Research papers publications

S.No.	Title of the paper	Name of the author/s	Department of the teacher	Name of journal	Year of publication	ISSN number	Link to the recognition in UGC enlistment of the Journal
1	Method development and validation of lenvatinib by HPLC and UV-Spectroscopy'	Dr.N.N. Inamdar	Pharmaceutical Chemistry	Indian Drugs	2018	0019-462X	http://www.indiandrugsonline.org/
2	The Chemistry and Bio-Medicinal Significance of Pyrimidines& Condensed Pyrimidines	Dr.N.N. Inamdar	Pharmaceutical Chemistry	Current Topics in Medicinal Chemistry	2016	1568-0266 e1873-4294	https://benthamscience.com/journals/current-topics-in-medicinal-chemistry/
3	Inhibitory Influence of Agmatine in Ethanol Withdrawal-Induced Depression in Rats: Behavioral and Neurochemical Evidences	Dr.N.R. Kotagale	Pharmacology	Alcohol. doi: 10.1016/j.alcohol.2019.09.002.	2019	0741-8329	https://www.journals.elsevier.com/alcohol
4	Agmatine reverses ethanol consumption in rats: Evidences for an interaction with imidazoline receptors	Dr.N.R. Kotagale	Pharmacology	Pharmacology Biochemistry and Behavior,doi: 10.1016/j.pbb.2019.172779	2019	0091-3057	https://www.journals.elsevier.com/pharmacology-biochemistry-and-behavior
5	Neuroprotective Offerings by Agmatine	Dr.N.R. Kotagale	Pharmacology	Neurotoxicology	2019	0161-813X	https://www.journals.elsevier.com/neurotoxicology
6	Effects of Withaniasomnifera Nicotine Induced Conditioned Place Preference in Mice	Dr.N.R. Kotagale	Pharmacology	Pharmacognosy Journal	2019	0975-3575	http://www.phcogj.com/
7	Agmatine Inhibits Behavioral Sensitization to 8Ethanol through Imidazoline Receptors	Dr.N.R. Kotagale	Pharmacology	Alcoholism-Clinical And Experimental Research	2019	1530-0277	https://onlinelibrary.wiley.com/journal/15300277
8	Neuroprotective effect of agmatine in mouse spinal cord injury model: Modulation by imidazoline receptors.	Dr.N.R.Kotagale	Pharmacology	Journal of natural science, biology and Medicine	2018	0976-9668	http://www.jnsbm.org/

9	Withaferin A attenuates Alcohol Abstinence Signs in Rats	Dr.N.R.Kotagale	Pharmacology	Pharmacognosy Journal	2018	0975-3575	http://www.phcogj.com/about-journal
10	Agmatine inhibits nicotine withdrawal induced cognitive deficits in inhibitory avoidance task in rats: Contribution of α2-adrenoceptors.	Dr.N.R.Kotagale	Pharmacology	Pharmacology Biochemistry and Behavior	2018	0091-3057	https://www.journals.elsevier.com/pharmacology-biochemistry-and-behavior
11	Acute orexigenic effect of agmatine involves interaction between central α2-adrenergic and GABAergic receptors.	Dr.N.R.Kotagale	Pharmacology	Biomedicine and Pharmacotherapy	2017	0753-3322	https://www.journals.elsevier.com/biomedicine-and-pharmacotherapy
12	Agmatine ameliorates adjuvant induced arthritis and inflammatory cachexia in rats	Dr.N.R.Kotagale	Pharmacology	Biomedicine and Pharmacotherapy	2017	0753-3322	https://www.journals.elsevier.com/biomedicine-and-pharmacotherapy
13	Effect of compression pressure on inhalation grade lactose as carrier for dry powder inhalations	Dr.N.R.Kotagale	Pharmacology	International Journal of Pharmaceutical Investigation	2016	2230-973X	https://www.jpionline.org/index.php/ijpi
14	Agmatine attenuates hyperactivity and weight loss associated with activity-based anorexia in female rats	Dr.N.R.Kotagale	Pharmacology	Pharmacology Biochemistry and Behavior	2015	0091-3057	https://www.journals.elsevier.com/pharmacology-biochemistry-and-behavior
15	Chronic agmatine treatment prevents behavioral manifestations of nicotine withdrawal in mice	Dr.N.R.Kotagale	Pharmacology	Eur J Pharmacol	2015	0014-2999	https://www.journals.elsevier.com/european-journal-of-pharmacology
16	Agmatine attenuates lipopolysaccharide induced anorexia and sickness behavior in rats	Dr.N.R.Kotagale	Pharmacology	Pharmacology Biochemistry and Behavior	2015	0091-3057	https://www.journals.elsevier.com/pharmacology-biochemistry-and-behavior

17	Imidazoline binding sites mediates anticompulsive-like effect of agmatine in marble-burying behavior in mice	Dr.N.R.Kotagale	Pharmacology	Eur J Pharmacol	2014	0014-2999	https://www.journals.elsevier.com/european-journal-of-pharmacology
18	Neuropeptide Y in the central nucleus of amygdala regulates the anxiolytic effect of agmatine in rats	Dr.N.R.Kotagale	Pharmacology	EurNeuropsychopharmacol	2014	0924-977X	https://www.journals.elsevier.com/european-neuropsychopharmacology
19	Imidazoline binding sites mediates anticompulsive-like effect of agmatine in marble-burying behavior in mice	Dr.N.R.Kotagale	Pharmacology	Eur J Pharmacol	2014	0014-2999	https://www.journals.elsevier.com/european-journal-of-pharmacology
20	Involvement of hypothalamic neuropeptide Y in pentazocine induced suppression of food intake in rats	Dr.N.R.Kotagale	Pharmacology	Neuropeptides	2014	0143-4179	https://www.journals.elsevier.com/neuropeptides
21	Agmatine attenuates nicotine induced conditioned place preference in mice through modulation of neuropeptide Y system	Dr.N.R.Kotagale	Pharmacology	Behav Brain Res	2014	0166-4328	https://www.journals.elsevier.com/behavioural-brain-research
22	Rapid and high yield Extraction method for Saponins from Safedmusli	Dr.S.L.Deore	Pharmacognosy	Pharmacognosy Journal	2015	0975-3575	http://www.phcogj.com/
23	Emulsion Micro Emulsion and Nano Emulsion: A Review	Dr.S.L.Deore	Pharmacognosy	Systematic Reviews in Pharmacy	2016	0975-8453 E-0976-2779	http://www.sysrevpharm.org/
24	Sunscreen: A review	Dr.S.L.Deore	Pharmacognosy	Pharmacognosy Journal	2016	0975-3575	http://www.phcogj.com/
25	BuccalMucoadhesive Films: A Review	Dr.S.L.Deore	Pharmacognosy	Systematic Reviews in Pharmacy	2016	0975-8453 E-0976-2779	http://www.sysrevpharm.org/

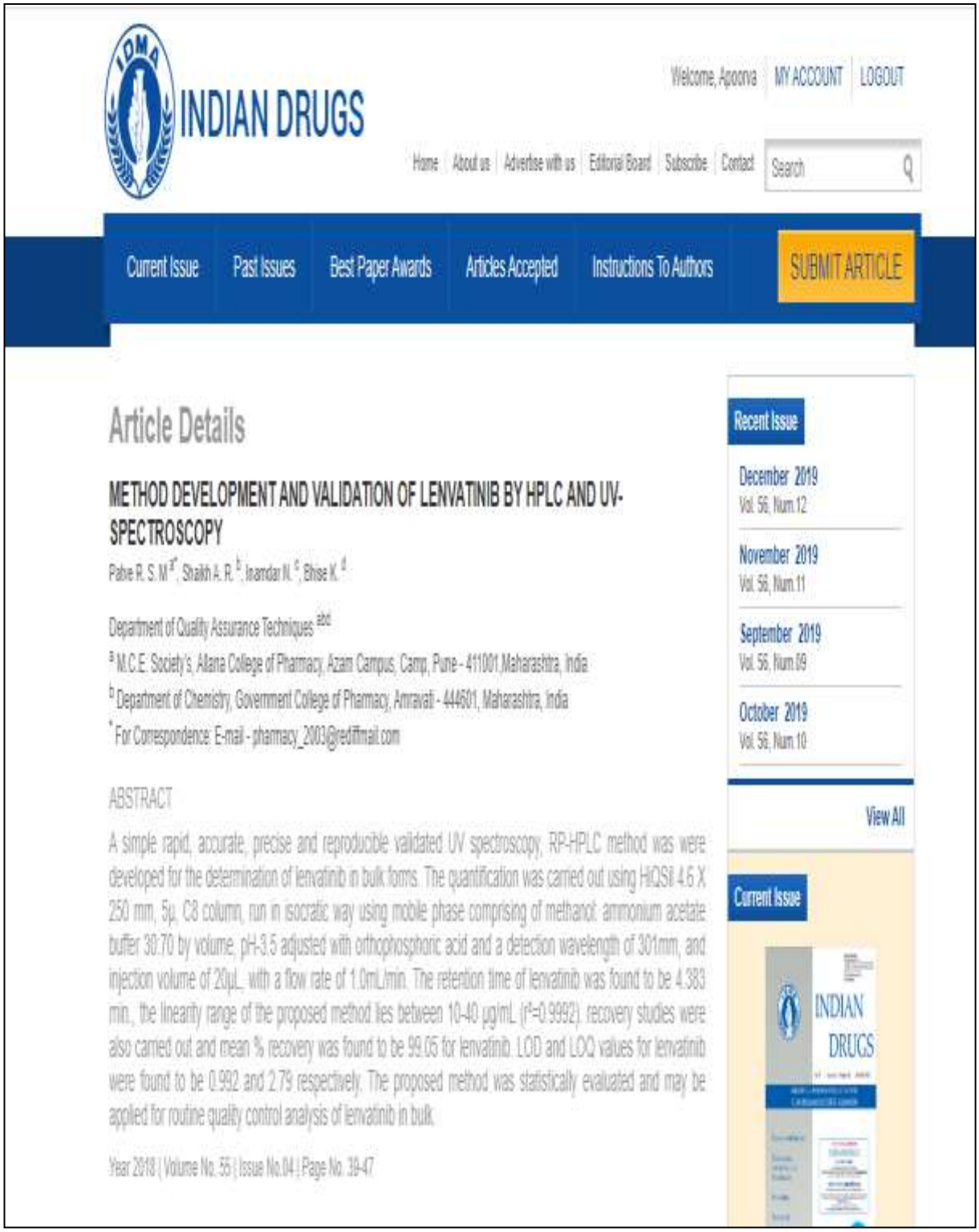
26	Solubility Enhancement of Nebivolol by Micro Emulsion Technique	Dr.S.L.Deore	Pharmacognosy	Journal of Young Pharmacists	2016	09751505, 09751483.	https://www.jyoungpharm.org/
27	Development and Evaluation of Herbal Sunscreen	Dr.S.L.Deore	Pharmacognosy	Pharmacognosy Journal	2017	0975-3575	http://www.phcogj.com/
28	Phytosynthesis of Silver Nanoparticles: Characterization, Biocompatibility Studies, and Anticancer Activity	Dr.S.L.Deore	Pharmacognosy	ACS Biomaterials Science and Engineering	2018	2373-9878	https://pubs.acs.org/journal/abseba
29	Optimization of Gastroadhesive System for Narrow Absorption Window Drugs Using Natural Polymers	Dr.M.A.Shende	Pharmaceutics	Indian Drugs	2016	0019-462X	http://www.indiandrugsonline.org/
30	Development and Optimization of Oral Gastroadhesive Matrices for Diltiazem Hydrochloride Using Some Natural Materials	Dr.M.A.Shende	Pharmaceutics	Research J. Pharm. and Tech	2016	0974-3618	http://rjptonline.org/
31	Formulation , & evaluation of curcumin loaded Nano crystal for diabetes therapy	Dr.G.S.Bangale	Pharmaceutics	Indian Drugs	2014	0019-462X	http://www.indiandrugsonline.org/
32	Enhanced tumor targeting & antitumor activity of gemcitabine encapsulated stealth liposomes	Dr.G.S.Bangale	Pharmaceutics	Indian Journal of Pharmaceutical Education and Research	2015	0019-5464	https://www.ijper.org/
33	Development & optimization of liposomal drug delivery system by 3^2 factorial design for cancer therapy	Dr.G.S.Bangale	Pharmaceutics	Indian Drugs	2018	0019-462X	http://www.indiandrugsonline.org/
34	PHYTOCHEMICAL SCREENING AND EVALUATION OF PHARMACOLOGICAL ACTIVITIES OF EULOPHIA NUDA LIND. TUBER EXTRACTS	Dr.V.P.Nagulwar	Pharmaceutical Chemistry	International Journal of Pharmaceutical Sciences and Research	2017	2320-5148	https://ijpsr.com/

35	Rapid and high yield Extraction method for Saponins from Safedmusli	Dr.B.A.Baviskar	Pharmaceutical Chemistry	Pharmacognosy Journal	2015	0975-3575	http://www.phcogj.com/

3.3.2- Any additional information (First page of Publications)

Dr. N. N. Inamdar

Method development and validation of Lenvatinib by HPLC and UV-Spectroscopy. Year 2018 | Volume No. 55 | Issue No.04 | Page No. 39-47



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Article Details

METHOD DEVELOPMENT AND VALIDATION OF LENVATINIB BY HPLC AND UV-SPECTROSCOPY

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ABSTRACT

A simple rapid, accurate, precise and reproducible validated UV spectroscopy, RP-HPLC method was were developed for the determination of lenvatinib in bulk forms. The quantification was carried out using HiQSil 4.6 X 250 mm, 5µ, C8 column, run in isocratic way using mobile phase comprising of methanol: ammonium acetate buffer 38:70 by volume, pH-3.5 adjusted with orthophosphoric acid and a detection wavelength of 301mm, and injection volume of 20µL, with a flow rate of 1.0mL/min. The retention time of lenvatinib was found to be 4.383 min., the linearity range of the proposed method lies between 10-40 µg/mL (r^2=0.9992). recovery studies were also carried out and mean % recovery was found to be 99.05 for lenvatinib. LOD and LOQ values for lenvatinib were found to be 0.992 and 2.79 respectively. The proposed method was statistically evaluated and may be applied for routine quality control analysis of lenvatinib in bulk.

