

BEST PRACTICE - 1

**Title: InnovateRx: Empowering
Research Excellence in
Pharmaceutical Sciences**

SMT. KISHORITAI BHOYAR COLLEGE OF PHARMACY, KAMPTEE

BEST PRACTISE -1

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The key objectives of this practice are as follows:

1. Foster an environment conducive to fostering innovative research ideas.
2. Inspire faculty members, post-graduate students, and research scholars to engage actively in research.
3. Generate funds to bolster research activities and provide necessary facilities.
4. Produce high-quality publications, patents, and consultancy services.

The Context

Research and development serve as the cornerstone of any educational institution focusing on pharmaceutical sciences due to its direct correlation with health and the drug discovery process. Our institute is dedicated to making significant contributions to pharmaceutical sciences and healthcare through a strong emphasis on research and innovation. To materialize this vision, a meticulously crafted action plan has been devised and strategically implemented.

The Practice

The institute has implemented various measures to promote a culture of research and development:

- ✓ Introduction of a research incentive policy encouraging faculty members to actively pursue research grants, publish in esteemed peer-reviewed journals, and engage in patent filings.
- ✓ Allocation of financial support for faculty members and students to participate in national research conferences, seminars, and workshops, facilitating knowledge exchange and skill enhancement.
- ✓ Establishment of a research committee to monitor and promote research activities, ensuring continual enhancements in each department's research quality.
- ✓ Rigorous monitoring and supervision of research work undertaken by undergraduate, postgraduate, and doctoral students by their respective guides and the Research Advisory committee constituted by RTM Nagpur University.
- ✓ Acquisition of anti-plagiarism software for analyzing manuscripts submitted to journals, Ph.D. theses submitted to the university, and research proposals submitted to funding agencies.
- ✓ Mandatory submission of certificates by research students and guides affirming

the originality of work and proper acknowledgment of references and contributions.

- ✓ Approval of animal protocols through IAEC following CPCSEA committee guidelines.
- ✓ Collaborative research and Organization of seminars and workshops aimed at enhancing theoretical and practical skills.

Evidence of Success

- ✓ The institute has made substantial strides in various research areas, including formulation and development, synthesis of new chemical entities, pharmacological and biological screenings, phytochemical isolation, purification, and characterization.
- ✓ A noteworthy achievement includes 267 publications and 678 presentations in highly reputable peer-reviewed journals over the last five years, garnering substantial citations, demonstrating the credibility and acceptance of the institute's research.
- ✓ Faculty members secured approximately 2.5 crore rupees in research grants from esteemed funding agencies.
- ✓ Furthermore, the institute and its faculty members have obtained 6 Indian patents and 2 international patents. This robust research output underscores the institute's commitment to integrity in drug discovery processes.
- ✓ This comprehensive approach has significantly elevated our research output, contributing to the institute's reputation in pharmaceutical sciences and propelling it forward in the realm of innovative drug discovery and development.
- ✓ Faculty and students have received several awards at scientific platform organized by Professional organizations and government agencies
- ✓ Significant research output through collaborative research work with reputed academic institutions.

Problems Encountered and Resources Required

- ✓ While departments have established their research areas, there's a need for more multidisciplinary research.
- ✓ Additional research funding is essential to advance R&D activities and supplement consultancy services for the pharmaceutical industry.

7. Notes (Optional)

Please add any other information that may be relevant for adopting/implementing the Best Practice in other Institutions (in about 150 words).

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Supportive Documents

1. List of Govt. research grants and funding
2. List of major Publications in last five years
3. List of Patents granted
4. List of Awards received by faculty and students
5. Significant Research Outcome

GRANTS/FUNDINGS BY GOVERNMENT AGENCIES

Faculty	Scheme	Funding agency	Year of award	Amount Sanctioned
Dr. B. G. Taksande	Start up research Grant	Science & Engineering Research Board (SERB)	2016	21,75,000/-
Dr. N. R. Kotagale Dr. B.G. Taksande	Extra Mural Research	Science & Engineering Research Board (SERB)	2016	39,67,679/-
Dr. K. J. Wadher	Skill and Personality Development for SC/ST	Department of Science and Technology	2017	9,09,129/-
Dr. A. T. Patil	Adjunct Professor scheme	AICTE	2017	6,00,000/-
Dr. M. J. Umekar	Skill and Personality Development centre	AICTE	2017	22,69,706/-
Dr. K. J. Wadher	Entrepreneurship development programme	EDII DST NIMET	2018	2,20,000/-
Dr. M. J. Umekar	Prerna	AICTE	2018	8,15,000/-
Dr. M. J. Umekar	Faculty Development Program	AICTE	2018	4,92,000/-
Dr. A. T. Patil	Faculty Development Program	AICTE	2018	4,56,000/-
Dr. Rashmi Trivedi	International Travel grant	AICTE	2019	75,000/-
Dr. Milind Umekar	MODROB	AICTE	2019	12,00,000/-

Dr. Milind Umekar	Short term training program	AICTE	2019	3,00,000/-
Dr. B. G. Taksande	Short term training program	AICTE	2019	2,50,000/-
Dr. K.J. Wadher	Research Promotion Scheme	AICTE	2020	22,35,294/-
Dr. Krishna Gupta	Short term training program	AICTE	2020	2,64,000/-
Dr. Rashmi Trivedi	ATAL FDP	AICTE	2020	93,000/-
Dr. Renuka Das & Mr. Manish Aglawe	AICTE LILAVATI AWARD	AICTE	2021	1,00,000/-
Mr. Manish Aglawe	Senior research fellowship	ICMR	2021	10,14,000/-
Dr. Milind Umekar	AICTE Spices	AICTE	2021	1,00,000/-
Dr. B.G. Taksande	Extra Mural Research	Science & Engineering Research Board (SERB)	2022	35,03,764/-
Dr. Brijesh Taksande	Extra Mural Research	ICMR	2023	45,15,050/-
Total: Two Crore, Fifty-Four Lakh, Seventy-Two Thousand, Six Hundred and Twenty-Two Only				2,54,72,622/-

LIST OF PUBLICATIONS IN HIGH IMPACT JOURNALS (2018-2023)

Sr No.	Title of paper	Name of journal	Year	Impact factor	publisher
1	Mitochondrial Dysfunction as a Signaling Target for Therapeutic Intervention in Major Neurodegenerative Disease	Neurotoxicity Research	2023	3.978	Springer Science
2	Mitophagy regulation in aging and neurodegenerative disease	Biophysical Reviews	2023	1.463	Springer Science
3	Agmatine prevents the manifestation of impulsive burying and depression-like behaviour in progesterone withdrawn female rats	Hormones and Behavior	2023	3.492	Elsevier
4	Nattokinase prevents β -amyloid peptide (A β 1-42) induced neuropsychiatric complications, neuroinflammation and BDNF signalling disruption in mice	European Journal of Pharmacology	2023	5	Elsevier
5	Recent Perspectives on Cardiovascular Toxicity Associated with Colorectal Cancer Drug Therapy	Pharmaceuticals	2023	5.215	MDPI
6	Overview on the Polyphenol Avenanthramide in Oats (<i>Avena sativa</i> Linn.) as Regulators of PI3K Signaling in the Management of Neurodegenerative Diseases	Nutrients	2023	6.706	MDPI
7	Molecular understanding of ER-MT communication dysfunction during neurodegeneration	Mitochondrion	2023	4.31	Elsevier

8	Achyranthes aspera ameliorates stress induced depression in mice by regulating neuroinflammatory cytokines	Pharmaceutics	2022	6.525	MDPI
9	Agmatine prevents development of tolerance to anti-nociceptive effect of ethanol in mice	Alcohol	2022	2.3	Elsevier
10	Involvement of molecular chaperone in protein-misfolding brain diseases.	Biomedicine and Pharmacotherapy	2022	7.5	Elsevier
11	Chronic agmatine treatment prevents olanzapine-induced obesity and metabolic dysregulation in female rats.	Brain research bulletin	2022	3.715	Elsevier
12	Alzheimer's disease and sleep disorders: Insights into the possible disease connections and the potential therapeutic targets	Asian Journal of Psychiatry	2022	13.89	Elsevier
13	Interweaving of reactive oxygen species and major neurological and psychiatric disorders	Annales Pharmaceutiques Françaises	2022	0.184	Elsevier
14	Phytotherapy: A promising approach for the treatment of Alzheimer's disease	Pharmacological Research-Modern Chinese Medicine	2022	1.07	Elsevier
15	Functional polysaccharide lentinan: Role in anti-cancer therapies and management of carcinomas	Pharmacological Research-Modern Chinese Medicine	2022	1.07	Elsevier
16	Analytical profiling of Lentinan in hybrid nanostructures for intranasal Delivery: Method development and Validation	Results in Chemistry	2022	2.3	Elsevier
17	An Overview of Diabetic Foot Ulcers and Associated Problems with Special Emphasis on	Life	2022	3.2	MDPI

Treatments with Antimicrobials					
18	Polysaccharide-based hydrogels for drug delivery and wound management: a review	Expert Opinion on Drug Delivery	2022	8.129	Taylor & Francis
19	Neurodegenerative disorders associated with genes of mitochondria. Future Journal of Pharmaceutical Sciences	Future Journal of Pharmaceutical Sciences	2021		Springer Science
20	Interweaving epilepsy and neurodegeneration: Vitamin E as a treatment approach	Biomedicine and pharmacotherapy	2021	7.5	Elsevier
21	Agmatine improves the behavioral and cognitive impairments associated with chronic gestational ethanol exposure in rats.	Brain Research Bulletin	2021	3.715	Elsevier
22	Possible involvement of agmatine in neuropharmacological actions of metformin in diabetic mice	European Journal of Pharmacology	2021	5	Elsevier
23	Evidences for agmatine alterations in A β 1-42induced memory impairment in mice	Neuroscience Letters	2021	3.197	Elsevier
24	Self-Assembling Dioscorea bulbifera loaded mixed micelles: Formulation optimization, in-vitro cytotoxicity and in-vivo pharmacokinetics	Journal of Drug Delivery Science and Technology	2021	5.062	Elsevier
25	Evaluation of antipsoriatic activity of gel containing Pongamia pinnata extract on Imiquimod-induced psoriasis	<i>Clinical Phytoscience</i>	2021		Springer Science

26	Development of topical thymoquinone loaded polymer-lipid hybrid vesicular gel: in-vitro and ex-vivo evaluation	Journal of Liposome Research	2021	5.586	Taylor and Francis Ltd.
27	Investigation of the influence of cellulose polymer on solid phase transformation of carbamazepine	Journal of Crystal Growth	2021	1.83	Elsevier
28	3D printing in pharmaceuticals: An emerging technology full of challenges.	Annales Pharmaceutiques Françaises	2021	1.36	Elsevier
29	Studies on meropenem and cefixime metal ion complexes for antibacterial activity.	Future Journal of Pharmaceutical Sciences	2021		Springer Science
30	Inhibitory Influence of Agmatine in Ethanol Withdrawal-Induced Depression in Rats: Behavioral Elsevier and Neurochemical Evidences	Alcohol	2020	2.558	Elsevier
31	Involvement of Agmatine in Antidepressant-like Effect of HMG-CoA Reductase Inhibitors in Mice	European Journal of Pharmacology	2020	5	Elsevier
32	Evidences for Agmatine alterations in A β 1-42 induced Memory Impairment in Mice	Neuroscience Letters	2020	3.197	Elsevier
33	Agmatine modulates anxiety and depression-like behaviour in diabetic insulin-resistant rats (PMID - 327584810)	Brain Research	2020	3.61	Elsevier
34	Agmatine reverses memory deficits induced by A β 1-42 peptide in mice: A key role of imidazoline receptors	Pharmacology Biochemistry and Behavior	2020	3.697	Elsevier

35	Involvement of hippocampal agmatine in β 1-42 amyloid induced memory impairment, neuroinflammation and BDNF signaling disruption in mice	NeuroToxicology	2020	3.379	Elsevier
36	LIPOID SPC-3-Based Coprecipitates for the Enhancement of Aqueous Solubility and Permeability of Ranolazine	Journal of Pharmaceutical Innovation	2020	2.538	Springer Science
37	Phospholipid complex-loaded self-assembled phytosomal soft nanoparticles: evidence of enhanced solubility, dissolution rate, ex-vivo permeability, oral bioavailability and antioxidant potential of Mangiferin.	Drug Delivery and Translational Research	2020	5.671	Springer Science
38	Agmatine reverses ethanol consumption in rats: Evidences for an interaction with imidazoline receptors	Pharmacology Biochemistry and Behavior	2019	3.697	Elsevier
39	Effect of Explant Source, Culture Media, and Growth Regulators on Callogenesis and Expression of Secondary Metabolites of <i>Curcuma Longa</i>	Journal of Herbs, Spices & Medicinal Plants	2019	0.256	Taylor and Francis Ltd.
40	Enhanced transdermal permeation and anti-inflammatory potential of phospholipids complex-loaded matrix film of umbelliferone: Formulation development, physico-chemical and functional characterization	European Journal of Pharmaceutical Sciences	2019	5.112	Elsevier
41	Development of self-assembled nanocarriers to enhance antitumor efficacy of docetaxel	Int J Biol Macromol.	2019	8.025	Elsevier

	trihydrate in MDA-MB-231 cell line				
42	Neuroprotective effect of agmatine in mouse spinal cord injury model: Modulation by imidazoline receptors	Journal of Natural Science, Biology and Medicine	2018	0.187	
43	Withaferin A attenuates Alcohol Abstinence Signs in Rats	Pharmacognosy Journal	2018	0.258	<u>Elsevier</u>
44	Agmatine inhibits nicotine withdrawal induced cognitive deficits in inhibitory avoidance task in rats: Contribution of $\alpha 2$ -adrenoceptors	Pharmacology Biochemistry and Behavior	2018	3.697	<u>Elsevier</u>
45	Design, evaluation and in vivo pharmacokinetic study of a cationic flexible liposomes for enhanced transdermal delivery of pramipexole	Journal of Drug Delivery Science and Technology	2018	5.062	Elsevier



Mitochondrial Dysfunction as a Signaling Target for Therapeutic Intervention in Major Neurodegenerative Disease

Shubhada V. Mangrulkar¹ · Nitu L. Wankhede² · Mayur B. Kale¹ · Aman B. Upaganlawar³ · Brijesh G. Taksande¹ · Milind J. Umekar¹ · Md. Khalid Anwer⁴ · Hamad Ghaleb Dailah⁵ · Syam Mohan^{6,7,8} · Tapan Behl⁷

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Abstract

Neurodegenerative diseases (NDD) are incurable and the most prevalent cognitive and motor disorders of elderly. Mitochondria are essential for a wide range of cellular processes playing a pivotal role in a number of cellular functions like metabolism, intracellular signaling, apoptosis, and immunity. A plethora of evidence indicates the central role of mitochondrial functions in pathogenesis of many aging related NDD. Considering how mitochondria function in neurodegenerative diseases, oxidative stress, and mutations in mtDNA both contribute to aging. Many substantial reports suggested the involvement of numerous contributing factors including, mitochondrial dysfunction, oxidative stress, mitophagy, accumulation of somatic mtDNA mutations, compromised mitochondrial dynamics, and transport within axons in neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis. Therapies therefore target fundamental mitochondrial processes such as energy metabolism, free-radical generation, mitochondrial biogenesis, mitochondrial redox state, mitochondrial dynamics, mitochondrial protein synthesis, mitochondrial quality control, and metabolism hold great promise to develop pharmacological based therapies in NDD. By emphasizing the most efficient pharmacological strategies to target dysfunction of mitochondria in the treatment of neurodegenerative diseases, this review serves the scientific community engaged in translational medical science by focusing on the establishment of novel, mitochondria-targeted treatment strategies.

Keywords Mitochondrial dysfunction · Oxidative stress · Mitochondrial quality control · Fusion · Fission · Mitochondrial medicine

Introduction

Neurodegenerative diseases are diverse group of devastating, and incurable condition, defined by the gradual deterioration and death of cells in the central nervous system. These pathological conditions, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease

(HD), and amyotrophic lateral sclerosis (ALS), are distinguished by the gradual loss of neuron cells, impaired motor or cognitive functions, and abnormal accumulation aggregated proteins. An increasing amount of research on NDD shows changes to the brain's reduction–oxidation (redox) equilibrium as well as bioenergetics deficits (Yap et al. 2009).

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Mitophagy regulation in aging and neurodegenerative disease

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Abstract

Mitochondria are the primary cellular energy generators, supplying the majority of adenosine triphosphate through oxidative phosphorylation, which is necessary for neuron function and survival. Mitophagy is the metabolic process of eliminating dysfunctional or redundant mitochondria. It is a type of autophagy and it is crucial for maintaining mitochondrial and neuronal health. Impaired mitophagy leads to an accumulation of damaged mitochondria and proteins leading to the dysregulation of mitochondrial quality control processes. Recent research shows the vital role of mitophagy in neurons and the pathogenesis of major neurodegenerative diseases. Mitophagy also plays a major role in the process of aging. This review describes the alterations that are being caused in the mitophagy process at the molecular level in aging and in neurodegenerative diseases, particularly Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis; also looks at how mitophagy can be exploited as a therapeutic target for these diseases.

Keywords Mitochondria · Mitophagy · Aging · Neurodegenerative diseases · Alzheimer's disease · Parkinson's disease · Amyotrophic lateral sclerosis

Background

Mitochondria are the cell's primary source of energy, regulating physiology and metabolism (Spinelli and Haigis 2018). Mitophagy is a process that eliminates damaged or unwanted mitochondria to maintain homeostasis and cellular metabolism (Ma et al. 2020). It is a selective type of autophagy that focuses on eliminating dysfunctional

mitochondria (Rodolfo et al. 2018). Mitochondrial metabolism, such as oxidative phosphorylation, generated a variety of reactive oxygen species (ROS) and submitochondrial particles. Mitochondria are highly susceptible to ROS damage due to their metabolic function (Chen and Zweier 2014). The damage to mitochondria is not solely caused by pathological conditions or oxidative stress; healthy mitochondria gradually accumulate oxidative damage hallmarks with time.

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Agmatine prevents the manifestation of impulsive burying and depression-like behaviour in progesterone withdrawn female rats

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ARTICLE INFO

Keywords

Agmatine
Depression
Premenstrual dysphoric disorder
Forced swim test
Marble burying behaviour

ABSTRACT

Premenstrual dysphoric disorder (PMDD) is characterized by various physical and affective symptoms, including anxiety, irritability, anhedonia, social withdrawal, and depression. The present study investigated the role of the agmatine system in animal model of progesterone withdrawal in female rats. Chronic progesterone exposure of female rats for 21 days and its abrupt withdrawal showed enhanced marble burying, increased immobility time, and reduced no. of entries in open arm as compared to control animals. The progesterone withdrawal-induced enhanced marble burying anxiety and immobility time was significantly attenuated by agmatine (5–20 mg/kg, i.p.), and its endogenous modulators like L-arginine (100 mg/kg, i.p.), nitro-L-arginine (25 mg/kg, i.p.) and arcanine (50 mg/kg, i.p.) by their once-daily administration from day 14–day 21 of the protocol. We have also analysed the levels of agmatine, progesterone, and inflammatory cytokines in the hippocampal region of progesterone withdrawn rats. There was a significant decline in agmatine and progesterone levels and an elevation in cytokine levels in the hippocampal region of progesterone withdrawn rats compared to the control animals. In conclusion, the present studies suggest the importance of the endogenous agmatine system in progesterone withdrawal-induced anxiety-like and depression-like behaviour. The data also projects agmatine as a potential therapeutic target for the premenstrual dysphoric disorder.

1. Introduction

Premenstrual dysphoric disorder (PMDD) is characterized by a range of physical and affective symptoms, including anxiety, irritability, anhedonia, social withdrawal, and depression (Hanley and Hooper, 2021). Cyclical premenstrual symptoms develop when estrogen and progesterone levels decrease during the late luteal phase of the menstrual cycle and remit at or soon after the onset of menses (American Psychiatric Association, 1995). Normally, these menstrual cycle-related ailments are mild and do not require therapeutic interventions, but approximately 5% of women are severely disabled by these symptoms (Halbreich, 2003). Both anxiety and depressed mood are among the symptoms frequently occurring during the luteal phase of the menstrual cycle (Hartlage and Arduini, 2002). Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat PMDD. However, the response rate is unsatisfactory and side effects are inevitable, especially in the long-term treatment. Thus, drug development is urgently needed

in the therapeutic management of PMDD.

Agmatine, an endogenous amine, has been implicated in the process of stress modulation and co-morbid psychiatric disorders, including depression (Li et al., 2003; Taksande et al., 2009; Kotagale et al., 2013a, 2013b; Chen et al., 2018; Fritov et al., 2018; Neis et al., 2018; Ostadhaft et al., 2018; Singh et al., 2017). Agmatine is biosynthesized following the decarboxylation of L-arginine by arginine decarboxylase (ADC) in the mammalian brain and other tissues (Regunathan and Reis, 2000). It is considered a neurotransmitter in the brain, being synthesized, stored in synaptic vesicles, accumulated by uptake, released by depolarization, and degraded by agmatinase into a polyamine, putrescine. Agmatine binds to α_2 -adrenoceptors and imidazoline binding sites, and blocks NMDA receptor channels and other ligand-gated cationic channels. Furthermore, agmatine inhibits nitric oxide synthase, and induces the release of some peptide hormones (Reis and Regunathan, 2000; Halami and Pluetz, 2007).

Agmatine is a pleiotropic molecule with many central and peripheral

Abbreviations: PMDD, Premenstrual Dysphoric Disorder.

