Criteria 3

Research, Innovations and Extension

Key Indicator 3.5

Collaboration

3.5.1 The number of MoUs, collaborations/linkages for Faculty exchange, Student exchange, Internship, Field trip, On-the- job training, research and other academic activities during the last five years

3.5.1 The number of MoUs, collaborations/linkages for Faculty exchange, Student exchange, Internship, Field trip, On-the-job training, research and other academic activities during the last five years

List of Collaboration made by faculties with other institutions and their outcome as publications

Sr. No.	Name of Faculty Member	Name of the collaborating agency with which collaborating publication is made	Year	Page No with Link
1	Gaurav V. Harlalka	Center for Human Disease Modeling, Duke University Medical Center, Durham, North Carolina, USA	2021-22	1
2	Gaurav V. Harlalka	RILD Wellcome Wolfson Centre, Royal Devon & Exeter NHS Foundation Trust, Barrack Road, Exeter, UK	2021-22	2
3	Mangesh Deokar	Department of Pharmacology, SVKM's Institute of Pharmacy, Dhule, (M.S.), India	2021-22	3
4	Darshan R. Telange	School of Pharmacy and Technology Management, SVKM's NMIMS (Deemed to be University), Shirpur, Maharashtra, India	2021-22	4
5	Gaurav V. Harlalka	RILD Wellcome Wolfson Medical Research Centre, RD&E (Wonford) NHS Foundation Trust, University of Exeter Medical School, Exeter, United Kingdom	2021-22	5
6	Deepak K. Lokwani	Department of Pharmaceutical Chemistry, Durgamata Institute of Pharmacy, Dharmapuri, Parbhani 431401, Maharashtra, India	2021-22	6
7	Prakash N. Kendre	Department of Ayurveda, Vijyashree Ayurved College and Hospital, JDA Scheme No.41/65, Vijay Nagar, Behind MPSEB Substation, Basha Jabalpur - 482 002, Madhya Pradesh, India	2021-22	7
8	Deepak K. Lokwani	Department of Chemical Technology, Dr. Babasaheb Ambedkar, Marathwada University, Aurangabad, Maharashtra, India	2021-22	8
9	Prakash N. Kendre	Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Kopargaon - 423 601, Maharashtra, India	2021-22	9
10	Shailesh Kewatkar	Department of Pharmacy, Jagdishprasad Jhabarwal Tibervala University, Jhunjhunu, Rajasthan 333001	2021-22	10

11	Mangesh Deokare	Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL, 33136	2021-22	**11**
12	Deepak K. Lokwani	Department of Pharmaceutical Chemistry, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharashtra 425405, India	2021-22	**12**
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15	Deepak K. Lokwani	Department of Chemistry, Radhabai Kale Mahila Mahavidyalaya, Ahmednagar, 414001, Maharashtra, India	2021-22	**15**
16	Sharad D. Tayade	Faculty of Pharmacy, Oriental University, Indore, Madhya Pradesh, India-453555	2021-22	**16**
17	Subhash V. Deshmane	Department of Quality Assurance, KJ's Institute, Trinity College of Pharmacy, Pune - 411 048, Maharashtra, India	2021-22	**17**
18	Sangameshwar Baburao Kanthale	Department of Pharmaceutics, SGMSPM'S Sharadchandra Pawar College of Pharmacy, Dumbarwadi, Tal: Junnar, Dist: Pune, Maharashtra 410504, India	2021-22	**18**
19	Subhash Deshmane	Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, India	**2020-21**	**19**
20	Gaurav V Harlalka	Department of Biological Science, International Islamic University1, H-10, Islamabad	2020-21	**20**
21	Darshan Telange	Department of Pharmaceutical Quality Assurance, R. C. Patel Institute of Pharmaceutical Education & Research, Karwand Naka, Shirpur, 425405, Dist.-Dhule,	2020-21	**21**
22	Darshan Telange	School of Pharmacy and Technology Management, SVKM's NMIMS, India	2020-21	**22**
23	Darshan Telange	Institute of Chemical Technology, Mumbai, Maharashtra, India	2020-21	**23**
24	Mahendra Ashok Giri	Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education & Research, Kopargaon, Maharashtra, India	2020-21	**24**

25	Prakash N Kendre	Department of Pharmaceutics, Sanjivani College ofPharmaceutical Education & Research, Kopargaon, Maharashtra, India.	2020-21	25
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30	Shailesh Kewatkar	Dr. D.Y. Patil institute of Pharmaceutical Research and Sciences 4, Pune - 411018, Maharashtra, India	2020-21	30
31	Shailesh Kewatkar	Department of Pharmacology, Vidyabharti College of Pharmacy, Amravati - 444602, Maharastra, India.	2020-21	31
32	Shailesh Kewatkar	Dr. Panjabrao Deshmukh Medical College, Amravati – 444603, Maharashtra, India	2020-21	32
33	Saddam Shaikh	Department of Pharmacognosy, Government College of Pharmacy, Karad, Maharashtra, India	2020-21	33
34	Prakash N. Kendre	Sanjivani College of Pharmaceutical Education and Research , Kopargaon, India	2019-20	34
35	Prakash N. Kendre	Modern College of Pharmacy, Nigdi, Pune, India	2019-20	35
36	Prakash N. Kendre	Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education & Research, Kopargaon, India;	2019-20	36
37	M. A. Giri	Department of Pharmacognosy, Sanjivani College of Pharmaceutical Education and Research, Pune University, Kopargaon, India and 3Department of Pharmaceutics, N. N. Sattha College of Pharmacy, BAT University, Ahmednagar, India	2019-20	37
38	Shailesh Kewatkar	Department of Pharmacognosy, Shri D. D. Vispute College of Pharmacy and Research Center, New Panvel, Navi Mumbai, Maharashtra, India	2019-20	38

39	Shailesh Kewatkar	JJT University, Jhunjhunu, Rajasthan, India	2019-20	**39**
40	Shailesh Kewatkar	JJT University, Jhunjhunu, Rajasthan, India and Mprex Healthcare, Pune, India	2019-20	**40**
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43	Sharuk L. Khan	Government College of Pharmacy, Aurangabad, Maharashtra, India 431005	2019-20	**43**
44	Gaurav V. Harlalka	RILD Building, Wellcome Wolfson Centre, University of Exeter Medical School, Exeter, UK	2019-20	**44**
45	Darshan R. Telangea	1Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's, NMIMS (Deemed to be University), Mumbai Campus, Mumbai, Maharashtra, INDIA	2019-20	**45**
46	Mahendra Ashok Giri	2Sanjivani College of Pharmaceutical Education and Research, Pune University, Kopargaon, Maharashtra, INDIA and 3Shri Sai Jyoti College of Pharmacy, Vattinagula Pally, Gandhipeth, Hyderabad, Telangana, INDIA	2019-20	**46**
47	Mahendra Ashok Giri	Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra, India	2019-20	**47**
48	Ajinkya Kailas Potea	Department of Pharmaceutics, RSM's N.N Sattha College of Pharmacy, Ahmednagar, India	2019-20	**48**
49	Sharuk L. Khan	Department of Pharmacognosy, JES's College of Pharmacy, Nandurbar, Maharashtra, India.	2019-20	**49**
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52	Shailesh Kewatkar	Department of Pharmacology, Vidya Bharti College of Pharmacy, Amravati, Maharashtra, India	2019-20	**52**
53	Gaurav V. Harlalka	Department of Biological Sciences, International Islamic University, Islamabad, H-10, Islamabad 44000, Pakistan	**2018-19**	**53**
54	Gaurav V. Harlalka	Department of Biological Sciences, International Islamic University, Islamabad, H-10, Islamabad 44000, Pakistan	2018-19	**54**
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RSCP

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ORIGINAL ARTICLE

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A recurrent rare intronic variant in *CAPN3* alters mRNA splicing and causes autosomal recessive limb-girdle muscular dystrophy-1 in three Pakistani pedigrees

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Abstract

Autosomal recessive limb-girdle muscular dystrophy-1 (LGMDR1) is an autosomal recessive disorder characterized by progressive weakness of the proximal limb and girdle muscles. Biallelic mutations in *CAPN3* are reported frequently to cause LGMDR1. Here, we describe 11 individuals from three unrelated consanguineous families that present with typical features of LGMDR1 that include proximal muscle wasting, weakness of the upper and lower limbs, and elevated serum creatine kinase. Whole-exome sequencing identified a rare homozygous *CAPN3* variant near the exon 2 splice donor

Kamal Khan, Sarmad Mehmood, and Chunyu Liu contributed equally.

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ARTICLE OPEN

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Evidence that the Ser192Tyr/Arg402Gln in *cis* Tyrosinase gene haplotype is a disease-causing allele in oculocutaneous albinism type 1B (OCA1B)

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Oculocutaneous albinism type 1 (OCA1) is caused by pathogenic variants in the *TYR* (tyrosinase) gene which encodes the critical and rate-limiting enzyme in melanin synthesis. It is the most common OCA subtype found in Caucasians, accounting for ~50% of cases worldwide. The apparent 'missing heritability' in OCA is well described, with ~25–30% of clinically diagnosed individuals lacking two clearly pathogenic variants. Here we undertook empowered genetic studies in an extensive multigenerational Amish family, alongside a review of previously published literature, a retrospective analysis of in-house datasets, and tyrosinase activity studies. Together this provides irrefutable evidence of the pathogenicity of two common *TYR* variants, p.(Ser192Tyr) and p.(Arg402Gln) when inherited in *cis* alongside a pathogenic *TYR* variant in *trans*. We also show that homozygosity for the p.(Ser192Tyr)/p.(Arg402Gln) *TYR* haplotype results in a very mild, but fully penetrant, albinism phenotype. Together these data underscore the importance of including the *TYR* p.(Ser192Tyr)/p.(Arg402Gln) in *cis* haplotype as a pathogenic allele causative of OCA, which would likely increase molecular diagnoses in this missing heritability albinism cohort by 25–50%.

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INTRODUCTION

Oculocutaneous albinism (OCA) refers to a group of genetically and clinically heterogeneous disorders characterised by abnormal melanin synthesis, resulting in decreased or absent pigmentation of eyes, skin and hair.

Ocular features are present in individuals with OCA and are characteristic of the disease. These include photophobia, nystagmus, foveal hypoplasia, iris transillumination and abnormal decussation of nerve fibres at the optic chiasm resulting in crossed asymmetry on visual evoked potential testing[1]. These ocular features may, however, be variable with no single defining characteristic found to be present in every individual with OCA[2]. The cutaneous phenotype may also vary, ranging from total absence to near-normal levels of pigmentation, and can be difficult to evaluate, particularly in individuals with a lightly pigmented ethnic background[3,4]. As such, OCA can be difficult to distinguish clinically from several other ocular disorders with overlapping phenotypical features, such as *GPR143*-associated X-linked ocular albinism, where the hypopigmentation is limited to the eye[1], *FRMD7*-associated X-linked idiopathic congenital nystagmus[5], *SLC38A8*-associated foveal hypoplasia (also known as FHONDA; foveal hypoplasia, optic nerve decussation defects and anterior segment dysgenesis)[6], and dominant *PAX6*-related ocular developmental disorders[7].

OCA1, associated with *TYR* gene variants, is the most common OCA subtype found in Caucasians accounting for ~50% of cases worldwide[8,9]. *TYR* encodes the enzyme tyrosinase, which is the critical and rate-limiting enzyme in the biosynthesis of melanin in follicular and epidermal melanocytes in hair and skin, as well as in uveal melanocytes in the iris, ciliary body and choroid, and retinal pigment epithelium cells in the eye[10]. Disease-associated variants in the *TYR* gene cause complete or partial OCA1 depending on their impact on the residual activity of the encoded mutant tyrosinase enzyme[11]. *TYR* gene variants that result in a severe reduction or complete abolition of enzyme activity are associated with OCA1A, characterised by an almost complete absence of hair, skin and eye pigmentation[10,11]. Hypomorphic *TYR* variants in which mutant tyrosinase possess residual catalytic activity are associated with OCA1B, where affected individuals present with a milder phenotype with reduced levels of pigmentation[10,11].

The apparent missing heritability in OCA is well described, with ~25–30% of clinically affected individuals lacking two clearly pathogenic sequence alterations within the same OCA gene; this proportion is higher in individuals with a partial OCA phenotype[11,12]. Several hypotheses have been proposed to explain this

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Original Research Article

Role of L-lysine in Ethanol Induced Behavioral Changes in Mice

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Conflict of interest: Nil

Abstract

Lysine, (S)-2,6,-diaminohexanoic acid, is a basic amino acid. Following ingestion, L-lysine is absorbed by the active transport process from the lumen of the small intestine into the enterocytes. L-lysine is a 5-HT_4 antagonist that can increase and decrease ethanol intake when they are given intraperitoneal administration. 5-HT_4 antagonist can block the rewarding and motivation effect as indicated by attenuation of sensitization to the locomotors stimulant effect of ethanol, decreased ethanol-induced conditioned placed preference, and reduced ethanol drinking. Young healthy mice (21–30 g) were group-housed (five per cage) in opaque polypropylene cages Animals were naive to drug treatment and experimentation at the beginning of all studies. Each experimental group was comprised of five mice. Testing was carried out in counterbalanced order concerning the treatment conditions in the noise-free room. Locomotor activity and conditioned place preference was assessed followed by acute and chronic exposure of ethanol to animals. The results revealed that acute as well as administration of L-lysine (20 and 40 mg/kg, i.p.) pre-treatment, 30 min before the test significantly reduced place preference in ethanol control-treated groups. In locomotor activity L-lysine (20 and 40 mg/kg, i.p.) pre-treatment, 30 min before the test significantly reduced locomotor count in ethanol control-treated groups in both acute and chronic groups. In conclusion, Results indicated that l-lysine exhibited an inhibitory influence against ethanol-induced behavioral changes in mice.

Keywords: L-lysine; 5-HT_4 antagonist, Ethanol dependence; Locomotor Activity; Conditioned Place Preference.

Introduction:

Ethanol is one of the most widely abused addictive drugs and has hazardous health consequences resulting from its chronic use[2]. Ethanol produces a striking array of behavioral effects in humans that are dependent on the dose of ethanol administered[3]. When used in low to moderate quantities, it relieves anxiety and fosters a feeling of well-being and euphoria. Alcohol abuse is a pattern of drinking that results in harm to one's health, interpersonal relationships, or ability to work[9]. Alcohol abuse can result in brain damage which causes impairments in executive functioning

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Research Article

Calcium Ion-Sodium Alginate-Piperine-Based Microspheres: Evidence of Enhanced Encapsulation Efficiency, Bio-Adhesion, Controlled Delivery, and Oral Bioavailability of Isoniazid

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Abstract. Isoniazid (INH) is a first-line chemotherapeutic drug employed in the management of tuberculosis. However, its extensive first-pass metabolism, short-life life, and low oral bioavailability confined its medical application. Therefore, the calcium ion-alginate-piperine microspheres (INH-CaSP Ms) was prepared to enhance encapsulation efficiency, controlled delivery, and oral bioavailability of INH. The INH-CaSP Ms was developed using a modified emulsification method and optimized via Box-Behnken design (BBD). Optimized INH-CaSP Ms were characterized for encapsulation efficiency, differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FT-IR), bio-adhesion, *in vitro* dissolution, *ex vivo* permeation, and oral bioavailability studies. Characterization studies confirmed the formation of microspheres. The INH-CaSP Ms showed spherical microspheres with enhanced encapsulation efficiency (~ 93.03 ± 1.54% w/w). The optimized INH-CaSP Ms exhibited higher bio-adhesion around (~ 81.41 ± 1.31%). The INH-CaSP Ms enhanced the dissolution rate of INH (~ 57%) compared to pure INH (~ 57%) and INH-SA Ms (~ 81%) in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.4). The same formulations improved the permeation rate of INH (~ 90%) compared to pure INH (~ 55%) and INH-SA Ms (~ 80%). The oral bioavailability results indicated that INH-CaSP Ms appreciably improved the oral bioavailability of INH via increasing the *Cmax*, *Tmax*, $t_{1/2}$, and *AUC* parameters compared to pure INH. The study demonstrates that the development of INH-CaSP Ms via cross-linked coordinate bond interaction between divalent cation calcium ion-alginate complex and anion piperine bio-enhancer is an effective approach for enhancing the encapsulation efficiency, bio-adhesion, controlled release, and oral bioavailability of INH.

KEY WORDS: Isoniazid; Sodium alginate; Piperine; Microspheres; Oral bioavailability.

INTRODUCTION

The oral route is the most desirable route for drug administration because of easy drug administration, non-invasive approach, convenience, high patient compliance, and feasibility for solid dosage formulations. Moreover, the prominent surface area (300–400 m^2) of the oral route provides an excellent attachment to the drug and promotes its absorption via enterocytes (1). Despite these positive benefits, the oral route displays multiple drawbacks such as drug stability and solubility issues in the GI tract, variable and poor absorption, extensive first-pass metabolism, and high P-gp efflux. This mechanism produces low oral bioavailability of many active pharmaceutical ingredients (APIs) (2). Various formulations have been introduced for enhancing the oral bioavailability of the drug. The nanoformulations are considered the best choice due to nanometer in size and demonstrated a significant improvement in oral bioavailability via localized and targeted drug delivery in the GI tract. It achieved the oral targeted delivery via enhancing drug residence duration, increased release, and assisting interaction with cells in the GI tract (2). This interaction can facilitate permeation absorption, thereby enhancing the oral bioavailability of the drug (3).

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PLOS GENETICS

RESEARCH ARTICLE

Biallelic variants in *TRAPPC10* cause a microcephalic TRAPPopathy disorder in humans and mice

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Abstract

The highly evolutionarily conserved transport protein particle (TRAPP) complexes (TRAPP II and III) perform fundamental roles in subcellular trafficking pathways. Here we identified biallelic variants in *TRAPPC10*, a component of the TRAPP II complex, in individuals with a severe microcephalic neurodevelopmental disorder. Molecular studies revealed a weakened interaction between mutant TRAPPC10 and its putative adaptor protein TRAPPC2L. Studies of patient lymphoblastoid cells revealed an absence of TRAPPC10 alongside a concomitant absence of TRAPPC9, another key TRAPP II complex component associated with a clinically overlapping neurodevelopmental disorder. The TRAPPC9/10 reduction phenotype was recapitulated in *TRAPPC10*$^{-/-}$ knockout cells, which also displayed a membrane trafficking defect. Notably, both the reduction in TRAPPC9 levels and the trafficking defect in these cells could be rescued by wild type but not mutant TRAPPC10 gene constructs. Moreover, studies of *Trappc10*$^{-/-}$ knockout mice revealed neuroanatomical brain defects and microcephaly, paralleling findings seen in the human condition as well as in a *Trappc9*$^{-/-}$ mouse model. Together these studies confirm autosomal recessive *TRAPPC10* variants as a cause of human disease and define TRAPP-mediated pathomolecular outcomes of importance to TRAPPC9 and TRAPPC10 mediated neurodevelopmental disorders in humans and mice.

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Explorations of novel pyridine-pyrimidine hybrid phosphonate derivatives as aurora kinase inhibitors

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ABSTRACT

For developing novel therapeutic agents with good anticancer activities, a series of novel pyridine-pyrimidine hybrid phosphonate derivatives 4(a–q) were synthesized by the Kabachnik-Fields method using CAN as catalyst. The compound 4o exhibited the most potent anticancer activity with an IC_{50} value of 13.62 μM, 17.49 μM, 5.81 μM, 1.59 μM and 2.11 μM against selected cancer cell lines A549, Hep-G2, HeLa, MCF-7, and HL-60, respectively. Compound 4o displayed seven times more selectivity towards Hep-G2 cancer cell lines compared to the human normal hepatocyte cell line LO2 (IC_{50} value 95.33 μM). Structure-Activity Relationship (SAR) studies were conducted on the variation in the aromatic ring (five-membered heterocyclic ring, six-membered heterocyclic ring) and the variation of substituents on the phenyl ring (electron donating groups, electron withdrawing groups). Furthermore, the mechanism of anticancer activity was clarified by further explorations in bioactivity by using in vitro aurora kinase inhibitory activity and molecular docking studies. The results showed that the compound **4o** at IC_{50} concentration demonstrated distinctive morphological changes such as cell detachment, cell wall deformation, cell shrinkage and reduced number of viable cells in cancer cell lines. Compound 4o induced early apoptosis and late apoptosis of 27.7% and 6.1% respectively.

Cancer is characterized as uncontrolled cell proliferation in the body. It is the second most life-threatening disease, taking approximately 9.6 million lives worldwide each year.[1] Different strategies are in the development stages for the treatment of cancer. Mitotic kinases play an essential role in mitosis, and are often observed to be over-expressed in human solid and many hematologic cancers.[2] Anti-mitotic agents, which disrupt mitotic spindle assembly, are one of the recent flourishing strategies, which include protein kinase inhibitors such as Aurora kinase. The literature survey highlighted that the over-expression of Aurora kinase leads to tumorigenesis via multiple mechanisms.[1] After being enlightened with this knowledge, a deep study was done on aurora kinase inhibitors.