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Recent Issue

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Current Issue

The Chemistry and Bio-Medicinal Significance of Pyrimidines& Condensed Pyrimidines. Curr Top Med Chem. 2016;16(28):3133-3174.

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The Chemistry and Bio-Medicinal Significance of Pyrimidines & Condensed Pyrimidines.

Jain KS[1], Arya N, Inamdar NN, Auti PB, Unawane SA, Puranik HH, Sanap MS, Inamke AD, Mahale VJ, Prajapati CS, Shishoo CJ.

Author information

Abstract

This review discusses the biological and medicinal significance of one of the most important and interesting heterocyclic ring systems, the pyrimidine and its condensed derivatives. Herein, various physiologically important molecules, as well as, therapeutically used drugs having a pyrimidine or condensed pyrimidine system in their chemical structures, have been covered. The chemistry and synthesis of pyrimidines have also been briefly discussed.

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Dr. N. R. Kotagale

Inhibitory Influence of Agmatine in Ethanol Withdrawal-Induced Depression in Rats: Behavioral and Neurochemical Evidences

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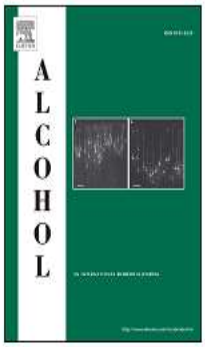

Inhibitory Influence of Agmatine in Ethanol Withdrawal-Induced Depression in Rats: Behavioral and Neurochemical Evidences

Niyamat Chimthanawala, Shruti Patil, Rishabh Agrawal, Nandkishor R. Kotagale, Milind J. Umekar, Brijesh G. Taksande

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Agmatine reverses ethanol consumption in rats: Evidences for an interaction with imidazoline receptors

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Agmatine reverses ethanol consumption in rats: Evidences for an interaction with imidazoline receptors

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Keywords:
Agmatine
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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-butanoic 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, I_1 agonist moxonidine (25 μg/rat, i.c.v.), and imidazoline I_2 agonist, 2-BFI (10 μg/rat, i.c.v.) and was blocked by imidazoline I_1 antagonist, efaroxan (10 μg/rat, i.c.v.), and I_2 antagonist, idazoxan (4 μg/rat, i.c.v.) at their ineffective doses per se. Thus, our result suggests the involvement of imidazoline I_1 and I_2 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 Organization, 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 mediates 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 (Aricioglu-Kartal and Uzbay, 1997; Li et al., 1999; Uzbay 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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Neuroprotective Offerings by Agmatine

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Review

Neuroprotective offerings by agmatine

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Neuroprotection
Spinal cord injury
Traumatic brain injury
Retinal ganglions
Molecular targets

ABSTRACT

Agmatine, an endogenous polyamine in CNS, is derived from arginine by dearboxylation. Like polyamines, agmatine has been studied for its neuroprotetive effects. At present, a large body of experimental evidences has been gathered that demonstrate the neuroprotective effects of agmatine. The neuroprotective effects have been observed in various CNS cell lines and animal models against the excitotocity, oxidative damage, corticosteroidid induced neurotoxicity, ischemic/hypoxic or oxygen-glucose deprivation toxicity, spinal cord injury and traumatic brain injury. The studies have been extended to rescue of retinal ganglion cells from toxicities. The mechanistic studies suggest that neuroprotection offered by agmatine can be assigned to its multimolecular biological effects. These include its action as glutamatergic receptor antagonist, α_2-adrenoceptor agonist, imidazoline binding site ligand, NOS inhibitor, ADP ribosylation inhibitor, and blocker of ATP-sensitive potassium and voltage-gated calcium channels, anti-apoptotic and antioxidant. Its action as regulator for polyamine synthesis, insulin release assists the neuroprotection.

The cumulative evidences of preclinical studies support the possible use of agmatine as an agent for neuronal damage and neurodegenerative diseases. However, it will be hasty to assert and promote agmatine as a novel therapeutic agent for neuroprotection. **The review is focused on the role of agmatine in different types and mechanisms of neural injuries.** The aspects of concern like dose range, pharmacokinetics of exogenous agmatine, levels of endogenous agmatine during events of injury etc. has to be addressed.

1. Introduction

Agmatine, a decarboxylated arginine, has been a known precursor for the synthesis of polyamines in plants and bacteria. Polyamines were found to exert neuroprotective effects in experimental models of neurotrauma (Gilad and Gilad, 1992). With the identification of agmatine and its biosynthetic activity in mammalian brain, it was hypothesized that agmatine might serve a neuroprotective role following neurotrauma. The hypothesis was upheld by its role of as endogenous ligand for imidazoline binding sites and its ability to interact with

Abbrevations: ADC, Arginine decarboxylase; Akt/protein kinase B, PI3K downstream effector protein; ARE, Antioxidant response element; ATF3, Activating transcription factor 3; Bax, Bcl-2 associated X protein; BCAO, Bilateral carotid artery occlusion; Bcl-2, B cell lymphoma 2; BMP, Bone morphogenetic protein; BrdU, Bromodeoxyuridine; CAST, Computer Assisted Stereological Toolbox; CE-T1WI, Contrast-enhanced T1-weighted images; CSO, Corticosterone; DWI, Serial diffusion-weighted images; DXM, Dexamethasone; eNOS, Endothelial nitric oxide synthase; ERK, Extracellular signal-regulated kinase; GCLc, Glutamate cysteine ligase, catalytic subunit; GFAP, Glial fibrillary acidic protein; Grp78, Glucose-regulated protein 78; GSTA2, Glutathione S-transferase α2; H & PI, Hoechst 33258 and propidium iodide; H&E, Hematoxylin and eosin; *hADC*, human hADC gene; HMGB1, high-mobility group box 1; HO-1, Heme oxygenase-1; Iba1, Calcium binding adaptor molecule 1; ICAM-1, Intercellular adhesion molecule 1; iNOS, Inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like-ECH-associated protein 1; LDH, Lactate dehydrogenase; LPS, Lipopolysaccharide (*E. coli* 026:B6); MAP-2, Microtubule-associated protein-2 (MAP-2); MAPK, Mitogen associated protein kinase; MCAO, middle cerebral artery occlusion; MMPs, Matrix metalloproteinases; mPFC, Medial prefrontal cortex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MT1-MMP, Membrane-type 1 matrix metalloproteinase; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NAME, Nω-nitro-L-arginine methyl ester; NeuN, Neuronal-specific nuclear protein; NF-κB, Nuclear factor-kappa B; NG2, Oligodendrocytes progenitor cells; NO, Nitric oxide; NQO1, NAD(P)H/quinone oxidoreductase; Nrf2, Nuclear factor (erythroid 2 derived)-like 2; OGD, Oxygen–glucose deprivation; Olig-2, Oligodendrocyte transcription factor-2; PI3K, Phosphatidylinositol- 3-kinase; PKC, Protein kinase C; RAGE, Receptor for advanced glycation end products; ROS, Reactive oxygen species; RT-PCR, Real-time PCR; T2WI, T2-weighted images; TBI, Traumatic brain injury; TGFβ-2, Transforming growth factor β-2; TLR, Toll-like receptor; TTC, Triphenyltetrazolium chloride; TUNEL, Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate (dUTP) nick end labeling assay; VEGF, Vascular endothelial growth factor; VEGFR2, VEGF receptor 2

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Effects of Withaniasomnifera Nicotine Induced Conditioned Place Preference in Mice

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Original Article

Effects of *Withania somnifera* Nicotine Induced Conditioned Place Preference in Mice

Nitin Govindrao Dumore[1,2*], Milind Janrao Umekar[1], Brijesh Gulabrao Taksande[1], Manish Manohar Aglawe[1], Nandkishor Ramdasji Kotagale[3]

ABSTRACT

Background: Herbal medicines can be novel treatment strategies for management of nicotine addiction. *Withania somnifera* (Ashwagandha) is an Indian medicinal plant of great medicinal value; used in many clinically proven conditions. **Objective:** In present study we aimed at investigating the effect of *withania somnifera* extract (WSE) on preventing nicotine mediated effects attributed for the development of addiction. **Materials and Methods:** Mice were treated with nicotine and/or WSE and subjected to nicotine induced conditioned place preference (CPP) in male albino mice was checked. **Results:** Application of two-way ANOVA showed that with preconditioning and post-conditioning values as a within-subjects (column) factor and treatment as an independent between subject (row) factor. Two-way ANOVA revealed significant effect of treatment [$F(3,40)=4.119$, $p<0.05$], time [$F(1,40)=23.76$, $p<0.001$] and interaction$_{\text{treatment x time}}$ [$F(3,40)=5.244$, $p<0.01$] on Intra-peritoneal (ip) administration of nicotine (1 mg/kg). WSE did not produce any changes in the preference to drug-paired compartment. Factors like treatment [$F(3,40) = 0.656$, $p>0.05$], time [$F(1,40) = 7.383$, $p<0.01$] and interaction$_{\text{treatment x time}}$ [$F(3,40) = 0.5748$, $p>0.05$] showed insignificant effects. *Withania somnifera* (50,100,200 mg/kg ip) co-administered with nicotine during the 6 days conditioning sessions completely abolished the acquisition of nicotine-induced CPP in mice. **Conclusion:** Above data indicate that *Withania somnifera* attenuate nicotine induced CPP. Hence it has potential as an anti-addictive therapy.

Key words: Condition place preference, Nicotine, *Withania somnifera*.

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INTRODUCTION

Quantification of the rewarding effect of addictive drug has widely assessed by employing self-administration or CPP test.[1] CPP occurs when the animals prefer one context more than others. This preference is known to associate with rewarding feeling paired previously with pleasing events.[2] Thus, CPP paradigm is widely used to explore the reinforcing effects of natural and pharmacological stimuli, including drugs of addiction. To understand and treat dependence disorders, researchers have utilized place conditioning to develop appropriate models of addiction.[3] Place conditioning is broadly defined as a pairing between an unconditioned stimulus (US) and a conditioned stimulus (CS) where the US is the administration of the drug or other reward to the model organism and the CS is the distinct environment in which the organism is placed after administration of the drug or reward.[4] CPP is based on a motivational aspect of the investigated drug and can be defined as an inclination for the model organism to choose the location paired with the drug.

Early CPP studies with nicotine found discrepant findings between laboratories, which included no effect, CPP, or CPA. In an attempt to clarify these discrepancies, tested nicotine for CPP by first assessing the most and least preferred sides of a three-chamber shuttle box which is termed as biased or unbiased protocol. These discrepancies were associated with animals strains and dos,[5] Nicotine showed CPP in the Lewis rats, but not in the Fischer-344.[6] Systemic administration of nicotine has been shown to produce both CPP and CPA in rodents through stimulation of nicotinic acetylcholine receptors (nAChrs).[7-8] Both CPP and CPA are observed at low and high doses, respectively. Pretreatment of mice with WSE dose-dependently prevented CPP acquisition – that is learning the association between affective interoceptive properties of morphine and environmental stimuli – an effect that might be attributed to a number of factors, including opposite motivational properties of WSE and WSE antagonism at U-opioid receptors. In agreement with a number of CPP studies with plant extracts,[9-10] WSE also blocked morphine-elicited CPP expression via involvement of $GABA_b$ receptors.[11] The results of the study demonstrated, in agreement with other study, that ethanol, under appropriate experimental conditions, elicited both CPP and CPA and that the standardized root extract of *Withania*

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Agmatine Inhibits Behavioral Sensitization to Ethanol through Imidazoline Receptors

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Agmatine Inhibits Behavioral Sensitization to Ethanol Through Imidazoline Receptors

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Background: Locomotor sensitization to repeated ethanol (EtOH) administration is proposed to play a role in early and recurring steps of addiction. The present study was designed to examine the effect of agmatine on EtOH-induced locomotor sensitization in mice.

Methods: Mice received daily single intraperitoneal injection of EtOH (2.5 g/kg, 20 v/v) for 7 consecutive days. Following a 3-day EtOH-free phase, the mice were challenged with EtOH on day 11 with a single injection of EtOH. Agmatine (10 to 40 μg/mouse), endogenous agmatine enhancers (L-arginine [80 μg/mouse], arcaine [50 μg/mouse], aminoguanidine [25 μg/mouse]), and imidazoline receptor agonist/antagonists were injected (intracerebroventricular [i.c.v.]) either daily before the injection of EtOH during the 7-day development phase or on days 8, 9, and 10 (EtOH-free phase). The horizontal locomotor activity was determined on days 1, 3, 5, 7, and 11.

Results: Agmatine (20 to 40 μg/mouse) administration for 7 days (development phase) significantly attenuated the locomotor sensitization response of EtOH challenge on day 11. Further, the agmatine administered only during EtOH-free period (days 8, 9, and 10) also inhibited the enhanced locomotor activity on the 11th day to EtOH challenge as compared to control mice indicating blockade of expression of sensitization. Daily treatment (i.c.v.) with endogenous agmatine enhancers like L-arginine (80 μg/mouse) or arcaine (50 μg/mouse) and aminoguanidine (25 μg/mouse) restrained the development as well as expression of sensitization to EtOH. Imidazoline I_1 receptor agonist, moxonidine, and I_2 agonist, 2-BFI, not only decreased the development and expression of locomotor sensitization but also potentiated the effect of agmatine when employed in combination. Importantly, I_1 receptor antagonist, efaroxan, and I_2 antagonist, idazoxan, blocked the effect of agmatine, revealing the involvement of imidazoline receptors in agmatine-mediated inhibition of EtOH sensitization.

