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RESEARCH PUBLICATIONS -2019

S.No	Faculty name	Title of the paper	Name of the journal	It is listed in UGC SCOPUS WEB Of Science	Link to abstract	Article count year wise
1.	Buchi N.Nalluri	Development of Zolmitriptan Mouth Dissolving Films: Formulation Variables, Mechanical Properties and *Invitro* Drug Release Studies	Asian Journal of Pharmaceutical and Clinical Research	Scopus preview - Scopus - Asian Journal of Pharmaceutical and Clinical Research	10.22159/ajpcr.2019.v12i4.32176	1
2.	Buchi N.Nalluri	Formulation and Evaluation of Ramipril Mouth Dissolving Films	International Journal of Applied Pharmaceutics	Scopus preview - Scopus - International Journal of Applied Pharmaceutics	10.22159/ijap.2019v11i3.32361	1
3.	Lakshmi Sudeepthi	Protective Effect of Curcuma Amada Acetone Extract Against High- Fat and High-Sugar Diet Induced Obesity and Memory Impairment	Nutritional Neurosciences	Scopus preview - Scopus - Nutritional Neuroscience	DOI: 10.1080/1028415X.2019.1616436	1
4.	Siva Reddy Challa & Ravindra Babu Pingili	Effect of Chrysin on the Formation of N-Acetyl-P-Benzoquinoneimine , A Toxic Metabolite of Paracetmol in Rats and Isolated Rat Hepatocytes	Chemico Biological Interactions	Scopus preview - Scopus - Chemico-Biological Interactions	DOI: 10.1016/j.cbi.2019.02.014	2
5.	Siva Reddy Challa & Ravindra Babu Pingili	A Comprehensive Review on Hepato Protective and Nephro Protective Activities on Chrysin Against Various Drugs and Toxic Agents	Chemico Biological Interactions	Scopus preview - Scopus - Chemico-Biological Interactions	DOI: 10.1016/j.cbi.2019.05.010	2
6.	Naveen Babu Kilaru & Ravindra Babu Pingili	A Cross-Sectional Observational Study on Drug Utilisation Pattern, Prevalence and Risk Factors for the Development of Diabetic Nephropathy Among Type 2 Diabetic Patients in a South Indian Tertiary Care Hospital	International Journal of Research in Pharmaceutical Sciences	Scopus preview - Scopus - International Journal of Research in Pharmaceutical Sciences	https://doi.org/10.26452/ijrps.v11i1.1791	2
7.	Naveen Babu Kilaru & Ravindra Babu Pingili	Assessment of Drug Utilization Pattern, and Risk Factors for the Development of Diabetic Neuropathy Among Type 2 Diabetic Patients in a South Indian Hospital: A Cross-Sectional Observational Study	Journal of Applied Pharmaceutical Science	Scopus preview - Scopus - Journal of Applied Pharmaceutical Science	DOI: 10.7324/JAPS.2019.91210	2

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8.	Naveen Babu Kilaru & Ravindra Babu Pingili	Assessment of Drug Utilization Pattern, Prevalence and Risk Factors for the Development of Diabetic Retinopathy Among Type 2 Diabetic Patients in a South Indian Tertiary Care Hospital: A Cross-Sectional Observational Study	International Journal of Research in Pharmaceutical Sciences	Scopus preview - Scopus - International Journal of Research in Pharmaceutical Sciences	DOI: 10.26452/ijrps.v11i2.2229	2
9.	Naveen Babu Kilaru	Development And Optamization of Sustained Release Mucoadhesive Composite Beads for Colon Targeting	International Journal of Biological Macromolecules	Scopus preview - Scopus - International Journal of Biological Macromolecules	https://doi.org/10.1016/j.ijbiomac.2019.07.190	1
10	T.Devadoss	Construction of a Novel Quinoxaline as a New Class of Nrf2 Activator	BMC chemistry	Scopus preview - Scopus - BMC Chemistry	Construction of a novel quinoxaline as a new class of Nrf2 activator (biomedcentral.com)	1
11	Siva Reddy Challa	Prevalence of Various Types of Cancers and an Observational Study of Various Haemoglobin Levels in Different Grade of Cancer: A South Indian Hospital Based Study	Journal of Clinical and Diagnostic Research	Web of Science Master Journal List - Search (clarivate.com)	https://doi.org/10.7860/JCDR/2019/41728.13209	1
12	Siva Reddy Challa & Ravindra Babu Pingili	Quercetin Reduced the Formation of N- Acetyl-P-Benzoquinoneimine , A Toxic Metabolite of Paracetmol in Rats and Isolated Rat Hepatocytes	Phytotherapy Research	Scopus preview - Scopus - Phytotherapy Research	https://doi.org/10.1002/ptr.6365	2
13	Siva Reddy Challa	*Morinda Citrifolia* (Noni) Fruit Protects the Exocrine Pancreatic Dysfunction Against L-Arginine Induced Acute Pancreatitis in Rats	Pharmacognosy Magazine	Web of Science Master Journal List - Search (clarivate.com)	https://10.4103/pm.pm_661_18	1
14	K Durga Devi	Design and Evaluation of Macrolide Antibiotic Ocular Films	Pakistan Journal of Pharmaceutical Research	Scopus preview - Scopus - Pakistan Journal of Pharmaceutical Sciences	DOI:10.22200/pjpr.201918-15	1
15	Siva Reddy Challa	Protective Effect of Fragarria Ananassa and Vacciniu m Corymbosum Fruit Extracts Against L-Arginine Induced Acute Pancreatitis in Rats	Indian Journal Of Animal Research	Scopus Web of science	10.18805/ijar.B-3737	1

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16	Siva Reddy Challa	Assessment of Success Rate of Directly Observed Treatment Short Course (DOTS) in Tuberculosis Patients of South India	Journal of Young Pharmacists	Web of science	https://mjl.clarivate.com/journal-profile	1

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Research Article

DEVELOPMENT OF ZOLMITRIPTAN MOUTH DISSOLVING FILMS: FORMULATION VARIABLES, MECHANICAL PROPERTIES, AND *IN VITRO* DRUG RELEASE STUDIES

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ABSTRACT

Objective: The objective of the present investigation is to prepare zolmitriptan (ZOL) mouth dissolving films (MDFs) and to investigate the influence of formulation variables on physicomechanical, chemical, and drug release properties of the prepared MDFs.

Methods: The MDFs were prepared by solvent casting technique using wet film applicator. The impact of hydroxypropyl methylcellulose of different viscosity grades (hydroxy propyl methyl cellulose [HPMC] E3, E5, and E15), plasticizers (glycerol and polyethylene glycol [PEG]-400), and solubilizing agents (polyvinyl pyrrolidone [PVP K30] and sodium lauryl sulfate [SLS]) on physicomechanical, chemical, and drug release properties were evaluated. The MDFs were also characterized by Fourier-transform infrared spectroscopy, differential scanning calorimetry, and X-ray diffractometry studies.

Results: The MDFs prepared were transparent and smooth and showed no recrystallization. The tensile strength of the MDFs increased significantly with an increase in polymer viscosities, and about a 2.63-fold increase in tensile strength was observed for HPMC E15 MDFs compared to E3, whereas an increase in film thickness resulted in brittle MDFs with low tensile strength. Similar results were observed with percent elongation and folding endurance of the MDFs. *In vitro,* drug release studies indicate that higher film thickness and polymer viscosities delayed the MDF disintegration and, in turn, the ZOL release. Addition of PVP K30 and SLS to HPMC E3 formulations resulted in 1.66- and 1.53-fold increase in ZOL release rates.