More and more evidence indicates that the heterocyclic scaffold is a significant tool for finding new active substances with many potential applications. Pyridine and pyrimidine derivatives have received great interest in recent pharmacological research, being effective in the treatment of various malignancies, such as myeloid leukemia, breast cancer, and idiopathic pulmonary fibrosis. The majority of FDA-approved drugs have a pyridine or pyrimidine core with various substituents.[3] Pyridine and pyrimidine derivatives have a variety of biological activities, such as hypoglycemic, anti-inflammatory, anti-virus, anti-cancer activity and so on[3]. In recent years, a series of anticancer compounds with a pyridine pyrimidine moiety have been designed and synthesized.[3] Pyrimidine derivatives such as VX-680, MLN 8054, and CYC-116 are Aurora Kinase inhibitors. AMG900 has been reported to demonstrate significant inhibitory activity against aurora kinase. AMG900 consists of pyridine pyrimidine framework in its structure. The pyridine pyrimidine framework played a key role in the interaction with Aurora kinase. Thus, developing such small molecules with a pyridine pyrimidine framework that can easily form hydrogen bonds with aurora

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ANALYTICAL STANDARDIZATION AND PROFILING OF AYUSH-64: AN AYURVEDIC TABLET FORMULATION

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ABSTRACT

Success of any healthcare product is based on its performance, which is further dependent upon the quality of the product. Quality of the polyherbal ayurvedic formulation is assured by developing proper analytical standards with the help of the guidelines provided by CCRAS (Central Council for Research in Ayurvedic Sciences), which will also ensure its authentication. Ayush-64 is a polyherbal formulation and its analytical standards were developed for various parameters like organoleptic properties, physical-chemical and chromatographic profiling etc. These standards were developed by studying and analyzing three batches of self-manufactured Ayush-64 tablets with the help of good manufacturing practices (GMP). These parameters were found to be sufficient to standardize and authenticate the quality of the formulation, which can be used further as a reference standard for quality control and quality assurance of the final product.

Keywords: Ayush-64 tablets, CCRAS, Standardization, Polyherbal formulation

INTRODUCTION

Ayush-64 is an antimalarial tablet invented and patented by CCRAS. It's a polyherbal tablet, widely used in treatment of malaria and allied fevers. In the past 80-100 years chemically synthetic products have been researched and manufactured in a very widespread revolutionary manner and still most of the population in the world relies on traditional health care practitioners for their day to day primary healthcare. Most of the populations of Indian and African sub-continents are using the traditional healthcare measures to meet their health requirements[1].

Commercialization of ayurvedic pharmacies in the past era with pharmaceutical practices of Ayurved drugs according to ancient methods created a need of quality and standardization[2]. Standardization ensures quality and therapeutic effect of a product. Ayurvedic/ herbal product cannot be considered as suitable or valid for medicinal use unless it proves the reproducibility of batch-to-batch manufacturing[3]. The present study reports on evaluating the analytical standards of polyherbal Ayush-64 tablets based on organoleptic properties, physico-chemical characterization and chromatographic profiling. Standardization of such ayurvedic products can be carried out using GMP (Good Manufacturing Practices) and GLP (Good Laboratory Practices) guidelines[4-6]. The present study was successfully conducted at Unijules Life Sciences Ltd. Nagpur (MS), India, a WHO-GMP approved Ayurvedic Pharmaceutical Company. All the chemicals used in the experimentation were of analytical grade and procured from Merck Specialties Pvt. Ltd. Mumbai (India).

MATERIALS AND METHODS

Ayush-64 tablet formulation was developed as per the composition (Table I) and procedure described by CCRAS (Central Council for Research in Ayurvedic Sciences). All the required ingredients were procured from authentic sources in Nagpur region. The quality and authenticity of all the ingredients was ensured as per the analytical specifications of API (Ayurvedic Pharmacopeia of India) at quality control laboratory of Unijules Life Sciences[7]. A separate *kashay* (decoction) of all the three items was made and *ghanasatva* (concentrated extract) was obtained. Formulation of Ayush-64 tablet was prepared by accurately weighing all the ingredients. One part each of ghansatva was mixed with two parts of powder of *Caesalpinia bonducella* (Latakaranj). Finally, tablets were prepared by wet granulation method, each

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Molecular dynamic simulations based discovery and development of thiazolidin-4-one derivatives as EGFR inhibitors targeting resistance in non-small cell lung cancer (NSCLC)

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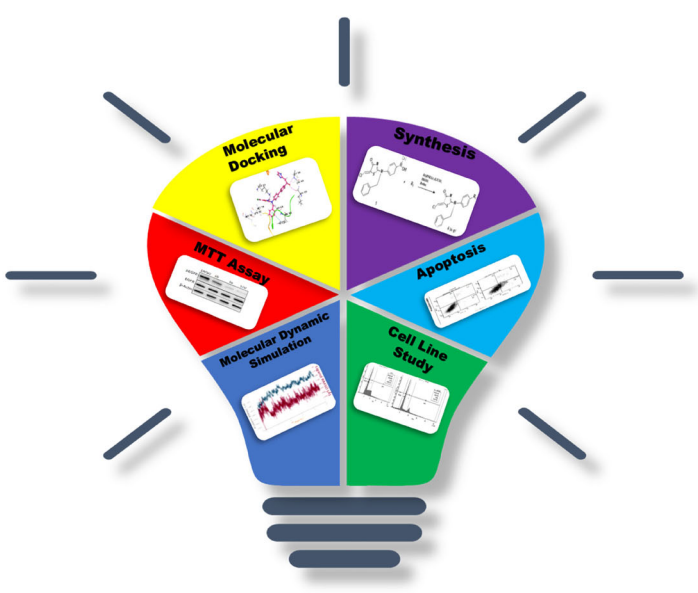
ABSTRACT

Targeting kinases with oncogenic driver mutations in malignancies with allosteric kinase inhibitors is a promising new treatment technique. EGFR inhibitors targeting the L858R/T790M/C797S mutation bearing thiazolidine-4-one scaffold were discovered, optimized, synthesized, and biologically evaluated. According to *in silico* and *in vitro* studies, compounds **6a** and **6b** resulted to be highly potent with IC_{50} values of 120 nM and 134 nM and good selectivity. Compound **6a** displayed significant antioxidant activity, with a DPPH radical scavenging value of 92.15%. The potency of compounds was also compared with ADMET and molecular dynamics simulations study. A comparative simulation of model protein and protein-ligand complex in presence and absence of compound **6a** has been carried out.



Abbreviations: Cys797 to Ser797 (C797S): Cysteine to Serine; T790M: Threonine 790 Methionine; EGFR: Epidermal Growth Factor Receptor; PDB: Protein Data Bank; ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity; MDS: Molecular Dynamic Simulations; Mol MW: Molecular Weight; NSCLC: Non-Small Cell Lung Cancer; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

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KEYWORDS
EGFR; allosteric; thiazolidine-4-one; ADMET; molecular docking; molecular dynamic simulations

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EFFECT OF HYDROPHILIC POLYMER ON DESIGN EXPERT ASSISTED ORO-DISPERSIBLE STRIP (ODS) OF ISOSORBIDE MONONITRATE

ABSTRACT

Oral conventional formulations like tablets, capsules and liquids have many limitations. Due to this and patient incompliance, there is a need to develop new formulations with better efficiency and stability. The aim of the present study was to develop and optimize fast dissolving Oro-dispersible strips (ODS) of isosorbide mononitrate by 3^2-full factorial design. HPMC E15 (X_1) concentration and glycerin (X_2) concentration were selected as the independent variables, whereas, *in vitro* disintegration time (Y_1), percent drug release (Y_2) and tensile strength (Y_3) were selected as dependent variables. Fast dissolving Oro-dispersible strips of isosorbide mononitrate were prepared by the solvent casting method.Tensile strength, disintegration time and *in vitro* dissolution of ODS of the strip were found to be within accepted range for optimized formulation. Statistical validity of the polynomials was established by ANOVA using Design-Expert software. The study suggests isosorbide mononitrate fast dissolving Oro-dispersible strip as potential alternative dosage form in management of angina pectoris.

Keywords:Oro-dispersible strips, Full factorial design, Solvent casting method, Isosorbide mononitrate

INTRODUCTION

The origin of Fast Dissolving Drug Delivery Systems (FDDDS) can be traced back to the late 1970's as a potential substitute for other oral dosage forms like tablets, capsules, syrups and other formulations. Their major benefit is for pediatric and geriatric patients suffering from dysphasia problems. The FDDDS possesses the advantages of conventional tablets and liquid formulation[1,2]. The ease of administration and better patient compliance makes FDDDS a formulation of choice for pediatric, geriatric and mentally challenged persons[3].

Delivery of the drug to the site of action successfully is the prime moto of any drug delivery system. The drug delivery system should be safe, effective, convenient and economical with highest patient compliance[4,5]. In FDDDS, the drug gets disintegrated, dissolved or swallowed and then reaches into the systemic circulation to show desired therapeutic effect[6,7].

Oro-dispersible strips (ODS) is one of the convenient novel drug delivery systems for the delivery of the drugs. It is based upon the technology of trans-dermal patch and consists of a very thin oral strip, to be placed on the patient's tongue or any oral mucosal tissue. This film then gets instantly wet by saliva and the strip rapidly hydrates and adheres onto the site of application[8].

Ease of administration, dosing accuracy, self-medication and patient compliance are the advantages offered by ODS over the other dosage forms[9]. For ODS administration, there is no need of water and can administered anytime, anywhere. These strips provide better disintegration and dissolution in the oral cavity due to its large surface area[10].

Isosorbide mononitrate is the long-acting metabolite of isosorbide dinitrate utilized as the vasodilator's specialist in the administration of angina pectoris by expanding the vessels. It brings down the circulatory strain and decreases the left ventricular pre-load and after-load, in this manner prompts a decrease of myocardial oxygen necessity. Usual dose of isosorbide mononitrate is 10-60 mg. The limit of absolute oral bioavailability of isosorbide mononitrate is about 90-95% and absorption is about 100%. Oral fast dissolving Oro-dispersible strips of isosorbidemononitrate will be convenient for geriatric patients and adults with swallowing difficulty[11].

The present research work involves the formulation and optimization of Oro-dispersible strips of isosorbide mononitrate by applying 3^2-factorial designs to understand the effect of formulation variables likes concentration of polymer (HPMC E15) and concentration of plasticizer (glycerin) on *in vitro* evaluation parameter.

METHODS

Isosorbide mononitrate was procured from Piramal Laboratories Ltd. Mumbai, India. HPMC E15 was obtained from Loba Chemie, Mumbai, India. Glycerin, citric acid and mannitol were procured from SD Fine Chem Ltd., Mumbai, India. All the materials used in this study were of analytical grade. Double distilled water was used throughout the study. The drug and all materials

Review Article

Phytochemicals: A Novel Approach for the Management of Coronavirus Disease 2019

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The severe acute respiratory syndrome coronavirus 2, formerly known as 2019 novel coronavirus, the causative pathogen of coronavirus disease 2019 is a major source of disaster in the 21st century. In the second meeting of the Emergency Committee, the World Health Organization declared that coronavirus disease 2019 is a "public-health emergency of international concern" on 30 January, 2020. Coronavirus is transmitted *via* airborne droplets from human to human or human to animal. Through membrane angiotensin-converting enzyme 2 exopeptidase receptor coronavirus enters in human cell. For the treatment of this sudden and lethal disease during coronavirus disease 2019, there are no specific anti-virus drugs or vaccines. Still, the development of these medicines will take months, even years. Currently there is need of supportive care and non-specific treatment to improve the symptoms of coronavirus disease 2019 infected patient. For this specific indication, rapid performance of herbal medicine or phytochemicals can contribute as an alternative measure. Phytochemicals are a powerful group of chemicals that are derived from plants origin hence causing fewer side effects because of less use of additives, preservatives or excipients. Hence, this review will focus on some phytochemicals which may control and prevent severe acute respiratory syndrome coronavirus 2. Further, the existing healing options, drugs accessible, ongoing trials and current diagnostics to treat severe acute respiratory syndrome coronavirus 2 have been discussed. We suggested phytochemicals extracted from herbal plants are potential novel therapeutic approaches, completely targeting severe acute respiratory syndrome coronavirus 2 and its pathways.

Key words: Severe acute respiratory syndrome coronavirus 2, phytochemicals, herbal medicine, coronavirus disease 2019

Coronaviruses (CoVs) classified to the subfamily Orthocoronavirinae in the family Coronaviridae and order Nidovirales. The subfamilies Orthocoronavirinae again contain four genera, namely Alphacoronavirus (α-CoV), Betacoronavirus (β-CoV), Gammacoronavirus (γ-CoV) and Deltacoronavirus (δ-CoV). From that, α and β-CoV genera are known to infect mammals, whilst δ and γ-CoVs are identified to infect birds. Coronavirus Disease 2019 (COVID-19) is not the first severe respiratory infection epidemic originated by the corona virus. In the past few decades, CoVs have caused three outbreak infections, namely, COVID-19, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)[1,2]. This article gives a bird's eye view about this new virus i.e. COVID-19 and phytochemicals which may be effective in the treatment of COVID-19 as given in fig. 1. In view of the fact that awareness about this new virus is speedily developing, readers are urged to modernize themselves repeatedly.

HISTORY

Novel Coronavirus (nCoV)-precipitated pneumonia, which was named by the World Health Organization (WHO) on the February 11, 2020 as COVID-19, has swiftly accelerated in epidemic scale since it first appeared during December 2019, inside Wuhan city, China. The international virus classification commission, on the same day, declared that the nCoV was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Right now, the

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Mutations in *MINAR2* encoding membrane integral NOTCH2-associated receptor 2 cause deafness in humans and mice

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Discovery of deafness genes and elucidating their functions have substantially contributed to our understanding of hearing physiology and its pathologies. Here we report on DNA variants in *MINAR2*, encoding membrane integral NOTCH2-associated receptor 2, in four families underlying autosomal recessive nonsyndromic deafness. Neurologic evaluation of affected individuals at ages ranging from 4 to 80 y old does not show additional abnormalities. *MINAR2* is a recently annotated gene with limited functional understanding. We detected three *MINAR2* variants, c.144G > A (p.Trp48*), c.412_419delCGGTTTTG (p.Arg138Valfs*10), and c.393G > T, in 13 individuals with congenital- or prelingual-onset severe-to-profound sensorineural hearing loss (HL). The c.393G > T variant is shown to disrupt a splice donor site. We show that *Minar2* is expressed in the mouse inner ear, with the protein localizing mainly in the hair cells, spiral ganglia, the spiral limbus, and the stria vascularis. Mice with loss of function of the Minar2 protein (*Minar2*$^{tm1b/tm1b}$) present with rapidly progressive sensorineural HL associated with a reduction in outer hair cell stereocilia in the shortest row and degeneration of hair cells at a later age. We conclude that MINAR2 is essential for hearing in humans and mice and its disruption leads to sensorineural HL. Progressive HL observed in mice and in some affected individuals and as well as relative preservation of hair cells provides an opportunity to interfere with HL using genetic therapies.

autosomal recessive | deafness | hearing loss | MINAR2 | NOTCH2

Hearing loss (HL) is one of the most common sensory deficits, affecting ~1 in 500 newborns (1). Genetic factors are implicated in the majority of cases, with more than 80% of the inherited form exhibiting autosomal recessive transmission (2). No additional findings are present in over 70% of the cases, which are then classified as nonsyndromic HL (Hereditary Hearing Loss Homepage, https://hereditaryhearingloss.org/) (2, 3). Genetic testing for etiologic evaluation has become a standard of care in people with congenital or childhood-onset sensorineural HL, which is caused by pathologies of the inner ear and auditory nerve (4, 5). Recent studies have shown that screening all recognized HL genes for variants reveals underlying cause in about half of the affected individuals, leaving a significant portion of people with HL with an unknown etiology (6–9). In the era of emerging genetic therapies for HL, finding the etiology of HL in affected individuals has become a critical task. This is especially relevant for progressive HL, as genetic therapies may potentially stop progression while cochlear hair cells are still alive (10–12).

MINAR2 (previously known as uncharacterized protein KIAA1024L and mouse gene *A730017C20Rik*) has recently been identified, and based on its structural similarity to MINAR1, named as major intrinsically disordered NOTCH2-associated receptor 2 or membrane integral NOTCH2-associated receptor 2 (13). A mutant mouse model of *Minar2* showed motor deficits similar to those seen in Parkinson disease, with no information about hearing abnormalities (13). A *Minar2* mutant mouse line, *Minar2*^{tm1b}, has also recently been reported to show no auditory brainstem responses at 14 wk old as part of a large HL screen (Mouse Genome Informatics [MGI]: 2442934) (11). Functional aspects of MINAR2 and consequences of its dysfunction in humans remain unknown.

In this study, to better map the landscape of hereditary HL, we sought DNA variants underlying deafness in 13 affected individuals from four families. We identified three different *MINAR2* variants in the families cosegregating with HL. We further showed that homozygous *Minar2*^{tm1b} mutant mice develop rapidly progressive HL associated with changes in outer hair cell stereocilia. Finally, via in vitro studies we demonstrated that *MINAR2* suppresses NOTCH2, suggesting that notch signaling might play a role in pathogenesis.

Significance

Molecular components of hearing in mammalians are not completely delineated. Via a genetic approach conducted in families with sensorineural hearing loss, this study presents MINAR2 as an indispensable element of hearing in humans. Similarly, disruption of Minar2 in mice leads to progressive hearing loss associated with alterations in the stereocilia of hair cells, the receptors of hearing, while hair cells remain intact until later in life. We present *MINAR2* as a gene working in the inner ear that is essential for hearing in humans and mice. Degeneration of sensory epithelium is a common consequence of hereditary deafness precluding genetic therapies. The preservation of hair cells in mutant mice at young ages makes MINAR2 a good candidate for intervention.

The authors declare no competing interest.

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ORIGINAL ARTICLE

Design, synthesis, and pharmacological evaluation of [1, 3] dioxolo-chromeno[2,3-*b*]pyridines as anti-seizure agents

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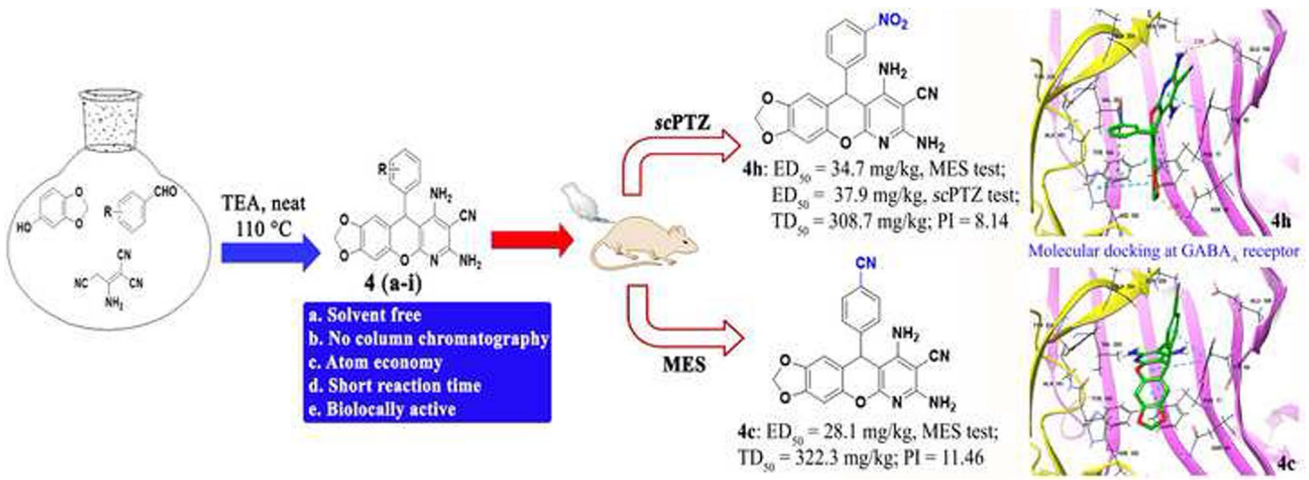
Abstract

An efficient one-pot three-component reaction for the synthesis of [1,3]dioxolo[4′,5′:6,7]chromeno[2,3-*b*]pyridines **4**(**a–i**) has been developed. Synthesis was achieved by reacting sesamol (**1**), aromatic aldehydes **2**(**a–i**), and 2-aminopropene-1,1,3-tricarbonitrile (**3**) in the presence of triethylamine at 100 °C under neat reaction condition. Simple operational procedure, broad substrate scope, column chromatography free separations, and high yield of products make it an efficient and largely acceptable synthetic strategy. Synthesized compounds **4**(**a–i**) were further screened for preliminary anticonvulsant activity using MES and *sc*PTZ tests. These analogs were also checked for neurotoxicity and hepatotoxicity. Selected active compounds have been then screened quantitatively to determine ED_{50} and TD_{50} values. Analog **4h** was found effective in both preclinical seizure models with significant therapeutic/toxicity profile (**4h**: ED_{50} = 34.7 mg/kg, MES test; ED_{50} = 37.9 mg/kg, *sc*PTZ test; TD_{50} = 308.7 mg/kg). Molecular dynamic simulation for 100 ns of compound **4h**-complexed with $GABA_A$ receptor revealed good thermodynamic behavior and fairly stable interactions (**4h**, **Docking score** = − 10.94). In conclusion, effective synthetic strategy, significant anticonvulsant activity with good toxicity profile and detailed molecular modeling studies led us to anticipate the emergence of these analogs as valid leads for the development of future effective neurotherapeutic agents.