Conclusions: Inhibition of EtOH sensitization by agmatine is mediated through imidazoline receptors and project agmatine and imidazoline agents in the pharmacotherapy of alcohol addiction.

Key Words: Agmatine, Ethanol, Locomotor Sensitization, Imidazoline Receptors.

BEHAVIORAL SENSITIZATION IS a persistent and progressive rise in locomotor and motivational response following repeated exposure to drugs of abuse including ethanol (EtOH; Calipari et al., 2015; van de Wetering and Schenk, 2017). Contemporary theories suggest that behavioral sensitization plays an important role in early and recurring steps of addiction (Robinson and Berridge, 1993). Behavioral sensitization displays 2 temporarily distinguishable phases, namely development and expression. The induction or development phase is believed to be mediated through ventral tegmental area (VTA) while the expression phase, which corresponds to enduring behavioral hypersensitivity, involves the nucleus accumbens (NAc) (Shaham and Hope, 2005). The alcohol-induced behavioral sensitization is believed to occur due to neuronal adaptation in dopaminergic, glutamatergic, and GABAergic circuitry in VTA, NAc, prefrontal cortex, and amygdala (Di Chiara, 2000; Koob et al., 1998; Meyer et al., 2005; Richtand, 2006; Shim et al., 2002; Steketee and Kalivas, 2011; Vezina and Leyton, 2009; Zislis et al., 2007). Similarly, other neurochemical systems including serotonergic and opioidergic have also been implicated in EtOH sensitization (Knapp et al., 2007; Overstreet et al., 2006; Winkler et al., 2016). Although EtOH acts on multiple neurological substrates, the mechanism for its behavioral sensitization or drug seeking behavior remains poorly defined.

Agmatine, an endogenous polyamine formed by decarboxylation of L-arginine by the enzyme, arginine decarboxylase, is a biologically active substance, influencing multiple physiological functions and having a number of promising pharmacological actions. It has received considerable attention due to its neuromodulatory and neuroprotective properties. Agmatine is densely localized in the brain areas (VTA, NAc, etc.) responsible for reinforcement, reward, and

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Neuroprotective effect of agmatine in mouse spinal cord injury model: Modulation by imidazoline receptors.

Original Article

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 efaroxan (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.[3,11,12] Its peripheral administration enhanced morphine analgesia dose-dependently in neuropathic rats.[13] 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.[15] Imidazoline binding sites are a family

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Withaferin A attenuates Alcohol Abstinence Signs in Rats

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Original Article

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.

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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 hyper-excitability, 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, anti-depressant, 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 preference[14] 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 α2-adrenoceptors.

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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 μg/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 μg/rat), a biosynthetic precursor of agmatine and arcaine (50 μg −100 μg/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 μg/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 μg/rat, icv) antagonized the memory enhancing effect of agmatine (20 μg/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 $\alpha_2$adrenergic receptors. 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 (Ashare 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 (McClernon 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 (Bence et al., 2003), orexigenic (Taksande et al., 2011), anti-compulsive (Dixit 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-adrenoreceptors (Li et al., 1994), imidazoline binding sites (Raasch et al., 2001; Reis and Regunathan, 2000), blocks *N*-methyl-D-aspartate (NMDA) receptors (Yang and Reis, 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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Original article

Acute orexigenic effect of agmatine involves interaction between central α_2-adrenergic and GABAergic receptors

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ABSTRACT

Agmatine and GABA have been abundantly expressed in brain nuclei involved in regulation of energy homeostasis and promoting stimulation of food intake in rodents. However, their mutual interaction, if any, in the elicitation of feeding behavior is largely remains unclear. The current study provides experimental evidence for the possible interaction of agmatine, adrenergic and GABAergic systems in stimulation of feeding in satiated rats.

Satiated rats fitted with intracerebroventricular (i.c.v.) cannulae and were administered agmatine, alone or jointly with (a) $GABA_A$ receptor agonist, muscimol, diazepam or antagonist bicuculline and flumazenil, $GABA_A$ positive modulator, allopregnanolone or negative modulator of $GABA_A$ receptor, dehydroepiandrosterone (b) In view of the high affinity of agmatine for α_2-adrenoceptors and the close association between α_2-adrenoceptors and GABAergic system, the effect of their modulators on feeding elicited by agmatine/GABAergic agonists were also examined. I.c.v. administration of agmatine (40–80 μg/rat) induces the significant orexigenic effect in satiated rats. The orexigenic effect of agmatine was potentiated by muscimol (25 ng/rat, i.c.v.); diazepam (0.5 mg/kg, i.p.); allopregnanolone (0.5 mg/kg, s.c.) and blocked by bicuculline (1 mg/kg, i.p.) and dehydroepiandrosterone (4 mg/kg, s.c.). However, it remained unaffected in presence of flumazenil (25 ng/rat, i.c.v.). The orexigenic effect of agmatine and GABAergic agonists was potentiated by a α_2-adrenoceptors agonist, clonidine (10 ng/rat, i.c.v.) and blocked by its antagonist, yohimbine (5 μg/rat, i.c.v.). Yohimbine also blocked the hyperphagic effect elicited by ineffective dose combination of agmatine (5 μg/rat, i.c.v.) with muscimol (25 ng/rat, i.c.v.) or diazepam (0.5 mg/kg, i.p.) or allopregnanolone (0.5 mg/kg, s.c.). The results of the present study suggest that agmatine induced α_2-adrenoceptors activation might facilitate GABAergic activity to stimulate food intake in satiated rats.

1. Introduction

Agmatine is an endogenous amine synthesized from an amino acid, L-arginine by arginine decarboxylase. It is stored in synaptic vesicles, accumulated by uptake, released by depolarization and consequently proposed as a new neuromodulator in the mammalian brain [1,2]. Agmatine exhibits interesting pharmacological profile in several neuropsychiatric disorders including depression [3,4], anxiety [5,6], epilepsy [7], psychosis [8,9], nociception [10], inflammatory cachexia [11] and is also implicated in the modulation of addictive behavior [12,13]. It activates α_2-adrenoceptors [14] and imidazoline receptors [15], antagonizes NMDA receptors [16] and inhibits nitric oxide (NO) synthase [17]. Agmatine and α_2-adrenoceptors have important functional interactions, including the inhibitory effect on nicotine-induced behavioral sensitization in mice [12] and potentiating effect on morphine-induced analgesia, conditioned place preference and anticonvulsant effects in rats [18–21]. We have recently

Abbreviations: aCSF, artificial cerebrospinal fluid; ANOVA, analysis of variance; DHEA, dehydroepiandrosterone; GABA, gamma-aminobutyric acid; i.c.v., intracerebroventricular; i.p., intraperitoneally; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; NPY, neuropeptide Y; PVN, paraventricular nucleus; s.c., subcutaneous.

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Agmatine ameliorates adjuvant induced arthritis and inflammatory cachexia in rats

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Agmatine ameliorates adjuvant induced arthritis and inflammatory cachexia in rats

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ABSTRACT

The present study investigated the pharmacological effect of agmatine in Complete Freud Adjuvant (CFA) induced arthritis and cachexia in rats. The rats were injected with CFA (0.1 ml/rat) to induced symptoms of arthritis. Day 8 onwards of CFA administration, rats were injected daily with agmatine for next 7 days, and arthritis score, body weights and food intake were monitored daily (g). Since cachexia is known to produce severe inflammation, malnutrition and inhibition of albumin gene expression, we have also monitored the total proteins, albumin, TNF-α and IL-6 levels in arthritic rats and its modulation by agmatine. In the present study, CFA treated rats showed a progressive reduction in both food intake and body weight. In addition analysis of blood serum of arthritis animals showed a significant reduction in proteins and albumin and significant elevation in tumor necrosis factor (TNF)-α and Interleukins (IL)-6. Chronic agmatine (20–40 mg/kg, ip) treatment not only attenuated the signs of arthritis but also reverses anorexia and body weight loss in CFA treated rats. In addition, agmatine restored total protein and albumin and reduces TNF-α and IL-6 levels in arthritis rats. These results suggest that agmatine administration can prevent the body weights loss and symptoms of arthritis via inhibition of inflammatory cytokines.

1. Introduction

Cachexia syndrome exhibits significant loss of body weight, muscle atrophy, fatigue, weakness and chronic loss of appetite. It is a devastating condition and occurs in many chronic pathological processes including cancer, renal failure, HIV infection and in chronic inflammatory illness such as rheumatoid arthritis [1–4]. Rheumatoid arthritis is usually associated with accelerated protein breakdown [5,6] leading to increase morbidity and premature mortality [7]. Increasing evidence from both animal and clinical studies suggests that an inflammatory response, mediated by a dysregulated production of pro-inflammatory cytokines, plays a role in the genesis of cachexia. However, the mechanisms leading to cachexia remain largely unclear.

Agmatine, an endogenous amine is synthesized through decarboxylation of L-arginine by arginine decarboxylase (ADC). It is a putative neurotransmitter [8,9] and exhibits biological effects by interacting with several receptors. Agmatine activates α_2-adrenoceptors and imidazoline receptors [9,10], and antagonize N-methyl D-aspartate (NMDA) receptors [11]. Additionally, it competitively inhibits nitric oxide (NO) synthase [12]. In experimental studies, agmatine showed a variety of pharmacological effects including anticonvulsant, anxiolytic, antinociceptive, antidepressant, and neuroprotective effects [9,10,13–20]. Several studies have reported that agmatine blocks spinal nociceptive reflexes, prevents inflammation, spinal cord injury and nerve injury induced pain [21,22]. Further, agmatine also attenuates mechanical hypernociception induced by Complete Freund's Adjuvant (CFA) in mice [23] and streptozotocin induced diabetic neuropathy in rats [22]. In fact, a recent clinical trial confirm that agmatine is safe and effective for treating pain and improving quality of life in patients suffering from lumbar disk-associated radiculopathy [24]. However, the information pertaining to involvement of agmatine in chronic inflammatory state like rheumatoid arthritis is much limited. In view of complimentary role of agmatine in pain and inflammation, therefore we hypothesized that agmatine may play role also in inflammatory cachexia in adjuvant-induced arthritis in rats.

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Effect of compression pressure on inhalation grade lactose as carrier for dry powder inhalations

Original Research Article

Effect of compression pressure on inhalation grade lactose as carrier for dry powder inhalations

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Abstract

Introduction: This study focused on the potential effects of compression forces experienced during lactose (InhaLac 70, 120, and 230) storage and transport on the flowability and aerosol performance in dry powder inhaler formulation. **Materials and Methods:** Lactose was subjected to typical compression forces 4, 10, and 20 N/cm^2. Powder flowability and particle size distribution analysis of un-compressed and compressed lactose was evaluated by Carr's index, Hausner's ratio, the angle of repose and by laser diffraction method. Aerosol performance of un-compressed and compressed lactose was assessed in dispersion studies using glass twin-stage-liquid-impenger at flow rate 40-80 L/min. **Results:** At compression forces, the flowability of compressed lactose was observed same or slightly improved. Furthermore, compression of lactose caused a decrease in *in vitro* aerosol dispersion performance. **Conclusion:** The present study illustrates that, as carrier size increases, a concurrent decrease in drug aerosolization performance was observed. Thus, the compression of the lactose fines onto the surfaces of the larger lactose particles due to compression pressures was hypothesized to be the cause of these observed performance variations. The simulations of storage and transport in an industrial scale can induce significant variations in formulation performance, and it could be a source of batch-to-batch variations.

Key words: Aerosolisation, compression pressure, dry powder inhalation, lactose, particle size

INTRODUCTION

Dry powder inhalers (DPI) are commonly used to treat respiratory diseases such asthma, bronchitis, emphysema and chronic obstructive pulmonary disease. In DPI, the deposition of the drug at the target site is maximum.[1] An aerosolized drug will be deposited either in the extrathoracic region (mouth, throat, and oropharynx) or within the lungs where drug particles can deposit in the bronchial region (also called central deposition) and in the alveolar region of the lung (known as peripheral deposition). Lung deposition studies determine the quantity of an aerosolized drug.[1] The study provides information on the regional distribution of the inhaled compound within the lungs, which could be expressed as the ratio of central to peripheral deposition.[2] Dry powder drug particles, designed for respiratory delivery, require a small aerodynamic diameter to avoid impaction in the throat and upper airways.[3] However, micronized particles of this size tend to be highly cohesive, and thus, a much larger nontherapeutic carrier particle is typically incorporated in DPI formulations to reduce drug particle agglomeration, improve aerosol redispersion, and facilitate dose metering.[4]

Pharmaceutical formulations have therapeutic doses in the microgram range (e.g., 200-400 µg) and cannot be metered without the addition of a diluent. Lactose as a diluent used for specific formulation type, which are generally referred to as carrier-based formulations and the powder blend contains an ordered mix of drug particles, uniformly adhered to the larger

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Agmatine attenuates hyperactivity and weight loss associated with activity-based anorexia in female rats

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Agmatine attenuates hyperactivity and weight loss associated with activity-based anorexia in female rats

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ABSTRACT

Anorexia nervosa is a debilitating eating disorder characterized by hypophagia, body weight loss, amenorrhea and intense fear of weight gain. In present study, the effect of subchronic agmatine treatment on development of activity based anorexia (ABA) in female rats has been investigated. Animals were injected with saline or agmatine (10–40 mg/kg, ip) just before the onset of dark phase and shifted to experimental cage with wheel for ABA test for 10 days. A pre-weighed quantity of food pellets (10 g) was placed daily for a restricted period of only 2 h (1700–1900 h) and food intake was monitored (g) manually by weighing the leftover food. Rats restricted to ABA paradigm, showed greater wheel running, suppressed food consumption, disrupted estrous cycle and weight loss. On the other hand, subchronic agmatine (10–40 mg/kg, ip, for 10 days) treatment decreased wheel running activity, pronounced increased in food intake and restored body weights as compared to saline treated animals. Further, agmatine treatment decreased corticosterone levels in ABA rats, thereby stabilizing HPA axis in ABA rats. Subchronic agmatine treatment also prevented the disruptions of estrous cycle. Considering the common resistance of anorexia nervosa to current pharmacotherapy, the preliminary data on reduction of physical activity by agmatine, may have potential therapeutic importance. Thus, the role of agmatine in feeding behavior is likely to provide insight into the circumstances that facilitate treatment in eating disorders like anorexia nervosa.

