellow precipitate formed was filtered, washed with hot water, and collected. The crude acridin-9(10H)-one was recrystallized from acetic acid.

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Research Paper

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Nutritional Impact of Foods Made from Spirulina on Children of Selected Anganwadis of Siddipet District in Telangana State in India

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ABSTRACT

In the present investigation, we sought to study the impact of introducing spirulina based nutritional supplementation to the children of Siddipet District in Telangana, India. It was observed that beneficiaries are the social community who need help, support and awareness. An integrated, spectrum and holistic study approach was made to reach the beneficiary community. Several attempts were made to find out the answers to questions raised in the concurrent development of malnourished child health status in two ICDS projects, with 30 anganwadis in Bharat Nagar and 34 anganwadis in Cheriyal under Siddipet District, with the guidance and help of District Collector and team of company, Sukrutha Organics. The Study encompasses both primary and secondary source of information, covering anganwadis of ICDS, Bharat Nagar and Cheriyal, out of which 2119 children each were selected for the study by using information collected by anganwadi teachers scheduled as tool for data collection. Peanut Chikkis (Brittle) and Biscuits made by the addition of Spirulina were distributed among the test group and no supplement was given in the control group of children who were enrolled under Anganwadis of Bharat Nagar and Cheriyal ICDS of Siddipet District. Descriptive analysis was made to draw inferences. The study has come out with some major findings, in spreading the knowledge about the ill effects of malnutrition and benefits of spirulina and foods made with spirulina.

KEYWORDS: Malnutrition; Spirulina supplementation; healthy snacking.

Introduction

India's malnutrition problem results not from calorie intake but from dependence on a carbohydrate-based diet, low in protein and fat. We compromise on the intake of protein, fat and vitamins – all of which are essential for growth and inducing disease-fighting immunity at a young age. It is vital that Indian children get a balanced and nutrient-rich diet which includes all micro- and macronutrients need to bring about a healthy growth.

Poor maternal health and anemia during pregnancy is another reason for induction of stunting in children. This could have roots from adolescent anemia (Uliyar et al., 2000). This compromises resistance to diseases and nutrition value of breast milk. Poor pre-pregnancy body-mass index (BMI) and insufficient weight gain during pregnancy are common, as is blood and urine micronutrient deficiency. All of these, cause low birth weight, damaging the physiological development of a child. In many Indian households, women are taught to eat last, even when expecting.

Malnutrition or malnourishment is a condition that results from eating a diet in which nutrients are either not enough or are too much such that the diet causes health problems. It may involve calories, protein, carbohydrates, vitamins or minerals (Sandhu et al., 2010; Liu et al., 1991, Zhang and Liu, 1999). Not enough nutrients are called undernutrition or undernourishment while too much is called overnutrition. Malnutrition is often used specifically to refer to under nutrition where there is not enough a calorie, protein, or micronutrients. If under nutrition occurs during pregnancy, or before two years of age, it may result in permanent problems with physical and mental development. Extreme under nourishment, known as starvation, may have symptoms that include: a short height, thin body, very poor energy levels, and swollen legs and abdomen. People also often get infections and are frequently cold. The symptoms of deficiencies depend on the micronutrient that is lacking.

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Design, synthesis and characterization of novel paracetamol derivatives to target breast cancer

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Most breast cancers are Estrogen Receptor-positive type. In the mammary epithelial, estrogen controls many cellular activities such as proliferation, differentiation and migration. There are two genetically distinct and functional estrogen receptors (ERs), ERα and ERβ, belonging to the superfamily of nuclear receptors for steroid/thyroid harmones. Estrogenexert its functions in different tissues by binding with its receptors, including alpha and beta (ERα and ERβ). Estrogen Receptor alpha (ERα) controls breast tissue development and progression of breast cancer. Paracetamol is one of the most widely used medicines. A recent experimental study suggests that paracetamol may have several pharmacological effects other than its well known analgesic/antipyretic properties. The docking study was performed on different paracetamol derivatives using Schrodinger 2015 (maestro 10.1) on Human Estrogen Receptor Alpha Ligand-Binding Domain (1XP6) and Endothelial nitric oxide synthase (3NLE). The *in silico* studies indicate that N-(4-((1*H*-1,2,3-triazol-4-yl)methoxy)phenyl) acetamide derivatives exhibit comparable docking score and good hydrogen bond interactions at Ligand binding domain of ERα and 3NLE. Based on the docking studies, a new series of N-(4-((1*H*-1,2,3-triazol-4-yl)methoxy)phenyl) acetamide derivatives have been synthesized by employing click chemistry approach. Nine compounds have been evaluated for their cytotoxicity in MCF-7 cell line and anti oxidant activity. Many of the synthesized compounds exhibit potent cytotoxic and anti oxidant activity. In particular **5c**, **5g**, and **5b** compounds show most potent cytotoxicity with IC_{50} value of 19.83, 20.57, 20.83 µg/mL respectively and **5e** and **5f** show most potent anti oxidant activity with IC_{50} value of 0.4, 0.5 µg/mL respectively.

Keywords: N-(4-((1*H*-1,2,3-Triazol-4-yl)methoxy)phenyl)acetamide, click chemistry, docking, estrogen receptor, MCF-7 cell line, anti-oxidant activity

Estrogen receptor-positive (ER+) breast cancer is the most common type of breast cancer diagnosed today. There are many established risk factors forbreast cancer, including age, genetic alterations, family history, mammographic breast density, menstrual and menopausal his-tory, radiation exposure, and life style. In particular, thehormones, estrogen and/or progesterone, are known to be capable of increasing breast cancer risk[1-3]. According to the American Cancer Society, about two out of every three cases of breast cancer are hormone receptor positive. Most of these cases are ER+ or receptive to both estrogen and progesterone. In Estrogen receptor positive breast cancer the level of Estrogen is a key factor for the initiation and progression of breast cancer[4-7]. In the mammary epithelial, estrogen controls many cellular activities such as proliferation, differentiation and migration[8,9]. There are two genetically distinct and functional estrogen receptors(ERs), ERα and ERβ, belonging to the superfamily of nuclear receptors for steroid/thyroid harmones. The structural differences between the two ERs indicate that they serve distinct actions[10]. Estrogen exert its functions in different tissues by binding with its receptors, including alpha and beta (ERα and ERβ), the former is the major one involved in breast cancer and chosen as an important target for endocrine therapy in clinic[11].

Paracetamol is a widely used over-the-counter pain medication and medication to reduce fever[12]. Paracetamol is used in the management of more severe pain such as post surgical and cancer pain in combination with opioid analgesics. In addition to well known use pain relief and fever reduction, recent laboratory and pre-clinical studies have demonstrated

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RESEARCH ARTICLE

BENTHAM SCIENCE

Synthesis, Antiproliferative, and Antioxidant Activities of Substituted *N*-[(1,3,4-Oxadiazol-2-yl) Methyl] Benzamines

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Abstract: ***Background*:** Oxadiazole emerged as an important class of heterocyclic compound with diverse biological activities like anticancer, antitubercular, anticonvulsant, anti-tubulin, antimicrobial, anti-inflammatory, antioxidant *etc.*

***Objective*:** The objective of this study is to synthesis series of twelve substituted *N*-[(1,3,4-oxadiazol-2-yl)methyl]benzamines (**6a-l**) and their evaluation as antiproliferative and antioxidant agents.

***Methods*:** The substituted *N*-[(1,3,4-oxadiazol-2-yl)methyl]benzamines (**6a-l**) analogues were synthesized as per the reported procedure. The antiproliferative activity was tested against nine different panels cancer cell lines (leukemia, colon, renal, non-small cell lung, breast, CNS, melanoma, prostate, and ovarian cancer) at 10 μM drug concentrations as per the NCI US Protocol.

***Results*:** 2-(5-((3-Chloro-4-fluorophenylamino)methyl)-1,3,4-oxadiazol-2-yl)phenol (**6e**) revealed the significant antiproliferative activity among the series of title compounds (**6a-l**). The compound, **6e** showed maximum sensitivity towards CCRF-CEM, MCF-7, MOLT-4, T-47D, and SR cell lines with percent growth inhibitions (%GIs) of 79.92, 56.67, 39.62, 34.71 and 33.35, respectively. Furthermore, the compounds, **6e** and **6c** showed promising antioxidant activity with an IC50 value of 15.09 and 19.02 μM, respectively in DPPH free radicals (FR) scavenging activity.

***Conclusion*:** The present study may support a significant value in cancer drug discovery programme.

Keywords: Anti-proliferative agents, antioxidants, oxadiazoles, one dose assay, DPPH, free radicals scavenging activity.

1. INTRODUCTION

Cancer is the second leading cause of deaths worldwide. In 2015, 8.8 million cancers related deaths were reported, and the newer case of cancers would rise by nearly 19.3 million in the year 2025 [1]. The incidence of cancer was drastically increased in the last decades and its treatment has gained great importance. Chemotherapy is an important approach for cancer treatment, however, lack of selectivity and emergence of drug resistance and genotoxicity diminished their efficacy [2]. Therefore, the development of effective and safe anticancer agents remains a critically important area in medicinal chemistry. We reported herewith the preparation of oxadiazoles because they are important class

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Medicinal Chemistry & Drug Discovery

2-Mercapto Benzthiazole Coupled Benzyl Triazoles as New COX-2 Inhibitors: Design, Synthesis, Biological Testing and Molecular Modeling Studies

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A series of 2-mercapto benzothiazole linked with triazoles (**3a-u**) were designed based on our previous experimental evaluation of benzothiazole allied oxadiazoles and synthesized in two step starting from the 2-mercaptan precursor. The structure of the benzothiazoles were confirmed by infrared (IR), nuclear magnetic resonance (NMR) and mass (LC–MS) spectral data. The *insilico* binding mode interpretations in both COX-1/COX-2 was investigated, their probable binding energies were predicted and ADMET properties were calculated. The molecular level interactions of the designed library indicated, the aryl ring united with triazole was occupying as mefenamic acid in COX-2 active site. All the benzothiazoles **3a-u** were evaluated for their COX inhibitory activities as per the standard protocol reported elsewhere. 2-(((1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl) methyl)thio)benzo[d]thiazole **3i**, 4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzoic acid **3t** and 4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzamide **3u** based benzthiazoles showed the most significant COX-2 inhibitory activity with an IC_{50} of 4.1, 4.3 and 5.4 μM respectively. The time dependant increase in inhibition of inflammation of above COX-2 inhibitors in *invivo* anti-inflammatory evaluation was noticed. Additionally, 2-(((1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]thiazole **3g** expressed the significant DPPH scavenging activity with 80.45 percent inhibition at 100 μM and an IC_{50} of 27.8 μM. Furthermore, the 50 ns molecular dynamic simulations of 2-(((1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]thiazole **3i** to interpret the constant residue interactions might liable for the COX selectivity was presented. Later, they also have been tested for cancer lines at NCI and obtained data were provided.

Introduction

Inflammation is a spontaneous course of action to an injury or infection caused by pathological substances. The inflammatory pain is one among the other major cardinal signs and is induced by the release of chemicals, preferably inflammatory mediators.[1] The oxidative stress due to reactive oxygen free radicals and pain associated with autoimmune disorders like rheumatoid arthritis turns situation in to chronic conditions.[2] The involvement of cyclooxygenases (COX-1 and COX-2) in the conversion of prostanoids from arachidonic acid made them as privileged target for most of the Non Steroidal Anti-Inflammatory Drugs (NSAIDS) to reduce inflammatory pain.[3] The inhibition strategy of COX enzymes is an attractive way to circumvent the pain and majority of the COXIBs were become popular as COX inhibitors.[4] Though, COXIBs were potent anti-inflammatory agents and COX inhibitors; but they failed to inhibit the specific isoform COX-2 enzyme and resulted in gastric side effects which are linked with physiological activities COX-1 isoform.[5] Thus, the selective isoform specific COX-2 inhibitors needed to address the modern scenario.

Benzothiazoles is an important class of bicyclic compounds reported with diverse medicinal and industrial applications,[6] Anticonvulsant,[7-8] anticancer,[9] anti-inflammatory,[10-11] antimicrobial,[12] antitubercular,[13] insecticidal[14] and many other biological activities were reported for benzothiazoles. Benzothiazoles (containing sulphur) is an isosteric analogue of benzoxazoles (containing oxygen). The design of our scaffold is based on the structure of reported anti-inflammatory agents, Flunoxaprofen (**A**), Benoxaprofen (**A**),[15] PF-469327 (**B**) (mPGES-

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and biological evaluation of chalcone-linked thiazole-imidazopyridine derivatives as anticancer agents

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Abstract
A novel library of chalcone linked thiazole-imidazopyridine (**12a–j**) derivatives were designed, synthesized, and their structures were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral studies. Further, all compounds were tested for their anticancer effects on four human cancer cell lines including MCF-7 (breast carcinoma), A549 (lung carcinoma), DU-145 (prostate carcinoma) and MDA MB-231 (breast carcinoma) by employing MTT method, using etoposide as the positive control. Among them, compound **12b** displayed more potent anticancer activity against four cancer cell lines when compared to the positive control.

Keywords Imidazo[4,5-b]pyridine · Zolpidine · Licochalcone A · Chalcone and anticancer activity

Introduction

Now days, cancer is the second leading cause of death after heart disease in developed and undeveloped countries (John and Ross 2010), which is initiated by external (Park et al. 2010; Meffert et al. 2003; Clemens 1991) and internal factors (Mantovani et al. 2008; Clayton et al. 2011; Porta et al. 2011). Cancer treatment has become an important and challenging therapeutic task in medicinal chemistry. The three main treatment strategies employed are surgery, radiation therapy, and chemotherapy. Of these, chemotherapy is one of the important therapy used for the treatment of cancer, which employs chemotherapeutic agents. However, this is associated with various side effects. Hence, the discovery of potent anticancer agents without side effects is a challenge in development of cancer chemotherapeutics for the future generations.

Nitrogen-containing heterocyclic molecules has always attracted significant interest in pharmaceutical industry because of their biological applications. Nitrogen containing imidazo[4,5-b]pyridines are versatile nitrogenized fused hetero-aromatic units that have exhibited potent anticancer properties against a panel of cell lines (Agarwal et al. 2016; Ahsan et al. 2015; Durgesh et al. 2018a, 2018b, 2018c; Hatti et al. 2015a, 2015b; Madhavi et al. 2017b; Murthy et al. 2019; Pragathi et al. 2019; Rao et al. 2019; Reddy et al. 2016a, 2016b; Reddy et al. 2019; Shahinshavali et al. 2019; Spandana et al. 2018a, 2018b; Sreenivasulu et al. 2017; 2018; 2019; 2020; Subramanyam et al. 2018; Suma et al. 2019; Yakantham et al. 2019). It is a structural analog of a purine base. Its derivatives easily interact with the proteins of DNA and RNA. They also show a variety of biological properties like antimitotic (Temple 1990),

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Research Article

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Formulation and *in vitro* evaluation of superporous hydrogel based gastroretentive drug delivery system of vildagliptin

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ABSTRACT: Numerous medications, which have a tight restorative window and are consumed predominantly in the stomach have been created as a gastroretentive conveyance framework. Vildagliptin, an antidiabetic, is exceedingly temperamental at fundamental pH and is widely retained from the stomach. Henceforth there is a need to build up a gastroretentive framework. In this investigation a superporous hydrogel was created as a gastroretentive medication conveyance framework. Superporous hydrogels were readied utilizing a gas forming method utilizing N', N'- BIS as the crosslinking operator and polyvinyl Alcohol as a composite specialist. Swelling practices of the superporous hydrogel in acidic arrangement were concentrated to explore their applications for gastric maintenance gadget. The ideal arrangement state of superporous hydrogels was gotten from the swelling and *in vitro* medication discharge thinks about. FT-IR, SEM and DSC contemplates were utilized to portray the similarity between polymers. As the grouping of crosslinker expanded from 0.5 to 3% the porosities diminished. In reenacted gastric liquid superporous hydrogels demonstrated a decent increment in harmony swelling limit. Checking electron infinitesimal pictures plainly showed the arrangement of interconnected pore and slim channels. Portrayal thinks about uncovered that the expansion in crosslinker focus is beneficial from the swelling proportion, and yet the decline in porosity may prompt abatement in medication discharge rate by dispersion through these narrow channels. The medication discharge from superporous hydrogels appeared for a drawn out timeframe. Structure the discharge energy it uncovered that sedate pursues the Non – Fickian mechanism. FTIR and DSC ponders uncovered that there were no critical collaborations between the drug and polymers. In light of the portrayal thinks about, it was uncovered that superporous hydrogels could be utilized as a gastroretentive medication conveyance framework for vildagliptin in perspective on their swelling and delayed medication discharge qualities in acidic pH.

KEYWORDS: Vildagliptin; superporous hydrogel; crosslinking agent; polyvinyl alcohol; swelling ratio.

1. INTRODUCTION

In the present time focusing of the medication at a specific site has turned into a significant piece of pharmaceutical research. Be that as it may, different issues are watched while focusing of medication atom at explicit destinations, for example, quick end, debasement and short living arrangement time. In the course of the most recent couple of decades, the engaged has been made in structuring of gadget that can hold in the upper piece of the gastrointestinal tract (GIT) as far as improving medication home time of medication at focusing on locales. There are different advancements have been utilized for a gastroretentive gadget, for example, low-density systems [1], high-density systems [2], bioadhesive systems[3] and expanding systems[4]. However, these frameworks are influenced by different factors, for example, gastric liquid substance, brutal gastric condition, gastric constriction and nourishment content. These components bring about lessening gastric maintenance time. Superporous hydrogels based GRDDS have been structured by numerous scientists as a gastric maintenance gadget. They have the attributes to retain a lot of water and swell due to having a hydrophilic practical gathering in their structure. This swelling property is dependable to keep the detailing

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Research Article

Evaluation of In Vitro antiurolithiatic activity of *Terminalia Chebula*

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ABSTRACT

Population in an industrialized world is afflicted by urinary stone disease. Kidney stones are common in all kinds of urolithiasis.The present study explored the evaluation of in vitro anti urolithiatic activity of *Terminalia Chebula*. It was observed that the highest calcium oxalate crystals dissolution was observed in the Ethanol extract of *Terminalia Chebula*. It was found that Ethanol extract of *Terminalia Chebula* has shows efficiency to dissolve calcium oxalate.

Keywords: Anti urolithiatic activity, Ethanol extract, *Terminalia Chebula*, Neeri.

INTRODUCTION

Plants provide food, raw materials for medicine and various other requirements for the very existence of life from the origin of human beings.(1)..Even the current conventional medicine is using a lot of plant derived chemicals as therapeutic agents. The overuse of synthetic drugs results in higher incidence of adverse drug reactions has motivated humans to return to nature for safe remedies. Herbs and herbal drugs have created interest among the people by its clinically proven effects .(2). Therefore, there is a compelling need for detailed scientific validation of all traditional medicinal plant drugs to establish their efficacy and safety in light of modern science .(1).Kidney stone disease is a multi-factorial disorder resulting from the combined influence of epidemilogical,biochemical and genetic risk factors.(3). Urolithiasis is considered as the third most common affliction of the urinary tract. It refers to the solid non-metallic minerals in the urinary tract. It is a complex process that is a consequence of an imbalance between promoters and inhibitors in the kidney. The formation of kidney stones involves several phytochemical events beginning with crystal nucleation, aggregation and end with retention within the urinary tract. Among the several types of kidney stones, the most common are calcium oxalate stones representing upto 80% of the analyzed stones(4) .Calcium containing stones may be in the form of pure calcium oxalate(50%) or calcium phosphate(5%) and a mixture of both(45%) followed by magnesium phosphate(15-20%),uric acid(10%) and cystine(1%)(5) . It is estimated that at least 10% of the population in the industrialized part of the world is afflicted by urinary tract diseases and among these kidney stones are common with an annual incidence of 0.5 -1.9%. About 12% of the population of India is expected to have urinary stones and out of that 50% of cases encounter loss of one or both 2 kidneys with or without renal damage upto some extent(2) . Stone disease is 2-3 times more common in males, than in females(5). It has a reoccurence rate of 70-81% in males and 47-60% in females.In spite of substantial progress in pathophysiolgy and treatment of urolithiasis, there is no satisfactory drug being used in clinical therapy. Kidney dialysis, endoscopic stone removal and extra corporeal shock wave lithotripsy are prohibitively costly and reoccurrence is quite 1 common with these procedures(1) Data from in vitro and in vivo clinical trials revealed that phytotherapeutic agents could be useful as alternative therapy in the management of urolithiasis. Medicinal plants and their products are more useful, because they promote the repair mechanism in natural way(1). Pharmacological and phytochemical prospecting of medicinal plants based on traditional knowledge can lead to the discovery of new drug and development of pharmacologically important products for human health care(6) .Green medicines were safe and more dependable than the costly synthetic drugs,many of which have side effects(7) The selected plant Tridax procumbens have occupied an important place in Indian culture and folk medicines. This plant have been extensively in ayurvedic system of medicine and is used throughout India. It is used in Ayurvedic medicine for liver disorders,. hepatoprotection, gastritis and heatburn(8).The plant shows various pharmacological activities like immunomodulatory, Anti-diabetic, Anti-hepatotoxic, Anti-oxidant, Anti-inflammatory, Analgesic etc(9)

Materials and Methods

Plant Materials

The seeds of *Terminalia chebula* were collected from Sangareddy of Telangana in the month of January 2018. The plant was authenticated by D. Venkateshwara Rao, DeputyDirector, Telangana. Forest Academy, Dullapally, Hyderabad, Rangareddy District. The seeds were washed with tap water and dried under shade.

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Mini-review

A review on HCV inhibitors: Significance of non-structural polyproteins

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ABSTRACT

Hepatitis C virus (HCV) mortality and morbidity is a world health misery with an approximate 130–150 million chronically HCV tainted and suffering individuals and it initiate critical liver malfunction like cirrhosis, hepatocellular carcinoma or liver HCV cancer. HCV NS5B protein one of the best studied therapeutic target for the identification of new drug candidates to be added to the combination or multiple combination medication recently approved. During the past few years, NS5B has thus been an important object of attractive medicinal chemistry endeavors, which induced to the surfacing of betrothal preclinical drug molecules. In this scenario, the current review set limit to discuss research published on NS5B and few other therapeutic functional inhibitors concentrating on hit investigation, hit to lead optimization, ADME parameters evaluation, and the SAR data which was out for each compound type and similarity taken into consideration. The discussion outlined in this specific review will surly helpful and vital tool for those medicinal chemists investigators working with HCV research programs mainly pointing on NS5B and set broad spectrum identification of creative anti HCV compounds. This mini review also tells each and every individual compound ability related how much they are active against NS5B and few other targets.

1. Introduction

The HCV is an infectious disease caused by Hepatitis C virus, which primarily affects the liver to develop liver Cirrhosis and carcinoma. The HCV causing virus is mainly transmitted to humans by transfusion of human body fluids similar to HIV [1]. According to the world health organization (WHO), 3–5 lakh death cases among 130–150 million hepatitis C virus infected individuals are being reporting each year across the world [2]. The existence of hepatitis C was suggested in the 1970s and is discovered in 1989 [3]. Hepatitis C infects only humans, chimpanzees according to few studies it is also found the in blood samples of horses in the form of non primate hepacivirus (NPHV) [4]. About 85% viral persistence in the liver of HCV infected individuals is reported. The infection is petite, if the diagnosis become delayed it leads into chronic infection (in 70–80% of cases) and development of liver cirrhosis increases the death aspects of the infected individuals (Fig. 1).

In few cases, those with cirrhosis will go on to develop liver failure and life threatening cancer [5]. The symptoms of HCV is not provoked immediately and thus majority of infected individuals may not be physically ill [2]. HCV infections can be quickly detected

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Pharmacological screening of aqueous extract of *Sesbania grandiflora* for anti-glaucomic activity in Rabbits

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The present work was designed to investigate the antiglaucoma activity of *Sesbania grandiflora* (SG) aqueous leaf extract against alpha chymotrypsin induced experimental glaucoma in rabbits. The experimental increase in IOP was achieved using alpha chymotrypsin induced glaucoma model. Once the IOP was increased significantly, aqueous leaf extract of SG and standard were given topically every day into the right eye of rabbits. IOP was measured by Schiotz indentation tonometer on every alternate day till a significant reduction of IOP was observed. The results were compared with standard 0.1% brinzolamide. A significant increase in IOP was observed on the 7th day after inducing glaucoma. Significant reduction of IOP was observed on the 6th day after giving plant extract when compared with the standard. The results show that the leaf extract showed significant occulohypotensive activity and this effect was comparable to the standard brinzolamide. Further investigation into the mechanism of action and isolation of compounds which are responsible for antiglaucoma activity is to be established.