Graphical abstract



Keywords Design · Synthesis · [1,3]Dioxolochromeno[2,3-*b*]pyridines · Anticonvulsants · Molecular docking

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Potential Herbal Anti-Cancer Drug Formulations Using Modern Drug Delivery Methods

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ABSTRACT

Objectives: The goal of the current effort is to create and assess chewing gum containing a potassium salt of curcumin extract for its ability to carry medication into the buccal cavity and fight cancer. It helps with the treatment of metabolic syndrome, arthritis, anxiety, and hyperlipidemia as well as oxidative and inflammatory diseases. Chewing gums containing curcumin were created to examine its anticancer properties.

Method: To increase the solubility of potassium Curcuminate, a solid dispersion of the compound was created utilising cyclodextrin. For the purpose of improving solubility, the obtained solid dispersion of potassium curcuminate was examined. Curcuminate Sucrose, castor oil, chewing gum base, potassium curcuminate, and other ingredients were then combined to create chewing gums. The prepared chewing gum was assessed for colour, flavour, hardness, and drug-excipient compatibility.

Results: The compatibility study's findings demonstrated that there was no interaction between the chosen medicine and excipients. When compared to curcumin and other common anticancer medications like 5-Fu, Mito-C, and Paclitaxel, potassium curcuminate has greater anticancer activity: 85% against prostate cancer cells, 80% against liver cancer cells, and 92% on average against colon cancer cells. In-vivo studies of the chewing gums were optimised based on in-vitro drug release.

Conclusion: According to the results of this study, chewing gum containing the potassium salt of the cancer-fighting compound curcumin can be deemed a good delivery mechanism.

Keywords: Chewing gums, Cancer, Anticancer, Tumor, Normal cells, Curcumin.

INTRODUCTION

The oral route is arguably the one that both patients and doctors favour among the other administration methods. Drugs administered orally, however, have drawbacks such hepatic first pass metabolism and gastrointestinal enzymatic degradation that make oral administration of some medication types inappropriate. [1] The outermost layer of the oral mucosa is made up of stratum distendum, stratum filamentosum, stratum suprabasale, and stratum basale, all of which are stratified squamous epithelium and are mucous-covered. Lamina propria and submucosa cover the area beneath the basal lamina. The lamina propria serves as a mechanical support and also carries the blood vessels and nerves, whilst the epithelium acts as a mechanical barrier to protect underlying tissues. The oral mucosa contains keratinized areas. [2] In general, the oral mucosa is an intermediate layer of leaky epithelia between the epidermis and the intestinal mucosa. The buccal mucosa's permeability is thought to be 4–4000 times greater than that of skin. Because of the various forms and functions of various oral mucosae, there are significant variances in permeability between different parts of the oral cavity, as seen by the wide range in this reported value. [3] In general, the oral mucosa is an intermediate layer of leaky epithelia between the epidermis and the intestinal mucosa. The buccal mucosa's permeability is thought to be 4–4000 times greater than that of skin. Because of the various forms and functions of various oral mucosae, there are significant variances in permeability between different parts of the oral cavity, as seen by the wide range in this reported value. [4] In general, buccal mucosae are more permeable than sublingual, and buccal mucosae are more permeable than palatal. [5] The sublingual mucosa is relatively thin and non-keratinized, the buccal mucosa is thicker and non-keratinized, and the palatal mucosa is intermediate in thickness but keratinized. These tissues are ranked according to their relative thickness and degree of keratinization. [6] The paracellular and transcellular routes are the two penetration routes for passive drug transport over the oral mucosa. These two routes can be used simultaneously by permeants, although depending on the physiochemical characteristics of the diffusant, one is typically chosen over the other. Since the cytoplasm and intercellular gaps

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Research Article
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A Study on Medicinal Plants and Its Hepatoprotective Activity

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9.

Abstract

We, the human being possess a huge wealth of medicinal plants which have been explored and validated for their therapeutic properties. Still there are so many plants whose medicinal properties are not yet published and lots of research works are needed to be carried out on such medicinal plants.Herbal drugs play a vital role in the management of various liver disorder, most of them speed up the natural healing process of liver. Numerous medicinal plants and their formulations are used in liver disorders in ethno medicinal practices as well as traditional system of medicine in India. Various types of treatment modalities are available to treat liver diseases. In allopathic medical practices, herbs play role in the management of various liver disorders. Since however, we do not have satisfactory remedy for disorders of liver, the search for finding out effective hepatoprotective drugs continues.

Keyword:-Herbal, Medicinal plant, Hepatoprotective, liver, modern drugs, herbal medicine.

Introduction

In recent times natural products are becoming an integral part of human health care system, because there is a now popular concern over toxicity and side effects of modern drugs. There is also a

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Research paper

Design, synthesis, and biological evaluation of novel quinoline derivatives as small molecule mutant EGFR inhibitors targeting resistance in NSCLC: *In vitro* screening and ADME predictions

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ADME study
Molecular dynamics simulations

ABSTRACT

Here in, we report the design, synthesis and *in vitro* anticancer activity of a novel series of 24 quinoline analogues of substituted amide and sulphonamide derivatives. The anticancer activity of the synthesised compounds was evaluated against the HCC827, H1975 (L858R/T790 M), A549 (WT EGFR), A-549 and BEAS-2B cell lines. The majority of quinoline compounds demonstrated a significant cytotoxic effect. Compound **21** was found to be the most potent, with IC_{50} values of 0.010 μM, 0.21 μM, 0.99 μM and 2.99 μM as compared to Osimertinib with IC_{50} values with of 0.0042 μM, 0.04 μM, 0.92 μM and 2.67 μM. Compound **21** exhibited promising inhibitory enzymatic activity against the EGFR L858R/T790 M with IC_{50} value of 138 nM, comparable to Osimertinib's 110 nM. Employing a Western blot assay on the phosphorylation of EGFR and the signalling pathways transmission in HCC827 cells, the anticancer activity of the synthesised compounds **18** and **21** was evaluated in terms of its mechanism of action. All the compounds were subjected to a comparative molecular docking study against various EGFR enzyme types, including the wild-type (PDB: 4I23) and T790 M mutant (PDB: 2JIV) enzymes. Furthermore, compounds were examined at the allosteric binding site of the EGFR enzyme with the L858R/T790 M/C797S mutation (PDB ID: 5D41). The MD simulation study was also performed for EGFR-compound **21** complex which indicates the stability compound **21** in both ATP and allosteric site of enzyme. Further, in silico ADME prediction studies of all derivatives were found promising, signifying the drug like properties.

1. Introduction

Non-small-cell lung cancer, often known as NSCLC, is the most lethal form of the disease and the main cause of cancer-related mortality on a global scale. It is estimated that 12.9% of all newly diagnosed cases of cancer are lung cancer, making it the most prevalent form of the disease and the leading cause of cancer-related deaths. Approximately 85% of lung cancers are NSCLC [1,2] and life-threatening malignancy worldwide, accounting for around one-third of all cancer-related deaths each year. It has been stated that the median age at which lung cancer is diagnosed is between 63 and 70 years, and that NSCLC accounts for 85% of lung cancer cases in individuals over the age of 65. Although the progression of NSCLC is slower than that of small cell lung cancer, the disease has frequently metastasized by the time it is detected in other parts of the body. Therefore, identification and therapy at an early stage are crucial [3]. Consequently, people with early-stage disease have surgery or radiation, and patients with more advanced disease are frequently treated initially with systemic chemotherapy, immunotherapy, or targeted therapy. The standard treatment consists of cytotoxic chemotherapy, which is nonspecific and nonselective, and it only produces a moderate improvement in the patient's chances of survival while causing severe harm to the patient. At first, targeted medications are only successful in treating a specific, limited subset of patients. However, over time, most patients develop resistance to additional

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Original Article

Formulation Development and Evaluation of Herbal Nanoparticles containing Ointment of Leaves extract of *Rhynchosia rothii*

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Abstract

In our previous work we have reported wound healing activity of leaves extract of *Rhynchosia rothii* in which we got excellent activity. Therefore in present study, the development of *Rhynchosia rothii* loaded Lycoat RS 720-BSA conjugated polymeric nanoparticles and subsequent ointment formulation has been aimed. Maillard Reaction was used to develop the Lycoat RS 720-BSA conjugate. The solvent evaporation approach was used to produce nanoparticles with *Rhynchosia rothii* loaded on them. The nanoparticles had a 257nm particle size and exhibited a spherical shape. The zeta potential in the formulation was -22.4 mV. Entrapment efficiency was 88.32% in the enhanced batch. The extracted content of the optimized batch was found to be 78.10%. A continuous release pattern was found by the *in-vitro* diffusion investigation, with 94.24% diffusion after 24 hours. The *Rhynchosia rothii* extract was created as an absorbent ointment formulation with a pH of 6.80–6.92 and a spread ability of 80.00–110.16 g.cm/s. It also has a distinctive aroma. Ointment containing herbal nanoparticles from the F4 batch has produced positive results. A new method of promoting nanoparticles in herbal medication delivery systems is by employing them in nanoparticles and an ointment. From present investigations we concluded that prepared ointment can be used clinically for the treatment of wounds if optimized further using more in vitro and in vivo models along with toxicity predictions.

Keywords: Herbal Nanoparticles, Lycoat RS-720, Solvent evaporation, Ointment, BSA

INTRODUCTION

For the treatment of skin conditions, a variety of topical dermatologic treatments, spanning from solids to liquids, are offered [1, 2]. The majority of ointments are made up of a base that primarily serves as a vehicle or carrier for the medications. The type of base also affects how well it works; therefore choosing an ointment base is a crucial step in formulation [3]. In contrast to fatty alcohols, traditional ointment bases have been oleaginous in nature, consisting of hydrocarbons like petrolatum, beeswax, and vegetable oils that do not permit the addition of any water. Topically applied ointments can serve a variety of functions, including protective, antimicrobial, emollient, antipruritic, keratolytic, and astringent. If the end product is to fulfill any of the aforementioned functions, the base of the ointment is crucial. The ointment base composition regulates the transfer of medications from the base to the human tissues as well as the depth of penetration [3, 4].

Particulate dispersions or solid particles with a size between 10 and 1000 nm are referred to as nanoparticles [5]. Their small size, variable composition, surface functionalization, and stability, which provide unique opportunities to interact with and target the tumor microenvironment, make them particularly alluring for the therapy of cancer [6, 7]. Polymeric nanoparticles are nanoparticles made of biocompatible and biodegradable polymers, either natural or manmade. Due to their small particle size and prolonged blood circulation, they have received specific attention during inspections for medication delivery and drug targeting [8].

The protein that is most abundant in plasma is BSA. It demonstrates significant buildup in the body's inflammatory and malignant regions [9]. It has a lengthy 19-day blood circulation half-life and several binding sites [10]. A serum albumin protein generated from cows is called bovine serum albumin. It is widely used as a benchmark for protein concentration. Lycoat RS 720 is a pea starch-based synthetic polymer. It exhibits strong film-forming and solution stability. It is the polymer with a regulated and sustained release [11, 12].

There are many species of *Rhynchosia* (Fabaceae) that are found in tropical and subtropical regions of the world. As an antibacterial, antidiabetic, abortive, healing, hepatoprotective, healer of boils, rheumatoid arthritis pain, and skin infection treatment, some plants from this genus have been utilized in traditional medicine [13]. So far, the genus *Rhynchosia* has yielded a total of 77 identified compounds, including as flavonoids, isoflavonoids, flavan-3-oils, xanthones, biphenyls, simple polyphenols, and sterols. Interestingly, prenylated C-glycosylflavonoids and isoflavonoids are abundant in the genus *Rhynchosia rothii* [13, 14].

RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF PHARMACEUTICAL TABLET DOSAGE FORM CONTAINING AMBRISENTAN

ABSTRACT

The objective of the current study was to develop a simple, precise and accurate RP-HPLC assay method and its validation for determination of ambrisentan in pharmaceutical tablet dosage form. Gradient RP-HPLC separation was achieved on an analytical Primsil C18 R column (250 mm × 4.6 mm; 5 µm particle size) using mobile phase containing mixture of acetonitrile: water (65:35 V/V). The developed method was validated for specificity, linearity, precision, accuracy and robustness study. The method was linear in the drug concentration range of 10-50 µg mL^{-1} with a correlation coefficient 0.998. The percent RSD values were found to be less than 2 %, indicating the developed method was also robust. The method was completely validated and shows satisfactory result for the all method parameter. Hence it is concluded that the proposed method is precise, simple, sensitive, accurate, rugged and rapid and can be applied successfully for the estimation of ambrisentan in pharmaceutical dosage form.

Keywords: Ambrisentan, chromatographic analysis, RP-HPLC, method validation, system suitability

INTRODUCTION

Ambrisentan, chemically (2*S*)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid, is a pulmonary antihypertensive agent. Ambrisentan is one of several newly developed vasodilator drugs that selectively target the endothelin type A (ETA) receptor, inhibiting its action and preventing vasoconstriction[1-3]. High performance liquid chromatography (HPLC) is the most versatile and widely used analytical technique. It utilizes a liquid mobile phase to separate the components of a mixture[4]. These components (or analytes) are first dissolved in a solvent, and then forced to flow through a chromatographic column under high pressure. In the column, the mixture is resolved into its components. The interaction of solute with mobile and stationary phases can be manipulated through different choices of both solvent and stationary phases[5]. As a result, HPLC acquires a high degree of versatility not found in other chromatographic systems and it has the ability to separate a wide variety of chemical mixtures[6]. Validation parameters to be studied before finalization of the method include specificity, linearity, range, accuracy, precision, limit of detection, limit of quantitation, ruggedness and robustness[7]. To the best of our knowledge, the assay of ambrisentan (AMB) is not official in pharmacopoeias of IP, USP and BP. The detailed survey of literature revealed that very few methods have been reported for the estimation of AMB alone. Hence the aim of present study was to develop, validate and stabilize RP-HPLC method for ambrisentan in pharmaceutical dosage form'.

MATERIALS AND METHODS

Chemicals and reagent

The standard ambrisentan, marketed preparation and other required chemicals used for the present investigation were procured from Cipla Pharmaceuticals Ltd., Mumbai (India). The entire chemicals used were of HPLC grade.

Instruments

RP-HPLC method development and validation was done on Younglin (S.K.) Gradient system UV Detector HPLC instrument UV- detector and column Primisil C18, 250×4.6 mm, 5 µm particle size. The instruments used were UV- spectrophotometer (Waters), ultra sonic cleaning bath (Spectralab model USB), pH analyser (Labindia), weighing balance (Shimadzu), Fuming chamber (Labexel), hot air oven (Thermo Lab 905) and magnetic stirrer (Whilmatic).

Trials for selection of chromatographic conditions

Seven trials for selection of chromatographic condition were carried out using C18 (250×4.6 mm, 5µm) column with different mobile phases, methanol-water and acetonitrile-water with different ratios. The pH of the mobile phase was adjusted to 3.2 ± 0.05 with ortho phosphoric acid and solution was filtered through nylon filter (0.45 µm), and flow rate was adjust at 0.7 mL min^{-1}, and injection volume was 20 µm[8-11].

Original Article

TO ENHANCE THE SOLUBILITY OF IVERMECTIN WITH PHYSICAL MIXING METHOD FOR THE PREPARATION OF ORODISPERSIBLE TABLETS

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Abstract

This study was aimed to enhance solubility of ivermectin and developed the orodispersable tablet (ODT) in solid unit dosage forms which administer orally it is dissolve and disintegrate instantly within few seconds. Fast disintegrating tablet is useful for paediatric, geriatric, it improve the patient compliance. In this article the ivermectin fast disintegrating tablet were prepared by using superdisintegrant ingredient like cross carmellose sodium. The solubility of ivermectin was enhanced by using solid dispersion techniques in these technique PEG 600 are used it increased the solubility of FDT. Total 06 formulation prepared and evaluated. And the formulation F2 was shown best result as per ICH guideline. Optimized formulation F2 contained cross carmallose sodium and show better result in disintegration time 16 sec and maximum in vitro drug release of FDT is 98 %.

Keywords: Ivermectin, Crosscarmellose sodium, Sodium starch glycolate. ODT.

INTRODUCTION

Drug delivery system is tool for in market external product life. The oral route is mostly preferred route of administration of therapeutic drug because it has low cost have accurate dosing self-medication and easy to administer and high patient compliance. The most popular dose is conventional tablet.

The oral route of administration is used for mostly conventional drugs like tablets, capsules & solution. Mostof the things of oral route of administration consist of the desire characteristics like easy to administration flexibility of dosage form, fast disintegration and also convenience. FDT have most advantages like easy manufacturing, accurate dosing, good stability, and also ideal alternative for both geriatric and paediatric patients. Fast disintegrating tablet absorbed fastly orally disintegrating tablet is developed by combined hardness, dosage uniformity, stability, and other parameters.

Ivermectin (IVM) is new wide spectrum, efficient, less toxic antibioticses antiparasitic agent, to internal ectoparasite Be respectively provided with it is good kill effect, it is preferable especially for the repelling and killing efficacy of nematode and arthropod.

The mostly found drawback of these dosage form is difficulty in swelling for many patient above 50% peoples are affect by this difficulty but in recent trademark the fast disintegration drug delivery started to gain popularity and it is also acceptable a new drug delivery system because of easy administration and it is also show better patient compliance according to the centre of drug evaluation and research USFDA define FDT it is a solid dosage form which contains medicinal substance which

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REVIEW ARTICLE

Stereolithography 3D printing technology in pharmaceuticals: a review

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ABSTRACT

Three-dimensional printing (3DP) technology is an innovative tool used in manufacturing medical devices, producing alloys, replacing biological tissues, producing customized dosage forms and so on. Stereolithography (SLA), a 3D printing technique, is very rapid and highly accurate and produces finished products of uniform quality. 3D formulations have been optimized with a perfect tool of artificial intelligence learning techniques. Complex designs/shapes can be fabricated through SLA using the photopolymerization principle. Different 3DP technologies are introduced and the most promising of these, SLA, and its commercial applications, are focused on. The high speed and effectiveness of SLA are highlighted. The working principle of SLA, the materials used and applications of the technique in a wide range of different sectors are highlighted in this review. An innovative idea of 3D printing customized pharmaceutical dosage forms is also presented. SLA compromises several advantages over other methods, such as cost effectiveness, controlled integrity of materials and greater speed. The development of SLA has allowed the development of printed pharmaceutical devices. Considering the present trends, it is expected that SLA will be used along with conventional methods of manufacturing of 3D model. This 3D printing technology may be utilized as a novel tool for delivering drugs on demand. This review will be useful for researchers working on 3D printing technologies.

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Additive manufacturing; customized dosage form; photocurable resins; solid freeform fabrication; three-dimensional printing; vat polymerization

Introduction

Three-dimensional printing (3DP) technology has opened new frontiers in pharmaceutical and other sectors. Simple tools and poor-standard object of some materials cannot yield high-quality products from any bulk substances. This is the limitation of typical or common methods of manufacture [1,2]. In contrast, the 3DP technique is sophisticated, rapid, highly automated, easy to use, customized and cost effective [3–6]. The 3DP technology is used to make 3D objects by laying layers on top of each other. Biological materials, alloys, tissues/cells, metals, wood, thermoplastics, etc. are used in making 3D objects [7,8]. Anatomical prostheses, biological tissues, heart valves, hearing aids and different parts or models of machinery are among the well known examples of 3D objects [9–13]. Innovative scanning and printing systems hold promise in the area of medicine [14]. Over the last three decades, pharmaceutical companies have been looking at 3DP technology to understand the roles it will play and how best to use it. Against a background in which new formulations, biomedical devices and medicines were being developed daily, Professor Clive Roberts, from the University of Nottingham, said that many researchers have designed and prepared many different dosage forms using 3DP techniques [15]. As with most complex 3D architectures, medical devices were printed directly using 3DP technology in the early 2000s [16,17]. Devices specific to a patient's anatomy were also fabricated. Optimized tools and techniques are a prerequisite for making formulations of the desired shapes and sizes. In August 2015, Aprecia Pharmaceuticals printed the first 3D drug that was approved by the FDA. This was Spritam (Levetiracetam) [18,19], a porous structure printed layer by layer and reformulated to treat dysphagia. When it comes in contact with saliva, it dissolves rapidly and delivers a high dose (1 g) of an antiepileptic drug from a tightly packed pill [20]. The non-uniform quality of some finished products is mainly caused by manufacturing processes such as milling, mixing, granulation and compression. Certain tools related to drug release, drug content and product stability are affected by these operations [21,22]. 3DP is proving to be the solution in overcoming such challenges [23].

Now a day's we can serve better with readdressing of artificial intelligence (AI). In the various filed, AI igniting with notice development [24,25]. Minimum time and cost is the new perspectives of AI in optimization of 3D products that, creating interest in the researchers for launching the products in market [26]. Design of experiments is also mostly used in optimization, but computer aided artificial neural network(ANN) have more attention and delight [27]. Extended drug release ibuprofen tablet fabricated with crosslinked polymers printed with artificial neural network [28]. A perfect tool of AI learning techniques develops pharmaceutical formulations in 3DP. Web bases software M3DISEEN [29] and accurate optimal parameters are the best example of AI [30]. 3D printed tablets of atomoxetine fabricated by ANN release the tailored drug release from immediate to prolong [31].A solid three-dimensional object of any shape can be prepared starting from a digital model through an automated sequential layering process [32]. It means this technique shares the theme of a sequential layer of material addition of 3D envelope [33,34]. 3DP allows more complex designs or shapes to be fabricated compared with conventional manufacturing processes [35]. Objects can be fabricated using 3DP methods through digital files [36–38].