Conclusion: Overall, F7 formulation showed quicker disintegration (within 11 s) and ZOL release rates (within 180 s) along with good physicomechanical properties. These results indicated that the disintegration and drug release of ZOL can be enhanced to a greater extent by optimizing formulation variables in MDFs.

Keywords: Formulation variables, Mouth dissolving films, Tensile strength, Wet film applicator, Zolmitriptan.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i4.32176

INTRODUCTION

The design of age-specific dosage forms stays to be a challenging task due to the wide range of pharmaceutical and clinical lookouts that must be considered in the design of dosage forms [1]. Palatability and ease of swallowing are imperative factors that are to be considered during the design of dosage forms, especially to pediatrics, who have distinct inclinations and swallowing capabilities [2].

Conventional oral drug delivery systems such as tablets and capsules may not fulfill the necessities of pediatric and geriatric patients due to their differential abilities in swallowing the dosage forms [3,4]. In this context, the novel mucosal delivery systems have gained popularity in which the mouth dissolving films (MDFs) are the new and novel drug delivery systems for the peroral delivery of drugs to overcome patient impediments [5], and on contact with saliva, it dissolves within a few seconds without the need of water making them particularly suitable for pediatric and geriatric patients [6].

Zolmitriptan (ZOL) is a serotonin agonist used for the treatment of migraine [7]. ZOL undergoes hepatic first-pass metabolism, and its absolute bioavailability is 40–50% of the administered dose with a half-life of 2.5–3 h [8]. At present, ZOL is marketed as oral disintegrating (ZOMIG-ZMT®) and immediate release tablets (ZOMIG®). Formulation of ZOL as MDFs may address the issues of low bioavailability along with providing the quicker onset of actions. Hence, keeping in perspective of the patient compliance and need of the better therapeutic efficacy when compared to the existing marketed formulations, in the present investigation, an attempt was made to deliver the ZOL as MDFs. Moreover, no work was published so far detailing the influence of formulation variables such as film thickness, plasticizers, and polymer viscosities on physicomechanical properties such as tensile strength, the percent elongation of ZOL MDFs along with thorough evaluation on drug loading effect on crystallization, and characterization using photographic, differential scanning calorimetry (DSC) and X-ray diffractometry (X-RD) studies. Hence, the present investigation was aimed at the formulation and evaluation of ZOL MDFs for physicomechanical, chemical, and drug release properties.

MATERIALS AND METHODS

Materials

ZOL was obtained from Mylan Laboratories, Hyderabad. HMPC E3, E5, and E15 were obtained from Colorcon Asia Ltd., India. Methanol, polyvinyl pyrrolidone (PVP K30), and sodium lauryl sulfate (SLS) were purchased from Loba Chemie, Mumbai. Aspartame and pineapple flavor were obtained from Darwin Laboratories, Vijayawada. All the ingredients of analytical grade were used.

Methods

Preparation of artificial saliva

Accurately weighed quantities of sodium chloride – 0.844 g, potassium chloride – 1.2 g, calcium chloride dihydrate – 0.193 g, magnesium chloride hexahydrate – 0.111 g, and potassium phosphate dibasic – 0.342 g were added one by one to 500 mL of distilled water, and then, the volume was made up to 1000 mL using the distilled water. The pH was adjusted with 0.1N HCl to 5.7 [9].

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Original Article

FORMULATION AND EVALUATION OF RAMIPRIL MOUTH DISSOLVING FILMS

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ABSTRACT

Objective: The present investigation was aimed at preparation and evaluation of mouth dissolving films (MDFs) of Ramipril to enhance patient convenience, compliance and to improve bioavailability.

Methods: MDFs with 0.5% w/w Ramipril were prepared by a solvent casting method using a wet film applicator. The effects of film formers, wetting/solubilizing, saliva stimulating agents and film modifiers on the physicomechanical and *in vitro* Ramipril release from MDFs were evaluated.

Results: The MDFs prepared were transparent, smooth and showed no re-crystallization upon storage. MDFs casted with hydroxypropyl methylcellulose (HPMC) E3 as film former and polyethylene glycol (PEG-400) as plasticizer showed superior Ramipril release rates and good physicomechanical properties when compared to MDFs with E5 and E15 as film formers. HPMC E3 MDFs with polyvinyl pyrrolidone K30 (PVP K30) and sodium lauryl sulphate (SLS) gave superior drug release properties than MDFs without PVP K30 and SLS. The HPMC E3 MDFs with citric acid (CA) as saliva stimulating and xylitol as soothing agent gave significantly superior *in vitro* drug release than the MDFs without CA and xylitol. Release kinetics data reveals diffusion as a drug release mechanism.

Conclusion: From the obtained results, it can be concluded that the administration of Ramipril as MDF may provide a quick onset of action with enhanced oral bioavailability and therapeutic efficacy.

Keywords: Hydroxy propyl methyl cellulose, Mouth dissolving films, Ramipril, Wet film applicator

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INTRODUCTION

Hypertension is a chronic medical condition involving the elevated blood pressure levels. The delayed treatment of hypertension can lead to several other fatal disorders like congestive heart failure, kidney failure, stroke, etc. Moreover, the hypertension can occur in sudden, severe and acute attacks requiring immediate treatment [1]. Most of the anti-hypertensives are available in the oral or parenteral dosage forms, which have certain limitations such as swallowing and chocking difficulties, delayed onset of action, first pass metabolism, the requirement of skilled personnel and pain during delivery. These limitations and a need for the quicker onset of action with better patient acceptability has paved the way for the development of mouth dissolving films (MDFs) as an alternative to other dosage forms [2]. The MDFs are a very thin polymeric strip, which get hydrated instantly by saliva when placed on a patients tongue and then disintegrates and/or dissolves to release the medication within the pre-oral cavity [3]. The oral cavity composed of striated squamous epithelia with very thin membranes and fine capillary network provides 4-4000 times greater absorption than other parts of skin [4]. The drug is directly absorbed into the systemic circulation which by-passes the first pass metabolism, improving the bioavailability of the drug [5].

Ramipril is a new generation anti-hypertensive drug and is an angiotensin-converting enzyme (ACE) inhibitor. Ramipril is a prodrug/precursor which is converted into active metabolite 'Ramiprilat' in liver by carboxylesterase. Ramipril inhibits the actions of ACE lowering the production of angiotensin II [6]. This results in relaxation of arteriole smooth muscle leading to a decrease in total peripheral resistance, reducing blood pressure. Ramipril undergoes first-pass metabolism and has an oral bioavailability of about 28-30% [7]. Presently, Ramipril is marketed in the form of oral disintegrating tablets (ALTACE®) and immediate release tablets (CARDACE®).

Few reports were published on formulation and evaluation of ramipril oral disintegrating, immediate release tablets, buccal patches and films. In most of the works reported so far, MDFs were prepared in petri plates, moulds etc. and the films were dried at 40-45 °C overnight and this procedure may not result in uniformity of thickness and drug content and thereby, vary the drug release rates [7-12]. Moreover, no works on the influence of formulation variables like film thickness, polymer viscosities, surfactants and saliva stimulating agents were reported. Also, the reported works were not evaluated thoroughly for the drug loading effect on the re-crystallization and characterization using photographic, Fourier-transform infrared spectroscopy studies (FTIR), etc. By considering all the above facts, the present investigation was aimed to prepare MDFs using wet film applicator, an industrially scalable technique and evaluate them systematically.