Keywords: Alphachymotrypsin, Brinzolamide, Intraocular pressure (IOP), Schiotz tonometer.

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Introduction

Glaucoma is described as a group of eye conditions leading to the interruption of visual information from the eye to the brain[1]. It is the second most important cause of blindness after cataract[2,3]. There are many risk factors for glaucoma but the most important is the rise in intraocular pressure which causes damage to the optic nerve[4,5]. Although surgical options exist, medical management to control IOP is the mainstay of the treatment[6]. There are different synthetic medications available in the market but their cost, side effects and contraindications limit their use in patients. Since many ages, Botanical compounds were used as a cure for various diseases and ailments. They have a very long history of medical use. 74% of today's modern drugs that are used directly in traditional medicine have their origin from the natural compounds[7]. Classical texts of Ayurveda have attributed wide-ranging therapeutic indications of this selected herb. *Sesbania grandiflora* popularly known as Agasthya leaves are known to possess wide therapeutic applications. It is used as an analgesic and CNS depressant[8], in smoke-related diseases[9], antioxidant and anti urolithiatic[10], cardioprotective[11], protective effect on kidneys[12], including eye diseases[13-15]. The plant was reported to contain Alkaloids, Glycoside, Tannins, Carbohydrates, etc[16-18]. However, relatively little scientific information is presented on the usage of this drug in treating ocular diseases such as glaucoma. Hence, in the present study, we studied the occulohypotensive activity of this plant in reducing IOP.

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Materials and Methods

Chemicals

Alpha chymotrypsin (Sisco Research Laboratories, Hyderabad, India), brinzolamide, indomethacin, midazolam, phenobarbitol and xylocaine are commercial samples procured in Apollo pharmacy, Hyderabad.

Animals

New Zealand rabbits of either sex weighing 2 kgs were used. The animals were treated in accordance with the institutional guidelines (CPCSEA approval no. 1358/ac/10) to make use of animals in research. The animals were acclimatized for a period of 2 weeks, *ad libitum* food and water was provided and 12 h light/dark cycle was maintained. After two weeks of habituation in the animal house facility, the animals were trained to accept tonometry.

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Development and Validation of a Stability-indicating Method for the Simultaneous Estimation of Sofosbuvir and Ledipasvir by RP-HPLC

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Research Paper

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Development and Optimization of Lovastatin-loaded Transdermal Proniosomal Gel using Box-Behnken Design

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ABSTRACT

In this study, a proniosome-based transdermal drug delivery system of lovastatin was developed by coacervation phase separation method. On the basis of the pilot trials, a 3-factor, 3-level Box–Behnken design was employed to characterize the effect of Cholesterol, soya lecithin and Tween 80 on dependent variables (particle size, entrapment efficiency, and drug release). TEM analysis of optimized formulation has demonstrated the presence of individual Proniosomes in spherical shape. Lovastatin optimized proniosomal formulation F1 shown better particle size and percentage entrapment efficiency and drug release of 99.49% within 24h in slow and controlled manner when compared with control. Kinetic analysis of drug release profiles showed that the systems predominantly released Lovastatin in a zero-order manner with a strong correlation coefficient (R^2= 0.9990). The particle size and Zeta potential of the optimized lovastatin proniosomal gel was found to be 138.82 nm and -11.4 mV respectively. Optimized batch of Proniosomes was used for the preparation of Lovastatin - based proniosomal hydrogel by incorporating hydrated Proniosomes to Carbopol matrix to enhance the stability and viscosity of the system. The enhanced skin permeation for prolonged time may lead to improved efficacy and better patient compliance.

KEYWORDS: Lovastatin; Proniosomal gel; Box-Behnken Design; Soya lecithin; TEM.

Introduction

In recent years, transporting the drug molecules to the desired site in the biological systems has become a very specific and sophisticated area of pharmaceutical research (Gyati Shilakari et al., 2016). Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have distinct advantages over conventional dosage forms because the particles can act as drug containing reservoirs. Therefore, these carriers play an increasingly important role in drug delivery (Singh et al., 2010). Transdermal drug delivery system (TDDS) is among the most widely employed system to overcome the issues associated with oral route (Wen et al., 2014). Due to which it exhibits high level of patient compliance with low levels of intra and inter-patient variability (Aggarwal and Dhawan, 2010). Among various strategies, vesicular systems like niosomes exhibits substantial potential to overcome such barrier. It also acts as drug reservoir and provides the controlled release of drug (Morrow et al., 2007; Vyas and Khar, 2004). Proniosomes was introduced to overcome such problems as it provides ease of transportation, distribution, storage and dosing. Proniosomes are usually dry powder or gel, which can be hydrated just before use resulting in the formation of niosomes. Proniosome gel when applied to skin under occlusive conditions, they get hydrated with the skin moisture and converted to niosomes (Kaushik et al., 2004).

Lovastatin is an antihyperlipedimic drug used to reduce cholesterol in the treatment of hyperlipidemias particularly in type 2a and 2b hyper lipoproteinaemias. It is given prophylactically for both primary and secondary prevention of ischemic heart diseases. The absorption of Lovastatin following oral administration is approximately 30% because it undergoes high first pass metabolism (Sweetman, 2005).

In the present study, a Coacervation phase separation method was used for the preparation and optimization of Lovastatin proniosomes, as this method is simple and easy to scale up. The proniosomes are thus of interest from a technical viewpoint and allow a wider scope to be used to study the influence of various formulation variables. To enhance the stability and viscosity of the system, the proniosomes were mixed with carbopol gel as described earlier (Pankaj et al., 2013).

Materials and Methods

Materials

Lovastatin calcium was received as a gift sample from Aurobindo Pharma Ltd, Hyderabad. Tween 80 and Soya lecithin was received as a gift sample from Lipoid GmbH, Germany. Cholesterol 95% stabilized was purchased

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REVIEW ARTICLE

Phytochemical Screening and *In-Vitro* Antioxidant activity of senna Occidentalis

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ABSTRACT:
The aim of this article is to evaluate antioxidant activity of leaf extract of Senna occidentalis by using in vitro assay. Extraction was carried out with ethanol extract by using Soxhlet apparatus. The in-vitro antioxidant activity ethanol extract has been investigated by 1, 1-diphenyl,2-picryl–hydrazyl free radical (DPPH) method. The ethanol extract exhibited maximum antioxidant activity. The results have been compared with the standard ascorbic acid. The Ethanolic leaf extract of Senna occidentalis shows IC_{50} value at 7 µg/ml.

KEYWORDS: Antioxidant activity, DPPH, Free radicals, Ethanolic extract, Ascorbic acid.

INTRODUCTION:

The term "antioxidant" is mostly used for two entirely different groups of substances: industrial chemical that are added to products to prevent oxidation, and naturally occurring compounds that are present in foods and tissue. The former, industrial antioxidants, have diverse uses: acting as preservatives in food and cosmetics, and being oxidation-inhibitors in fuels.[1]A substance that inhibits oxidation, especially one used to counteract the deterioration of stored food products.Antioxidants are an inhibitor of the process of oxidation, even at relatively smallconcentration and thus have diverse physiological role in the body. Antioxidant constituents of the plant material act as radical scavengers, and helps in converting the radicals to less reactive species. A variety of free radical scavenging antioxidants is found in dietarysources like fruits, vegetables and tea, etc.[2] Oxidative stress is characterized as an imbalance between the production of reactive species and antioxidant defense activity, and its enhanced state has been associated with many of the chronic diseases such as cancer, diabetes, neurodegenerative and cardiovascular diseases.[3]

There is our days, an increasing interest in the measurement and use of plant antioxidants for scientific research as well as industrial (dietary, pharmaceutical and cosmetic) purposes. This is mainly due to their strong biological activity, exceeding those of many synthetic antioxidants which have possible activity as promoters of carcinogenesis.[4]

The traditional medicine all over the world is nowadays revalued by an extensive activity of research on different plant species and their therapeutic principles. Experimental evidence suggests that free radicals (FR) and reactive oxygen species (ROS) can be involved in a high number of diseases (Richards and Sharma, 1991, Niwa, 1991). As plants produce a lot of antioxidants to control the oxidative stress caused by sunbeams and oxygen, they can represent a source of new compounds with antioxidant activity. Ayurveda, the Indian traditional health care system (ayus=life, veda=knowledge, meaning science of life), is the oldest medical system in the world and is being revived in its complete form under the name of Maharishi Ayurved (Glaser, 1988). The World Health Organization has approved its efficacy (Zaman, 1974). This system provides an approach to prevention and treatment of different diseases by a large number of medical procedures and pharmaceuticals. One of the clinical specialties' of Ayurveda is Rasayana. Rasayana is not only a drug therapy but is a specialized procedure

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Research Article

FORMULATION AND EVALUATION OF PRONIOSOMAL GEL-BASED TRANSDERMAL DELIVERY OF ATORVASTATIN CALCIUM BY BOX–BEHNKEN DESIGN

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ABSTRACT

Objective: The aim of this study was to investigate the combined influence of three independent variables in the preparation of atorvastatin proniosomes by coacervation-phase separation method.

Methods: On the basis of the preliminary trials, a 3-factor, 3-level Box–Behnken design was employed to study the effect of cholesterol, soya lecithin, and Span 60 independent variable on dependent variables (particle size and % entrapment efficiency). Transmission electron microscopy analysis of optimized formulation has demonstrated the presence of individual proniosomes in spherical shape.

Results: Atorvastatin optimized proniosomal formulation F2 shown better particle size and % entrapment efficiency, and also, the drug release was 99.72% within 24 h in slow and controlled manner when compared with control. Kinetic analysis of drug release profiles showed that the drug release was followed by zero-order manner with Korsmeyer–Peppas model, which implies super case II release kinetics. The particle size and zeta potential of the optimized atorvastatin proniosomal gel were found to be 65.72 and −10.5, respectively. The optimized batch of proniosomes was used for the preparation of atorvastatin-based proniosomal hydrogel by incorporating hydrated proniosomes to carbopol matrix to enhance the stability and viscosity of the system.

Conclusion: The enhanced skin permeation, for a prolonged period of time, may lead to improved efficacy and better patient compliance. This study suggests that proniosomal gel-containing atorvastatin could perform therapeutically better effects than the conventional formulations.

Keywords: Atorvastatin, Proniosomes, Box–Behnken Design, Span 60, Zeta potential.

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INTRODUCTION

Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have distinct advantages over conventional dosage forms because the particles can act as drug-containing reservoirs [1]. The use of non-ionic surfactant vesicles (niosomes) as drug carrier systems has distinct advantages over conventional dosage [2]. They can increase the drug efficacy, reduce drug side effects, increase the drug solubility, and develop an effective topical delivery [3]. Transdermal drug delivery system is among the most widely employed system to overcome the issues associated with oral route, increases the therapeutic efficacy of many drugs by preventing their conversion to undesirable metabolites, and also helps in maintaining uniform plasma levels *in vivo* [4]. Due to which, it exhibits a high level of patient compliance with low levels of intra- and inter-patient variability [5]. Among various strategies, vesicular systems such as niosomes exhibit substantial potential to overcome such barrier [6,7]. Proniosomal gel when applied to skin under occlusive conditions get hydrated with the skin moisture and converted to niosomes [8]. The additional convenience of the transportation, distribution, storage, and dosing would make "dry niosomes" a promising industrial product. These dry niosomes are hydrated immediately before use and thus avoids some of the problems [9,10] Atorvastatin calcium is a 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor used in the treatment of hyperlipidemia [11]. It has an oral bioavailability of <12%. It also undergoes high first-pass metabolism. It is highly soluble in acidic pH and absorbed more in the upper part of the gastrointestinal tract [12].

In the present study, the coacervation-phase separation method was used for the preparation and optimization of atorvastatin proniosomes, from a technical viewpoint, and allowed a wider scope to be used to study the influence of various formulation variables. To enhance the stability and viscosity of the system, the proniosomes were mixed with carbopol gel [13].

MATERIALS AND METHODS

Materials

Atorvastatin calcium was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad. Span 60 and soya lecithin were purchased from SD Fine Chemicals (Mumbai, India). Cholesterol 95% stabilized was purchased from Acros Organics. Carbopol P 934 was obtained from MSN Laboratories, Hyderabad. Dialysis tubing was purchased from HiMedia Laboratories (Mumbai, India). All other chemicals and solvents were of analytical grade and were used without further purification.

Methodology

Drug-excipient compatibility study

Fourier-transform infrared (FTIR) studies

The drug-excipient compatibility studies were performed to check the interaction between drug and excipients. The FTIR spectra of drug sample and its physical mixture with excipients were carried out by potassium bromide disc method using Shimadzu IRAffinity 1 Spectrophotometer in the region of 4000–400 cm^{-1}.

Differential scanning calorimetry (DSC) studies

DSC of drug sample and its physical mixture with excipients was carried out using a Perkin Elmer DSC-7 Differential Scanning Calorimeter (PerkinElmer, CT, USA) equipped with a TAC 7/DX Instrument Controller. Analyses were performed in triplicate on 5 mg samples under nitrogen purge.

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Synthesis, anti-diabetic evaluation and molecular docking studies of 4-(1-aryl-1*H*-1, 2, 3-triazol-4-yl)-1,4-dihydropyridine derivatives as novel 11-β hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibitors

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ABSTRACT

11-Beta-Hydroxysteroid dehydrogenase-1(11β-HSD1) inhibitors are one of the emerging classes of molecules to fight against diabetic complications. A novel series of 4-(1-substituted-1*H*-1,2,3-triazol-4-yl)-1,4-dihydropyridine derivatives were synthesized and evaluated for their anti-diabetic activity. Two compounds showed anti-diabetic activity very effectively. To clarify the mechanism of action of these compounds, the most potent compounds (5g and 5h) of the synthesized analogs were further studied by testing its 11-Beta Hydroxysteroid dehydrogenase-1 inhibitory activity through *in vitro* enzymatic experiments. The results showed that the 11β-HSD1 inhibitory activity of compounds 5g and 5h was stable and efficient. Molecular docking studies revealed compounds 5g (−9.758) and 5h (−8.495) to have a stable binding patterns to the human 11-Beta-Hydroxysteroid dehydrogenase-1.

1. Introduction

Adipose tissue is an important source in governing energy equity and glucose homeostasis. As an energy repository, adipose tissue responds to the body's metabolic signaling by controlling lipid depot and mobilization. Adipocytes liberate free fatty acid (FFA) as a nutrient source when glucose levels are decreasing, whereas they store ample energy as triglycerides in an energy excess environment. Insulin resistance can uplift the FFA limits, and excessive FFA leads to deterioration of metabolic state by stimulating liver glucose output and by impeding glucose uptake by peripheral tissues and the generation of a reactive oxygen system (ROS), which, in turn, provoke insulin resistance [1]. Adipose tissue is an important portion of the endocrine system, which liberates many adipokines, such as leptin, GBP-28, Nicotinamide phosphoribosyltransferase, (NAmPRTase), omentin, and adipose tissue-specific secretary factor (ADSF), to control glucose homeostasis and whole body insulin sensitivity. Thus, adipocyte dysfunctioning may lead to pathogenic characteristics of obesity and metabolic disorders such as type 2 diabetes [2]. Glucocorticoid is an antagonizing hormone of insulin that triggers hepatic glucose production and inhibits insulin-dependent glucose uptake in peripheral tissues such as adipose tissue and skeletal muscle. Excess glucocorticoid in Cushing's syndrome, develops obesity and many clinical complications correlated with insulin resistance, such as type 2 diabetes, hypertension and dyslipidemia [3]. The target tissue activity of glucocorticoid is measured not only by considering its circulating status but also by the local glucocorticoid stimulation, which is controlled by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and 11β-HSD2. 11β-HSD1, which is widely expressed in the liver, adipose tissue, gonads, and brain, and potentiate the glucocorticoid activation (cortisol in human and corticosterone in rodents) from inoperative 11-keto steroids (cortisone in human and 11-dehydrocorticosterone in rodents). This process multiplies locally centralized glucocorticoid action, whereas 11β-HSD2 is widely expressed in aldosterone-sensitive target tissues such as kidney, colon, salivary glands and placenta and also catalyzes counter reactions [4]. High glucocorticoid levels in adipocytes reduce insulin-dependent glucose uptake, accelerates FFA secretion and alters adipokine profiles, thus develop in insulin resistance [5]. Therefore, 11β-HSD1 is expected to play a critical role in governing glucose and lipid metabolism in adipose tissue. Many preclinical studies have been reported to illustrate the role of 11β-HSD1 in acquiring insulin resistance and the development of obesity [6]. Mice studies have been reported where the

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RESEARCH ARTICLE

Evaluation of *In Vitro* Antiurolithiatic Activity of *Vigna radiata*

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ABSTRACT:
The present study was undertaken to evaluate the in vitro antiurolithiatic activity of the medicinal plantvigna radiata aqueous extract.It showed its maximum efficiency in the dissolution of calcium oxalate crystals.. Our result have clearly indicated that the Aqueousextract of seeds of*vignaradiata* were quite promising for further studies in this regard. In this study Neeri was used as standard drug.

KEYWORDS: In vitro antiurolithiatic activity, Aqueous extract, urolithiasis, *vigna radiata*, Neeri.

INTRODUCTION:

Plants provide food, raw materials for medicine and various other requirements for the very existence of life from the origin of human beings[1]. Urinary stone formation affects 10–12% of the population in industrialised countries. From epidemiological data, calcium oxalate (CaOx) is the most common component of the calculi[2]. The formation of such concretions involves several physicochemical events, e.g. nucleation, growth and aggregation, but the mechanism(s) of these processes remain incompletely understood[3]. Furthermore, although some drugs used to prevent the disease have some positive effects, they are not effective in all patients and often have adverse effects that compromise their use in long-term medical treatment.[4]

Kidney stone disease is a multi-factorial disorder resulting from the combined influence of epidemiological, biochemical and genetic risk factors[3]. Urolithiasis is considered as the third most common affliction of the urinary tract. It refers to the solid non-metallic minerals in the urinary tract.

It is a complex process that is a consequence of an imbalance between promoters and inhibitors in the kidney. The formation of kidney stones involves several phytochemical events beginning with crystal nucleation, aggregation and end with retention within the urinary tract. Among the several types of kidney stones, the most common are calcium oxalate stones representing up to 80% of the analyzed stones[4].

Calcium containing stones may be in the form of pure calcium oxalate(50%) or calcium phosphate(5%) and a mixture of both(45%) followed by magnesium phosphate (15-20%), uric 5 acid(10%) and cystine (1%)[5]. Many patients still undergo surgery to remove the stones; thus in Morocco, as in many countries, most patients (≈70%) use medicinal plants as an alternative therapy for many diseases, including lithiasis. The aerial parts of *Herniariahirsuta*, widely distributed in the Mediterranean area, is used in folk medicine as a diuretic and to treat kidney stones[6]Though technological advancements have made dramatic improvement in the removal of urinary stones still some of the drawbacks of these methods exists which includes their being too costly for a common man and recurrence of stone formation along with a number of other side effects.[7]

Management of stone disease depends on the size and location of the stones. Stones larger than 5 mm or stones that fail to pass through should be treated by some interventional procedures such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), or percutaneous nephrolithotomy (PNL)[8]

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Research Article

NEW STABILITY-INDICATING ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY METHOD DEVELOPMENT AND VALIDATION OF LENVATINIB MESYLATE IN BULK DRUG AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Objective: The objective of the present study was to develop and validate a new stability-indicating method for the quantification of lenvatinib mesylate in bulk drug and pharmaceutical dosage form using ultra performance liquid chromatography (UPLC).

Methods: The optimized chromatographic conditions for elution of drug included UPLC HSS C18 (100 mm × 2.1 mm, 1.8 m) column, mixture of 0.1% orthophosphoric acid and acetonitrile (50:50 v/v%) mobile phase run on an isocratic mode at a flow rate of 0.3 mL/min, 240 nm detection wavelength, and column oven temperature maintained at 30°C.

Results: The retention time for lenvatinib was found to be 1.24 min. The developed method was validated for various validation parameters in accordance with the International Conference on Harmonization guidelines. The method obeyed Beer's law in the concentration range of 2.5–15 µg/mL with a correlation coefficient of 0.9996. The percentage relative standard deviation and percentage recovery were determined to be 0.4 and 99.66–100.30%, respectively. The developed method was found to be accurate, precise, specific, linear, rugged, and robust. Forced degradation studies were conducted by exposing the drug to diverse stress conditions such as acidic, basic, peroxide, neutral, photolytic, and thermal conditions. The net degradation was obtained within the limits.

Conclusion: The developed method for the estimation of lenvatinib can be employed to routine analysis of pharmaceutical dosage form.

Keywords: Lenvatinib mesylate, Ultra performance liquid chromatography, Stability indicating, Method development, Validation.

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INTRODUCTION

Lenvatinib mesylate (Fig. 1) [1,2] chemically known as 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. It is a white to pale reddish-yellow powder, slightly soluble in water and practically insoluble in ethanol. It is a pKa value of 5.05. It belongs to anticancer category and utilized for the treatment of various kinds of thyroid cancer [3,4]. It acts as receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor receptors [5]. It also inhibits other RKTs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor receptors.

Ultra performance liquid chromatography (UPLC) [6-8] is a relatively new technique giving new possibilities in liquid chromatography, especially concerning the decrease of time and solvent consumption. UPLC chromatographic system is designed in a special way to withstand extreme system back pressures.

In accordance to literature review, it was known that there were only few methods such as reverse-phase high-performance liquid chromatography (RP-HPLC) [9-11], ultraviolet (UV) spectroscopy [11], and liquid chromatography coupled with tandem mass spectrometry method [12-14] developed for the estimation of lenvatinib.

As there was no UPLC method developed for the estimation of lenvatinib, the present study was intended to develop and validate a stability-indicating UPLC method for the quantitative determination of lenvatinib in bulk drug and pharmaceutical dosage form.

METHODS

Chemicals and reagents

Lenvatinib mesylate working standard was supplied as a gift sample from Spectrum Labs, Hyderabad. Lenvima capsules were purchased from a local pharmacy. All the chemicals used for the development of the method were of AR grade purchased from Merck, Mumbai. All the solvents used were of HPLC grade purchased from Sigma-Aldrich, Mumbai.

Analytical conditions and instruments

The ACQUITY UPLC system equipped with binary solvent manager, sample manager, UV detector, and UPLC HSS C18 (100 mm × 2.1 mm, 1.8 µ) column was used for the determination of lenvatinib. The analytical conditions included 0.1% orthophosphoric acid and acetonitrile (50:50 v/v%) as mobile phase run on an isocratic mode at a flow rate of 0.3 mL/min. The column was kept at 30°C and detection was done at 240 nm wavelength. Additional equipment included pH meter, ultrasonic bath sonicator, and weighing balance.

Preparation of mobile phase

Mixture of 0.1% aqueous orthophosphoric acid buffer and acetonitrile in the ratio of 50:50 v/v% was used as mobile phase.

Preparation of standard and sample solution

10 mg of lenvatinib working standard was dissolved in 100 ml of diluent. 1 mL of the above standard stock solution was diluted to 10 mL diluent.

Average weight of 20 lenvima capsules was calculated and an amount equivalent to 10 mg of lenvatinib was dissolved in 100 mL of diluent.

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RJPT

RESEARCH ARTICLE

Evaluation of *In Vitro* Anthelmintic Activity of Spirulina Powder

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ABSTRACT:

The aim of the present study was to evaluate the In-vitro antihelmenthic activity of Spirulina Powder. Currently, our understanding on the underlying mechanisms for Spirulina's activities, especially the antihelmenthic, is limited. The Spirulina Powder was taken for anthelmintic activity against Indian earthworm Pheretimaposthuma. The results were expressed in terms of time required for paralysis and death of Pheretimaposthuma. Albendazole was used as a standard control group. Spirulina Powder shows the significant activity at 150 mg/ml concentration.

KEYWORDS: Spirulina, Pheretimaposthuma, anthelmintic, *In-vitro*, Albendazole.

INTRODUCTION:

Helminthic infections are very common in man. Helminthic infections are large threat to human beings health in developing countries. It contributes malnutrition, anemia and pneumonia. Majority of the infections are due to worms are generally limited to topical regions. The World Health Organization reveals that over two billion people are suffering from parasitic worm infections[1]. It is estimated that by the year 2025, about 57% of the population in developing countries will be influenced[2]. The prevalence of parasitic helminths typically displays a negative binomial distribution within an infected population such that relatively few persons carry heavy parasite burdens. Without treatment, those individuals are most likely to become ill and to perpetuate infection within their community[3]. Helminthes infections are now being recognized as cause of many acute as well as chronic ill health among the various human beings as well as cattle's. More than half of the population of the world suffers from infection of one or the other and majority of cattle's suffers from worm infections[4].