1. Introduction

Anorexia nervosa (AN) is a debilitating eating disorder characterized by hypophagia, body weight loss, amenorrhea and intense fear of weight gain. This eating disorder is particularly prevalent in young women than men. It is associated with high rates of depression, perfectionism, obsessive behavior and has the highest mortality rates among all psychiatric disorders (Bulik et al., 2007). In other words AN is characterized by self-imposed starvation and obsessive fear of obesity (Becker et al., 2009; Kaye et al., 2009; Klein et al., 2004). Thus, patients are motivated to restrict their eating, particularly the consumption of highly palatable, high energy density foods and continue to avoid till they get severely underweight (Klein et al., 2004). In addition to eating restraint, hyperactivity is featured in up to 75% of AN patients (Hebebrand et al., 2003). Indeed, excessive exercise has been reported to precede, follow, or coincide with the onset of strict dieting/food restriction (Davis and Kaptein, 2006). In this sense, hyperactivity not only promotes the progression, but also likely impedes the successful treatment and recovery of AN (Carter et al., 2004).

Although abnormalities of serotonergic system have been implicated in the development and persistence of AN in women, the treatment with SSRIs proved unsuccessful (Kaye et al., 1998). In contrast, dysregulation of reward and mood related systems have been identified in AN patients (Kaye et al., 2009). The dopaminergic (DA) system that regulates reward processing, movement, and feeding behavior has been reported to alter in AN patients. These patients exhibit reductions in homovanillic acid, a major metabolite of DA (Kaye et al., 1999) and increased DA D2 and DA D3 receptor binding sites (Frank et al., 2005). Furthermore, polymorphisms in DA D2 receptor are associated with AN (Bulik et al., 2005; Burden et al., 1993; Monteleone and Maj, 2008). Recent findings suggest that drugs targeting at DA receptors may be effective in treating AN. Several open label studies have reported that the treatment with atypical antipsychotics increases body weight and reduces hyperactivity and anxiety about eating and body shape in AN patients (Barbarich et al., 2004; Dennis et al., 2006; Leggero et al., 2010). However, such treatments reduced obsession about weight gain while increasing the rate of weight gain and rate of relapse in AN.

Neuroendocrinological studies in AN patients have found normal homeostatic physiological responses to starvation like elevated levels of orexigenic peptide, NPY and reduced levels of anorexigenic, CART and leptin in their CSF (Misra and Klibanski, 2010). Although no medication have been approved by FDA for treatment of AN, standard treatment for AN consist of nutritional rehabilitation, psychotherapy and adjunctive pharmacotherapy. However, eating disorders require comprehensive therapy with drugs having multidimensional activity.

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Chronic agmatine treatment prevents behavioral manifestations of nicotine withdrawal in mice

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Behavioural pharmacology

Chronic agmatine treatment prevents behavioral manifestations of nicotine withdrawal in mice

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ABSTRACT

Smoking cessation exhibits an aversive withdrawal syndrome characterized by both increases in somatic signs and affective behaviors including anxiety and depression. In present study, abrupt withdrawal of daily nicotine injections (2 mg/kg, s.c., four times daily, for 10 days) significantly increased somatic signs viz. rearing, grooming, jumping, genital licking, leg licking, head shakes with associated depression (increased immobility in forced swim test) as well as anxiety (decreased the number of entries and time spent in open arm in elevated plus maze) in nicotine dependent animals. The peak effect was observed at 24 h time point of nicotine withdrawal. Repeated administration of agmatine (40–80 μg/mouse, i.c.v.) before the first daily dose of nicotine from day 5 to 10 attenuated the elevated scores of somatic signs and abolished the depression and anxiety like behavior induced by nicotine withdrawal in dependent animals. However, in separate groups, its acute administration 30 min before behavior analysis of nicotine withdrawal was ineffective. This result clearly shows the role of agmatine in development of nicotine dependence and its withdrawal. In extension to behavioral experiments, brain agmatine analyses, carried out at 24 h time point of nicotine withdrawal demonstrated marked decrease in basal brain agmatine concentration as compared to control animals. Taken together, these data support the role of agmatine as common biological substrate for somatic signs and affective symptoms of nicotine withdrawal. This data may project therapies based on agmatine in anxiety, depression and mood changes associated with tobacco withdrawal.

1. Introduction

Smoking cessation exhibits an aversive withdrawal syndrome in animals characterized by both increases in somatic signs and affective behaviors analogous to that observed in nicotine dependent individuals (Cinciripini et al., 2013; Kota et al., 2007). The affective changes primarily include anxiety, reward deficits (Hughes and Hatsukami, 1986; Parrott, 1993) and depressive symptoms (Covey et al., 1998; Tsoh et al., 2000). These behavioral changes associated with nicotine withdrawal may contribute to the maintenance of nicotine dependence and smoking habit (Maskos et al., 2005; Picciotto and Corrigall, 2002). Behavioral effects of nicotine including addiction and withdrawal are regulated through its interactions with central nicotinic acetylcholine receptors (nAChRs) and multiple other neurotransmitters receptors systems in different brain areas (Di Chiara, 2000; Zislis et al., 2007). However, the molecular mechanism responsible for its dependence and withdrawal is still poorly understood.

Agmatine, a biogenic amine, has been implicated in the process of drug addiction (Halaris and Piletz, 2007; Otake et al., 1998; Reis and Regunathan, 2000). Agmatine is pleiotropic molecule with many central and peripheral functions. Its systemic administration evokes anxiolytic (Lavinsky et al., 2003) antidepressant (Li et al., 2003; Taksande et al., 2009), antinociceptive (Onal et al., 2004), anticonvulsive (Bence et al., 2003), anti-inflammatory (Satriano et al., 2001), antiproliferative (Isome et al., 2007), antipsychotic (Kotagale et al., 2012), neuroprotective (Olmos et al., 1999) effects and causes facilitation of working memory in experimental animals (Liu and Bergin, 2009). Agmatine binds to α_2-adrenoreceptors (Li et al., 1994), imidazoline binding sites (Raasch et al., 2001; Reis and Regunathan, 2000), blocks N-methyl-d-aspartate (NMDA) receptors (Yang and Reis, 1999) and inhibits nitric oxide synthase (NOS) (Auguet et al., 1995, Galea et al., 1996).

Agmatine is abundantly expressed in brain region like ventral tegmental area (VTA), nucleus accumbens (NAc) and amygdala that are associated with processing of drug addiction (Reis and Regunathan, 2000; Zhu et al., 2008). Agmatine attenuate the

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Agmatine attenuates lipopolysaccharide induced anorexia and sickness behavior in rats

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Agmatine attenuates lipopolysaccharide induced anorexia and sickness behavior in rats

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ABSTRACT

Sickness behavior is characterized by lethargy, reduced appetite, anhedonia and anxiety. It can be induced in experimental animals by bacterial endotoxin, lipopolysaccharide (LPS). We investigated the impact of intracerebroventricular agmatine injections (5–20 μg/rat, icv) on sickness behavior induced by LPS (100 μg/rat, ip) in rats. Rats challenged with LPS demonstrated hyperthermia, anorexia, anxiety, depression like phenomenon and reduction in body weights. Additionally, mediators of sickness behaviors, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) level in LPS treated rat serum were also increased. The present study revealed that these LPS induced symptoms of sickness behavior including anorexia were normalized by pretreatment with agmatine. The IL-6 and TNF-α serum levels were also normalized in agmatine pretreated rats. It is anticipated that agmatine may suppress LPS induced sickness behavior by inhibiting proinflammatory pathway and/or activity circuitry in brain. This study suggests that agmatine may be an important therapeutic target in the treatment of anorexia and other neurological abnormalities associated with bacterial infection.

1. Introduction

Agmatine, an endogenous amine is synthesized through decarboxylation of L-arginine by arginine decarboxylase (ADC) and widely distributed throughout the body including brain. It is a neurotransmitter and/or neuromodulator (Raasch et al., 1995; Reis and Regunathan, 2000) and exhibits several biological effects by interacting with certain receptors and neuronal pathways in CNS. Agmatine activates α_2-adrenoceptors and imidazoline receptors (Reis and Regunathan, 2000; Halaris and Plietz, 2007), and blocks N-methyl D-aspartate (NMDA) receptors (Yang and Reis, 1999), nicotinic receptors and 5-HT3 receptors. Additionally, it competitively inhibits nitric oxide (NO) synthase (Auguet et al., 1995). In experimental studies, agmatine showed a variety of pharmacological effects including anticonvulsant, anxiolytic, antinociceptive, antidepressant, antistress and neuroprotective effects (Reis and Regunathan, 2000; Halaris and Plietz, 2007; Gilad and Gilad, 2000; Gilad et al., 2005; Olmos et al., 1999; Wang et al., 2006; Zhu et al., 2003, 2008; Taksande et al., 2010, Taksande et al., 2013). In addition, it augments the release of insulin from pancreatic β-cells (Sener et al., 1989), leutinizing hormone-releasing hormone (LHRH) from the hypothalamus (Kalra et al., 1995) and gastrin secretion. Several reports indicated that agmatine may be a useful substance in the treatment of number of CNS disorders ranging from pain to substance abuse and dependence. Few studies have demonstrated its orexigenic activity (Taksande et al., 2011; Prasad and Prasad, 1996) and suggest that agmatine may be an additional regulator of feeding behavior (Taksande et al., 2011; Prasad and Prasad, 1996). However, the role of agmatine in infection associated anorexia and sickness behavior remains poorly investigated.

Sickness behavior is a behavioral complex induced typically by infections, inflammation, tissue injury or immune trauma and mediated by proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α. Its characteristic features include anxiety, anorexia, depressed activity, hyperthermia, loss of interest in usual activities and sleepiness etc. (Becskei et al., 2008). In experimental animals, sickness behavioral response can be induced by administration of gram negative bacterial component, lipopolysaccharide (LPS) released during sepsis or severe infection. Importantly, Sastre et al. (1998) reported that LPS reduces endogenous agmatine levels by stimulating its degrading enzyme, agmatinase and/or inhibiting stimulatory enzyme ADC. The results of recent studies that agmatine suppresses LPS induced hyperthermia, hepatic failure (Aricioglu and Regunathan, 2005; El-Agamy et al., in press) and NO synthesis in cultured microglia (Abe et al., 2000) indicated its role in sickness behavior. Considering the presence of agmatine in brain system known to be involved in food consumption, inflammation, pain, anxiety and depressive behavior (Taksande et al., 2009, Taksande et al., 2010; Fairbanks et al., 2000) we hypothesized that agmatine would prevent responses to infection such as sickness behavior. This study investigated the effect of agmatine on various indicators of sickness behavior including anorexia, hyperthermia, anxiety, depression, and body weight changes following i.p.

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Imidazoline binding sites mediates anticompulsive-like effect of agmatine in marble-burying behavior in mice

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Behavioural pharmacology

Imidazoline binding sites mediates anticompulsive-like effect of agmatine in marble-burying behavior in mice

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ABSTRACT

Agmatine is a cationic amine formed by decarboxylation of L-arginine by the mitochondrial enzyme arginine decarboxylase and widely distributed in mammalian brain. Although the precise function of endogenous agmatine has been largely remained unclear, its exogenous administration demonstrated beneficial effects in several neurological and psychiatric disorders. This study was planned to examine the role of imidazoline binding sites in the anticompulsive-like effect of agmatine on marble-burying behavior. Agmatine (20 and 40 mg/kg, ip), mixed imidazoline I_1/α_2 agonists clonidine (60 μg/kg, ip) and moxonidine (0.25 mg/kg, ip), and imidazoline I_2 agonist 2- BFI (10 mg/kg, ip) showed significant inhibition of marble burying behavior in mice. In combination studies, the anticompulsive-like effect of agmatine (10 mg/kg, ip) was significantly potentiated by prior administration of moxonidine (0.25 mg/kg, ip) or clonidine (30 μg/kg,) or 2-BFI (5 mg/kg, ip). Conversely, efaroxan (1 mg/kg, ip), an I_1 antagonist and idazoxan (0.25 mg/kg, ip), an I_2 antagonist completely blocked the anticompulsive-like effect of agmatine (10 mg/kg, ip). These drugs at doses used here did not influence the basal locomotor activity in experimental animals. These results clearly indicated the involvement of imidazoline binding sites in anti-compulsive-like effect of agmatine. Thus, imidazoline binding sites can be explored further as novel therapeutic target for treatment of anxiety and obsessive compulsive disorders.

1. Introduction

Obsessive compulsive disorder (OCD) is characterized by recurrent and persistent thoughts, impulses or images (obsessions), and/or repetitive, seemingly purposeful behaviors (compulsions), e.g., doubting, checking and washing (Rasmussen and Eisen, 1992; Sasson et al., 1997). Although OCD is classified as an anxiety disorder, patients with OCD demonstrate a high incidence of comorbid depression (Sasson et al., 1997). The first line therapy of OCD includes selective serotonin reuptake inhibitors (SSRIs) to which 40–60% of the patients did not respond satisfactorily (Pallanti and Quercioli, 2006). Refractory patients, however respond to antidopaminergics and N-methyl-D-aspartate (NMDA) receptor antagonists (Denys, 2006), suggesting that multiple neurotransmitters are probably involved in the regulation of compulsive behavior.