MATERIALS AND METHODS

Materials

Ramipril was obtained from Mylan Laboratories, Hyderabad. Hydroxypropyl methyl cellulose (HPMC E3, E5 and E15) samples were obtained from Colorcon Asia Ltd., India. Ethanol, polyvinyl pyrrolidone (PVP) K30, sodium lauryl sulphate (SLS) and citric acid (CA) were purchased from Loba Chemie, Mumbai. Pineapple flavour was obtained from Darwin laboratories, Vijayawada. Xylitol was obtained from Rouquette Laboratories, France. All the ingredients of analytical grade were used.

Methods

Preparation of artificial saliva

Artificial saliva was prepared by dissolving 0.844 g of sodium chloride, 1.2 g of potassium chloride, 0.193 g of calcium chloride dehydrate, 0.111 g of magnesium chloride hexahydrate and 0.342 g of potassium phosphate dibasic one by one in 500 ml of distilled water and then the final volume was made up to 1000 ml using the distilled water. The pH was adjusted with 0.1N HCl to 5.7 [13].

Preparation of ramipril MDFs

Ramipril MDFs were prepared as per the formula is given in table 1 by using the solvent casting method to a batch size of 5 g. Ramipril was dissolved in a mixture of solvents (water and ethanol) in a

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Protective effect of *Curcuma amada* acetone extract against high-fat and high-sugar diet-induced obesity and memory impairment.

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Abstract

Objectives: *Curcuma amada* Roxb. (Mango ginger) was evaluated for anti-obesity, anti-amnesic and neuroprotection using high-fat and high-sugar diet (HFHS)-induced obesity and cognitive impairment in rats. **Methods:** Animals were exposed to HFHS diet to evaluate lipid parameters and subjected to Y maze test and Pole climbing test to evaluate the memory. In addition, oxidative stress parameters, acetyl cholinesterase activity (AChE), neurochemicals and histopathology were assessed in the brain. **Results:** HFHS diet led to increased body weight and lipid parameters (total cholesterol, low-density lipoprotein [LDL], and very low-density lipoprotein [VLDL], triglycerides [TG]) but not high-density lipoprotein (HDL). Elevated serum glutamate oxalate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT), oxidative biomarker, decreased enzymatic and non-enzymatic antioxidants, Acetylcholinesterase (AChE) activity and reduced percentage of spontaneous alternation behaviour (% SAB in Y-maze test) as well as reduced serotonin and dopamine levels and neurodegeneration were observed in HFHS diet-fed rats. *Curcuma amada* (CAAE1, 100 mg/kg and CAAE2, 300 mg/kg) treatment to HFHS diet-fed rats (21 days after HFHS diet feeding alone) showed dose-dependent activity and ameliorated the HFHS diet-induced alterations in lipid parameters related to obesity, hepatological parameters, memory, oxidative stress, neurochemicals and neurodegeneration. Furthermore, 300 mg/kg of *C. amada* (CAAE2) augmented the memory by inhibiting acetylcholinesterase (AChE) activity; it also ameliorated the effect of antioxidants such as glutathione, superoxide dismutase (SOD), and total thiol and mitigated the effect of malondialdehyde (MDA). CAAE2 also controlled the level of dopamine and serotonin and reduced the neurodegeneration in the hippocampus CA1 region. **Discussion:** The results of the present study indicated that treatment with *C. amada* 300 mg/kg (CAAE2) attenuated the HFHS diet-induced obesity, memory loss, oxidative stress, and neurodegeneration. These study results indicated that the administration of *C. amada* offers a potential treatment option for obesity and memory loss, and it requires further preclinical and clinical evaluations.

KEYWORDS: Obesity; Western diet; cognitive impairment; neurodegeneration; oxidative stress

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Effect of chrysin on the formation of *N*-acetyl-*p*-benzoquinoneimine, a toxic metabolite of paracetamol in rats and isolated rat hepatocytes

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Keywords:
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ABSTRACT

Paracetamol (N-acetyl-para amino phenol) is the most commonly used analgesic and antipyretic around the world. Its causes hepatotoxicity and nephrotoxicity at overdose or even at therapeutic doses. It is primarily metabolized by glucuronidation and sulfate conjugation. It is also metabolized by cytochrome-P450 system (CYP2E1, CYP1A2 and CYP 3A4), leading to the formation of *N*-acetyl-*p*-benzoquinoneimine (NAPQI). The present study was planned to investigate the influence of chrysin (known CYP2E1 and CYP3A4 inhibitor) on the bioactivation of paracetamol to NAPQI using rat liver microsomes *in vitro* and rats *in vivo*. Paracetamol (30 mg/kg) was administered orally without or with silymarin (100 mg/kg), a known CYP2E1 inhibitor and chrysin (100 and 200 mg/kg) to rats for 15 consecutive days. The area under the plasma concentration–time curve ($AUC_{0-\infty}$) and the peak plasma concentration (C_{max}) of paracetamol were dose-dependently increased with chrysin (100 and 200 mg/kg) compared to paracetamol control group. On the other hand, the $AUC_{0-\infty}$ and C_{max} of NAPQI were decreased significantly with chrysin (100 and 200 mg/kg). The elevated liver and kidney function markers were significantly reduced by chrysin and silymarin compared to paracetamol control group ($P < 0.01$). Histopathological studies of liver and kidney also well correlated with liver and kidney function tests. Chrysin also reduced the formation of NAPQI in the incubation samples of rat hepatocytes. The present study (both *in vivo* and *in vitro*) results revealed that chrysin might be inhibited the CYP2E1, CYP1A2 and CYP3A4-mediated metabolism of paracetamol; thereby decreased the formation of NAPQI and protected the liver and kidney.

1. Introduction

N-acetyl-*p*-benzoquinoneimine (NAPQI) is a toxic metabolite of paracetamol formed primarily via cytochrome P-450 2E1 (CYP2E1) and CYP3A4 metabolic pathway when administered at therapeutic doses or overdose [1,2]. Metabolic activation of paracetamol to NAPQI by cytochrome P450 enzymes is the critical initiating event of hepatic toxicity (as shown in Fig. 1). Excess NAPQI depletes glutathione (GSH) and subsequently results in covalent binding of NAPQI with cellular proteins, which triggers initiation of the injury process with mitochondrial oxidative stress, ultimately leading to apoptosis and hepatocellular necrosis [3–5]. *N*-Acetylcysteine (NAC) is currently the drug of choice for the management of paracetamol overdose. NAC, a precursor of GSH, diminishes paracetamol toxicity by increasing GSH levels and acts as an antioxidant to antagonize NAPQI-induced oxidative stress [6]. However, in order for NAC to be effective, this antidote should be administered relatively early (i.e., within 8 h) after APAP overdose [7,8].