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Nattokinase prevents β -amyloid peptide ($A\beta_{1-42}$) induced neuropsychiatric complications, neuroinflammation and BDNF signalling disruption in mice

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ARTICLE INFO

Keywords:

Nattokinase

Alzheimer's disease

β -amyloid ($A\beta_{1-42}$) peptide

Neuroinflammation

Depression

Anxiety

Memory impairment

ABSTRACT

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder characterized by abnormal accumulation of extracellular β -amyloid ($A\beta$) plaques and neuronal damage. Although AD is typically considered a cognitive neurodegenerative disorder, almost all people diagnosed with AD develop neuropsychiatric complications at some stage in their life span. The present study investigated the effect of chronic Nattokinase (NK) administration on β -Amyloid peptide ($A\beta_{1-42}$) induced neuropsychiatric conditions (depression-like behaviour, anxiety, and memory impairment) in mice. $A\beta_{1-42}$ peptide injected mice demonstrated depression, anxiety, and impairment of cognitive abilities evaluated as increased immobility time in forced swim test (FST), decreased open arm time/entries in elevated plus maze (EPM) and reference and working memory error in radial arm maze (RAM) respectively with elevation in Interleukin-6 (IL-6), Tumour necrosis factor- α (TNF- α), reduction in Interleukin-10 (IL-10) and Brain-derived neurotrophic factor (BDNF) immunoreactivity within the hippocampus. Chronic administration of NK (50–100 mg/kg, i.p.) from day 8–27, prevented depression-like behaviour, anxiety, and memory impairment and normalized the neurochemical alteration within the hippocampus of mice injected with $A\beta_{1-42}$ peptide. The effect of NK on psychiatric complications, learning, and memory was comparable to peripheral donepezil treatment. This study suggests that NK improves learning, memory impairment, and neuropsychiatric complications possibly through the downregulation of neuroinflammatory pathways and restoring BDNF signalling in AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder most often associated with memory deficits and cognitive decline (Marrero and Koch, 2014). The primary causes of AD are largely unknown and there remain no effective treatment options for the majority of patients (DeTure and Dickson, 2019). The cardinal pathological features of the disease include abnormal amyloid plaque formation and neurofibrillary tangles deposition in the brain. $A\beta$ peptide is the main component of senile plaques and a major contributing factor for neurodegeneration associated with AD acting through neurotoxic mechanisms and neuroinflammation (Kojima et al., 2008). The pathology of AD is not only limited to neurotoxicity within certain brain areas but also involves abnormal cerebral vasculature due to decreased cerebral blood

flow and blood-brain barrier dysfunction (Kopani and Schneider, 2016). This typical neurovascular damage in AD provides direct access to fibrinogen in the central nervous system (Alm et al., 2010). Hence, AD condition is commonly characterized by elevated fibrinogen, decreased fibrinolysis, increased clot formation, and elevated levels of coagulation factors and activated platelets (Cortes-Castelli et al., 2012). Abnormal deposition of fibrinogen in the brain of AD patients contributed to $A\beta$ deposition, decreased cerebral blood flow, exacerbated neuroinflammation, and eventual neurodegeneration (Nelson et al., 2016). On the other hand, reducing fibrinogen levels not only ameliorates cerebral amyloid angiopathy but also reduces neuroinflammation and improves cognitive performance in AD mouse models (Singh et al., 2021). Importantly, fibrinogen in the cerebral spinal fluid has been identified as a useful biomarker to distinguish between AD and cognitively normal or

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Review

Recent Perspectives on Cardiovascular Toxicity Associated with Colorectal Cancer Drug Therapy

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Abstract: Cardiotoxicity is a well-known adverse effect of cancer-related therapy that has a significant influence on patient outcomes and quality of life. The use of antineoplastic drugs to treat colorectal cancers (CRCs) is associated with a number of undesirable side effects including cardiac complications. For both sexes, CRC ranks second and accounts for four out of every ten cancer deaths. According to the reports, almost 39% of patients with colorectal cancer who underwent first-line chemotherapy suffered cardiovascular impairment. Although 5-fluorouracil is still the backbone of chemotherapy regimen for colorectal, gastric, and breast cancers, cardiotoxicity caused by 5-fluorouracil might affect anywhere from 1.5% to 18% of patients. The precise mechanisms underlying cardiotoxicity associated with CRC treatment are complex and may involve the modulation of various signaling pathways crucial for maintaining cardiac health including TKI ErbB2 or NRG-1, VEGF, PDGF, BRAF/Ras/Raf/MEK/ERK, and the PI3/ERK/AMPK/mTOR pathway, resulting in oxidative stress, mitochondrial dysfunction, inflammation, and apoptosis, ultimately damaging cardiac tissue. Thus, the identification and management of cardiotoxicity associated with CRC drug therapy while minimizing the negative impact have become increasingly important. The purpose of this review is to catalog the potential cardiotoxicities caused by anticancer drugs and targeted therapy used to treat colorectal cancer as well as strategies focused on early diagnosing, prevention, and treatment of cardiotoxicity associated with anticancer drugs used in CRC therapy.

Keywords: colorectal cancer; cardiotoxicity; chemotherapy; oxidative stress; apoptosis; 5-fluorouracil

1. Introduction

Colorectal cancer (CRC) is the leading cause of morbidity and mortality worldwide. CRC is the third most common cancer in women and the fourth most common cancer in men overall. In recent years, the prevalence of CRC has been rapidly rising worldwide. Globally, it was predicted that there would be 1.93 million newly diagnosed CRC cases and 0.94 million deaths from CRC in 2020, resulting in 10% of the total cancer incidence (more than 19.29 million new cases) and 9.4% of the total cancer-related deaths (9.96 million deaths). With an expected 419,536 fatalities for women and 515,637 deaths for men in

Review

Overview on the Polyphenol Avenanthramide in Oats (*Avena sativa* Linn.) as Regulators of PI3K Signaling in the Management of Neurodegenerative Diseases

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Abstract: Avenanthramides (Avns) and their derivatives, a group of polyphenolic compounds found abundantly in oats (*Avena sativa* Linn.), have emerged as promising candidates for neuroprotection due to their immense antioxidant, anti-inflammatory, and anti-apoptotic properties. Neurodegenerative diseases (NDDs), characterized by the progressive degeneration of neurons, present a significant global health burden with limited therapeutic options. The phosphoinositide 3-kinase (PI3K) signaling pathway plays a crucial role in cell survival, growth, and metabolism, making it an attractive target for therapeutic intervention. The dysregulation of PI3K signaling has been implicated in the pathogenesis of various NDDs including Alzheimer's and Parkinson's disease. Avns have been shown to modulate PI3K/AKT signaling, leading to increased neuronal survival, reduced oxidative stress, and improved cognitive function. This review explores the potential of Avn polyphenols as modulators of the PI3K signaling pathway, focusing on their beneficial effects against NDDs. Further, we outline the need for clinical exploration to elucidate the specific mechanisms of Avn action on the PI3K/AKT pathway and its potential interactions with other signaling cascades involved in neurodegeneration. Based on the available literature, using relevant keywords from Google Scholar, PubMed, Scopus, Science Direct, and Web of Science, our review emphasizes the potential of using Avns as a therapeutic strategy for NDDs and warrants further investigation and clinical exploration.

Keywords: avenanthramide; AKT-protein kinase B; Alzheimer's disease; Parkinson's disease; oxidative stress; neuroprotection



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1. Introduction

Since ancient times, cultivated oats have been an important cereal crop for human consumption worldwide. Recently, interest in oats has been increased due to their nutritional properties and associated health benefits [1]. In the world grain ranking, oats were placed sixth for their nutritional values and regarded as most suitable for cultivation under variable climatic and soil conditions [2,3]. Cereal oats contain numerous bioactive compounds with high nutritive values including cellulose, arabinoxylan, β -glucans, proteins, unsaturated fatty acids, vitamins, minerals, phenols, and dietary fiber [4,5]. Studies suggest that the regular consumption of oat grains is associated with a lower risk of various chronic diseases [6,7]. Meta-analysis studies also revealed that regular oat intake lowers blood cholesterol and improves insulin sensitivity and post-prandial glycemic control [6,7]. The water-soluble β -glucan contained in oat seeds mainly lowers cholesterol levels, leading to a reduced risk of heart disease in humans [8,9]. Further, pharmacological studies indicate that



Review

Molecular understanding of ER-MT communication dysfunction during neurodegeneration

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ABSTRACT

Biological researchers are seeing organelles in a new light. These cellular entities have been believed to be singular and distinctive structures that performed specialized purposes for a very long time. But in recent past years, scientists have learned that organelles become dynamic and make physical contact. Additionally, biological processes are regulated by organelles interactions and its alteration play an important role in cell malfunctioning and several pathologies, including neurodegenerative diseases. Mitochondria-ER contact sites (MERCs) have received considerable attention in the domain of cell homeostasis and dysfunction, specifically in the area of neurodegeneration. This is largely due to the significant role of this subcellular compartment in a diverse array of vital cellular functions, including Ca^{2+} homeostasis, transport, bioenergetics and turnover, mitochondrial dynamics, apoptotic signaling, ER stress, and inflammation. A significant number of disease-associated proteins were found to physically interact with the ER-Mitochondria (ER-MT) interface, causing structural and/or functional alterations in this compartment. In this review, we summarize current knowledge about the structure and functions of the ER-MT contact sites, as well as the possible repercussions of their alteration in notable neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and fronto-temporal dementia. The constraints and complexities in defining the nature and origin of the highlighted defects in ER-MT communication, as well as their concise contribution to the neurodegenerative process, are illustrated in particular. The possibility of using MERCs as a potential drug target to prevent neuronal damage and ultimately neurodegeneration is the topic of our final discussion.

1. Introduction

For many decades, the standard understanding of organelles in textbooks has been that they form discrete contained entities within a cell and function autonomously and in isolation from one another. Now, however, it is understood that interactions between organelles play critical roles in many facets of cellular health (Pallagum et al., 2016). Membrane contact sites are regions of two neighboring membranes that are near together but do not fuse. They act as “hotspots” for signaling, inter-organelle communication, and the transport of lipids and ions. Understanding the relationships between the endoplasmic reticulum (ER) and mitochondria or studying ER-MT tethering proteins has

attracted a lot of attention recently (Fioravanti and Pellegrini, 2015). The mitochondria and ER are tubular organelles with an intricate network structure, which forms membrane contact sites or inter-organelle connections called mitochondria-ER contact sites (MERCs). MERCs was discovered in the late 1950s by electron microscopy (EM) of rat tissue (BERNHARD and ROULLER, 1956), with an inter-organelle distance varying between 10 and 80 nm depending on the type of the cell and the amount of stress that cells go through, and it is estimated that 5–12 percent of the outer mitochondrial surface remains integrated to the ER (Csédes et al., 2006; Stoica et al., 2014; Wu et al., 2017). By using focused ion beam scanning electron microscopy (FIB-SEM), researchers were able to reconstruct the ER-MT contact sites in three

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Achyranthes aspera ameliorates stress induced depression in mice by regulating neuroinflammatory cytokines



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ABSTRACT

Background and aim: *Achyranthes aspera* Linn. (*A. aspera*) (family: Amaranthaceae) is highly recognized in ethnomedicine and traditional systems of Indian medicine as a nerve restorative for several psychiatric disorders. Study presented here was designed to appraise the antidepressant-like effects of *A. aspera* in murine model of chronic unpredictable mild stress (CUMS) induced depression.

Experimental procedures: Rodents were exposed to different stressor in unpredictable manner during CUMS protocol once a day for 4 weeks. Mice were intraperitoneally injected with *A. aspera* extract (2.5, 5 and 10 mg/kg) or fluoxetine (10 mg/kg) or betaine (20 mg/kg) once daily during day 15–28 of the CUMS protocol. Sucrose preference, motivation and self-care, immobility latency and plasma corticosterone were evaluated after 24 h of last stressor. After behavioral assessments TNF- α , IL-6 and BDNF immunoccontent was determined in hippocampus and prefrontal cortex.

Results and conclusion: *A. aspera* extract as well as betaine improved sucrose preference, increased grooming frequency and latency in splash test and ameliorated depression-like condition in CUMS mice in Porsolt test. *A. aspera* treatment decreased the elevated plasma corticosterone and reversed the effect of CUMS on TNF- α , IL-6 and BDNF immunoccontent in mice. The results of the present study suggest *A. aspera* as a promising indigenous medicine for stress associated neurobehavioral and comorbid complications.

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1. Introduction

Depression is a universal psychiatric condition characterized by defeated interest, motivation and anhedonia with frequent suicidal tendencies.¹ Chronic stress exposure leads to and prominently involved in instigation of clinical depression and mood disorders.² Repeated stress exposure results in hypothalamic pituitary adrenal (HPA) axis hyperactivity and increases the individual's

susceptibility to many psychiatric and neurological complications. HPA axis hyperactivation characterized by increased levels of corticosteroids and its normalization may be a critical strategy for therapeutic interventions and mechanism of antidepressant agents. In addition, several reports proposed that neuro-inflammation is the key pathological factor involved in pathogenesis of depression.³ Psychological and physical stressors can activate immune and inflammation processes,⁴ through release of inflammatory cytokines like IL-6, and TNF- α .⁵ Several antidepressant drugs reversed the depression through reduction in inflammatory markers and corticosterone levels.⁶ The neurotrophic theory of depression propose that brain derived neurotrophic factor (BDNF) is critically associated the etiopathophysiology of depressive comorbidities.⁷ Chronic stress exposure leads to decreased BDNF expression in the brain limbic system which can be restored following antidepressant therapy.⁸

Current pharmacological approaches to the management of

Abbreviations: *A. aspera*, *Achyranthes aspera*; CUMS, Chronic Unpredictable Mild Stress; TNF- α , Tumor Necrosis Factor- Alpha; IL-6, Interleukin-6; BDNF, Brain Derived Neurotrophic Factor; HPA, Hypothalamic Pituitary Adrenal; SPT, Sucrose Preference Test; OFT, Open Field Test; FST, Forced Swim Test.

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Agmatine prevents development of tolerance to anti-nociceptive effect of ethanol in mice



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ABSTRACT

Drug tolerance is directly correlated with drug abuse and physical dependence. The development of tolerance is manifested as the decline in pharmacological responses of drugs following repeated administration of the constant dose. The present study evaluated the effect of agmatine in ethanol-induced anti-nociception and tolerance in the tail-flick assay in mice. In an acute protocol, ethanol (1 and 2 g/kg, i.p. [intraperitoneally]) and agmatine (20 and 40 µg/mouse, i.c.v. [intracerebroventricularly]) produced significant analgesic effects in mice, as was evident from the increased baseline tail-flick latency when tested 20 minutes after their administration. Agmatine in a per se non-effective dose (5 µg/mouse, i.c.v.), L-arginine (40 µg/mouse, i.c.v.), and arcaine (25 µg/mouse, i.c.v.) significantly potentiated the anti-nociceptive effect of ethanol. Blood ethanol analysis showed no significant differences in blood ethanol concentration between ethanol/saline- and ethanol/agmatine-treated mice, suggesting that the effects of agmatine were not due to any possible effects on the pharmacokinetics of ethanol. In a separate study, mice were injected with ethanol (2 g/kg, i.p., 12%) or saline (1 mL/kg, i.p.) once daily for 9 days. On days 1, 3, 5, 7, and 9 of the experiment, they were subjected to the tail-flick test. Agmatine (5–20 µg/mouse, i.c.v.), L-arginine (40 µg/mouse, i.c.v.), arcaine (25 µg/mouse, i.c.v.), aCSF (2 µL/mouse, i.c.v.), or saline (1 mL/kg, i.p.) was administered daily prior to the first daily ethanol or saline injections, and reaction latencies were determined in the tail-flick assay. Injections of agmatine, L-arginine, and arcaine prevented the development of tolerance to ethanol-induced analgesia. Given that agmatine and its endogenous modulation can prevent tolerance to the anti-nociceptive effects of ethanol, these data suggest it as a possible new therapeutic strategy for the treatment of alcohol use disorder and associated complications.

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Introduction

Alcohol use disorder is a leading risk factor for the global diseases burden and causes substantial health damage (Shield et al., 2020). Currently, management of alcohol addiction largely depends on modulation of multiple biological targets, such as alcohol dehydrogenase, GABA, NMDA, serotonin, opioids, and their respective receptor systems (Wang, Chen, Chen, Lee, & Cheng,

2020). Unfortunately, the available drugs have failed to meet the health care expectations, and their clinical utility has been diminished by serious adverse effects (Rehm & Imtiaz, 2016). Hence, there is an immediate need for alternative therapies for the treatment of alcoholism.

Chronic ethanol consumption leads to tolerance, with successive decline in or weaker pharmacological actions. The development of tolerance to different effects of ethanol normally progresses to excessive ethanol consumption and withdrawal syndrome. Ethanol-induced analgesia is a strong motivator for drinking, as shown in human (Muskel, Maisto, De Vita, & Ditre, 2018) and animal studies (Yu, Hwa, Makhijani, Beshes, & Kash, 2019), and its tolerance contributes to escalating use and relapse (Powers, Zrolensky, & Ditre, 2019). As ethanol tolerance can lead to

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Review

Involvement of molecular chaperone in protein-misfolding brain diseases

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ABSTRACT

Protein misfolding causes aggregation and build-up in a variety of brain diseases. There are several molecules that are linked with the protein homeostasis mechanism. Molecular chaperones are one of such molecules that are responsible for protection against protein misfolded and aggregation-induced neurotoxicity. Many studies have explored the participation of molecular chaperones in Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, and Huntington's diseases. In this review, we highlighted the constructive role of molecular chaperones in neurological diseases characterized by protein misfolding and aggregation and their capability to control aberrant protein interactions at an early stage thus successfully suppressing pathogenic cascades. A comprehensive understanding of the protein misfolding associated with brain diseases and the molecular basis of involvement of chaperone against aggregation-induced cellular stress might lead to the progress of new therapeutic intervention-related to protein misfolding and aggregation.

1. Introduction

In a functioning cell, protein biogenesis is a vital process that ensures the conservation of correctly folded protein. Polypeptides are synthesized and delivered to the proper cellular compartment, where they are folded into their native structure. Thus, failure in this process can capture the site of investigators as there are number of molecules that assist protein folding and are under extensive search for decades. Moreover, recently several disorders have been associated with misfolded and

aggregation of protein [1–6]. An accumulation of a large amount of unfolded or misfolded polypeptides resulting from the number of pathogenetic sources such as mutations, inefficient folding, error in synthesis, etc. may cause cell toxicity, as defense mechanisms enable to withstand.

One of such molecules that assist protein homeostasis is molecular chaperons. They are expressed ubiquitously under physiological conditions and play important role in various cellular processes [7]. They assist protein folding by binding their substrates briefly with the folded

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Research report

Chronic agmatine treatment prevents olanzapine-induced obesity and metabolic dysregulation in female rats

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ABSTRACT

Antipsychotic-induced obesity affects millions of people and is a serious health condition worldwide. Olanzapine is the most widely prescribed antipsychotic agent with high obesogenic potential. However, the exact mechanism by which it causes its metabolic dysregulation remains poorly understood. In this study, we investigated the effect of agmatine in olanzapine-induced metabolic derangements in Female Sprague-Dawley rats. Repeated olanzapine administration for 28 days increased body weight while treatment with agmatine from days 15 to 28 prevented the body weight gain induced by olanzapine without any alteration in food intake. Repeated agmatine treatment decreased the elevated feeding efficiency and adiposity index, as well as improved dysregulated lipid metabolism induced by olanzapine. Increased activity of fatty acid synthase (FAS) and decreased expression of carnitine palmitoyl transferase-1 (CPT-1) were detected in chronic olanzapine-treated rats. Although agmatine treatment did not alter FAS activity, it increased CPT-1 activity. It is possible that the inhibitory effect of agmatine on weight gain and adiposity might be associated with increased mitochondrial fatty acid oxidation and energy expenditure in olanzapine-treated rats. We suggest that agmatine can be explored for the prevention of obesity complications associated with chronic antipsychotic treatment.

1. Introduction

Obesity and associated metabolic dysregulation is a pressing priority for the global healthcare system. Particularly, obesity associated with chronic use of atypical antipsychotics is alarming and affects millions of people worldwide (Charlson et al., 2018; Hamre, 2013; Yeo and O'Rahilly, 2021). Olanzapine is the main atypical antipsychotic drug highly prescribed for the treatment of schizophrenia (Joffe et al., 2008; Lieberman et al., 2005). However, olanzapine is also one of the most obesogenic agents among second-generation antipsychotic drugs. Clinical studies have reported that nearly 86 % of patients on olanzapine therapy have shown weight gain or obesity (Kahn et al., 2008; Lieberman et al., 2005; McEvoy et al., 2007). Its long-term use causes derangements in the blood lipid and glucose profile (Himmerich et al., 2015). These metabolic adverse effects including hyperglycemia, decreased insulin sensitivity, obesity and dyslipidemia are the risk factors for cardiovascular

disease leading to an increased mortality rate in schizophrenic patients (Daumit et al., 2008; Meyer et al., 2008). Moreover, chronic olanzapine treatment significantly enhanced the risk for the development of type-II diabetes in psychotic patients (Koro et al., 2002; Lambert et al., 2006). Although existing medications might offer limited relief from the metabolic dysregulation induced by antipsychotics, there is a need for effective medication which can treat the obesity induced by olanzapine.

Agmatine is an endogenous polyamine compound biosynthesized through the decarboxylation of L-arginine by arginine decarboxylase (ADC) (Reis and Regunathan, 2000). It is implicated as a potential central neuromodulator and/or neurotransmitter in the mammalian brain, synthesized, stored in synaptic vesicles, accumulated by uptake, released by depolarization, and degraded by the enzyme agmatinase and diamine oxidase (DAO). It has a multi-receptorial affinity and acts via various neuronal pathways (Balarin and Plets, 2007; Reis and Regunathan, 2000). Agmatine activates both 11/12 imidazoline and

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Review article

Alzheimer's disease and sleep disorders: Insights into the possible disease connections and the potential therapeutic targets

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ABSTRACT

One of the comorbid conditions in an individual with Alzheimer's disease is a sleep disorder. Clinical features of sleep disorders involve various sleep disturbances such as Obstructive Sleep Apnea (OSAS), Excessive Daytime Sleepiness (EDS), Rapid Eye Movement (REM), Breathing Disorders, Periodic limb movements in sleep (PLMS), etc. The primary tools used for the identification of such disturbances are Polysomnography (PSG) and Wrist actigraphy. This review will highlight and explain the different approaches used in the treatment of sleep disorders. Non-pharmacological treatments include Peter Hauri rules, sleep education program, and light therapy which play a key role in the regulation of sleep-wake cycles. Pharmacological therapy described in this article may be useful in treating sleep destruction in patients with Alzheimer's disease. Along with the Non-pharmacological and pharmacological treatment, here we discuss five commonly recognized plant-based nutraceuticals with hypothesized impact on sleep disorders: caffeine, chamomile, cherries, L-tryptophan, and valerian by the proper emphasis on the known mechanism of their action.

1. Alzheimer's disease

Alzheimer's disease (AD) was first identified in the year 1907 by Aloisius Alzheimer who described the symptoms of a 51-year-old woman, Auguste Deter, who was under his care at the state asylum in Frankfurt Germany. After the death of Auguste Deter, Alzheimer used the silver staining histological technique to examine her brain microscopically and found the neuritic plaques, neurofibrillary tangles, and amyloid angiopathy which lead to increased knowledge and understanding of this disease (Stepanski and Wyatt, 2003).

The World Health Organization recognized AD as a global public health priority. It is the most common cause of dementia and accounts for 80% of all dementia cases (Crous-Bou et al., 2017). AD is mostly seen in people age 65 and more. Lower percentages of cases are seen in the younger population. Although older age is a risk factor AD is not a normal part of aging and involves temporal lobes frequently (Upaganlawar et al., 2021).

Abbreviations: AD, Alzheimer's Disease; Aβ, Amyloid-Beta Plaques; NFTs, Neurofibrillary Tangles; APP, Amyloid Precursor Protein; APOE, Apolipoprotein E; OSAS, Obstructive Sleep Apnea; EDS, Excessive Daytime Sleepiness; REM, Rapid Eye Movement; SWS, Slow-Wave Sleep; SDAT, Senile Dementia of Alzheimer's Type; SDB, Sleep-Disordered Breathing; PLMS, Periodic Limb Movements in Sleep; PSG, Polysomnography; MSLT, Multiple Sleep Latency Test; PSQI, Pittsburgh Sleep Quality Index; PROMIS, Patient-Reported Outcomes Measurement Information System; ESS, Epworth Sleepiness Scale; GABA, Gamma-Amino Butyric Acid; 5-HTP, 5-Hydroxy Tryptophan; RBD, Rapid Eye Behavior Disorder.

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GENERAL REVIEW

Interweaving of reactive oxygen species and major neurological and psychiatric disorders

Entrelacement des espèces réactives de l'oxygène et des troubles neurologiques et psychiatriques majeurs

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HIGHLIGHTS

- Reactive oxygen species have functions in normal physiology and also cause various disorders.
- Mitochondria produce most of the reactive oxygen species.
- Reactive oxygen species plays role in the pathogenesis of major neurological disorders.

KEYWORDS

Reactive oxygen species;
Alzheimer's disease;
Parkinson's disease;
Huntington's disease;
Depression;
Schizophrenia.

Summary Reactive oxygen species are found to be having a wide range of biological effects ranging from regulating functions in normal physiology to alteration and damaging various processes and cell components causing a number of diseases. Mitochondria are an important organelle responsible for energy production and in many signalling mechanisms. The electron transport chain in mitochondria, where oxidative phosphorylation takes place, is also coupled with the generation of reactive oxygen species (ROS). Changes in normal homeostasis and overproduction of reactive oxygen species by various sources are found to be involved in multiple

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Phytotherapy: A promising approach for the treatment of Alzheimer's disease

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ARTICLE INFO

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurological disease and the most common form of dementia, affecting more than 10 million people all over the world. Clinically, AD is characterized by progressive deficits in memory, cognitive impairment, and altered behavior. Although researches have largely continued, there is still no appropriate treatment option for disease-modifying AD. However, symptomatic treatment options exist. Medicinal plants have been used in different systems of medicine from ancient times for the treatment of diseases. Numerous herbs have been shown to improve brain function and may have a role to play in AD treatment. In this review, we provide a systematic review on the role of medicinal plants and herbs useful for the treatment of Alzheimer's disease, the effect of these herbs on hormones, herb-drug interactions as well as stability-related testing for the herbal pharmaceutical medicines.