Agmatine [4- (amino butyl) guanidine] is an endogenous amine, widely present in mammalian brain and proposed as a novel neurotransmitter in the central nervous system (Li et al., 1994; Reis and Regunathan, 2000). It is a metabolite of L-arginine via arginine decarboxylase and hydrolyzed to putrescine and urea by agmatinase (Reis and Regunathan, 2000; Halaris and Piletz, 2007). Besides its function to regulate formation of intracellular polyamines, agmatine has been ascribed roles in several biological processes like neuroprotection (Olmos et al., 1999), chronic pain (Onal et al., 2004; Kotagale et al., 2013), epilepsy (Bence et al., 2003), stress (Zhu et al., 2008), depression (Zomkowski et al., 2002), schizophrenia (Kotagale et al., 2012) and modulation of addictive behavior (Kotagale et al., 2010; Taksande et al., 2010). The localization of agmatine like immunoreactivity has been demonstrated in several brain regions implicated in the regulation of anxiety-like behavior including amygdala (Otake et al., 1998). Moreover, numerous studies have demonstrated its anxiolytic profile in rodents (Lavinsky et al., 2003; Gong et al., 2006). Likewise, agmatine was also effective in the marble-burying paradigm and decreased the number of marbles buried (Krass et al., 2010). However, the exact mechanism of its anxiolytic action has largely remained elusive.

Agmatine is a biologically active substance and considered as an endogenous ligand at I_1/I_2 imidazoline binding sites. Brain regions that regulate endocrine and affective functions have abundant imidazoline binding sites and their endogenous ligands

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Neuropeptide Y in the central nucleus of amygdala regulates the anxiolytic effect of agmatine in rats

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Neuropeptide Y in the central nucleus of amygdala regulates the anxiolytic effect of agmatine in rats

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Abstract
In the present study, modulation of anxiolytic action of agmatine by neuropeptide Y (NPY) in the central nucleus of amygdala (CeA) is evaluated employing Vogel's conflict test (VCT) in rats. The intra-CeA administration of agmatine (0.6 and 1.2 μmol/rat), NPY (10 and 20 pmol/rat) or NPY Y1/Y5 receptors agonist [Leu^{31}, Pro^{34}]-NPY (30 and 60 pmol/rat) significantly increased the number of punished drinking licks following 15 min of treatment. Combination treatment of subeffective dose of NPY (5 pmol/rat) or [Leu^{31}, Pro^{34}]-NPY (15 pmol/rat) and agmatine (0.3 μmol/rat) produced synergistic anxiolytic-like effect. However, intra-CeA administration of selective NPY Y1 receptor antagonist, BIBP3226 (0.25 and 0.5 mmol/rat) produced anxiogenic effect. In separate set of experiment, pretreatment with BIBP3226 (0.12 mmol/rat) reversed the anxiolytic effect of agmatine (0.6 μmol/rat). Furthermore, we evaluated the effect of intraperitoneal injection of agmatine (40 mg/kg) on NPY-immunoreactivity in the nucleus accumbens shell (AcbSh), lateral part of bed nucleus of stria terminalis (BNSTl) and CeA. While agmatine treatment significantly decreased the fibers density in BNSTl, increase was noticed in AcbSh. In addition, agmatine reduced NPY-immunoreactive cells in the AcbSh and CeA. Immunohistochemical data suggest the enhanced transmission of NPY from the AcbSh and CeA. Taken together, this study suggests that agmatine produced anxiolytic effect which might be regulated via modulation of NPYergic system particularly in the CeA.

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Imidazoline binding sites mediates anticompulsive-like effect of agmatine in marble-burying behavior in mice

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Behavioural pharmacology

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1. Introduction

Obsessive compulsive disorder (OCD) is characterized by recurrent and persistent thoughts, impulses or images (obsessions), and/or repetitive, seemingly purposeful behaviors (compulsions), e.g., doubting, checking and washing (Rasmussen and Eisen, 1992; Sasson et al., 1997). Although OCD is classified as an anxiety disorder, patients with OCD demonstrate a high incidence of comorbid depression (Sasson et al., 1997). The first line therapy of OCD includes selective serotonin reuptake inhibitors (SSRIs) to which 40–60% of the patients did not respond satisfactorily (Pallanti and Quercioli, 2006). Refractory patients, however respond to antidopaminergics and N-methyl-D-aspartate (NMDA) receptor antagonists (Denys, 2006), suggesting that multiple neurotransmitters are probably involved in the regulation of compulsive behavior.

Agmatine [4- (amino butyl) guanidine] is an endogenous amine, widely present in mammalian brain and proposed as a novel neurotransmitter in the central nervous system (Li et al., 1994; Reis and Regunathan, 2000). It is a metabolite of L-arginine via arginine decarboxylase and hydrolyzed to putrescine and urea by agmatinase (Reis and Regunathan, 2000; Halaris and Piletz, 2007). Besides its function to regulate formation of intracellular polyamines, agmatine has been ascribed roles in several biological processes like neuroprotection (Olmos et al., 1999), chronic pain (Onal et al., 2004; Kotagale et al., 2013), epilepsy (Bence et al., 2003), stress (Zhu et al., 2008), depression (Zomkowski et al., 2002), schizophrenia (Kotagale et al., 2012) and modulation of addictive behavior (Kotagale et al., 2010; Taksande et al., 2010). The localization of agmatine like immunoreactivity has been demonstrated in several brain regions implicated in the regulation of anxiety-like behavior including amygdala (Otake et al., 1998). Moreover, numerous studies have demonstrated its anxiolytic profile in rodents (Lavinsky et al., 2003; Gong et al., 2006). Likewise, agmatine was also effective in the marble-burying paradigm and decreased the number of marbles buried (Krass et al., 2010). However, the exact mechanism of its anxiolytic action has largely remained elusive.

Agmatine is a biologically active substance and considered as an endogenous ligand at I_1/I_2 imidazoline binding sites. Brain regions that regulate endocrine and affective functions have abundant imidazoline binding sites and their endogenous ligands

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Involvement of hypothalamic neuropeptide Y in pentazocine induced suppression of food intake in rats

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Involvement of hypothalamic neuropeptide Y in pentazocine induced suppression of food intake in rats

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ABSTRACT

The potent orexigenic peptide neuropeptide Y (NPY) has been considered as a possible endogenous ligand for a subpopulation of sigma receptors (SigR). However, their mutual interaction with reference to feeding behavior remains poorly understood. In the present study, we explored the possible interaction between sigma1 receptors (Sig1R) agonist, pentazocine, and NPY on food intake in satiated rats. While pentazocine dose-dependently reduced the food intake, NPY significantly increased it at 2, 4 and 6 h post injection time points. In combination studies, pretreatment with NPY (0.1 nmol/rat, intra-PVN) normalized the inhibitory effect of pentazocine (60 μg/rat, intra-PVN) on food intake. Similarly, pre-treatment with pentazocine (30 μg/rat, intra-PVN) significantly antagonized the orexigenic effect of NPY (0.5 and 1.0 nmol/rat, intra-PVN). Moreover, pentazocine treatment decreased NPY immunoreactivity in arcuate (ARC), paraventricular (PVN), dorsomedial (DMH) and ventromedial (VMH) nuclei of hypothalamus. However, no change was observed in lateral hypothalamus (LH). Study implicates the reduced NPY immunoreactivity for the anorectic effect observed following pentazocine injections. Therefore, the concomitant activation of the NPYergic system along with the Sig1R agonist treatment may serve a useful purpose in the management of the unwanted side effects related to energy homeostasis.

1. Introduction

Appetite regulation is a complex process involving the interactions between number of neuromodulators and neurotransmitters (Cooper and Sanger, 1984; Levine et al., 1985; Mandenoff et al., 1984) and controlled by a superfluous mechanism related to a variety of central and peripheral systems. Within the central nervous system neuropeptide Y (NPY), agouti related protein (AGRP), cocaine- and amphetamine-regulated transcript peptide (CART) and other peptidergic cascade system plays important role in controlling the appetite (Lambert et al., 1998; Satoh et al., 1997). Several lines of evidence suggest a role for central NPY in the regulation of food intake and body weight. NPY is the most powerful central enhancer of appetite (Kalra et al., 1991; Kask et al., 1998; Kageyama et al., 2012; Kohno and Yada, 2012; Pedrazzini et al., 2003). Its expression is predominant in arcuate nucleus of hypothalamus (ARC) and projects to second order neurons located in paraventricular nucleus (PVN), lateral hypothalamus (LH), perifornical area (PFA), ventromedial (VMH) and dorsomedial (DMH) nuclei and to other brain regions (Sousa-Ferreira et al., 2011; Mahaut et al., 2010). Feeding related and other effects of NPY predominantly involves its interaction with Y1 receptors while few lines of investigations have suggested that affinity for sigma receptors (SigRs) also contribute to some of the biological effects of NPY (Ault and Werling, 1998; Bouchard et al., 1993; Meurs et al., 2007).

Sigma receptors (SigRs), a distinct class of receptors, are not members of the opioid receptor family (Vaupel, 1983; Steinfels et al., 1987). Recent evidences suggested two subtypes of SigR, while Sig1R has high affinity for (+) isomers of benzomorphans and haloperidol, Sig2R shows slight preference for the (−) isomers of benzomorphans and possess high affinity for haloperidol (Banister and Kassiou, 2012). High densities of Sig1R binding sites are found in limbic structures, including PVN in hypothalamus (Contreras et al., 1987; McLean and Weber, 1988).

Tam and Mitchell (1991) reported that NPY did not bind to SigR under different binding conditions including different temperatures, membrane preparations, protease inhibitor and sources of the peptides. Later it has been proposed that NPY may be the endogenous ligand at a subpopulation of SigRs and competes for

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Agmatine attenuates nicotine induced conditioned place preference in mice through modulation of neuropeptide Y system

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Research report

Agmatine attenuates nicotine induced conditioned place preference in mice through modulation of neuropeptide Y system

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HIGHLIGHTS

- Agmatine attenuated the acquisition of nicotine-induced CPP.
- NPY and [Leu^{31}, Pro^{34}]-NPY potentiated the inhibitory effect of agmatine.
- BIBP3226 blocked the effect of agmatine on nicotine induced CPP.
- Agmatine modified NPY-immunoreactive profile induced by nicotine.

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ABSTRACT

The purpose of the present study was to examine the effect of agmatine on nicotine induced conditioned place preference (CPP) in male albino mice. Intra-peritoneal (ip) administration of nicotine (1 mg/kg) significantly increased time spent in drug-paired compartment. Agmatine (20 and 40 mg/kg, ip) co-administered with nicotine during the 6 days conditioning sessions completely abolished the acquisition of nicotine-induced CPP in mice. Concomitant administration of neuropeptide Y (NPY) (1 pg/mouse, icv) or [Leu^{31}, Pro^{34}]-NPY (0.1 pg/mouse, icv), selective NPY Y1 receptor agonist potentiated the inhibitory effect of agmatine (10 mg/kg, ip) on nicotine CPP. Conversely, pretreatment with NPY Y1 receptor antagonist, BIBP3226 (0.01 ng/mouse, icv) blocked the effect of agmatine (20 mg/kg, ip) on nicotine induced CPP. In immunohistochemical study, nicotine decreased NPY-immunoreactivity in nucleus accumbens shell (AcbSh), bed nucleus of stria terminalis, lateral part (BNSTl), arcuate nucleus (ARC) and paraventricular nucleus (PVN). Conversely, administration of agmatine prior to the nicotine significantly reversed the effect of nicotine on NPY-immunoreactivity in the above brain nuclei. This data indicate that agmatine attenuate nicotine induced CPP via modulation of NPYergic neurotransmission in brain.

1. Introduction

Nicotine, a major psychoactive constituent of tobacco induces conditioned place preference (CPP) and facilitates intracranial self-stimulation in experimental animals [5,14]. It mediates positive reinforcing effects via the activation of central nicotinic acetylcholine receptors (nAChRs). Behavioral effects of nicotine including addiction are regulated through its interactions with multiple neurotransmitters receptor systems in different brain areas [10,47]. However, the molecular mechanism responsible for its rewarding effect and its dependence is still poorly understood.

Neuropeptide Y (NPY), a 36 amino acids peptide, binds to five receptor subtypes (Y1, Y2, Y4, Y5 and y6) and plays a crucial role in feeding [7], depression [15], convulsion [24] and anxiety [6]. Furthermore, several studies have suggested a role of NPY in addiction to drugs of abuse, including nicotine. NPY is abundantly expressed in numerous brain areas involved in regulation of addictive process including ventral tegmental area (VTA) and nucleus accumbens (Acb) [11]. Number of studies has suggested the existence of interaction between nicotine and NPYergic systems. Nicotine administration dose-dependently increased NPY mRNA levels and NPY immunoreactivity in hypothalamic nuclei and down regulates NPY Y1 receptors [23]. Moreover, NPY and NPY Y1 receptor agonist attenuated abdominal constriction following nicotine withdrawal [33]. Recently, Nakhate et al. [27] demonstrated that, NPY in the hypothalamic arcuate nucleus (ARC) and paraventricular nuclei (PVN), plays an important role in the regulation of acute, chronic

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Dr. S.L.Deore

Rapid and high yield Extraction method for Saponins from Safedmusli

PHCOG J ORIGINAL ARTICLE

Rapid and high yield Extraction method for Saponins from *Safed musli*

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ABSTRACT

Objectives: We aimed to develop, compare and optimise rapid and high yield extraction method for saponins of *Safed musli* using conventional extraction techniques and as well as modern microwave assisted solvent extraction method. **Materials and methods:** Roots of *Safed musli* (*Chlorophytum borivilianum*) are extracted by maceration, soxhlet, sonication and microwave methods. Extract further fractionated to obtain total saponins. Microwave assisted solvent extraction (MASE) method is optimised using Taguchi L9 orthogonal array design. Total saponins are estimated by High Performance Thin Layer chromatography (HPTLC) from all extracts obtained by different methods. **Results:** Factors namely temperature, irradiation time, irradiation power and powder size which potentially affects extraction efficiency are considered while optimizing MASE by statistical orthogonal array design procedure and saponins are quantified using HPTLC. Under developed optimum conditions, MASE showed significantly higher yield (5.11%) and drastic reduction in extraction time (4 min) than conventional extraction methods. **Conclusion:** Saponins of *Safed musli* shown highest yield in MASE and then maceration, soxhlet and sonication followed. The developed and optimised method of saponin extraction by MASE can have huge industrial applications after scale up.