In most developing and less developed countries, helminth infections are a major health concern because they predispose humans to other infections such as fungal and bacterial infections[5]. Intestinal infections with worms can more easily treated than those the infections that occur in other locations in the body, because the worms need to be killed by the drug and the drug need not be absorbed when given by oral route[6].

Anthelmintics are drugs that may act locally to expel worms from the GIT or systemically to eradicate adult helminths or development forms that invade organs and tissues[7]. Most of the existing anthelmintics produce side effects such as abdominal pain, loss of appetite, nausea, Vomiting, headache and diarrhoea[8]. Anthelmintics from the natural sources may play a key role in the treatment of these parasite infections[9]. Because of the increasing anthelmintic resistance and the impact of conventional anthelmintics on the environment, it is important to look for alternative strategies against parasitic worms. Earthworms have been used widely for the initial evaluation of anthelmintic compound in vitro[10-13].

Spirulina is free-floating filamentous microalgae growing in alkaline water bodies. With its high nutritional value, Spirulina has been consumed as food for centuries in Central Africa. It is now widely used as nutraceutical food supplement worldwide. Recently,

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STABILITY INDICATING UPLC METHOD DEVELOPMENT AND VALIDATION FOR THE DETERMINATION OF CRIZOTINIB IN PHARMACEUTICAL DOSAGE FORMS

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Keywords:
Crizotinib, UPLC, Stability indicating method, Method development, Validation

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ABSTRACT: A stability indicating method was developed for the estimation of Crizotinib in pharmaceutical dosage form by using Ultra Performance Liquid Chromatography (UPLC). The separation was done on isocratic mode with Hibra C18 (100 mm × 2.1 mm, 2 µ) column and 0.1% Ortho-phosphoric acid and acetonitrile (45:55% v/v) as mobile phase at a flow rate of 0.3 mL/min and at room temperature. The detection was done at a wavelength of 327 nm. A good linearity was observed in the concentration range of 37.5 µg/mL - 225 µg/mL, with a correlation coefficient of 0.999. The method was validated according to the ICH guidelines. The developed method was found to be accurate and precise, with % recovery 99.9% - 100.18% and % relative standard deviation 1.1. The drug was found to be stable at forced degradation conditions and the net degradation was found to be within the limits. The developed method can be used for the quality control of Crizotinib in pharmaceutical dosage form.

INTRODUCTION: Crizotinib **Fig. 1**, chemically designated as 3- [(1*R*)- 1- (2, 6-dichloro-3-fluoro-phenyl) ethoxy]- 5- (1- piperidin- 4- ylpyrazol-4-yl) pyridin-2-amine, is a white to pale yellow powder, slightly soluble in methanol, ethanol and water and has a pKa of 5.6 and 9.4. It is used in the treatment of lung cancer by acting as an oral receptor tyrosine kinase inhibitor [1]. According to the literature survey, very few methods HPLC methods [2, 3], LC-MS/MS method [4], Spectrofluorimetry [5], UPLC-MS/MS method [6] and LC-ESI–MS/MS method [7] were developed.

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The proposed method aimed to develop and validate a stability indicating method for the estimation of Crizotinib in pharmaceutical dosage form by UPLC.

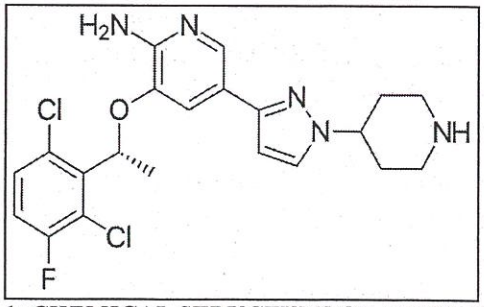

FIG. 1: CHEMICAL STRUCTURE OF CRIZOTINIB

MATERIAL AND METHODS:

Reagents and Chemicals: Crizotinib standard drug was supplied as gift sample by spectrum labs, Hyderabad (India).

Research Article

STABILITY INDICATING UPLC METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF DASATINIB IN PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

The present work describes the stability indicating method development and validation for the determination of Dasatinib in pharmaceutical dosage form using Ultra Performance Liquid Chromatography with UV detection. The optimized chromatographic conditions used were Acquity UPLC HSS C18 (100mm × 2.1mm, 1.8µ) column, 0.1% Orthophosphoric acid and acetonitrile in the ratio (50:50%v/v) as mobile phase run on an isocratic mode at a flow rate of 0.2ml/min. The column oven temperature was maintained at room temperature. The detection wavelength was found to be 321nm.The developed method was validatedas per ICH guidelines and found to be specific, rugged and robust. A linear response was found in the concentration range of 12.5µg/ml to 75µg/ml with correlation coefficient of 0.999, indicating that the method obeys Beer's law. The % recovery for Dasatinib was found to be 99.80% to 100.19% indicating the method was accurate. The % relative standard deviation was found to be 0.7 indicating the method was precise. The drug was found to be stable at stressed conditions and the net degradation was found to be within the limits. The developed method can be used for the quality control of Dasatinib in pharmaceutical dosage form.

Keywords: Dasatinib, Stability Indicating, Method development, Validation, UPLC.

INTRODUCTION

Dasatinib (Figure 1) is chemically designated as *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide monohydrate. It is a white to off – white solid which is slightly soluble in methanol, ethanol and water and has pKa values of 3.1 and 6.8 (two basic pKas) and 10.8 (acidic pKa). It is an anticancer drug used to treat chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) [1,2]. The literature survey reveals that there are few methods for the estimation of Dasatinib such as colorimetric method [3], UV-Visible spectrophotometric method [4], RP-HPLC methods [5-10] and UPLC method [11]. The objective of the present study is to develop a stability indicating method for the determination of Dasatinib in pharmaceutical dosage form by UPLC and validate it.

Material and methods

Chemicals and Reagents

The Dasatinib standard drug was procured from Spectrum Labs, Hyderabad, Telangana, India as a gift sample. The Dasatinib tablets (Dasanat) were purchased from local pharmacy. All the chemicals used were of AR grade and purchased from sigma Aldrich. All the solvents used were of HPLC grade and purchased from Merck, Mumbai, India.

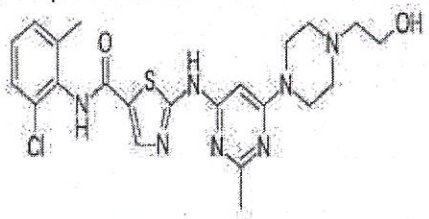

Figure 1: Chemical structure of Dasatinib

Apparatus and Chromatographic conditions:

Waters UPLC ACQUITY instrument core system includes ACQUITY UPLC binary solvent manager, ACQUITY UPLC sample manager andACQUITY UPLC single column manager with Acquity UPLC HSS C18 (100mm x 2.1 mm, 1.8µ) column maintained at room temperature, Waters Empower 2 PC workstation, a solvents tray and UV detector was used for the determination of Dasatinib in tablet dosage form. All the parameters of UPLC were run on Empower software. Other instruments used were electronic balance, digital pH meter and Ultrasonic

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Evaluation of *in vitro* Antiurolithiatic Activity of *Gossypium Herbaceum*

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Abstract:
The present study was undertaken to evaluate the in vitro antiurolithiatic activity of the medicinal plant Gossypium herbaceum. Both Ethanolic and Aqueous extracts showed their maximum efficiencies in the dissolution of calcium oxalate crystals Ethanolic extract was even more efficient than Aqueous extract in dissolution of calcium oxalate crystals. Our results have clearly indicated that the aqueous and ethanolic extracts of Gossypium herbaceum were quite promising for further studies in this regard. In this study Neeri was used as standard drug.
Keywords: In vitro antiurolithiatic activity, aqueous extracts, urolithiasis, Gossypium herbaceum

INTRODUCTION:

Urolithiasis is derived from the greek words ouron means urine and lithos means stone. Urolithiasis is characterized by the formation of the stone in the kidneys or urinary tract in a large number of people. Nearly 10-15% of the population is currently suffering from kidney stones.

Urinary tract stones (kidney stones) composed of calcium oxalate, either alone or mixed with calcium phosphate. World Health Organization(WHO) estimated that about 12% of men and 55% of women have at least one episode of kidney stone during their life time.[1] The cause of urolithiasis is still unknown but probably positive family history, overweight, obesity or increased body mass index (BMI).[2] Epidemiological studies revealed that urolithiasis is more common in men than in women and is more prevalent between the ages of 20-40 in both sexes. [3] Ammonium urate, mono sodium urate monohydrate, uric acid anhydrous, uric acid mono and di hydrate are commonly existing urate stones. [4,5] Drugs with multiple mechanisms of protective action provide minimizing the diseases.

Plants provide food, raw materials for medicine and various other requirements for the very existence of life from the origin of human beings[6]. The majority of the global population utilizes medicinal plants for their health care. Even the current conventional medicine is using a lot of plant derived chemicals as therapeutic agents. The overuse of synthetic drugs results in higher incidence of adverse drug reactions has motivated humans to return to nature for safe remedies. Herbs and herbal drugs have created interest among the people by its clinicallyproven effects[7].

*Gossypium Herbaceum*L. belongs to Malveceae and commonly called as cotton plant [8, 9]. It is oldest Indian herbal drug, which is included in our present study is widely used by tribal people. Ayurvedic system has already noticed the importance of this plant. It has several experimentally proven pharmacological activities, which includes Antitumor [10], Antimutagenic [11], Anticonvulsant [12] antibacterial, antihelmenthic [13] and antifungal activities [14]. The cotton seed has already proved antiUrolithiatic so based on the literature review the present study was carried out antiurolithiatic activity of leaves of Gossypium Herbaceum.

MATERIALS AND METHODS:

PLANT MATERIALS

The leaves of Gossypium herbaceum was collected in the month of august 2017 from Maddur village, Medak dist. of Telangana, India. The plant was authenticated by D. Venkateshwara Rao, DeputyDirector, Telangana. Forest Academy, Dullapally, Hyderabad, Rangareddy District. The leaves were washed with tap water and dried under shade.

PREPARATION OF PLANT EXTRACT

The leaves were shade dried and powdered. The crude plant extract was prepared by Soxhlet extraction method. 50g of powdered plant material was extracted with 500ml of ethanol and water individually. The process of extraction was carried out up to 6 cycles, till the solvent in siphon tube of an extractor became colorless. The two extracts were filtered separately, and evaporated to dryness using rotary evaporator. Further the dried extracts were maintained in a refrigerator at 4°C for further antiurolithiatic activity.

CHEMICALS USED

Neeri, Sodium oxalate, Tris buffer, calcium chloride, Potassium permanganate(KMnO4), Sulphuric acid(H2SO4).

INVESTIGATION OF IN VITRO ANTIUROLITHIATIC ACTIVITY TEST BY TITRIMETRY

The experimental kidney stones of calcium oxalate (CaOx) were prepared in the laboratory by taking equimolar solution of calcium chloride dehydrate in distilled water and sodium oxalate in 10 ml of 2N H2SO4. Both were allowed to react in sufficient quantity of distilled water in a beaker, the resulting precipitate was calcium oxalate. The precipitate was freed from traces of sulphuric acid by ammonia solution, washed with distilled water and dried at 60oC. The dissolution percentage of calcium oxalate was evaluated by taking exactly 1 mg of calcium oxalate and 10 mg of the extract, packed it together in semi permeable membrane of egg as shown in the model designed given below .This was allowed to suspend in a conical flask containing 100 ml of 0.1M Tris buffer. First group served as blank containing only1 mg of calcium oxalate. The second group served as positive control containing 1 mg of calcium oxalate and along with the 10mg standard drugs, i.e. Neeri. The 3rd, 4th groups along with 1 mg of calcium oxalate contain methanolic and aqueous, extracts. The conical flasks of all groups were kept in an incubator preheated to37oC for 2 h. Remove the contents of semi permeable membranes from each group into separate test tubes, add 2 ml of 1Nsulphuricacid to each test tube and titrated with 0.9494 N KMnO4 till a light pink colour end point obtained. The amount of remaining undissolved calcium oxalate is substracted from the total quantity used in the experiment in the beginning to know the total quantity of dissolved calcium oxalate by various solvent extracts.[15]

RESULTS AND DISCUSSION:

Drug therapy has developed in response to population health care needs. There are many crucial areas in medicine such as liver diseases, arthritis, old age related problems, certain viral infections and cancer where the conventional medicine is devoid of satisfactory treatment. These are among the promising areas of research and development of medicines from the vast highly potential plant resources. Plants are also attractive sources for the development of novel and very effective and safe therapeutic agents against kidney procumbens. Herbal medicines are also in great demand in the developed world for primary health care because of their efficacy, safety and lesser side effects. Unlike allopathic medicines which target is only one aspect of urolithiatic pathophysiology, most of plant based therapy have been shown to be effective at different stages of stone pathophysiology. About

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Elucidation of chemosensitization effect of acridones in cancer cell lines: Combined pharmacophore modeling, 3D QSAR, and molecular dynamics studies

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ABSTRACT

Overexpression of P-glycoprotein (P-gp) leads to the emergence of multidrug resistance (MDR) in cancer treatment. Acridones have the potential to reverse MDR and sensitize cells. In the present study, we aimed to elucidate the chemosensitization potential of acridones by employing various molecular modelling techniques. Pharmacophore modeling was performed for the dataset of chemosensitizing acridones earlier proved for cytotoxic activity against MCF7 breast cancer cell line. Gaussian-based QSAR studies also performed to predict the favored and disfavored region of the acridone molecules. Molecular dynamics simulations were performed for compound 10 and human P-glycoprotein (obtained from Homology modeling). An efficient pharmacophore containing 2 hydrogen bond acceptors and 3 aromatic rings (AARRR.14) was identified. NCI 2012 chemical database was screened against AARRR.14 CPH and identified 25 best-fit molecules. Potential regions of the compound were identified through Field (Gaussian) based QSAR. Regression analysis of atom-based QSAR resulted in r^2 of 0.95 and q^2 of 0.72, whereas, regression analysis of field-based QSAR resulted in r^2 of 0.92 and q^2 of 0.87 along with r^2_{cv} as 0.71. The fate of the acridone molecule (compound 10) in the P-glycoprotein environment is analyzed through analyzing the conformational changes occurring during the molecular dynamics simulations. Combined data of different in silico techniques provided basis for deeper understanding of structural and mechanistic insights of interaction phenomenon of acridones with P-glycoprotein and also as strategic basis for designing more potent molecules for anti-cancer and multidrug resistance reversal activities.

1. Introduction

The success of cancer chemotherapy is limited by the development of drug resistance (Baumert and Hilgeroth, 2009). Multidrug resistance (MDR) is defined as resistance to several unrelated drug classes, such as anthracyclines, Vinca alkaloids or topoisomerase inhibitors, and novel cytostatic agents, including tyrosine receptor kinase inhibitors or protease inhibitors (Borst et al., 2000; Kruh and Belinsky, 2003).

Multidrug resistance occurs by overexpression of ATP-binding cassette (ABC) family protein family members, in which P-glycoprotein (P-gp), an *mdr1* gene product, is one of the barriers to chemotherapeutic treatment of cancer. P-gp is polyspecific, transporting a wide range of structurally diverse compounds out of the cell (Becker et al., 2009). P-gp has been shown to bind ATP and drug analogues (Ambudkar et al., 1999) have ATPase activity, and catalyze ATP dependent drug efflux to effectively reduce intracellular accumulation in resistant cells. This efflux mechanism of P-gp could also be referred to as "flippase" activity of the transporter (Sharom, 2011). This association of *mdr1* P-glycoprotein expression in tumor has become an important target for the reversal of MDR or for blocking the transport activity of P-gp (Lehne, 2000). Despite large number of studies conducted to elucidate the P-gp efflux mechanism, these remain controversial. However, it is believed

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1476-9271/

Original Article

Protective Effect of A_{2B} Receptor Antagonist (TRP 1) on Acetic Acid Induced Ulcerative Colitis in Rats: *in vitro, in vivo* and *in silico* Methods

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ABSTRACT

Aim: Present study was elucidate the protective effect of pyridinone derivatives such as 7-amino-5-oxo-2- Phenyl-5H, 8H-dihydro-[1, 2, 4] triazolo [1, 5-α] pyridine - 6-carbonitril (TRP 1) by *in vitro, in vivo and in silico.* **Methods:** Radioligand binding assay was performed on human adenosine receptors (A_{2B}) and assess A_{2B} antagonist effect by adenylyl cyclase activity. *In vitro* study was carried out to determine the neutralize capacity against DPPH*, NO*, SO*, LPO* free radicals. TRP 1 at the doses 1 mg/kg bd.wt. and 10 mg/kg bd.wt p.o, was administered consecutively for 14 days in albino rats. Ulcerative colitis was induced with single dose of 2 ml of 3% acetic acid intrarectal on 14th day in treated rats. At the end of treatment, colonic tissue was collected and subjected for estimation of macroscopic score, glutathione, catalase, MPO and inflammatory parameters such as IL 1β, TNF α and IL 6. *In silico* study was carried out to evaluate the binding energy and IC_{50} toward IL 1β, TNF α and IL 6. **Results:** TRP 1 was antagonized the A_{2B} receptors at the concentration of 30000 nM. *In vitro* study was revealed that TRP1 (1 mg/ml) was significantly neutralizes the free radicals of DPPH*, SO*, NO*and LPO*. In *in vivo* studies, intrarectal administration of acetic acid caused significantly (***P<0.001) increased macroscopic score, colon weight, colonic MPO, IL 6, IL 1β and TNF-α (*P<0.05), while TRP 1 treated colitis rats antioxidants system such as GSH (**P<0.01), catalase (*P<0.05) activity was significantly improved, decreases inflammatory mediators such TNF α (*P<0.05), IL 1β (**P<0.01) , IL 6 (**P< 0.01) and also suppresses the MPO activity (*P<0.05). *In silico* study was reported that the IC_{50} of TPR 1 against IL 1β, IL 6 and TNF-α was 7.5 mM, 28.65 mM and 45.87 mM respectively. **Conclusion:** Our data demonstrated that the TRP 1 treatment improved clinical score in acetic acid induced colitis in rats. It also inhibited the proinflammatory cytokine IL-6, IL 1β and TNF α and improvements of antioxidant in colitis rats through A_{2B} receptor antagonist property.

Key words: 7-amino-5-oxo-2- phenyl)-5H, 8H-dihydro-[1,2,4] triazolo [1,5-α] pyridine - 6-carbonitril (TRP 1), Ulcerative colitis, Acetic acid, Myeloperoxydase (MPO), Glutathione (GSH), Catalase, TNF α, IL 1β and IL 6.

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INTRODUCTION

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is a lifelong disabling gastrointestinal disease.[1,2,3] Although etiology of inflammatory bowel disease (IBD) is unknown it appears that an abnormal response of the mucosal innate immune system to luminal bacteria may trigger inflammation which is perpetual by disregulation of cellular immunity[4,5,6] and imbalances between proinflammatory cytokines, such as

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RESEARCH ARTICLE

Comparative In vitro antidiabetic and antioxidant activity of *Pulicaria wightinia, Curcuma inodora ,Derris scandens* leaf extracts

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ABSTRACT:
In preventing the progression of various metabolic diseases, medicinal plants play very important role. The present study was focused on three different medicinal plants, *Pulicaria wightiania, Derris scandens and Curcuma inodora* commonly found in Narsapur forest of Medak district Telangana, (India), were screened for the potency of antioxidant and antidiabetic activity by various *In-vitro* methods. Three plants leaves were extracted using methanol and ethanol as solvents based on their solubility. Methanol extracts of *Pulicaria wightiania, Derris scandens* and ethanolic extract of *Curcuma inodora* plants leaves were examined. Antioxidant activities of three different extracts were evaluated by DPPH scavenging assay and putative antidiabetic activity was determined by *in-vitro* methods such as Glucose uptake by Yeast cells method, α-glucosidase inhibition activity assays. A dose dependent significant DPPH scavenging activity was found with three different plants when compared with standard drug ascorbic acid. The three plants leaf extracts exhibited a significant inhibitory action on α-glucosidase enzyme. The data obtained clearly suggests that the plant extract is capable of effectively enhancing glucose uptake which in turn suggests that it is capable of enhancing effective glucose utilization thereby controlling blood glucose level. The results suggest that these plants possess potential antioxidant and antidiabetic components.

KEYWORDS: Antidiabetic activity, *Pulicaria wightiania*, *Derris scandens* and *Curcuma inodora* Alpha - glucosidase enzyme, Glucose uptake, Yeast cells.

INTRODUCTION:
The world 'Diabetic Capital 'is India with 50.8 million diabetics[1] Preventing the absorption of carbohydrates after food intake is one of the therapeutic approaches for reducing postprandial hyperglycemias in patients with diabetes mellitus. Alpha glucosidase is the enzyme that catalyzes the cleavage of glycoside bonds in oligosaccharides and thus compounds inhibiting this enzyme could help prevent postprandial hyperglycemias by decreasing the rate of carbohydrate degradation to glucose[2].

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The plant extracts have long been used for the ethno-medical treatment of diabetes in various systems of medicine and are currently accepted as an alternative for diabetic therapy. However, for many plant extracts, there is no clear understanding of the mechanism of action. Therefore, natural α-glucosidase inhibitors from plant sources offer an attractive strategy for the control of postprandial hyperglycemias. The mechanism of glucose transport across the yeast cell membrane has been gaining significant importance as An in- vitro screening method for evaluating the hypoglycemic effects of various medicinal plants[3]. As there are disturbances in antioxidant defence systems in diabetes mellitus[4] ,treatment with antioxidant may contribute to the prevention and delaying of diabetic complications[5] This is currently the basis of the "unifying hypothesis" that

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ANTIPROLIFERATIVE ACTIVITY OF RUTIN ON HELA CELL LINE INDUCED CERVICAL CANCER IN RATS

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Keywords:

Rutin, HeLa cell line, Antiproliferative effect, Antioxidant activity

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ABSTRACT: In present study antiproliferative activity of Rutin was evaluated on HeLa cell line induced cervical cancer in rats. For this study, 30 rats were divided into 5 groups and each group containing 6 rats each. Group I- normal saline treatment for 45 days, Group II- cancer cells (1×10^6 cells in 0.1ml/rat), Group III– 5-Fluorouracil (20mg/kg + 1×10^6 cells in 0.1ml/rat), Group IV- Rutin (50mg/kg + 1×10^6 cells in 0.1ml/rat), Group V- Rutin (70mg/kg + 1×10^6 cells in 0.1ml/rat). After 24 h of tumour inoculation intraperitoneally, Rutin was administered daily for 45 days. After administration of last dose followed by 18 hrs fasting, rats were sacrificed for observation of antiproliferative activity. The change in body weight, body circumference of tumour bearing hosts and simultaneous alterations in haematological profile, serum (Triglycerides, Total protein, Total cholesterol, GGT, ALP and glucose) and liver biochemical parameters (lipid peroxidation, GSH and antioxidant enzymes-CAT, GPx) were estimated. The changes in tissue enzymes-Glucose-6 phosphate dehydrogenase, Hexokinase, Succinate dehydrogenase and CytochromeP450 levels were also estimated. Rutin maintained the body circumference and body weight of proliferation bearing rat. Haematological profile reverted towards normal levels in Rutin treated rat. Treatment with Rutin restored serum biochemical parameters towards normal levels and decreased levels of lipid peroxidation and increased levels of reduced glutathione and other antioxidant enzymes. The Rutin treatment restored Glucose-6 phosphate dehydrogenase, Hexokinase, Succinate dehydrogenase and CytochromeP450 levels in proliferation induced rat. Rutin exhibited antiproliferative effect by modulating haematological parameters, lipid peroxidation and augmenting antioxidant defense system in proliferation bearing rat.

INTRODUCTION: Cervical cancer is the third most common type of cancer in women worldwide[1]. This cancer develops slowly; starting from a precancerous dysplasia designated cervical intraepithelial neoplasia that may further develop to invasive cervical carcinoma.