1. Introduction

Alzheimer's disease has been the most frequent cause of dementia globally, and its incidence is increasing, owing in part to the globe's aging population. Dementia affects an estimated 0.7 percent of the world population or 51.6 million individuals. Between 1990 and 2019, the overall number of people affected greater than doubled. Alzheimer's disease is responsible for up to 80 percent of the overall dementia diagnosis. Even though the total fatality rate from cardiovascular diseases (CVD) and stroke in the USA is dropping, the portion of fatalities linked to AD is growing, rising by 89 percent between 2000 and 2014 [1,2].

Although treatment options for people with AD are still supportive and can improve memory and alertness, they can also reduce the overall progression of the condition. The degenerative characteristics associated with Alzheimer's disease, Amyloid β (A β) and tau protein, are the primary targets for prospective therapies; although, early success in comparative investigation and smaller clinical studies is not yet replicable in relatively large administrations. [3–5] Diet and exercise are the only proven methods that can help prevent cognitive decline and maintain a healthy lifestyle. These interventions are first-line suggestions for all patients regardless of their cognitive function. [6] While certain FDA-approved medications are approved for the management

of AD, the results are frequently disappointing, and there is a space for alternative therapies, particularly herbal therapy.

Several of today's modern manufactured pharmaceuticals have their origins in the plant world, and herbal remedies led to the main pharmacopoeias only around two hundred years ago. When fundamental and clinical pharmacology established themselves as important fields of medicine, traditional remedies saw a dramatic fall. [7] Nonetheless, herbal therapy is still being studied for a variety of ailments, including psychiatric and neurological problems. There are several explanations for this problem. Firstly, patients are unsatisfied with conventional therapy, secondly, the individuals consider herbal remedies as being consistent with their own beliefs and values, also patients desire control over their medical choices. [8] The specificity of phytoconstituents and extracted chemicals for Brain receptors suggests that herbal medicines may play an essential role in the management of neurological illnesses. Furthermore, animal and human research have shown a scientific foundation for the use of therapeutic plants. [9,10]

The generic antioxidant and anti-inflammatory action of herbal medications, as well as their particular cholinesterase inhibitory effect, lend support to their usage in Alzheimer's disease. Herbal medications are also becoming more popular owing to their claimed efficacy, safety, and cost. To evaluate the effectiveness of these herbal remedies alone or

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Review

Functional polysaccharide lentinan: Role in anti-cancer therapies and management of carcinomas

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ARTICLE INFO

Keywords:
Lentinan
Lentinus edodes
Anti-tumour
Immunomodulation
Shiitake mushrooms

ABSTRACT

Introduction: To conduct a retrospective data collection on prevalence of functional food lentinan as its role in anti-cancer therapies and management of carcinomas.

Methods: The methodical review was carried out on various indexed databases Scopus, Web of sciences and PubMed, in addition to the Google Scholar database. The work focuses on observational studies like anti-tumour, cytotoxic and immunomodulating of functional food lentinan.

Results: World Health Organisation (WHO) classifies cancer as the second leading cause of death worldwide, approximately 1 in 6 deaths occurring are because of cancer, and WHO estimates ~14.1 million new cancer cases and ~10 million deaths per year. In recent years' natural products like mushrooms have emerged as an anti-cancer and immunomodulating agent and have overcome the drawbacks of conventional chemotherapeutic strategies. Similarly, Lentinan (LNT) a bioactive molecule obtained from *Lentinus edodes* with a chemical backbone of β -1, 3-glucan with two β -1, 6-glucose chains. The literature has suggested lentinan as a chemotherapeutic has improved quality of life and has promoted the efficacy of chemotherapy and radiation therapy during cancer treatment. The anti-tumour and biological response modifier and the ability of immunoregulation of lentinan have drawn the attraction to oncologists and pharmacologists.

Conclusion: Hence this review describes the possible mechanism of Lentinan as anti-tumour, cytotoxic and immunomodulating moiety in treating various cancers.

1. Introduction

Cancer is the major concern of mortality accompanying by high morbidity among the world, which is building colossal pressure on society [1]. As stated by the world health organization (WHO) cancer is classified as the second leading cause of death worldwide, approximately 1 in 6 deaths occurring are because of cancer, and WHO estimates ~14.1 million new cancer cases and ~10 million deaths per year [2]. The current conventional therapies available for management are surgery, chemotherapy, and radiotherapy but causing serious side effects and leading to poor prognosis [3]. Hence to overcome the drawbacks of current treatment regimens for combatting cancer and to control the increasing rate of cancer worldwide it is necessary to search for a novel anti-cancer drug accompanying high safety [4]. In recent years, the utilization of herbal bioactive has increased as a food supplement and medicinal purpose and become a core attraction of researchers due to their low toxicity and high specificity. Mushrooms are fungi that have

been used as food and drug for since long time. Polysaccharides are the most active constituents in mushrooms which are reported to have immunomodulatory, anticancer, and antiviral activities, among them one is lentinan obtained from *Lentinus edodes* (phylum Basidiomycota, family Pleurotaceae [5]. Lentinan (LNT) is a β -1, 3-glucan with two β -1, 6-glucose branches having every five glucose moiety residing in the backbone and the triple helical structure is widely responsible to impart anti-tumour and anti-cancer activity and unlike existing synthetic anti-cancer agents [6]. Lentinan is said to possess no toxic side effects and on the application as an anti-cancer agent, studies have revealed that LNT has significantly prolonged the life span of candidates under investigation and expressively improved the quality of life [4,7]. Literature demonstrated many in-vivo and in-vitro studies which signify that lentinan is accountable for modulation of humoral and cellular mediators of interleukin (IL) [8], activators of macrophages [9], T-helper, and natural killer (NK) [10] and hence can be proved as a good candidate for anti-cancer therapy. LNT has been traditionally used by many countries

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Analytical profiling of Lentinan in hybrid nanostructures for intranasal Delivery: Method development and Validation

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Keywords

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ABSTRACT

Lentinan (LNT) a polysaccharide obtained from mushroom *Lentinus edodes*, possesses potent anticancer and antitumor activity. To improve the bioavailability, encapsulation of LNT in polymer-lipid hybrid nanostructures (PLHNs) is done and administration via nasal pathway will bypass hepatic first-pass metabolism, which possibly will give high prospect for treatment of brain tumors. The estimation of entrapped LNT within Hybrid Nanostructures is one of the important parameters for the characterization of nanoparticles. Therefore, an analytical method was developed and validated for estimating plain LNT and LNT-PLHNs in Nasal Simulated Fluid (NSF) by conjugating with Congo Red (CR) in dilute alkaline solutions by employing high-performance liquid chromatography (HPLC). The developed method was validated for selectivity, linearity, precision, accuracy, robustness. The linearity was checked over the concentration range of 2–10 µg/mL, the limit of detection (LOD) and limit of quantification (LOQ) were 38.02 ± 0.21 ng/mL and 86.71 ± 0.82 ng/mL respectively. The mean percent recovery of LNT was 99.18 %, relative standard deviation (RSD) of 0.386 % and intra- and interday coefficient of variation was <2 %. The developed HPLC method was found suitable for assessing percent entrapment efficiency (%EE), *in-vitro* drug release, intracellular uptake study and stability profile of LNT-PLHNs obtained by solvent injection technique.

Introduction

Numerous advancements have been seen for development of polysaccharides Lentinan (LNT) as a modern medicine for treatment of various cancers as it possess antitumor, immunomodulating, antioxidant, radical scavenging properties [1]. Generally, to improve and enhance the advantageous functional properties of bioactive molecules and exploring their potential in sites-of-action, the nano-drug delivery systems have shown that they have substantially assisted in enhancing the effectiveness [2]. LNT is a mushroom polysaccharide obtained from *Lentinus edodes* (phylum Basidiomycota, family: Pleurotaceae and chemically it is β-1, 3-glucan with two β-1, 6-glucose branches having every-five-glucose moiety residing in the backbone (Fig. 1A) [3]. LNT exhibits anti-tumour and anti-cancer activity dissimilar to preexisting synthetic anti-cancer molecules because of the presence of triple helical structure. LNT causes activation of T-cells, NK cells and macrophages which initiate a strong host mediated antitumor activity and simultaneously inhibits chemical and viral carcinogenesis, therefore this attribute makes LNT as a vital drug of choice for immunotherapy

[1,4]. Various studies suggests that LNT have very less toxic side effects and application of it as an anti-cancer molecule it has significantly improved and prolonged the life span of patients under study [5]. Since last few years there has been upsurge in enhancing the patient compliance and in which non-invasive administration of drugs plays an important role. Among the various patient friendly dosage forms after oral drug delivery, the second most explored drug delivery route in last few decades is administration of drugs via nasal pathway because it enables improved bioavailability, bypass of hepatic first-pass metabolism and moreover it gives high prospect for treatment of various brain disorders and diseases by direct targeting to brain from intranasal delivery [6]. In spite of several benefits of nasal route, one the limitation imposed by this route is absorption of drugs having high molecular weight through nasal mucosa and to overcome this barrier encapsulation of such drugs into nano-carriers have a significant role [7]. Till date several nanostructures have been developed among which inclusion of lipids and polymers in nanoparticles have enhanced the characteristic properties of drug delivery and drug targeting with high physical stability and biocompatibility [8]. The major issues faced during

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Review

An Overview of Diabetic Foot Ulcers and Associated Problems with Special Emphasis on Treatments with Antimicrobials

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Abstract: One of the most significant challenges of diabetes health care is diabetic foot ulcers (DFU). DFUs are more challenging to cure, and this is particularly true for people who already have a compromised immune system. Pathogenic bacteria and fungi are becoming more resistant to antibiotics, so they may be unable to fight microbial infections at the wound site with the antibiotics we have now. This article discusses the dressings, topical antibacterial treatment, medications and debridement techniques used for DFU and provides a deep discussion of DFU and its associated problems. English-language publications on DFU were gathered from many different databases, such as Scopus, Web of Science, Science Direct, Springer Nature, and Google Scholar. For the treatment of DFU, a multidisciplinary approach involving the use of diagnostic equipment, skills, and experience is required. Preventing amputations starts with patient education and the implementation of new categorization systems. The microbiota involved in DFU can be better understood using novel diagnostic techniques, such as the 16S-ribosomal DNA sequence in bacteria. This could be achieved by using new biological and molecular treatments that have been shown to help prevent infections, to control local inflammation, and to improve the healing process.

Keywords: diabetic foot ulcers; diabetes mellitus; Wagner grade; diabetic neuropathy; antimicrobials; biofilms

1. Introduction

More than 415 million people throughout the world are diagnosed with diabetes, and that number is expected to climb to 640 million (1 in 10) by the year 2040, according to the

REVIEW

Open Access

Neurodegenerative disorders associated with genes of mitochondria



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Abstract

Background: Over the last decade, aggregating evidences suggested that there is a causative link between mutation in gene associated with mitochondrial dysfunction and development of several neurodegenerative disorders.

Main text: Recent structural and functional studies associated with mitochondrial genes have shown that mitochondrial abnormalities possibly lead to mitochondrial dysfunction. Several studies on animal models of neurodegenerative diseases and mitochondrial genes have provided compelling evidence that mitochondria is involved in the initiation as well as progression of diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and Friedreich ataxia (FA).

Conclusion: In this mini-review, we have discussed the different etiologic and pathogenesis connected with the mitochondrial dysfunction and relevant neurodegenerative diseases that underlie the dominant part of mitochondrial genes in the disease development and its progress.

Keywords: Mitochondrial genes, Parkinson's disease, Alzheimer's disease, Huntington's disease, Mutation, Friedreich ataxia

Background

Mitochondria basically allied with formation of adenosine triphosphate (ATP) through oxidative phosphorylation process. However, mitochondria also take part in a lots of necessary cellular functions like iron and calcium homeostasis, steroids, pyrimidines and heme biosynthesis [1, 2]. Mitochondria have both inner and outer membrane, which is impermeable to charged ions including all other molecules. The ATP generation process occurs at the inner membrane of mitochondria through electrons donation by nicotinamide adenine dinucleotide (NAD) or flavin adenine dinucleotide (FAD) equivalents formed by the tricarboxylic acid (TCA) cycle. This process is called as the electron transport system [3, 4]. Mitochondrial DNA (mtDNA) involves circular structure of 569, 16 base pairs which are active in the synthesis of proteins and mitochondrial ribonucleic acids

(RNSs). This mtDNA encodes 13 polypeptides, 22 ribosomal RNAs and 22 transfer RNAs, all of which are important for ATP formation and electron transport, consequently for normal cellular physiology. There are many human diseases which are strongly related with mutated mitochondrial genes [5–8]. Oxidative damage and subsequent dysfunction are occurring to mitochondria which is known to be a major site of free radical generation in cells [9]. Mitochondrial genome (mtDNA) is more susceptible to oxidative damage as compared to the nuclear DNA [10]. Due to the decline of defense mechanism in the cell, oxidative stress occurs and damages the nucleic acids. If the damage DNA is not repaired then it is considered being highly mutagenic upon DNA replication [11].

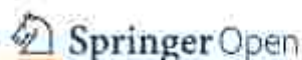
Basic mitochondrial genetics

It is well known that mitochondria contribute to ageing and neurodegeneration through accumulation of mtDNA mutation and generation of reactive oxygen species (ROS) [12]. Excessive production of ROS stimulates several

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Review

Interweaving epilepsy and neurodegeneration: Vitamin E as a treatment approach

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ARTICLE INFO

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ABSTRACT

Epilepsy is the most common neurological disorder, affecting nearly 50 million people worldwide. The condition can be manifested either due to genetic predisposition or acquired from acute insult which leads to alteration of cellular and molecular mechanisms. Evaluating the latest and the current knowledge in regard to the mechanisms underlying molecular and cellular alteration, hyperexcitability is a consequence of an imbalanced state wherein enhance excitatory glutamatergic and reduced inhibitory GABAergic signaling is considered to be accountable for seizures associated damage. However, neurodegeneration contributing to epileptogenesis has become increasingly appreciated. The components at the helm of neurodegenerative alterations during epileptogenesis include GABAergic neuronal and receptor changes, neuroinflammation, alteration in axonal transport, oxidative stress, excitotoxicity, and other cellular as well as functional changes. Targeting neurodegeneration with vitamin E as an antioxidant, anti-inflammatory and neuroprotective may prove to be one of the therapeutic approaches useful in managing epilepsy. In this review, we discuss and converse about the seizure-induced episodes as a link for the development of neurodegenerative and pathological consequences of epilepsy. We also put forth a summary of the potential intervention with vitamin E therapy in the management of epilepsy.

1. Introduction

Epilepsy is one of the most common neurological disorders, affecting nearly 50 million people across the globe [1]. The condition is characterized by recurrent seizures resulting from abnormal neuronal networks leading to synchronous discharges which disrupt normal neuronal activity that manifest several signs and symptoms alike electroclinical seizures counting abnormal level of consciousness and motor manifestations seen during different seizures [2]. The term encompasses a huge variety of syndromes with no single etiology and can be associated with neurological, psychological, cognitive, and social sequelae which may affect the quality of life in patients who do not respond to traditional treatment [3]. The condition can be manifested either due to genetic

predisposition or acquired from acute insult which leads to alteration of cellular and molecular mechanisms in the affected region that generate seizures immediately or after a latent period and lasts until the manifestation of recurring seizures [4].

Out of the several types, Temporal lobe epilepsy (TLE) is the most frequently acquired form contributing approximately 30% of the seizures in adults, typified by spontaneous recurrent motor seizures especially in the hippocampus [5]. Numerous brain insults contributing to acquired TLE include brain injury, infection, status epilepticus (SE), brain tumors, genetic or congenital abnormalities [6,7].

Reviewing current knowledge in regards to the mechanisms underlying molecular and cellular alteration, it is assumed that neuronal hyperexcitability may arise of imbalance wherein enhance excitatory

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Agmatine improves the behavioral and cognitive impairments associated with chronic gestational ethanol exposure in rats

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ARTICLE INFO

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Memory impairment

ABSTRACT

Chronic maternal ethanol exposure leads to poor intelligence, impaired cognition and array of neurological symptoms in offsprings and commonly referred as fetal alcohol spectrum disorder (FASD). Despite high prevalence and severity, the neurochemical basis of FASD remains largely unexplored. The present study evaluated the pharmacological effects of agmatine in cognitive deficits associated with FAS in rat's offsprings prenatally exposed to alcohol. Pregnant rats received ethanol in liquid modified diet during the entire gestational period of 21 days. Offsprings were treated with agmatine (20–80 mg/Kg, i.p.) during early postnatal days (PND: 21–35) and subsequently evaluated for anxiety in elevated plus maze (EPM), depression in forced swim test (FST) and learning and memory in Morris's water maze (MWM) during post adolescent phase. Hippocampal agmatine, BDNF, TNF- α and IL-6 levels were also analyzed in prenatally ethanol exposed pups. Offsprings prenatally exposed to ethanol demonstrated delayed righting reflex, reduced exploratory behavior along with anxiety, depression-like behavior and impaired memory. These behavioral abnormalities were correlated with a significant reduction in hippocampal agmatine and BDNF levels and elevation in TNF- α and IL-6 immunoreactivity. Chronic agmatine (40 and 80 mg/Kg, i.p.) administration for 15 days (PND: 21–35), improved entries and time spent in open arm of EPM, decreased immobility time in FST. It also reduced latency to reach the platform location; increased the number of entries, time spent in platform quadrant and also number of crossing over platform quadrant when subjected to MWM test in prenatally ethanol exposed offsprings. This study provides functional evidences for the therapeutic potential of agmatine in cognitive impairment and other neurological complications associated with FASD.

1. Introduction

Gestational ethanol exposure leads to poor intelligence, impaired cognition and array of psychiatric symptoms in offspring like anxiety and depression, commonly referred as fetal alcohol spectrum disorder (FASD). Multifaceted rodent, non-human primates and clinical studies have established in parallel the cognitive deficits, behavioral disorders and motor skills impairment as a consequence of prenatal ethanol exposure (Farber et al., 2010; Qodim et al., 2011; Guneri et al., 2009; Mairson et al., 2013). Several mechanisms explained the effect of prenatal ethanol exposure on CNS development (Archibald et al., 2001; Astley et al., 2009; Sullivan, 2014) including dysregulation of several neurotransmitter systems or receptors, transcription factors and tropic factors (Bartram et al., 2012; Bressa et al., 1994). The role of

neuro-immune system especially microglia and pro-inflammatory mediators has been significantly evident in neurodevelopmental physiology (Sajin and Glaz, 2011; Kattenmann et al., 2011) and pathophysiology of FASD (Drew and Kania, 2014; DeVito and Stone, 2001). Correspondingly, cognitive impairment is attributed to abnormal hippocampal and cortical glutamatergic plasticity and altered N-methyl D-aspartate receptor (NMDAR) expression (Abbott et al., 2016; Goodfellow et al., 2016).

In recent years, researchers have generated considerable interest in agmatine that allosterically modulates rather than block NMDAR activity via binding at polyamine site (Yang and Reis, 1999). Agmatine is an endogenous amine synthesized from amino acid, L-arginine by decarboxylation (Reis and Reganathan, 2000; Halaris and Pletiz, 2007). It has multi receptorial affinity and activates α_2 -adrenoceptors,

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Possible involvement of agmatine in neuropharmacological actions of metformin in diabetic mice

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ABSTRACT

The risk of psychiatric and neurological disorders is significantly higher in patients with diabetes mellitus. Diabetic patients are more susceptible to depression, anxiety and memory impairment as compared with non-diabetic individuals. Metformin, a biguanide used for the management of type 2 diabetes mellitus (T2DM), promotes neurogenesis, enhances spatial memory function and protects the brain against oxidative imbalance beyond its effect on glucose metabolism. However, the exact mechanism of its neuropharmacological actions in T2DM is not known. We investigated the role of the agmatinergic system in neuropharmacological actions of metformin in diabetic mice. Diabetes was induced by the streptozotocin (STZ) injection and confirmed by high blood glucose levels. After 28 days, STZ treated mice exhibited memory impairment in radial arm maze, depression-like behavior in forced swim test and anxiety-like behavior in elevated plus maze along with increased expression of pro-inflammatory cytokines like TNF- α , IL-1 β , IL-6, IL-10 also, reduced agmatine and BDNF levels in the hippocampus and prefrontal cortex compared to the control animals. Metformin and agmatine alone or in combination, by once-daily administration during 14–27 day of the protocol significantly reversed the STZ induced high blood glucose levels, memory impairment, depression and anxiety-like behavior. It also reduced neuro-inflammatory markers and increased agmatine and BDNF levels in the hippocampus and prefrontal cortex. The present study suggests the importance of endogenous agmatine in the neuropharmacological action of metformin in diabetic mice. The data projects agmatine and metformin combination as a potential therapeutic strategy for diabetes associated memory impairment, depression, anxiety, and other comorbidities.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder directly linked with neurological complications and cognitive impairment (van Slooten et al., 2020). The molecular mechanism involved in diabetes associated with the psychiatric disturbance remains elusive. The therapeutic options to treat neurological disorders in diabetic patients are limited because these drugs act on central nervous system, impair the glycemic control and aggravate the complications in DM (de Groot et al., 2001; Lustman and Clouse, 2005; Musselman et al., 2003). Coincidentally, one of the most established antidiabetic agents, metformin is reported to provide benefits in combating the neurological complications associated with DM.

Metformin (biguanide) is widely used in the management of type 2 diabetes mellitus (T2DM) and also to enhance patient's longevity

(Bazilki et al., 2015). In addition to glucose metabolism regulation, metformin promotes neurogenesis, enhances spatial memory function and protects the brain against oxidative imbalance (Ahmed et al., 2017; Correia et al., 2008; Pintana et al., 2012). It also exerts anxiolytic, antidepressant and memory facilitating effects, especially in diabetic condition (Fen et al., 2018; Gao et al., 2014; Pintana et al., 2012; Zhao et al., 2014). Metformin is effective in psychiatric complication, showing neuroprotective action by regulating neuro-inflammatory pathway (Mudgal et al., 2019; Wang et al., 2016). However, the clear mechanism of action and associated signaling pathways for its neuropharmacological actions is not known. A recent study established that metformin treatment is associated with increased agmatine production by microbiota of T2DM patients (Fryer et al., 2019).

Agmatine is an endogenous polyamine and is established preclinically as a potential neuromodulator to manage diverse psychiatric

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Short communication

Evidences for agmatine alterations in $A\beta_{1-42}$ induced memory impairment in mice

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ABSTRACT

Alzheimer's disease is an age related progressive neurodegenerative disorder characterized by decline in cognitive functions, such as memory loss and behavioural abnormalities. The present study sought to assess alterations in agmatine metabolism in the beta-amyloid ($A\beta_{1-42}$) Alzheimer's disease mouse model. $A\beta_{1-42}$ injected mice showed impairment of cognitive functioning as evidenced by increased working and reference memory errors in radial arm maze (RAM). This cognitive impairment was associated with a reduction in the agmatine levels and elevation in its degrading enzyme, agmatinase, whereas reduced immunoreactivity was observed in its synthesizing enzyme arginine decarboxylase expression within hippocampus and prefrontal cortex. Chronic agmatine treatment and its endogenous modulation by L-arginine, or arcaine or aminoguanidine prevented the learning and memory impairment induced by single intracranial $A\beta_{1-42}$ peptide injection. In conclusion, the present study suggests the importance of the endogenous agmatineric system in β -amyloid induced memory impairment in mice.