Key words: HPTLC, Microwave assisted solvent extraction, Maceration Saponins, Orthogonal test L9 (34) Sonication, Taguchi Design.

INTRODUCTION

In Ayurveda, Siddha, Unani, *Safed musli* roots are very popular and well known for its aphrodisiac as well as immune-modulatory activity and hence it is important ingredient of 50 Ayurvedic and Unani preparations. *Safed musli* is also one of the important ingredients of very popular and useful Ayurvedic formula-Chyawanprash. Thirteen species of *Chlorophytum*, reported from India, sold as '*Safed musli*' in the Indian drug market. From research it is confirmed that the therapeutic effects of *Safed musli* are due to the presence of large amount of saponins. Among all species, *Chlorophytum borivilianum* produces the highest yield and highest saponin content. Its International drug market value is more than 300-700 tons per year. But factors like poor seed germination and dormancy are affecting uniform supply of this musli in market.[1] A solution to overcome such situation is the development of Rapid and high yield extraction method in order to obtain valuable metabolites. Traditionally the very common method for extraction of this saponin has been Soxhlet extraction. But the Soxhlet extraction method requires long heating time, bulk amount of organic solvents which again involves high risk of thermal decomposition of drug substances and pollution.[2] Despite of large preference to this method, researchers needs new fast and reliable methods of extraction. Microwave assisted Solvent extraction[3] offers simultaneous heating of sample material and solvent to obtain improved yield. The principle of MASE depends on dielectric properties of the solvent as well as of matrix where cell bursting is caused due to localized internal superheating followed by penetration of solvent into matrix and thus dissolution of the active components.[3] This surely enables improved and selective extraction of active phytochemicals with less time.[4] Hence the present work is reporting a new MASE method for fast and efficient extraction of Saponins from the roots of *Chlorophytum borivilianum* and comparison with conventional extraction techniques and optimization using Taguchi L9 orthogonal array design.[5]

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Emulsion Micro Emulsion and Nano Emulsion: A Review

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Review Article

Emulsion Micro Emulsion and Nano Emulsion: A Review

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ABSTRACT

Lipid dosage forms are attractive delivery systems for hydrophobic drug molecules. Emulsion is one of the popular system since many decades. Pharmaceutical applications of emulsions widened especially after micro and nano-emulsion emergence. This paper is an attempt to summarise comparative aspects like definition, theories, types, methods of preparations, advantages, disadvantages and methods of analysis of emulsion, micro-emulsion and nano-emulsion.

Key words: Emulsion, Micro emulsion, Nano emulsion, Surface tension, Zeta potential

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INTRODUCTION

Emulsions are dispersions made up of two immiscible liquid phases which are mixed using mechanical shear and surfactant. Amphiphilic surface-active molecules are called as 'surfactants' which are responsible to reduce naturally existing attractive forces in the form of surface tension.[1] Choice of surfactant on the basis of hydrophilic-lipophilic balance (HLB) value or critical packing parameter (CPP) helps to develop desired emulsion. Surfactants with low HLB[3-6] values as shown in Figure 1 are useful to form W/O emulsion and that of with high HLB values[8-10] are used to form O/W emulsion.[2-4] critical packing parameter (CPP) is ratio of hydrophilic and hydrophobic parts of surfactant molecule. CPP also gives idea of nature of aggregates.[5] recently two new concepts are emerged in emulsion that is as follows:

Micro-emulsion is clear, thermodynamically stable, isotropic liquid mixture. It is prepared by using oil, water, surfactant and a co-surfactant. It incorporates very small size particles up to nano size as compared to conventional emulsion.[6,7] IUPAC defines micro-emulsion as dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm.[1-6] Nano-emulsions are very similar to micro-emulsions that are dispersions of nano scale particles but obtained by mechanical force unlike to micro-emulsions which forms spontaneously.[7-9]

1.4.2 Emulsion

Emulsions are dispersions made up of two immiscible liquid phases which are mixed using mechanical shear and surfactant. Particle size of this conventional emulsion grows continuously with time and hence finally separation occurs at gravitational force thus these emulsions are thermodynamically unstable.

Theories: According to the surface-tension theory of emulsification, the emulsifiers or stabilizers lower the interfacial tension between the two immiscible liquids, reducing the repellent force between the two liquids and diminishing the attraction between the molecules of the same liquid[3] The oriented-wedge theory assumes the formation of monomolecular layers of the emulsifying agent which are curved around the droplet of the internal phase of an emulsion. This theory is based on the presumption that certain emulsifying agents orient themselves around a liquid droplet in a manner reflective of their solubility in that particular liquid. The plastic-or interfacial-film theory describes that the emulsifying agent is located at the boundary between the water and oil, forming a thin film by being adsorbed onto the surface of the internal phase droplets. The film avoids the contact and subsequent coalescence of the dispersed phase; a tougher and more pliable film will result in greater physical stability of the emulsion.[1]

- *Surface tension theory*- this theory assumes that, when surface tension between two phases lessens then emulsion can be formed
- *Repulsion theory*- this theory explains a phenomenon by which emulsifying agent forms a film containing globules on one of the immiscible phases with ability to repel each other. Thus immiscible globules remain suspended in the dispersion medium due to these repulsive forces.
- *Viscosity modification*- according to this theory emulsifying agents raises viscosity of the medium and thus miscible viscous suspension of globules is formed.

Types[3]

Following are different types of emulsions

Water-in-oil (w/o)

Oil-in-water (o/w)

Water-in-oil-in-water (w/o/w)

Oil-in-water-in-oil (o/w/o)

Methods of preparations[4]

- **Dry Gum Method**: Triturate mixture of emulsifier and oil with addition of water which will form primary emulsion. Further add water to dilute and mix continuously to form emulsion.
- **Wet Gum Method**: Initially triturate oil with water and then with emulsifier to form primary emulsion. Further add water, dilute and mix to form emulsion.
- ***In Situ* Soap Method**: Take oil and lime water (calcium hydroxide solution). Mix with stirring to form emulsion.
- **Mechanical Method**: Take oil, water and emulsifier together, mix well and stir by machine to form emulsion

Advantages[5]

- To solubilise hydrophobic or oil soluble drugs
- To enhance drug absorption through
- To enhance topical absorption of drugs
- To mask the disagree able taste and odour of drugs
- To enhance palatability of nutrient oils

Sunscreen: A review

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Review Article

Sunscreens: A review

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ABSTRACT
Sunlight despite of source of life and energy creating major health challenges like sunburn, pigmentation, wrinkles, dermatitis, urticaria, ageing, immune-suppression and number of skin cancers too. Sun protective clothes and or sunglasses provide insufficient and less convenient approach to get rid of all these health hazards. So sunscreen protection is popular mean among various regions of world. Present article have summarize types and classification, regulations, terminologies, evaluation methods, labeling, dosage and controversies of sunscreens. Natural chemical classes like phenolics (tannins, flavonoids), carotenoids, vitamins, oils are also discussed.

Key words: UV rays, SPF, COLIPA, IPD, PPD, ISO, Polyphenols, Antioxidant.

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INTRODUCTION

In India, cosmetic is defined as any article intended to be rubbed, poured, sprinkled, or sprayed on, or introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness or altering the appearance, and includes any article intended for use as a component of cosmetic.[1] Now-a-days one cosmetic product category sunscreen have gain wide popularity due to additional health benefits apart from beautification.[2-3] Either separate sunscreens or many other sunscreen loaded cosmetic products for skin care, hair care, lips care and eye care are available in market.[4-7] This review is tried to summarize all possible issues related to sunscreens.

Ultra-Violet radiations and human skin[8-9]

Ultraviolet (UV) radiation is defined as that portion of the electromagnetic radiation lies between X-rays and visible light which is from 200 to 400 nm. This ultraviolet radiation comprises 3 categories depending on wavelength as follows:

- **UV-A Radiation**: This radiation ranges between 320 to 400 nm. UV-A is most responsible radiation for immediate tanning or darkening of the skin due to excess production of melanin in the epidermis, premature photo ageing, suppression of immunologic functions, and even necrosis of endothelial cells and damage of dermal blood vessels.
- **UV-B Radiation**: This radiation ranges between 280 to 320 nm. UV-B radiations are known as burning rays as they are 1000 times more capable of causing sunburn than UV-A. UV-B rays act mainly on the epidermal basal cell layer of the skin but more genotoxic than UV-A radiations. Ultraviolet B (UVB) rays vary with time and season are major cause of sunburn. Sunburned skin is a leading risk factor for melanoma and non-melanoma skin cancer.
- **UV-C Radiation**: This radiation ranges between 200 to 280 nm. UV-C radiations are filtered by stratospheric ozone layers so less effective and hazardous.

The human skin is the largest organ of the body of surface area of approximately 1.5–2.0 m2. Skin acts as effective barrier against the harmful effects of environmental and xenobiotic agents.[9-10] Among all factor chronic exposure of UV radiations is key factor in instigation of skin problems like cracks, burns, immune suppression, wrinkles, dermatitis, urticaria, ageing, hypopigmentation, hyperpigmentation and most complicated skin cancers.[11] Role of infrared radiations in skin damage is unclear.

Mechanism of photoreaction

Photo-oxidative mechanism depending on light-driven reactive oxygen species (ROS) generation is now accepted to cause skin photoaging and photocarcinogenesis.[12] UVA rays mediated photo-oxidative damage effectively reaches through the upper layers of skin into the human dermis and dermal capillary system. Substantial protein and lipid oxidation occurs in human skin epidermis and dermis together with a significant depletion of enzymatic and non-enzymatic antioxidants in the stratum corneum, epidermis and dermis. The immediate as well as persistent pigment darkening (IPD or PPD) responses of human skin are due to photo-oxidation of pre-existing melanins and its precursors respectively. Also up-regulation of hemeoxygenase-1 (HO-1), ferritin, glutathione peroxidase, Cu–Zn-dependent superoxide dismutase (SOD1), manganese-dependent superoxide dismutase (SOD2), and catalase occurs after solar irradiation.[13]

UV rays contact initiates photo oxidative reactions to activate protein kinase C enzyme and reactive oxygen species which further reacts with protein lipids and DNA to form cyclobutane pyridine dimmers. This leads to erythema, edema, skin sunburn and cell apoptosis. UV irradiation activates cell surface growth factor and cytokine receptors on keratinocytes and fibroblasts in human skin, critical in the regulation of cell proliferation and survival.[14] UV-driven formation of H2O2 regulates the tyrosine kinase activity of the epidermal growth factor receptor (EGF–R) and emerging evidence suggests the inhibition of protein tyrosine phosphatases as a consequence of UV-induced ROS formation. According to response to sun radiation Fitzpatrick's skin type classification[15] is most popular for decision of types of skin:

Protection:

Use of physical barriers[16] to sunlight like sun protective clothing, sunglasses, hats, umbrella, shade and possible avoidance of sunlight can be

BuccalMucoadhesive Films: A Review

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Review article

Buccal Mucoadhesive Films: A Review

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ABSTRACT
Traditional oral dosage forms prone to first pass metabolism and degradation due to enzymes but mucoadhesive films able to bypass first pass metabolism and related degradation. It also offers more patient compliance without risk of chocking in case of paediatric and geriatric patients. Present review has summarised basics of mucoadhesion, composition, method of preparation, characterisation parameters, advantages and disadvantages of buccal mucoadhesive films.

Key words: *Buccal, Mucoadhesive* film, Tensile strength, Folding endurance, Solvent casting.

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INTRODUCTION

Drugs are normally administered by following routes through various dosage forms:[1]

Site	Administration	Dosage forms
Oral	Through the mouth	Powders, tablet, capsules, granules, solutions, suspensions, syrups, emulsions
Topical	Skin	Creams, lotions, ointments, gels, solutions, suspensions,
Parenteral	Subcutaneous, intramuscular, intravenous	Solutions, suspensions, emulsions
Trans-mucosal	Nasal, *Buccal* /sublingual, vaginal, ocular and rectal	Tablet, gels, emulsions, films, suppositories
Nasal	Inhalation	Sprays, powders

Oral route is most preferred route of drug administration but solubility and first pass metabolism sensitivity of drug are important characteristic to be accepted by this route. Parental rout is painful drug administration system. Topical drugs are limited for topical or local treatment only.[1]
High molecular weight drugs, poor skin penetrating drugs, poor water insoluble drugs, and extensive first pass metabolism prone drugs need alternative routes. *Mucoadhesive* route is becoming popular alternative for most of the drugs.
Mucoadhesive drug delivery system through *Buccal*, sublingual, rectal and nasal mucosa can be faster and systemic mode of non-invasive drug administration to bypass first pass metabolism. Faster delivery and enhanced bio availability of drugs is observed through *mucoadhesive* administration.[2] Following are various *mucoadhesive* drug delivery systems:

Mucus

A thin, continuous jelly layer of transparent and viscid discharge of epithelial surface is called as mucus made up of glycol proteins located in various body cavities from respiratory and gastrointestinal tract. This mucus layer of thickness of about 50-450 µm in humans actually creates adhesive interface for drugs.[10]
There is continuous secretion of mucus to balance removal of mucus layer during digestion, solubilisation and due to bacteria mediated degradation.[11] Composition of mucus varies according to anatomical locations but overall composition remains as shown in Table 1:

Table 1: Composition of mucus

Sr. no.	Components	Amount (Percentage)
1	Water	90-95
2	Lipids	0.5-6.0
3	Minerals	1-1.5
4	Proteins	0.5-1.5

This mucus layer performs following functions:[12-14]
Protective: allows selective transport and protects epithelial surface from acid diffusion through lumen
Barrier: allows selective absorption for drugs
Adhesion: mucus layer with cohesive properties allows firm adhesion surface for molecules
Lubrication: moisture present in mucus provides lubrication to mucosal layer

Mucus membrane	Surface area	Thickness	Layers	Mucus secretion/ day	Turnover time of mucus
Buccal[2-4]	30 cm	500–800 µm	epithelium, basement membrane, and connective tissues	800-1000 ml	5–6 days
Nasal[2-4]	60 mm	150-200 cm	columnar cells, goblet cells, and basal cells	20 mL	10–15 min
Ocular[2-4]		3–10 µm	epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium	2–3 µL	15–20 h
Vaginal[5-6]	6 to 10 cm	3–10 µm	lamina propia and stratified squamous epithelium	1-4 ml	7 days
Rectal[1,3,8]	300 cm	10–20 cm	Epithelium consists of a single layer of cylindrical cells and goblet cells	3 ml	7 days

Solubility Enhancement of Nebivolol by Micro Emulsion Technique

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Original Article

Solubility Enhancement of *Nebivolol* by Micro Emulsion Technique

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ABSTRACT

Nebivolol is a third-generation beta-a drenoceptor antagonist. It differs from other beta-a drenoceptor an tagonists as it combines highly selective beta (1)-adrenoceptor antagonist properties with nitric oxide-mediated vasodilator actions and beneficial effects on endothelial function. But this very useful drug use is limited due to challenge of poor water solubility (0.0403 mg/ml). Present study deals with enhancement of solubility of *Nebivolol* by micro emulsion technique. Various oils, surfactants, and co-surfactants were used to check solubility of *Nebivolol*. Pseudoternary phase diagrams were constructed using various combinations of ingredients i.e. oil: surfactant: co-surfactant. Micro emulsion batches were prepared by phase titration method. Developed micro emulsion was evaluated for various physicochemical, stability parameters, *in-vitro* and *ex-vivo* parameters. Results showed stable micro emulsion form of *Nebivolol* improved solubility.