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Several molecules present in the diet, including flavonoids, can inhibit the growth of cancer cells with an ability to act as "chemopreventers" [2]. Their cancer-preventive effects have been attributed to various mechanisms, including the induction of cell-cycle arrest and/or apoptosis as well as the antioxidant functions. The antioxidant activity of chemo preventers has recently received a great interest, essentially because oxidative stress participates in the initiation and progression of different pathological conditions, including cancer. Since antioxidants are capable of preventing oxidative damage, the wide use of natural food-

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Research Article

FORMULATION OF FLUCONAZOLE AS TOPICAL ANTIFUNGAL GELS BY MICROSPONGE BASED DELIVERY SYSTEMS

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ABSTRACT

The purpose of present work was to formulate fluconazole loaded microsponge-based topical delivery system for modified release. Microsponges with varied drug–polymer ratios were prepared by emulsion solvent diffusion technique using ethyl cellulose as release retard material. Prepared microsponges were studied for particle size and physical characterization. Scanning Electron Microscopy (SEM) images showed the microsponges porous and spherical in shape. The microsponges were then incorporated in carbopol gel and evaluated for pH, viscosity, spreadability, drug content, *in vitro* release. The *In vitro* drug release showed that microsponges with 1:1.5 drug–polymer ratios (F3) were more efficient to give sustained release of 74.2% at the end of 8h. All the microsponge gel formulations (i.e.F1-F10) showed better results like pH between 6.5-7.0, viscosity between 25,030-47,390 cps, spreadability 2-4cm/s and drug content of 76.20±0.02% to 96.41±0.01%. Hence, the fabricated microsponge based formulation of fluconazole would be anticipation and promising substitute to conventional therapy of skin infections.

Keywords: Fluconazole, microsponge, ethyl cellulose, SEM

INTRODUCTION

Fluconazole is a synthetic antifungal agent belonging to the group of triazole. It is one of the commonly used antifungal agents for most kinds of fungal infections including superficial and invasive fungal infections (Vinod *et al.*, 2012). Regrettably fluconazole oral administration has limitations such as nausea, vomiting, bloating and abdominal discomfort. Alongside most of the time the parenteral administration of fluconazole led to skin rashes and itching (Doaa *et al.*, 2012). For these reasons, now a day's advance localized and transdermal delivery has gained a lot of importance (Niethard *et al.*, 2005; Kulkarni *et al.*, 2011). The conventional gel formulation of fluconazole causes cutaneous irritation and prolonged use led to dermal hypersensitivity. So, a novel system necessitates which will increase the presence of active agents either on skin surface or within epidermis, concurrently reducing hasty transdermal penetration. Many researchers have attempted to develop novel transdermal formulations of fluconazole. Accordingly, the goal of our research is to formulate and evaluate fluconazole microsponge loaded carbopol gel for safe, effective and stable gel and evaluate the in-vitro sustained release performance. Microsponge-based delivery systems (MDS) give assurance of drug localization on skin surface and within epidermis without entering in systemic circulation in greater extent; thereby reducing systemic and local cutaneous adversities. They also offer an advantage of programmable release and are biologically safe. Additionally, this technology presents quite a lot of benefits via drug entrapment by means of better formulation flexibility, abridged side effects, improved elegance and superior stability (D'souza and More, 2008; Vyas *et al.*, 2010; Vyas and Khar, 2002; Won, 1987).

MATERIALS AND METHODS

Fluconazole was obtained as a gift sample from RMS Research labs Pvt Ltd Hyderabad, India. Ethyl cellulose was gifted by Yeluri formulations, Hyderabad, India. Polyvinyl alcohol, triethyl citrate and ethyl acetate were purchased from Emerck (India) Ltd., Mumbai. All other chemicals and solvents used are of analytical grade.

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Anticataract potential of *Boerhavia diffusa* roots on galactose induced cataractogenesis

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Cataract has been a major cause of bilateral blindness worldwide, and it is responsible for 50-80% of the bilaterally blindness in India. Oxidative stress is the major risk factor causing cataract. *Boerhavia diffusa*, commonly known as spreading hogweed or tarvine and locally, punarnava, is known for its antioxidant potential. Here, we evaluated anticataract potential of alcoholic extract of *B. diffusa* roots using galactose induced cataract model on Wistar albino rats. The rats were divided into five groups. The first group was taken as control, the second as disease control group and all other three groups test groups, given three doses of plant extracts i.e. 100, 200 and 400 mg/kg body wt., respectively for 28 days. Periodically slit lamp photographs were taken to know the percentage incidence and progression of cataract. The plant extract significantly delayed the onset and maturation of galactose induced cataract. Biochemical analyses were performed at the end of the study. The analyses revealed the plant extract at highest dose exhibited an efficient antioxidant effect. It has shown 69% inhibition on galactitol accumulation. Aldose reductase (AR) inhibitory activity was also performed on isolated rat lenses. The significant percentage inhibition of AR was shown at a dose of 70 µg/mL. In conclusion, our results demonstrated that the alcoholic extract of *Boerhavia diffusa* roots delay the process of cataractogenesis in galactose induced cataract.

Keywords: Aldose reductase, Antioxidant potential, Cataract, Galactitol, Punarnava, Oxidative stress, Spreading hogweed, Tarvine

Cataract, a visual impairment causing disturbance in lens transparency occurs mainly due to opacification or optical dysfunction of the crystalline lens. It reduces the amount of incoming light and results in deterioration of the vision[1]. Apart from senile cataract, various other factors, such as oxidative stress, diabetes, excessive exposure to ionising radiation, inflammatory diseases of the eye increase the risk of cataract. In all these factors, oxidative damage plays a most important role in causing cataract[2]. Surgically, cataractous lens can be replaced with artificial lens; however, epidemiologically the problem persist owing to the cost and post operational complications of surgery[3]. There are no plants which are proven clinically but more work is now going on curcumin, though at pre-clinical stage only[4,5]. Surgery is the alternative for treating cataract.

Aldose reductase (AR), also known as aldehyde reductase, is NADPH dependant oxidoreductase which catalyses the reduction of galactose into galactitol. Galactitol can't be further metabolised. When the concentration of galactitol increases it causes pronounced increase in lens hydration. It leads to osmotic imbalance and formation of vacuoles in the eye[6].

Few plants have been reported in the ancient literature for ophthalmic use, but most of them have no scientific data. *Boerhavia diffusa* (Fam.: Nyctaginaceae), commonly called Tarvine or Spreading hogweed, locally known as 'punarnava', is a herbaceous perennial plant well distributed all over India and has been shown to have a wide range of biological activities such as anthelmintic[7], anticancer[8], antidiabetic[9], antidepressant[10,11], antihaemolytic[12], antifungal[13], antileishmanial[14], antimetastatic[15], antimicrobial[16], antioxidant[17], free radical scavenger[18], hepatoprotective[19], immunomodulatory[20] and neuroprotective[21] activities. It is also having many folklore uses, including eye problems[22-24]. However, scientific information on the use of this plant in treating eye diseases is not available yet. Hence, we

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Research Paper

Formulation and *In vitro* Evaluation of Floating Microspheres of Misoprostol

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ABSTRACT

Misoprostol is a synthetic prostaglandin PGE1 analogue, which has proved to be an effective anti-secretory agent for oral use. The major indications of Misoprostol are in the prevention and treatment of NSAID-induced gastric and duodenal ulcers. Its half-life is 20-40 minutes. More than one third of patients with ulcers are resistant to H_2 antagonists. So, these patients can be healed on Misoprostol. The objective of the present study was to formulate gastroretentive floating drug delivery system of an antiulcer drug Misoprostol. Floating microspheres of Misoprostol were prepared by an emulsification solvent evaporation technique using hydroxy propyl methyl-cellulose (HPMC K 100M) and ethyl cellulose. The percentage yield and drug entrapment efficiencies of these floating microspheres were within the range between: 70 ± 2.8 to 98 ± 2.9 % and 39.27 to 82.39 %, respectively. The determined mean particle size for all the microspheres were 250 ± 7.28 to 400 ± 2.32 µm. The flowability of these microspheres was found good. A high performance liquid chromatography (HPLC) method with ultra-violet (UV) detection was selected for the method of analysis. The drug release was found to delay for 12 hours with the increasing drug to polymer ratio. The drug release kinetics followed Korsemeyer-Peppas and Higuchi model with anomalous (non-Fickian) diffusion mechanism for the drug release. The FTIR and DSC studies showed that there was an absence of chemical interaction between the drug and the excipients. The *in vitro* drug release from Misoprostol floating microspheres showed the drug release was dependent on the drug to polymer ratio. The drug release was found delayed with the increasing drug to polymer ratio.

KEYWORDS: Floating microspheres; emulsion solvent evaporation method; Misoprostol.

Introduction

Oral route is always the most popular and preferred route for drug delivery to the systemic circulation due to its low cost of therapy, ease of administration, patient compliance, etc. During the past few decades, considerable effort has been directed towards the development of numerous oral drug delivery systems from which the incorporated drugs are released over a defined period at a predetermined and controlled rate. Nevertheless, conventional oral dosage forms provide no control over drug delivery, contributing to fluctuations in plasma drug level (Shargel and Andrew, 1999). The oral controlled release drug delivery has recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages such as ease of doing administration, patient compliance and flexibility in formulation (Nayak and Malakar, 2010). From the pharmacokinetic point of view, an ideal sustained and controlled release dosage form should attain the desired therapeutic concentration of drug in plasma and maintains constant for the entire duration of treatment, which is possible through administration of conventional dosage form in a particular dose and at particular frequencies. In addition, this should be compared with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels, once the steady state is reached (Hwang et al., 1998). Despite excellent *in vitro* release patterns, the drug absorption through oral delivery is unsatisfactory and highly variable among individuals. The reasons for this are essentially physiological and usually affected by the gastrointestinal transit of the dosage form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability (Hwang et al., 1998).

Variable and short gastric retention of a dosage form can result is an incomplete drug release. Again, some drugs are absorbed in the particular segment of the gastrointestinal tract (GIT) only are absorbed to a different extent in various segments of GIT. Such and drug candidates are said to have an 'absorption window'. However, in case of 'narrow absorption window' drugs, only the drug released in the region foregoing and in close vicinity of the absorption window is available for absorption. To overcome these restrictions, various gastroretentive systems have been designed to retain in

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Synthesis, Antioxidant, Antibacterial and Cytotoxic Activity of Novel Chromone Derivatives

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ABSTRACT

The present work was aimed to synthesize novel chromone derivatives to target estrogen receptor positive breast cancer. About 80% of all breast cancers are "ER-positive. The chromone scaffold is a privileged scaffold for exploration of anticancer agents. 3(4-oxo-4H-chromen-3-yl)acrylic acid amides derivatives designed, synthesized by employing the molecular hybridization approach between different aromatic, aliphatic amines and 3(4-oxo-4H-chromen-3-yl)acrylic acid. The docking study of 3(4-oxo-4H-chromen-3-yl)acrylic acid amides were performed using Schrodinger 2015 (maestro 10.1) on human estrogen receptor α-Ligand-Binding domain (1XP6), Tyrosyl-t-RNA synthetase protein (1JIK), DNA gyrase protein (4DUH), nitric oxide synthase (3NLE) and evaluated in vitro antioxidant activity, antibacterial activity, cytotoxicity against human Breast Cancer Cell Line (MCF-7). The in silico studies indicated that 3(4-oxo-4H-chromen-3-yl)acrylic acid amides derivatives exhibited comparable docking score and good hydrogen bond interactions with the amino acids present in the active site of 3NLE and 1XP6. Many of the synthesized compounds exhibited potent antioxidant and cytotoxic activity. The most potent antioxidant activity was observed for compound A_5 with IC_{50} value of 0.5 µg/ml, most potent anticancer activity was observed for compound A_1 with IC_{50} value of 37.13 µg/ml and potent antibacterial activity was observed for compound A_1 with Minimum Inhibitory Concentration (MIC) value of 100 µg/ml against Escheriea coli and Proteus vulgaris.

Keywords: 3(4-oxo-4H-chromen-3-yl)acrylic acid amides, Estrogen receptor, Breast cancer, Antioxidant activity, Antibacterial activity

INTRODUCTION

Estrogen receptor-positive (ER+) breast cancer is the most common type of breast cancer diagnosed today. According to the American Cancer Society, about two out of every three cases of breast cancer are hormone receptor positive. Most of these cases are ER+ or receptive to both estrogen and progesterone [1]. In Estrogen receptor positive breast cancer the level of Estrogen is a key factor for the initiation and progression of breast cancer [2 5]. In the mammary epithelial, estrogen controls many cellular activities such as proliferation, differentiation and migration [6,7]. There are two genetically distinct and functional Estrogen Receptors (ERs), ERα and ERβ, belonging to the superfamily of nuclear receptors for steroid/thyroid hormones. The structural differences between the two ERs indicate that they serve distinct actions [8]. Estrogen exert its functions in different tissues by binding with its receptors, including alpha and beta (ERα and ERβ), the former is the major one involved in breast cancer and chosen as an important target for endocrine therapy in clinic [2,9].

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [10]. Chromone (1) (4H-chromen-4-one, 4H-1-benzopyran-4-one) is an important class of oxygen-containing heterocyclic compounds with a benzoannelated γ-pyrone ring and they are part of the flavonoid family. The chromone and related compounds are widespread in the plant kingdom from algae to conifers. Chromones have found to be active in a number of plant cycles, including growth regulation, indole acetic acid oxidation and dormancy inhibition as well as exhibiting cytokinin-type behavior and stimulating oxygen uptake in plant tissue [11]. Chromone derivatives are abundant in nature and exhibit a wide range of pharmacological activity like antibacterial, antifungal [12,13], anticancer [14], antioxidant [15], anti-HIV [16], antiulcer [17], immunostimulators [18], biocidal [19], wound healing [20], antiinflammatory [21], and immune stimulatory [22]. Many chromone derivatives are also photoactive and can be used easily in various photo induced reactions affording diverse heterocyclic compounds [23]. Chromone derivatives are also active at benzodiazepine receptors [24] and on lipoxygenase and cyclooxygenase [25]. In addition to this, they have been shown to be possessing antimutagenic properties [26] as well as the ability to inhibit electron transport through inhibition at Nicotinamide Adenine Dinucleotide Hydrogen (NADH): Ubiquinone oxidoreducatase and phorbol ester-induced ornithine decarboxylase [27,28]. Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator. These compounds also possess Low mammalian toxicity and are present in large amounts in the diet of humans due to their origin in plants [25]. Acrylic acid derivatives have wide range of therapeutically importance such as, Anti-tumor activity [29], antioxidant activity [30] and antibacterial [31] activity.

SCIENTIFIC REPORTS

OPEN

Nimbolide upregulates RECK by targeting miR-21 and HIF-1α in cell lines and in a hamster oral carcinogenesis model

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Reversion-inducing cysteine-rich protein with Kazal motifs (RECK), a potent inhibitor of matrix metalloproteinases (MMPs) is a common negative target of oncogenic signals and a potential therapeutic target for novel drug development. Here, we show that sequential RECKlessness stimulates angiogenesis and Notch signalling in the 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis model, a paradigm for oral oncogenesis and chemointervention. We also report the chemotherapeutic effect of nimbolide, a limonoid from the neem tree (*Azadirachta indica*) based on the upregulation of RECK as well as modulation of the expression of key molecules involved in invasion and angiogenesis. We demonstrate that nimbolide upregulates RECK by targeting miR-21, and HIF-1α resulting in reduced MMP activity and blockade of VEGF and Notch signalling. Nimbolide reduced microvascular density, confirming its anti-angiogenic potential. Molecular docking analysis revealed interaction of nimbolide with HIF-1α. Additionally, we demonstrate that nimbolide upregulates RECK expression via downregulation of HIF-1α and miR-21 by overexpression and knockdown experiments in SCC4 and EAhy926 cell lines. Taken together, these findings provide compelling evidence that targeting RECK, a keystone protein that regulates mediators of invasion and angiogenesis with phytochemicals such as nimbolide may be a robust therapeutic approach to prevent oral cancer progression.

Reversion-inducing cysteine rich protein with Kazal motifs (RECK), a membrane bound glycoprotein that plays a pivotal role in remodelling the extracellular matrix (ECM) by regulating the activity of matrix metalloproteinases (MMPs) is a potent inhibitor of tumor invasion, metastasis and angiogenesis[1–3]. The RECK protein containing multiple epidermal growth factor-like (EGF-like) repeats and serine-protease inhibitor (SPI) motifs is anchored via the C-terminal glycosylphosphatidylinositol (GPI) to the cell membrane. RECK primarily inhibits MMP-2, and -9 as well as a-disintegrin and metalloproteinase (ADAM-10). RECK regulates Notch signalling, which plays a critical role in angiogenesis[4]. RECK is widely expressed in normal tissues and nonneoplastic cell lines, but its expression is frequently downregulated in several tumours and in fibroblasts transformed by various oncogenes. Hence, RECKlessness is considered a hallmark of cancer[5].

RECK downregulation is reported to stimulate invasion and angiogenesis in several tumours including liver, lung, breast, prostate, oral and digestive tract cancers[4–6]. The RECK gene is a common negative target of oncogenic signals as well as histone deacetylase (HDAC) that act on the binding site of the transcription factor Sp1 on the RECK gene promoter[7]. In addition, hypoxia and groups of miRs also cause transcriptional repression of RECK gene expression leading to upregulation of MMPs and ECM degradation[2,8,9]. Several synthetic and natural

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Pueraria tuberosa potentially attenuates Arsenic induced oxidative stress mediated cardiotoxicity, blood toxicity and dyslipidemia in rats

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ORIGINAL RESEARCH ARTICLE

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ABSTRACT

Background: The present study was carried out to evaluate protective effect of hydroalcoholic extract of *Pueraria tuberosa* (tuber) in arsenic induced cardiotoxicity in Wistar albino rats.

Material and Methods: Dose selection of *Pueraria tuberosa* was made on the basis of acute oral toxicity study (5, 50, 300, 1000 mg/kg body weight) as per OECD guidelines. Cardiotoxicity was produced in adult wistar rats randomly divided into six animals in six groups for 25 days. Group I rats were administered with drinking water for 30 days. Positive Control (Group II) rats were treated with sodium arsenate (1mg/kg).Group III rats were treated with sodium arsenate (1mg/kg) and Vitamin E (100 mg/kg).Group IV ,V,VI rats were treated with sodium arsenate (1mg/kg) and hydroalcoholic extract of *Pueraria tuberosa* (50mg/kg, 100mg/kg, 200mg/kg). After 30 days of the treatment, blood samples were collected and analyzed for the serum parameters *viz.* HDL (High density lipoprotein), Total cholesterol, LDL (Low density lipoprotein), Troponin, Triglycerides and LDH. Antioxidant parameters like Malondialdehyde, catalase, Reduced glutathione and glutathione reductase were estimated. Blood parameters like Haemoglobin, Mean corpuscular haemoglobin (MCH), Mean corpuscular volume (MCV), Mean corpuscular haemoglobin concentration (MCHC), RBC, WBC, Erythrocyte sedimentation rate, DNA fragmentation, body weight, organ weight were also estimated. The heart is removed and sectioned for histopathological examination.

Results: The hydroalcoholic extract of *Pueraria tuberosa* (tuber) inhibits the oxidative stress hypothesis mechanism and influence of calcium homeostasis.

Conclusion: It was concluded that the extract of *Pueraria tuberosa* (tuber) acts on intracellular calcium ions are increased in the myocardial cells to regulate myocardial hypertrophy.

Keywords: Arsenic trioxide, Cardiotoxicity, blood toxicity, *Peurariatuberosa*, DNA fragmentation.

INTRODUCTION

Cardiotoxicity is defined by the National Cancer Institute as the toxicity that affects the heart. This definition includes a direct effect of the drug on the heart but also an indirect effect due to enhancement of haemodynamic flow alterations or due to thrombotic events. Cardiotoxicity is the occurrence of heart electrophysiology dysfunction or muscle damage (Akhlaghia, 2010) reported as a result of cardiotoxicity, heart is not being able to pump blood throughout body. The heart becomes weaker and is not as efficient in pumping and circulating blood. This is due to caused by adverse effects of heavy metals intake (arsenic, mercury, lead, aluminium). Cardiotoxicity resulting from exposure to environmental toxicants and pollutants is known for a long time. For every new treatment, it will be essential to thoroughly assess toxic effects on the heart. The application of cutting-edge molecular biology approaches has provided significant and novel insights into cardiac toxicity and its mechanisms.

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Research Article

SYNTHESIS, CHARACTERIZATION, AND ANTICANCER ACTIVITY OF SOME NOVEL ACRIDINE DERIVATIVES

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ABSTRACT

Objective: The objective of the study was to synthesize and evaluate the anticancer activity of some novel acridine derivatives.

Methods: The present works involve condensation of acridine and various 2, 4-Thiazolidine-2,4-dione derivatives (2a–2h) with chloroacetyl chloride to give a novel acridine derivatives (5a–5l), respectively.

Results: All the newly synthesized molecules (5a–5l) were characterized by FTIR, H^1-NMR, and mass spectral analysis along with physical data. The biological potentials of the new synthesized compounds are evaluated for their *in vitro* anticancer activity by MTT assay.

Conclusion: The synthesized compounds 5a, 5f, and 5h exhibited good anticancer activity against MCF-7 and SKVO3 cancer cell lines at a concentration of 0.5 mg/mL^{-1}.

Keywords: Acridine, 2, 4-Thiazolidinedione, Substituted aldehydes, Chloroacetyl chloride, Anticancer activity, MCF-7, SKVO3 cells.

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INTRODUCTION

Acridine was first isolated by Carl Grabe and Heinrich Caro in Germany in 1870 from high boiling fraction of coal tar [1]. The antimicrobial property [2] of acridine was discovered Ehrlich and Benda in 1917. Bernthsen reported the primary synthesis of acridine, in which diphenylamine was reacted with benzoic acid using zinc chloride and high temperatures. The synthesis of acridine and its derivatives has attracted considerable attention from untreated and medicinal chemists for many natural life, as a number of natural source have been report to have this heterocyclic nucleus. Chemically, acridine is also known by the names of dibenzopyridine, 2,3,5,6-dibenzopyridine, and 10-azaanthracene. It has an irritating odor and crystallizes in colorless to light yellow needles with melting point of 110°C and boiling point of 346°C.

Acridine is a class of heterocyclic compounds which merit special attention because it belongs to a group of substances with activity in medicinal chemistry. This try cyclic nucleus derivatives are associated with anti-inflammatory [3,4], anticancer [5], antimicrobial [6], antitubercular [7,8], antiparasitic [9], antimalarial [10,11], antiviral [12,13], and fungicidal activities [14]. The basic in nature of pyridine, quinoline, and acridine is more or less similar compounds which possess no benzene ring, one benzene ring, and two benzene rings, respectively. Acridone is the one of the heterocyclic compounds with a tricyclic ring having nitrogen at 10^{th} positions and keto group at 9^{th} positions with the formula $C_{13}H_9N$. Acridines are substituted derivative of the parent ring. It is a planar molecule so as to be structurally related to anthracene by means of one of the central CH groups replaced by nitrogen.

In view of the facts mentioned above and the wide applications of acridine molecule and its derivatives in medicinal chemistry, an attempt has been made to synthesize novel 3-(2-(9-oxoacridin-10(9H)-yl) acetyl)-5-(benzylidene) thiazolidine-2,4-dione moiety as new anticancer agents.

METHODS

The synthesized compound was screened for sterile and anticancer activities. Fourier transform IR spectrometer (model Shimadzu 8700) in the range of 400–4000 cm^{-1} using KBr pellets and values are report in cm^{-1} and the spectra were interpreted. ^{1}H-NMR spectra were recorded on DPX-200 MHz NMR spectrometer using DMSO-d_6 and chemical shift (δ) is reported in parts per million downfield from internal reference tetramethylsilane and the spectra were interpreted. Mass spectra were record on mass spectrophotometer (model Shimadzu) by LC–MS and the spectra were interpreted. Pre-coated silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compound: n-Hexane: ethyl acetate (7:3) [15-17].

General procedures

Step 1: Preparation of N-phenyl anthracitic acid

In a 500 ml round-bottomed flask are placed a combination of o-Chlorobenzoic acid (20 g, 0.128 mol), Aniline (11.8 ml, 0.128 mol) and Copper metallic (0.5 g). To this solution 100 ml of amyl alcohol is delivered with constant stirring. To this mixture, dry potassium carbonate (20 g) was slowly added with stirring and the reaction mixture was allowed to reflux for 6 h in a light liquid paraffin oil bath at 135–140°C. Then the amyl alcohol was removed by using steam distillation and combination poured into two 2 L of hot water and acidified with targeted hydrochloric acid. The bluish-black precipitate formed was filtered, washed with hot water, and collected. The crude acid was dissolved in aqueous 10% sodium hydroxide solution, boiled in the presence of activated charcoal, and filtered. On acidification of the filtrates with concentrated hydrochloric acid, light yellowish precipitate was obtained, which was washed with hot water. The crude acid was recrystallized from aqueous methanol to give a light yellow solid.