1. Introduction

Alzheimer's disease (AD) is an age related progressive neurodegenerative condition characterized by decline in cognitive functions and behavioural abnormalities. Although amyloid beta ($A\beta$) plays a central and causative role in the disease development [1,2], recent evidence suggests the importance of alterations in arginine metabolism in AD pathogenesis [3,4]. L-Arginine is a semi-essential amino acid that can be metabolized to several important biologically active compounds including Nitric Oxide (NO), L-ornithine and agmatine [5]. It has been recognized that agmatine stands at the crossroad of arginine metabolism to regulate the synthesis of NO and polyamines [5–7] and is involved in cognitive processing [8–10]. Hence, altered agmatine concentrations during AD and memory impairment may have important functional significance [6].

Agmatine has been projected as a neuromodulator in mammalian brain and participates in diverse neuronal functions through interaction with multiple receptors [5,11]. It antagonizes N-methyl-D-aspartate (NMDA) receptors, inhibits nitric oxide synthase (NOS) and activates I_1/I_2 imidazoline receptors and α_2 -adrenoceptor [9].

Agmatine is predominantly localized in brain regions directly associated with memory processing including hippocampus, cortex, locus coeruleus and forebrain and has been demonstrated to play a vital role in learning and memory [8–10,12,13]. Agmatine offers protection against $A\beta_{25-35}$ -induced memory impairment [14] and several recent studies suggested the therapeutic implication of agmatine in $A\beta$ peptide induced cognitive impairment [15–17]. Agmatine inhibits apoptosis and antioxidant pathway in a streptozotocin-induced AD [15] and AD-like alterations caused by brain insulin resistance [16]. Importantly, intracerebroventricular infusion of rats with $A\beta_{25-35}$, a neurotoxic domain of full length $A\beta_{1-42}$ decreased endogenous agmatine levels in the hippocampus and prefrontal cortex [3]. However, functional correlation of agmatine reduction with memory impairment and whether it is related to impaired synthesis or enhanced degradation is not evidently known. We hypothesized that endogenous agmatineric pathway might be altered in the $A\beta_{1-42}$ induced memory impairment.

Although, literature on L-arginine metabolism in the pathogenesis of AD largely focuses on arginase/ornithine pathway, there are evidences for dysregulation of agmatine pathways [3,4]. Hence, it is essential to understand how the agmatine metabolic profile changes following

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Self-Assembling *Dioscorea bulbifera* loaded mixed micelles: Formulation optimization, *in-vitro* cytotoxicity and *in-vivo* pharmacokinetics

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ABSTRACT

Dioscorea bulbifera (DB) is one among the traditionally used medicinal plant which has been reported to have anticancer property and capable of inducing apoptosis of tumors, but the poor water solubility restricts its pharmacological application. The study aims at improving the aqueous solubility of *Dioscorea bulbifera* and enhancing the bioavailability by formulating Pluronic F-127 and Soluplus® incorporated polymeric mixed micelles (PL-SO-MMs). Micelles were prepared by thin film dispersion method, using 3² factorial design-response surface methodology with Particle size (nm) and entrapment efficiency (EE%) as indicators. Transmission electron microscopy (TEM) images revealed that prepared Mixed Micelles were nano-spherical and having average particle size of 61.45 ± 0.4 nm and zeta potential in range of -18.11 ± 1.2 mV to -21.70 ± 0.9 mV and with acritical micelle concentration (CMC) of 0.821 ± 0.002 % w/v. The cell toxicity assays of DB loaded Polymeric mixed micelles was performed on MCF7 and MDAMB-231 showed higher cell toxicity compared with free DB. The IC₅₀ values of DB and DB loaded PL-SO-MMs on MCF7 and MDAMB-231 were 8.92 µg/ml, 12 µg/ml and 3.07 µg/ml, 8.1 µg/ml respectively. In conclusion, the Mixed Micelles (PL-SO-MMs) developed in the present study were proven as promising drug delivery system for *Dioscorea bulbifera*.

1. Introduction

Applications of nanoparticles in drug delivery are escalating with advancement in technology and of various nanocarriers being researched till date, among which micellar systems are found to be promising drug delivery system. This nano-sized drug delivery system provides increased solubility and stability of the hydrophobic drug and *in-vivo* advantages versus the free drug. The stability of the mixed micelles depends on copolymers self-aggregation tendency. The critical micelle concentration (CMC) of the amphiphilic polymers is influenced by the hydrophilic-lipophilic balance (HLB) of the polymer [1,2]. Nanocarriers are a very important constituent of novel drug formulation as they protect and stabilize sensitive agents and increase bioavailability with fewer side effects.

Mixed micelles is a novel nano delivery system made up of a combination of two or more amphiphilic block copolymers presents several advantages such as, selective Targeting, improving drug-loading capacities, greater stability, protection of drug against oxidation and premature drug degradation and importantly, reduction in side effects

[3,4]. Poorly water-soluble drugs can be easily entrapped into the hydrophobic inner core and the core is surrounded by a hydrophilic outer shell that can self-assemble into polymeric micelles in an aqueous solution [5]. The degradation rate and the drug release rate can be adjusted by varying the ratio of a hydrophilic and lipophilic polymer [6]. Mixed micelles can self-assemble with two or more similar structures and performance block copolymers. Mixed micelles can provide multiple functionality micelles by constituent copolymers.

Soluplus® (SO) a graft copolymer consisting of polyethylene glycol (PEG), polyvinyl caprolactam, and polyvinyl acetate shows an excellent self-assembling micelle forming property. The block polymer shows enhanced micellar property because of its amphiphilic character, ultimately leading to formation of micelle in various aqueous mediums and increasing the bioavailability of drug by enabling the solubilisation of poorly water-soluble drugs [7]. Pluronic F-127 known as Poloxamers are also among the class of block copolymers, structurally consisting of poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO), possessing amphiphilic characteristics and various association and adsorption properties. Particularly, this polymer improves the aqueous

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ORIGINAL CONTRIBUTION

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Evaluation of antipsoriatic activity of gel containing *Pongamia pinnata* extract on Imiquimod-induced psoriasis



Kamlesh Wadher^{*}, Shital Dabre, Anjali Gaidhane, Sagar Trivedi and Milind Umekar

Abstract

Background: *Pongamia pinnata* (Fabaceae) is among those categories of plants mentioned in Ayurveda and traditionally known to use in several types of disease and disorders. The objective of the present work was to investigate the anti-psoriatic activity of *Pongamia pinnata* leaves extracts in Herbal gel formulation.

Results: Hydroalcoholic leaves extract of *Pongamia pinnata* was first subjected to phytochemical screening and quantification of phytoconstituents. Herbal gel was prepared containing *Pongamia pinnata* extracts using Carbopol 934 as gelling agent. The prepared gel formulations were studied for pH, viscosity, Spreadability and in vitro diffusion studies. The Imiquimod-induced psoriatic mouse model, showed a prominent anti-psoriatic activity of the extract as evident through index grading. Treatment with extract confirmed a noteworthy reduction in psoriasis in the treated groups as there was a considerable diminution in the thickness and scaling of skin.

Conclusions: Lack of proper treatment and disadvantages associated with allopathic medicines pave the way to extensive research in natural products with anti-psoriatic activity. The present research scientifically justified the anti-psoriatic activity of the Hydroalcoholic extracts of *Pongamia pinnata* leaves.

Keywords: *Pongamia pinnata*, Anti-psoriatic activity, Imiquimod, Medicinal plant

Background

Psoriasis is a hyper-proliferative neutrophilic skin disorder affecting around 5–6% of the world population, with prevalence rate in adult from 0.5%–11.4% [23]. The pathogenesis of psoriasis is associated with increased production of inflammatory cytokines that cause hyperkeratosis [13, 19]. Psoriasis is a multifactorial with numerous key factors such as, genetic vulnerability, environmental triggers, skin barrier disruption and immune dysfunction [18]. On the basis of extent of inflammation, localization of rash and severity, psoriasis can be categorized as, Vulgaris (plaque), guttate, inverse, pustular and erythrodermic [6, 15]. Vulgaris (plaque) has reported to affects around 85%–90% of psoriatic patients affecting physically and mentally a lot [7, 12].

Traditional medicines are gaining importance on account of the associated side effects of synthetic medicines [25]. *Pongamia* is a genus having one species only *Pongamia pinnata* (Linn.) [Syn. *Pongamia glabra* (Vent.) *Derris indica* (Lamk.)] which belongs to family Fabaceae and subfamily Papilionaceae is native in tropical and temperature regions of Asia. It is among that category of plants which has wide applicability in the treatment of diseases such as for treatment of piles, ulcers, skin diseases, and wounds and rheumatic joints [20]. Most scientist and researchers have worked on various extracts and chemical constituents, and reported the anti-oxidant, antimicrobial, antiparasite, anti-inflammatory, anti-convulsant, anti-diabetic, antihyperammonemic, cytotoxicity, anthelmintic, insecticidal and immunomodulatory activities [1].

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ARTICLE



Development of topical thymoquinone loaded polymer-lipid hybrid vesicular gel: *in-vitro* and *ex-vivo* evaluation

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ABSTRACT

Thymoquinone (TH), a naturally occurring moiety shows excellent anticancer properties and in the present study, TH loaded polymer hybrid lipid vesicles (TH PLH) were formulated, and *in-vitro* cytotoxicity towards breast cancer cell lines (MCF-7 and MBD-MB 231 cells) was determined. TH PLH was primed by the ethanol spraying method and were characterized for various attributes like particle size, morphology, percentage drug entrapment, elasticity, rheological, zeta potential, etc. The prepared TH PLH Vesicles showed an average particle size from 344.7 ± 3.7 nm to 351.9 ± 2.3 nm and showed very narrow distribution with polydispersity index ranging from 0.245 ± 0.36 to 0.271 ± 0.66 . The surface charge on the vesicles was confirmed by zeta potential ($p -21.3 \pm 1.08$ mV to $p -19.98 \pm 3.4$ mV). The globular moulded vesicles were in the nano-size range and had high flexibility and an approximately 10-fold increase in elasticity properties. TH PLH Vesicular gel was formulated by means of Carbopol 934 and was evaluated for physical appearance, pH, rheological behaviour, and skin irritation test. Cytotoxicity study reveals paramount inhibition on cells by TH vesicle-loaded gel. These results showed the high potential of TH PLH vesicles for topical anticancer application.

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KEYWORDS

Thymoquinone; polymer-lipid hybrid vesicle; anticancer activity; breast cancer

1. Introduction

One of the notable, common, and prevailing types of cancer, typically diagnosed in females is breast cancer. It is becoming the leading reason for death in women with an increase in its global incidence by over 20% in the last few decades (Tang *et al.* 2017). The contemporary treatment for breast cancer is associated with many complications along with side effects and possible metastasis that could account for the increase in mortality rate over the years. metastasis (Ghoncheh *et al.* 2016, Plummer *et al.* 2016).

Subsequently, there is a critical ought to create a secure and safe treatment for breast cancer. The main difficulties in the current therapy are the non-specific delivery of drug, drug resistance, poor pharmacokinetic characteristics, and systemic toxicity (Moo *et al.* 2018). A systematic method to deliver the drug to the target site in cancer includes systemic administration and topical delivery of the drug that may lead to improved therapeutic effect and decrease potential side effects (Saha *et al.*, 2017, Navya *et al.* 2019). One approach is nano-drug delivery which has various advantages including improved specificity by overcoming tumour barriers (Rosenblum *et al.* 2018). A recently emerged technique is to produce mixed vehicles from lipids and co-polymers to overcome the limitations of conventional liposomes (Tang *et al.* 2017). An amalgamation of polymer and lipid base gives rise to a vehicle that exhibits greater viscoelastic properties in comparison to pure liposomes and is more stable than the conventional vesicular system (Fauquignon *et al.* 2019).

Polymer-lipid based hybrid vesicles (PLH vesicles) are composed of a polymer with a hydrophilic section consisting of PEG that ensures longer blood circulation half-life by reducing reticuloendothelial system (RES) uptake. A polymer-lipid based hybrid vesicles enhance the accumulation of drug in tumours, prevent its metabolism and lysosomal degradation, and avoids unnecessary exposure of the drug to normal tissue. This improved permeability and retention ability to ensure a certain passive targeting to tumour cells, an advantageous feature of PLH vesicles encapsulated drugs over free drugs (Rao and Prestidge 2016). Hybrid vesicles resulting from the combined self-assembly of both copolymers and lipids is a promising method to overcome the limitations of a vesicular system like liposomes and polymersomes. The main expected benefit of such hybrid structures would be bio functionality and modulation of the membrane properties such as permeability and elasticity.

Medicinal plants have been a valuable source for decades of numerous cancer chemotherapeutic agents and in view of this, Thymoquinone (TH), proves to be potential for its wide array of biological actions like anti-oxidant, anti-inflammatory antitumor, and anticancer properties (Sun *et al.* 2019). A naturally occurring bioactive compound obtained from the black seed oil from the plant, *Nigella sativa* is TH (2-methyl-5-isopropyl-1,4-benzoquinone), which reportedly has certain anticancer properties. Schneider-Stock *et al.* demonstrated prominent cytotoxic activities against several cancer cell lines including human cervical adenocarcinoma Cervical Cancer



Investigation of the influence of cellulose polymer on solid phase transformation of carbamazepine

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ABSTRACT

Crystalline anhydrous drugs can get potentially transformed in to the hydrate form during manufacturing processes that involve water. To control the solid-state form of the drug it is important to understand the process of manipulating these transformations. The use of polymers to inhibit solid state transformations is an imperative concept in drug delivery. Recently tremendous investigation is going on using various polymers to prevent the anhydrous to hydrate transformation during manufacturing. The aim of this work was to investigate the influence of specific ratio of hydroxypropyl methylcellulose K 4 M on the phase transformation and release profile of carbamazepine. The surface topography of the crystal for assessing the crystal habit was done using scanning electron microscope, Fourier Transform Infrared Spectrophotometer and differential scanning calorimetry. Powder dissolution profile concluded that anhydrous exhibited significantly higher dissolution rate. HPMC K4 M was found to inhibit the transformation of carbamazepine to carbamazepine dihydrate in the gel layer of hydrated tablets and in aqueous solutions. Upon exposure to aqueous medium, the anhydrous form rapidly converts to the dihydrate. However, premixing of anhydrous with HPMC K4M in specific ratio, in the presence of water exhibited inhibition of the solution mediated phase transformation of carbamazepine anhydrous to dihydrate.

1. Introduction

The solubility and the ability of the drug moiety to cross the biological membrane is the major parameter which regulates the bioavailability of drug in body and ultimately affecting the therapeutic efficiency [1]. Nevertheless, the maximum marketed prevailing drugs have poor solubility and lack the necessary permeability properties, hence this has resulted to formulate a strategy to overcome this existing problems [2,3]. Carbamazepine (5H-dibenzazepine-5-carboxamide; CBZ), an iminosulbene derivative with a tricyclic structure, belongs to class II according to the Biopharmaceutical classification system due to its low solubility and low permeability. As a result, the focal point of ongoing research is to improve the dissolution or release of these drugs from the formulations [4]. Four polymorphic forms and one dihydrate form of CBZ are reported whose, solubility and dissolution rate have been found to be influenced by the polymorphic form [5]. Among all polymorphs, CBZ Anhydrous (CBZ-A) known to be the most stable at room temperature. It has been reported that, the anhydrous converts to

CBZ dihydrate (CBZ-DH) via solution mediated mechanism though with different kinetics in humid condition [6].

There is decrease in solubility and thus bioavailability of CBZ-A forms once they convert to the CBZ-DH. Kinetics of this transformation is a critical point for the bioavailability as this phase transformation results in a reduction of dissolution and bioavailability and explains partly erratic dissolution of CBZ tablets stored at different temperatures and relative humidity. Transformation from anhydrous to dihydrate form may negatively impact product quality and dissolution or bioavailability. Therefore, it is important to understand whether and how processing conditions might have resulted in solid phase changes and possible implications to dosage form performance.

This study was carried out to (1) characterize certain basic solid state properties of anhydrous and dihydrates of carbamazepine and conditions of their inter-conversion and (2) to study the effects of cellulose polymer on phase transitions and potential impact on dissolution of dosage form. A probable mechanism suggested by many researchers for polymers inhibiting the solid state transformation of various drugs is

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GENERAL REVIEW

3D printing in pharmaceuticals: An emerging technology full of challenges



L'impression 3D dans le secteur pharmaceutique : une technologie émergente pleine de défis

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HIGHLIGHTS

- 3D printing technology: Boon for the research and development of printed materials and devices.
- 3D printing considered to be next technological revolution in the pharmaceutical and medical arena.
- Personalization of medicine, tissues engineering and formulation of precise dosage forms.
- There are many challenges which exemplifies the limitations of this technology.
- Without developing concrete regulatory pathways, the future of the 3D printing in pharmaceutical sector is uncertain.

KEYWORDS

Personalized medicine;
3 dimensional printing technology;
Pharmaceutical application

Summary Although in its infancy, when compared with the other sectors, year 2005 marked the rapid evolution of 3 Dimensional printing (3DP) technologies in pharma sector with a huge potential in the dosage form designing and personalisation of the medication. 3DP is an innovative and highly promising way for the instant manufacturing in contrast with the tailored made conventional manufacturing. Various 3DP technologies are categorized into the various areas on the basis of the type of material used, deposition techniques and the solidification/fusion techniques. 3DP technologies have multiple pharmaceutical applications including formulation

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RESEARCH

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Studies on meropenem and cefixime metal ion complexes for antibacterial activity

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Abstract

Background: The metal ion complexes of meropenem and cefixime with cadmium, silver, palladium, zinc, nickel, cobalt and copper were synthesized and characterized by UV, FTIR and ^1H -NMR spectrophotometry. The antibacterial effects of the complexes were studied using cup and plate method against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa* and *K. pneumoniae* for normal and resistant strains of bacteria. The minimum inhibitory concentration of the metal ion complexes was determined by broth dilution method.

Results: UV spectroscopic studies suggested that meropenem ligand form complex with different metal ions and FTIR spectrum confirmed the proposed structure. Similarly, UV spectrum of cefixime metal ion complexes at λ_{max} 202–295 nm and meropenem metal ion complexes at λ_{max} 249–304 nm was observed in all the complexes. FTIR peaks for a proposed structure were observed in all the meropenem and cefixime metal ion, indicating the formation of complexes, and retained the functional groups of drugs. Meropenem as well as cefixime metal ion complexes exhibited more antibacterial activity against all the selected bacterial strains. Specifically, the lowest minimum inhibitory concentration against *P. aeruginosa* and *K. pneumoniae* was observed to be 100 and 150 $\mu\text{g/ml}$, respectively.

Conclusion: The present study concluded that the meropenem and cefixime metal complexes can exhibit the better treatment than individual drug on normal as well as resistant bacteria.

Keywords: Meropenem, Cefixime, Metal ion complex, Antibacterial, MIC, Resistance

Background

Metal ion exhibits antibacterial activity against most of the bacteria. Currently, complexes of antibiotics with metal ions focus the attention for new drugs as well as those endeavoring to increase the activity of antibiotics in use. Therefore, the role of antibiotic-metal complexes (AMC) in the field of pharmaceutical research has been constantly expanding. Moreover, it is necessary for the present situation to search for new, more effective and more broadly acting drugs due to an alarming increase in the growing number of drug-resistant bacteria [1]. This growing interest and research activities in the search for new combinations of metal ions with various classes

of antibiotics and other pharmaceuticals are currently observed. For overcoming the effects of resistant microorganisms such complexes have been intensively studied in recent years [2–5]. As reported in the literature, the use of metalloantibiotics, nanoparticles with metal ions, green nanoparticles and similar type of novel formulations allows for reduction of dose introduced into the body, enhancement of bioavailability and benefiting from the pharmaceutical effects of both ligand antibiotics and metal ions [6].

The interaction of metal ions with drugs and proteins, green-synthesized nanoparticles and metal ions has been recognized internationally as an important area for research. Metals existing in the nature due to their variable oxidation states, number and types of coordinated ligands and coordinative geometry after complexation can provide variety of properties, whereas the ligands can not only control the reactivity of the metal, but also play

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Inhibitory influence of agmatine in ethanol withdrawal-induced depression in rats: Behavioral and neurochemical evidence

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ABSTRACT

Although ethanol withdrawal depression is one of the prominent reasons for ethanol consumption reinstatement and ethanol dependence, its neurochemical basis is not clearly understood. The present study investigated the role of the agmatineric system in ethanol withdrawal-induced depression using the forced swim test (FST) in rats. Chronic exposure of animals to ethanol for 21 days and its abrupt withdrawal produced depression-like behavior, as evidenced by increased immobility time in the FST, compared to the pair-fed control animals. The ethanol withdrawal-induced depression was significantly attenuated by agmatine (20–40 µg/rat, i.c.v. [intracerebroventricularly]), moxonidine (50 µg/rat, i.c.v.), 2-BFI (20 µg/rat, i.c.v.), L-arginine (80 µg/rat, i.c.v.), amino-guanidine (25 µg/rat, i.c.v.), and arcaine (50 µg/rat, i.c.v.) by their once-daily administration during the withdrawal phase (Days 21, 22, and 23). The antidepressant effect of agmatine in ethanol-withdrawn rats was potentiated by the imidazoline receptor I₁ agonist moxonidine (25 µg/rat, i.c.v.) and the imidazoline receptor I₂ agonist, 2-BFI (10 µg/rat, i.c.v.) at their sub-effective doses. On the other hand, it was completely blocked by the imidazoline receptor I₁ antagonist, efaroxan (10 µg/rat, i.c.v.) and the imidazoline receptor I₂ antagonist, idazoxan (4 µg/rat, i.c.v.). In addition, agmatine levels were significantly reduced in brain samples of ethanol-withdrawn rats as compared to the pair-fed control animals. In conclusion, the present study suggests the importance of the endogenous agmatineric system and the imidazoline receptors system in ethanol withdrawal-induced depression. The data project agmatine as a potential therapeutic target for the alcohol withdrawal-induced depression.

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Introduction

Alcohol addiction and depression are two of the most costly and widespread neurological disorders, affecting millions of people worldwide. Several clinical studies have shown strong and consistent correlation between depression and alcohol addiction (Pavlovic et al., 2018; Pettinati, O'Brien, & Dondan, 2013). In addition, preclinical studies have supported the functional link between alcoholism and depression by demonstrating depression-like behavior in rodents during ethanol withdrawal (Chen et al., 2019; Rami & Rahman, 2017). Although ethanol withdrawal

depression is one of the leading causes for ethanol consumption reinstatement and ethanol dependence, its neurochemical basis is not clearly understood. Thus, understanding the neural mechanisms involved in mediating the co-morbidity of depression and alcoholism may be crucial in exploring new pharmacological treatments for this condition.