Chrysin (5, 7-dihydroxyflavone) is a naturally occurring flavonoid and has been used as traditional medicine from ancient. It exhibits several important and diverse pharmacological activities, including antioxidant [9,10], anticancer, hepatoprotective [11], cardioprotective [12], renoprotective [13], neuroprotective [14], respiroprotective [15] and nephroprotective [16]. Several studies reported that chrysin has anti-inflammatory effect by inhibiting several cytokines, nitric oxide, prostaglandin E and COX-2 [17]. Flavonoids have been shown to be cytochrome P-450 (CYP) and drug transporter inhibitors However significant or even life-threatening pharmacokinetic interactions of flavonoids or flavonoid containing food/herbal products with conventional drugs have been observed in animal and clinical studies [18,19]. For example, *in vitro* studies have reported that flavonoids are P

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ABSTRACT

Paracetamol (N-acetyl-para amino phenol) is the most commonly used analgesic and antipyretic around the world. Its causes hepatotoxicity and nephrotoxicity at overdose or even at therapeutic doses. It is primarily metabolized by glucuronidation and sulfate conjugation. It is also metabolized by cytochrome-P450 system (CYP2E1, CYP1A2 and CYP 3A4), leading to the formation of *N*-acetyl-*p*-benzoquinoneimine (NAPQI). The present study was planned to investigate the influence of chrysin (known CYP2E1 and CYP3A4 inhibitor) on the bioactivation of paracetamol to NAPQI using rat liver microsomes *in vitro* and rats *in vivo*. Paracetamol (80 mg/kg) was administered orally without or with silymarin (100 mg/kg), a known CYP2E1 inhibitor and chrysin (100 and 200 mg/kg) to rats for 15 consecutive days. The area under the plasma concentration–time curve ($AUC_{0-\infty}$) and the peak plasma concentration (C_{max}) of paracetamol were dose-dependently increased with chrysin (100 and 200 mg/kg) compared to paracetamol control group. On the other hand, the $AUC_{0-\infty}$ and C_{max} of NAPQI were decreased significantly with chrysin (100 and 200 mg/kg). The elevated liver and kidney function markers were significantly reduced by chrysin and silymarin compared to paracetamol control group ($P < 0.01$). Histopathological studies of liver and kidney also well correlated with liver and kidney function tests. Chrysin also reduced the formation of NAPQI in the incubation samples of rat hepatocytes. The present study (both *in vivo* and *in vitro*) results revealed that chrysin might be inhibited the CYP2E1, CYP1A2 and CYP3A4-mediated metabolism of paracetamol; thereby decreased the formation of NAPQI and protected the liver and kidney.

1. Introduction

N-acetyl-*p*-benzoquinoneimine (NAPQI) is a toxic metabolite of paracetamol formed primarily via cytochrome P-450 2E1 (CYP2E1) and CYP3A4 metabolic pathway when administered at therapeutic doses or overdose [1,2]. Metabolic activation of paracetamol to NAPQI by cytochrome P450 enzymes is the critical initiating event of hepatic toxicity (as shown in Fig. 1). Excess NAPQI depletes glutathione (GSH) and subsequently results in covalent binding of NAPQI with cellular proteins, which triggers initiation of the injury process with mitochondrial oxidative stress, ultimately leading to apoptosis and hepatocellular necrosis [3–5]. *N*-Acetylcysteine (NAC) is currently the drug of choice for the management of paracetamol overdose. NAC, a precursor of GSH, diminishes paracetamol toxicity by increasing GSH levels and acts as an antioxidant to antagonize NAPQI-induced oxidative stress [6]. However, in order for NAC to be effective, this antidote should be administered relatively early (i.e., within 8 h) after APAP overdose [7,8].

Chrysin (5, 7-dihydroxyflavone) is a naturally occurring flavonoid and has been used as traditional medicine from ancient. It exhibits several important and diverse pharmacological activities, including antioxidant [9,10], anticancer, hepatoprotective [11], cardioprotective [12], renoprotective [13], neuroprotective [14], respiroprotective [15] and nephroprotective [16]. Several studies reported that chrysin has anti-inflammatory effect by inhibiting several cytokines, nitric oxide, prostaglandin E and COX-2 [17]. Flavonoids have been shown to be cytochrome P-450 (CYP) and drug transporter inhibitors However significant or even life-threatening pharmacokinetic interactions o flavonoids or flavonoid containing food/herbal products with conven tional drugs have been observed in animal and clinical studies [18,19] For example, *in vitro* studies have reported that flavonoids are P

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A comprehensive review on hepatoprotective and nephroprotective activities of chrysin against various drugs and toxic agents

Ravindra Babu Pingili[a,b,*], A. Krishnama ijari Pawar[c], Siva Reddy Challa[b], Tanvija Kodali[d], Sirisha Koppula[d], Vyshnavi Toleti[d]

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ABSTRACT

Chrysin belongs to the flavonoids and has been used as traditional medicine from ancient and has been reported to exhibit a wide range of pharmacological properties. The biochemical and molecular mechanisms involved in the hepato- and nephroprotective activities of chrysin were discussed in this review. Chrysin exhibited hepatoprotective activity against 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, carbon tetrachloride, cisplatin, D-galactosamine, doxorubicin, ethanol, lipopolysaccharide/D-galactosamine, methotrexate, ammonium chloride, paracetamol, diethylnitrosamine, streptozotocin, *tert*-butyl hydroperoxide, thioacetamide, 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP), ischemia/reperfusion-induced hepatotoxicity and nephroprotective activity against cisplatin, doxorubicin, paracetamol, gentamicin, streptazotocin, *N*-nitrosodiethyl amine, 5-fluorouracil, adenine, carbon tetrachloride, copper, 2,3,7,8-tetrachlorodibenzo- p-dioxin, colistin, No-nitro-L-arginine-methylester and ethanol in various animal models due to its antioxidant, anti-apoptotic activities. In this review, we provide an overview of the possible mechanisms by which chrysin reduced the hepatotoxicity and nephrotoxicity of different toxicants. This will help the toxicologists, pharmacologists and chemists to develop new safer pharmaceutical products with chrysin and other toxicants.

1. Introduction

Liver is the largest organ, accounting for approximately 2%–3% of average body weight. The liver has 2 lobes and located in the right upper quadrant of the abdominal cavity beneath the right hemidiaphragm, it is protected by the ribcage and maintains its position through peritoneal reflections, referred to as ligamentous attachments. Although not true ligaments, these attachments are avascular and are in continuity with the Glisson capsule or the equivalent of the visceral peritoneum of the liver [1]. Liver plays a central role in metabolism and distribution of nutrients and detoxification of toxic metabolites and xenobiotics. The liver is a metabolically active organ that utilizes carbohydrates for synthesis of cholesterol and fatty acids, stores glucose as glycogen and free fatty acids as triglycerides (TG). The liver plays a critical role in maintaining blood glucose levels during fasting by synthesis of glucose from amino acids (gluconeogenesis) and releasing glucose from glycogen (glycogenolysis). The liver absorbs fat (TG) and cholesterol from the diet and synthesizes fatty acids and cholesterol from acetyl-CoA derived from glucose. It catabolizes cholesterol to bile acids, which facilitate biliary secretion of cholesterol and intestinal absorption of dietary fats and cholesterol. It also obtains free fatty acids from the adipose tissues when glucagon increases to activate hormone-activated lipase to mobilize TG. The liver assembles TG to very low-density lipoprotein (VLDL) for excretion into blood circulation. VLDL transports TG to adipose tissues for storage and to muscle and other tissues for energy metabolism. (see Tables 1 and 2)