Keywords: *Nebivolol*, Pseudo ternary phase diagrams, Micro emulsion, Co-surfactant, S_{mix}

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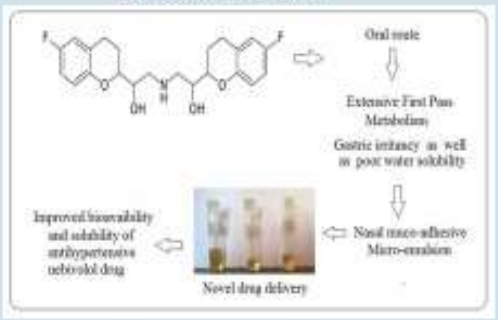
PICTORIAL ABSTRACT



INTRODUCTION

Management of hypertension and heart failure with the help of beta-blockers as antihypertensive plays critical role in reduction of cardiac deaths.[1] Novel and highly cardio selective *Nebivolol* is a better beta-blocker in comparison to other beta-blockers and hence more effective and preferred drug.[2] Along with beta blocker effects, *Nebivolol* is vasodilator, anti-atherosclerotic agent and anti *friabilator* agent.[3] Hence, it is very useful antihypertensive drug diabetic and systolic hypertensive patients and with known associated vascular diseases. But the oral administration of drug *Nebivolol* causes gastrointestinal disturbances as well as extensive first pass metabolism and thus faces challenges of poor bioavailability.[4] Hence to reduce first-pass metabolism and improve bio availability lipid-based formulation in the form of micro emulsion is prepared and found promising.[5,6]

MATERIALS AND METHODS

Pre-formulation Studies

Pre-formulation studies are preliminary studies to understand physicochemical behavior of a new drug and possible hurdles in dosage form development. It generates supportive data for necessary modifications to design, develop and evaluate formulation.

Solubility Study of Drug in Oil

To select the best oil for preparation of micro emulsion formulation, saturated solubility studies were carried out in different oils, i.e. soya bean oil, castor oil, olive oil, labrafill 1944 and oleic acid etc. Excess amount of drug i.e. *Nebivolol* added to the 200 mg of each oil in glass vial. Then allowed them to solubilize in sonicator for 30 min.[7] further mixture containing vials were kept in orbital shaker for 72 hr. to from homogenous mixture. This was done by preparing saturated solutions of the drug in these oils and analyzing their drug content spectrophotometrically.

Surfactant and Co-Surfactant Screening

The final selection after solubility analysis was done on the basis of HLB value of co-surfactant. Among all surfactant screened, the highest solubilisation capacity was exhibited by Tween 80 (27.8289 mg/mL) followed by Cremophor RH 40 (26.1842 mg/ml) and Labrasol (23.8815 mg/mL). Tween 80 was therefore selected for further investigation, while final selection would rely on emulsification properties with co surfactant mixtures. For solubility studies surfactants and co surfactants were chosen from the GRAS (generally regarded as safe) category. Nonionic surfactants are reported to be less toxic than ionic surfactants.[7,8] Solubility of *Nebivolol* in various surfactants and co surfactants is given in Figure 2

Optimization of formulation

Pseudo ternary phase diagrams were constructed using various combinations of ingredients i.e. oil: surfactant: co surfactant. Surfactant and co-surfactant were mixed (S: Co-s) in a ratio S mix (2:1, 1:2, 1:1). In order to get concentration range of component for the existing range of micro emulsion region, oil and S_{mix} were mixed in a 1:9 to 9:1 ratio. Considering turbidity or cloudiness as an end point, pseudo ternary phase diagrams were constructed by water titration method. Pseudo ternary phase diagram is plotted by using Chemix software.[8,9] After 24 h, when mixture formed equilibrium at room temperature then evaluated

Development and Evaluation of Herbal Sunscreen

Pharmacogn J. 2017; 9(1): 83-97

Original Article

Development and Evaluation of Herbal Sunscreen

Mukund Manikrao Donglikar[1] and Sharada Laxman Deore[2*]

ABSTRACT

Thus present research work deals with the development and evaluation of topical photo protective formulation, containing antioxidant, wound healing, anti-inflammatory and rather photo protective poly phenols like curcumin, quercetin, resveratrol and safranal. The present research work provides stable natural photo protective formulation with antioxidant potential, high SPF and more important uniform UVA/UVB protection.

Key words: Sunscreen, Resveratrol, Quercetin, Curcumin, Safranal, SPF.

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INTRODUCTION

From the dawn of mankind, Sun is source of life and energy. But recent studies accepts sun as main culprit of deleterious effects including acute effects (e.g., sunburn and drug-induced photo toxicity) and chronic risks of frequent sun ray exposure like sunburn, crack, melanoma and pigmentation, cancer and immune suppresion.[1] Sun rays are most harmful environmental factor which affects skin, cause sun burn, skin cancers and photo ageing. Due to these harmful effects of UV radiations there is need to develop sunscreen formulation to heal, prevent sun burn, suntan, skin cancer and premature skin ageing and to increase level of Sun Protection Factor.[2]

The goal of sunscreen formulation is to block UV-rays and increase the level of protection from the UV-rays. The key components of UV protection are flavonoids, phenolic compounds or herbal oils due to their UV rays absorption capacity in UV-A region and their antioxidant activity.[3] Cell mutation, DNA damage, hormone alteration and eczema like allergic reaction are some adverse effects of the synthetic sun-screen agents. Sunscreen formulations available in market don not have properties like wound healing, anti-inflammatory, cooling and anti-ageing. Again free radical mediated skin damages cannot be cured until and unless free radical scavengers are not available in photo protective products.[4]

During the market survey, it is found that there are many sunscreen formulations available in markets which are used in protection of skin from UV rays. Various formulations have different sun protection activity on basis of their efficacy of UV rays absorption but maximum formulations are of high cost and incorporated synthetic molecules are with potential toxicity and even carcinogenesis.[5] Hence there is need to develop and evaluate effective and safe sunscreen product which can give solution to sunburn, wounds, cracks, wrinkles, premature ageing and antioxidant ingredients to help in protection of long term damaging effects of sunrays mediated free radicals.

Curcumin, quercetin, resveratrol and safranal belong to class of poly phenolics and are potent antioxidants as well as photo protective. But additionally curcumin is wound healing, antiseptic; quercetin is anticancer, resveratrol is antiaging and safranal is emollient.[5-11] So sunscreen product incorporated with these ingredients can give desired all-in-one product.

Curcumin (diferuloylmethane) is a yellow odorless pigment isolated from the rhizome of turmeric (*Curcuma longa*). Curcumin possesses anti-inflammatory, antitumoral, and antioxidant properties. It has been found that topical application of curcumin in epidermis of CD-1 mice significantly inhibited UVA-induced ornithine decarboxylase ornithine decarboxylase (ODC) activity. The inhibitory effects of curcumin were attributed to its ability to scavenge reactive oxygen species reactive oxygen species (ROS). Curcumin can prevent UV irradiation-induced apoptotic changes in human epidermoid carcinoma A431 cells.[7]

Quercetin is polyphenolic compound present in *citrus* species shows strong immune modulatory, antioxidant, anti-inflammatory effects and act as a. Quercetin and rutin were tested as potential topical sunscreen factors in human beings and found to provide protection in the UVA and UVB range.[8]

Resveratrol is chemically fat soluble stilbenes belong to polyphenolic class. It is of trans and a cis configuration. It acts as a potent antioxidant and as well anticancer and anti-inflammatory.[5,6]

Safranal, an organic aromatic compound present in stigmas of crocus flowers (*Crocus sativus*). It exhibits high antioxidant and free radical scavenging efficacy. It is also found to be anticancer.[9,10]

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Phytosynthesis of Silver Nanoparticles: Characterization, Biocompatibility Studies, and Anticancer Activity

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Phytosynthesis of Silver Nanoparticles: Characterization, Biocompatibility Studies, and Anticancer Activity

Kiran Jadhav*, Sharada Deore, Dinesh Dhamecha*, Rajeshwari H R, Satveer Jagwani, Sunil Jalalpure and Raghvendra Bohara

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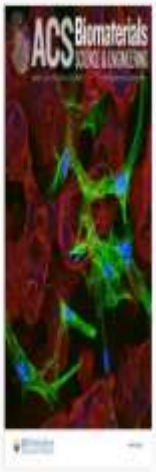
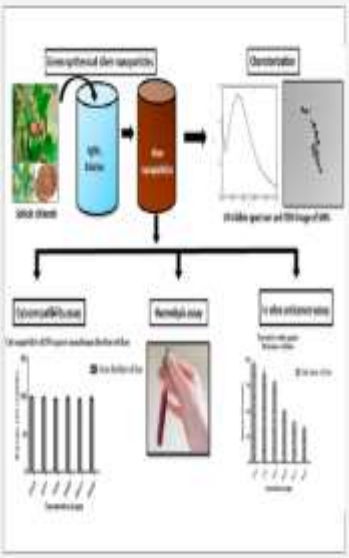
SUBJECTS: Anatomy, Metal nanoparticles, Cancer, Nanoparticles Cells



ACS Biomaterials Science & Engineering

Abstract

Silver nanoparticles (SNPs), owing to their wide range of biomedical applications, have recently attracted remarkable interest for use in cancer nanomedicine. The present research work investigated the anticancer activity of phytosynthesized SNPs against human cancer cell lines. Phytosynthesis of SNPs was achieved by using an aqueous extract of *Salacia chinensis* (SC) bark as a green source to reduce silver nitrate to silver nanoparticles. Characterization of synthesized nanoparticles demonstrated a UV–visible peak at 443 nm, ζ-potential (zetasizer) of −25.6 ± 0.34 and particle size (transmission electron microscopy analysis) in the range of 40–80 nm, which validates formation of stable silver nanoparticles. The absence of cytotoxicity against normal human fibroblasts and blood erythrocytes confirms the biocompatible nature of green synthesized SNPs. In vitro anticancer assay demonstrated IC_{50} values of 6.31, 4.002, 5.228, 8.452, 14.37, 7.46, and 6.55 μg/mL against liver (Hep G2), lungs (L-132), pancreas (MIA-Pa-Ca-2), breast (MDA-MB-231), oral (KB cells), prostate (PC-3), and cervical (HeLa) cancer cell lines respectively, which confirms its potent anticancer action. The results of the present study give an experimental proof that the SC mediated green synthesized SNPs could serve as a promising anticancer agent to overcome limitations of existing conventional cancer chemotherapeutics.



KEYWORDS: silver nanoparticles, green chemistry, anticancer activity, biocompatibility, Salacia chinensis

Dr. M.A.Shende

Optimization of Gastroadhesive System for Narrow Absorption Window Drugs Using Natural Polymers

Article Details

OPTIMIZATION OF GASTROADHESIVE DELIVERY SYSTEM FOR NARROW ABSORPTION WINDOW DRUG USING NATURAL POLYMERS

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ABSTRACT

A system comprising mechanisms of gastric retention by gastroadhesion has been investigated employing combination of hibiscus esculentus mucilage and xanthan gum for diltiazem hydrochloride. Various formulations of diltiazem hydrochloride were prepared by wet granulation technique using Box-Behnken approach and were tested for compatibility, swelling behaviour, in vitro drug release, mucoadhesive strength and accelerated stability. The percent cumulative drug release at 8th hr (Y1), time to release 80 % of drug (Y2), mucoadhesive strength (Y3) and mucoadhesive time (Y4) were used as the formulation responses in order to optimize the formulation. The accelerated stability studies revealed that the tablets retained their characteristics even after stressed storage conditions. The DLT mucoadhesive matrices were 49.99 mg hibiscus esculentus mucilage, 44.97 mg xanthan gum and 4.48 ton compression load fulfilled the optimal criteria of best sustained release rate and bioadhesive characteristics with t80% of 7.6 h, Q8h of 89.83 % and bioadhesive strength of 22.14 g.