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Original Article

A Novel Hemizygous Variant in the *AFF2* Gene Causing Fragile XE (FRAXE) Syndrome: First Report from Pakistan

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Abstract

Background: Fragile XE (FRAXE) is an X-linked recessive condition that affects 1 in 50,000 of new born males with intellectual disability (ID). It is characterized by mild Intellectual disability (ID), speech delay cognitive impairment, and in some cases with phenotypes of Autism Spectrum disorder (ASD).
Methodology: In this study, a family was investigated with two male siblings having neuro developmental delay. Whole exome sequencing analysis (WES) was carried out to identify the pathogenic variant. Sanger sequencing was performed in normal and affected family members and co-segregation analysis was done.
Results: Two probands were affected in a family diagnosed with intellectual disability. A novel hemizygous variant (c.3348G>T, p.Asp1150Tyr) in *AFF2* gene was identified as the causal variant cause in affected individuals. This variant was novel from Pakistani population.
Conclusion: In this study, a novel hemizygous variant (c.3348G>T, p.Asp1150Tyr) identified in *AFF2*. These findings paved the way for further studies on genetic and clinical spectrum of rare X-linked recessive disease involved in ID.
Key words: *AFF2*, hemizygous, intellectual disability, neurological disorders.

Introduction

Cognition is the result of cellular, biological and multiple molecular events in the nervous system. Minor defect in any of these events can results in intellectual disability or cognitive impairment.[1,2] It can also be termed as neuro-development disorder as it results from defect in synapse formation.[3,4]

Overall, in general population, the prevalence of intellectual disability (ID) is 2-3%.[5,6] Its clinical and genetic heterogeneity make the diagnosis challenging for scientists and physicians.[7,8] More than 900 genes are reported to cause intellectual disability so far.[9,10].

The X-linked intellectual disability is a heterogeneous group of genetic disorders. There are more than 141 genes linked with disease located on x-chromosome.[11] Its prevalence is high in males as x-chromosome genes contribute to cognition. Among x-linked intellectual disability, Fragile X syndrome (FXS) is common and characterized by moderate to severe disability (OMIM - 309548).[12] There is high repeat expansion of a CGG in *FMR1* gene which cause methylation, that ultimately halts the production of *FMR1* protein leads to (FXS) syndrome.[13]

The *AFF2* gene (also as *FMR2* gene) cause non-specific x-lined intellectual disability with prevalence as 1/25,000 to 100,000 in new born male. Micro deletion in *AFF2* genes leads to Fragile XE (FRAXE) syndrome [14]. It is characterized by mild to moderate intellectual disability.[15]

In FRAXE syndrome, learning, thinking ability and cognitive function, affected badly. Also there is delay in speech; hyperactivity, poor writing skills, and very short attention span are common symptoms of people affected with this syndrome. It

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Authors Contribution

IA, GVH & AM conceptualized the project and drafting, revision & writing of manuscript. IA & MI did the literature search and data collection. IA, MI & AM performed the statistical analysis.

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Lymphatic transport system to circumvent hepatic metabolism for oral delivery of lipid-based nanocarriers

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ABSTRACT

The oral route of administration for lipid-based nanocarriers is of immense importance for the drugs having low bioavailability because of extensive first-pass metabolism. These drug delivery systems have reportedly improved oral bioavailability via lymphatic transport. The solubility issues of a drug are addressed by directly encapsulating them into the lipid. Subsequently, various lipid-based nanocarriers have enhanced the therapeutic activity of drugs via lymphatic transport with negligible side effects. Animal studies have depicted significant improvement in the oral bioavailability of drugs by avoiding first-pass metabolism. A detailed clinical study for large animals is needed to investigate the safety and efficacy of various lipid-based nanocarriers. In this review, we have described the potential and pertinence of the oral route of administration for lipid-based nanocarriers. The importance of lymphatic transport systems as a liver bypass transport system is also described herein. Various carriers such as liposomes, nanostructured lipid carriers, lipid-drug conjugate, etc. are discussed in brief with recent examples. The transport of lipids and absorption of drugs across the lymphatic pathway and various factors associated with nanocarriers affecting the lymph node targeting are also highlighted. Various *in vivo* and *in vitro* research models along with a brief focus on *in silico* prediction of the lymphatic transfer are described. The insights on future perspectives with an emphasis on the translational barriers may help the researchers working in this area.

1. Introduction

Lymph biology is being explored as an alternative to blood biology regarding the orally administered drug delivery systems. Presently, the lymphatic system is studied vigorously with greater consideration for drug delivery. The lymphatic system is considered as the drain of the vasculature, submissively filtering fluid and proteins from the interstitial spaces along with lipid from the intestine into the blood [1]. The structure and function of lymphatics differ for various organs. Lymphatics in intestines carry out the transport of lipid-soluble vitamins, fats, and maintain an aqueous balance [2]. The oral route of administration is the most commonly used as compared to various other routes such as intravenous, subcutaneous, pulmonary, transdermal, nasal, etc. Certainly, there are numerous advantages of using oral formulations such as easy administration, convenience, patient compliance, cost-effectiveness, etc. But it also has a major unavoidable disadvantage i.e., low bioavailability due to gastric sensitivity, reduced intestinal absorption, and hepatic first-pass metabolism. The molecular size and solubility of a drug are critical parameters that decide the route of administration. Upon oral administration, the drug is absorbed in the

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Use of combined nanocarrier system based on chitosan nanoparticles and phospholipids complex for improved delivery of ferulic acid

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ABSTRACT

A novel nanocarrier system of phospholipids complex loaded chitosan nanoparticles (FAPLC CNPs) was developed to improve the oral bioavailability and antioxidant potential of FA. FAPLC CNPs were optimized using a Box-Behnken Design (BBD). FAPLC CNPs were characterized using differential scanning calorimetry, Fourier transforms infrared spectroscopy, powder x-ray diffractometry, proton nuclear magnetic resonance, solubility, in vitro dissolution, ex vivo permeation, and in vivo antioxidant activity in carbon tetrachloride (CCl_4)-induced albino rat model. The characterization studies indicated a formation of the complex as well as FAPLC CNPs. The FAPLC CNPs exhibited a lower particle size ~123.27 nm, PDI value ~0.31, and positive zeta potential ~32 mV respectively. Functional characterization studies revealed a significant improvement in the aqueous solubility, dissolution, and permeation rate of FAPLC and FAPLC CNPs compared to FA and FA CNPs. The FAPLC CNPs showed significant enhancement of in vivo antioxidant activity of FA by restoring the elevated marker enzymes in the CCl_4-intoxicated rat model compared to FA CNPs. Moreover, the pharmacokinetic analysis demonstrated a significant enhancement of oral bioavailability of FA from FAPLC CNPs compared to FA CNPs. These findings show that FAPLC CNPs could be used as an effective nanocarrier for improving the oral delivery of FA.

1. Introduction

Ferulic acid (FA) (IUPAC name: [E]-3-[4-hydroxy-3-methoxy-phenyl] prop-2-enoic acid), a phenolic acid derivative, found in wheat, rice, barley, citrus, and some beverages such as coffee and beer. It is a potent free radical scavenger [1,2]. FA produces several biological activities such as antioxidant [3], neurodegenerative disorder [4], antidiabetic [5], anticancer [6], and pulmonary protective effect [7], etc. The antioxidant activity of FA attributes to the presence of unsaturated side chain, phenolic nucleus, hydroxyl and methoxy group attached to the phenyl ring, which ultimately provides stabilization to the structure via resonance [8]. Moreover, FA has low toxicity and therefore, it has been widely used in the pharmaceutical and food industry [9]. Despite these potential medical applications, FA exhibits low bioavailability, rapid metabolism, and elimination via oral administration [10]. Additionally, being a BCS class II drug (low solubility and high permeability), FA shows a poor absorption profile from the gastrointestinal tract via conventional delivery systems. Therefore, we need to develop novel and smart nanocarriers which can improve the biopharmaceutical properties of FA.

Literature analysis demonstrated that only some nanoformulations have been attempted by the authors for enhancing the biopharmaceutical properties of FA. These include nanostructured lipid carrier (NLCs) [11], conjugates [12], phospholipids complex [13], hydrogel [14], and PLGA nanoparticles [15]. Analysis of these work demonstrated only partial improvement in the dissolution rate of FA, whereas, optimization, solubility, permeability, oral bioavailability, and antioxidant activity evaluation were found to have lacked. Likewise, the findings of phospholipids complex work have shown the limited improvement of FA solubility ~ (3-fold only) without analysis of dissolution rate, permeability, oral bioavailability, and antioxidant status of FA [13]. Moreover, the obtained low solubility of FA in employed soy lecithin based phospholipids can form strong aggregates and agglomeration product, which could exhibit low dissolution of FA form this phospholipids complex. The existed drawbacks of these single nanocarriers were overcome in the present research work by the formation of novel nanocarriers using a combination of phospholipids complex and chitosan nanoparticles through solvent evaporation and ionic gelation technology, which can accomplish the benefits of each carrier and circumvent their limitations.

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Research Article

Egg White Protein Carrier-Assisted Development of Solid Dispersion for Improved Aqueous Solubility and Permeability of Poorly Water Soluble Hydrochlorothiazide

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Abstract. Hydrochlorothiazide (HTZ) is a first-line drug used in the treatment of hypertension suffered from low oral bioavailability due to poor aqueous solubility and permeability. Hence, lyophilized egg white protein-based solid dispersion (HTZ-EWP SD) was developed to explore its feasibility as a solid dispersion carrier for enhanced aqueous solubility and permeability of HTZ. The HTZ-EWP SD was prepared using the kneading method. HTZ-EWP SD was characterized using scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Fourier transforms infrared spectroscopy (FT-IR), powder X-ray diffractometer (PXRD), solubility, *in vitro* dissolution, and *ex vivo* permeation studies. The physico-chemical evaluation suggested the formation of the solid dispersion. Optimized HTZ-EWP SD4 drastically enhanced (~32-fold) aqueous solubility (~16.12 ± 0.08 mg/mL) over to pure HTZ (~ 0.51 ± 0.03 mg/mL). The dissolution study in phosphate buffer media (pH 6.8) revealed that HTZ-EWP SD4 significantly enhanced the release rate of HTZ (~ 87 %) over to HTZ (~ 25 %). The permeation rate of HTZ from optimized HTZ-EWP SD4 was enhanced significantly (~ 84 %) compared to pure HTZ (~ 24 %). Optimized HTZ-EWP-SD4 enhanced the rate of HTZ dissolution (~ 86 %) in FeSSIF (fed state simulated intestinal fluid), compared to a low dissolution rate (~ 72 %) in FaSSIF (fasted state simulated intestinal fluid) state after 2-h study. Obtained results conclude that lyophilized egg white protein can be utilized as an alternative solid dispersion carrier for enhancing the solubility and permeability of HTZ.

KEY WORDS: complexation; dissolution; egg white protein; permeability; solubility.

INTRODUCTION

Hydrochlorothiazide (HTZ, Fig. 1) (IUPAC Name: [6-chloro-1, 1-dioxo-3, 4-dihydro-2H-1, 2, 4–benzothiadiazine-7-sulphonamide], a thiazide diuretic, is employed as first-line therapy in the management of hypertension alone and blend with other cardiovascular drugs (1). HTZ produces the antihypertensive action by reducing the reabsorption of Na^+ and Cl^- ion in the distal tubule with Na-Cl co-transporter, which increases the excretion of Na^+, K^+, H^+, and water (2). Despite the health benefit of HTZ, its medical application is confined by low aqueous solubility (~ 0.72 mg/mL), slow dissolution rate, low membrane permeability (logP = - 0.15) (3), rapid metabolism to hydrolysis product of HTZ, and shorter half-life (~ 6 h) (4, 5). Moreover, the Biopharmaceutical Classification System (BCS) is categorized BCS class IV drug, i.e., low solubility and low permeability (6). Following oral administration, HTZ demonstrates low and variable oral bioavailability in the range of (~ 60 – 80%) (7). Therefore, HTZ, a potential drug candidate, was selected as a model drug to improve its low aqueous solubility and permeability.

Literature analysis revealed that several formulations have been developed and explored for enhancing the solubility and permeability of HTZ. These include pellets (8, 9), β-cyclodextrin complex (10, 11), micelles (12), nanoparticles (3), solid dispersion (13), nanoemulsion (14), self-nano emulsified drug delivery system (SNEDDS) (1), and microsphere (2). The outcome of these studies has shown that none of the authors has investigated the solubility and permeability of HTZ, however, in its place; they investigated the pharmacological activity of HTZ. Hence, there is an alternative formulation strategy is required to overcome the solubility and permeability of HTZ.

Among the reported formulations, the solid dispersion approach has been considered as a preferable approach for

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Hypotension: A comprehensive review

Rasika Dnyandeo Bhalke, Mahendra Ashok Giri, Rasal Yash Anil, Narhe Mansi Balasaheb, Parjane Abhishek Nanasaheb and Vishal Vijay Pande

Abstract
Hypotension is a decrease in systemic blood pressure below accepted low values. While there is not an accepted standard hypotensive value, pressures less than 90/60 are recognized as hypotensive. Hypotension is a relatively benign condition that is under-recognized mainly because it is typically asymptomatic. It only becomes a concern once pumping pressure is not sufficient to perfuse key organs with oxygenated blood. This leads to symptoms impacting the quality of life of a patient. Hypotension is classified based on the biometric parameters of the blood pressure measurement. It may be absolute with changes in systolic blood pressure to less than 90 mm Hg or mean arterial pressure of less than 65 mm Hg. It may be relative to a decrease in diastolic blood pressure to less than 40 mm Hg. It may be orthostatic with a decrease in systolic pressure or 20 mm Hg or greater or a decrease in diastolic pressure of 10 mm Hg or greater on positional change from lying to standing. It may be profound which is defined as being medication-dependent. In acute conditions, the hypotensive shock is a possible and life-threatening condition.

Keywords: Genetic combining ability, specific combining ability, okra, variance, growth, yield and quality

Introduction
Low blood pressure is known as Hypotension. It is the blood pressure low enough that flow of blood to the organ of the body is inadequate. Normal blood pressure is 120/80mm of Hg whereas hypotension blood pressure is 90/60mm of Hg.

Types of hypotension
1. Chronic Asymptomatic hypotension.
2. Orthostatic hypotension.
3. Neurally Mediated hypotension.

Chronic Asymptomatic Hypotension
It has no signs or symptoms & needs no treatment.

Orthostatic Hypotension (OH)
It occurs when standing up from a sitting down position.It can give a dizzy feel. Orthostatic hypotension occurs if your body isn't able to adjust blood pressure and blood flow fast enough for the change in position. This type of low blood pressure usually lasts for only a few seconds or minutes after immediate standing. After sitting or lying down for a short time brings blood pressure to normal. It may occur in all age groups.

Orthostatic Hypotension causes
Two types of causes

I. Non neurogenic causes
It is caused by cardiac impairment, hypovolemia, venous pooling. It is of the following two types.

a. Acute non neurogenic
In this type hypotension is frequently caused by decrease in intravascular blood flow. It is accompanied by myocardial infarction.

b. Chronic non neurogenic causes
It is associated with disorders causing cardiac impairment, anemia, diabetic insipidus.

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Tailoring hybrid organic-inorganic film-forming topical gel: a tuneable approach for tramadol HCl delivery

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ABSTRACT

Drug release properties for transdermal route can be better modified as per requirement which is mostly dependent upon the carrier system. In case of organic film-forming systems, the physical properties may not be achieved for successful delivery of drug through transdermal route. A novel organic-inorganic hybrid film-forming gel may fulfil these expectations to many extend. The present study focuses on the development of the organic-inorganic hybrid film-forming gel. A smooth, transparent, clear film-forming gel of tramadol was prepared for application on the intact skin with better comfort and modified drug release rate properties. The key properties of the adhesive films produced from the hybrid gels were investigated and the results showed that the incorporation of appropriate PVA: TEOS: Glycerine: HCl in the ratio of 46:12.5:25.5:6 respectively. Resultant hybrid film-forming gel has modified the physical properties and improved drug release properties. Furthermore, the investigations of skin irritation suggested no irritation to skin after topical application. This study has provided an alternative to the presently available organic gel and films for transdermal delivery of drugs with better patient compliance and modified physical and chemical stability.

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TEOS; PVA; hybrid-organic-inorganic film-forming gel; tramadol HCl; transdermal route etc

Introduction

Many of the drug delivery systems have been developed till date by many researchers with different characteristics. Efficient drug delivery systems can be developed further by doing modifications in the available drug delivery systems. These modifications can be possible using variety of compatible polymeric components. These modifications may include grafting of polymers, cross-linking of polymers and many more other approaches using various techniques.

Hybrid systems are made-up of composites of two different materials with different physical and or chemical properties. Hybrid film-forming gels refers to the combination of organic and inorganic components in one system either at macroscopic level or molecular level [1].

Single hybrid system is a homogenous phase of both organic and inorganic materials and shows characteristics that are different at their individual level. These resultant characteristics may be beneficial based upon the appropriate contributions of both the materials combined together using suitable methodology and techniques. Mechanical properties of hybrid systems are so improved so that patient acceptance will enhance with excellent drug release properties and stability of the final formulation. Mostly inorganic phase provides mechanical strength while organic phase delivers bonding. The word hybrid comes from the Latin word 'hybrida', which is related to the meaning 'mongrel'. The easy way to construct transparent and homogeneous hybrid materials is to increase the affinity between organic polymer and inorganic phases [2].

Optical transparency is the most important characteristic of these hybrids and it arises because dispersion of material in the matrix is in the order of tens of nanometres, far less than the wavelength of visible and ultraviolet light. As a result, light is not lost due to scattering.

Moreover, the hybrid materials offer the advantages like higher flexibility and mechanical strength, greater temperature, range of usability, increased durability, improved electrical, magnetic or redox properties [3–5].

The synthesis of hybrid materials includes two methodologies:

(A) Building block approach
(B) *In-situ* formation of the components
   a. In situ formation of inorganic materials
   b. Formation of organic polymers in presence of preformed inorganic materials

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ORIGINAL ARTICLE

Phospholipid complex-loaded self-assembled phytosomal soft nanoparticles: evidence of enhanced solubility, dissolution rate, ex vivo permeability, oral bioavailability, and antioxidant potential of mangiferin

Darshan R. Telange[1] · Nazish K. Sohail[2] · Atul T. Hemke[2] · Prashant S. Kharkar[3] · Anil M. Pethe[4]

Abstract

In this study, self-assembled phytosomal soft nanoparticles encapsulated with phospholipid complex (MPLC SNPs) using a combination of solvent evaporation and nanoprecipitation method were developed to enhance the biopharmaceutical and antioxidant potential of MGN. The mangiferin-Phospholipon® 90H complex (MPLC) was produced by the solvent evaporation method and optimized using central composite design (CCD). The optimized MPLC was converted into MPLC SNPs using the nanoprecipitation method. The physicochemical and functional characterization of MPLC and MPLC SNPs was carried out by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FT-IR), powder X-ray diffractometer (PXRD), proton nuclear magnetic resonance (^{1}H-NMR), solubility, in vitro dissolution, oral bioavailability, and in vivo antioxidant studies. A CCD formed stable MPLC with the optimal values of 1:1.76, 50.55 °C, and 2.02 h, respectively. Characterization studies supported the formation of a complex. MPLC and MPLC SNPs both enhanced the aqueous solubility (~ 32-fold and ~ 39-fold), dissolution rate around ~ 98% via biphasic release pattern, and permeation rate of ~ 97%, respectively, compared with MGN and MGN SNPs. Liver function tests and in vivo antioxidant studies exhibited that MPLC SNPs significantly preserved the CCl_4-intoxicated liver marker and antioxidant marker enzymes, compared with MGN SNPs. The oral bioavailability of MPLC SNPs was increased appreciably up to ~ 10-fold by increasing the main pharmacokinetic parameters such as C_{max}, T_{max}, and AUC. Thus, MPLC SNPs could be engaged as a nanovesicle delivery system for improving the biopharmaceutical and antioxidant potential of MGN.

Keywords Mangiferin · Solubility · In vitro dissolution rate · Oral bioavailability and in vivo antioxidant potential

Introduction

Mangiferin (MGN), a xanthonoid predominantly found in the leaves, bark, fruits, and root bark of plants such as *Mangifera indica* (Family: Anacardiaceae) and others, is a super-antioxidant [1–6]. Following oral administration, it offers a score of health benefits such as antioxidants [7], blood lipid-lowering agents [8], anti-proliferative [9], skeletal muscle contractile [10], and brain oxygenation [11]. Recently Imran et al. [4] have extensively reviewed the potential of MGN in managing lifestyle-related disorders. Enormous literature reports are available demonstrating the utility of MGN in a variety of diseases and disorders. MGN is being consistently explored in life sciences, particularly during the last decade or so, as seen from the number of published papers. Yang et al. reported the protective effect of MGN on cerebral ischemia-reperfusion

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ORIGINAL ARTICLE

LIPOID SPC-3-Based Coprecipitates for the Enhancement of Aqueous Solubility and Permeability of Ranolazine

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Abstract

Purpose The study was aimed at exploring the feasibility of LIPOID SPC-3 as a coprecipitate carrier to enhance the aqueous solubility and permeability of ranolazine, a BCS class II drug.