It is the major organ capable of converting excess fatty acids to ketone bodies, which provide energy to the brain and muscle during starvation. Therefore, the liver plays a critical role in maintaining whole body lipid, glucose, and energy metabolism. It is also the major organ for detoxification of drugs and xenobiotics and the principal organ for amino acid metabolism. It uptakes alanine and glutamine from muscles, kidney, and other tissues, and catabolizes amino acid nitrogen to urea for disposal in the urine. The liver is the major organ

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A cross-sectional observational study on drug utilisation pattern, prevalence and risk factors for the development of diabetic nephropathy among type 2 diabetic patients in a south indian tertiary care hospital

Madhavi Mannam[1], Lavanya Nalluri[1], Dhanalakshmi Pinnika[1], Mounika Pothuraju[1], Ravindrababu Pingili[2], Anjani Kumar C[3], Jaidev Sudagani[4], Naveen Babu Kilaru*[5]

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ABSTRACT

Diabetic nephropathy is the leading cause of the end-stage renal disease (ESRD) worldwide, and it is estimated that ~ 20% of type 2 diabetic patients reach ESRD during their lifetime. The objective of the present study was to assess the drug utilization pattern, risk factors, and prevalence of diabetic nephropathy in patients with type 2 diabetes mellitus in a south Indian tertiary care hospital. A cross-sectional observational study was conducted on 613 subjects (254 with and 359 without diabetic nephropathy). Prevalence of diabetic nephropathy was measured, and risk factors for the development of diabetic nephropathy were determined by calculating odds ratios using graphpad prism statistical software, and drug utilization pattern was assessed. Metformin (47.05%), a combination of Glimepiride and Metformin (30.71%), a combination of insulin isophane and insulin regular (29.41%), teneligliptin (10.45%), insulin regular (9.80%) were the anti-diabetic medications mostly given to the T2DM patients with nephropathy. The present study revealed that the risk factors for the development of diabetic nephropathy were multiple.

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INTRODUCTION

Diabetic nephropathy is one of the most common microvascular complications of type 2 diabetes mellitus (T2DM) and the leading cause of end-stage renal disease worldwide (Lopes, 2009; Ohga *et al.*, 2007). Diabetic kidney disease (DKD) is a thoughtful complication that takes place in 20% to 40% of all diabetics (Gheith *et al.*, 2016; Chen, 2014). The prevalence of diabetes around the world has reached epidemic proportions. While diabetes is already estimated to affect more than 8% of the global population (nearly more than 350 million people), this is predictable to grow to over 550

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Assessment of Drug Utilization Pattern, Prevalence and Risk Factors for the Development of Diabetic Retinopathy among Type 2 Diabetic Patients in A South Indian Tertiary Care Hospital: A cross-sectional observational study

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ABSTRACT

Diabetic retinopathy (DR) is a leading cause of visual impairment and blindness in the working-age population across the globe. The objective of the present study was to assess the drug utilization pattern, risk factors and prevalence of diabetic retinopathy in patients with type 2 diabetes mellitus in a south Indian tertiary care hospital. A cross-sectional observational study was conducted on 745 subjects (386 with diabetic retinopathy and 359 without diabetic retinopathy). Prevalence of diabetic retinopathy was measured and risk factors for the development of diabetic retinopathy were determined by calculating odds ratios using graph-pad prism statistical software and drug utilization pattern was assessed. Retinopathy was significantly higher in the subjects who are married, uneducated, housewives, urban residents, no income group and risk factors were comorbidities (other diseases, hypertension, endocrine diseases, history of cardiovascular diseases, HbA1c, high serum creatinine, duration of diabetes (5-10 years and >10 years, physical inactivity, junk foods (weekly once and weekly twice), soft drinks occasionally and tea/ coffee (daily twice). Metformin (38.21%), combination of Insulin Isophane and Insulin Regular (16.75%), Insulin Regular (15.18%), combination of Glimepiride and Metformin (11.51%), Glimepiride (7.85%), combination of Metformin and Vildagliptin (7.85%) were most commonly prescribed antidiabetic drugs to the T2DM patients with retinopathy.

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INTRODUCTION

With 387 million people diagnosed with diabetes mellitus worldwide and a prevalence of 8.2% as per the Diabetes atlas 2014, diabetes mellitus has become a global burden (Fernandes *et al.*, 2016; Guariguata *et al.*, 2014). Diabetic retinopathy (DR) is a leading cause of visual impairment and blindness in the working-age population across the globe (Cheung *et al.*, 2010; Klein, 2007). In 2010, of an estimated 285million people worldwide with

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Assessment of drug utilization pattern and risk factors for the development of diabetic neuropathy among type 2 diabetic patients in a south Indian hospital: A cross-sectional observational study

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is a well-known microvascular complication of type 2 diabetes mellitus (T2DM). DPN is defined as peripheral nerve dysfunction in diabetics after exclusion of other causes. To assess the prevalence of peripheral neuropathy in T2DM and the associated risk factors among in outpatients department in a south Indian hospital. A cross-sectional observational study was conducted on 868 subjects (509 with DPN and 359 without DPN). Prevalence of diabetic peripheral neuropathy was measured and risk factors for the development of diabetic peripheral neuropathy were determined by calculating odds ratios and drug utilization pattern was assessed. The prevalence of DPN in T2DM was significantly higher in the subjects who are married, uneducated, housewives, and urban residents. Many associated risk factors could affect T2DM leading to DPN such as hypertension, other diseases, endocrine diseases, history of cardiovascular diseases (CVD), >9 HbA1c, low high-density lipoproteins (HDL), high serum creatinine, long duration of diabetes, physical inactivity, and habit of taking junk foods (weekly once and weekly twice, soft drinks occasionally). The present study revealed that risk factors for the development of DPN were hypertension, endocrine diseases, history of CVD, poor glycemic control (>9 HbA1c), low HDL, high serum creatinine, long duration of diabetes, physical inactivity, habit of taking junk foods and soft drinks. Early detection of the identification of DPN in T2DM is needed in order to slow progression and complications. Metformin (40.47%), combination of glimepiride and metformin (29.93%), combination of human insulin and insulin isophane (22.7%) were mostly given to the T2DM patients with neuropathy.

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Key words:
Diabetic neuropathy, prevalence, hyperglycemia, odds ratio.

ABSTRACT

Diabetic peripheral neuropathy (DPN) is a well-known microvascular complication of type 2 diabetes mellitus (T2DM). DPN is defined as peripheral nerve dysfunction in diabetics after exclusion of other causes. To assess the prevalence of peripheral neuropathy in T2DM and the associated risk factors among in outpatients department in a south Indian hospital. A cross-sectional observational study was conducted on 868 subjects (509 with DPN and 359 without DPN). Prevalence of diabetic peripheral neuropathy was measured and risk factors for the development of diabetic peripheral neuropathy were determined by calculating odds ratios and drug utilization pattern was assessed. The prevalence of DPN in T2DM was significantly higher in the subjects who are married, uneducated, housewives, and urban residents. Many associated risk factors could affect T2DM leading to DPN such as hypertension, other diseases, endocrine diseases, history of cardiovascular diseases (CVD), >9 HbA1c, low high-density lipoproteins (HDL), high serum creatinine, long duration of diabetes, physical inactivity, and habit of taking junk foods (weekly once and weekly twice, soft drinks occasionally). The present study revealed that risk factors for the development of DPN were hypertension, endocrine diseases, history of CVD, poor glycemic control (>9 HbA1c), low HDL, high serum creatinine, long duration of diabetes, physical inactivity, habit of taking junk foods and soft drinks. Early detection of the identification of DPN in T2DM is needed in order to slow progression and complications. Metformin (40.47%), combination of glimepiride and metformin (29.93%), combination of human insulin and insulin isophane (22.7%) were mostly given to the T2DM patients with neuropathy.