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Development and Optimization of Oral Gastroadhesive Matrices for Diltiazem Hydrochloride Using Some Natural Materials

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RESEARCH ARTICLE

Development and Optimization of Oral Gastroadhesive Matrices for Diltiazem Hydrochloride Using Some Natural Materials

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ABSTRACT:

The present aim of this wok was to formulate gastric retentive tablets by gastroadhesion with a view to provide better absorption employing combination of *hibiscus esculentus* mucilage and xanthan gum for diltiazem hydrochloride. Various formulations of diltiazem hydrochloride were prepared by wet granulation technique using Box-Behnken approach and were tested for compatibility, swelling behaviour, *in-vitro* drug release, mucoadhesive strength and accelerated stability. The percent cumulative drug release at 8th hr (Y_1), time to release 80% of drug (Y_2), mucoadhesive strength (Y_3) and mucoadhesive time (Y_4) were used as the formulation responses in order to optimize the formulation. The accelerated stability studies revealed that the tablets retained their characteristics even after stressed storage conditions. The DLT mucoadhesive matrices were 49.99 mg *hibiscus esculentus* mucilage, 44.97 mg xanthan gum and 4.48 ton compression load fulfilled the optimal criteria of best sustained release rate and bioadhesive characteristics with $t_{80\%}$ of 7.6 h, Q8h of 89.83 % and bioadhesive strength of 22.14 g. The formulated tablets ascertained first order kinetics and followed peppas mechanism.

KEYWORDS: Diltiazem hydrochloride, *Hibiscus esculentus*, Xanthan gum, Gastroadhesive, Box-Behnken

INTRODUCTION:

Response surface methodology (RSM) was a collection of statistical and mathematical techniques that has been successfully used to determine the effects of several variables and optimize processes. Optimization of formulation design can be used in formulation and development of pharmaceutical products due to the wide array of parameters and variables that must be controlled to achieve desire release pattern and meet other performance criteria. Box–Behnken designs do not have axial points, thus all design points fall within the safe operating zone. These designs also ensure that all factors are never set at their high levels, simultaneously.[1,2]

Furthermore; Box–Behnken designs have fewer design points. Also, each factor requires only three levels instead of the five required for central composite designs (unless alpha is equal to one), which may be experimentally more convenient and less expensive to run than central composite designs with the same number of factors.

Oral sustained release formulations have drawbacks in respect to variation of gastric emptying time results in variable drug absorption. Too rapid gastrointestinal transit can lead to inadequate drug release from the dosage form above the absorption zone, resulting in diminished effectiveness of the given dose when the drug presents an absorption window. Prolongation of gastric residence time of a rate controlled oral drug delivery system can rectify these problems by minimizing the inter-subject variability known as 'peak and trough' effect, and also improve the bioavailability, specially for drugs having a narrow absorption window

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Dr. G.S. Bangale

Formulation and evaluation of curcumin loaded Nanocrystal for diabetes therapy

Article Details

FORMULATION AND EVALUATION OF CURCUMIN LOADED NANOCRYSTAL FOR DIABETES THERAPY

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ABSTRACT

The aim of the present investigation was to design and characterize nanocrystal formulation of curcumin for diabetes therapy. Formulation was prepared by High Pressure Homogenization. HPH cycles and pressure range were screened by preliminary batches (T1 & T2). 15 cycles were optimized and the pressure range was kept at 500-2000 bar. A Taguchi design was used to optimize type of polymers, Drug: polymer ratio, amount of SLS and HPH pressure. Formulations were characterized for particle size, % entrapment efficiency and in vitro drug release. Optimized formulation (NC 4) showed a particle size of 147.8nm, % EE of 85.35%, % DR of 77.46% and was used for further study. Zeta potential and PDI was found to be -39.63 and 0.252 respectively. Stability study was carried out for 3 weeks. It indicated no significant change in particle size, Zeta Potential, PDI and settling.

Year 2014 | Volume No. 51 | Issue No.12 | Page No. 5-11

Development and optimization of liposomal drug delivery system by 3^2 factorial design for cancer therapy

Article Details

DEVELOPMENT AND OPTIMIZATION OF LIPSOMAL DRUG DELIVERY SYSTEM BY 32 FACTORIAL DESIGN FOR CANCER THERAPY

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ABSTRACT

The objective of the present study was to develop nano range liposomal formulation for cancer therapy and optimize the formulation by response surface method, i.e. 3^2 factorial design, in order to minimize more efforts, time and material use when formulation like the liposomes are developed. Two independent variables, namely, the concentration of lipid (X^1) and the concentration of cholesterol (X^2), were set at three different levels. High and low levels of each variable were coded as 1 and -1, respectively, and the mean value was coded as zero. The dependent variables for factorial batches measured as vesicle size (Y^1) was 61.5 to 72.3%, and % encapsulation efficiency (Y^2) was found to be 127 to 240 nm. Stepwise regression analysis was used to find out the control factors that significantly affect response variables. The results were subjected to ANOVA and multiple regression analysis that led to equations describing the effect of independent variables on the selected responses. The level of significance selected was 5% ($p<0.05$). Contour plot and response surface plot were constructed & overlay plot was used to optimize the formulation by keeping the desired responses. The optimized formulation CL-10 has vesicle size of 132 nm & PDI value of 0.241. Zeta potential of formulation was -20.4, conforming the formulations stability. Vesicular morphology measured by SEM & TEM study indicates that the vesicle was spherical in nature. Stability study of optimized formulation was carried out for 6 months as per ICH guidelines at 4^0C and 37^0C and indicates no significant changes in parameters like % drug release, vesicle size, % EE supported by student t test ($p=0.05$).

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Enhanced tumor targeting &anti-tumor activity of gemcitabine encapsulated stealth liposomes

Pharmaceutical Research

Enhanced Tumor Targeting and Antitumor Activity of Gemcitabine Encapsulated Stealth Liposome's

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ABSTRACT

Introduction: Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Gemcitabine is new cytotoxic drug but some of limitations while its use likes it suppress the activity of Bone marrow i.e. effect on blood forming cells, lower half life-7-18 min.unable to deliver by oral & other route. Higher dose-1000-1250 mg/m2 require against malignancies. Effective against various solid tumor like colon, lungs, breast etc. Several attempt was made to enhance efficacy of gemcitabine against tumor including novel stealth liposomal technology might proves to avoids above limitation. **Method:** A present investigation focuses on to enhance encapsulation of gemcitabine inside the vesicle by adopting pH gradient methods followed by solvent evaporation. The resulting formulation of liposomes are characterize by vesicle size, zeta potential by zeta sizer along with encapsulation efficiency by centrifugation. The optimization of formulation was carried out by statistically by 32 factorial design. The optimized formulation further subjected for *in vitro* antitumor activity i.e. cell line study and *in vivo* performance by using animal model. **Results:** The stealth liposomal formulation comparatively evaluated with conventional liposomes and pure drug based on cell line study proves that stealth liposomes are effectively retarding the % tumor cell growth than others. Bio distribution profile of stealth liposomes in various organs assure for prolong circulation half of formulation and maximum tumor concentration of drug even after 24 hrs study. There is no sign of toxicity after administration supported by data obtained through toxicity studies. **Conclusion:** The final outcomes of research was antitumor activity of gemcitabine improved by PEGylation (stealth) technology which also minimize unwanted toxicities associated with gemcitabine via other route of administration.

Key words: Gemcitabine, Pharmacokinetic, pH gradient, Stealths Liposome, Zeta potential.

INTRODUCTION

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems. Cancer is not just one disease but many diseases. There are more than 200 different types of cancer.[1-4] For instance, although there are numerous anticancer agents that are highly cytotoxic to tumor cells *in vitro*, the lack of selective antitumor effect *in vivo* precludes their use in clinic. One of the major limitations of antineoplastic drugs is their low therapeutic index (TI), i.e. the dose required to produce anti-tumor effect is toxic to normal tissues.[5]

Liposomes are spherical vesicles composed of lipid bilayers arranged around a central aqueous core. The particle size of liposomes ranges from 20 nm to 10 μm in diameter. They can be composed of natural constituents such as phospholipids and may mimic naturally occurring cell membranes. Liposomes have the ability to incorporate lipophilic and hydrophilic drugs within their phospholipid membrane or they can encapsulate hydrophilic compounds within the aqueous core.[6]

Gemcitabine is new cytotoxic drug but some limitations restrict its use, for example it suppress the activity of Bone marrow i.e. effect on blood forming cells. Higher water

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Phytochemical Screening and Evaluation of Pharmacological Activities of *EulophiaNuda*Lind. Tuber Extracts

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PHYTOCHEMICAL SCREENING AND EVALUATION OF PHARMACOLOGICAL ACTIVITIES OF *EULOPHIA NUDA* LIND. TUBER EXTRACTS

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Keywords:

Eulophia nuda, Antibacterial activity, Antifungal activity, Hepatoprotective activity

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ABSTRACT: *Eulophia nuda* Lind. belongs to family Orichidaceae and is a rare and endangered orchid. Present research work was carried out on tuber extracts of *Eulophia nuda* for the evaluation of antimicrobial activities and hepatoprotective. Preliminary phytochemical screening revealed presence of phytochemical constituents like alkaloids, flavonoids, steroids, glycosides (cardiac), tannins, saponins, carbohydrates in three tuber extracts prepared by using solvents (chloroform, acetone and ethanol). Antibacterial activity was carried out with Disc Diffusion method against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Acetone extract was more effective against *Staphylococcus aureus* with maximum zone of inhibition 18 mm compared to standard antibiotic Ampicillin with zone of inhibition 20 mm. Antifungal studies was carried out using well diffusion method against *Candida albicans*, *Aspergillus niger* and *Aspergillus flavus*. Chloroform extract was more effective against *Aspergillus niger* having zone of inhibition 17 mm compared with standard antifungal Fluconazole (20mm). Acetone extract shown the zone of inhibition of 16 mm against *Aspergillus flavus* compared to standard Fluconazole (22mm). Hepatoprotective activity was carried out as per OECD guidelines 425 using Wistar albino rats. Effect of these extracts on CCl_4 induced hepatotoxic rats was studied by SGOT, SGPT and ALP parameters compared with standard LIV 52. From the research work, it was concluded that *Eulophia nuda* tuber extracts are active as antibacterial, antifungal and hepatoprotective which could be used for the development of some promising formulations, furthermore, structural elucidation of isolated components from the extracts of *Eulophia nuda* can be carried out using studies like IR and NMR.

INTRODUCTION: Traditional herbal medicines are naturally occurring; plant derived substances with minimal or no industrial processing that have been used to treat illness with local or regional healing practices.

QUICK RESPONSE CODE

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Herbal medicines also known as botanical / phyto-medicine refers to using a plant, seeds, berries, roots, leaves, barks, tubers or flowers for their medicinal purposes [1]. The family Orichidaceae to which orchid belongs is the largest family amongst monocotyledons contains almost 600 - 800 genera / species.

The genus *Eulophia* is terrestrial with almost round pseudo bulbs enveloped by a few sheath carrying 3 - 4 lanceolate, plicate, acuminate, long plicate, long grooved stalks which have several leaf like bracts. The plants blooms in springs with tall thick fleshy

Dr.B.A.Baviskar

Rapid and high yield Extraction method for Saponins from Safedmusli

PHCOG J ORIGINAL ARTICLE

Rapid and high yield Extraction method for Saponins from *Safed musli*

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ABSTRACT

Objectives: We aimed to develop, compare and optimise rapid and high yield extraction method for saponins of *Safed musli* using conventional extraction techniques and as well as modern microwave assisted solvent extraction method. **Materials and methods:** Roots of *Safed musli* (*Chlorophytum borivilianum*) are extracted by maceration, soxhlet, sonication and microwave methods. Extract further fractionated to obtain total saponins. Microwave assisted solvent extraction (MASE) method is optimised using Taguchi L9 orthogonal array design. Total saponins are estimated by High Performance Thin Layer chromatography (HPTLC) from all extracts obtained by different methods. **Results:** Factors namely temperature, irradiation time, irradiation power and powder size which potentially affects extraction efficiency are considered while optimizing MASE by statistical orthogonal array design procedure and saponins are quantified using HPTLC. Under developed optimum conditions, MASE showed significantly higher yield (5.11%) and drastic reduction in extraction time (4 min) than conventional extraction methods. **Conclusion:** Saponins of *Safed musli* shown highest yield in MASE and then maceration, soxhlet and sonication followed. The developed and optimised method of saponin extraction by MASE can have huge industrial applications after scale up.

Key words: HPTLC, Microwave assisted solvent extraction, Maceration Saponins, Orthogonal test L9 (34) Sonication, Taguchi Design.

INTRODUCTION

In Ayurveda, Siddha, Unani, *Safed musli* roots are very popular and well known for its aphrodisiac as well as immune-modulatory activity and hence it is important ingredient of 50 Ayurvedic and Unani preparations. *Safed musli* is also one of the important ingredients of very popular and useful Ayurvedic formula-Chyawanprash. Thirteen species of *Chlorophytum*, reported from India, sold as '*Safed musli*' in the Indian drug market. From research it is confirmed that the therapeutic effects of *Safed musli* are due to the presence of large amount of saponins. Among all species, *Chlorophytum borivilianum* produces the highest yield and highest saponin content. Its International drug market value is more than 300-700 tons per year. But factors like poor seed germination and dormancy are affecting uniform supply of this musli in market.[1] A solution to overcome such situation is the development of Rapid and high yield extraction method in order to obtain valuable metabolites. Traditionally the very common method for extraction of this saponin has been Soxhlet extraction. But the Soxhlet extraction method requires long heating time, bulk amount of organic solvents which again involves high risk of thermal decomposition of drug substances and pollution.[2] Despite of large preference to this method, researchers needs new fast and reliable methods of extraction. Microwave assisted Solvent extraction[3] offers simultaneous heating of sample material and solvent to obtain improved yield. The principle of MASE depends on dielectric properties of the solvent as well as of matrix where cell bursting is caused due to localized internal superheating followed by penetration of solvent into matrix and thus dissolution of the active components.[3] This surely enables improved and selective extraction of active phytochemicals with less time.[4] Hence the present work is reporting a new MASE method for fast and efficient extraction of Saponins from the roots of *Chlorophytum borivilianum* and comparison with conventional extraction techniques and optimization using Taguchi L9 orthogonal array design.[5]

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