Methods LIPOID SPC-3-based coprecipitates of ranolazine (RNZ-SPC-CP) were developed using the solvent method. The developed formulation was physico-chemically characterized using scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), powder x-ray diffractometry (PXRD), and drug content. Functional evaluation of RNZ-SPC-CP formulations was carried out by solubility analysis, in vitro dissolution studies, fed vs. fasted state dissolution comparison, and ex vivo permeation studies.

Results The SEM studies revealed dissimilar morphological characteristics of pure ranolazine, LSPC-3, and RNZ-SPC-CP formulations. The physico-chemical analysis confirmed the formation of the coprecipitate. Optimized RNZ-SPC-CP1 demonstrated a noteworthy increase (~18-fold) in water solubility (~92.23 ± 1.02 μg/mL) over that of pure ranolazine (~4.94 ± 0.06 μg/mL) and physical mixture (PM) (~30.21 ± 2.12 μg/mL). Optimized RNZ-SPC-CP1 appreciably enhanced the rate and extent of ranolazine dissolution (~85%), compared with that of pure ranolazine (~21%) and PM (~35%). Similarly, the permeation rate of ranolazine from optimized RNZ-SPC-CP1 formulation was found to be enhanced significantly (~83%) over that of pure ranolazine (~19%) and PM (~32%). In the fed state, the RNZ-SPC-CP1 improved the rate and extent of ranolazine dissolution, compared with those of fasted state dissolution.

Conclusions The results conclude that RNZ-SPC-CP could be used as a promising approach for enhancing the aqueous solubility and permeation rate of ranolazine.

Keywords Coprecipitates · Dissolution · Permeability · Phospholipids · Solubility

Introduction

Ranolazine (IUPAC name: *N*-(2,6-dimethyl phenyl)-2-[4-[2-hydroxy-3-(2-methoxy phenoxy) propyl]-propyl piperazine-acetamide]), a piperazine derivative, is used predominantly for the management of chronic stable angina pectoris (CSAP). It is a selective sodium channel blocker, which inhibits the late phase of Na^+ current in ischemia [1]. Upon oral administration, ranolazine produces a low and variable pharmacokinetic profile, resulting in poor oral bioavailability (i.e., ~35 to 50%). This is mainly attributed to its shorter half-life (~2 to 6 h), rapid clearance (>70%), and rapid hepatic first-pass metabolism by cytochrome P-450 3A (CYP3A) and CYP2D6, respectively [2–4]. Moreover, it is categorized as a Biopharmaceutics Classification System (BCS) class II drug, which exhibits low solubility and high permeability [5]. Earlier published reports have also shown that ranolazine plasma concentration is highly undesirable and fluctuate following oral administration [2]. Therefore, a unique formulation approach is strongly needed to improve the solubility, dissolution rate, permeability, and oral bioavailability of ranolazine.

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Antimutagenic Activity of Cassia Auriculata Linn Fractions along with Anticancer Activity in Male Albino Mice

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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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Original Research Article

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ABSTRACT

Background: In recent years, there has been a surge in interest in studying plant-derived materials and their impact on DNA. Herbal products include a number of natural substances that may help protect cells against mutagen-induced cell damage.
Aim: The purpose of this research was to assess the genotoxic effects of Cassia Auriculata Linn flavonoids (CAF) and Cassia Auriculata Linn saponin (CAS) rich fractions on mouse bone marrow cells utilizing chromosomal aberration test and micronucleus assay.
Methodology: The suppressive impact of CAF and CAS on 7, 12-dimethylbenz (α) anthracene (DMBA) and Croton oil induced skin tumor promotion in mice with topical administration twice

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Evaluation of the Antigenotoxic Potential of Methanolic Leaves Extract of *Triticum aestivum* in Mice

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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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Original Research Article

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ABSTRACT

Mutations are changes to the nucleotide sequence of the genetic material of an organism. Reactive oxygen species (ROS) play an important role in process like mutagenesis, carcinogenesis and aging by their ability to damage cellular DNA. Inhibition of mutagenesis or carcinogenesis is generally not based on one specific mechanism. Protection against cancer can occur at different stages of the complicated processes of carcinogenesis. Naturally occurring antioxidants have been extensively studied for their capacity to protect organisms and cells from oxidation. *Triticum aestivum (T. aestivum)* have revealed its medicinal potential for some human diseases; therefore, this study aimed to evaluate the genotoxic and antigenotoxic potential of methanolic extract. To accomplish this, the methanolic extract of *T. aestivum* was evaluated for its antigenotoxic effect using the chromosomal aberrations and micronucleus assay of bone marrow cells of mice.

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IN-VITRO ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY OF *SALIX ALBA* L. ALONG WITH SIMULTANEOUS HPTLC ANALYSIS OF SALICIN AND FERULIC ACID

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Keywords:

Salix alba L, Salicin, Ferulic acid, High performance thin layer chromatography, Antioxidant and anti-inflammatory

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ABSTRACT: Now a day's interest towards natural and has been growing due to the unhealthy consequences of chemicals in the health industry; though, herbal substances possess several quality control and confirm pharmacological action issues. This present study was designed to determine the effects of *Salix alba* L. methanolic extract (MESAL) for its antioxidant and anti-inflammatory activity in rat models. Further to establish and validate a sensitive, fast and reproducible high performance thin layer chromatographic (HPTLC) method of two biomarker compounds Salicin and Ferulic acid from MESAL. The anti-inflammatory activity was studied by the carrageenan-induced rat paw oedema method while DPPH free radical scavenging ability was utilized to determine the antioxidant activity. Additionally, the separation was performed by HPTLC with quantification of markers (Salicin and Ferulic acid). Among the different combinations of mobile phases used, the best separation was achieved in Toluene: Ethyl acetate: Methanol: Formic Acid (5:3:1:1v/v/v/v). The MESAL exhibited antioxidant activity with a maximal inhibitory concentration (IC_{50}) value of 400 µg/ml, and exerted anti-inflammatory activity, wherein 70 % protection was shown at 400 mg/ml. In contrast, HPTLC method gave compact spots of Salicin and Ferulic acid at R_f 0.22 ± 0.02 and 0.68 ± 0.02, respectively. The MESAL displayed potent antioxidant and anti-inflammatory properties. Statistical analysis proves that the HPTLC method is repeatable and selective for the estimation of the said drugs, thus can be used for routine analysis and quality control of raw material of *Salix alba* L.

INTRODUCTION: Noteworthy work is essential to evaluate herbal drugs for their quality, safety, and efficacy; there is required for a well-defined particular strategy for routine analysis of herbal raw materials and formulations with regard to constituents responsible for their efficacy [1, 2].

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S. alba L., universally recognized as White Willow (particularly, the bark) is the original source of salicin, a weaker precursor of aspirin [3].

The chemical component like glycosides (1.5-11%) predominantly salicylates (salicin, salicortin, populin, fragilin, tremulacin); tannins (8-20%); aromatic aldehydes and acids distinctively salidroside, vanillin, syringin, salicylic acid, caffeic and ferulic acids; Salicyl alcohol (saligenin); Flavonoids have been isolated and identified from the plant [4-6]. *Salix alba* L. has been used as antioxidant, antiacetyl cholinesterase, anti-

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ANTIOXIDANT ACTIVITY OF *CASSIA AURICULATA* AND *CASSIA FISTULA* EXTRACT ALONG WITH WOUND HEALING ACTIVITY OF ITS POLYHERBAL FORMULATION

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Keywords:

Antioxidant, *Cassia fistula*, *Cassia auriculata*, Polyherbal formulation, Wound healing activity

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ABSTRACT: Due to emergent concerns about unhealthy consequences of chemicals in the health industry, the interest towards natural and herbal substances has been growing every day. In this study, the antioxidant effect of Cassia *fistula* [CFF] and *Cassia auriculata* [CAF] extract was evaluated. Also discover wound healing activity of polyherbal formulation (CFF and CAF). The antioxidant activity of the extract was evaluated by using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity. Total phenolic content (TPC) was determined to screen the prepared extracts by using the Folin-Ciocalteu phenol reagent method. The polyherbal formulation (CFF and CAF) using the excision wound model. The CFF and CAF extracts showed variable degrees of antioxidant activity. The formulated gel accelerates the wound healing process which may be due to enhancing the cellular defense mechanisms, proliferation, suppression of inflammation, and contraction of the collagen tissue and could be delayed by reactive oxygen species or microbial infection. The results suggest that extracts have antioxidant properties, which may be a potentially promising agent and favorable for wound healing, and this plant extract used in polyherbal formulation may be useful in the management of abnormal healing.

INTRODUCTION: Wound healing is the natural process of repair that follows injury to the skin and other soft tissues. It is an interaction of the complex cascade of cellular and biochemical actions healing to the restoration of structural and functional integrity with the recovery of the strength of injured tissues [1].

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Healing involves continuous cell-cell interaction and cell-matrix interactions that allow the process to continue in different overlapping phases, which include inflammation, wound contraction, re-epithelialization, tissue remodeling, and formation of granulation tissue with angiogenesis [2]. These events are controlled by several mediators, including platelets, inflammatory cells, cytokines, growth factors, and matrix metalloproteinases and their inhibitors [3].

Numerous factors such as microbial infection, necrotic tissue, and interference with blood supply, lymphatic blockage, oxidative stress and disease condition such as diabetes delay the wound healing

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RESEARCH ARTICLE

Comparative Pharmacognostical and Phytochemical Study of *Cassia auriculata* and *Cassia fistula*

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Abstract

Cassia auriculata L. (CAL) popularly identified as Tanner's Cassia and *Cassia fistula L.* (CFL) is generally known as Golden Shower. Both plants belong to the Family, Fabaceae. These plants are used in skin disease, as hepatoprotective, as anticancer agent and as antioxidant agent. The intention of current article is to put forward the comparative pharmacognostical analysis of *Cassia auriculata* and *Cassia fistula* roots in terms of macroscopic evaluation, microscopic evaluation, physicochemical evaluation, extractive values and phytochemical analysis. Thin Layer Chromatography study was carried out for CAL and CFL and data pertaining to the above cited evaluations were recorded for both, CAL and CFL roots. The present study may help in differentiating among these species and these pharmacognostic parameters may serve as a tool for identification, authentication and standardization of CAL and CFL.

Keywords: *Cassia auriculata*, *Cassia fistula*, Microscopy, Phytochemical evaluation

1. Introduction

CAL is usually well-known as Tanner's Cassia, which fit in to the Family Fabaceae. The said plant is spread in Indian county and subcontinents. In Indian traditional system of medicine, the leaf and flower along with Triphala are utilized in the management of diabetic problems. The root of *cassia* is alexeteric and reported to be useful in thirst and respiratory problems. The leaves showed anthelmintic potential and they are supportive in the management of ulcers. The flowers are also reported to be useful in the treatment of throat complications[1,2]. Preclinical and clinical research have showed that roots have ephroprotective potential, leaves also showed liver protective action along with other health benefits[3–11].

CFL normally identified as Golden Shower belonging to Family Fabaceae, also well-known as Amaltas. The herb is found throughout the country. It is scattered in numerous countries including Asia, Mexico, East Africa, South Africa and West Indies along with Brazil. The root is generally consumed as a stimulant and febrifuge. It also shows potential as a strong laxative. In ayurvedic literature, root is used in skin problems like leprosy. The flowers are useful in treating cough and related problems, even flatulence. In Unani system of medicine, the leaf of CFL diminishes the edema. The flowers are used as a purgative. The seeds are used as an emetic. The described uses of CFL are as antibacterial, liver protective, wound healing, anti feedant, larvicidal, antifungal, protease inhibitor, anticancer and antifertility, antioxidant action[12–20].

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Review Article

PHARMACEUTICAL AND BIOPHARMACEUTICAL ASPECTS OF QUANTUM DOTS-AN OVERVIEW

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ABSTRACT

In the twenty-first century, nanotechnology has become cutting-edge technology. It is interdisciplinary and multidisciplinary, covering numerous fields such as medicine, engineering, biology, physics, material sciences, and chemistry. The present work aims to cover the optical properties, method of preparations, surface modifications, bio-conjugation, characterization, stability, and cytotoxicity of quantum dots (QDs).

Articles were reviewed in English literature reporting the pharmaceutical and bio-pharmaceutical aspects of QDs which were indexed in Scopus, web of science, google scholar and PubMed without applying the year of publication criterion.

One significant value of utilizing nanotechnology is that one can alter and control the properties in a genuinely unsurprising way to address explicit applications' issues. In science and biomedicine, the usage of functional nanomaterials has been broadly investigated and has become one of the quick-moving and stimulating research directions. Different types of nanomaterial (silicon nanowires, QDs, carbon nanotubes, nanoparticles of gold/silver) were extensively utilized for biological purposes. Nanomedicine shows numerous advantages in the natural characteristics of targeted drug delivery and therapeutics. For instance, protection of drugs against degradation, improvement in the drug's stability, prolonged circulation time, deceased side effects, and enhanced distribution in tissues. The present review article deals with the quantum dots, their optical properties, method of preparations, surface modifications, bio-conjugation, characterization, stability, and cytotoxicity of quantum dots. The review also discusses various biomedical applications of QDs.

The QDs-based bio-nanotechnology will always be in the growing list of unique applications, with progress being made in specialized nanoparticle development, the detection of elegant conjugation methods, and the discovery of new targeting ligands.

Keywords: Quantum dots, Optical properties, Microwave-assisted method, Cytotoxicity, Cell imaging, Sentinel lymph-node mapping

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INTRODUCTION

In 1981, Ekimov and Onushenko described the Quantum dots (QDs), also called nanoscale semiconductor crystals [1]. The quantum dots are made up of material from periodic table group II-VI (CdSe) or III-V (InP) [2–6]. The most well studied and broadly utilized QDs are the cadmium selenide (Cd/Se) [3]. The cores and QDs targeting are protected by surface modification, and such changes significantly improve QDs sizes [7]. There are two kinds of fluorescent-based quantum dots, namely graphene and carbon quantum dots [8]. Quantum dots possess quantum confinement property and, on excitation from visible to infra-red wavelength, emit fluorescence [9, 10]. Usually, in the crystal core of a single QD, around 100-100,000 atoms are present. The size of QDs usually lies in between 2-10 nm diameter, which generally grows up to 5-20 nm in diameter after encapsulation of polymer [11, 12]. QDs comprise a semiconductor core, which is over-covered by shell and cap. The anatomy of QDs is represented in fig. 1 [13]. Semiconducting character and optical properties depend on the inorganic core. In QDs synthesis, the organic surfactants are developed and eventually shape ligands on the core surface [14–17]. The nature of the capping agent produced significantly relies on the final application of QDs. Frequently used ligands in QDs synthesis are alcohols, essential amines, and thiols [18, 19]. Bio-conjugation with carbohydrates, viruses, natural products, DNA fragments, and peptides assist by ligands through the covalent coupling and electrostatic or hydrophobic interactions [20, 21]. Determination of solubility, colloidal stability, control particle morphology, particle size distribution, and accumulation chiefly depends on ligands [22–24]. The present work aims to cover the optical properties, method of preparations, surface modifications, bio-conjugation, characterization, stability, and cytotoxicity of QDs. Articles were reviewed in English literature reporting the pharmaceutical and bio-pharmaceutical aspects of QDs which were indexed in Scopus, web of science, google scholar and PubMed without applying the year of publication criterion. The keywords used for searching the literature are quantum dots, quantum dots in drug delivery system, methods of preparation of quantum dots, applications of quantum dots, recent advances in quantum dots, pharmaceutical and biopharmaceutical applications of quantum dots etc.

QDs core consists of several substances like cadmium, zinc, lead chalcogenides (CdS, CdSe, CdTe), copper salt (CuCl), arsenides (InAs, GaAs), semiconducting phosphides (InP, GaP), and nitrides (GaN). The shell of CdSe, ZnSe, PbS, ZnS, ZnTe, CdS, ZnO generally enclosed the core [3]. The core of nanomaterials guarded by outer covering from photoinitiated degradation and removing surface defects enhances the luminescence properties. Besides, cadmium, silver, copper, manganese, and rare earth metal ions can be used to dope the core of nanocrystals to enhance photoluminescence properties [25, 26]. QDs can be assembled, permitting particle shape, size, and chemical composition to be changed by suit a given application. The design and size of QDs are the properties that are frequently manipulated; this will decide if the QDs are chemically excited in NIR or UV light [27–29]. The biological targeting molecules (e. g., antibodies) or biocompatible polymeric materials (e. g., PEG) can be functionalized on the amenable external surface of QDs to improve their physiological system performance. The most commonly utilized QDs consist of graphene QDs, carbon QDs, and cadmium-based QDs [30–32]. QDs are found to be photochemically stable with symmetric, narrow, and strong fluorescence emission. QDs are


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An effort to tailor the solid dispersion loaded, surface-modified, microporous-cryogel formulation of acitretin for the treatment of psoriasis

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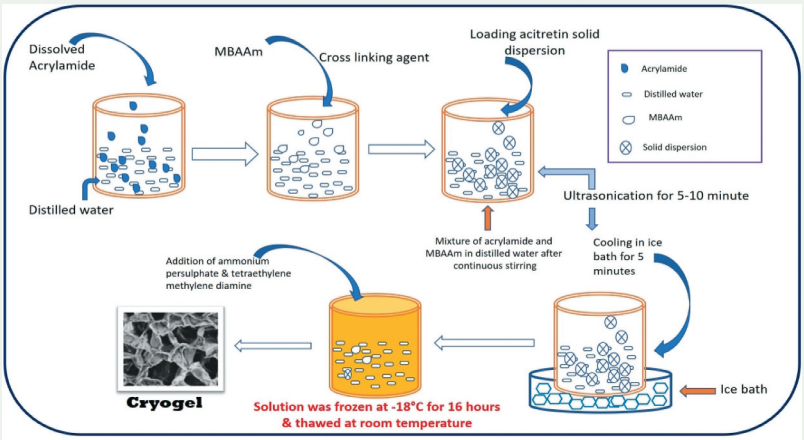
ABSTRACT

Acitretin is the drug of choice for the treatment of psoriasis, but due to its poor solubility, the development of oral and topical formulations of acitretin has been restricted. The aim of the present investigation was to enhance the solubility of acitretin. Solid dispersions of acitretin were prepared using a lipidic solubilizer, Gelucire® 44/14. These solid dispersions were characterized through FT-IR, DSC, XRD, drug content and solubility studies. The most solubilized dispersion was loaded on an N, N-methylenebisacrylamide microporous cryogel. Physical parameters of the solubilized drug such as the porosity, rheological behaviour, surface properties, appearance, drug content and diffusion behaviour were studied. It was concluded that the solubilized form of acitretin, loaded on a surface-modified cryogel, is the best option for the treatment of psoriasis. The hydration of the skin was excellent, and the permeability of the acitretin into the skin was better.



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KEYWORDS
Acitretin; Gelucire® 44/14; N, N-methylenebisacrylamide; solid dispersion; cryogel; microporous

Introduction

Most of the drugs available today have greater potential in the management of various diseases, but certain properties of these drugs have restricted the development of different dosage forms. With recent advancements in the field of science and technology and in the manufacture of modified excipients with excellent features, it is possible to overcome these hurdles in the development of newer dosage forms.

Psoriasis is a condition in which skin cells build up and form scales, rashes and itchy, dry patches that are very uncomfortable to the patients physically as well as socially [1]. There are many problems associated with psoriasis, including inflammation, redness of the skin, sharply demarcated papules and rounded plaques. Regular hydration of the skin is required to avoid serious skin damage [2]. Many drugs are used to treat psoriasis and the symptoms associated with it. WThese drugs include methotrexate, cyclosporine and acitretin. Treatment with topical steroids for prolonged periods may be dangerous. This may suppress the body's immune system. Drugs such as methotrexate may be hepatotoxic and may impair kidney function [3].

Acitretin is the drug of choice for the treatment of psoriasis, but due to its poor solubility (0.0729 mg/L), its use and the development of oral formulations have been restricted [4]. Hence, the development of topical formulations is the need of the hour. Acitretin is retinoid, a form of vitamin A. It is used in the treatment of psoriasis because of its role in epithelial cell growth, sebum production and collagen synthesis [5].

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ORIGINAL PAPER

An effort to augment solubility and efficiency of the oral bosentan-bucco-adhesive drug delivery system using graft co-polymer as the carrier

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Abstract

Although there are rapid developments in molecular science and synthetic chemistry for investigation of many essential drug molecules, poor solubility and bioavailability issues are major constraint in the design of more efficient formulations. This research study focuses on the enhancement of solubility and development of the bucco-adhesive drug delivery system of bosentan using Soluplus® (polyvinyl-caprolactam-polyvinyl-acetate-polyethylene glycol graft co-polymer) as a carrier. A 3^2-factorial design was implemented to develop bucco-adhesive tablets using hydroxypropyl methyl cellulose (HPMC) K100 LV (X_1) and Carbopol 934 P (X_2) as independent variables at various levels whereas $t_{50\%}$(Y_1) (time required to release 50% of drug), Rel_{4h} (Y_2) (percentage of the drug release in 4 h) and bio-adhesive strength (Y_3) were considered as set response parameters. The positive effect of the surface response quadratic model demonstrated the change in the already set dependent variables of $t_{50\%}$, Rel_{4h} and bio-adhesive strength. The FT-IR study confirmed the suitability of all the components used in the design of formulation. DSC and XRD study have confirmed the encapsulation of bosentan in the Soluplus® carrier and amorphous form of bosentan, respectively. Overall, 6.832-fold increase in solubility was observed for bosentan-solid dispersion. High-water uptake and swelling of bucco-adhesive tablets (containing bosentan-solid dispersion) was observed due to presence of the highly hydrophilic-Soluplus®. $Rel_{4h}$was found to be $97.86 \pm 0.57\%$ for optimized formulation (F4) and was decreased with increasing polymer content. The values of $t_{50\%}$ were found to be enhanced from 1.11 to 2.32 h at the lower to higher levels of both the polymers respectively.