INTRODUCTION

With 387 million people diagnosed with diabetes mellitus worldwide and a prevalence of 8.2% as per the Diabetes Atlas 2014 (Joaoda *et al.*, 2016). Diabetic peripheral neuropathy (DPN) is a well-known microvascular complication of type 2 diabetes mellitus (T2DM) and is defined as peripheral nerve dysfunction in diabetics (Boulton *et al.*, 1998; Candrilli *et al.*, 2007; Sumner *et al.*, 2003; William and Laurence, 2005). Some of the risk factors of DPN include age > 60 years, females, obesity, and hypertension (Bruce *et al.*, 2008). Regular consumption of even a moderate amount of alcohol interferes with blood glucose and increases the risk of peripheral neuropathy (Emanuele *et al.*, 1998). Similarly, smoking and long duration of diabetes mellitus are found to increase the risk of DPN. One hundred and ten million people worldwide are estimated to be likely affected by DPN (Tesfaye, 2004). The prevalence of DPN varies largely across regions from 5% to 60% (Davies *et al.*, 2006; Tesfaye and Selvarajah, 2012; Tesfaye *et al.*, 1996; Young *et al.*, 1993).

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evelopment and optimization of sustained release mucoadhesive omposite beads for colon targeting

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ABSTRACT

The present work investigates a blend of Linum Seed mucilage(LSM) and Hibiscus Leaf gum(HLG) as mucoadhesive carriers for Capecitabine(CPTB) loaded mucoadhesive composite bead formulation (CMB), in an attempt to achieve sustained release of CPTB (BCS Class I drug) in the colon region. Optimization using Box-Behnken Design(BBD) was used to study the effect of quantities of mucoadhesive carriers(LSM,HLG) and enteric polymer pectin (in curing solution) on response factors such as %drug loading (%DL) and %drug release (%DR). CMB prepared by ion-gelation technique showed uniform bead size, spherical surface morphology, maximum drug encapsulation efficiency. The optimized CMB(F18) exhibited maximum %drug loading(28.94%), favorable *in vitro* drug release of CPTB(54.43%) in 12 h, where, the release kinetics follow zero order non-Fickian diffusion mechanism. CMB's exhibited significantly higher swelling upon exposure to alkaline media than acidic media similarly *ex vivo* mucoadhesive study also revealed that major fraction of beads were washed off within 2 h in 1.2pH media whereas in 7.4pH alkaline media major portion of the beads remain adhered even after 24 h Moreover accelerated stability testing of CMB(F18) revealed shelf life of about 2.59 years. Hence the study confirms that the combination of LSM&HLG as ideal mucoadhesive carriers and can favorably target highly soluble drugs to the colon region.

1. Introduction

Natural mucilages and gums are hydrocolloids with relatively high molecular weight formed as pathological or metabolic products either intracellularly or extracellularly. In the current scenario, mucilages and gums have manifested diverse pharmaceutical applications as viscosity enhancers, disintegrating agents, binders, emulsifying agents and as release modifiers [1]. Natural mucilages and gums are also proved to have potential application for competent use as excipients replacing synthetic excipients with favoured properties like wettability, swelling, biodegradability and biocompatibility [2]. Mucoadhesive drug delivery systems are confronting release systems which have gratified role in extending the GI residence time, drug targeting and local action of dosage form [3].

Linum Seed Mucilage (LSM) is a polysaccharide extracted from Linum usitatisimum seeds and Hibiscus Leaf Gum (HLG) is a polysaccharide extracted from Hibiscus rosa sinensis leaves. Both the polysaccharides are established mucoadhesive agents employed in formulating mucoadhesive gels, mucoadhesive tablets and mucoadhesive buccal formulations [4,5]. Literature revealed vacancy of ionotropically cross linked mucoadhesive beads containing combination of LSM and HLG meant for controlled and targeted drug release.

Capecitabine (CPTB) is an orally administered BCS (Biopharmaceutical Classification System) Class I anti-cancer agent used chemotherapeutically in treating various cancer types including breast cancer and colorectal cancer. Chemically CPTB is a prodrug which converts enzymatically into 5-FluoroUracil (5FU) in tumor tissues. 5 FU acts by inhibiting DNA synthesis in tumor and thus prevent cancer cell growth. CPTB has a short elimination half-life of 0.5 to 1 h and is available as immediate release dosage form (Xeloda®) with twice daily dosing. The aforementioned dosage regimen leaves a dosing gap in between and creates extraneous plasma drug concentration which causes severe side effects which is clinically undesirable. Hence the need to design a Sustained release (SR) dosage form which maintains extended drug levels in the body is of major concern for the current work. Earlier several attempts like infusion [6], gastro retentive tablet [7], extended release tablet [8], micro beads [9] to achieve controlled release.

Colon targeting is a pragmatic approach for treating colon related ailments like ulcerative colitis, inflammatory bowel disease, colorectal

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BMC Chemistry

RESEARCH ARTICLE Open Access

Construction of a novel quinoxaline as a new class of Nrf2 activator

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Abstract

Background: The transcription factor Nuclear factor erythroid-2-related factor 2 (NRF2) and its principal repressive regulator, Kelch-like ECH-associated protein 1 (KEAP1), are perilous in the regulation of inflammation, as well as maintenance of homeostasis. Thus, NRF2 activation is involved in cytoprotection against many inflammatory disorders. *N*′-Nicotinoylquinoxaline-2-carbohdyrazide (NQC) was structurally designed by the combination of important pharmacophoric features of bioactive compounds reported in the literature.

Methods: NQC was synthesised and characterised using spectroscopic techniques. The compound was tested for its anti-inflammatory effect using Lipopolysaccharide from *Escherichia coli* (LPS*Ec*) induced inflammation in mouse macrophages (RAW 264.7 cells). The effect of NQC on inflammatory cytokines was measured using enzyme-linked immune sorbent assay (ELISA). The Nrf2 activity of the compound NQC was determined using 'Keap1:Nrf2 Inhibitor Screening Assay Kit'. To obtain the insights on NQC's activity on Nrf2, molecular docking studies were performed using Schrödinger suite. The metabolic stability of NQC was determined using mouse, rat and human microsomes.