Agmatine, an endogenous amine, has received considerable attention in the process of drug addiction and associated complications. Agmatine is biosynthesized following decarboxylation of L-arginine, and is considered as a neuromodulator in the brain with many central and peripheral functions (Hilari & Piletz, 2007; Moretti et al., 2014; Reis & Regimathan, 2000). Systemic administration of agmatine exerts anxiolytic (Lavinsky, Arteni, & Netto, 2003; Taksande et al., 2014), anti-nociceptive (Agarwal et al., 2014), anti-inflammatory (Taksande, Gawande, Chopde, Umekar, & Kotagale, 2017), neuroprotective (Dixit et al., 2018), and anti-

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Agmatine Improves the Behavioral and Cognitive Impairments Associated with Chronic Gestational Ethanol Exposure in Rats

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Involvement of agmatine in antidepressant-like effect of HMG-CoA reductase inhibitors in mice

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ABSTRACT

3-Hydroxy-3-methyl-glutaryl-co-enzyme-A (HMG-CoA) reductase inhibitors (statins) are popularly used for the treatment of obesity and hypercholesterolemia with established safety profile. Statins exhibit a wide range of neurobehavioral effects in addition to their peripheral actions, and may be beneficial in treatment of psychiatric conditions. Present study investigated the role of agmatine and imidazoline receptors in antidepressant-like effect of statins in mouse forced swimming test (FST). The antidepressant-like effect of atorvastatin (5 mg/kg, p.o.) and simvastatin (10 mg/kg, p.o.) was potentiated by pretreatment with agmatine (5 mg/kg, i.p.) as well as the drugs known to increase endogenous agmatine levels in brain viz., L-arginine (40 µg/mouse, i.c.v.), an agmatine biosynthetic precursor; arcaine (50 µg/mouse, i.c.v.), agmatinase inhibitor; and aminoguanidine (6.5 µg/mouse, i.c.v.), a diamine oxidase inhibitor. Further, both the statins increased agmatine levels within hippocampus and prefrontal cortex. Conversely, prior administration of I₁ receptor antagonist, efaroxan (1 mg/kg, i.p.) and I₂ receptor antagonist, idazoxan (0.25 mg/kg, i.p.) blocked the antidepressant-like effect of statins and their synergistic combination with agmatine. These results demonstrate the involvement of agmatine and imidazoline receptors in antidepressant-like effect of statins and suggest as a potential therapeutic target for the treatment of depressive disorders.

1. Introduction

Statins, used for the treatment of obesity and hypercholesterolemia inhibits *de novo* cholesterol biosynthesis through 3-hydroxy-3-methyl-glutaryl-co-enzymes-A (HMG-CoA) reductase enzyme. Lipophilic statins exhibits a wide range of neurobehavioral effects in addition to their peripheral actions, and may be beneficial in treatment of psychiatric and neurological conditions (Chauvet et al., 2016; Kumar et al., 2012). They possess some cholesterol independent pleiotropic effect including neuroprotection, neurogenesis and brain plasticity (Chen et al., 2003; Ludka et al., 2017). Further, chronic administration of statins enhances the expression of brain derived neurotrophic factor (BDNF) and inhibits inflammatory cytokines, oxidative stress and neuronal apoptosis in hippocampus (Piernartzi et al., 2010; Martins et al., 2015). This beneficial neuropharmacological profile further led to exploration of their antidepressant effects in rodents (Ludka et al., 2013, 2014, 2016; Shahsavarian et al., 2014; Taulguri et al., 2019; Zhang et al., 2019) and

as an adjuvant in the clinical depression (Salagre et al., 2016). However, the exact mechanism of their antidepressant-like effects is still remained poorly investigated.

Agmatine is a biogenic amine synthesized following decarboxylation of amino acid L-arginine (Nels et al., 2017; Pilcz et al., 2013). It is metabolized to putrescine and guanido-butanolic acid by an enzyme agmatinase and diamine oxidase respectively (Huang et al., 2003; Regunathan, 2006). Agmatine, projected as a neuromodulator, is involved in the pathogenesis of several neurological and psychiatric disorders (Talaris and Pilcz, 2007; Laube and Bernsteln, 2017). It exhibits antidepressant (Nels et al., 2014; Taksande et al., 2014), anxiolytic (Taksande et al., 2010), neuroprotective (Hoodimandi et al., 2018; Kotagale et al., 2019), anti-inflammatory (Guan et al., 2017), anti-convulsant effect (Sahremand et al., 2018; Singh et al., 2017) and also involved in regulation of stress (Gawell et al., 2017; Zhu et al., 2007) and drug addiction (Chimthanasavala et al., 2020; Kotagale et al., 2015, 2018; Taksande et al., 2019; Urby et al., 2000; Wang et al.,

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Evidences for Agmatine alterations in $A\beta_{1-42}$ induced Memory Impairment in Mice

Madhura P. Dixit (Investigation) (Formal analysis) (Methodology), Shubham N. Rahmatkar (Methodology), Prachi Raut (Investigation) (Methodology), Milind J. Umekar (Supervision) (Validation), Brijesh G. Taksande (Supervision) (Validation) (Visualization) (Writing - original draft) (Writing - review and editing), Nandkishor R. Kotagale (Conceptualization) (Data curation) (Formal analysis) (Investigation) (Methodology) (Writing - original draft) (Writing - review and editing)

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Research report

Agmatine modulates anxiety and depression-like behaviour in diabetic insulin-resistant rats

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HIGHLIGHTS

- Agmatine inhibited depression, anxiety in HFD fed rats.
- HFD fed rats showed reduced agmatine levels and enhanced agmatinase expression in hippocampus.
- Agmatine reversed the increased IL-6 and TNF- α level in hippocampus in HFD fed rats.
- Agmatine increased the BDNF expression in HFD fed rats.

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ABSTRACT

Epidemiological studies indicated that mood disorders like depression and anxiety are highly prevalent in type-II diabetes mellitus (T2DM). However, the neurobiological mechanisms underlying the relationship between T2DM and depression have yet to be identified. Thus, understanding the neural mechanisms that mediate the co-morbidity of depression and type-II diabetes mellitus may unlock new pharmacological treatments for this condition. The present study investigated the role of the agmatinergic system in T2DM induced depression using forced swim test (PST) and anxiety in the elevated plus-maze (EPM) in rats. T2DM was induced by the combination of high-fat diet (HFD) and streptozotocin (STZ) injection and confirmed by high blood glucose levels. After 12 weeks, HFD fed and STZ injected rats exhibited depression-like behaviors and anxiety. It was associated with increased expression of pro-inflammatory cytokines like IL-6 and TNF- α , and reduced BDNF immunoreactivity in the hippocampal tissues. The T2DM-induced depression, anxiety, and neuroinflammatory markers were significantly inhibited by agmatine (10–20 mg/kg, i.p.), by once-daily administration during 9th to 12th week of the protocol. Agmatine levels were significantly reduced in the hippocampus of T2DM rats as compared to the normal fed (NF) control animals. In conclusion, the present study suggests the importance of endogenous agmatine in T2DM induced anxiety and depressive-like behavior in rats. The data projects agmatine as a potential therapeutic target for T2DM-associated depression, anxiety, and comorbidities.

1. Introduction

The risks of neuropsychiatric disorders are higher in patients with type 2 diabetes mellitus (T2DM) (van Sloten et al., 2020). A large number of studies have demonstrated the epidemiological and neurobiological links between mood disorders like depression, anxiety, and T2DM (Mazzanti et al., 2014; Moulton et al., 2015; Pan et al., 2010). It has been reported that diabetic patients are more susceptible to have depression and anxiety than non-diabetic individuals (Lustman et al.,

2005). Co-morbidity of depression and anxiety with T2DM increases the mortality rates by micro and macrovascular complications leading to multi-organ damage (Gaspert and Blesse, 2000; Semenkovich et al., 2015). The pathophysiology of mood disorders in diabetic patient is highly complicated and multifactorial, like functional insulin-resistance, inflammation, oxidative stress, dysregulation of neurotransmitter systems including norepinephrine and serotonin, and decreased brain-derived neurotrophic factor (BDNF) (Gahbe et al., 2007; Lustman et al., 2005; Muselman et al., 2003; Winokur et al., 1988).

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Agmatine reverses memory deficits induced by A β _{1–42} peptide in mice: A key role of imidazoline receptors

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ABSTRACTS

Agmatine is a biogenic amine synthesized following decarboxylation of L-arginine by the enzyme arginine decarboxylase and exhibits favourable outcome in neurodegenerative disorders. Present study was designed to examine the relationship between agmatine and the imidazoline receptors in memory deficits induced by A β _{1–42} peptide in mice. Mice were treated with single intracerebroventricular (i.c.v.) injection of A β _{1–42} peptide (3 μ g) and evaluated for learning and memory in Morris water maze (MWM) and subjected to A β _{1–42}, TNF- α and IL-6 and BDNF immunoccontent analysis within the hippocampus. While the learning and memory impairment was evident in the mice subjected to MWM test following A β _{1–42} peptide administration, there was a significant increase in A β _{1–42}, TNF- α and IL-6 and reduction in BDNF immunoccontent within the hippocampus. Daily intraperitoneal (i.p.) treatment with agmatine (10 and 20 mg/kg); imidazoline I₁ receptor agonist, moxonidine and imidazoline I₂ receptor agonist, 2-BF starting from day 8 to 27 post-A β _{1–42} injection, significantly prevented the cognitive deficits and normalized the A β _{1–42} peptide, IL-6, TNF- α and BDNF immunoccontent in hippocampus. On the other hand, pre-treatment with imidazoline I₁ receptor antagonist, clazosan and imidazoline I₂ receptor antagonist, BU 224 attenuated the effects of agmatine on learning and memory in MWM, IL-6, TNF- α and BDNF content. In conclusion, the present study provides functional evidence for the involvement of the imidazoline receptors in agmatine induced reversal of A β _{1–42} induced memory deficits in mice. The data projects agmatine and imidazoline receptor agonists as a potential therapeutic target for the treatment of AD.

1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by progressive loss of memory, diminished spatial skills and disoriented behavior. The primary pathogenic mechanism involves the accumulation of β -amyloid (A β) peptide in the senile plaques and intracellular aggregates tau proteins in the neurofibrillary tangles (Hardy and Higgins, 1992; Hardy and Selkoe, 2002). The pharmacotherapy offers only symptomatic relief and do not treat or prevent the progression of AD (Yiannopoulou and Papageorgiou, 2020). Thus, identification of new molecular targets and receptorial system are necessary to abolish the progressive neurodegeneration and resulting memory loss in AD (Saccarechovsk et al., 2019). Current research strategies mainly focus on modulating molecular events involve in A β production, its removal and prevention of hyperphosphorylation of tau protein, employing endogenous molecules as a biological target (Cheng et al., 2020; Xin et al., 2018; Zuccarello et al., 2020).

Agmatine, an endogenous aminoguanidine compound synthesized from L-arginine by arginine decarboxylase has been projected as a neuromodulator in the brain (Laube and Bernstein, 2017; Halaris and Piletz, 2007). It exhibits neuroprotective (Dixit et al., 2018; Kotagale et al., 2019), anxiolytic (Taksande et al., 2014), anti-depressant (Taksande et al., 2009), antinociceptive (Onal et al., 2004), anticonvulsive (Bence et al., 2003), anti-compulsive (Dixit et al., 2014) and also inhibits the process of addiction (Kotagale et al., 2018; Taksande et al., 2019a, 2019b). Agmatine is localized in major brain regions (hippocampus, cortex, locus coeruleus) which are directly associated with cognition and has demonstrated a vital role in learning and memory (Arzeni et al., 2003; Rushaidhi et al., 2012, 2013). Agmatine prevents memory deficits induced by intracerebroventricular injection of A β _{25–35} peptide (Bergin et al., 2015; Liu et al., 2011) and offers neuroprotection against A β peptide-induced hippocampal toxicity (Bhoslmundi et al., 2019). Agmatine also ameliorates cognitive impairment in AD-associated with diabetes mellitus (Sang et al., 2014;

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Full Length Article

Involvement of hippocampal agmatine in β_{1-42} amyloid induced memory impairment, neuroinflammation and BDNF signaling disruption in miceNandkishor Kotagale^{a,b}, Shubham Rahmatkar^a, Sarita Chauragade^a, Madhura Dixit^a, Milind Umekar^a, Chandrabhan Chopde^b, Brijesh Taksande^{a,*}^a Division of Neuroscience, Department of Pharmacology, Sant. Kishorilal Bhoyar College of Pharmacy, New Campus, Nigam, Maharashtra, 441 002, India^b Government College of Pharmacy, Amravati, Maharashtra, 444 604, India

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ABSTRACT

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder characterized by abnormal accumulation of extracellular β -amyloid ($A\beta$) plaques and neuronal damage. The present study investigated the effect of chronic intra-hippocampal agmatine administration on β -Amyloid ($A\beta$) induced memory impairment in mice. $A\beta_{1-42}$ peptide injected mice demonstrated impairment of cognitive abilities evaluated as reference memory error and working memory error in radial arm maze (RAM) and decreased exploration time for novel object as well as recognition index in novel object recognition (NOR) test along with elevation in $A\beta_{1-42}$ peptide, β -Site APP cleaving enzyme 1 (BACE 1), microtubule-associated protein tau (MAPt), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and reduction in neprilysin and brain derived neurotrophic factor (BDNF) immunoreactivity within hippocampus and prefrontal cortex. Importantly, this was associated with a reduction in the agmatine levels following $A\beta_{1-42}$ peptide administration. Chronic administration of agmatine from day 8–27, prevented the memory impairment in mice and normalized the neurochemical alteration within prefrontal cortex and hippocampus induced by $A\beta_{1-42}$ peptide administration. However, it did not modulate the amyloid precursor protein and BACE expression. This study suggests that agmatine improves learning and memory impairment possibly through the down regulation of neuroinflammatory pathways in AD.

1. Introduction

Alzheimer's disease (AD) is a chronic, complex and progressive neurodegenerative disorder that affects a large percentage of the elderly population worldwide. At neuropathological level it demonstrates abnormal deposition of extracellular β -amyloid ($A\beta$) senile plaques and intracellular neurofibrillary tangles (Kossmann and Müller, 2010; Platenik et al., 2014; Qi et al., 2013). Accumulations of the $A\beta$ lead to neuroinflammation followed by neuronal damage and results in synaptic dysfunction particularly within hippocampus (Bronzeoli et al., 2016). Hippocampus is considered as an important brain nuclei associated with cognitive process, spatial navigation and gets severely affected during AD progression (West et al., 1994, 2004; Muñoz et al., 2015). Many factors contribute to synaptic dysfunction within hippocampus including dysregulation of brain derived neurotrophic factor (BDNF) signaling (Tapia-Arancibia et al., 2008). BDNF is critically important for neuronal survival, neuronal plasticity and synaptic transmission and its mRNA expression is reported to be reduced in hippocampus and cortical areas of AD patients (Hock et al., 2006).

AD is commonly associated with alteration in most of the neurotransmitter system in brain (Gsell et al., 2004). Agmatine is a biogenic amine synthesized from the amino acid, L-arginine by enzyme arginine decarboxylase (ADC) and implicated in neuromodulation and neuroprotection (Laube and Bernstein, 2017; Neis et al., 2017; Dixit et al., 2018). It has anxiolytic (Taksande et al., 2014), anti-depressant (Taksande et al., 2009), antinociceptive (Aglaive et al., 2014), anti-convulsive (Bence et al., 2003), anti-compulsive (Dixit et al., 2014) and anti-inflammatory effects (Taksande et al., 2015a, 2015b, 2017) and also modulates the process of drug addiction (Kotagale et al., 2015; Taksande et al., 2019; Chinnappa et al., 2020). Agmatine binds to α_2 -adrenoreceptors, imidazoline binding sites, blocks N-methyl-D-aspartate (NMDA) receptors and inhibits nitric oxide synthase (NOS) (Neis and Regunathan, 2000).

Being predominantly localized in brain regions directly associated with cognition including the hippocampus, cortex and locus coeruleus, agmatine has demonstrated a vital role in learning and memory (Liu et al., 2011; Moosavi et al., 2013). Its chronic treatment improved working and spatial memory in water maze and novel object

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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 ($92.23 \pm 1.02 \mu\text{g/mL}$) over that of pure ranolazine ($4.94 \pm 0.06 \mu\text{g/mL}$) and physical mixture (PM) ($30.21 \pm 2.12 \mu\text{g/mL}$). 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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Phospholipid complex-loaded self-assembled phytosomal soft nanoparticles: evidence of enhanced solubility, dissolution rate, ex vivo permeability, oral bioavailability, and antioxidant potential of mangiferin

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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 (¹H-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 CCl₄-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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Agmatine reverses ethanol consumption in rats: Evidences for an interaction with imidazoline receptors

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ABSTRACT

Alcohol is one of the most widely abused recreational drugs, largely linked with serious health and social concerns. However, the treatment options for alcohol-use disorders have limited efficacy and exhibit a range of adverse drug reactions. Large numbers of preclinical studies have projected a biogenic amine, agmatine as a promising potential treatment option for drug addiction, including alcoholism. In the present study, administration of agmatine (20–40 mg/kg, i.p.) resulted in significant inhibition of ethanol self-administration in the right p-VTA in operant conditioning paradigm. Further, acute intracranial administration of agmatine (20 and 40 µg/rat) significantly reduced the ethanol consumption in the two bottle choice paradigm. Agmatine is degraded to putrescine and guanido-butyric acid by the enzyme agmatinase and diamine oxidase respectively and inhibition of these enzymes results in augmentation of endogenous agmatine. In the present study, diamine oxidase inhibitor, aminoguanidine and agmatinase inhibitor, arcaine were used to block the agmatine metabolic pathways to increase brain agmatine levels. Drugs that augment endogenous agmatine levels like L-arginine (80 µg/rat, i.c.v.) or arcaine (50 µg/rat, i.c.v.) and aminoguanidine (25 µg/rat, i.c.v.) also reduced the ethanol consumption following their central administration. The pharmacological effect of agmatine on ethanol consumption was potentiated by imidazoline receptor agonists, I₂ agonist moxonidine (25 µg/rat, i.c.v.), and imidazoline I₂ agonist, 2-BFI (10 µg/rat, i.c.v.) and was blocked by imidazoline I₂ antagonist, efexoran (10 µg/rat, i.c.v.), and I₂ antagonist, idazoxan (4 µg/rat, i.c.v.) at their ineffective doses per se. Thus, our result suggests the involvement of imidazoline I₂ and I₂ receptors in agmatine induced inhibition of ethanol consumption in rats.

1. Introduction

Chronic ethanol consumption leads to serious health and social consequences. A huge mortality worldwide is attributed to alcoholism, even greater than deaths caused by infections or violence (World Health Organisation, 2014). Unfortunately, there are only three medications approved by the Food and Drug Administration for the treatment of alcohol abuse and alcoholism: disulfiram, naltrexone and acamprosate (Liang and Olsen, 2014). Medication compliance issues, adverse side effects and the modest efficacy of these compounds reveal the need for better targets of alcoholism in order to develop newer effective medications.

Although, there are different pathways underlying alcohol seeking behavior, the biological process that builds and reinforces alcohol addiction is not yet fully understood. Although alcohol can affect multiple neurotransmitter receptors, including GABA, NMDA, 5-HT₃ etc.

(Trudell et al., 2014; Morrow et al., 2001) the studies are inconclusive in finding their direct correlation with alcohol intake. In recent years, several studies were executed to identify exactly how does the endogenous systems like neuropeptides, β -endorphins, endocannabinoids mediate reinforcing the effects of alcohol (Kokare et al., 2008; Ron and Messing, 2013; Henderson-Redmond et al., 2015).

Agmatine, an endogenous biogenic amine, has been implicated in the process of drug addiction. It attenuates ethanol, nicotine as well as morphine withdrawal symptoms (Azicoglu-Kartal and Ucbay, 1997; Li et al., 1999; Ucbay et al., 2000; Kotagale et al., 2015, 2018). Further, it reduces impaired performance on a cerebellar-dependent balance tested in a rat model of third trimester binge-like ethanol exposure (Lewis et al., 2007) and ultrasonic vocalization deficits in female rat pups exposed neonatally to ethanol (Wellmann et al., 2010). Agmatine decreases the morphine, cocaine, fentanyl self-administration (Morgan et al., 2002), inhibits the ethanol induced locomotor sensitization

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Effect of Explant Source, Culture Media, and Growth Regulators on Callogenesis and Expression of Secondary Metabolites of *Curcuma Longa*

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ABSTRACT

The effects of explant source, medium composition, and growth regulators were examined in callus lines of *Curcuma longa*. Callus cultures were induced from leaf sheath, leaf lamina, leaf base, apical buds, and lateral buds. The growth potential of established callus lines varied with a combination of phytohormones and culture medium. The greatest callus induction (79%) after 21 d was observed with MS medium supplemented with 3 mg L⁻¹ 2,4-D and 0.8 mg mL⁻¹ kinetin. Phytochemical and chromatographic analysis of callus extract after 6th sub-culture revealed the presence of 53.6 mg g⁻¹ of total polyphenols and 36.1 mg g⁻¹ curcumin dry wt. with higher *in-vitro* anti-oxidant activity compared to turmeric rhizome extract. The lateral bud callus of *C. longa* may be used as a starting material for the synthesis of secondary metabolites of pharmaceutical interest.

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Turmeric; callus induction; *in-vitro* culture; secondary metabolites; MS medium; curcumin

Introduction

Curcuma longa (Zingiberaceae) commonly called turmeric, known as the "golden spice" and "spice of life," is extensively used in Ayurveda, Unani, and Siddha medicine and as a home remedy for various diseases.^[1] Turmeric is an erect perennial herb, grown as an annual, with short stem, large oblong leaves, and bears ovate, pyriform, or oblong brownish branched rhizomes.^[2]

Callus is an undifferentiated mass of parenchymatous cells. Optimized culture conditions by variations in plant growth regulators and nutrient medium supplemented with vitamins can lead to callus induction, subsequent differentiation, and organogenesis. Cell division, cell growth, and tissue differentiation in plants can be achieved with the stimulus of endogenous growth substances or by the addition of exogenous growth regulators to the nutrient medium.^[3]

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Enhanced transdermal permeation and anti-inflammatory potential of phospholipids complex-loaded matrix film of umbelliferone: Formulation development, physico-chemical and functional characterization

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ABSTRACT

In the present study, umbelliferone - phospholipids complex - loaded matrix film (UPLC - MF) was developed with a goal of improving transdermal permeation and anti-inflammatory potential of umbelliferone (UMB). Umbelliferone - phospholipids complex (UPLC) was prepared using solvent evaporation method. UPLC-MF was prepared by simple and reproducible solvent casting method. Prepared UPLC and UPLC-MF were both physico-chemically characterized by Fourier transforms infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD), proton nuclear magnetic resonance spectroscopy (¹H NMR), weight variation, thickness, tensile strength, folding endurance, % elongation, moisture content and uptake. Functional characterization of UPLC and UPLC-MF was carried out by solubility analysis, in vitro dissolution, diffusion, and ex vivo permeation via dialysis and biological membrane. UPLC - MF was also evaluated for in vivo anti-inflammatory activity using carrageenan-induced Albino rat paw model. Design-based optimal values for formulation and process variables of UPLC were observed to be 1:1.78, 50 °C and 2 h, respectively. Physico-chemical characterization confirmed the formation of the complex and the film. UPLC demonstrated a higher aqueous solubility (~11-fold), compared to pure UMB. Rate and extent of dissolution of UMB from UPLC was enhanced significantly to that of pure UMB. Compared to UMB-MF, the diffusion and permeation rate of UMB from UPLC-MF enhanced significantly. The UPLC - MF improved the anti-inflammatory potential of UMB by significant enhancement of edema inhibition (%), compared to UMB-MF. The obtained results showed that the present combined formulation system could be employed as a promising strategy for improving transdermal permeation of UMB.

1. Introduction

Umbelliferone (UMB), a coumarin derivative, is widely distributed in nature, particularly several plants and fruits such as carrot, coriander, garden angelica, golden apple and bitter orange (Jard et al., 1971). It is a natural antioxidant and therefore, widely used in diet for obvious health benefits (Hoult and Paydt, 1996). Previous studies have shown that upon oral administration, UMB produced a number of biological activities including, antifungal (Pan et al., 2017), anti-cancer (Kumar et al., 2012; Yu et al., 2015), anti-diabetic (Ramesh and Puganelli, 2006), and most importantly, the antioxidant and anti-inflammatory activities (Singh et al., 2010; Ranfah et al., 2014). The anti-

inflammatory activity of UMB is most likely due to potent inhibition of the peripheral and centrally-acting pain mediators (Singh et al., 2010). Regardless of UMB positive and therapeutic profile, its relatively higher hydrophobicity and poor absorption limits its potential utility as a promising drug candidate (Lacatusu et al., 2013). The matter is worse its extensive first-pass metabolism via glucuronidation, shorter half-life ($t_{1/2}$) and rapid clearance from the body, comprising its anti-inflammatory potential due to lower bioavailability (Bütschli et al., 1977).