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RESEARCH ARTICLE

Design, fabrication, and characterization of graft co-polymer assisted ocular insert: a state of art in reducing post-operative pain

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ABSTRACT

Purpose: Targeted delivery of drugs at appropriate concentrations to ocular tissues is required to avoid wastage. Hence, advanced systems that maximize the release of poorly soluble drugs and deliver them at ocular sites must be designed.

Methods: In this study, Soluplus® (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol–graft copolymer) was selected as a solubilizer as well as film former for preparing ocular inserts and polyethylene glycol 400 (PEG-400) as a plasticizer. On the basis of an initial phase solubility study, the maximum concentration of Soluplus® possible was used for developing the inserts. An optimized formulation was obtained using a 3^2-factorial design. Two factors at three levels were used to design the ocular inserts. Soluplus® (X_1) and the plasticizer, PEG-400 (X_2), were set as the independent variables at various levels, and the Rel_{4h} (drug release in 4 h, Y_1) and tensile strength (Y_2) were set as the dependent variables. A pre-formulation study was conducted to select suitable materials.

Results: Various physico-chemical parameters of the optimized formulation, including the tensile strength and folding endurance, were studied using FT-IR, DSC, XRD, and SEM. An *in vitro* dissolution study was conducted to determine the amount of drug released. There was no redness, swelling, or watering of the rabbit eye.

Conclusion: It was concluded that the ocular inserts of the poorly soluble nepafenac developed using a graft-co-polymer enhanced the solubility and utilization of the drug for a prolonged period.

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KEYWORDS
Ocular insert; ophthalmic drug delivery; Nepafenac; graft-co-polymer; Soluplus®

Introduction

In designing a formulation, the issues of absorption, distribution, metabolism, and elimination must be considered. When it comes to the delivery of pharmaceuticals, the eye offers unique opportunities and challenges. Though the absorption by this route is incompetent, there are few side effects with conventional ocular dosage forms. Most ocular formulations such as eye drops and suspensions are used to administer active drugs topically on the tissues around the ocular cavity. These dosage forms are easy to administer but suffer from inherent drawbacks. Ocular drug delivery is generally used to treat eye diseases. But problem of rapid and extensive elimination of conventional eye drops from the eye have been noticed here which lead to extensive loss of drug. Less amount of drug penetrates the corneal layer and reaches the internal tissue of eye. Drug loss occurs at lachrymal drainage and then drug dilution by tears. Hence, ocular bioavailability is reduced which leads to unwanted toxicity and side effect. Eye is a portal for drug delivery which is generally used for local therapy instead of systemic therapy. Due to high blood concentration of drug, there is risk of eye damage which can be overcome by local therapy [1,2]. Traditional topical formulations are highly concentrated, and corneal drug absorption with these formulations is low. There are ocular and systemic side effects because the precorneal residence time of eye drops is low [3]. Frequent administration of concentrated solutions is required to achieve the therapeutic effect. This results in the short residence of high drug concentrations in the tear film, followed by long periods of underdosing [4–6]. This leads to poor patient compliance. Several approaches have been adopted to overcome these issues. The use of various ophthalmic vehicles, such as suspensions, ointments, inserts, and aqueous gels, has been investigated to extend the ocular residence time of topically applied medications [7–9].

Sterile preparations with a solid or semisolid consistency, and of sizes and shapes designed for ophthalmic application, are generally known as ophthalmic inserts. These inserts are placed in the lower fornix and, sometimes, on the cornea or in the upper fornix. An ophthalmic insert is a polymeric vehicle consisting of the drug and is mainly used for topical therapy [10]. Increased ocular residence, the possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life are the prime advantages offered by ophthalmic inserts over conventional dosage forms [8–16]. Many of the such topical eye inserts are designed using polymeric components offering continuous release of drug without loss due to drainage and reducing the frequent administration [17].

The reduction of systemic absorption, which occurs freely with eye drops, is achieved with the use of these devices. Patient compliance is improved because of the lower frequency of administration and lower incidence of side effects [18–20]. The difficult problem of limited precorneal drug residence time is overcome by the use of ocular inserts [21,22]. The prime objective of using ophthalmic inserts is to increase the time of contact between the

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RESEARCH Open Access

A facile approach to fabrication and characterization of novel herbal microemulsion-based UV shielding cream

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Abstract

Background: Since many decades, phytoconstituents are well known for their potential therapeutic benefits but the development of herbal products has been limited due to difficulties like collection, isolation, stability and aqueous solubility of the phytoconstituents. The present study focuses on the development of microemulsion-based sunscreen cream formulation containing therapeutically active phytoconstituents like lycopene, β-carotene and curcumin which are reported for both antioxidant and ultraviolet radiation barrier properties. But the major hurdle in the development of the formulation is poor solubility and stability of these 3 components. Microemulsion preparation helps to enhance the solubility and stability of the final product. Screening of oils, surfactants and cosurfactants were done based on solubility studies followed by the construction of pseudo-ternary phase diagrams, sesame oil, span 80 to tween 80 (surfactant) and isopropyl alcohol (co-surfactant) which were selected to stable microemulsion.

Result: Based on a solubility study of components and pseudo-ternary phase diagrams, surfactant to co-surfactant (Smix) with 2:1 ratio and oil to Smix with 2:8 ratio were selected for preparation of the final microemulsion. Results show an average globule size of 208 nm, conductance 0.935 moh/cm, pH 7.1, zeta potential − 17.5 mV, refractive index 1.002, polydispersibility index 0.342, percent transmittance 90.68% and viscosity 82.45 cps. In a drug content study, the presence of lycopene, β-carotene and curcumin was found to be 87.53, 85.08 and 90.65%, respectively. Finally, microemulsion-based sunscreen cream was prepared and evaluated for various parameters like pH, extrudability, spreadability and drug content study. The sun protection factor (SPF) of microemulsion and cream was found to be 36.32 and 37.65, respectively. The stability study data shows better stability of the final formulation.

Conclusion: Formulation of microemulsion-based sunscreen cream may be a better option in the design and development of herbal phytoconstituents.

Keywords: Microemulsion, Surfactant, Lycopene, Curcumin, β-Carotene, Sunscreen cream

Background

Everyone is very conscious about their health, and nowadays, people are even very sensible about looks and external appearance. In short, the world is fond of cosmetics and skin protection against many harmful environmental effects which are on prime importance. One of the harmful factors is the ultra-violet rays coming from the sun. This sunburn may darken the skin and severe consequences may lead to skin damage or cancer. Human exposure to harmful ultraviolet (UV) radiations has very dangerous side effects such as skin melanoma, photoaging, skin pigmentation, sunburn and various painful effects. Ultraviolet radiations increase oxidative stress on skin cells by frequent formation of reactive oxygen species (ROS) leading to initiation and promotion of cancer [1].

There are several products available in the market which are sold by many companies and claiming on the

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Evaluation of the diuretic activity of ethanolic and aqueous extracts of *Tabernaemontana divaricata* in rats

Short Title: Diuretic potential of *Tabernaemontana divaricata* plant extracts

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Conflicts of interest: There are no conflicts of interest

Research Article

Anti-inflammatory, Anti-oxidant and Anti-microbial Properties of Polyherbal Formulation in Acne Treatment

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ABSTRACT

Nowadays, individual herbs are insufficient to achieve a desired therapeutic effect. When it is optimized as multiple herbs composition in a particular ratio it will give a therapeutic effect in a better way with reduced toxicity. In order to develop such an intervention, the present study was intended to develop a polyherbal cream from extracts of *Santalum album, Rubia cordifolia, Ocimum sanctum, Emblica officinalis, Glycyrrhiza glabra, Persea americana, Simmondsia chinensis, Vitis vinifera*. The present study emphasizes on screening of polyherbalism as anti-inflammatory, antioxidant and anti-microbial in Acne treatment. The polyherbal cream showed significant activity against *P. acnes* and *S. auerus* with diameter of 10 mm and 15 mm inhibition zone respectively. The polyherbal cream exhibited moderate antioxidant activity with IC50 value of 8.9 mg/ml. Topical anti-inflammatory activity was assessed by carrageenan induced paw oedema compared with Diclofenac. The percentages of edema inhibition were 79.9 % ($p < 0.01$) after five hours. The outcome of the study suggested that polyherbal cream could be possible to use as the natural anti-acne formulations.

Keywords: Polyherbal cream, Anti-acne, Anti-inflammatory, Anti-microbial, antioxidant.

INTRODUCTION

Herbal treatments applied topically have gained considerable attention due to their widespread use and ill-defined benefit/risk ratio[1]. Topical application of cream and ointment at pathological sites offer great advantages in a faster release of a drug directly to site of action[2]. The concept of polyherbalism has mentioned in "Sarangdhar Samhita". This stated that products with combined extracts of plants are considered more effective rather than individual ones. The active phytoconstituents of individual plants have been recognized butare generally present in small quantities, which is not enough to produce the desired therapeutic action for curing acne. Medicinal plants with antimicrobial, antioxidant and anti-inflammatory properties used in the treatment of acne. Polyherbalism results in cheaper medication by reducing the duration of therapy or individual cost for anti-acne medications[3].

Acne vulgaris (acne) is one of the most commonly encountered skin diseases and usually affects nearly everybody during their lifetime[4]. Pathophysiology of acne is attributed to different notable factors such as androgen-mediated stimulation of sebaceous gland activity, follicular hyper keratinization, hormonal imbalance, inflammation and external bacterial infection. Propionibacterium acnes and Staphylococcus epidermidis are the major bacteria found on skin causes acne[5,6]. A number of topical and systematic therapies are available for acne; various antibiotics, comedolytic agents, and anti-inflammatory drugs are available as a topical therapy, whereas modern systematic cure includes antibiotics, hormones, zinc and laser treatment[7]. However, an excessive use of these drugs over a long time can lead to the rising resistance of bacteria. These drugs have limitations with respect to toxicity and side effects also such as skin drying, headache, nausea etc. To overcome these limitations, there is an imperative need for the development of effective, safe and low-cost anti-acne drugs. Exploration of herbal resources may provide valuable leads that can be further developed as anti-acne drugs [8].

Santalum album seed exhibited significant antioxidant and antimicrobial activity due to rich and diverse presence of saturated fatty acid[9]. The plant bioactives of *Rubia cordifolia* exhibited antioxidant and anti-microbial activities and has been found to have efficacy, traditionally in treatment of acne[10]. *Ocimum sanctum* contains fixed oil and linolenic acid having the ability to block cycloxygenase and lipoxygenase pathways of arachidonic acid metabolism. Therefore, they show anti-inflammatory activities[11]. *Emblica Officinalis* contains two hydrolysable tannins Emblicanin A and B which have antioxidant properties along with anti-microbial activities[12]. *Glycyrrhiza glabra L.* showed existence of numerous useful metabolites such as: flavonoids, saponins, alkaloids and so on. Because of these

ORIGINAL ARTICLE

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Isolation, Identification and Characterization of Ximenynic Acid with Anti-Aging Activity from *Santalum Album*

Rakesh S Shivatare[*1], Ramesh Musale[1], Priya Lohakare[1], Dipika Patil[1], Durga Choudhary[2], Gayatri Ganu[2], Dheeraj H Nagore[3], Shailesh M Kewatkar[4]

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Ximenynic acid, Santalum album, isolation, Characterization, Antiaging assay

ABSTRACT

Medicinal plants and its products have been used as a remedial agent in most irising countries for treating diseases. Furthermore, an increasing reliance on the use of medicinal plants in industrialized societies has been traced for the extraction and development of several drugs and chemotherapeutics from these herbal plants. Novel acetylenic fatty acids named Ximenynic acid (XMA) were successfully isolated from the seeds of *Santalum album* L by N-Hexane extraction. Ximenynic acid (or Santalbic acid) is one of the few acetylenic fatty acids occurring at higher levels in plant seed oils. Ximenynic acid predominantly exists in the seed oil of *Santalaceae*, *Olacaceae*, and *Opiliaceae* families. The structure of XMA was characterized by UV-visible spectroscopy, Infrared Spectrum (IR), NMR Spectroscopy, Differential scanning calorimetry (DSC), Thermal Gravimetric Analysis (TGA), X-ray diffraction (XRD), Fourier Transform Infrared Spectroscopy (FT-IR), LCMS spectral analysis. The antiaging activities were assessed by anti-collagenase enzyme assay. Structural analysis revealed that XMA was a crystalline material with a melting point of 38.25°C and an average molecular weight of 278 kDa. Which is composed of carboxylic acid, butylenic acid, methylene, allylic in their structure. The antiaging assay showed that XMA exhibited significant collagenase inhibition activity as compared with Catechin. These findings suggested that the acetylenic fatty acids XMA could be served as a novel antiaging in Pharmaceutical as well as the cosmetic industry.

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INTRODUCTION

Plants are considered an essential source of medicines for humans. Plant parts like leaves, flowers, roots, stems, seeds, and fruit are used as food resources for human as well as a safe medicine for the treatment of different diseases. Plant-derived herbal medicine is used as the main source for the treatment of diseases since ancient times (Hussain *et al.*, 2013) .Ethnopharmacology of natural products isolated from herbal plants possesses pharmacological and therapeutic efficacy for treating diseases (Pan *et al.*, 2013). Aging is a natural process in all living organisms. Anti-aging has always been an interest in mankind. After much

ORIGINAL ARTICLE

In vitro Antioxidant Activity and Stability Indicating High-performance Thin-layer Chromatographic Method for Ximenynic Acid in *Santalum album* Seed Extract

Rakesh S. Shivatare[1], Ramesh Musale[1], Priya Lohakare[1], Dipika Patil[1], Durga Choudhary[2], Gayatri Ganu[3], Dheeraj H. Nagore[3,4], Sohan Chitlange[5], Shailesh M. kewatkar[6]

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Abstract

Introduction: Due to emergent concern about the unhealthy consequences of chemicals in the health industry, the interest toward natural and herbal substances have been growing every day; though, regrettably they possess several quality control issues. In this study, the antioxidant effect of *Santalum album* seed extract was evaluated. Furthermore, discover effortless, accurate, responsive, and stability-indicating high-performance thin-layer chromatographic (HPTLC) assay method for the detection and quantification of ximenynic acid in *S. album* seed extract. **Materials and Methods:** Antioxidant activity was evaluated by 2, 2-diphenyl-1, 1-picrylhydrazyl (DPPH) radical scavenging method. The HPTLC method contains aluminum plates precoated with silica gel 60 F254 as a stationary phase. The mobile phase was a combination of toluene: chloroform:methanol: formic acid (2:5:0.3:0.3 v/v/v/v). Densitometric analysis of ximenynic acid was carried out in the absorbance mode at 550 nm using Camag thin-layer chromatography scanner-3. **Results:** Antioxidant potential was observed in DPPH scavenging assay (EC = 4.0 ± 0.02 mg/mL) and by *S. album* seed extract. The HPTLC method was validated as per the ICH guidelines for specificity, precision, linearity, robustness, and accuracy. The method was established to give dense and symmetrical band for ximenynic acid at retention factor 0.45 ± 0.02. The repeatability of the method was found to be 1.25 relative standard deviations and recovery values from 99.94 to 100.10% for ximenynic acid. **Conclusion:** These findings indicate that *S. album* seed extract may have antioxidant potential. Statistical analysis confirmed that the projected method is repeatable, selective, and accurate for estimating the content of ximenynic acid. Since the projected mobile phase successfully resolves the ximenynic acid, this HPTLC method can be useful for identification and quantitation of these phytochemicals in herbal extracts and pharmaceutical dosage form.

Key words: Antioxidant activity, high-performance thin-layer chromatographic, *Santalum album*, ximenynic acid

INTRODUCTION

Herbal medicine plays an important role in the health care of many urbanized, developing countries. The use of herbal products is increasing worldwide due to the distinct advantages.[1] Nearly 80% of African and Asian population depend on traditional medicines for their primary health care.[2] These medicines are readily available in the market from health food stores without prescriptions.[3] In general, it is believed that the risk associated with herbal drugs is very less, but reports on serious reactions are

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Research Article

IN VIVO AND *IN VITRO* INVESTIGATIONS OF PHARMACOLOGICAL POTENTIALS OF *CASSIA OBTUSIFOLIA* PLANT

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ABSTRACT

Objectives: *Cassia obtusifolia* L. belonging to the Family Caesalpiniaceae, proposed to have abundant pharmacological potential and widely consumed as laxative, diuretic, and stomachic. The aim of the present research was to study the anti-inflammatory, analgesic, antipyretic, and antioxidant potentials of *C. obtusifolia* plant.

Methods: Various acute and chronic animal models such as Carrageenan-induced paw edema, tail immersion method, acetic acid-induced writhing, and *in vitro* methods were used to study the profound pharmacological and antioxidant potentials.

Results: The results for pharmacological study were statistically analyzed by one-way ANOVA followed by Dunnett's multiple comparisons using INTA software.

Conclusion: The present study reveals that *C. obtusifolia* possesses comparable anti-inflammatory, analgesic, antipyretic, and antioxidant potential.

Keywords: *Cassia obtusifolia*, Anti-inflammatory, Antioxidant, Carrageenan, Antipyretic.

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INTRODUCTION

Drugs presently used for the management of pain and inflammatory conditions are either narcotics, for example, opioids or non-narcotics, for example, salicylates and corticosteroids, and for example, hydrocortisone. Being synthetically designed these drugs possess well-recognized side and toxic effects. On the contrary, many medicines from plant origin had been used for long time. Exploring the healing power of plants, people from centuries have been trying to alleviate and treat diseases with different plant extracts and formulations [1]. Plants represent a large intact source of structurally novel compounds that might serve as the basis for the development of novel drugs. Screening of the plants for their biological activity merely depends on their chemotaxonomic investigation or ethnobotanical knowledge for a particular disease. Identification of a specific compound against a specific disease is a challenging extensive process [2]. Literature research for several medicinal plants possesses active constituents with significant anti-inflammatory and analgesic activities.

Cassia obtusifolia L. belonging to Caesalpiniaceae family, also known as sicklepod is extensively used as a traditional medicine [3]. The foremost active components of *C. obtusifolia* include anthraquinones, naphthopyrones, and lactones which are assumed to possess various medicinal potentials. The plant is also widely consumed as laxative, diuretic, stomachic, and digestive aid [4].

Hence, an attempt has been made to conduct studies for ascertaining anti-inflammatory, antipyretic, and analgesic potential of the medicinal plant *C. obtusifolia* using different animal models. Different *in vitro* methods were also used to study the antioxidant potential of *C. obtusifolia* plant.

METHODS

Chemicals

All AR grade solvents such as ethanol, ethyl acetate, sodium carbonate, sodium phosphate, hydrogen peroxide, and trichloroacetic acid were procured from Merck Life Science Private Ltd, Vikhroli (East), Mumbai, India. Gallic acid, Folin–Ciocalteu reagent;1, and 1-diphenyl-2-picrylhydrazyl (DPPH) were procured from SD-Fine Chem Ltd., Fischer Scientific Pvt. Ltd, Pune, India, and HiMedia Lab. Ltd., Mumbai, respectively. Marketed tablet formulations of indomethacin, pentazocine, and paracetamol were used as standard drugs that were procured from the local market.

Procurement and authentication of plant

The leaves of the plant were collected from fields of Sant Tukaram Nagar, Pimpri, Pune, and authenticated by the Botanical Survey of India, Pune, and were given the voucher specimen number SMK-1.

Extraction procedure

Leaves of *C. obtusifolia* Linn. (2 kg) were dried under shade and grinded to get the coarse powdered material. The extraction of the powdered leaves was carried out by the maceration (water) process. Then, the solution was filtered and to this filtrate, alcohol was added to get precipitate of the polysaccharides. Then, the resulting solution was filtered and the filtrate was evaporated to 1/4th of the total volume. After evaporating 1/4th of the total volume of the solution, it was successively extracted with ethyl acetate. The ethyl acetate extract was evaporated to get the brownish-yellow colored flavonoid-rich fraction of *C. obtusifolia* Linn. (FRCO) (1% w/w) which gave a positive response to the Shinoda test for the flavonoids [5-7].

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Discovery of Naturally Occurring Flavonoids as Human Cytochrome P450 (CYP3A4) Inhibitors with the Aid of Computational Chemistry

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Keywords
Human Cytochrome P450 (CYP3A4); Flavonoids; Doxorubicin; Molecular docking; PyRx Virtual Screening Tool.