Results: NQC was found to be non-toxic at the dose of 50 µM on RAW 264.7 cells. NQC showed potent anti-inflammatory effect in an in vitro model of LPS*Ec* stimulated murine macrophages (RAW 264.7 cells) with an IC_{50} value 26.13 ± 1.17 µM. NQC dose-dependently down-regulated the pro-inflammatory cytokines [interleukin (IL)-1β (13.27 ± 2.37 µM), IL-6 (10.13 ± 0.58 µM) and tumor necrosis factor (TNF)-α] (14.41 ± 1.83 µM); and inflammatory mediator, prostaglandin E_2 (PGE_2) with IC_{50} values, 15.23 ± 0.91 µM. Molecular docking studies confirmed the favourable binding of NQC at Kelch domain of Keap-1. It disrupts the Nrf2 interaction with kelch domain of keap 1 and its IC_{50} value was 4.21 ± 0.89 µM. The metabolic stability studies of NQC in human, rat and mouse liver microsomes revealed that it is quite stable with half-life values; 63.30 ± 1.73, 52.23 ± 0.81, 24.55 ± 1.13 min; microsomal intrinsic clearance values; 1.14 ± 0.31, 1.39 ± 0.87 and 2.96 ± 0.34 µL/min/g liver; respectively. It is observed that rat has comparable metabolic profile with human, thus, rat could be used as an in vivo model for prediction of pharmacokinetics and metabolism profiles of NQC in human.

Conclusion: NQC is a new class of NRF2 activator with potent in vitro anti-inflammatory activity and good metabolic stability.

Keywords: *N*′-nicotinoylquinoxaline-2-carbohydrazide, NRF2, KEAP1, Anti-inflammatory, Metabolic stability, Molecular docking

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Original Article

Oncology Section

Prevalence of Various Types of Cancers and an Observational Study of Various Haemoglobin Levels in Different Grade of Cancer: A South Indian Hospital Based Study

SILVYA MATHANGI[1], SIVA REDDY CHALLA[2], NAGA AKHILA BHUVANESWARI KONDRU[3], DIVYA ARANGI[4], SRI LEKHYA CHOWDARY KAMBHAM[5], GOPICHAND MAMILLAPALLI[6], MV SUBBA RAO[7]

ABSTRACT

Introduction: The status report on the global burden of cancer worldwide by the International Agency for Research on Cancer using GLOBOCAN 2018 estimated 18.1 million newer cancer cases and 9.6 million cancer deaths in 2018. Particularly, breast cancer ranks second according to incidence of cancers in women in the world. There is growing evidence that anaemia has an impact on treatment outcome, prognosis and survival of cancer patients.

Aim: To assess the prevalence of different types of cancers and frequency of pre-diagnosed haemoglobin levels in cancer patients.

Materials and Methods: A cross-sectional study was carried out for two months period between September 2017 and October 2017 in a Tertiary cancer care hospital, A South Indian hospital based study. A total of 90 patients were recruited into the study based on inclusion criteria. The collected data was analysed by calculating the percentage frequency.

Results: Breast cancer (n=45, 50%), gastrointestinal cancers (n=14, 16%), urogenital cancers (n=14, 16%), Hodgkin's lymphoma (n=5, 6%), non-Hodgkin's lymphoma (n=1, 1%), other advanced metastatic carcinomas (n=9, 10%), sarcomas (n=2, 2%) were reported. In our study population breast cancer patients were highly prevalent. In breast cancer patients, the maximum number of patients was diagnosed with Infiltrating Ductal Carcinoma (IDC). In IDC patients, majority of patients were diagnosed in Grade II IDC.

Conclusion: Prevalence of breast cancer patients was high in our study population of cancer patients. Most of the patients diagnosed in Grade II were found to have less haemoglobin levels while it was not observed in Grade I. Our result implies that anaemia could be one of the poor prognostic factors for cancer progression.

Keywords: Anaemia, Breast, Carcinoma, Infiltrating ductal carcinoma, Sarcoma

INTRODUCTION

Globally, second leading cause of death is cancer. Patients with cancer generally have a poor prognosis in developing countries, including India, because of lack of cancer awareness, delay in diagnosis and lack of patient affordable treatment services including targeted therapy, radiation therapy and chemotherapy [1]. The status report on the global burden of cancer worldwide by the International Agency for Research on Cancer using GLOBOCAN 2018 estimated 18.1 million newer cancer cases and 9.6 million cancer deaths in 2018 [2]. Particularly, breast cancer ranks second according to incidence of cancers in women in the world [2,3]. There is growing evidence that anaemia has an impact on treatment outcome, prognosis and survival of cancer patients.

Anaemia is an important and common problem adding substantial burden to the cancer patients besides affecting physical, functional, emotional well-being, and quality of life. It has negative impact on treatment outcome, prognosis and survival [4,5]. It has been reported that between 30-90% of patients with cancer have anaemia [6]. Literature suggests that Iron deficiency (ID) plays a major role in the pathogenesis of anaemia in cancer patients and has an estimated impact on 19–63 % patients of different cancer types [5]. In a meta-analysis anaemic patients had shorter survival time than those without anaemia. The overall estimated increase in risk was 65% (54-77% in patients with different types of malignant tumours) [6]. Iron Deficiency Anaemia (IDA) is diagnosed when Haemoglobin (Hb) levels are less than 13 g/dL in men and 12 g/dL in women according to World Health Organisation (WHO) limits for haemoglobin [7]. Chronic, tumour-related anaemia is diagnosed when Haemoglobin (Hb) levels are below 12 g/dL [8].

In this study we aimed to assess the prevalence of different types of cancers, frequency of breast cancer patients with respect to site of carcinoma, stage of carcinoma and receptor positivity and the frequency of cancer patient population with respect to pre-diagnosed haemoglobin levels.

MATERIALS AND METHODS

Study Design and Participants

It was a cross-sectional study which was carried out for a two months period between September 2017 and October 2017 in a Tertiary cancer care hospital, City Cancer Centre, Vijayawada, Andhra Pradesh, India.

Ethical Consideration

The study protocol was approved by Institutional Ethics Committee of City Cancer Centre. All the participants were informed about study details and informed consent was obtained before the initiation of study. The protocol number was IEC/HCGCCC/333/ACD/05/17.

Inclusion and Exclusion Criteria

Inclusion criteria: The patients both males and females visited the hospital in two months specified period with age greater than 18-year-old. Patients laboratory data accompanied by haemoglobin levels prior to their diagnosis with cancer.

Exclusion criteria: Patients who were not willing to participate and patients with insufficient data were excluded.

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WILEY

RESEARCH ARTICLE

Quercetin reduced the formation of *N*-acetyl-*p*-benzoquinoneimine, a toxic metabolite of paracetamol in rats and isolated rat hepatocytes

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N-acetyl-*p*-benzoquinoneimine (NAPQI) is toxic metabolite of paracetamol formed primarily by cytochrome P4502E1 (CYP2E1) metabolic pathway when administered at therapeutic doses or overdose. The influence of quercetin (flavonoid) on the bioactivation of paracetamol to NAPQI was investigated using rat liver microsomes and rats in vivo. Paracetamol (80 mg/kg) was administered orally without or with silymarin (100 mg/kg), a known inhibitor of CYP2E1, CYP3A4 and quercetin (10 and 20 mg/kg) to rats for 15 consecutive days. Area under the plasma concentration–time curve ($AUC_{0-\infty}$) and the peakplasma concentration (C_{max}) of paracetamol were dose-dependently increased with quercetin (10 and 20 mg/kg) compared to paracetamol control group ($p < 0.001$). On the other hand, the $AUC_{0-\infty}$ and C_{max} of NAPQI were decreased significantly with quercetin. The same results were observed with silymarin also. The elevated liver and kidney functional enzymes/compounds were significantly reduced by quercetin and silymarin compared to paracetamol control group. The formation of NAPQI was reduced in the incubation samples in presence of quercetin in experiment using isolated rat hepatocytes. The presentstudy results revealed that quercetin might be inhibited the CYP2E1-mediated metabolism of paracetamol; thereby decreased the formation of NAPQI and protected the liver and kidney.