Till date, only a few attempts have been made to improve the oral bioavailability of UMB. These include PLGA nanoparticles (Kumar et al., 2012), solid lipid nanoparticles (SLN) (Lacatusu et al., 2013) and

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Neuroprotective Effect of Agmatine in Mouse Spinal Cord Injury Model: Modulation by Imidazoline Receptors

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Abstract

Objective: The involvement of imidazoline receptors in the effect of agmatine was studied in locomotor recovery following experimental SCI (ESCI) in mice. **Methods:** ESCI was induced in mice using compression method. Locomotor function score (0–10) was measured on day 14 following ESCI. **Results:** Agmatine (2.5, 5, and 10 mg/kg) treatment through intraperitoneal route for 14 days following ESCI, dose-dependently improved the motor function score. Clonidine (0.1 mg/kg; imidazoline I1 receptor agonist) or moxonidine (0.5 mg/kg; I2 receptor agonist) treatment 15 min before agmatine (2.5 mg/kg) daily for 14 days following ESCI, significantly potentiated the effect of *per se* agmatine. On the other hand, 15 min before treatment of efroxan (1 mg/kg; imidazoline I1 receptor antagonist) or idazoxan (3 mg/kg; imidazoline I2 receptor antagonist) significantly blocked the motor function score of agmatine (10 mg/kg). **Conclusion:** These data suggest that imidazoline receptors may modulate the locomotor recovery following ESCI in agmatine treated mice, perhaps through I1/I2 receptors.

Keywords: Agmatine, imidazoline receptors, locomotor recovery, motor function score, spinal cord injury

INTRODUCTION

Spinal cord injury often results in disability or loss of movement and sensation below the site of injury. At present, few treatments for spinal cord injury are available, however with less significant functional improvement. Agmatine, an endogenous amine, exists in mammalian brain and has been proposed as a novel neurotransmitter/neuromodulator.^[1] The distribution of agmatine-containing neurons is concentrated in regions of the brain that subserve visceral and neuroendocrine control, processing of emotions, pain perception, cognition, and memory. Agmatine has been implicated in several biological processes such as neuroprotection,^[2] antinociception,^[3] convulsions,^[4] stress,^[5] depression,^[6] and anxiety.^[7] It is interesting to note that agmatine also dose-dependently attenuates neuropathic pain in rodents.^[8] Its intraperitoneal administration reversed long-lasting hypersensitivity, hyperalgesia, and allodynia induced by neuropathic pain.^[9–11] Further, agmatine also attenuated the pain associated with diabetic neuropathy.^[12–14] Its peripheral administration enhanced morphine analgesia dose-dependently in neuropathic rats.^[15] Moreover, systemically administered agmatine significantly reduces the mechanical and thermal hyperalgesia

as well as allodynia in neuropathic mice caused by spinal cord injury.

Agmatine binds to several target receptors such as imidazoline, N-methyl-D-aspartate (NMDA), nicotinic cholinergic, α_2 -adrenergic, serotonergic receptors, and inhibits nitric oxide synthase. Agmatine is co-localized with imidazoline receptor in several brain areas. Moreover, several pharmacological effects of agmatine are mediated through imidazoline receptors. The role of imidazoline receptor in nociception is fairly well established. Imidazoline binding sites have currently attracted attention in nociception as well as drug addiction.^[14] Moreover, the brain structures involved in the drug abuse and pain perception including hypothalamus, hippocampus, and amygdala are rich in imidazoline binding sites and its endogenous ligands.^[13] Imidazoline binding sites are a family

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Withaferin A attenuates Alcohol Abstinence Signs in Rats

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ABSTRACT

Background: *Withania somnifera* (WS) have been reported to inhibit acquisition and expression conditioned place preference, self-administration and withdrawal anxiety of psychostimulants. In the present work, we have assessed the effect of Withaferin A on somatic and affective symptoms of ethanol withdrawal syndrome in rats. **Methods:** Animals had given free access to ethanol uninterrupted for 21 days through liquid diet. Withaferin A (5, 10 and 20 mg/kg) was injected (ip) either during the development of ethanol dependence phase (days 15–21 or 30 min before ethanol withdrawal assessment). Withdrawal signs characterized by changes in somatic signs were measured in the open field followed by evaluation of anxiety parameters, locomotion, and depressive behavior. **Results:** Withaferin A treatment 30 min before 24 h post-ethanol withdrawal assessment did not alter the scores of somatic behavioral signs in ethanol abstinence animals. However, withaferin A (10 and 20 mg/kg, ip) from day 15–21 prevented the ethanol withdrawal-induced elevated scores of somatic behaviors, hyperlocomotion, depressive behavior, and anxiety. Withaferin A treatment did not influence the blood ethanol levels in dependent and withdrawn animals. However, withaferin A administration attenuated the elevated plasma corticosterone and ACTH levels in ethanol withdrawn rats, suggesting withaferin A induced anti-stress effect and stabilization of HPA axis activity could have facilitated the inhibitory effect of withaferin A on ethanol withdrawal syndrome. **Conclusion:** The finding supports further investigation of Withaferin A and other bioactive components of WS in alcohol addiction.

Key words: Anxiety, Corticosterone, Ethanol withdrawal, HPA axis, Withaferin A.

INTRODUCTION

Alcohol withdrawal syndrome is potentially life-threatening in addicted people and associated maladies constitute a serious health and social issues.¹ Abstinence from chronic ethanol consumption leads to the manifestation of a variety of somatic and affective symptoms attributed to central nervous system hyperexcitability, like irritability, anxiety, restlessness and dysphoria.² Despite the tremendous advances made in the treatment of alcoholism and/or its abstinence, remarkably, the majority of these agents, including naltrexone and benzodiazepines etc. have unpleasant side effect.^{3,4}

Withaferin A is a steroidal lactone, an active compound isolated from *Withania somnifera* (WS) (Family- Solanaceae). WS, known as ashwagandha in Ayurveda or its active principles, including withaferin A has been used as an antioxidant, adaptogen, antistress,^{5,6} anti-inflammatory, neuroprotective, anxiolytic, antidepressant, immunomodulatory, memory enhancer, anti-ulcer and anti-carcinogenic agents.^{7–12} In addition, WS extract has been inhibited the morphine-induced acquisition and expression in conditioned place preference,¹³ ethanol conditioned place preference¹⁴ and self-administration,¹⁵ ethanol withdrawal-induced anxiety in rats.¹⁶ In the present work, we have assessed

the effect of withaferin A on somatic and affective symptoms of ethanol withdrawal syndrome in rats.

MATERIALS AND METHODS

Subjects

Adult healthy Sprague Dawley rats weighing 200–220 g (3–4 months old) were group housed (four per cage) under controlled temperature (25±2°C) and light (12 h light/dark cycle, light on at 07.00 am) environment with free access to food and water. Experimental protocols were approved by the Institutional Animal Ethical Committee and executed in strict accordance with the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, Govt. of India. The behavioral assessments were conducted during the light cycle.

Drugs

Withaferin A was purchased from Natural Remedies Private Limited, Bangalore, India and administered intraperitoneally (ip) as a solution (1 ml/kg) in dimethylsulphoxide (DMSO) prepared just before the experiments. Ethanol (99% w/v) (Merck, India)

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Agmatine inhibits nicotine withdrawal induced cognitive deficits in inhibitory avoidance task in rats: Contribution of α_2 -adrenoceptors

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ABSTRACT

Nicotine abstinence following chronic exposure is associated with impairments in memory and variety of cognitive functions. Daily nicotine (2 mg/kg, sc, four times daily) administration for 14 days and its abrupt withdrawal significantly impaired avoidance learning in inhibitory avoidance task as indicated by a significant decrease in the step through latency. Animals injected with agmatine (10–40 μ g/rat, icv) from day 7 to 14 before the first daily dose of nicotine (2 mg/kg, sc) showed increased step through latencies during retrieval test. Similarly Intracerebroventricular injection of L-arginine (25–100 μ g/rat), a biosynthetic precursor of agmatine and arginine (50 μ g + 100 μ g/rat), an agmatinase inhibitor, also increased the step through latency during retrieval test in nicotine withdrawn animals. In separate experiments, α_2 -adrenoceptor agonist, clonidine (0.5–1 μ g/rat, icv) not only demonstrated significant increase in the step through latency as in nicotine withdrawn rats but also potentiated the pharmacological effect of agmatine. In contrast, pre-treatment of α_2 -adrenoceptor antagonist, yohimbine (0.5 μ g/rat, icv) antagonized the memory enhancing effect of agmatine (20 μ g/rat, icv) in nicotine withdrawn rats. In addition, brain agmatine analysis carried out at 72 h time point of nicotine withdrawal showed marked decrease in basal brain agmatine content as compared to control. Overall, the data indicate that agmatine attenuates nicotine withdrawal induced memory impairment through modulation of α_2 -adrenoceptors. Thus, agmatine might have therapeutic implications in the treatment of cognitive deficits following nicotine withdrawal.

1. Introduction

Nicotine generally acts as a cognitive enhancer and known to influence several domains of learning and memory. In fact, nicotine treatment can improve cognitive performance in schizophrenics and in attention deficit hyperactivity disorder (Moss et al., 2009; Tidey et al., 2013). However, its withdrawal results in severe deficits in learning and memory functioning. Nicotine abstinence in smokers is usually associated with difficulty in attentiveness and inferior working memory (Aubare et al., 2014; Cook et al., 2003; Wesnes et al., 2013). More specifically, smoking abstinence impairs executive functions which may promote smoking behavior and relapse (McClellan et al., 2016). However, the molecular mechanism and related neural substrate responsible for these cognitive deficits are not clearly known.

Agmatine is a biogenic amine synthesized from amino acid, L-arginine by enzyme arginine decarboxylase (ADC) and implicated in the development of drug addiction (Aricioglu-Kartal and Uzbay, 1997;

Uzbay et al., 2000; Uzbay, 2012). It exhibits anxiolytic (Taksande et al., 2010, 2014) antidepressant (Li et al., 2003; Taksande et al., 2009), antinociceptive (Onal et al., 2004), anticonvulsive (Beuce et al., 2003), orexigenic (Taksande et al., 2011), anti-compulsive (Oxli et al., 2014), neuroprotective (Olmos et al., 1999) effects, inhibits inflammatory markers (Taksande et al., 2015a, 2015b, 2017) and causes facilitation of working memory in experimental animals (Liu and Bergin, 2009). Agmatine binds to α_2 -adrenoceptors (Li et al., 1994), imidazoline binding sites (Rausch et al., 2001; Reis and Regunathan, 2000), blocks N-methyl-D-aspartate (NMDA) receptors (Yaug and Reiz, 1999) and inhibits nitric oxide synthase (NOS) (Auguet et al., 1995; Galea et al., 1996). Agmatine also inhibited the nicotine induced sensitization and conditioned place preference (Kotagale et al., 2010, 2014).

It is important to note that, agmatine is predominantly localized in brain regions directly associated with memory processing including hippocampus, cortex, locus ceruleus, and forebrain and demonstrated a vital role in learning and memory (Halaris and Piletz, 2007). Prolonged

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Development of self-assembled nanocarriers to enhance antitumor efficacy of docetaxel trihydrate in MDA-MB-231 cell line

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ABSTRACT

Self-assembled nanocarriers (SANs) as a novel colloidal controlled delivery for docetaxel trihydrate (DTX) were engineered by high-pressure homogenization method to overcome the several clinical problems. Drug-excipient compatibility was studied using DSC and FTIR spectroscopy. The fabricated SANs was characterized by particle size, zeta potential, and SEM. QbD based central composite design of experiment was employed for formula optimization. The cell viability of DTX-hydroalcoholic solution (DTX-HA) and DTX-loaded SANs has been determined in MDA-MB-231 cell line by MTT assay. The stability study of selected SANs formulations were carried out at various storage conditions as per ICH guidelines. The summary of results obtained shows high drug content with higher entrapment efficiency ($91.23 \pm 3.41\%$ w/w) of DTX-loaded SANs. It shows diffusion controlled release of DTX over the period of 12 h which is higher than DTX-HA solution, releases the DTX within 4 h. The MTT assay expressed lower cellular viability and improved cell inhibition leads to increase cytotoxicity of formulations towards cells. The stability study reveals stability of DTX-loaded SANs formulations at various storage conditions over a period of three months. The strong experimental evidence confirms the SANs as an effective approach to formulate the controlled delivery system of antineoplastic with improved stability.

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1. Introduction

Biocompatible nanostructured lyotropic liquid crystalline particles (LLC NPs) are efficient and safer for delivery of drugs. These are formed by the combination of both natural and synthetic lipids, surfactants, solvents and stabilizers. The surfactant plays an important role in the formulation. Polar head and a non-polar tail of surfactant help to bind the organic and aqueous phases in LLC. Six different types of LLC phases have been described by the various research groups which include lamellar, hexagonal, cubic, nematic, gel and intermediate phases [1,2].

Cubic LLC phases are able to accommodate water-soluble, lipid-soluble as well as amphiphilic molecules [3]. They are typically 100–200 nm in size and highly ordered bicontinuous cubic nanostructure of water channels through the lipid matrix [4–7] and exert controlled delivery of drugs via tortuous diffusion through the regular channel structure. Since they are formed by the self-assembly of hydrophilic as well as lipophilic molecules at specific temperature and pressure condition they termed as self-assembled nanocarriers (SANs).

Mechanical fragmentation of the cubic lipid-water phase in a three-phase region leads to fabrication of cubic phases but the excessive addition of water results into the formation of their colloidal dispersion. Excess of water may hamper the stability of colloidal dispersion. Incorporation of tri-block copolymers like Pluronic® F127 can helps to stabilize the dispersion by avoiding particle aggregation [8].

SANs are formed by combination of biologically compatible lipids and water which make them well suited for body tissues [9,10]. The small size of the SANs ensures easier transportation across the physiological barrier and increases the amount of drug penetration [11–13]. The large interfacial area provides a complex diffusion pathway for sustained or controlled release of entrapped drug molecules. In addition, due to the low viscosity, the colloidal dispersion of cubic phases can be incorporated into other product formulations [14,15]. SANs encapsulated large drug-preload and offer sustained release of the entrapped drug than other lipid-based systems [6,7,16,17].

Recently self-assembly of PEGylated D,L-octapeptide was designed by one of the research group to self-assemble it in the core-shell nanoparticles and their self-assembling properties were studied by alternating enantiomeric sequences. They have concluded that self-assembly would be the effective carriers for high drug loading and sustained drug release of curcumin [18]. Due to the small particle size, the self-assembled nanocarriers like micelles can also been used as a carrier

* Corresponding author at: Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, M.S. 440033, India. Tel.: +91-712-2900324; Fax: +91-712-2900355; Mobile: +91-7719895521.

E-mail address: nr@nranikar@iitb.ac.in (N.R. Rarokar).

Smt. Kishoritai Bhoyar College of Pharmacy- List of Patents

Sr. no.	Application no.	Status	Title	Inventors	Remarks
1.	6294433	Granted	Gas Chromatography - Mass for qualitative analysis of chemical compounds.	Dr. Milind Umekar, Mr. Shyam Rangari, Dr. Sushil Burle, Ms. Swati Lade, Ms. Monali Dakhole, Ms. Ruchika Chimurkar, Ms. Sarita Ukey, Ms. Shweta Raut	UK Design Patent
2.	202022103266	Granted	Dissolving device for vaginal formulation containing probiotics	Dixit, Madhura, Kale, Vinita, Trivedi, Rashmi, Umekar, Milind	German Utility Patent
3.	397075	Granted	Green Synthesised Nanoparticles	Dr. UMEKAR Milind J, Ms. RAUT Neha S, Ms. RAMTEKE Ashwini, Ms. LENDE Shweta	Indian Patent
4.	396840	Granted	Novel Bioactive Benzotrazole Derivatives and Process for Preparing Thereof	Dr. UMEKAR Milind J Dr. HEMKE Atul Ms. SAWALAKHE Diksha	Indian Patent
5.	387169	Granted	Bepotastine Besilate Ophthalmic Insert composition	Dr. Gupta Krishna R., Askarkar Sonali Suresh, Dr. Umekar Milind J.	Indian Patent
6.	410623	Granted	Liposomal Transdermal Gel Composition Comprising Pramipexole	Dr. UMEKAR Milind J TRIVEDI Rashmi Dr. KOTAGALE N. R.	Indian Patent
7.	430147	Granted	TOPICAL CARRIER MEDIATED DRUG DELIVERY SYSTEM	Dr. MILIND J. Umekar; Dr. KAMLESH Wadher; Sagar Trivedi	Indian Patent
8.	440976	Granted	Formulation containing Bupropion loaded nanoparticles for Intranasal administration.	Mahajan Tejashri, Dr. Taksande Jayshree, Dr. Umekar Milind J.	Indian Patent

Urkunde

über die Eintragung des
Gebrauchsmusters Nr. 20 2022 103 266

Bezeichnung:

Auflösungsvorrichtung für Probiotika enthaltende Vaginalformulierung

IPC:

G01N 33/15

Inhaber/Inhaberin:

Dixit, Madhura, Nagpur, Maharashtra, IN
Kale, Vinita, Nagpur, Maharashtra, IN
Trivedi, Rashmi, Nagpur, Maharashtra, IN
Umekar, Milind, Nagpur, Maharashtra, IN

Tag der Anmeldung:

10.06.2022

Tag der Eintragung:

21.06.2022

Die Präsidentin des Deutschen Patent- und Markenamts



Cornelia Rudloff-Schäffer

München, 21.06.2022





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THE PATENT OFFICE

पेटेंट प्रमाणपत्र
PATENT CERTIFICATE
(Rule 74 of The Patents Rules)

क्रमांक : 022118173
SL No :



पेटेंट सं. / Patent No	397075
आवेदन सं. / Application No	202121047332
फाइल करने की तारीख / Date of Filing	19/10/2021
पेटेंटी / Patentee	Smt. Kishorital Bhojar College of Pharmacy

प्रमाणित किया जाता है कि पेटेंटी को, उपरोक्त आवेदन में वर्णित GREEN SYNTHESIZED NANOPARTICLES नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख अक्टूबर 2021 के उन्नीसवें दिन से बीस वर्ष की अवधि के लिए पेटेंट अनुदान किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled GREEN SYNTHESIZED NANOPARTICLES as disclosed in the above mentioned application for the term of 20 years from the 19th day of October 2021 in accordance with the provisions of the Patents Act, 1970.



अनुदान की तारीख
Date of Grant : 18/05/2022

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, अक्टूबर 2023 के उन्नीसवें दिन की और उसके शेषाव अवधि वर्ष में उसी दिन देय होगी।

Note. - The fees for renewal of this patent, if it is to be maintained will fall / has fallen due on 19th day of October 2023 and on the same day in every year thereafter.



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PATENT CERTIFICATE
(Rule 74 of The Patents Rules)

क्रमांक : 022118131
SL No :



पेटेंट सं. / Patent No.	396840
आवेदन सं. / Application No.	202121046439
फाइल करने की तारीख / Date of Filing	12/10/2021
पेटेंटी / Patentee	Smt. Kishorital Bhoyar College of Pharmacy

प्रमाणित किया जाता है कि पेटेंटी को, उपरोक्त आवेदन में उद्घाटित NOVEL BIOACTIVE BENZOTRAZOLE DERIVATIVES AND PROCESS FOR PREPARING THEREOF नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख अक्टूबर 2021 के बारहवें दिन से बीस वर्ष की अवधि के लिए पेटेंट अनुवत्त किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled NOVEL BIOACTIVE BENZOTRAZOLE DERIVATIVES AND PROCESS FOR PREPARING THEREOF as disclosed in the above mentioned application for the term of 20 years from the 12th day of October 2021 in accordance with the provisions of the Patents Act, 1970.



अनुदान की तारीख : 13/05/2022
Date of Grant

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, अक्टूबर 2023 के बारहवें दिन को और उसके फायदा प्रत्येक वर्ष में उसी दिन देना होगा।

Note. - The fees for renewal of this patent, if it is to be maintained will fall / has fallen due on 12th day of October 2023 and on the same day in every year thereafter.



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PATENT CERTIFICATE
(Rule 74 Of The Patents Rules)

क्रमांक : 022116426
SL No :



पेटेंट सं. / Patent No.	387169
आवेदन सं. / Application No.	201721013104
फाइल करने की तारीख / Date of Filing	12/04/2017
पेटेंटी / Patentee	1.DR. GUPTA KRISHNA R. 2.ASKARKAR SONALI SURESH 3.DR. UMEKAR MILIND J.

प्रमाणित किया जाता है कि पेटेंटी को उपरोक्त आवेदन में व्यापकृत BEPOTASTINE BESILATE OPHTHALMIC INSERT COMPOSITION नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख 12th day of April 2017, से बीस वर्ष की अवधि के लिए पेटेंट अनुवृत्त किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled BEPOTASTINE BESILATE OPHTHALMIC INSERT COMPOSITION. as disclosed in the above mentioned application for the term of 20 years from the 12th day of April 2017 in accordance with the provisions of the Patents Act, 1970.



अनुदान की तारीख : 22/01/2022
Date of Grant :

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस यदि इसे बनाए रखा जाना है 12th day of April 2019 को और उसके संबंधित प्रत्येक वर्ष के उसी दिन के बाद होगी।

Note - The fees for renewal of this patent. If it is to be maintained will fall / has fallen due on 12th day of April 2019 and on the same day in every year thereafter



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पेटेंट प्रमाणपत्र
PATENT CERTIFICATE
(Rule 74 of The Patents Rules)

क्रमांक : 022120517
SL No :



पेटेंट सं. / Patent No. : 410263
आवेदन सं. / Application No. : 201821031737
फाइल करने की तारीख / Date of Filing : 24/08/2018
पेटेंटी / Patentee : SMT. KISHORITAI BHOYAR COLLEGE OF PHARMACY

प्रमाणित किया जाता है कि पेटेंटी को, उपरोक्त आवेदन में यथाप्रकटित LIPOSOMAL TRANSDERMAL GEL COMPOSITION COMPRISING PRAMIPEXOLE, नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख अगस्त 2018 के चौबीसवें दिन से बीस वर्ष की अवधि के लिए पेटेंट अनुदत्त किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled LIPOSOMAL TRANSDERMAL GEL COMPOSITION COMPRISING PRAMIPEXOLE, as disclosed in the above mentioned application for the term of 20 years from the 24th day of August 2018 in accordance with the provisions of the Patents Act, 1970.



अनुदान की तारीख : 28/10/2022
Date of Grant :

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के सर्वाधिकार के लिए फीस, यदि इसे बनाए रखा जाना है, अगस्त 2020 की चौबीसवीं दिन की और उसके पश्चात प्रत्येक वर्ष में उसी दिन देय होगी।

Note - The fees for renewal of this patent, if it is to be maintained will fall / has fallen due on 24th day of August 2020 and on the same day in every year thereafter.