ABSTRACT: Purpose: The human cytochrome P450 3A4 (CYP3A4) is the biggest individual from the CYP3A subfamily and records for 30–60% of the total for CYP450 adult liver. Hereditary varieties in CYP3A4 are a noteworthy hotspot for inter-patient changeability in plasma concentration, adverse effects and pharmacological response to medications. This research was done to discover naturally occurring novel CYP3A4 inhibitors from flavonoids. Methods: The molecular docking method was used to optimize the inhibiting activity of flavonoids against CYP3A4. PyRx Virtual Screening Tool 0.8 and BIOVIA Discovery Studio 2019 was used for simulation. Results: Flavonoids like Pongamoside A, Pongamoside B, and Pongamoside D have more binding affinity (kcal/mol) i.e. -11.6, -10.9, -10.8 respectively than Doxorubicin which have -10.7 against CYP3A4. Although, Daidzein, Genistein, and Luteolin form more hydrogen bonds than doxorubicin. Conclusion: The rational synthesis of natural analogues in reference to synthetic drugs, could generate drugs with improved therapeutic effect for chemoprevention. CYP3A4 plays a major role in the metabolism of various drugs; by the help of flavonoids, we can control the selective drug metabolism by inhibiting CYP3A4. Despite this, these molecules are not marketed for cancer treatment because of high polarity. If we could overcome this problem, these molecules can acts as effective anticancer agents in the future. Still, if we want to use these compounds clinically, there is a need to generate more scientific evidence and quality data by using *in vivo* and *in vitro* models.

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INTRODUCTION

Flavonoids are a well-known category of polyphenolic compounds. These are the regular dietary materials of the human, as many of the plants contains flavonoids. There are plenty of plants that exerts good pharmacological properties including anticancer activity just because of the presence of flavonoids. Flavonoids are the essential plant shades that act as chemical messengers, physiological controllers, and cell cycle inhibitors [1]. Flavonoids stand out amongst the most tried and broadly distributed substances of plant sources. They are found in natural products, vegetables, leguminous plants and even a few sorts of greenery. The skeleton of flavonoids comprises of 1-benzopyran. It is a C6-C3-C6 framework, in which sweet-smelling rings are associated, shaping a focal pyran or pyron cycle. Contingent upon the position to which ring is associated with the chromane, flavonoids are grouped into isoflavonoids and neoflavonoids [2].

Amongst the different other natural substances, flavonoids hold much consideration because of their noteworthy range of pharmacological activities, such as cell reinforcement, antimutagenic, antibacterial, antiangiogenic, anti-

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NOTE

Variants in *NIPAL4* and *ALOXE3* cause autosomal recessive congenital ichthyosis in Pakistani families

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Autosomal recessive congenital ichthyosis (ARCI) encompasses clinically diverse and genetically heterogeneous group of cornification disorders, and clinically characterized by generalized scaling, variable erythroderma with a global prevalence of approximately 7:1 million.[1]

Patients with ARCI are born as collodion babies or with congenital ichthyosiform erythroderma (CIE) and later develop lamellar ichthyosis (LI) with coarse brown scales or CIE with fine white scales.[2] To date 12 disease causing genes have been identified in *ARCI* including *NIPAL4*, *TGM1*, *ALOXE3*, *ALOX12B*, *ABCA12*, *CASP14*, *CERS3*, *PNPLA1*, *SDR9C7*, *LIPN*, *SULT2B1*, and *CYP4F22*.[3]

NIPLA4 gene is one of the causative genes for autosomal recessive congenital ichthyosis, typically in ARCI type III.[4] However, the function of *NIPAL4* gene is still unclear, it has been hypothesized that it is a magnesium transporter based on the fact that protein family member *NIPA2* was supposed to be a magnesium transporter.[5]

Mutations in *ALOXE3* gene cause lamellar ichthyosis, congenital ichthyosiform erythroderma (CIE), and pleomorphic ichthyosis. Oxygenation of the linoleate moiety of ceramides catalyzed by *ALOXE3* constitutes an essential step in the formation of the corneocyte lipid envelope.[6]

In this study, two Pakistani families (Family 1 and Family 2) with a history of ARCI were investigated. Written informed consent was obtained from patients or their legal guardians and ethical approval was obtained from the Institutional Ethical Committee of IIUI, Pakistan. Pedigree analysis was indicative of an autosomal recessive mode of inheritance in families 1 and 2 (Figure 1). At the time of clinical examination, the affected individuals IV: 1; IV: 4 in Family 1 were 17 and 9 years old, while affected individuals IV: 5, IV: 6, and V: 4 in Family 2 were 8, 3, and 10 years of ages, respectively. Disease was observed at the age of 3 months in patient IV: 1 and was observed in patient IV: 4 at the time of birth in Family 1. Both affected members of family 1 (IV: 1, IV: 4) have short stature. Disease symptoms were typically seen at the time of birth in affected individuals (IV: 5, IV: 6, and V: 4) of Family 2. On the basis of basic clinical dermatological assessment, ARCI was the major finding in all affected members of the investigated families.

In order to identify the disease causing mutation, single affected individuals (IV: 1; Family 1 and IV: 5; Family 2) were initially selected to perform whole exome sequence and then validated by Sanger sequencing (details in Supporting Information). This identified a homozygous splice-site variant (NM_001099287.1:c.464-1G>A; Chr5:156894056G>A [GRCh37]) in the intron 2 of *NIPAL4* gene (Figure 1F) in Family 1, and a homozygous nonsense variant (NM-02168.2:C.631C>T; Chr17:80178 51G>A [GRCh37]) in exon 5 of *ALOXE3* gene of family-2 (Figure 1G), as the likely causes of each condition. No other variants were observed in both genes. The *NIPAL4* variant c.464-1G>A is a reported disease causing variant with HGMD accession ID CS075164.[4] This is a first instance where c.464-1G>A splice-site variant in *NIPAL4* is identified in homozygous form, being present in two affected half-sisters from a Pakistani family (Family 1; Figure 1). III: 4 (father of IV: 4) from Family 1 is also distantly related to III: 3 (mother of IV: 4). The Family 1 is from Azad Kashmir region in Pakistan (Table S3). According to HGMD professional, 18 mutations (Table S1) in *NIPAL4* are known to cause different forms of ichthyosis to date.

In Family 2, a homozygous nonsense variant c.631C>T results in premature termination (p.Arg211*). While the same *ALOXE3* variant is also reported in HGMD (accession ID CM1610944)[7] this is the first study reporting homozygous *ALOXE3* c.631C>T; (p.Arg211*) nonsense variant. This family is from Multan city in Punjab, Pakistan (Table S3). So far 22 variants (Table S2) in *ALOXE3* have been implicated in various forms of ichthyosis (HGMD Professional 2018.3).

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Original Article

Supramolecular Complexes of Phospholipids and β-Cyclodextrin with Bioactive β-Carotene: A Comparative Physico-Chemical and Functional Evaluation

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ABSTRACT

Background: β-carotene, a chief component of carotenoids family exhibits multiple numbers of pharmacological activities. However, its poor aqueous solubility and low dissolution rate restricts it to become a potential drug candidate. Hence, β-carotene-phospholipids complex (BPLC) and β-carotene-β-cyclodextrin complex (BCDC) were prepared with an objective of enhancing its aqueous solubility and dissolution rate. **Materials and Methods:** BPLC and BCDC were synthesized using solvent evaporation and kneading method respectively. BPLC and BCDC, were characterized by particle size and zeta potential analysis, complexation rate, drug loading, Fourier transform infrared spectroscopy and differential scanning calorimetry. Functional characterization of above formulations was performed by solubility and *in vitro* dissolution studies. **Results and Conclusion:** Particle size analysis result of BCDC and BPLC formulations were found to be suitable for oral route of administration. FT- IR and DSC studies supported the formation of BCDC and BPLC formulation. Solubility results displayed that BPLC (1:1) significantly enhanced the aqueous solubility upto (28-fold), compared to BCDC (1:2) (18-fold) and β-carotene. Dissolution studies showed that BPLC (1:1) considerably improved the release rate of β-carotene in PBS (pH 7.4) compared to BCDC (1:2) and β-carotene suspension. Hence, above comparison confirmed that phospholipids could be promising carrier compared to β-cyclodextrin for overall enhancement of aqueous solubility and *in vitro* dissolution rate of β-carotene.

Key words: β-carotene, Phospholipids, β-cyclodextrin, Solubility, *in vitro* dissolution.

INTRODUCTION

β-carotene (β-CTE), a chief component of carotenoids family shows existence in many fruits, vegetables and microalgae such as mangos, cantaloupe, peppers, pumpkin, sweet potatoes, carrots, leaves, fish and sea foods etc. It acts as a great source of vitamin A and hence, it finds application in the maintenance of normal functioning of human eye.[1] Moreover, it is an approved food ingredients and thus, has been employed majorly in countless food, cosmetic and most importantly, in pharmaceutical products.[2] Earlier studies have reported a number of clinical benefits of β-CTE such as antioxidant,[3] anticancer, cardio-protective and anti-ageing activities.[4,5] Regardless of therapeutic advantages of β-CTE, its clinical utility is primarily restricted by its poor aqueous solubility (< 0.6 µg/mL), low oral bioavailability (~ 11 – 30%) and easy susceptibility to degradation due to high sensitivity to molecular oxygen, light and temperature. In this situation, overcoming

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Int. J. Pharm. Investigation, 2020;10(4):569-574 Original Article

Antiparkinsonian and Antioxidant Effects of Hydroalcoholic Extract of *Camellia sinensis*, *Asparagus racemosus*, *Mucuna pruriens* and their Combination

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ABSTRACT

Objectives: Because of environmental risk factors Parkinson's disease rate doubled in last decades. In upcoming decades rate of Parkinson's disease is expected to be 12 million people in aging population. Present treatments are having huge side effects and requires more combinations. Hence objective of this study is to provide herbal combination for Parkinson's disease with reduced side and adverse effects. **Methods:** The antiparkinsonian activity of HECS, HEAR, HEMP and Mixture was evaluated by using haloperidol induced catalepsy, reserpine induced hypolocomotion, tacrine induced vacuous chewing movements and orofacial brusts. Antioxidant activity was assessed by using DPPH radical and H_2O_2 scavenging assay. The results were analyzed by repeated measure ANOVA followed by Dunnett's test. **Results:** Significant reduction (P<0.05) in haloperidol-induced catalepsy was observed in the all groups at the doses of 30 and 100 mg/kg when given orally. Mixture 30 mg/kg showed extremely significant (P<0.001) reduction in duration of catalepsy. Pretreatment with Mixture at 100mg/kg was significantly (P<0.05) reduces Reserpine induced hypolocomotion which is more significant as compared with other treatments. Similarly, HECS 30 mg/kg and mixture was more effective (P<0.05) than remaining extracts in reducing tacrine induced Vacuous chewing movements. In tacrine induced orofacial brust Mixture and HEAR 30 mg/kg shows extremely significant (P<0.001) reduction of orofacial brusts. Similarly Mixture and HECS 100 mg/kg is more effective than other treatment in tacrine induced tongue protrusion. In DPPH scavenging assay, all the extracts exhibited free radical scavenging activity. In DPPH assay the IC_{50} value of ascorbic acid, HECS, HEAR, HEMP and Mixture (1:1:1) was 14.99, 18.44, 26.51, 23.19 and 20.47 µg/ml respectively. **Conclusion:** 1:1:1 mixture show extremely significant antioxidant and anti-parkinsonian activity as compare with individual hydroalcoholic extract. Thus the studied combination possess potent antiparkinsonian effect.

Key words: Antioxidant, Antiparkinsons, *Camellia sinensi*, *Asparagus racemosus, Mucuna prurines*, Haloperidol, Reserpine, Tacrine.

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INTRODUCTION

Parkinson's Disease (PD) is a complex multi-framework, neurodegenerative sickness. In spite of the fact that dominatingly saw as motor ailment, it likewise has incapacitating non-motor highlights, which are as often as possible missed and not treated. The degeneration of dopaminergic neurons is viewed as the underlying driver of the trademark traditional engine side effects and non-motor indications. Significant treatment objectives are to increase striatal dopamine levels with antecedent replacement and additionally decrease its breakdown. As the ailment advances, a consistent increment in the portion of levodopa is inescapable. Be that as it may, higher dosages cause engine intricacies of dyskinesia and dystonia and bargain clinical treatment. Based on the studies, it is known that mitochondrial dysfunction, Neuronal death in substantial nigra and changed oxidative stress are the two crucial cellular stress parameters playing important role in PD pathogenesis. In parkinsons disease tremors, bradykinesia, stiffness in limbs and torso and postural instability are the four main symptoms. The focal point of the executives is the alleviation of the clinically prevailing motor side effects of PD. In any case, presently, there is an expanding acknowledgment of the non-motor highlights of PD, which additionally need consideration. These highlights are rest aggravations, constipation, psychological decay, melancholy, dread, tension, bladder issues, weight changes, weakness and loss of vitality, autonomic brokenness/hypotension and sexual issues. These can be predominant and incapacitating in a sizeable number of patients, influencing a mind-blowing nature. PD additionally has pre-malady manifestations like blockage and loss of smell, decreased outward appearances, soft tone, rest changes, wooziness which go before months to decades before clinical determination of PD. The current restorative technique against PD essentially depends on reestablishing the ideal degree of dopamine (DA) and its related flagging pathways, for which Levodopa or L-DOPA (L-3, 4-dihydroxyphenylalanine), a forerunner of dopamine is regulated to the PD patients. L-DOPA gives introductory advantage by hindering the malady movement; be that as it may, long haul benefits are impossible. Additionally, it is likewise directed in blend with carbidopa, a fringe decarboxylase inhibitor. This aides in reducing the reaction of L-DOPA which principally incorporate gastrointestinal and cardiovascular issues. Another procedure for PD treatment is the utilization of monoamine oxidase B (MAO-B) inhibitors. The movement of MAO-B compound is expanded by virtue of DA metabolism which hoists oxidative stress and mitochondrial dysfunctions. Until this point, mitochondrial brokenness and adjusted oxidative stress are viewed as the conceivable system prompting neuronal cell death. Therefore, therapeutic approaches

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Evaluation Of *Camellia sinensis*, *Withania somnifera* and their Combination for Antioxidant and Antiparkinsonian Effect

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Abstract:

Aims: *Camellia sinensis* and *Withania somnifera*, well known for antioxidant potentials, in present work hydroalcoholic extract of *Camellia sinsnsis* (HECS), *withania somnifera* (HEWS) and 1:1 combination mixture has been studied for protective effect against haloperidol, reserpine and tacrine induced neuronal damage.

Mehods: Albino Mice either sex were treated with haloperidol (0.5 mg/kg) and wistar rats either sex were treated with reserpine (1 mg/kg) and tacrine (5 mg/kg) intraperitoneally. HECS, HEWS and mixture was administered at different doses of 30 mg/kg and 100 mg/kg (p.o) indifferent groups 30 min prior to haloperidol, reserpine and tacrine. Behavioural changes due to neuronal damage and antioxidant status were analysed. Behavioural changes were observed by using bar test, Actophotometer and Plexiglas chamber.

Results: 1:1 mixture (HECS:HEWS) significantly (P<0.05) improved antioxidant status and behavioural activities altered by haloperidol induced catalepsy, reserpine induced hypolocomotion and tacrine induced vacuous chewing movement, orofacial brusts in a dose dependant manner.

Conclusion: 1:1 mixture possesses antioxidant activity and protects neuronal damage which is more noticeable at dose of 30 mg/kg against haloperidol induced catalepsy, reserpine induced hypolocomotion and tacrine induced vacuous chewing movements and orofacial brust.

Keywords: Antioxidant, Antiparkinson, *Camellia sinensis*, *Withania somnifers*, Haloperidol, Reserpine, Tacrine

INTRODUCTION:

Neurodegenerative diseases like Alzheimer's, Parkinson's, Huntington's and multiple sclerosis are associated with the process of memory loss and cognitive decline which results from selective degeneration of particular neuronal cells and the deposit of aggregated proteins. Parkinson's disease (PD) is mainly characterized as a movement disorder but non-motor symptoms are also involved. Since dopamine is associated with motor activity, the progressive loss of dopaminergic neurons in PD leads to muscle rigidity, tremors and bradykinesia as well as cognition, mental, sleeping, personality and behaviour disorders including depression and anxiety [1-2]. The mechanisms responsible for dopaminergic neuronal loss in PD are complex and yet unclear. Pathogenic factors such as oxidative and nitrosative stress, mitochondrial dysfunction, apoptosis, inflammatory responses and excitotoxicity have been proposed for the degeneration of dopaminergic neurons. Literature review suggests increased reactive oxygen species (ROS) and oxidative damage in the cascade of events leading to degeneration of dopaminergic neurons. This is mainly due to the observations that increased level of lipid peroxidation, modifications of proteins, and DNA and RNA oxidation products are seen in the brain of Parkinsonian patients [3-4]. Currently, there is no cure for PD and the drugs used for treatment are levodopa, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors, which provide only symptomatic relief. Levodopa has been considered the gold standard drug therapy for Parkinson's disease but it is limited only to relieving symptoms and its long term use may cause serious side effects that include involuntary movements (dyskinesia), the on-off effect may cause Parkinson's related movement problems to appear and disappear suddenly and unpredictably. The side effects of allopathic medicines for PD are highly alarming; hence, the current research is now focusing on herbs used in alternative systems of medicine as neuroprotective [5]. In this quest, some herbs have been found to be effective neuroprotectants. Phytoconstituents like polyphenols, flavonoids exhibit antiparkinsonian activity against experimentally induced PD. *Withania somnifera* and *Camellia sinensis* are an important plants used in Ayurveda for the treatment of various disorders of the CNS and are rich in polyphenols, flavonoids, alkaloids and lactones. *Camellia sinensis* is popularly known as Green Tea belonging to Theaceae family. The most important phytoconstituents of *Camellia sinensis* are polyphenolic compounds known as catechins including epigallocatechin gallate (EGCG), catechin (C), epicatechin (EC), gallocatechin (GC), gallocatechin gallate (GCG), epigallocatechin (EGC), and epicatechin gallate (ECG). Flavonols contribute to the antioxidant capabilities of tea leaves. The aglycones of the main flavonols in tea leaves are quercetin, kaempferol, and myricetin. Pharmacologically active constituents of *Camellia sinensis* have been shown to possess hepatoprotective, cardioprotective, neuroprotective, anticancer, antiobesity, antidiabetic, antibacterial, antiviral and antioxidant effects. Antioxidant property of catechin contributes to protection from neurodegeneration [6-7]. *Withania somnifera* commonly known as Ashwagandha, Asgand, Indian ginseng, and winter cherry belongs to the family Solanaceae is an important medicinal plant that has been used in Ayurvedic and indigenous medicine. The biologically active chemical constituents are alkaloids (isopelletierine, anaferine), steroidal lactones (withanolides, withaferins), saponins containing an

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Design & Development of Curcumin Loaded Zinc Oxide Nanoparticles Decorated Mesoporous Silica Liquid Stitches: A Proof of Concept in Animals

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ABSTRACT

The present research was aimed at synthesising and characterising curcumin-loaded zinc oxide nanoparticle-decorated mesoporous silica as a tissue adhesive (Liquid Stitches). The mesoporous silica nanoparticles facilitate adhesion to tissues through the nanobridging effect. The mesoporous silica was synthesised using a sol–gel methodology, and the drug was incorporated using the wetness impregnation method. The platform that was prepared was characterised using infrared spectroscopy, TEM, DSC, XRD, particle size analysis, BET analysis, a tissue model adhesion test, an antimicrobial assay and a wound model in Sprague Dawley rats. The average particle size was found to be 72.4 nm, while the surface area was found to be 654 m^2/g. The tissue model adhesion graphs showed significantly different values for the peak load, work done and deformation at peak load, which reflects a difference between the glue strengths of the mesoporous silica nanoparticles and the Cur-ZnO-MSN and the carrier medium (water). The animal study provided a proof of concept by glueing wounds in less than 1 minute and healing the wound within 5 days.

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KEYWORDS
Tissue glue; mesoporous silica; nanobridging; shear lap adhesion; liquid stitches; zinc oxide nanoparticles

Introduction

Wound healing or surgical incision healing is a complex procedure involving different stages like inflammatory reaction, cell proliferation and synthesis of the elements which make up the extracellular matrix, and the posterior period, called remodelling [1,2]. The minor cuts or wounds may be applied with topical dressings and wound-healing formulations but the major cuts, wounds, surgical incision needs permanent solutions like surgical sutures [3], Cyanoacrylate tissue glue or fibrin glue, etc. [4]. But it has been observed that cyanoacrylates possess toxicity like immunogenicity, local heat production and damage to the tissue or liberation of formaldehyde [5], fibrin glue possess immunogenic reaction as well as cost issue and the sutures may also be risky due to delayed healing and scar tissue formation. So, it was a need of the hour to design and develop an immediate glueing formulation which is safe, give better effect in case of fast wound healing and cost-effective. The unique combination of herbal drug curcumin, zinc oxide and the mesoporous silica platform has been developed in this study for wound healing. The use of Mesoporous silica nanoparticles (MSNs) has been proved to be effective in drug delivery [6], solubility enhancement [7], targeted delivery [8], sustained delivery, bioimaging, sensing, etc. [9]. The use of these Mesoporous silica nanoparticles (NPs) in tissue glueing and wound healing is being explored because the connection of injured tissues and healing of wounds and trauma is a potential challenge due to the complex nature of healing [10]. It has been proved that the use of mesoporous silica in drug delivery is safe and efficacious. It has been awarded the GRAS status by the USFDA as it is biocompatible and biodegradable in nature [11]. An MSN-based tissue glue can lead to the development of a potential substitute for currently available immunogenic reaction-causing glues such as cyanoacrylates. Its use may prevent the delays in healing and the scar tissue formation that is associated with application of stitches [12]. Moreover, mesoporous silica has a honeycomb-like structure and hence it has ability to acquire drug molecules. The action of a tissue glue is based on the nanobridging effect [11]. The numerous protein chains present in body tissues are adsorbed by the nanoparticles, and a connective bridge is created between them. This bridge facilitates the glueing and healing of the wound. Many nanoparticles, such as titanium dioxide nanoparticles, zinc oxide nanoparticles, silica nanoparticles loaded silver nanoparticles, etc., have been shown to exhibit this effect [13]. Curcumin has multiple effects like antiviral, antibacterial, antifungal, antioxidant mediated anticancer, etc. [14,15]. Even

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Research Article

B-SITOSTEROL: ISOLATION FROM *MUNTINGIA CALABURA* LINN. BARK EXTRACT, STRUCTURAL ELUCIDATION, AND MOLECULAR DOCKING STUDIES AS POTENTIAL INHIBITOR OF SARS-COV-2 M^{PRO} (COVID-19)

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ABSTRACT

Objective: A novel human coronavirus, labeled as SARS-CoV-2 (COVID-19), causing pneumonia is spreading around the world. At present, there are no specific treatments for COVID-19. β-sitosterol is well known for its multiple biological actions. This research aims to isolate and study the binding affinity of β-sitosterol for SARS-CoV-2 (COVID-19) main protease (M^{pro}).