Step 2: Preparation of acridin-9-one

N-Phenyl anthranilic acid (18 g, 0.084 mol) was taken in a 500 ml of round bottom flask to which polyphosphoric acid (180 g, 0.5327 mol) was added, shaken well, and refluxed on a water bath at 100°C for 3 h. Appearance of yellow color indicated the completion of reaction. Then, it was poured into 2 L of hot water and made alkaline by 25% ammonia solution. The yellow precipitate formed was filtered, washed with hot water, and collected. The crude acridin-9(10H)-one was recrystallized from acetic acid.

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Research Paper

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Nutritional Impact of Foods Made from Spirulina on Children of Selected Anganwadis of Siddipet District in Telangana State in India

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ABSTRACT

In the present investigation, we sought to study the impact of introducing spirulina based nutritional supplementation to the children of Siddipet District in Telangana, India. It was observed that beneficiaries are the social community who need help, support and awareness. An integrated, spectrum and holistic study approach was made to reach the beneficiary community. Several attempts were made to find out the answers to questions raised in the concurrent development of malnourished child health status in two ICDS projects, with 30 anganwadis in Bharat Nagar and 34 anganwadis in Cheriyal under Siddipet District, with the guidance and help of District Collector and team of company, Sukrutha Organics. The Study encompasses both primary and secondary source of information, covering anganwadis of ICDS, Bharat Nagar and Cheriyal, out of which 2119 children each were selected for the study by using information collected by anganwadi teachers scheduled as tool for data collection. Peanut Chikkis (Brittle) and Biscuits made by the addition of Spirulina were distributed among the test group and no supplement was given in the control group of children who were enrolled under Anganwadis of Bharat Nagar and Cheriyal ICDS of Siddipet District. Descriptive analysis was made to draw inferences. The study has come out with some major findings, in spreading the knowledge about the ill effects of malnutrition and benefits of spirulina and foods made with spirulina.

KEYWORDS: Malnutrition; Spirulina supplementation; healthy snacking.

Introduction

India's malnutrition problem results not from calorie intake but from dependence on a carbohydrate-based diet, low in protein and fat. We compromise on the intake of protein, fat and vitamins – all of which are essential for growth and inducing disease-fighting immunity at a young age. It is vital that Indian children get a balanced and nutrient-rich diet which includes all micro- and macronutrients need to bring about a healthy growth.

Poor maternal health and anemia during pregnancy is another reason for induction of stunting in children. This could have roots from adolescent anemia (Uliyar et al., 2000). This compromises resistance to diseases and nutrition value of breast milk. Poor pre-pregnancy body-mass index (BMI) and insufficient weight gain during pregnancy are common, as is blood and urine micronutrient deficiency. All of these, cause low birth weight, damaging the physiological development of a child. In many Indian households, women are taught to eat last, even when expecting.

Malnutrition or malnourishment is a condition that results from eating a diet in which nutrients are either not enough or are too much such that the diet causes health problems. It may involve calories, protein, carbohydrates, vitamins or minerals (Sandhu et al., 2010; Liu et al., 1991, Zhang and Liu, 1999). Not enough nutrients are called undernutrition or undernourishment while too much is called overnutrition. Malnutrition is often used specifically to refer to under nutrition where there is not enough a calorie, protein, or micronutrients. If under nutrition occurs during pregnancy, or before two years of age, it may result in permanent problems with physical and mental development. Extreme under nourishment, known as starvation, may have symptoms that include: a short height, thin body, very poor energy levels, and swollen legs and abdomen. People also often get infections and are frequently cold. The symptoms of deficiencies depend on the micronutrient that is lacking.

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Design, synthesis and characterization of novel paracetamol derivatives to target breast cancer

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Most breast cancers are Estrogen Receptor-positive type. In the mammary epithelial, estrogen controls many cellular activities such as proliferation, differentiation and migration. There are two genetically distinct and functional estrogen receptors (ERs), ERα and ERβ, belonging to the superfamily of nuclear receptors for steroid/thyroid harmones. Estrogenexert its functions in different tissues by binding with its receptors, including alpha and beta (ERα and ERβ). Estrogen Receptor alpha (ERα) controls breast tissue development and progression of breast cancer. Paracetamol is one of the most widely used medicines. A recent experimental study suggests that paracetamol may have several pharmacological effects other than its well known analgesic/antipyretic properties. The docking study was performed on different paracetamol derivatives using Schrodinger 2015 (maestro 10.1) on Human Estrogen Receptor Alpha Ligand-Binding Domain (1XP6) and Endothelial nitric oxide synthase (3NLE). The *in silico* studies indicate that N-(4-((1*H*-1,2,3-triazol-4-yl)methoxy)phenyl) acetamide derivatives exhibit comparable docking score and good hydrogen bond interactions at Ligand binding domain of ERα and 3NLE. Based on the docking studies, a new series of N-(4-((1*H*-1,2,3-triazol-4-yl)methoxy)phenyl) acetamide derivatives have been synthesized by employing click chemistry approach. Nine compounds have been evaluated for their cytotoxicity in MCF-7 cell line and anti oxidant activity. Many of the synthesized compounds exhibit potent cytotoxic and anti oxidant activity. In particular **5c**, **5g**, and **5b** compounds show most potent cytotoxicity with IC_{50} value of 19.83, 20.57, 20.83 µg/mL respectively and **5e** and **5f** show most potent anti oxidant activity with IC_{50} value of 0.4, 0.5 µg/mL respectively.

Keywords: N-(4-((1*H*-1,2,3-Triazol-4-yl)methoxy)phenyl)acetamide, click chemistry, docking, estrogen receptor, MCF-7 cell line, anti-oxidant activity

Estrogen receptor-positive (ER+) breast cancer is the most common type of breast cancer diagnosed today. There are many established risk factors forbreast cancer, including age, genetic alterations, family history, mammographic breast density, menstrual and menopausal his-tory, radiation exposure, and life style. In particular, thehormones, estrogen and/or progesterone, are known to be capable of increasing breast cancer risk[1-3]. According to the American Cancer Society, about two out of every three cases of breast cancer are hormone receptor positive. Most of these cases are ER+ or receptive to both estrogen and progesterone. In Estrogen receptor positive breast cancer the level of Estrogen is a key factor for the initiation and progression of breast cancer[4-7]. In the mammary epithelial, estrogen controls many cellular activities such as proliferation, differentiation and migration[8,9]. There are two genetically distinct and functional estrogen receptors(ERs), ERα and ERβ, belonging to the superfamily of nuclear receptors for steroid/thyroid harmones. The structural differences between the two ERs indicate that they serve distinct actions[10]. Estrogen exert its functions in different tissues by binding with its receptors, including alpha and beta (ERα and ERβ), the former is the major one involved in breast cancer and chosen as an important target for endocrine therapy in clinic[11].

Paracetamol is a widely used over-the-counter pain medication and medication to reduce fever[12]. Paracetamol is used in the management of more severe pain such as post surgical and cancer pain in combination with opioid analgesics. In addition to well known use pain relief and fever reduction, recent laboratory and pre-clinical studies have demonstrated

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RESEARCH ARTICLE

BENTHAM SCIENCE

Synthesis, Antiproliferative, and Antioxidant Activities of Substituted *N*-[(1,3,4-Oxadiazol-2-yl) Methyl] Benzamines

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Abstract: ***Background*:** Oxadiazole emerged as an important class of heterocyclic compound with diverse biological activities like anticancer, antitubercular, anticonvulsant, anti-tubulin, antimicrobial, anti-inflammatory, antioxidant *etc.*

***Objective*:** The objective of this study is to synthesis series of twelve substituted *N*-[(1,3,4-oxadiazol-2-yl)methyl]benzamines (**6a-l**) and their evaluation as antiproliferative and antioxidant agents.

***Methods*:** The substituted *N*-[(1,3,4-oxadiazol-2-yl)methyl]benzamines (**6a-l**) analogues were synthesized as per the reported procedure. The antiproliferative activity was tested against nine different panels cancer cell lines (leukemia, colon, renal, non-small cell lung, breast, CNS, melanoma, prostate, and ovarian cancer) at 10 μM drug concentrations as per the NCI US Protocol.

***Results*:** 2-(5-((3-Chloro-4-fluorophenylamino)methyl)-1,3,4-oxadiazol-2-yl)phenol (**6e**) revealed the significant antiproliferative activity among the series of title compounds (**6a-l**). The compound, **6e** showed maximum sensitivity towards CCRF-CEM, MCF-7, MOLT-4, T-47D, and SR cell lines with percent growth inhibitions (%GIs) of 79.92, 56.67, 39.62, 34.71 and 33.35, respectively. Furthermore, the compounds, **6e** and **6c** showed promising antioxidant activity with an IC50 value of 15.09 and 19.02 μM, respectively in DPPH free radicals (FR) scavenging activity.

***Conclusion*:** The present study may support a significant value in cancer drug discovery programme.

Keywords: Anti-proliferative agents, antioxidants, oxadiazoles, one dose assay, DPPH, free radicals scavenging activity.

1. INTRODUCTION

Cancer is the second leading cause of deaths worldwide. In 2015, 8.8 million cancers related deaths were reported, and the newer case of cancers would rise by nearly 19.3 million in the year 2025 [1]. The incidence of cancer was drastically increased in the last decades and its treatment has gained great importance. Chemotherapy is an important approach for cancer treatment, however, lack of selectivity and emergence of drug resistance and genotoxicity diminished their efficacy [2]. Therefore, the development of effective and safe anticancer agents remains a critically important area in medicinal chemistry. We reported herewith the preparation of oxadiazoles because they are important class

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Chemistry SELECT Full Papers

Medicinal Chemistry & Drug Discovery

2-Mercapto Benzthiazole Coupled Benzyl Triazoles as New COX-2 Inhibitors: Design, Synthesis, Biological Testing and Molecular Modeling Studies

Satyanarayana Yatam,[a] Surender Singh Jadav,[b, c] Krishna Prasadh Gundla,[a] Kalyani Paidikondala,[a] Ashok Reddy Ankireddy,[a] Bathini Nagendra Babu,*[c, d] Mohamed Jawed Ahsan,[e] and Rambabu Gundla*[a]

A series of 2-mercapto benzothiazole linked with triazoles (**3a-u**) were designed based on our previous experimental evaluation of benzothiazole allied oxadiazoles and synthesized in two step starting from the 2-mercaptan precursor. The structure of the benzothiazoles were confirmed by infrared (IR), nuclear magnetic resonance (NMR) and mass (LC–MS) spectral data. The *insilico* binding mode interpretations in both COX-1/COX-2 was investigated, their probable binding energies were predicted and ADMET properties were calculated. The molecular level interactions of the designed library indicated, the aryl ring united with triazole was occupying as mefenamic acid in COX-2 active site. All the benzothiazoles **3a-u** were evaluated for their COX inhibitory activities as per the standard protocol reported elsewhere. 2-(((1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl) methyl)thio)benzo[d]thiazole **3i**, 4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzoic acid **3t** and 4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzamide **3u** based benzthiazoles showed the most significant COX-2 inhibitory activity with an IC_{50} of 4.1, 4.3 and 5.4 μM respectively. The time dependant increase in inhibition of inflammation of above COX-2 inhibitors in *invivo* anti-inflammatory evaluation was noticed. Additionally, 2-(((1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]thiazole **3g** expressed the significant DPPH scavenging activity with 80.45 percent inhibition at 100 μM and an IC_{50} of 27.8 μM. Furthermore, the 50 ns molecular dynamic simulations of 2-(((1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]thiazole **3i** to interpret the constant residue interactions might liable for the COX selectivity was presented. Later, they also have been tested for cancer lines at NCI and obtained data were provided.

Introduction

Inflammation is a spontaneous course of action to an injury or infection caused by pathological substances. The inflammatory pain is one among the other major cardinal signs and is induced by the release of chemicals, preferably inflammatory mediators.[1] The oxidative stress due to reactive oxygen free radicals and pain associated with autoimmune disorders like rheumatoid arthritis turns situation in to chronic conditions.[2] The involvement of cyclooxygenases (COX-1 and COX-2) in the conversion of prostanoids from arachidonic acid made them as privileged target for most of the Non Steroidal Anti-Inflammatory Drugs (NSAIDS) to reduce inflammatory pain.[3] The inhibition strategy of COX enzymes is an attractive way to circumvent the pain and majority of the COXIBs were become popular as COX inhibitors.[4] Though, COXIBs were potent anti-inflammatory agents and COX inhibitors; but they failed to inhibit the specific isoform COX-2 enzyme and resulted in gastric side effects which are linked with physiological activities COX-1 isoform.[5] Thus, the selective isoform specific COX-2 inhibitors needed to address the modern scenario.

Benzothiazoles is an important class of bicyclic compounds reported with diverse medicinal and industrial applications,[6] Anticonvulsant,[7-8] anticancer,[9] anti-inflammatory,[10-11] antimicrobial,[12] antitubercular,[13] insecticidal[14] and many other biological activities were reported for benzothiazoles. Benzothiazoles (containing sulphur) is an isosteric analogue of benzoxazoles (containing oxygen). The design of our scaffold is based on the structure of reported anti-inflammatory agents, Flunoxaprofen (**A**), Benoxaprofen (**A**),[15] PF-469327 (**B**) (mPGES-

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and biological evaluation of chalcone-linked thiazole-imidazopyridine derivatives as anticancer agents

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Abstract
A novel library of chalcone linked thiazole-imidazopyridine (**12a–j**) derivatives were designed, synthesized, and their structures were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral studies. Further, all compounds were tested for their anticancer effects on four human cancer cell lines including MCF-7 (breast carcinoma), A549 (lung carcinoma), DU-145 (prostate carcinoma) and MDA MB-231 (breast carcinoma) by employing MTT method, using etoposide as the positive control. Among them, compound **12b** displayed more potent anticancer activity against four cancer cell lines when compared to the positive control.

Keywords Imidazo[4,5-b]pyridine · Zolpidine · Licochalcone A · Chalcone and anticancer activity

Introduction

Now days, cancer is the second leading cause of death after heart disease in developed and undeveloped countries (John and Ross 2010), which is initiated by external (Park et al. 2010; Meffert et al. 2003; Clemens 1991) and internal factors (Mantovani et al. 2008; Clayton et al. 2011; Porta et al. 2011). Cancer treatment has become an important and challenging therapeutic task in medicinal chemistry. The three main treatment strategies employed are surgery, radiation therapy, and chemotherapy. Of these, chemotherapy is one of the important therapy used for the treatment of cancer, which employs chemotherapeutic agents. However, this is associated with various side effects. Hence, the discovery of potent anticancer agents without side effects is a challenge in development of cancer chemotherapeutics for the future generations.

Nitrogen-containing heterocyclic molecules has always attracted significant interest in pharmaceutical industry because of their biological applications. Nitrogen containing imidazo[4,5-b]pyridines are versatile nitrogenized fused hetero-aromatic units that have exhibited potent anticancer properties against a panel of cell lines (Agarwal et al. 2016; Ahsan et al. 2015; Durgesh et al. 2018a, 2018b, 2018c; Hatti et al. 2015a, 2015b; Madhavi et al. 2017b; Murthy et al. 2019; Pragathi et al. 2019; Rao et al. 2019; Reddy et al. 2016a, 2016b; Reddy et al. 2019; Shahinshavali et al. 2019; Spandana et al. 2018a, 2018b; Sreenivasulu et al. 2017; 2018; 2019; 2020; Subramanyam et al. 2018; Suma et al. 2019; Yakantham et al. 2019). It is a structural analog of a purine base. Its derivatives easily interact with the proteins of DNA and RNA. They also show a variety of biological properties like antimitotic (Temple 1990),

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Research Article

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Formulation and *in vitro* evaluation of superporous hydrogel based gastroretentive drug delivery system of vildagliptin

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ABSTRACT: Numerous medications, which have a tight restorative window and are consumed predominantly in the stomach have been created as a gastroretentive conveyance framework. Vildagliptin, an antidiabetic, is exceedingly temperamental at fundamental pH and is widely retained from the stomach. Henceforth there is a need to build up a gastroretentive framework. In this investigation a superporous hydrogel was created as a gastroretentive medication conveyance framework. Superporous hydrogels were readied utilizing a gas forming method utilizing N', N'- BIS as the crosslinking operator and polyvinyl Alcohol as a composite specialist. Swelling practices of the superporous hydrogel in acidic arrangement were concentrated to explore their applications for gastric maintenance gadget. The ideal arrangement state of superporous hydrogels was gotten from the swelling and *in vitro* medication discharge thinks about. FT-IR, SEM and DSC contemplates were utilized to portray the similarity between polymers. As the grouping of crosslinker expanded from 0.5 to 3% the porosities diminished. In reenacted gastric liquid superporous hydrogels demonstrated a decent increment in harmony swelling limit. Checking electron infinitesimal pictures plainly showed the arrangement of interconnected pore and slim channels. Portrayal thinks about uncovered that the expansion in crosslinker focus is beneficial from the swelling proportion, and yet the decline in porosity may prompt abatement in medication discharge rate by dispersion through these narrow channels. The medication discharge from superporous hydrogels appeared for a drawn out timeframe. Structure the discharge energy it uncovered that sedate pursues the Non – Fickian mechanism. FTIR and DSC ponders uncovered that there were no critical collaborations between the drug and polymers. In light of the portrayal thinks about, it was uncovered that superporous hydrogels could be utilized as a gastroretentive medication conveyance framework for vildagliptin in perspective on their swelling and delayed medication discharge qualities in acidic pH.

KEYWORDS: Vildagliptin; superporous hydrogel; crosslinking agent; polyvinyl alcohol; swelling ratio.

1. INTRODUCTION

In the present time focusing of the medication at a specific site has turned into a significant piece of pharmaceutical research. Be that as it may, different issues are watched while focusing of medication atom at explicit destinations, for example, quick end, debasement and short living arrangement time. In the course of the most recent couple of decades, the engaged has been made in structuring of gadget that can hold in the upper piece of the gastrointestinal tract (GIT) as far as improving medication home time of medication at focusing on locales. There are different advancements have been utilized for a gastroretentive gadget, for example, low-density systems [1], high-density systems [2], bioadhesive systems[3] and expanding systems[4]. However, these frameworks are influenced by different factors, for example, gastric liquid substance, brutal gastric condition, gastric constriction and nourishment content. These components bring about lessening gastric maintenance time. Superporous hydrogels based GRDDS have been structured by numerous scientists as a gastric maintenance gadget. They have the attributes to retain a lot of water and swell due to having a hydrophilic practical gathering in their structure. This swelling property is dependable to keep the detailing

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Research Article

Evaluation of In Vitro antiurolithiatic activity of *Terminalia Chebula*

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ABSTRACT

Population in an industrialized world is afflicted by urinary stone disease. Kidney stones are common in all kinds of urolithiasis.The present study explored the evaluation of in vitro anti urolithiatic activity of *Terminalia Chebula*. It was observed that the highest calcium oxalate crystals dissolution was observed in the Ethanol extract of *Terminalia Chebula*. It was found that Ethanol extract of *Terminalia Chebula* has shows efficiency to dissolve calcium oxalate.

Keywords: Anti urolithiatic activity, Ethanol extract, *Terminalia Chebula*, Neeri.

INTRODUCTION

Plants provide food, raw materials for medicine and various other requirements for the very existence of life from the origin of human beings.(1)..Even the current conventional medicine is using a lot of plant derived chemicals as therapeutic agents. The overuse of synthetic drugs results in higher incidence of adverse drug reactions has motivated humans to return to nature for safe remedies. Herbs and herbal drugs have created interest among the people by its clinically proven effects .(2). Therefore, there is a compelling need for detailed scientific validation of all traditional medicinal plant drugs to establish their efficacy and safety in light of modern science .(1).Kidney stone disease is a multi-factorial disorder resulting from the combined influence of epidemilogical,biochemical and genetic risk factors.(3). Urolithiasis is considered as the third most common affliction of the urinary tract. It refers to the solid non-metallic minerals in the urinary tract. It is a complex process that is a consequence of an imbalance between promoters and inhibitors in the kidney. The formation of kidney stones involves several phytochemical events beginning with crystal nucleation, aggregation and end with retention within the urinary tract. Among the several types of kidney stones, the most common are calcium oxalate stones representing upto 80% of the analyzed stones(4) .Calcium containing stones may be in the form of pure calcium oxalate(50%) or calcium phosphate(5%) and a mixture of both(45%) followed by magnesium phosphate(15-20%),uric acid(10%) and cystine(1%)(5) . It is estimated that at least 10% of the population in the industrialized part of the world is afflicted by urinary tract diseases and among these kidney stones are common with an annual incidence of 0.5 -1.9%. About 12% of the population of India is expected to have urinary stones and out of that 50% of cases encounter loss of one or both 2 kidneys with or without renal damage upto some extent(2) . Stone disease is 2-3 times more common in males, than in females(5). It has a reoccurence rate of 70-81% in males and 47-60% in females.In spite of substantial progress in pathophysiolgy and treatment of urolithiasis, there is no satisfactory drug being used in clinical therapy. Kidney dialysis, endoscopic stone removal and extra corporeal shock wave lithotripsy are prohibitively costly and reoccurrence is quite 1 common with these procedures(1) Data from in vitro and in vivo clinical trials revealed that phytotherapeutic agents could be useful as alternative therapy in the management of urolithiasis. Medicinal plants and their products are more useful, because they promote the repair mechanism in natural way(1). Pharmacological and phytochemical prospecting of medicinal plants based on traditional knowledge can lead to the discovery of new drug and development of pharmacologically important products for human health care(6) .Green medicines were safe and more dependable than the costly synthetic drugs,many of which have side effects(7) The selected plant Tridax procumbens have occupied an important place in Indian culture and folk medicines. This plant have been extensively in ayurvedic system of medicine and is used throughout India. It is used in Ayurvedic medicine for liver disorders,. hepatoprotection, gastritis and heatburn(8).The plant shows various pharmacological activities like immunomodulatory, Anti-diabetic, Anti-hepatotoxic, Anti-oxidant, Anti-inflammatory, Analgesic etc(9)

Materials and Methods

Plant Materials

The seeds of *Terminalia chebula* were collected from Sangareddy of Telangana in the month of January 2018. The plant was authenticated by D. Venkateshwara Rao, DeputyDirector, Telangana. Forest Academy, Dullapally, Hyderabad, Rangareddy District. The seeds were washed with tap water and dried under shade.

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Mini-review

A review on HCV inhibitors: Significance of non-structural polyproteins

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ABSTRACT

Hepatitis C virus (HCV) mortality and morbidity is a world health misery with an approximate 130–150 million chronically HCV tainted and suffering individuals and it initiate critical liver malfunction like cirrhosis, hepatocellular carcinoma or liver HCV cancer. HCV NS5B protein one of the best studied therapeutic target for the identification of new drug candidates to be added to the combination or multiple combination medication recently approved. During the past few years, NS5B has thus been an important object of attractive medicinal chemistry endeavors, which induced to the surfacing of betrothal preclinical drug molecules. In this scenario, the current review set limit to discuss research published on NS5B and few other therapeutic functional inhibitors concentrating on hit investigation, hit to lead optimization, ADME parameters evaluation, and the SAR data which was out for each compound type and similarity taken into consideration. The discussion outlined in this specific review will surly helpful and vital tool for those medicinal chemists investigators working with HCV research programs mainly pointing on NS5B and set broad spectrum identification of creative anti HCV compounds. This mini review also tells each and every individual compound ability related how much they are active against NS5B and few other targets.

1. Introduction

The HCV is an infectious disease caused by Hepatitis C virus, which primarily affects the liver to develop liver Cirrhosis and carcinoma. The HCV causing virus is mainly transmitted to humans by transfusion of human body fluids similar to HIV [1]. According to the world health organization (WHO), 3–5 lakh death cases among 130–150 million hepatitis C virus infected individuals are being reporting each year across the world [2]. The existence of hepatitis C was suggested in the 1970s and is discovered in 1989 [3]. Hepatitis C infects only humans, chimpanzees according to few studies it is also found the in blood samples of horses in the form of non primate hepacivirus (NPHV) [4]. About 85% viral persistence in the liver of HCV infected individuals is reported. The infection is petite, if the diagnosis become delayed it leads into chronic infection (in 70–80% of cases) and development of liver cirrhosis increases the death aspects of the infected individuals (Fig. 1).