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पेटेंट कार्यालय
THE PATENT OFFICE

पेटेंट प्रमाणपत्र
PATENT CERTIFICATE
(Rule 74 of The Patents Rules)

क्रमांक : 022124123
SL No :



पेटेंट सं. / Patent No.	430147
आवेदन सं. / Application No.	202121051689
फाइल करने की तारीख / Date of Filing	11/11/2021
पेटेंटी / Patentee	SMT. KISHORITAI BHOYAR COLLEGE OF PHARMACY

प्रमाणित किया जाता है कि पेटेंटी को, उपरोक्त आवेदन में व्हायरस-मध्यस्थ TOPICAL CARRIER MEDIATED DRUG DELIVERY SYSTEM नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख नवम्बर 2021 के ग्यारहवें दिन से बीस वर्ष की अवधि के लिए पेटेंट अनुदान किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled TOPICAL CARRIER MEDIATED DRUG DELIVERY SYSTEM as disclosed in the above mentioned application for the term of 20 years from the 11th day of November 2021 in accordance with the provisions of the Patents Act, 1970.



अनुदान की तारीख
Date of Grant : 26/04/2023

Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, नवम्बर 2023 के ग्यारहवें दिन की और उसके पश्चात प्रत्येक वर्ष से उसी दिन देय होगी।

Note. - The fees for renewal of this patent, if it is to be maintained will fall / has fallen due on 11th day of November 2023 and on the same day in every year thereafter.



पेटेंट कार्यालय, भारत सरकार

The Patent Office, Government Of India

पेटेंट प्रमाण पत्र

Patent Certificate

(पेटेंट नियमावली का नियम 74)

(Rule 74 of The Patents Rules)

पेटेंट सं. / Patent No.

440976

आवेदन सं. / Application No.

201921050381

फाइल करने की तारीख / Date of Filing

06/12/2019

पेटेंटी / Patentee

SMT. KISHORITAI BHOYAR COLLEGE OF PHARMACY

प्रमाणित किया जाता है कि पेटेंटी को उपरोक्त आवेदन में व्यापकृतित **FORMULATION CONTAINING BUPROPION LOADED NANOPARTICLES FOR INTRANASAL ADMINISTRATION** नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख दिसम्बर 2019 के छठे दिन से बीस वर्ष की अवधि के लिए पेटेंट अनुदान किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled **FORMULATION CONTAINING BUPROPION LOADED NANOPARTICLES FOR INTRANASAL ADMINISTRATION** as disclosed in the above mentioned application for the term of 20 years from the 6th day of December 2019 in accordance with the provisions of the Patents Act, 1970.



अनुदान की तारीख
Date of Grant

27/07/2023

पेटेंट नियंत्रक
Controller of Patents

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, दिसम्बर 2021 के छठे दिन को और उसके समान प्रत्येक वर्ष में उसी दिन देय होगी।

Note. - The fees for renewal of this patent, if it is to be maintained, will fall / has fallen due on 6th day of December 2021 and on the same day in every year thereafter.

Indian Academy of Neurosciences



IAN Travel Award

To

Raj Katariya

*Smt. Kishoritai Bhoyar College of Pharmacy
Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, India*

For presenting paper entitled

*Unveiling the Neuroprotective Mechanisms of Agmatine in
Huntington's Disease: Implications for Therapeutic Interventions*

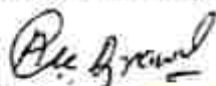


At the

**XLI Annual Meeting of Indian Academy of Neurosciences
Jiwaji University, Gwalior - 474011, Madhya Pradesh, India
October 04-06, 2023**



**Vinay K. Khanna
Secretary HQ**



**Ashok K. Agrawal
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**Ishan Patro
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ASSOCIATION OF PHARMACEUTICAL TEACHERS OF INDIA (APTI)
AND
PSIT-PRANVEER SINGH INSTITUTE OF TECHNOLOGY (PHARMACY), KANPUR

CERTIFICATE OF APPRECIATION

This is to certify that

Prof./Dr./Mr./Ms. *Monali Balkrushna Yerne*
From *SMT. Kishorita Bhojra College of Pharmacy.*

has secured **FIRST/SECOND/THIRD** position in **POSTER PRESENTATION** on the topic entitled

*In silico Design, Synthesis and Study of Substituted
Amino Acid chalcone hybrids for Biological Activity*

in the 26th Annual National Convention of the Association of Pharmaceutical Teachers
of India -2023 held at PSIT- Pranveer Singh Institute of Technology (Pharmacy),
Kanpur (India) from 2nd to 3rd September 2023.


Dr. Pranay Wal
Organising secretary


Dr. A K Rai
Head of the Institute


Dr. Deependra Singh
LOC Chairman


Dr. Milind J. Umekar
APTI president

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CONVENTION

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Kanpur



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AND
PSIT-PRANVEER SINGH INSTITUTE OF TECHNOLOGY (PHARMACY), KANPUR

CERTIFICATE OF APPRECIATION

This is to certify that

Prof./Dr./Mr./Ms. *Alvina Jazin Sajid Sheikh*

From *SMT. Kishoritai Bhoyar College of Pharmacy*

has secured **FIRST/SECOND/THIRD** position in **POSTER PRESENTATION** on the topic entitled

Insilico Design and Synthesis of Hydroxy Benzoic Acid as an analgesic and Anti-inflammatory agents.

in the 26th Annual National Convention of the Association of Pharmaceutical Teachers
of India - 2023 held at PSIT- Pranveer Singh Institute of Technology (Pharmacy),
Kanpur (India) from 2nd to 3rd September 2023.

Dr. Pranay Wal
Organising secretary

Dr. A K Rai
Head of the Institute

Dr. Deependra Singh
LOC Chairman

Dr. Milind J. Umekar
APTI president

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Established for Alzheimer's Research

National Level

**Memory
Game
Competition**

Certificate of Achievement

It is to be certified that

Md. Labid Khan

of

BMS College of Engineering, Bengaluru

is **RUNNER** of

National Level Competition on

"Model Creation for Cognition of Alzheimer's Disease Patients"

held on Aug 26, 2023

Dr. Milind J. Umekar
Chairman



Dr. Brijesh G. Taksande
Co-Chairman



Smt. Kishoribai Bhoyar College of Pharmacy, Kamptee



Club for Alzheimer's Research & Education

San Kishoritai Bhoyar College of Pharmacy, Kamptee

National Level

**Memory
Game
Competition**

Certificate of Achievement

It is to be certified that

Ms. Honey Rane

of

Smt. Kishoritai Bhoyar College of Pharmacy

is **RUNNER** of

National Level Competition on

"Model Creation for Cognition of Alzheimer's Disease Patients"

held on Aug 26, 2023

Dr. Milind J. Umekar
Chairman



Dr. Brijesh G. Taksande
Co-Chairman



Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee



Club for Alzheimer's Research & Education

National Level

**Memory
Game
Competition**

Certificate of Achievement

It is to be certified that

Mr. Mayur Kale (Pharmaceuticals)

of

Smt. Kishoritai Bhoyar College of Pharmacy

has successfully contributed as a **MENTOR of RUNNER** team
in National Level Competition on

"Model Creation for Cognition of Alzheimer's Disease Patients"

held on Aug 26, 2023

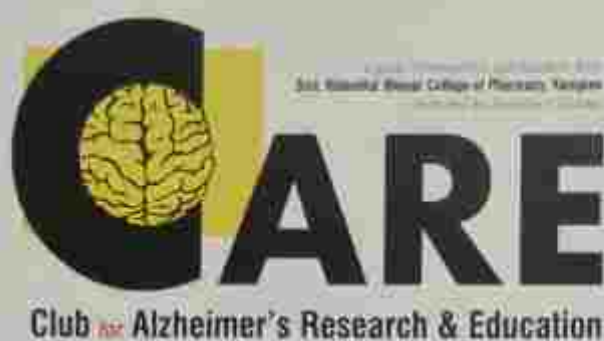
Dr. Milind J. Umekar
Chairman



Dr. Brijesh G. Taksande
Co-Chairman



Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee



National Level

Memory Game Competition

Certificate of Achievement

It is to be certified that

Mr. Tanmay Gujjar

of

Smt. Kishoritai Bhoyar College of Pharmacy

is **RUNNER** of

National Level Competition on

"Model Creation for Cognition of Alzheimer's Disease Patients"

held on Aug 20, 2023

Dr. Milind J. Umekar
Chairman



Dr. Brijesh G. Taksande
Co-Chairman



Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee

www.skb.edu.in | www.skbcare.in



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OF BEST POSTER PRESENTATION



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16th & 17th March 2023 | JNTUH, Hyderabad, India

This is to certify that Mr/Ms/Mrs/Dr. Kalyani Thombre has presented his/her
paper titled Synthesis of Novel Apigenin Derivatives and Evaluation as Antidepressant and Anticonvulsant Agents

..... which
has been awarded as **Best E-Poster Presentation** in the 2nd International Conference on "Current Advances in Pharmaceutical Industry and Development" Organized by Centre for Pharmaceutical Sciences, UCEST, Jawaharlal Nehru Technological University Hyderabad (JNTUH), India & Association of Pharmaceutical Research (APR) held on 16th & 17th March 2023.

A. Jaya Laxmi

Dr. A. Jaya Laxmi
Principal
JNTUH UCEST
Hyderabad, India

S. Reddy

Dr. M. Sunitha Reddy
Head of the Department
Centre for Pharmaceutical Sciences,
JNTUH UCEST, Hyderabad, India



R. Bhanu Satpathy

Mr. Rudra Bhanu Satpathy
Founder & CEO
Association of Pharmaceutical
Research (APR), India



RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY, NAGPUR



AVISHKAR RESEARCH CONVENTION 2022-2023

HOSTED BY



DADASAHEB BALPANDE COLLEGE OF PHARMACY, BESA, NAGPUR

16th - 17th December 2022



— CERTIFICATE —

This is to certify that Veishnavi Padale
has actively participated in selection trial of AVISHKAR 2022-2023 organized by
Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur hosted by Dadasaheb Balpande
College of Pharmacy, Besa, Nagpur in Poster / Model Competition and he/she has secured
winner / runner up position in UG/PG/PPG/TH Level.


Dr. Nilesh Mahajan
Co-ordinator, AVISHKAR
DCCOR Nagpur


Dr. Ujjwala Mahajan
Principal
DCCOR Nagpur


Dr. Mangesh Patil
Director, Student's Development
RTMNU, Nagpur


Dr. Bharat Bhoirane
Chairman, AVISHKAR
RTMNU, Nagpur



RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY, NAGPUR



AVISHKAR RESEARCH CONVENTION 2022-2023

HOSTED BY

DADASAHEB BALPANDE COLLEGE OF PHARMACY, BESA, NAGPUR

16th - 17th December 2022



— CERTIFICATE —

This is to certify that.....Kalyani Thombare.....

has actively participated in selection trial of AVISHKAR 2022-2023 organized by Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur hosted by Dadasaheb Balpande College of Pharmacy, Besa, Nagpur in Poster / Model Competition and he/she has secured winner / runner up position in UG/PG/PPG/TH Level.

Dr. Nilesh Mahajan
Co-ordinator, AVISHKAR
DBCOP, Nagpur

Dr. Ujwala Mahajan
Principal
DBCOP, Nagpur

Dr. Mangesh Pathak
Director, Student's Development
RTMNU, Nagpur

Dr. Bharat Bhanvase
Chairman, AVISHKAR
RTMNU, Nagpur



SAVITRIBAI PHULE PUNE UNIVERSITY

**15th MAHARASHTRA STATE INTER-UNIVERSITY
RESEARCH CONVENTION**

Aavishkar 2023

Certificate of Participation

This is to certify that Mr./Miss. ~~Kolpyakwar~~ Gauri Vinay of Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur has participated in State Inter University Research Convention for Postgraduate Students (PG) level at **"AAVISHKAR 2023"** under Pure Sciences category, held at Savitribai Phule Pune University, Pune from 12th to 15th January 2023.

Prof. Sanjay Dhale

Prof. Dr. Sanjeev Sanasane

Prof. Dr. Kanchanvi Kale



SAVITRIBAI PHULE PUNE UNIVERSITY

**15th MAHARASHTRA STATE INTER-UNIVERSITY
RESEARCH CONVENTION**

Aavishkar 2023

Certificate of Participation

*This is to certify that Mr./Miss. **Rahangdale Sandipkumar Ramesh** of **Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur** has participated in State Inter University Research Convention for Post PG Students (PPG) level at **"AAVISHKAR 2023"** under **Medicine and Pharmacy** category, held at Savitribai Phule Pune University, Pune from 12th to 15th January 2023.*

Prof. Sanjay Dhole
Director, IQAC

Prof. Dr. Sanjeev Sonawane
Pro-Vice Chancellor

Prof. Dr. Karbhari Kale
Vice Chancellor



RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY, NAGPUR

AVISHKAR RESEARCH CONVENTION 2022-2023



HOSTED BY
DADASAHEB BALPANDE COLLEGE OF PHARMACY, BESA, NAGPUR

16th - 17th December 2022



— CERTIFICATE —

This is to certify that.....Madhura Dixit.....

has actively participated in selection trial of AVISHKAR 2022-2023 organized by Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur hosted by Dadasaheb Balpande College of Pharmacy, Besa, Nagpur in Poster / Model Competition and he/she has secured winner / runner up position in UG/PG/PPG/TH Level.

Dr. Nilesh Mahajan
Co-ordinator, AVISHKAR
DBCOP, Nagpur

Dr. Ujwala Mahajan
Principal
DBCOP, Nagpur

Dr. Mangesh Pathak
Director, Student's Development
RTMNU, Nagpur

Dr. Bharat Bhanvase
Chairman, AVISHKAR
RTMNU, Nagpur



RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY, NAGPUR



AVISHKAR RESEARCH CONVENTION 2022-2023

HOSTED BY

DADASAHEB BALPANDE COLLEGE OF PHARMACY, BESA, NAGPUR

16th - 17th December 2022

— CERTIFICATE —

This is to certify that.....Neha Raut.....

has actively participated in selection trial of AVISHKAR 2022-2023 organized by Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur hosted by Dadasaheb Balpande College of Pharmacy, Besa, Nagpur in Poster / Model Competition and he/she has secured winner / runner up position in UG/PG/PPG/TH Level.

Dr. Nilesh Mahajan
Co-ordinator, AVISHKAR
DBCOP, Nagpur

Dr. Ujjwal Mahajan
Principal
DBCOP, Nagpur

Dr. Mangesh Pothak
Director, Student's Development
RTMNU, Nagpur

Dr. Bharat Bhavsar
Chairman, AVISHKAR
RTMNU, Nagpur



INTERNATIONAL CONFERENCE ON PHARMACOLOGY IN DRUG DISCOVERY AND DISEASE MANAGEMENT

Certificate of Award

This is to certify that

Ms. Pratiksha Nanepag

of Smt. Kishorital Bhoyar College of Pharmacy, New Kamptee, Nagpur

has been awarded **FIRST PRIZE** in **Poster Competition** in the INTERNATIONAL CONFERENCE
ON PHARMACOLOGY IN DRUG DISCOVERY AND DISEASE MANAGEMENT
organized by the Department of Pharmacology
Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India
on 25th and 26th of November 2022.

Dr. Jaya Thomas
HOD
Dept. of Pharmacology
Amrita School of Pharmacy



Dr. Sabitha M
Principal
Amrita School of Pharmacy

2nd International Conference on

**"Innovations in Chemical, Biological and Pharmaceutical Sciences"
(ICBPS-2022) November, 18-19, 2022**

Certificate

*This is to certify that Mr./Dr./Prof./Ms. Nitu L. Wankhede
presented a paper on Agmatine...modulates...neurodevelopmental...alterations...in
offspring induced by maternal stress
and awarded 1st / 2nd / 3rd position*

*2nd International Conference on "Innovations in Chemical, Biological and Pharmaceutical Sciences
(ICBPS-2022)" held on November 18-19, 2022 through online mode.*


Mr. Shashank Chaturvedi
(Co-Convener)


Dr. Rohitas Deshmukh
(Convener)


Prof. Meenakshi Bajpai
(Chairperson)



CERTIFICATE



This is certify that Mr. Sandeep has received Second prize as 'Young Toxicologist' for presenting Oral Presentation in "International Symposium on Toxicology & Applied Pharmacology" organized by National Institute of Pharmaceutical Education and Research, Raebareli (NIPER-R) on 29th-30th September, 2022.

Dr. Sandeep Chaudhary
Dean, NIPER-Raebareli

Dr. Saba Naqvi
Organizing Secretary



"Empowering Academia for
Advancing Pharmacy Education"

ASSOCIATION OF PHARMACEUTICAL TEACHERS OF INDIA (APTI)
AND
JSS COLLEGE OF PHARMACY, MYSURU
JSS ACADEMY OF HIGHER EDUCATION & RESEARCH, MYSURU

CERTIFICATE
OF APPRECIATION

This is to Certify that

Prof./Dr./Mr./Ms. Manish Aglawe
has presented a paper entitled "Agmatine - NPY interplay in paraventricular
nuclei regulate pubertal endocrine physiology"
and won the ~~FIRST~~ **SECOND** prize in ~~Poster~~ Oral presentation at 25th Annual National
Convention of the Association of Pharmaceutical Teachers of India-2022 (25th APTICON- 2022)
held at JSS College of Pharmacy, JSS Academy of Higher Education & Research, Mysuru, India from
2nd to 4th September 2022.




Dr. Milind J Umekar
President, APTI


Dr. Raman Dang
Secretary, APTI


Dr. T M Pramod Kumar
Organizing Chairman
25th APTICON 2022


Dr. Balamuralidhara V
Organizing Secretary
25th APTICON 2022



Department of Pharmaceuticals
Ministry of Chemicals and Fertilizers
Government of India



एक कदम स्वच्छता की ओर



9th International e-Conference of Federation of Indian Physiological Societies (FIPS)-2022

CERTIFICATE OF APPRECIATION

This Certificate is awarded to

Shivkumar S. Sammeta

for securing **Second Prize** for the Presentation entitled

"Agmatine: A potential regulator of gut-brain-axis in depression"

under Student oral presentation category during the International e-Conference on

"Reconnecting Physiology and Nature for Healthy Life"

Organized by FIPS and National Institute of Pharmaceutical Education and Research (NIPER) Hyderabad
from 25th to 27th March 2022

DR. SHASHI BALA SINGH

PRESIDENT, FIPS

DIRECTOR, NIPER-HYDERABAD

DR. DHARMENDRA K. KHATRI

ORGANIZING SECRETARY, FIPS



MoE's
INNOVATION CELL
(GOVERNMENT OF INDIA)

75
Azadi Ka
Amrit Mahotsav



INSTITUTION'S
INNOVATION
COUNCIL
(Ministry of HRD initiative)



AICTE- SPICES

sponsored

National Level



Scientific Poster Presentation Competition

Certificate

This is to certify that

Shalakra Dabhekar

is **WINNER** of

National Level -Scientific Poster Presentation Competition

(Faculty/Ph.D Category)

held on the occasion of

National Science Day 2022

under

Theme: Innovations in Pharmaceutical Science

On: Feb. 28, 2022

Dr. Milind J. Umekar
Convener

Co-ordinators

Dr. Brijesh G. Taksande Dr. Kamlesh J. Wadher Mr. Rajesh T. Lohiya Dr. Renuka J. Das

Organized By

Institute Innovation Council | Research & Development Cell



Smt. Kishoritai Bhoyar College of Pharmacy

Kamptee (Nagpur, MS), India



MoE's
INNOVATION CELL
(GOVERNMENT OF INDIA)



INSTITUTION'S
INNOVATION
COUNCIL
(Ministry of HRD Initiative)



AICTE- SPICES

sponsored

National Level



Scientific Poster Presentation Competition

Certificate

This is to certify that

Shivkumar Sammeta

is **RUNNER** of

National Level -Scientific Poster Presentation Competition
(PG Category)

held on the occasion of

National Science Day 2022

under

Theme: Innovations in Pharmaceutical Science

On: Feb. 28, 2022

Dr. Milind J. Umekar
Convenor

Co-ordinators

Dr. Brijesh G. Taksande Dr. Kamlesh J. Wadher Mr. Rajesh T. Lohiya Dr. Renuka J. Das

Organized By

Institute Innovation Council | Research & Development Cell



Smt. Kishoritai Bhoyar College of Pharmacy
Kamptee (Nagpur, MS), India



राष्ट्रसंत तुकडोजी महाराज
नागपूर विद्यापीठ

उत्कृष्ट संशोधक पुरस्कार
२०२१

डॉ. ब्रिजेश जी. ताकसांडे

संत किशोरिता भोयर कॉलेज ऑफ फार्मसी,
कामठी

ह्यांना संशोधन क्षेत्रातील
प्रशंसनीय कार्याच्या गौरवार्थ
उत्कृष्ट संशोधक पुरस्कार २०२१
दिनांक ०५ सप्टेंबर २०२१ रोजी आयोजित
शिक्षक दिना निमित्त देण्यात येत आहे.



Rashtrasant Tukadoji Maharaj
Nagpur University

**BEST RESEARCHER AWARD
2021**

Dr. Brijesh G. Taksande

Smt. Kishorita Bhoir College of Pharmacy
Kamptee

*has been honoured with
Best Researcher of the Year 2021
for his precious contribution
in the field of Research
on Teachers' Day, 5th September 2021*

Dr. Subhash R. Chandhari
Vice Chancellor



National Seminar on Panchgavya for Healthcare

"A Potential Area for Pharmaceutical Research"

8, 9 February 2020

Certificate

This is to certify that Prof. / Dr. / Mr. / Ms. Payal Kshirsagar
of Smt. Kishoribai Bhoyar College of Pharmacy, Kamptee.

Presented Poster in National Seminar on **Panchgavya for Healthcare**

A Potential Area for Pharmaceutical Research

His / Her topic for poster was Panchgavya ----- therapeutic perspective

:: Organized by ::

Anurag College of Pharmacy, Warthi, Bhandara

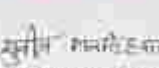
:: In Association with ::

Go Vigyan Anusandhan Kendra, Deolapori, Nagpur

Cumulation Prize.


Convener
Dr. Sampat Waze


Co-ordinator
Mr. Sachin Lohar


Co-ordinator, GVAK
Mr. Sunil Manunghikar


President, GVAK
Dr. Hemant Jambhakar



**C. P. & BERAR
E. S. COLLEGE, NAGPUR**



HOSTS

RTM NAGPUR UNIVERSITY, NAGPUR

SELECTION TRIALS FOR

AVISHKAR

2018

UNIVERSITY LEVEL



**UNIVERSITY
WINNER**

4 January 2019



C. P. & BERAR E. S. COLLEGE, NAGPUR

HOSTS



**RASHTRASANT TUKADOJI MAHARAJ
NAGPUR UNIVERSITY, NAGPUR**

SELECTION TRIALS FOR

AVISHKAR-2018
UNIVERSITY LEVEL

CERTIFICATE

This is to certify that

Mr./Ms. Manish M. Aglawe

of Kishoritai Bhojer College of Pharmacy

Selected in Rashtrasant Tukadoji Maharaj Nagpur University

"AVISHKAR-2018" Team to participate 12th Maharashtra State

Inter-University Research Convention at Gadchiroli.