Methods: Extraction and column chromatography was performed to isolate the β-sitosterol from an n-hexane extract of Muntingia calabura bark followed by thin-layer chromatography (TLC), high-performance TLC (HPTLC), Fourier-transform infrared (FTIR), and ultraviolet–visible spectroscopy. The molecular docking studies were performed on SARS-CoV-2 M^{pro} to determine the binding affinity of the β-sitosterol using PyRx Virtual Screening Tool.

Results: In the present study, preliminary phytochemical screening showed the presence of carbohydrate, steroid, terpenoid, and flavonoid compounds. A total of 115 fractions was collected from column chromatography using benzene as a solvent by an isocratic elution technique. HPTLC fingerprinting analysis showed the presence of β-sitosterol under 366 nm. FTIR characterization was performed of the same fraction which gives the absorption peaks which resembles the β-sitosterol structure.

Conclusion: The overall study concludes this method can be considered as a standard method for isolation of β-sitosterol from *M. calabura* bark. Favipiravir has a less binding affinity, i.e. −5.7 kcal/mol than β-sitosterol which has −6.9 kcal/mol. The number of hydrogen bonds formed by the favipiravir is much more, i.e., 4 than β-sitosterol which formed only 01 hydrogen bonds with SARS-CoV-2 M^{pro}.

Keywords: *Muntingia calabura*, β-sitosterol, SARS-CoV-2 (COVID-19), Molecular docking, High-performance thin-layer chromatography.

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INTRODUCTION

Muntingia calabura, also known as cherry, it has been an essential herb in the Ayurvedic and indigenous medical systems for over 4000 years. Belong to genus Muntingia which contains about 30 species of tropical fruiting trees in the flowering plant family Tiliaceae. *M. calabura* (Muntingiaceae) grows in the tropical and subtropical regions and its parts are used commonly in folk medicine for a varied variety of conditions. According to Ayurveda, varied medicinal properties are attributed to different parts of the mango tree. Cherry is one of the most popular of all tropical fruits. Various parts of the plant are used as a dentifrice, antiseptic, astringent, diaphoretic, stomachic, vermifuge, tonic, laxative, and diuretic and to treat diarrhea, dysentery, anemia, asthma, bronchitis, cough, hypertension, insomnia, rheumatism, toothache, leucorrhoea, hemorrhage, and piles. All parts are used to treat abscesses, broken horn, rabid dog or jackal bite, tumor, snakebite, stings, Datura poisoning, heatstroke, miscarriage, anthrax, blisters, wounds in the mouth, tympanitis, colic, diarrhea, glossitis, indigestion, bacillosis, bloody dysentery, liver disorders, excessive urination, tetanus and asthma, and hermaphrodite [1-3].

COVID-19 is an infectious disease caused by a coronavirus. A new human coronavirus, which has been labeled SARS-CoV-2, began spreading in December 2019 in Wuhan City, China [4]. As of now until 14 April 2020, there were 1,776,867 confirmed cases, 111,828 confirmed deaths, and 213 countries, areas, or territories with cases around the world (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). The World Health Organization declared this disease pandemic. At present, there are no specific vaccines or treatments for COVID-19. However, many ongoing clinical trials are evaluating potential treatments (https://www.who.int/health-topics/coronavirus#tab=tab_1). Favipiravir has recently been approved for a clinical trial to treat COVID-19. Favipiravir is a purine nucleoside which disturbs viral RNA synthesis, was originally developed by Toyama Chemical of Japan [5]. Therefore, in present work, we have taken favipiravir as a reference molecule for the docking study.

METHODS

Plant material

The plant specimen was collected from Gangapur road, Nashik, Maharashtra, India. Dr. A. Benniamin's, (Scientist-C), (Botanical Survey of India, Koregaon Road, Pune), identified and authenticated the voucher specimen of the plant by comparing morphological features. Voucher specimen no. BBJ-1 (Reference number BSI/WRC/Tech./2013).

Preparation of plant material for extraction

Air-dried bark was processed for size reduction using a cutter mill (portable mixer). The crushed material was passed through #40sieves (coarse powder) for uniform particle size, which gave efficient extraction and yield of extract. The 100 g powder was filled in a Soxhlet apparatus and extracted continuously with n-hexane and methanol. The extraction was conceded until the powder becomes colorless. Then, the content of the round bottom flask was kept for the solvent recovery system which promotes the green chemistry extraction methodology. Approximately 100 ml of n-hexane and methanol were recovered by

Review Article

Pharmacological Activity Investigation of Alkaline Water – A Review

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ABSTRACT

In present study various pharmacological investigation of alkaline water compiled, now days due to fast life acidity become a huge problem in metro cities which is origin for various diseases such a GERD, hypertension, skin diseases, hyperthyroidism, hyperlipidemia, cancer, diabetes etc. Various researches worked on activity of alkaline water and various clinical trials are in tunnel. Compile date elucidate the importance of alkaline water in various diseases treatments and future prospectus in clinical trials of various cancer and related diseases.

Keywords: Alkaline water, acidity, Cancer, Pharmacological investigation.

INTRODUCTION

Acidity is most important and ignored reason in development of different diseases like hypertension[1], skin diseases[2], hyperthyroidism[3], hyperlipidemia[4], cancer [5], diabetes[6] and related diseases etc. In allopathy physician only work on sign and symptoms of the diseases after performing various expensive diagnosis test like ECG, Kidney function, Blood test etc., but the root of this disease condition is completely ignored. The Natural alkaline water is one the solution to cure root of this diseases. In this article would like explore the various researches done on alkaline water and futuristic research possibilities.

Figure 1: Root cause of various life-threatening diseases

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Synthesis of 2,5-disubstituted-1,3,4-thiadiazole derivatives from (2S)-3-(benzyloxy)-2-[(*tert*-butoxycarbonyl) amino] propanoic acid and evaluation of anti-microbial activity

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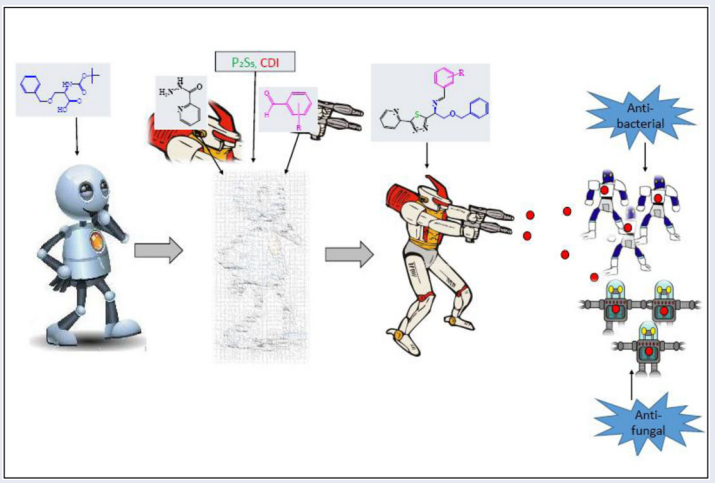
ABSTRACT

The new compounds **AP-1** to **AP-10** were synthesized from starting material (2S)-3-(benzyloxy)-2-[(*tert*-butoxycarbonyl) amino]propanoic acid (**1**). The intermediate 2,5-disubstituted-1,3,4-thiadiazole amine (**5**) was prepared by coupling of (2S)-3-(Benzyloxy)-2-[(tert-butoxycarbonyl) amino]propanoic acid (**1**) with pyridine-2-carboxylic acid hydrazide (**2**) in the presence of carbonyldiimidazole (CDI) followed by 1,3,4-thiadiazole ring formation via diacylhydrazines derivative (**3**) and deprotection with shorter reaction time and excellent yield. The structures of new compounds were confirmed by spectral analysis. The series of new synthesized compounds **AP-1** to **AP-10** were evaluated for their anti-microbial activities *in vitro* and compounds **AP-1**, **AP-3**, **AP-4**, and **AP-10** showed strong activities against all tested microorganisms.

GRAPHICAL ABSTRACT



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Anti-microbial; carbonyldiimidazole; evaluation; pyridine-2-carboxylic acid hydrazide; 1,3,4-thiadiazole

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ORIGINAL ARTICLE

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Pharmacognostical Standardisation of *Ailanthus Excelsa* Leaves and *Randia Dumetorum* Fruit Along with Antioxidant Activity and Free Radical Scavenging Capacity of Its Fractions

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Standardisation, Antioxidant Activity, Ailanthus Excelsa, Randia Dumetorum

ABSTRACT

The world is observing an unprecedented development in the usage of herbal product at national as well as international levels. This requires the improvement of current and aimed standards for estimating the quality, safety and efficacy of these drugs. The leaves of *Ailanthus excelsa* and the fruits of *Randia Dumetorum* are medicinal plants that are used for many diseases around the world. We then collected the flavonoids and saponin fraction extracted from the leaves of Ailanthus excelsa and the fruits of *Randia dumetorum*. To determine the reliability, quality and purity of these particles, we provide a crucial pharmacological profile along with the antioxidant activity. Pharmacological studies, such as morphological, physicochemical, TLC, and phytochemical analysis of all fractions containing total phenol and flavonoids, were performed according to specific methods. DPPH tests estimated the antioxidant action of all fractions, Hydrogen peroxide scavenging assay, and reducing power assay method. Previous phytochemical studies discovered the occurrence of saponins, flavonoids, tannins, and especially phenolic chemicals. All fractions have antioxidant effects, depending on the existence of a phenolic compound. The above parameters are vital to establishing pharmacological rules for the authentication of Ailanthus excelsa leaves and *Randia Dumetorum* fruits.

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INTRODUCTION

Presently there is an enormous deal of awareness in herbal medicine today. This interest is mainly because medicinal plants do not have adverse effects. A quarter of the world's population or 1.42 trillion people are not expected to rely on traditional medicines to treat various diseases (Kadam *et al.*, 2012). Traditional medical systems such as Ayurveda play an essential role in today's health field, especially in the treatment of malignant diseases (Shivatare *et al.*, 2014). However, the most significant barriers to the use of alternative drugs in industrialised countries are the lack of documentation and strict quality control. Research on traditional medicines needs to be documented. In this context, it is vital to try to standardise the plant substance that will be utilised as a remedy (Modi *et al.*, 2010; Shruthi *et al.*, 2010). Normalisation can be done through pharmacological and phyto-


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RESEARCH ARTICLE Open Access

Homozygous variants in the *HEXB* and *MBOAT7* genes underlie neurological diseases in consanguineous families

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Abstract

Background: Neurological disorders are a common cause of morbidity and mortality within Pakistani populations. It is one of the most important challenges in healthcare, with significant life-long socio-economic burden.

Methods: We investigated the cause of disease in three Pakistani families in individuals with unexplained autosomal recessive neurological conditions, using both genome-wide SNP mapping and whole exome sequencing (WES) of affected individuals.

Results: We identified a homozygous splice site variant (NM_000521:c.445 + 1G > T) in the hexosaminidase B (*HEXB)* gene confirming a diagnosis of Sandhoff disease (SD; type II GM2-gangliosidosis), an autosomal recessive lysosomal storage disorder caused by deficiency of hexosaminidases in a single family. In two further unrelated families, we identified a homozygous frameshift variant (NM_024298.3:c.758_778del; p.Glu253_Ala259del) in membrane-bound O-acyltransferase family member 7 (*MBOAT7)* as the likely cause of disease. *MBOAT7* gene variants have recently been identified as a cause of intellectual disability (ID), seizures and autistic features.

Conclusions: We identified two metabolic disorders of lipid biosynthesis within three Pakistani families presenting with undiagnosed neurodevelopmental conditions. These findings enabled an accurate neurological disease diagnosis to be provided for these families, facilitating disease management and genetic counselling within this population. This study consolidates variation within *MBOAT7* as a cause of neurodevelopmental disorder, broadens knowledge of the clinical outcomes associated with *MBOAT7*-related disorder, and confirms the likely presence of a regionally prevalent founder variant (c.758_778del; p.Glu253_Ala259del) in Pakistan.

Keywords: Neurological disorder, *HEXB*, *MBOAT7*, Exome sequencing, Sandhoff disease, Pakistan

Background

Neurological disorders cause structural, functional, biochemical or electrical abnormalities in the nervous system, resulting in cognitive impairment, seizures, muscle weakness, paralysis, poor coordination and mood alteration. Neurological disorders are an increasing burden in developing countries due to improving life expectancy, urbanisation of the population and improved health care and diagnosis. A higher prevalence of intellectual disability (ID) and epilepsy have been identified within Pakistani populations compared with more economically developed countries [1, 2]. In Pakistan, 82.5% of the parents are blood relatives due to religious, economic, social and cultural reasons in different regions [3]. The *HEXB* gene encodes the hexosaminidase beta subunit, which forms a heterodimer with the alpha subunit in hexosaminidase A (HEXA) and a homodimer in hexosaminidase B (HEXB), which are important enzymes within neuronal membrane components responsible for GM2 ganglioside degradation. Sandhoff disease (SD)(MIM 268800) is an autosomal recessive lysosomal lipid storage disorder caused by biallelic variants within the *HEXB* gene, resulting in deficiency of HEXA and HEXB enzymes [4] and intralysosomal accumulation of GM2

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BMC Medical Genetics

RESEARCH ARTICLE Open Access

Novel nonsense variants in *SLURP1* and *DSG1* cause palmoplantar keratoderma in Pakistani families

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Abstract

Background: Inherited palmoplantar keratodermas (PPKs) are clinically and genetically heterogeneous and phenotypically diverse group of genodermatoses characterized by hyperkeratosis of the palms and soles. More than 20 genes have been reported to be associated with PPKs including desmoglein 1 (*DSG1*) a key molecular component for epidermal adhesion and differentiation. Mal de Meleda (MDM) is a rare inherited autosomal recessive genodermatosis characterized by transgrediens PPK, associated with mutations in the secreted LY6/PLAUR domain containing 1 (*SLURP1*) gene.

Methods: This study describes clinical as well as genetic whole exome sequencing (WES) and di-deoxy sequencing investigations in two Pakistani families with a total of 12 individuals affected by PPK.

Results: WES identified a novel homozygous nonsense variant in *SLURP1*, and a novel heterozygous nonsense variant in *DSG1*, as likely causes of the conditions in each family.

Conclusions: This study expands knowledge regarding the molecular basis of PPK, providing important information to aid clinical management in families with PPK from Pakistan.

Keywords: Mal de Meleda, Palmoplantar keratoderma, *SLURP1*, *DSG1*, Mutation, Variant, Exome sequencing

Background

Palmoplantar keratoderma (PPK) is a heterogeneous entity of both genetics and acquired keratinization disorder, which is characterized by persistent marked epidermal thickening of palms and soles [1]. Hereditary PPKs comprising an increasing number of entities with different prognoses, which may be associate with cutaneous and extracutaneous manifestations [2].

Depending on different patterns of hyperkeratosis, PPKs are further classified into four distinct types: diffuse, striate, focal and punctate [3, 4]. So far, deleterious mutations in > 20 genes have been reported in pathogenesis of different forms of hereditary PPKs [3, 4]. In last few years, advent of cutting edge genetic techniques such as whole genome microarray scans and whole exome sequencing have incredibly accelerated the identification of disease causing variants in many genes involved in various inherited forms of PPKs, and thus significantly increasing understanding about intricate molecular mechanisms of heterogeneous disorders, consecutively aiding valuable genetic counselling and patient care [3].

Mal de Meleda (MDM), a type of transgradient palmoplantar keratoderma (PPK), is a rare autosomal recessive disorder. Luca Stulli, a Croatian born scientist in 1826 first described Mal de Meleda on the Adriatic Meleda island (now Mljet) [5]. The disease can feature other potentially disfiguring effects on the hands and feet that can severely impact function.

The disease onset is soon after birth and is clinically characterized by erythema, transgradients and progradients hyperkeratosis of palms and soles with well demarcated borders and hypohydrosis. Other associated features are brachydactyly, nail abnormalities and lichenoid plaques [6]. Rigorous keratoderma can lead to deformity in

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Glucosamine HCl-based solid dispersions to enhance the biopharmaceutical properties of acyclovir.

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Original Article

ABSTRACT

The objective of the work presented here was to assess the feasibility of using glucosamine HCl as a solid-dispersion (SD) carrier to enhance the biopharmaceutical properties of a BCS class III/IV drug, acyclovir (ACV). The solid-dispersions of acyclovir and glucosamine HCl were prepared by an ethanol-based solvent evaporation method. The prepared formulations characterized by photomicroscopy, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Fourier transforms infrared spectrophotometry (FTIR), powder x-ray diffractometry (PXRD) and drug content analysis. The functional characterization of ACV-SD was performed by aqueous solubility evaluation, dissolution studies, fasted *versus* fed state dissolution comparison, ex vivo permeability, and stability studies. Photomicroscopy and SEM analysis showed different surface morphologies for pure ACV, glucosamine HCl and ACV-SD. The physical-chemical characterization studies supported the formation of ACV-SD. A 12-fold enhancement in the aqueous solubility of ACV was observed in the prepared solid dispersions, compared to pure ACV. Results from *in vitro* dissolution demonstrated a significant increase in the rate and extent of ACV dissolution from the prepared ACV-SD formulations, compared to pure ACV. The rate and extent of ACV permeability across everted rat intestinal membrane were also found to be significantly increased in the ACV-SD formulations. Under fed conditions, the rate and extent of the *in vitro* dissolution of ACV from the formulation was appreciably greater compared to fasted conditions. Overall, the results from the study suggest the feasibility of utilizing glucosamine HCl as a solid dispersion carrier/excipient for enhancement of biopharmaceutical properties of acyclovir, and similar drugs with low solubility/permeability characteristics.

KEY WORDS: Acyclovir, ACL, glucosamine HCl, solid dispersion, solubility, permeability, excipients

INTRODUCTION

Modern drug discovery techniques, which include high throughput screening and combinatorial chemistry, have generated new molecules with solubility characteristics that result in lower and inconsistent oral bioavailability (1). Over half of all newly discovered drugs appears to fall into biopharmaceutics classification system's (BCS) class II (↓ solubility, ↑ permeability), Class III (↑ solubility, ↓ permeability) or class IV (↓ solubility, ↓ permeability) (2). These drugs exhibit dissolution and/or permeation rate-limited absorption. For these drugs, enhancement of dissolution rate and/or permeability is vital to attain suitable blood concentration to achieve optimal bioavailability for therapeutic effect (3-5). Thus, for a formulation development team, there is a consistent and well-justified need to explore

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Review Article

Quality by Design: A Roadmap for Quality Pharmaceutical Products

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Abstract

Quality by design (QbD) refers to a new approach to product development that could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product life cycle. QbD is increasingly becoming an important and widely used technique in the pharmaceutical industry. QbD can be considered to be system-based approach to the design, development, and delivery of any product or service to a consumer. It is an approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control. Process parameters and quality attributes are identified for each unit operation. Benefits, opportunities, and steps involved in QbD of pharmaceutical products are described. The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products, but quality should be built in by design. It includes the quality target product profile, critical quality attributes, and key aspects of QbD. It also gives comparison between product quality by end product testing and product quality by QbD. The foundation of QbD is ICH guidelines. Hence, if we identify the cause and effect relationship between the various inputs and responses by carefully designed experiments, we can control the quality of the product by simply controlling the inputs such as raw material specifications or process parameters.

Keywords: *Critical quality attributes, pharmaceutical manufacturing, process analytical technology, quality by design*

Introduction

Quality by design (QbD) means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. In pharmaceutical industry, QbD identifies characteristics that are critical to quality from the perspective of patients and health care team, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters (CPPs) can be varied to consistently produce a drug product with the desired characteristics. The main concept of QbD is that all final product critical quality attributes (CQAs) are affected by raw materials and process parameters. Hence, if we identify the cause and effect relationship between the various inputs and responses, we can control the quality of the product by simply controlling the inputs such as raw material specifications or process parameters. As a result, the final product will always conform to the quality specifications.[1]

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development or a combination of both. A more systematic approach to development (also defined as QbD) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management (QRM), and use of knowledge management (ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.[2]

Quality by Design

This concept was first outlined by well-known quality expert Joseph M. Juran

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