In few cases, those with cirrhosis will go on to develop liver failure and life threatening cancer [5]. The symptoms of HCV is not provoked immediately and thus majority of infected individuals may not be physically ill [2]. HCV infections can be quickly detected

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Pharmacological screening of aqueous extract of *Sesbania grandiflora* for anti-glaucomic activity in Rabbits

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The present work was designed to investigate the antiglaucoma activity of *Sesbania grandiflora* (SG) aqueous leaf extract against alpha chymotrypsin induced experimental glaucoma in rabbits. The experimental increase in IOP was achieved using alpha chymotrypsin induced glaucoma model. Once the IOP was increased significantly, aqueous leaf extract of SG and standard were given topically every day into the right eye of rabbits. IOP was measured by Schiotz indentation tonometer on every alternate day till a significant reduction of IOP was observed. The results were compared with standard 0.1% brinzolamide. A significant increase in IOP was observed on the 7th day after inducing glaucoma. Significant reduction of IOP was observed on the 6th day after giving plant extract when compared with the standard. The results show that the leaf extract showed significant occulohypotensive activity and this effect was comparable to the standard brinzolamide. Further investigation into the mechanism of action and isolation of compounds which are responsible for antiglaucoma activity is to be established.

Keywords: Alphachymotrypsin, Brinzolamide, Intraocular pressure (IOP), Schiotz tonometer.

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Introduction

Glaucoma is described as a group of eye conditions leading to the interruption of visual information from the eye to the brain[1]. It is the second most important cause of blindness after cataract[2,3]. There are many risk factors for glaucoma but the most important is the rise in intraocular pressure which causes damage to the optic nerve[4,5]. Although surgical options exist, medical management to control IOP is the mainstay of the treatment[6]. There are different synthetic medications available in the market but their cost, side effects and contraindications limit their use in patients. Since many ages, Botanical compounds were used as a cure for various diseases and ailments. They have a very long history of medical use. 74% of today's modern drugs that are used directly in traditional medicine have their origin from the natural compounds[7]. Classical texts of Ayurveda have attributed wide-ranging therapeutic indications of this selected herb. *Sesbania grandiflora* popularly known as Agasthya leaves are known to possess wide therapeutic applications. It is used as an analgesic and CNS depressant[8], in smoke-related diseases[9], antioxidant and anti urolithiatic[10], cardioprotective[11], protective effect on kidneys[12], including eye diseases[13-15]. The plant was reported to contain Alkaloids, Glycoside, Tannins, Carbohydrates, etc[16-18]. However, relatively little scientific information is presented on the usage of this drug in treating ocular diseases such as glaucoma. Hence, in the present study, we studied the occulohypotensive activity of this plant in reducing IOP.

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Materials and Methods

Chemicals

Alpha chymotrypsin (Sisco Research Laboratories, Hyderabad, India), brinzolamide, indomethacin, midazolam, phenobarbitol and xylocaine are commercial samples procured in Apollo pharmacy, Hyderabad.

Animals

New Zealand rabbits of either sex weighing 2 kgs were used. The animals were treated in accordance with the institutional guidelines (CPCSEA approval no. 1358/ac/10) to make use of animals in research. The animals were acclimatized for a period of 2 weeks, *ad libitum* food and water was provided and 12 h light/dark cycle was maintained. After two weeks of habituation in the animal house facility, the animals were trained to accept tonometry.

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Development and Validation of a Stability-indicating Method for the Simultaneous Estimation of Sofosbuvir and Ledipasvir by RP-HPLC

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Research Paper

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Development and Optimization of Lovastatin-loaded Transdermal Proniosomal Gel using Box-Behnken Design

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ABSTRACT

In this study, a proniosome-based transdermal drug delivery system of lovastatin was developed by coacervation phase separation method. On the basis of the pilot trials, a 3-factor, 3-level Box–Behnken design was employed to characterize the effect of Cholesterol, soya lecithin and Tween 80 on dependent variables (particle size, entrapment efficiency, and drug release). TEM analysis of optimized formulation has demonstrated the presence of individual Proniosomes in spherical shape. Lovastatin optimized proniosomal formulation F1 shown better particle size and percentage entrapment efficiency and drug release of 99.49% within 24h in slow and controlled manner when compared with control. Kinetic analysis of drug release profiles showed that the systems predominantly released Lovastatin in a zero-order manner with a strong correlation coefficient (R^2= 0.9990). The particle size and Zeta potential of the optimized lovastatin proniosomal gel was found to be 138.82 nm and -11.4 mV respectively. Optimized batch of Proniosomes was used for the preparation of Lovastatin - based proniosomal hydrogel by incorporating hydrated Proniosomes to Carbopol matrix to enhance the stability and viscosity of the system. The enhanced skin permeation for prolonged time may lead to improved efficacy and better patient compliance.

KEYWORDS: Lovastatin; Proniosomal gel; Box-Behnken Design; Soya lecithin; TEM.

Introduction

In recent years, transporting the drug molecules to the desired site in the biological systems has become a very specific and sophisticated area of pharmaceutical research (Gyati Shilakari et al., 2016). Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have distinct advantages over conventional dosage forms because the particles can act as drug containing reservoirs. Therefore, these carriers play an increasingly important role in drug delivery (Singh et al., 2010). Transdermal drug delivery system (TDDS) is among the most widely employed system to overcome the issues associated with oral route (Wen et al., 2014). Due to which it exhibits high level of patient compliance with low levels of intra and inter-patient variability (Aggarwal and Dhawan, 2010). Among various strategies, vesicular systems like niosomes exhibits substantial potential to overcome such barrier. It also acts as drug reservoir and provides the controlled release of drug (Morrow et al., 2007; Vyas and Khar, 2004). Proniosomes was introduced to overcome such problems as it provides ease of transportation, distribution, storage and dosing. Proniosomes are usually dry powder or gel, which can be hydrated just before use resulting in the formation of niosomes. Proniosome gel when applied to skin under occlusive conditions, they get hydrated with the skin moisture and converted to niosomes (Kaushik et al., 2004).

Lovastatin is an antihyperlipedimic drug used to reduce cholesterol in the treatment of hyperlipidemias particularly in type 2a and 2b hyper lipoproteinaemias. It is given prophylactically for both primary and secondary prevention of ischemic heart diseases. The absorption of Lovastatin following oral administration is approximately 30% because it undergoes high first pass metabolism (Sweetman, 2005).

In the present study, a Coacervation phase separation method was used for the preparation and optimization of Lovastatin proniosomes, as this method is simple and easy to scale up. The proniosomes are thus of interest from a technical viewpoint and allow a wider scope to be used to study the influence of various formulation variables. To enhance the stability and viscosity of the system, the proniosomes were mixed with carbopol gel as described earlier (Pankaj et al., 2013).

Materials and Methods

Materials

Lovastatin calcium was received as a gift sample from Aurobindo Pharma Ltd, Hyderabad. Tween 80 and Soya lecithin was received as a gift sample from Lipoid GmbH, Germany. Cholesterol 95% stabilized was purchased

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REVIEW ARTICLE

Phytochemical Screening and *In-Vitro* Antioxidant activity of senna Occidentalis

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ABSTRACT:
The aim of this article is to evaluate antioxidant activity of leaf extract of Senna occidentalis by using in vitro assay. Extraction was carried out with ethanol extract by using Soxhlet apparatus. The in-vitro antioxidant activity ethanol extract has been investigated by 1, 1-diphenyl,2-picryl–hydrazyl free radical (DPPH) method. The ethanol extract exhibited maximum antioxidant activity. The results have been compared with the standard ascorbic acid. The Ethanolic leaf extract of Senna occidentalis shows IC_{50} value at 7 µg/ml.

KEYWORDS: Antioxidant activity, DPPH, Free radicals, Ethanolic extract, Ascorbic acid.

INTRODUCTION:

The term "antioxidant" is mostly used for two entirely different groups of substances: industrial chemical that are added to products to prevent oxidation, and naturally occurring compounds that are present in foods and tissue. The former, industrial antioxidants, have diverse uses: acting as preservatives in food and cosmetics, and being oxidation-inhibitors in fuels.[1]A substance that inhibits oxidation, especially one used to counteract the deterioration of stored food products.Antioxidants are an inhibitor of the process of oxidation, even at relatively smallconcentration and thus have diverse physiological role in the body. Antioxidant constituents of the plant material act as radical scavengers, and helps in converting the radicals to less reactive species. A variety of free radical scavenging antioxidants is found in dietarysources like fruits, vegetables and tea, etc.[2] Oxidative stress is characterized as an imbalance between the production of reactive species and antioxidant defense activity, and its enhanced state has been associated with many of the chronic diseases such as cancer, diabetes, neurodegenerative and cardiovascular diseases.[3]

There is our days, an increasing interest in the measurement and use of plant antioxidants for scientific research as well as industrial (dietary, pharmaceutical and cosmetic) purposes. This is mainly due to their strong biological activity, exceeding those of many synthetic antioxidants which have possible activity as promoters of carcinogenesis.[4]

The traditional medicine all over the world is nowadays revalued by an extensive activity of research on different plant species and their therapeutic principles. Experimental evidence suggests that free radicals (FR) and reactive oxygen species (ROS) can be involved in a high number of diseases (Richards and Sharma, 1991, Niwa, 1991). As plants produce a lot of antioxidants to control the oxidative stress caused by sunbeams and oxygen, they can represent a source of new compounds with antioxidant activity. Ayurveda, the Indian traditional health care system (ayus=life, veda=knowledge, meaning science of life), is the oldest medical system in the world and is being revived in its complete form under the name of Maharishi Ayurved (Glaser, 1988). The World Health Organization has approved its efficacy (Zaman, 1974). This system provides an approach to prevention and treatment of different diseases by a large number of medical procedures and pharmaceuticals. One of the clinical specialties' of Ayurveda is Rasayana. Rasayana is not only a drug therapy but is a specialized procedure

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Research Article

FORMULATION AND EVALUATION OF PRONIOSOMAL GEL-BASED TRANSDERMAL DELIVERY OF ATORVASTATIN CALCIUM BY BOX–BEHNKEN DESIGN

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ABSTRACT

Objective: The aim of this study was to investigate the combined influence of three independent variables in the preparation of atorvastatin proniosomes by coacervation-phase separation method.

Methods: On the basis of the preliminary trials, a 3-factor, 3-level Box–Behnken design was employed to study the effect of cholesterol, soya lecithin, and Span 60 independent variable on dependent variables (particle size and % entrapment efficiency). Transmission electron microscopy analysis of optimized formulation has demonstrated the presence of individual proniosomes in spherical shape.

Results: Atorvastatin optimized proniosomal formulation F2 shown better particle size and % entrapment efficiency, and also, the drug release was 99.72% within 24 h in slow and controlled manner when compared with control. Kinetic analysis of drug release profiles showed that the drug release was followed by zero-order manner with Korsmeyer–Peppas model, which implies super case II release kinetics. The particle size and zeta potential of the optimized atorvastatin proniosomal gel were found to be 65.72 and −10.5, respectively. The optimized batch of proniosomes was used for the preparation of atorvastatin-based proniosomal hydrogel by incorporating hydrated proniosomes to carbopol matrix to enhance the stability and viscosity of the system.

Conclusion: The enhanced skin permeation, for a prolonged period of time, may lead to improved efficacy and better patient compliance. This study suggests that proniosomal gel-containing atorvastatin could perform therapeutically better effects than the conventional formulations.

Keywords: Atorvastatin, Proniosomes, Box–Behnken Design, Span 60, Zeta potential.

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INTRODUCTION

Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have distinct advantages over conventional dosage forms because the particles can act as drug-containing reservoirs [1]. The use of non-ionic surfactant vesicles (niosomes) as drug carrier systems has distinct advantages over conventional dosage [2]. They can increase the drug efficacy, reduce drug side effects, increase the drug solubility, and develop an effective topical delivery [3]. Transdermal drug delivery system is among the most widely employed system to overcome the issues associated with oral route, increases the therapeutic efficacy of many drugs by preventing their conversion to undesirable metabolites, and also helps in maintaining uniform plasma levels *in vivo* [4]. Due to which, it exhibits a high level of patient compliance with low levels of intra- and inter-patient variability [5]. Among various strategies, vesicular systems such as niosomes exhibit substantial potential to overcome such barrier [6,7]. Proniosomal gel when applied to skin under occlusive conditions get hydrated with the skin moisture and converted to niosomes [8]. The additional convenience of the transportation, distribution, storage, and dosing would make "dry niosomes" a promising industrial product. These dry niosomes are hydrated immediately before use and thus avoids some of the problems [9,10] Atorvastatin calcium is a 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor used in the treatment of hyperlipidemia [11]. It has an oral bioavailability of <12%. It also undergoes high first-pass metabolism. It is highly soluble in acidic pH and absorbed more in the upper part of the gastrointestinal tract [12].

In the present study, the coacervation-phase separation method was used for the preparation and optimization of atorvastatin proniosomes, from a technical viewpoint, and allowed a wider scope to be used to study the influence of various formulation variables. To enhance the stability and viscosity of the system, the proniosomes were mixed with carbopol gel [13].

MATERIALS AND METHODS

Materials

Atorvastatin calcium was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad. Span 60 and soya lecithin were purchased from SD Fine Chemicals (Mumbai, India). Cholesterol 95% stabilized was purchased from Acros Organics. Carbopol P 934 was obtained from MSN Laboratories, Hyderabad. Dialysis tubing was purchased from HiMedia Laboratories (Mumbai, India). All other chemicals and solvents were of analytical grade and were used without further purification.

Methodology

Drug-excipient compatibility study

Fourier-transform infrared (FTIR) studies

The drug-excipient compatibility studies were performed to check the interaction between drug and excipients. The FTIR spectra of drug sample and its physical mixture with excipients were carried out by potassium bromide disc method using Shimadzu IRAffinity 1 Spectrophotometer in the region of 4000–400 cm^{-1}.

Differential scanning calorimetry (DSC) studies

DSC of drug sample and its physical mixture with excipients was carried out using a Perkin Elmer DSC-7 Differential Scanning Calorimeter (PerkinElmer, CT, USA) equipped with a TAC 7/DX Instrument Controller. Analyses were performed in triplicate on 5 mg samples under nitrogen purge.

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Synthesis, anti-diabetic evaluation and molecular docking studies of 4-(1-aryl-1*H*-1, 2, 3-triazol-4-yl)-1,4-dihydropyridine derivatives as novel 11-β hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibitors

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ABSTRACT

11-Beta-Hydroxysteroid dehydrogenase-1(11β-HSD1) inhibitors are one of the emerging classes of molecules to fight against diabetic complications. A novel series of 4-(1-substituted-1*H*-1,2,3-triazol-4-yl)-1,4-dihydropyridine derivatives were synthesized and evaluated for their anti-diabetic activity. Two compounds showed anti-diabetic activity very effectively. To clarify the mechanism of action of these compounds, the most potent compounds (5g and 5h) of the synthesized analogs were further studied by testing its 11-Beta Hydroxysteroid dehydrogenase-1 inhibitory activity through *in vitro* enzymatic experiments. The results showed that the 11β-HSD1 inhibitory activity of compounds 5g and 5h was stable and efficient. Molecular docking studies revealed compounds 5g (−9.758) and 5h (−8.495) to have a stable binding patterns to the human 11-Beta-Hydroxysteroid dehydrogenase-1.

1. Introduction

Adipose tissue is an important source in governing energy equity and glucose homeostasis. As an energy repository, adipose tissue responds to the body's metabolic signaling by controlling lipid depot and mobilization. Adipocytes liberate free fatty acid (FFA) as a nutrient source when glucose levels are decreasing, whereas they store ample energy as triglycerides in an energy excess environment. Insulin resistance can uplift the FFA limits, and excessive FFA leads to deterioration of metabolic state by stimulating liver glucose output and by impeding glucose uptake by peripheral tissues and the generation of a reactive oxygen system (ROS), which, in turn, provoke insulin resistance [1]. Adipose tissue is an important portion of the endocrine system, which liberates many adipokines, such as leptin, GBP-28, Nicotinamide phosphoribosyltransferase, (NAmPRTase), omentin, and adipose tissue-specific secretary factor (ADSF), to control glucose homeostasis and whole body insulin sensitivity. Thus, adipocyte dysfunctioning may lead to pathogenic characteristics of obesity and metabolic disorders such as type 2 diabetes [2]. Glucocorticoid is an antagonizing hormone of insulin that triggers hepatic glucose production and inhibits insulin-dependent glucose uptake in peripheral tissues such as adipose tissue and skeletal muscle. Excess glucocorticoid in Cushing's syndrome, develops obesity and many clinical complications correlated with insulin resistance, such as type 2 diabetes, hypertension and dyslipidemia [3]. The target tissue activity of glucocorticoid is measured not only by considering its circulating status but also by the local glucocorticoid stimulation, which is controlled by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and 11β-HSD2. 11β-HSD1, which is widely expressed in the liver, adipose tissue, gonads, and brain, and potentiate the glucocorticoid activation (cortisol in human and corticosterone in rodents) from inoperative 11-keto steroids (cortisone in human and 11-dehydrocorticosterone in rodents). This process multiplies locally centralized glucocorticoid action, whereas 11β-HSD2 is widely expressed in aldosterone-sensitive target tissues such as kidney, colon, salivary glands and placenta and also catalyzes counter reactions [4]. High glucocorticoid levels in adipocytes reduce insulin-dependent glucose uptake, accelerates FFA secretion and alters adipokine profiles, thus develop in insulin resistance [5]. Therefore, 11β-HSD1 is expected to play a critical role in governing glucose and lipid metabolism in adipose tissue. Many preclinical studies have been reported to illustrate the role of 11β-HSD1 in acquiring insulin resistance and the development of obesity [6]. Mice studies have been reported where the

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RESEARCH ARTICLE

Evaluation of *In Vitro* Antiurolithiatic Activity of *Vigna radiata*

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ABSTRACT:
The present study was undertaken to evaluate the in vitro antiurolithiatic activity of the medicinal plantvigna radiata aqueous extract.It showed its maximum efficiency in the dissolution of calcium oxalate crystals.. Our result have clearly indicated that the Aqueousextract of seeds of*vignaradiata* were quite promising for further studies in this regard. In this study Neeri was used as standard drug.

KEYWORDS: In vitro antiurolithiatic activity, Aqueous extract, urolithiasis, *vigna radiata*, Neeri.

INTRODUCTION:

Plants provide food, raw materials for medicine and various other requirements for the very existence of life from the origin of human beings[1]. Urinary stone formation affects 10–12% of the population in industrialised countries. From epidemiological data, calcium oxalate (CaOx) is the most common component of the calculi[2]. The formation of such concretions involves several physicochemical events, e.g. nucleation, growth and aggregation, but the mechanism(s) of these processes remain incompletely understood[3]. Furthermore, although some drugs used to prevent the disease have some positive effects, they are not effective in all patients and often have adverse effects that compromise their use in long-term medical treatment.[4]

Kidney stone disease is a multi-factorial disorder resulting from the combined influence of epidemiological, biochemical and genetic risk factors[3]. Urolithiasis is considered as the third most common affliction of the urinary tract. It refers to the solid non-metallic minerals in the urinary tract.

It is a complex process that is a consequence of an imbalance between promoters and inhibitors in the kidney. The formation of kidney stones involves several phytochemical events beginning with crystal nucleation, aggregation and end with retention within the urinary tract. Among the several types of kidney stones, the most common are calcium oxalate stones representing up to 80% of the analyzed stones[4].

Calcium containing stones may be in the form of pure calcium oxalate(50%) or calcium phosphate(5%) and a mixture of both(45%) followed by magnesium phosphate (15-20%), uric 5 acid(10%) and cystine (1%)[5]. Many patients still undergo surgery to remove the stones; thus in Morocco, as in many countries, most patients (≈70%) use medicinal plants as an alternative therapy for many diseases, including lithiasis. The aerial parts of *Herniariahirsuta*, widely distributed in the Mediterranean area, is used in folk medicine as a diuretic and to treat kidney stones[6]Though technological advancements have made dramatic improvement in the removal of urinary stones still some of the drawbacks of these methods exists which includes their being too costly for a common man and recurrence of stone formation along with a number of other side effects.[7]

Management of stone disease depends on the size and location of the stones. Stones larger than 5 mm or stones that fail to pass through should be treated by some interventional procedures such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), or percutaneous nephrolithotomy (PNL)[8]

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Research Article

NEW STABILITY-INDICATING ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY METHOD DEVELOPMENT AND VALIDATION OF LENVATINIB MESYLATE IN BULK DRUG AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Objective: The objective of the present study was to develop and validate a new stability-indicating method for the quantification of lenvatinib mesylate in bulk drug and pharmaceutical dosage form using ultra performance liquid chromatography (UPLC).

Methods: The optimized chromatographic conditions for elution of drug included UPLC HSS C18 (100 mm × 2.1 mm, 1.8 m) column, mixture of 0.1% orthophosphoric acid and acetonitrile (50:50 v/v%) mobile phase run on an isocratic mode at a flow rate of 0.3 mL/min, 240 nm detection wavelength, and column oven temperature maintained at 30°C.

Results: The retention time for lenvatinib was found to be 1.24 min. The developed method was validated for various validation parameters in accordance with the International Conference on Harmonization guidelines. The method obeyed Beer's law in the concentration range of 2.5–15 µg/mL with a correlation coefficient of 0.9996. The percentage relative standard deviation and percentage recovery were determined to be 0.4 and 99.66–100.30%, respectively. The developed method was found to be accurate, precise, specific, linear, rugged, and robust. Forced degradation studies were conducted by exposing the drug to diverse stress conditions such as acidic, basic, peroxide, neutral, photolytic, and thermal conditions. The net degradation was obtained within the limits.

Conclusion: The developed method for the estimation of lenvatinib can be employed to routine analysis of pharmaceutical dosage form.

Keywords: Lenvatinib mesylate, Ultra performance liquid chromatography, Stability indicating, Method development, Validation.

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INTRODUCTION

Lenvatinib mesylate (Fig. 1) [1,2] chemically known as 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. It is a white to pale reddish-yellow powder, slightly soluble in water and practically insoluble in ethanol. It is a pKa value of 5.05. It belongs to anticancer category and utilized for the treatment of various kinds of thyroid cancer [3,4]. It acts as receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor receptors [5]. It also inhibits other RKTs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor receptors.

Ultra performance liquid chromatography (UPLC) [6-8] is a relatively new technique giving new possibilities in liquid chromatography, especially concerning the decrease of time and solvent consumption. UPLC chromatographic system is designed in a special way to withstand extreme system back pressures.

In accordance to literature review, it was known that there were only few methods such as reverse-phase high-performance liquid chromatography (RP-HPLC) [9-11], ultraviolet (UV) spectroscopy [11], and liquid chromatography coupled with tandem mass spectrometry method [12-14] developed for the estimation of lenvatinib.

As there was no UPLC method developed for the estimation of lenvatinib, the present study was intended to develop and validate a stability-indicating UPLC method for the quantitative determination of lenvatinib in bulk drug and pharmaceutical dosage form.

METHODS

Chemicals and reagents

Lenvatinib mesylate working standard was supplied as a gift sample from Spectrum Labs, Hyderabad. Lenvima capsules were purchased from a local pharmacy. All the chemicals used for the development of the method were of AR grade purchased from Merck, Mumbai. All the solvents used were of HPLC grade purchased from Sigma-Aldrich, Mumbai.

Analytical conditions and instruments

The ACQUITY UPLC system equipped with binary solvent manager, sample manager, UV detector, and UPLC HSS C18 (100 mm × 2.1 mm, 1.8 µ) column was used for the determination of lenvatinib. The analytical conditions included 0.1% orthophosphoric acid and acetonitrile (50:50 v/v%) as mobile phase run on an isocratic mode at a flow rate of 0.3 mL/min. The column was kept at 30°C and detection was done at 240 nm wavelength. Additional equipment included pH meter, ultrasonic bath sonicator, and weighing balance.

Preparation of mobile phase

Mixture of 0.1% aqueous orthophosphoric acid buffer and acetonitrile in the ratio of 50:50 v/v% was used as mobile phase.

Preparation of standard and sample solution

10 mg of lenvatinib working standard was dissolved in 100 ml of diluent. 1 mL of the above standard stock solution was diluted to 10 mL diluent.

Average weight of 20 lenvima capsules was calculated and an amount equivalent to 10 mg of lenvatinib was dissolved in 100 mL of diluent.