Dr. Sanjay Karandikar
Director
Students' Development
RTM Nagpur University, Nagpur

Dr. Sanjay Dhole
Convener
Avishkar 2018
RTM Nagpur University, Nagpur

Dr. Milind Dharbarte
Principal
C. P. & Berar E. S. College
Nagpur



RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY,
NAGPUR

BHIWAPUR MAHAVIDYALAYA
BHIWAPUR

University Level

Avishkar

2019-2020

1st Rank

Dr. Jobi George
Principal & Organizer



RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY, NAGPUR
Backward Class Youth Relief Committee's
BHIWAPUR MAHAVIDYALAYA, BHIWAPUR
Internal Quality Assurance Cell



HOSTS
RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY'S
SELECTION TRIALS AT UNIVERSITY LEVEL
FOR

AVISHKAR RESEARCH CONVENTION 2019-2020

CERTIFICATE

This is to certify that Mr./Ms./Mrs. Anita Rajkumar Pounikar

of Smt. Kishoritai Bhoyar college of pharmacy Kamptee

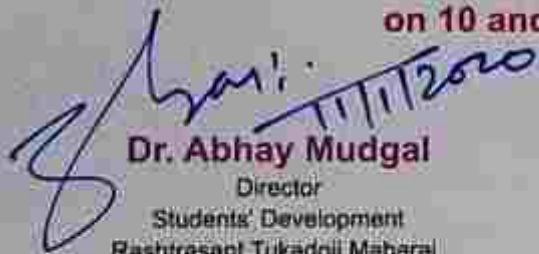
has participated / and been selected at UG / ☒ PG / PPG / TH level under the

Category Medicine And pharmacy in the

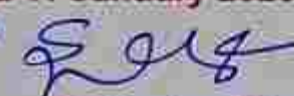
'Selection Trials at University Level for **AVISHKAR 2019-2020**'

held at Bhiwapur Mahavidyalaya, Bhiwapur

on 10 and 11 January 2020


Dr. Abhay Mudgal

Director
Students' Development
Rashtrasant Tukadoji Maharaj,
Nagpur University


Dr. Sanjay Dhoble

Chairman
Avishkar Committee
Rashtrasant Tukadoji Maharaj,
Nagpur University


Dr. Jobi George

Principal
Bhiwapur Mahavidyalaya,
Bhiwapur



University of Mumbai

Avishkar
2019-20

14th Maharashtra State
Inter-University Research Convention

January 28-31, 2020



Certificate of Participation

This is to certify that Ms. Pounikar Anita Rajkumar of Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur has participated and presented a research project titled 'Novel Apigenin Derivatives as Antioxidant, Antimicrobial and Anticancer Agent in Medicine and Pharmacy category and PG level at the 14th Maharashtra State Inter-University Avishkar Research Convention: 2019-20 organized by University of Mumbai on January 28-31, 2020.

Kalina, Mumbai
January 31, 2020


Prof. Sahas Pednekar
Vice-Chancellor,
University of Mumbai


Dr. Ajay Deshmukh
Registrar,
University of Mumbai

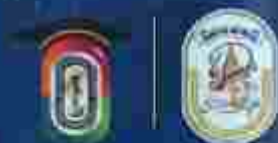



Prof. Ravindra Kulkarni
Pro Vice-Chancellor,
University of Mumbai


Dr. Smil Patil
Director,
Department of Students' Development,
University of Mumbai and
Organizing Secretary



Smt. Kishoritai Bhoyar
College of Pharmacy



Celebrating

World Science Day

On: Nov. 09, 2019

It is to certify that

Shraddha Bhondekar

is an

Winner

for Scientific Presentation (Poster) Competition

under

APTI sponsored

One Day National Level Symposium

on

**“New Hypotheses for Breakthrough
Innovations in Drug Discovery”**

Dr. Milind J. Umekar
Convener & VP-APTI

Dr. Brijesh G. Taksande
Co-convener



RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY, NAGPUR

Backward Class Youth Relief Committee's
BHIWAPUR MAHAVIDYALAYA, BHIWAPUR
Internal Quality Assurance Cell

HOSTS

RASHTRASANT TUKADOJI MAHARAJ NAGPUR UNIVERSITY'S
SELECTION TRIALS AT UNIVERSITY LEVEL

FOR

AVISHKAR RESEARCH CONVENTION 2019-2020

CERTIFICATE

This is to certify that Mr./Ms./Mrs. Sandip R. Rahangdale
of Smt. Kishoritai Bhoyar College of Pharmacy Kamptee
has participated / and been selected at UG / PG / PPG / TH level under the
Category Medicine And pharmacy in the

'Selection Trials at University Level for AVISHKAR 2019-2020'

held at Bhiwapur Mahavidyalaya, Bhiwapur

on 10 and 11 January 2020


Dr. Abhay Mudgal
Director
Students' Development
Rashtrasant Tukadoji Maharaj,
Nagpur University


Dr. Sanjay Dhoble
Chairman
Avishkar Committee
Rashtrasant Tukadoji Maharaj,
Nagpur University


Dr. Jobi George
Principal
Bhiwapur Mahavidyalaya,
Bhiwapur



Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur



VIDARBHA YOUNG SCHOLARS' CONFERENCE-2019

Organized by

Innovative, Incubation & Linkages, Intellectual Quality Assurance Cell and Technology Park

Certificate

This is to certify that Dr./Mr./Ms. Sonita M. Chauragade of _____
has participated in the

Vidarbha Young Scholars' Conference-2019 held on 29-30 March, 2019. S/he has presented a paper entitled

Agmatine modulates - - - - - haugh imidazole receptors
in the Oral/Poster session of this conference.


Dr. Abhay D. Deshmukh
Organizing Secretary


Dr. Rakesh S. Badole
Convener


Prof. R. H. Kalde
Director, Technology Park


Prof. S. R. Zade
Director IQAC


Prof. M. M. Rai
Director, III


Prof. G. S. Khadke
Dean, Faculty of Sci & Tech



भारतीय आयुर्विज्ञान अनुसंधान परिषद्
INDIAN COUNCIL OF MEDICAL RESEARCH

Sponsored

3rd International Conference on Innovations in Pharmaceutical Sciences (ICIPS)
(3rd and 4th August, 2018)

(Theme: Focus on Innovations to Remain Globally Competitive in Pharma Sector)

Organized by



SCHOOL OF PHARMACY, GURU NANAK INSTITUTIONS TECHNICAL CAMPUS (AUTONOMOUS)

Accredited by NBA, Accredited by NAAC with A+ Grade
Bhimipatnam, R.R. District, Hyderabad, Telangana-501 505, INDIA

CERTIFICATE OF PRESENTATION

This is to Certify that Dr./Prof./Mr./Mrs./Miss Deshmukh RA of
SKB College of Pharmacy, Nagpur has presented a paper titled ROLE OF IMIDAZOLINE RECEPTOR
IN AMPHETAMINE INDUCED HYPERLOCOMOTION AND STEREOTYPE IN RATS, HAS WON 1st PRIZE in the
Oral / Poster Scientific Session of ICMR Sponsored 3rd International Conference on Innovations in Pharmaceutical
Sciences (ICIPS-2018) held on 3rd and 4th August at GNTC SCHOOL OF PHARMACY, Hyderabad, India.

Dr. S. S. Nair
President ICMR

Dr. P. S. Jaiswal
Dr. Chair

Dr. T. C. Chhabra
Convener

Dr. M. Ramesh Babu
Executive Officer

23rd ANNUAL NATIONAL CONVENTION OF
ASSOCIATION OF PHARMACEUTICAL TEACHERS OF INDIA

APTICON - 2018

October 5th-6th, 2018



*Innovative Teaching And Learning Strategies In Pharmacy -
Requirements & Barriers*

Certificate

This is to certify that Prof./Dr./Mr./Ms. S. V. Dabhekar has participated
in Poster / Oral presentation / Competitive Event in 23rd Annual National Convention of Association of
Pharmaceutical Teachers of India (APTICON-2018), held at Swami Keshvanand Institute of Pharmacy, Jaipur
and has won First Prize in Pharmacology.

Dr. P.D. Chaudhari
President APTI

Dr. Raman Dang
Secretary APTI

Mr. Ajay Phatak
Chairman LOC

Dr. Rajesh Asija
Convener

Prof. Hemlata Dullar
Co-Convener

Dr. Jayesh Dairvedi
Organizing Secretary

Dr. Rahul K. Gang
Organizing Secretary



Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur

SCIENCE WEEK CELEBRATION

National Mathematics Day 2017 and National Science Day 2018

26-28 February 2018

Certificate

This is to certify that

Mr./Ms. Nidhi Khedpande of
S. K. B. College of Pharmacy has attended in Intercollegiate Seminar
Competition / Science Exhibition Competition under Science Week Celebration, organized by
Internal Quality Assurance Cell and Technology Park, Rashtrasant Tukadoji Maharaj
Nagpur University, Nagpur from 26th to 28th February 2018 as a contestant / participant and
secured First position. This programme has been catalyzed and supported by National
Council for Science and Technology Communication (NCSTC), DST, Government of India and
Rajiv Gandhi Science and Technology Commission, Government of Maharashtra.


Dr. G. S. Khadekar
Convener NMD 2017


Dr. M. M. Rai
Convener NSD 2018


Dr. R. B. Kakde
Director, Technology Park

SMT. KISHORITAI BHOYAR COLLEGE OF PHARMACY, KAMPTEE

AWARDS RECEIVED BY STUDENTS AND FACULTY MEMBERS IN SCIENTIFIC CONFERENCES/CONVENTIONS FOR RESEARCH AND INNOVATION (2017-18 to 2022-23)

1. **Mr. Raj Katariya:** IAN Travel Award at XLI Annual meeting of Indian Academy Neuroscience at Jiwaji University Gwalior on 4-6th Oct 2023
2. **Ms. Monali Yerne:** First Prize in poster presentation at APTICON, PSIT Kanpur 2-3 September 2023
3. **Ms. Alvina Sheikh:** Second Prize in poster presentation at APTICON, PSIT Kanpur 2-3 September 2023
4. **Honey Rane, Tanmay Gujjar, Mayur Kale:** Second prize in National level competition on model creation for cognition of Alzheimer's disease patients organized by CARE club of SKB college of pharmacy on 26 Aug 2023
5. **Ms. Kalyani Thombre:** Awarded best E poster presentation award at 2nd international conference on current advances in Pharmaceutical Industry and development JNTUH Hyderabad 16-17th March 2023
6. **Vaishnavi Padole:** Winner in PG Pharmacy category at RTMNU organized research convention AVISHKAR 2022 -23 on 16-17 December 2022
7. **Kalyani Thombre:** Runner up in PG Pharmacy category at RTMNU organized research convention AVISHKAR 2022 -23 on 16-17 December 2022
8. **Gauri Koypekwar:** Runner up in PG Pure Science category at RTMNU organized research convention AVISHKAR 2022 -23 on 16-17 December 2022
9. **Sandip Rahangdale:** Winner in PPG Pharmacy category at RTMNU organized research convention AVISHKAR 2022 -23 on 16-17 December 2022
10. **Madhura Dixit:** Winner in TH Pharmacy category at RTMNU organized research convention AVISHKAR 2022 -23 on 16-17 December 2022
11. **Neha Raut:** Runner up in TH Pharmacy category at RTMNU organized research convention AVISHKAR 2022 -23 on 16-17 December 2022
12. **Ms. Pratiksha Nanepag:** First Prize in e-Poster competition at International Conference on Pharmacology in Drug Discovery & Disease Management, Amrita School of Pharmacy, Kochi, Kerala 25-26th Nov 2022
13. **Ms. Nitu Wankhede:** Second Prize in oral presentation at International Conference on Innovation in Chemical, biological and Pharmaceutical Sciences, Institute of Pharmaceutical Research, GLA University, Mathura 18-19th Nov 2022
14. **Mr. Sandip Rahangdale:** Second Prize in oral presentation at International Symposium for Toxicology & Applied Pharmacology, NIPER, Raibareli 29-30th Sept 2022
15. **Mr. Manish Aglawe:** Second Prize in oral presentation at APTICON, Mysore 02-04 Sept 2022
16. **Mr. Shivkumar Sammeta:** second prize in oral presentation at FIPS, NIPER, Hyderabad, 25-27th March 2022
17. **Ms. Shalakra Dabhekar:** (Research Scholar category) first prize at poster presentation competition on National Science Day, SKBCOP, Kamptee 28 Feb 2022
18. **Mr. Shivkumar Sammeta:** (PG Student Category) first prize at poster presentation competition on National Science Day, SKBCOP, Kamptee 28 Feb 2022
19. **Dr. Brijesh Taksande:** Best Scientist/Researcher Award -2021 by RTM Nagpur University Nagpur

20. **Ms. Mrunali Dhokne, Dishant Bhadnag, Kartikey Mishra, Rahashri Chindalohare, Viraj Dalal, Shraddha Shelke:** Consolation Prize in Digital Poster by Academic Decipher, Mumbai 2021
21. **Mr. Pranali Chandurkar, Rajashri Chindalohare, Shraddha Shelke:** Second prize for National Level review article writing competition organized by DECIPHER Mumbai 2021
22. **Hemant Kanhere, Payal Kshirsagar:** Consolation Prize at Panchagavya Conference, organized by Anurag COP, Warthi, Bhandara 2020
23. **Mr. Manish Aglawe:** first prize for oral presentation at Avishkar organized by RTM Nagpur university, Nagpur 4th Jan 2019
24. **Ms. Madhura Dixit:** First prize in teachers' category for oral presentation at Avishkar organized by RTM Nagpur university, Nagpur 2019
25. **Anita Pounikar:** First prize in post graduate category for oral presentation at Avishkar organized by RTM Nagpur university, Nagpur 2019
26. **Nidhi Sahu:** First prize in graduate category for oral presentation at Avishkar organized by RTM Nagpur university, Nagpur 2019
27. **Ms. Shradha Bhondekar:** First Prize for scientific poster presentation competition in one day national level symposium at SKBCOP KAMPTTEE on World Science Day 9th Nov 2019
28. **Ms. Rajshree Fating:** Second Prize for scientific poster presentation competition in one day national level symposium at SKBCOP KAMPTTEE on World Science Day 9th Nov 2019
29. **Mr. Sandip Rahangdale:** First prize for oral presentation in research scholar category at Avishkar organized by RTM Nagpur university, Nagpur 2019
30. **Dr. C. T. Chopde:** Received Teacher of Excellence award by APTI 2019
31. **Ms. Sarita Chauragade:** Received First Prize for Oral presentation Scientific Competition by IQAC RTM NAGPUR UNIVERSITY 2018
32. **Ms. Rupali Deshmukh:** Secured First Prize for poster presentation at ICMR Sponsored International Conference at Hyderabad on 3rd and 4th August 2018
33. **Ms. Shalakra Dhabekar:** Received Best poster presentation at APTI conference Jaipur 5-6 Oct 2018
34. **Ms. Nidhi Khedpande:** Received First prize at RTMNU organized oral presentation competition on National Science Day, from 26th to 28th February, 2018

Research Outcome and Major Scientific Contribution

Case study : Pharmacology Department

Lab Development

Infrastructure
ICT based Class
Room

Exp. Laboratory
02

Research Lab.
01(Pharmacology)
01(Bio-analytical)
01(Video tracking)

Animal House
Library



Motorized stereotaxic
instruments



Operant conditioning
chamber



ELIZA Reader

EQUIPMENTS

1. HPLC (PDA Detectors)
2. Elevated plus maze
3. Light dark box
4. Morris water mazes
5. Radial Arm Maze,
6. Actophotometer
7. Vogel's conflict test
8. Convulsimeter,
9. Rotarod apparatus
10. Conditioned Place Preference
11. Plethysmometer
12. Passive Avoidance
13. Fear extinction
14. Autoanalyser

Research strength & expertise

Research Interests and Strengths

- ✓ Understanding the mechanisms underlying various CNS disorders and to explore their modifying strategies
- ✓ Neuropharmacology: front line area

Research Components

- ✓ Standardization and sharpening of skills in range of neurobehavioral paradigms.
- ✓ Stereotaxic surgeries for intra-cranial drug administration
- ✓ Neurochemical analysis in discrete brain areas
- ✓ Application of Immunohistochemistry to examine neural activity

Chronology of Major Investigations

Established the role of agmatine in neuropsychiatric conditions

- ✓ A Biogenic amine
- ✓ Neurotransmitter
- ✓ Diverse Biological Properties
- ✓ High Potential for drug discovery

Obsessive compulsive behavior
Dixit et al., 2014,
Eur J Pharmacol (IF 3.26)

Nicotine Withdrawal syndrome
Kotagale et al., 2015,
Eur J Pharmacol (IF 3.26)

Ethanol sensitization
Taksande et al., 2019, *Alcoholism : Clin & Expt Res* (IF 3.03)

2020-22

Alzheimer's diseases
Kotagale et al., 2020
Neurotoxicology ((IF 3.37)
Brain Research Bulletin
(IF 3.4)

2019-20

2017

Cachexia
Taksande et al., 2017,
Biomed and Pharmacother (IF 4.54)

2015

2014

AGM- NPY Interaction
Taksande et al., 2011,
British J Pharmacol (IF 7.73)

2013

Anxiety
Taksande et al., 2013,
Eur NP Pharmacology (IF 3.85)

2012

Schizophrenia
Kotagale et al., 2012,
Pharmacol Biochem Behav (IF 2.77)

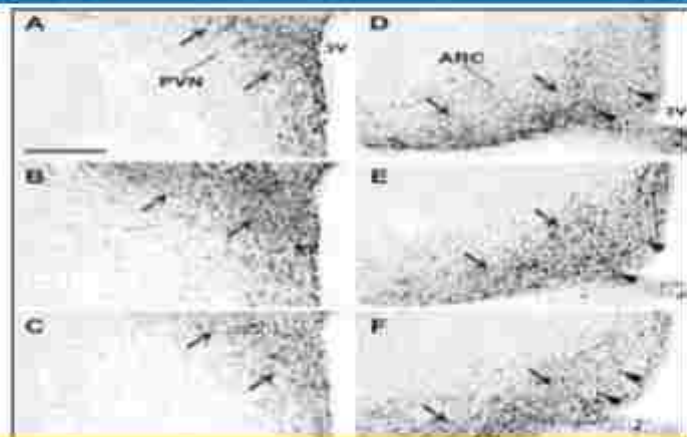
2011

2009

Depression
Taksande et al., 2009,
Neuropharmacol (IF 4.4)

Projected agmatine as a novel therapeutic target in neurological disorders

Agmatine and NPY colocalized at magnacellular neuron of hypothalamus



(Taksande et al., 2011, British Journal of Pharmacology)

Agmatine activates $\alpha 2$ adrenergic receptors to release

NPY

ARC & PVN

Orexigenic effect
(Taksande et al., 2011)
Anorexia nervosa
(Taksande et al., 2015)
Inflammatory cachexia
(Taksande et al., 2017)

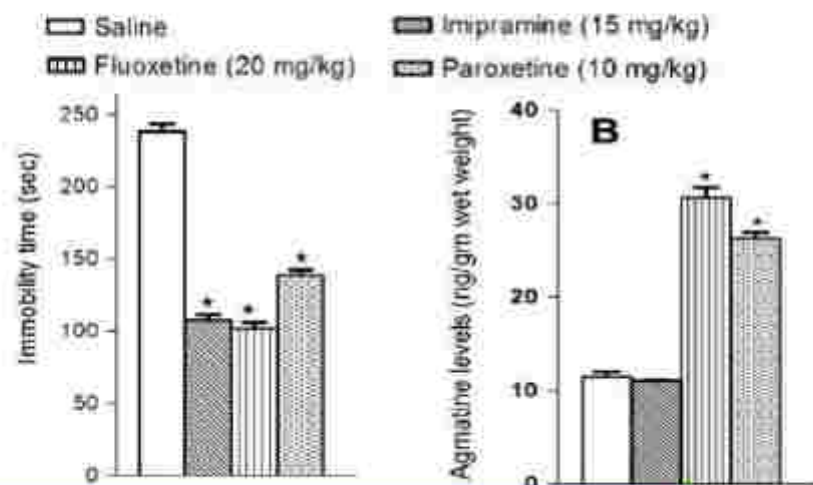
CeA

Induced anxiolytic effect
(Taksande et al., 2014)
Obsessive compulsive
disorder
(Dixit et al., 2014)

AcbSh & BNSTl

Nicotine induced conditioned
place preference
(Kotagale et al., 2014)
Nicotine withdrawal
syndrome
(Kotagale et al., 2015, 2017)

Agmatine is an endogenous regulator of stress and its levels decline in suicides victims



(Taksande et al., 2009, Neuropharmacology)

Clinically used antidepressants like SSRIs enhanced endogenous agmatine levels

CUMS induced anhedonia
Taksande et al., 2014
LPS induced sickness
behavior
(Taksande et al., 2015)

Diabetes Associated
psychiatric
complications
(Kale et al., 2020)

A β induced depression
and neuroinflammation
(Kotagale et al., 2020)

Research Recognitions & Awards



**Prof. Unvas Prize 2011 by
Indian Pharmacological society
at IPSCON Manipal**



**Best Researcher/Scientist
Award -2021
RTM Nagpur University,
Nagpur**



**Special Recognition for
Scientific program Coordination
at Indian Pharmaceutical
congress Nagpur 2023**

RESEARCH PROJECT SPONSORED BY SERB-DST

1. Investigations on central agmatine signaling in alcohol addiction **(Completed)**
2. Importance of central agmatinergeric signaling in neurobiology of Alzheimer's Diseases **(Completed)**
3. Role of Central Agmatine Signalling in the Etiopathogenesis of Huntington's Diseases **(On-going)**

Total Outlay : 96,46,443/- INR



Research Awards to Students



MR. MANISH AGLAWE RECEIVED
**FIRST PRIZE FOR ORAL
PRESENTATION AT AVISHKAR**
ORGANIZED BY RTM NAGPUR
UNIVERSITY, NAGPUR 2018



MS. MADHURA DIXIT & MR. SANDEEP
RAHANGDALE RECEIVED FIRST PRIZE
in THEIR RESPECTIVE CATEGORY
FOR ORAL PRESENTATION AT
AVISHKAR ORGANIZED BY RTM
NAGPUR UNIVERSITY, NAGPUR 2019

Research Awards to Students



Ms. Utkarsha Ramteke received Second Prize for poster presentation at Innopharm organized by M.P. Council of Science & Technology, Vigyan Bhawan, Bhopal MP, India from Feb 11-12, 2017.



Mr. Shreyans S. Gujar received Third Prize for poster presentation at Innopharm 2 organized M.P. Council of Science & Technology, Vigyan Bhawan, Bhopal MP, India from Feb 11-12, 2017



Ms. Shreesha Nambiar received Second Prize for poster presentation at ICMR sponsored National Conference on 25-26 March 2017, organized Kamla Nehru College Of Pharmacy, Nagpur.



Mr. Shubham N. Rahmatkar received First Prize for poster presentation at DST-SERB, ICMR & CSIR Sponsored National Conference on 27-29 July 2017, organized Nanavati college of Pharmacy, Mumbai



Ms. Nidhi Khedpande received First prize at RTMNU organized oral presentation competition on National Science Day, from 26th to 28th February, 2018 :



Ms. Rupali Deshmukh secured First Prize for poster presentation at ICMR Sponsored International Conference at Hyderabad on 4th August 2018,



Ms. Ashwini Charpe received First Prize for poster presentation at UDPD RAIPUR



Ms. Sarita Chauragade received First Prize for poster presentation at RTM NAGPUR UNIVERSITY

Research Awards to Students

Congratulations
to



Mentors






Mr. Shivkumar S. Sammeta
M. Pharm- II, Department of
Pharmacology

Mr. Sandip R. Rahangdale
Asst. Prof., Department of
Pharmacology

Dr. Brijesh G. Taksande
Dean Research & Accreditation,
HOD Pharmacology

Dr. Milind J. Umekar
Professor & Principal

 **Smt. Kishoritai Bhojar College of Pharmacy** 

On Securing **2nd Rank** in **Dr. S. K. Manchanda** Oration Award at
9th Annual Symposium of
Federation of Indian Physiological Societies (FIPS)-2022
International Conference

Organized by
**National Institute of Pharmaceutical Education & Research (NIPER),
Hyderabad**
In Association with PSI, SAPI, APPI & ISCAP

Academic & Research Collaboration



**UDPS RTM NAGPUR
UNIVERSITY NAGPUR**



**INSTITUTE OF CHEMICAL
TECHNOLOGY MUMBAI**



**GOVT. COLLEGE OF
PHARMACY, AMRAVATI**



**Go-Vigyan Anusandhan
Kendra Deolapar**