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RESEARCH ARTICLE

Evaluation of *In Vitro* Anthelmintic Activity of Spirulina Powder

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ABSTRACT:

The aim of the present study was to evaluate the In-vitro antihelmenthic activity of Spirulina Powder. Currently, our understanding on the underlying mechanisms for Spirulina's activities, especially the antihelmenthic, is limited. The Spirulina Powder was taken for anthelmintic activity against Indian earthworm Pheretimaposthuma. The results were expressed in terms of time required for paralysis and death of Pheretimaposthuma. Albendazole was used as a standard control group. Spirulina Powder shows the significant activity at 150 mg/ml concentration.

KEYWORDS: Spirulina, Pheretimaposthuma, anthelmintic, *In-vitro*, Albendazole.

INTRODUCTION:

Helminthic infections are very common in man. Helminthic infections are large threat to human beings health in developing countries. It contributes malnutrition, anemia and pneumonia. Majority of the infections are due to worms are generally limited to topical regions. The World Health Organization reveals that over two billion people are suffering from parasitic worm infections[1]. It is estimated that by the year 2025, about 57% of the population in developing countries will be influenced[2]. The prevalence of parasitic helminths typically displays a negative binomial distribution within an infected population such that relatively few persons carry heavy parasite burdens. Without treatment, those individuals are most likely to become ill and to perpetuate infection within their community[3]. Helminthes infections are now being recognized as cause of many acute as well as chronic ill health among the various human beings as well as cattle's. More than half of the population of the world suffers from infection of one or the other and majority of cattle's suffers from worm infections[4].

In most developing and less developed countries, helminth infections are a major health concern because they predispose humans to other infections such as fungal and bacterial infections[5]. Intestinal infections with worms can more easily treated than those the infections that occur in other locations in the body, because the worms need to be killed by the drug and the drug need not be absorbed when given by oral route[6].

Anthelmintics are drugs that may act locally to expel worms from the GIT or systemically to eradicate adult helminths or development forms that invade organs and tissues[7]. Most of the existing anthelmintics produce side effects such as abdominal pain, loss of appetite, nausea, Vomiting, headache and diarrhoea[8]. Anthelmintics from the natural sources may play a key role in the treatment of these parasite infections[9]. Because of the increasing anthelmintic resistance and the impact of conventional anthelmintics on the environment, it is important to look for alternative strategies against parasitic worms. Earthworms have been used widely for the initial evaluation of anthelmintic compound in vitro[10-13].

Spirulina is free-floating filamentous microalgae growing in alkaline water bodies. With its high nutritional value, Spirulina has been consumed as food for centuries in Central Africa. It is now widely used as nutraceutical food supplement worldwide. Recently,

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STABILITY INDICATING UPLC METHOD DEVELOPMENT AND VALIDATION FOR THE DETERMINATION OF CRIZOTINIB IN PHARMACEUTICAL DOSAGE FORMS

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Keywords:
Crizotinib, UPLC, Stability indicating method, Method development, Validation

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ABSTRACT: A stability indicating method was developed for the estimation of Crizotinib in pharmaceutical dosage form by using Ultra Performance Liquid Chromatography (UPLC). The separation was done on isocratic mode with Hibra C18 (100 mm × 2.1 mm, 2 µ) column and 0.1% Ortho-phosphoric acid and acetonitrile (45:55% v/v) as mobile phase at a flow rate of 0.3 mL/min and at room temperature. The detection was done at a wavelength of 327 nm. A good linearity was observed in the concentration range of 37.5 µg/mL - 225 µg/mL, with a correlation coefficient of 0.999. The method was validated according to the ICH guidelines. The developed method was found to be accurate and precise, with % recovery 99.9% - 100.18% and % relative standard deviation 1.1. The drug was found to be stable at forced degradation conditions and the net degradation was found to be within the limits. The developed method can be used for the quality control of Crizotinib in pharmaceutical dosage form.

INTRODUCTION: Crizotinib **Fig. 1**, chemically designated as 3- [(1*R*)- 1- (2, 6-dichloro-3-fluoro-phenyl) ethoxy]- 5- (1- piperidin- 4- ylpyrazol-4-yl) pyridin-2-amine, is a white to pale yellow powder, slightly soluble in methanol, ethanol and water and has a pKa of 5.6 and 9.4. It is used in the treatment of lung cancer by acting as an oral receptor tyrosine kinase inhibitor [1]. According to the literature survey, very few methods HPLC methods [2, 3], LC-MS/MS method [4], Spectrofluorimetry [5], UPLC-MS/MS method [6] and LC-ESI–MS/MS method [7] were developed.

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The proposed method aimed to develop and validate a stability indicating method for the estimation of Crizotinib in pharmaceutical dosage form by UPLC.

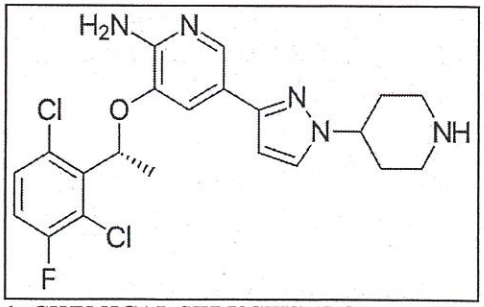

FIG. 1: CHEMICAL STRUCTURE OF CRIZOTINIB

MATERIAL AND METHODS:

Reagents and Chemicals: Crizotinib standard drug was supplied as gift sample by spectrum labs, Hyderabad (India).

Research Article

STABILITY INDICATING UPLC METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF DASATINIB IN PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

The present work describes the stability indicating method development and validation for the determination of Dasatinib in pharmaceutical dosage form using Ultra Performance Liquid Chromatography with UV detection. The optimized chromatographic conditions used were Acquity UPLC HSS C18 (100mm × 2.1mm, 1.8µ) column, 0.1% Orthophosphoric acid and acetonitrile in the ratio (50:50%v/v) as mobile phase run on an isocratic mode at a flow rate of 0.2ml/min. The column oven temperature was maintained at room temperature. The detection wavelength was found to be 321nm.The developed method was validatedas per ICH guidelines and found to be specific, rugged and robust. A linear response was found in the concentration range of 12.5µg/ml to 75µg/ml with correlation coefficient of 0.999, indicating that the method obeys Beer's law. The % recovery for Dasatinib was found to be 99.80% to 100.19% indicating the method was accurate. The % relative standard deviation was found to be 0.7 indicating the method was precise. The drug was found to be stable at stressed conditions and the net degradation was found to be within the limits. The developed method can be used for the quality control of Dasatinib in pharmaceutical dosage form.

Keywords: Dasatinib, Stability Indicating, Method development, Validation, UPLC.

INTRODUCTION

Dasatinib (Figure 1) is chemically designated as *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide monohydrate. It is a white to off – white solid which is slightly soluble in methanol, ethanol and water and has pKa values of 3.1 and 6.8 (two basic pKas) and 10.8 (acidic pKa). It is an anticancer drug used to treat chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) [1,2]. The literature survey reveals that there are few methods for the estimation of Dasatinib such as colorimetric method [3], UV-Visible spectrophotometric method [4], RP-HPLC methods [5-10] and UPLC method [11]. The objective of the present study is to develop a stability indicating method for the determination of Dasatinib in pharmaceutical dosage form by UPLC and validate it.

Material and methods

Chemicals and Reagents

The Dasatinib standard drug was procured from Spectrum Labs, Hyderabad, Telangana, India as a gift sample. The Dasatinib tablets (Dasanat) were purchased from local pharmacy. All the chemicals used were of AR grade and purchased from sigma Aldrich. All the solvents used were of HPLC grade and purchased from Merck, Mumbai, India.

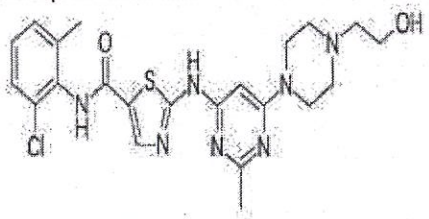

Figure 1: Chemical structure of Dasatinib

Apparatus and Chromatographic conditions:

Waters UPLC ACQUITY instrument core system includes ACQUITY UPLC binary solvent manager, ACQUITY UPLC sample manager andACQUITY UPLC single column manager with Acquity UPLC HSS C18 (100mm x 2.1 mm, 1.8µ) column maintained at room temperature, Waters Empower 2 PC workstation, a solvents tray and UV detector was used for the determination of Dasatinib in tablet dosage form. All the parameters of UPLC were run on Empower software. Other instruments used were electronic balance, digital pH meter and Ultrasonic

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Evaluation of *in vitro* Antiurolithiatic Activity of *Gossypium Herbaceum*

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Abstract:
The present study was undertaken to evaluate the in vitro antiurolithiatic activity of the medicinal plant Gossypium herbaceum. Both Ethanolic and Aqueous extracts showed their maximum efficiencies in the dissolution of calcium oxalate crystals Ethanolic extract was even more efficient than Aqueous extract in dissolution of calcium oxalate crystals. Our results have clearly indicated that the aqueous and ethanolic extracts of Gossypium herbaceum were quite promising for further studies in this regard. In this study Neeri was used as standard drug.
Keywords: In vitro antiurolithiatic activity, aqueous extracts, urolithiasis, Gossypium herbaceum

INTRODUCTION:

Urolithiasis is derived from the greek words ouron means urine and lithos means stone. Urolithiasis is characterized by the formation of the stone in the kidneys or urinary tract in a large number of people. Nearly 10-15% of the population is currently suffering from kidney stones.

Urinary tract stones (kidney stones) composed of calcium oxalate, either alone or mixed with calcium phosphate. World Health Organization(WHO) estimated that about 12% of men and 55% of women have at least one episode of kidney stone during their life time.[1] The cause of urolithiasis is still unknown but probably positive family history, overweight, obesity or increased body mass index (BMI).[2] Epidemiological studies revealed that urolithiasis is more common in men than in women and is more prevalent between the ages of 20-40 in both sexes. [3] Ammonium urate, mono sodium urate monohydrate, uric acid anhydrous, uric acid mono and di hydrate are commonly existing urate stones. [4,5] Drugs with multiple mechanisms of protective action provide minimizing the diseases.

Plants provide food, raw materials for medicine and various other requirements for the very existence of life from the origin of human beings[6]. The majority of the global population utilizes medicinal plants for their health care. Even the current conventional medicine is using a lot of plant derived chemicals as therapeutic agents. The overuse of synthetic drugs results in higher incidence of adverse drug reactions has motivated humans to return to nature for safe remedies. Herbs and herbal drugs have created interest among the people by its clinicallyproven effects[7].

*Gossypium Herbaceum*L. belongs to Malveceae and commonly called as cotton plant [8, 9]. It is oldest Indian herbal drug, which is included in our present study is widely used by tribal people. Ayurvedic system has already noticed the importance of this plant. It has several experimentally proven pharmacological activities, which includes Antitumor [10], Antimutagenic [11], Anticonvulsant [12] antibacterial, antihelmenthic [13] and antifungal activities [14]. The cotton seed has already proved antiUrolithiatic so based on the literature review the present study was carried out antiurolithiatic activity of leaves of Gossypium Herbaceum.

MATERIALS AND METHODS:

PLANT MATERIALS

The leaves of Gossypium herbaceum was collected in the month of august 2017 from Maddur village, Medak dist. of Telangana, India. The plant was authenticated by D. Venkateshwara Rao, DeputyDirector, Telangana. Forest Academy, Dullapally, Hyderabad, Rangareddy District. The leaves were washed with tap water and dried under shade.

PREPARATION OF PLANT EXTRACT

The leaves were shade dried and powdered. The crude plant extract was prepared by Soxhlet extraction method. 50g of powdered plant material was extracted with 500ml of ethanol and water individually. The process of extraction was carried out up to 6 cycles, till the solvent in siphon tube of an extractor became colorless. The two extracts were filtered separately, and evaporated to dryness using rotary evaporator. Further the dried extracts were maintained in a refrigerator at 4°C for further antiurolithiatic activity.

CHEMICALS USED

Neeri, Sodium oxalate, Tris buffer, calcium chloride, Potassium permanganate(KMnO4), Sulphuric acid(H2SO4).

INVESTIGATION OF IN VITRO ANTIUROLITHIATIC ACTIVITY TEST BY TITRIMETRY

The experimental kidney stones of calcium oxalate (CaOx) were prepared in the laboratory by taking equimolar solution of calcium chloride dehydrate in distilled water and sodium oxalate in 10 ml of 2N H2SO4. Both were allowed to react in sufficient quantity of distilled water in a beaker, the resulting precipitate was calcium oxalate. The precipitate was freed from traces of sulphuric acid by ammonia solution, washed with distilled water and dried at 60oC. The dissolution percentage of calcium oxalate was evaluated by taking exactly 1 mg of calcium oxalate and 10 mg of the extract, packed it together in semi permeable membrane of egg as shown in the model designed given below .This was allowed to suspend in a conical flask containing 100 ml of 0.1M Tris buffer. First group served as blank containing only1 mg of calcium oxalate. The second group served as positive control containing 1 mg of calcium oxalate and along with the 10mg standard drugs, i.e. Neeri. The 3rd, 4th groups along with 1 mg of calcium oxalate contain methanolic and aqueous, extracts. The conical flasks of all groups were kept in an incubator preheated to37oC for 2 h. Remove the contents of semi permeable membranes from each group into separate test tubes, add 2 ml of 1Nsulphuricacid to each test tube and titrated with 0.9494 N KMnO4 till a light pink colour end point obtained. The amount of remaining undissolved calcium oxalate is substracted from the total quantity used in the experiment in the beginning to know the total quantity of dissolved calcium oxalate by various solvent extracts.[15]

RESULTS AND DISCUSSION:

Drug therapy has developed in response to population health care needs. There are many crucial areas in medicine such as liver diseases, arthritis, old age related problems, certain viral infections and cancer where the conventional medicine is devoid of satisfactory treatment. These are among the promising areas of research and development of medicines from the vast highly potential plant resources. Plants are also attractive sources for the development of novel and very effective and safe therapeutic agents against kidney procumbens. Herbal medicines are also in great demand in the developed world for primary health care because of their efficacy, safety and lesser side effects. Unlike allopathic medicines which target is only one aspect of urolithiatic pathophysiology, most of plant based therapy have been shown to be effective at different stages of stone pathophysiology. About

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Elucidation of chemosensitization effect of acridones in cancer cell lines: Combined pharmacophore modeling, 3D QSAR, and molecular dynamics studies

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ABSTRACT

Overexpression of P-glycoprotein (P-gp) leads to the emergence of multidrug resistance (MDR) in cancer treatment. Acridones have the potential to reverse MDR and sensitize cells. In the present study, we aimed to elucidate the chemosensitization potential of acridones by employing various molecular modelling techniques. Pharmacophore modeling was performed for the dataset of chemosensitizing acridones earlier proved for cytotoxic activity against MCF7 breast cancer cell line. Gaussian-based QSAR studies also performed to predict the favored and disfavored region of the acridone molecules. Molecular dynamics simulations were performed for compound 10 and human P-glycoprotein (obtained from Homology modeling). An efficient pharmacophore containing 2 hydrogen bond acceptors and 3 aromatic rings (AARRR.14) was identified. NCI 2012 chemical database was screened against AARRR.14 CPH and identified 25 best-fit molecules. Potential regions of the compound were identified through Field (Gaussian) based QSAR. Regression analysis of atom-based QSAR resulted in r^2 of 0.95 and q^2 of 0.72, whereas, regression analysis of field-based QSAR resulted in r^2 of 0.92 and q^2 of 0.87 along with r^2_{cv} as 0.71. The fate of the acridone molecule (compound 10) in the P-glycoprotein environment is analyzed through analyzing the conformational changes occurring during the molecular dynamics simulations. Combined data of different in silico techniques provided basis for deeper understanding of structural and mechanistic insights of interaction phenomenon of acridones with P-glycoprotein and also as strategic basis for designing more potent molecules for anti-cancer and multidrug resistance reversal activities.

1. Introduction

The success of cancer chemotherapy is limited by the development of drug resistance (Baumert and Hilgeroth, 2009). Multidrug resistance (MDR) is defined as resistance to several unrelated drug classes, such as anthracyclines, Vinca alkaloids or topoisomerase inhibitors, and novel cytostatic agents, including tyrosine receptor kinase inhibitors or protease inhibitors (Borst et al., 2000; Kruh and Belinsky, 2003).

Multidrug resistance occurs by overexpression of ATP-binding cassette (ABC) family protein family members, in which P-glycoprotein (P-gp), an *mdr1* gene product, is one of the barriers to chemotherapeutic treatment of cancer. P-gp is polyspecific, transporting a wide range of structurally diverse compounds out of the cell (Becker et al., 2009). P-gp has been shown to bind ATP and drug analogues (Ambudkar et al., 1999) have ATPase activity, and catalyze ATP dependent drug efflux to effectively reduce intracellular accumulation in resistant cells. This efflux mechanism of P-gp could also be referred to as "flippase" activity of the transporter (Sharom, 2011). This association of *mdr1* P-glycoprotein expression in tumor has become an important target for the reversal of MDR or for blocking the transport activity of P-gp (Lehne, 2000). Despite large number of studies conducted to elucidate the P-gp efflux mechanism, these remain controversial. However, it is believed

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1476-9271/

Original Article

Protective Effect of A_{2B} Receptor Antagonist (TRP 1) on Acetic Acid Induced Ulcerative Colitis in Rats: *in vitro, in vivo* and *in silico* Methods

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ABSTRACT

Aim: Present study was elucidate the protective effect of pyridinone derivatives such as 7-amino-5-oxo-2- Phenyl-5H, 8H-dihydro-[1, 2, 4] triazolo [1, 5-α] pyridine - 6-carbonitril (TRP 1) by *in vitro, in vivo and in silico.* **Methods:** Radioligand binding assay was performed on human adenosine receptors (A_{2B}) and assess A_{2B} antagonist effect by adenylyl cyclase activity. *In vitro* study was carried out to determine the neutralize capacity against DPPH*, NO*, SO*, LPO* free radicals. TRP 1 at the doses 1 mg/kg bd.wt. and 10 mg/kg bd.wt p.o, was administered consecutively for 14 days in albino rats. Ulcerative colitis was induced with single dose of 2 ml of 3% acetic acid intrarectal on 14th day in treated rats. At the end of treatment, colonic tissue was collected and subjected for estimation of macroscopic score, glutathione, catalase, MPO and inflammatory parameters such as IL 1β, TNF α and IL 6. *In silico* study was carried out to evaluate the binding energy and IC_{50} toward IL 1β, TNF α and IL 6. **Results:** TRP 1 was antagonized the A_{2B} receptors at the concentration of 30000 nM. *In vitro* study was revealed that TRP1 (1 mg/ml) was significantly neutralizes the free radicals of DPPH*, SO*, NO*and LPO*. In *in vivo* studies, intrarectal administration of acetic acid caused significantly (***P<0.001) increased macroscopic score, colon weight, colonic MPO, IL 6, IL 1β and TNF-α (*P<0.05), while TRP 1 treated colitis rats antioxidants system such as GSH (**P<0.01), catalase (*P<0.05) activity was significantly improved, decreases inflammatory mediators such TNF α (*P<0.05), IL 1β (**P<0.01) , IL 6 (**P< 0.01) and also suppresses the MPO activity (*P<0.05). *In silico* study was reported that the IC_{50} of TPR 1 against IL 1β, IL 6 and TNF-α was 7.5 mM, 28.65 mM and 45.87 mM respectively. **Conclusion:** Our data demonstrated that the TRP 1 treatment improved clinical score in acetic acid induced colitis in rats. It also inhibited the proinflammatory cytokine IL-6, IL 1β and TNF α and improvements of antioxidant in colitis rats through A_{2B} receptor antagonist property.

Key words: 7-amino-5-oxo-2- phenyl)-5H, 8H-dihydro-[1,2,4] triazolo [1,5-α] pyridine - 6-carbonitril (TRP 1), Ulcerative colitis, Acetic acid, Myeloperoxydase (MPO), Glutathione (GSH), Catalase, TNF α, IL 1β and IL 6.

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INTRODUCTION

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is a lifelong disabling gastrointestinal disease.[1,2,3] Although etiology of inflammatory bowel disease (IBD) is unknown it appears that an abnormal response of the mucosal innate immune system to luminal bacteria may trigger inflammation which is perpetual by disregulation of cellular immunity[4,5,6] and imbalances between proinflammatory cytokines, such as

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RESEARCH ARTICLE

Comparative In vitro antidiabetic and antioxidant activity of *Pulicaria wightinia, Curcuma inodora ,Derris scandens* leaf extracts

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ABSTRACT:
In preventing the progression of various metabolic diseases, medicinal plants play very important role. The present study was focused on three different medicinal plants, *Pulicaria wightiania, Derris scandens and Curcuma inodora* commonly found in Narsapur forest of Medak district Telangana, (India), were screened for the potency of antioxidant and antidiabetic activity by various *In-vitro* methods. Three plants leaves were extracted using methanol and ethanol as solvents based on their solubility. Methanol extracts of *Pulicaria wightiania, Derris scandens* and ethanolic extract of *Curcuma inodora* plants leaves were examined. Antioxidant activities of three different extracts were evaluated by DPPH scavenging assay and putative antidiabetic activity was determined by *in-vitro* methods such as Glucose uptake by Yeast cells method, α-glucosidase inhibition activity assays. A dose dependent significant DPPH scavenging activity was found with three different plants when compared with standard drug ascorbic acid. The three plants leaf extracts exhibited a significant inhibitory action on α-glucosidase enzyme. The data obtained clearly suggests that the plant extract is capable of effectively enhancing glucose uptake which in turn suggests that it is capable of enhancing effective glucose utilization thereby controlling blood glucose level. The results suggest that these plants possess potential antioxidant and antidiabetic components.

KEYWORDS: Antidiabetic activity, *Pulicaria wightiania*, *Derris scandens* and *Curcuma inodora* Alpha - glucosidase enzyme, Glucose uptake, Yeast cells.

INTRODUCTION:
The world 'Diabetic Capital 'is India with 50.8 million diabetics[1] Preventing the absorption of carbohydrates after food intake is one of the therapeutic approaches for reducing postprandial hyperglycemias in patients with diabetes mellitus. Alpha glucosidase is the enzyme that catalyzes the cleavage of glycoside bonds in oligosaccharides and thus compounds inhibiting this enzyme could help prevent postprandial hyperglycemias by decreasing the rate of carbohydrate degradation to glucose[2].

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The plant extracts have long been used for the ethno-medical treatment of diabetes in various systems of medicine and are currently accepted as an alternative for diabetic therapy. However, for many plant extracts, there is no clear understanding of the mechanism of action. Therefore, natural α-glucosidase inhibitors from plant sources offer an attractive strategy for the control of postprandial hyperglycemias. The mechanism of glucose transport across the yeast cell membrane has been gaining significant importance as An in- vitro screening method for evaluating the hypoglycemic effects of various medicinal plants[3]. As there are disturbances in antioxidant defence systems in diabetes mellitus[4] ,treatment with antioxidant may contribute to the prevention and delaying of diabetic complications[5] This is currently the basis of the "unifying hypothesis" that

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ANTIPROLIFERATIVE ACTIVITY OF RUTIN ON HELA CELL LINE INDUCED CERVICAL CANCER IN RATS

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Keywords:

Rutin, HeLa cell line, Antiproliferative effect, Antioxidant activity

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ABSTRACT: In present study antiproliferative activity of Rutin was evaluated on HeLa cell line induced cervical cancer in rats. For this study, 30 rats were divided into 5 groups and each group containing 6 rats each. Group I- normal saline treatment for 45 days, Group II- cancer cells (1×10^6 cells in 0.1ml/rat), Group III– 5-Fluorouracil (20mg/kg + 1×10^6 cells in 0.1ml/rat), Group IV- Rutin (50mg/kg + 1×10^6 cells in 0.1ml/rat), Group V- Rutin (70mg/kg + 1×10^6 cells in 0.1ml/rat). After 24 h of tumour inoculation intraperitoneally, Rutin was administered daily for 45 days. After administration of last dose followed by 18 hrs fasting, rats were sacrificed for observation of antiproliferative activity. The change in body weight, body circumference of tumour bearing hosts and simultaneous alterations in haematological profile, serum (Triglycerides, Total protein, Total cholesterol, GGT, ALP and glucose) and liver biochemical parameters (lipid peroxidation, GSH and antioxidant enzymes-CAT, GPx) were estimated. The changes in tissue enzymes-Glucose-6 phosphate dehydrogenase, Hexokinase, Succinate dehydrogenase and CytochromeP450 levels were also estimated. Rutin maintained the body circumference and body weight of proliferation bearing rat. Haematological profile reverted towards normal levels in Rutin treated rat. Treatment with Rutin restored serum biochemical parameters towards normal levels and decreased levels of lipid peroxidation and increased levels of reduced glutathione and other antioxidant enzymes. The Rutin treatment restored Glucose-6 phosphate dehydrogenase, Hexokinase, Succinate dehydrogenase and CytochromeP450 levels in proliferation induced rat. Rutin exhibited antiproliferative effect by modulating haematological parameters, lipid peroxidation and augmenting antioxidant defense system in proliferation bearing rat.

INTRODUCTION: Cervical cancer is the third most common type of cancer in women worldwide[1]. This cancer develops slowly; starting from a precancerous dysplasia designated cervical intraepithelial neoplasia that may further develop to invasive cervical carcinoma.

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Several molecules present in the diet, including flavonoids, can inhibit the growth of cancer cells with an ability to act as "chemopreventers" [2]. Their cancer-preventive effects have been attributed to various mechanisms, including the induction of cell-cycle arrest and/or apoptosis as well as the antioxidant functions. The antioxidant activity of chemo preventers has recently received a great interest, essentially because oxidative stress participates in the initiation and progression of different pathological conditions, including cancer. Since antioxidants are capable of preventing oxidative damage, the wide use of natural food-

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Research Article

FORMULATION OF FLUCONAZOLE AS TOPICAL ANTIFUNGAL GELS BY MICROSPONGE BASED DELIVERY SYSTEMS

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ABSTRACT

The purpose of present work was to formulate fluconazole loaded microsponge-based topical delivery system for modified release. Microsponges with varied drug–polymer ratios were prepared by emulsion solvent diffusion technique using ethyl cellulose as release retard material. Prepared microsponges were studied for particle size and physical characterization. Scanning Electron Microscopy (SEM) images showed the microsponges porous and spherical in shape. The microsponges were then incorporated in carbopol gel and evaluated for pH, viscosity, spreadability, drug content, *in vitro* release. The *In vitro* drug release showed that microsponges with 1:1.5 drug–polymer ratios (F3) were more efficient to give sustained release of 74.2% at the end of 8h. All the microsponge gel formulations (i.e.F1-F10) showed better results like pH between 6.5-7.0, viscosity between 25,030-47,390 cps, spreadability 2-4cm/s and drug content of 76.20±0.02% to 96.41±0.01%. Hence, the fabricated microsponge based formulation of fluconazole would be anticipation and promising substitute to conventional therapy of skin infections.

Keywords: Fluconazole, microsponge, ethyl cellulose, SEM

INTRODUCTION

Fluconazole is a synthetic antifungal agent belonging to the group of triazole. It is one of the commonly used antifungal agents for most kinds of fungal infections including superficial and invasive fungal infections (Vinod *et al.*, 2012). Regrettably fluconazole oral administration has limitations such as nausea, vomiting, bloating and abdominal discomfort. Alongside most of the time the parenteral administration of fluconazole led to skin rashes and itching (Doaa *et al.*, 2012). For these reasons, now a day's advance localized and transdermal delivery has gained a lot of importance (Niethard *et al.*, 2005; Kulkarni *et al.*, 2011). The conventional gel formulation of fluconazole causes cutaneous irritation and prolonged use led to dermal hypersensitivity. So, a novel system necessitates which will increase the presence of active agents either on skin surface or within epidermis, concurrently reducing hasty transdermal penetration. Many researchers have attempted to develop novel transdermal formulations of fluconazole. Accordingly, the goal of our research is to formulate and evaluate fluconazole microsponge loaded carbopol gel for safe, effective and stable gel and evaluate the in-vitro sustained release performance. Microsponge-based delivery systems (MDS) give assurance of drug localization on skin surface and within epidermis without entering in systemic circulation in greater extent; thereby reducing systemic and local cutaneous adversities. They also offer an advantage of programmable release and are biologically safe. Additionally, this technology presents quite a lot of benefits via drug entrapment by means of better formulation flexibility, abridged side effects, improved elegance and superior stability (D'souza and More, 2008; Vyas *et al.*, 2010; Vyas and Khar, 2002; Won, 1987).

MATERIALS AND METHODS

Fluconazole was obtained as a gift sample from RMS Research labs Pvt Ltd Hyderabad, India. Ethyl cellulose was gifted by Yeluri formulations, Hyderabad, India. Polyvinyl alcohol, triethyl citrate and ethyl acetate were purchased from Emerck (India) Ltd., Mumbai. All other chemicals and solvents used are of analytical grade.

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Anticataract potential of *Boerhavia diffusa* roots on galactose induced cataractogenesis

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Cataract has been a major cause of bilateral blindness worldwide, and it is responsible for 50-80% of the bilaterally blindness in India. Oxidative stress is the major risk factor causing cataract. *Boerhavia diffusa*, commonly known as spreading hogweed or tarvine and locally, punarnava, is known for its antioxidant potential. Here, we evaluated anticataract potential of alcoholic extract of *B. diffusa* roots using galactose induced cataract model on Wistar albino rats. The rats were divided into five groups. The first group was taken as control, the second as disease control group and all other three groups test groups, given three doses of plant extracts i.e. 100, 200 and 400 mg/kg body wt., respectively for 28 days. Periodically slit lamp photographs were taken to know the percentage incidence and progression of cataract. The plant extract significantly delayed the onset and maturation of galactose induced cataract. Biochemical analyses were performed at the end of the study. The analyses revealed the plant extract at highest dose exhibited an efficient antioxidant effect. It has shown 69% inhibition on galactitol accumulation. Aldose reductase (AR) inhibitory activity was also performed on isolated rat lenses. The significant percentage inhibition of AR was shown at a dose of 70 µg/mL. In conclusion, our results demonstrated that the alcoholic extract of *Boerhavia diffusa* roots delay the process of cataractogenesis in galactose induced cataract.

Keywords: Aldose reductase, Antioxidant potential, Cataract, Galactitol, Punarnava, Oxidative stress, Spreading hogweed, Tarvine

Cataract, a visual impairment causing disturbance in lens transparency occurs mainly due to opacification or optical dysfunction of the crystalline lens. It reduces the amount of incoming light and results in deterioration of the vision[1]. Apart from senile cataract, various other factors, such as oxidative stress, diabetes, excessive exposure to ionising radiation, inflammatory diseases of the eye increase the risk of cataract. In all these factors, oxidative damage plays a most important role in causing cataract[2]. Surgically, cataractous lens can be replaced with artificial lens; however, epidemiologically the problem persist owing to the cost and post operational complications of surgery[3]. There are no plants which are proven clinically but more work is now going on curcumin, though at pre-clinical stage only[4,5]. Surgery is the alternative for treating cataract.

Aldose reductase (AR), also known as aldehyde reductase, is NADPH dependant oxidoreductase which catalyses the reduction of galactose into galactitol. Galactitol can't be further metabolised. When the concentration of galactitol increases it causes pronounced increase in lens hydration. It leads to osmotic imbalance and formation of vacuoles in the eye[6].

Few plants have been reported in the ancient literature for ophthalmic use, but most of them have no scientific data. *Boerhavia diffusa* (Fam.: Nyctaginaceae), commonly called Tarvine or Spreading hogweed, locally known as 'punarnava', is a herbaceous perennial plant well distributed all over India and has been shown to have a wide range of biological activities such as anthelmintic[7], anticancer[8], antidiabetic[9], antidepressant[10,11], antihaemolytic[12], antifungal[13], antileishmanial[14], antimetastatic[15], antimicrobial[16], antioxidant[17], free radical scavenger[18], hepatoprotective[19], immunomodulatory[20] and neuroprotective[21] activities. It is also having many folklore uses, including eye problems[22-24]. However, scientific information on the use of this plant in treating eye diseases is not available yet. Hence, we

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Research Paper

Formulation and *In vitro* Evaluation of Floating Microspheres of Misoprostol

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ABSTRACT

Misoprostol is a synthetic prostaglandin PGE1 analogue, which has proved to be an effective anti-secretory agent for oral use. The major indications of Misoprostol are in the prevention and treatment of NSAID-induced gastric and duodenal ulcers. Its half-life is 20-40 minutes. More than one third of patients with ulcers are resistant to H_2 antagonists. So, these patients can be healed on Misoprostol. The objective of the present study was to formulate gastroretentive floating drug delivery system of an antiulcer drug Misoprostol. Floating microspheres of Misoprostol were prepared by an emulsification solvent evaporation technique using hydroxy propyl methyl-cellulose (HPMC K 100M) and ethyl cellulose. The percentage yield and drug entrapment efficiencies of these floating microspheres were within the range between: 70 ± 2.8 to 98 ± 2.9 % and 39.27 to 82.39 %, respectively. The determined mean particle size for all the microspheres were 250 ± 7.28 to 400 ± 2.32 µm. The flowability of these microspheres was found good. A high performance liquid chromatography (HPLC) method with ultra-violet (UV) detection was selected for the method of analysis. The drug release was found to delay for 12 hours with the increasing drug to polymer ratio. The drug release kinetics followed Korsemeyer-Peppas and Higuchi model with anomalous (non-Fickian) diffusion mechanism for the drug release. The FTIR and DSC studies showed that there was an absence of chemical interaction between the drug and the excipients. The *in vitro* drug release from Misoprostol floating microspheres showed the drug release was dependent on the drug to polymer ratio. The drug release was found delayed with the increasing drug to polymer ratio.

KEYWORDS: Floating microspheres; emulsion solvent evaporation method; Misoprostol.

Introduction

Oral route is always the most popular and preferred route for drug delivery to the systemic circulation due to its low cost of therapy, ease of administration, patient compliance, etc. During the past few decades, considerable effort has been directed towards the development of numerous oral drug delivery systems from which the incorporated drugs are released over a defined period at a predetermined and controlled rate. Nevertheless, conventional oral dosage forms provide no control over drug delivery, contributing to fluctuations in plasma drug level (Shargel and Andrew, 1999). The oral controlled release drug delivery has recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages such as ease of doing administration, patient compliance and flexibility in formulation (Nayak and Malakar, 2010). From the pharmacokinetic point of view, an ideal sustained and controlled release dosage form should attain the desired therapeutic concentration of drug in plasma and maintains constant for the entire duration of treatment, which is possible through administration of conventional dosage form in a particular dose and at particular frequencies. In addition, this should be compared with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels, once the steady state is reached (Hwang et al., 1998). Despite excellent *in vitro* release patterns, the drug absorption through oral delivery is unsatisfactory and highly variable among individuals. The reasons for this are essentially physiological and usually affected by the gastrointestinal transit of the dosage form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability (Hwang et al., 1998).

Variable and short gastric retention of a dosage form can result is an incomplete drug release. Again, some drugs are absorbed in the particular segment of the gastrointestinal tract (GIT) only are absorbed to a different extent in various segments of GIT. Such and drug candidates are said to have an 'absorption window'. However, in case of 'narrow absorption window' drugs, only the drug released in the region foregoing and in close vicinity of the absorption window is available for absorption. To overcome these restrictions, various gastroretentive systems have been designed to retain in

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Synthesis, Antioxidant, Antibacterial and Cytotoxic Activity of Novel Chromone Derivatives

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ABSTRACT

The present work was aimed to synthesize novel chromone derivatives to target estrogen receptor positive breast cancer. About 80% of all breast cancers are "ER-positive. The chromone scaffold is a privileged scaffold for exploration of anticancer agents. 3(4-oxo-4H-chromen-3-yl)acrylic acid amides derivatives designed, synthesized by employing the molecular hybridization approach between different aromatic, aliphatic amines and 3(4-oxo-4H-chromen-3-yl)acrylic acid. The docking study of 3(4-oxo-4H-chromen-3-yl)acrylic acid amides were performed using Schrodinger 2015 (maestro 10.1) on human estrogen receptor α-Ligand-Binding domain (1XP6), Tyrosyl-t-RNA synthetase protein (1JIK), DNA gyrase protein (4DUH), nitric oxide synthase (3NLE) and evaluated in vitro antioxidant activity, antibacterial activity, cytotoxicity against human Breast Cancer Cell Line (MCF-7). The in silico studies indicated that 3(4-oxo-4H-chromen-3-yl)acrylic acid amides derivatives exhibited comparable docking score and good hydrogen bond interactions with the amino acids present in the active site of 3NLE and 1XP6. Many of the synthesized compounds exhibited potent antioxidant and cytotoxic activity. The most potent antioxidant activity was observed for compound A_5 with IC_{50} value of 0.5 µg/ml, most potent anticancer activity was observed for compound A_1 with IC_{50} value of 37.13 µg/ml and potent antibacterial activity was observed for compound A_1 with Minimum Inhibitory Concentration (MIC) value of 100 µg/ml against Escheriea coli and Proteus vulgaris.

Keywords: 3(4-oxo-4H-chromen-3-yl)acrylic acid amides, Estrogen receptor, Breast cancer, Antioxidant activity, Antibacterial activity

INTRODUCTION

Estrogen receptor-positive (ER+) breast cancer is the most common type of breast cancer diagnosed today. According to the American Cancer Society, about two out of every three cases of breast cancer are hormone receptor positive. Most of these cases are ER+ or receptive to both estrogen and progesterone [1]. In Estrogen receptor positive breast cancer the level of Estrogen is a key factor for the initiation and progression of breast cancer [2 5]. In the mammary epithelial, estrogen controls many cellular activities such as proliferation, differentiation and migration [6,7]. There are two genetically distinct and functional Estrogen Receptors (ERs), ERα and ERβ, belonging to the superfamily of nuclear receptors for steroid/thyroid hormones. The structural differences between the two ERs indicate that they serve distinct actions [8]. Estrogen exert its functions in different tissues by binding with its receptors, including alpha and beta (ERα and ERβ), the former is the major one involved in breast cancer and chosen as an important target for endocrine therapy in clinic [2,9].

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [10]. Chromone (1) (4H-chromen-4-one, 4H-1-benzopyran-4-one) is an important class of oxygen-containing heterocyclic compounds with a benzoannelated γ-pyrone ring and they are part of the flavonoid family. The chromone and related compounds are widespread in the plant kingdom from algae to conifers. Chromones have found to be active in a number of plant cycles, including growth regulation, indole acetic acid oxidation and dormancy inhibition as well as exhibiting cytokinin-type behavior and stimulating oxygen uptake in plant tissue [11]. Chromone derivatives are abundant in nature and exhibit a wide range of pharmacological activity like antibacterial, antifungal [12,13], anticancer [14], antioxidant [15], anti-HIV [16], antiulcer [17], immunostimulators [18], biocidal [19], wound healing [20], antiinflammatory [21], and immune stimulatory [22]. Many chromone derivatives are also photoactive and can be used easily in various photo induced reactions affording diverse heterocyclic compounds [23]. Chromone derivatives are also active at benzodiazepine receptors [24] and on lipoxygenase and cyclooxygenase [25]. In addition to this, they have been shown to be possessing antimutagenic properties [26] as well as the ability to inhibit electron transport through inhibition at Nicotinamide Adenine Dinucleotide Hydrogen (NADH): Ubiquinone oxidoreducatase and phorbol ester-induced ornithine decarboxylase [27,28]. Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator. These compounds also possess Low mammalian toxicity and are present in large amounts in the diet of humans due to their origin in plants [25]. Acrylic acid derivatives have wide range of therapeutically importance such as, Anti-tumor activity [29], antioxidant activity [30] and antibacterial [31] activity.

SCIENTIFIC REPORTS

OPEN

Nimbolide upregulates RECK by targeting miR-21 and HIF-1α in cell lines and in a hamster oral carcinogenesis model

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Reversion-inducing cysteine-rich protein with Kazal motifs (RECK), a potent inhibitor of matrix metalloproteinases (MMPs) is a common negative target of oncogenic signals and a potential therapeutic target for novel drug development. Here, we show that sequential RECKlessness stimulates angiogenesis and Notch signalling in the 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch (HBP) carcinogenesis model, a paradigm for oral oncogenesis and chemointervention. We also report the chemotherapeutic effect of nimbolide, a limonoid from the neem tree (*Azadirachta indica*) based on the upregulation of RECK as well as modulation of the expression of key molecules involved in invasion and angiogenesis. We demonstrate that nimbolide upregulates RECK by targeting miR-21, and HIF-1α resulting in reduced MMP activity and blockade of VEGF and Notch signalling. Nimbolide reduced microvascular density, confirming its anti-angiogenic potential. Molecular docking analysis revealed interaction of nimbolide with HIF-1α. Additionally, we demonstrate that nimbolide upregulates RECK expression via downregulation of HIF-1α and miR-21 by overexpression and knockdown experiments in SCC4 and EAhy926 cell lines. Taken together, these findings provide compelling evidence that targeting RECK, a keystone protein that regulates mediators of invasion and angiogenesis with phytochemicals such as nimbolide may be a robust therapeutic approach to prevent oral cancer progression.

Reversion-inducing cysteine rich protein with Kazal motifs (RECK), a membrane bound glycoprotein that plays a pivotal role in remodelling the extracellular matrix (ECM) by regulating the activity of matrix metalloproteinases (MMPs) is a potent inhibitor of tumor invasion, metastasis and angiogenesis[1–3]. The RECK protein containing multiple epidermal growth factor-like (EGF-like) repeats and serine-protease inhibitor (SPI) motifs is anchored via the C-terminal glycosylphosphatidylinositol (GPI) to the cell membrane. RECK primarily inhibits MMP-2, and -9 as well as a-disintegrin and metalloproteinase (ADAM-10). RECK regulates Notch signalling, which plays a critical role in angiogenesis[4]. RECK is widely expressed in normal tissues and nonneoplastic cell lines, but its expression is frequently downregulated in several tumours and in fibroblasts transformed by various oncogenes. Hence, RECKlessness is considered a hallmark of cancer[5].

RECK downregulation is reported to stimulate invasion and angiogenesis in several tumours including liver, lung, breast, prostate, oral and digestive tract cancers[4–6]. The RECK gene is a common negative target of oncogenic signals as well as histone deacetylase (HDAC) that act on the binding site of the transcription factor Sp1 on the RECK gene promoter[7]. In addition, hypoxia and groups of miRs also cause transcriptional repression of RECK gene expression leading to upregulation of MMPs and ECM degradation[2,8,9]. Several synthetic and natural

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Pueraria tuberosa potentially attenuates Arsenic induced oxidative stress mediated cardiotoxicity, blood toxicity and dyslipidemia in rats

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ABSTRACT

Background: The present study was carried out to evaluate protective effect of hydroalcoholic extract of *Pueraria tuberosa* (tuber) in arsenic induced cardiotoxicity in Wistar albino rats.

Material and Methods: Dose selection of *Pueraria tuberosa* was made on the basis of acute oral toxicity study (5, 50, 300, 1000 mg/kg body weight) as per OECD guidelines. Cardiotoxicity was produced in adult wistar rats randomly divided into six animals in six groups for 25 days. Group I rats were administered with drinking water for 30 days. Positive Control (Group II) rats were treated with sodium arsenate (1mg/kg).Group III rats were treated with sodium arsenate (1mg/kg) and Vitamin E (100 mg/kg).Group IV ,V,VI rats were treated with sodium arsenate (1mg/kg) and hydroalcoholic extract of *Pueraria tuberosa* (50mg/kg, 100mg/kg, 200mg/kg). After 30 days of the treatment, blood samples were collected and analyzed for the serum parameters *viz.* HDL (High density lipoprotein), Total cholesterol, LDL (Low density lipoprotein), Troponin, Triglycerides and LDH. Antioxidant parameters like Malondialdehyde, catalase, Reduced glutathione and glutathione reductase were estimated. Blood parameters like Haemoglobin, Mean corpuscular haemoglobin (MCH), Mean corpuscular volume (MCV), Mean corpuscular haemoglobin concentration (MCHC), RBC, WBC, Erythrocyte sedimentation rate, DNA fragmentation, body weight, organ weight were also estimated. The heart is removed and sectioned for histopathological examination.

Results: The hydroalcoholic extract of *Pueraria tuberosa* (tuber) inhibits the oxidative stress hypothesis mechanism and influence of calcium homeostasis.

Conclusion: It was concluded that the extract of *Pueraria tuberosa* (tuber) acts on intracellular calcium ions are increased in the myocardial cells to regulate myocardial hypertrophy.

Keywords: Arsenic trioxide, Cardiotoxicity, blood toxicity, *Peurariatuberosa*, DNA fragmentation.

INTRODUCTION

Cardiotoxicity is defined by the National Cancer Institute as the toxicity that affects the heart. This definition includes a direct effect of the drug on the heart but also an indirect effect due to enhancement of haemodynamic flow alterations or due to thrombotic events. Cardiotoxicity is the occurrence of heart electrophysiology dysfunction or muscle damage (Akhlaghia, 2010) reported as a result of cardiotoxicity, heart is not being able to pump blood throughout body. The heart becomes weaker and is not as efficient in pumping and circulating blood. This is due to caused by adverse effects of heavy metals intake (arsenic, mercury, lead, aluminium). Cardiotoxicity resulting from exposure to environmental toxicants and pollutants is known for a long time. For every new treatment, it will be essential to thoroughly assess toxic effects on the heart. The application of cutting-edge molecular biology approaches has provided significant and novel insights into cardiac toxicity and its mechanisms.

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Review Article

Chronic Hypoxia as a Potential Factor in Human Life-threatening Diseases

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ABSTRACT

The review article focuses on the importance of adequate oxygen levels in the body as cure and therapy for many ailments. It is known that hypoxia is the cause for cellular damage and if it can be applied to major patho-physiology's, it can be observed that slow and chronic hypoxic conditions are the cause for most of the diseases. On the contrary, providing each cell of the body with proper oxygen may be helpful in maintaining the immunity of the body and therefore treating many disease conditions. This theory, if tested may show positive results in heart related diseases, neuronal disorders, stresses, digestive disorders and the unresolved cancer too. Slow decrease in the levels of atmospheric oxygen could be a reason to induce chronic hypoxia. According to Dr. Otto Warburg, a Noble laurate, a normal cell when deprived of oxygen, may get converted to a cancerous cell, whereas a cancerous cell cannot survive in aerobic conditions. If this part of his research be concentrated on, there could be fruitful results in the treatment of cancer. To maintain adequate levels of oxygen in the body, simple yogic breathing practices are helpful. And to maintain the adequate atmospheric oxygen, trees and plants which cleanse the atmospheric air are useful. Clinical surveys on volunteers who have been practicing regular breathing exercises can prove the fact that proper and concentrated respiration could prevent many diseases. Thus, supplementing breathing exercises along with the regular treatment for cancer patients could be helpful in alleviating cancer and other diseases.

KEYWORDS: Chronic Hypoxia; Yoga-Breathing exercises; Hypoxia in Cancer; Oxygen deprivation; Oxygen therapy.

Introduction

It is universally known that the most basic and vital functions of the body cannot be performed in the absence of oxygen. But the fact, that providing the body with adequate amounts of oxygen could be used as the cure for major disorders, is being ignored. Hypoxia, deprivation of oxygen, is known to be the major cause of cellular damage, which in turn can cause damage to the corresponding organs and their functions.

Oxygen is the only component of the air that we can breathe and is capable of supporting life. Air is mainly composed of approximately 21% oxygen, 78% nitrogen and other trace components. However, the addition of any gas, except oxygen, to air reduces the oxygen concentration through displacement and dilution. Deprivation of oxygen at a higher percentage acutely, is supposed to have many disastrous effects on the body. A list of the effects corresponding to the percentage of oxygen concentration are given in the Table 1.

Hypoxia as Root Cause of Cancer

If the percentage of oxygen is decreased at a smaller rate and for a longer time, that is in cases of chronic hypoxia, there could be many physiological and pathological changes in the body. All the cells have multiple responses to low or zero oxygen concentrations. In the complete absence of oxygen, cells undergo cell death through apoptosis, and not necrosis (Brunelle and Chandel, 2002).

TABLE 1

Effects of oxygen-deficient exposure.

Oxygen concentration (% vol)	Health effects
19	Some adverse physiological effects occur, but they may not be noticeable.
15-19	Impaired thinking and attention. Increased pulse and breathing rate. Reduced coordination. Decreased ability to work strenuously. Reduced physical and intellectual performance without awareness.
12-15	Poor judgment. Faulty coordination. Abnormal fatigue upon exertion. Emotional upset.
10-12	Very poor judgment and coordination. Impaired respiration that may cause permanent heart damage. Possibility of fainting within a few minutes without warning. Nausea and vomiting.
<10	Inability to move. Fainting almost immediate. Loss of consciousness. Convulsions. Death.