KEYWORDS
CYP2E1, CYP3A4, hepatocytes, paracetamol, quercetin, silymarin

1 | INTRODUCTION

Paracetamol is a widely used analgesic and antipyretic drug for therapeutic purposes. But repeated use of or an overdose of paracetamol may cause severe liver injury and failure. At therapeutic doses, paracetamol is excreted in the urine in the forms of paracetamol glucuronide and paracetamol sulfate. An overdose of paracetamol forms a toxic metabolic intermediate, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), primarily via the cytochrome P450 2E1 (CYP2E1) enzyme pathway as shown in Figure 1. But CYP1A2 and CYP3A4 are also play a minor role in the formation of NAPQI (Nelson, 1995; Pumford, Halmes, & Hinson, 1997). NAPQI requires glutathione (GSH) for detoxification by forming its GSH-adduct. Once the intracellular stores of GSH are depleted, excess NAPQI may react with cellular proteins, thus causing liver cell necrosis (Kon, Kim, Jaeschke, & Lemasters, 2004; Terneus, Kiningham, Carpenter, Sullivan, & Valentovic, 2007). Currently, *N*-acetylcysteine (NAC) is the drug of choice for the management of paracetamol overdose. NAC, a precursor of GSH, diminishes paracetamol toxicity by increasing GSH levels and acts as an antioxidant to antagonize NAPQI-induced oxidative stress (Smilkstein et al., 1991). However, in order for NAC to be effective, this antidote should be administered relatively early (i.e., within 8 hr) after paracetamol overdose (Latchoumycandane, Goh, Ong, & Boelsterli, 2007; Smilkstein, Knapp, Kulig, & Rumack, 1988). Paracetamol is also a P-glycoprotein (P-gp) substrate (Ravindra, Krishnamanjari, & Siva, 2015).

Quercetin, a plant-derived aglycone form of flavonoid glycosides, has been used as a nutritional supplement and may be beneficial

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Quercetin, a plant-derived aglycone form of flavonoid glycosides, has been used as a nutritional supplement and may be beneficial

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ORIGINAL ARTICLE

Morinda Citrifolia (Noni) Fruit Protects the Exocrine Pancreatic Dysfunction Against L-Arginine Induced Acute Pancreatitis in Rats

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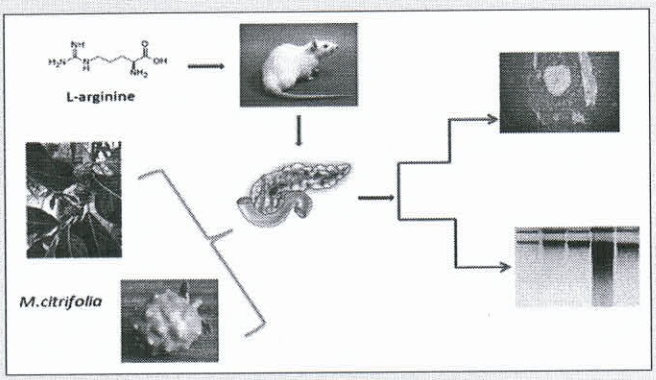
ABSTRACT

Background and Objective: *Morinda citrifolia* (MC) commonly known as Noni is being used for many ailments and is considered as wellness drink. It is traditionally used for anti-inflammatory, anti-aging, and immunostimulant properties. The present study has been initiated to investigate the protective effects of MC fruit extract (MCFE) on L-arginine-induced acute pancreatitis (AP) in rats. **Materials and Methods:** Male Sprague-Dawley rats were randomly divided into groups of control, disease control, positive control, and treatment groups. AP is induced by the administration of a single dose of L-arginine (2 × 2.5 g/kg, intraperitoneally, 1 h apart). Positive control received melatonin (10 mg/kg); treatment groups received 200 mg/kg and 400 mg/kg MCFE 6 days before administration of L-arginine. After 12 h of induction, the serum samples were analyzed for biomarker enzymes such as amylase, lipase, C-reactive protein, superoxide dismutase, glutathione, catalase, tissue nitrate, lactate dehydrogenase, and myeloperoxidase. Histopathological studies and deoxyribonucleic acid (DNA) fragmentation assay were performed from the isolated pancreatic tissue. **Results:** MCFE administration showed a dose-dependent significant ($P < 0.001$) protective effect by improving the levels of antioxidant enzymes and reducing the elevated levels of amylase and lipase. The acinar cell damage was limited in histopathological findings and an intact DNA when compared to disease control. **Conclusion:** MCFE administration showed a protective effect against AP in rats, and it may be due to the attenuation of oxidative stress. Further investigation for the exact molecular mechanism is needed.

Key words: Amylase, arginine, lipase, *Morinda citrifolia*, oxygen free radicals, pancreatitis

SUMMARY

- Noni juice demonstrated a protective effect against L-arginine induced acute pancreatitis which was in accordance with the positive control Melatonin. The protective effect is observed to be due to the presence of active constituents such as desacetylasperulosidic acid, 6-α-hydroxyadoxoside, 6-β-7-β-epoxy 8-episplendoside, americanin A which showed the antioxidant effects. The exploration of molecular level mechanism may lead to the development of essential therapeutic targets in acute pancreatitis.



Abbreviations used: AP: Acute Pancreatitis; MCFE: *Morinda citrifolia* fruit extract; DNA: Deoxyribonucleic acid; GI: Gastrointestinal; ROS: Reactive oxygen species; CRP: C-reactive protein; Kcl: Potassium chloride; UPLC: Ultrahigh-pressure liquid chromatography; LC-MS/MS: Liquid chromatography–mass spectrometry; OECD: Organization of economic cooperation and development; LD_{50}: Lethal dose 50; SOD: Superoxide dismutase; H_2O_2: Hydrogen peroxide; TCA: Trichloroacetic acid; DNPH: Di nitrophenylhydrazine; EDTA: Ethylenediaminetetraacetic acid; TBA: Thiobarbituric acid; MDA: Malondialdehyde; LDH: Lactate dehydrogenase; β-NADH: β-Nicotinamide adenine dinucleotide; SDS page: Sodium dodecyl sulfate-polyacrylamide gel electrophoresis; ANOVA: Analysis of variance; iNOS: Inducible nitric oxide

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INTRODUCTION

Acute pancreatitis (AP), a self-limiting disease is one of the most frequent diseases of pancreas and the most common cause for hospital admission among the Gastrointestinal diseases in many countries. AP is regarded as one of the leading acute diseases worldwide with increasing evidence of age-standardized rates over the past decades. Although it is self-limiting, up to 20% of the patients may encounter mild edematous to severe necrotizing form.[1] Pathogenesis involves the activation of intracellular pancreatic zymogen which triggers systemic and local inflammatory response by releasing mediators from macrophages and neutrophils, which eventually lead to multiorgan dysfunction.[2] One of the pivotal mechanisms of AP is based on the involvement of reactive oxygen species (ROS), which provoke the development of pancreatitis through

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Research Article

Design and Evaluation of Macrolide Antibiotic Ocular Films

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Abstract

Azithromycin is a semi synthetic macrolide antibiotic mainly obtained from erythromycin. Oral administration of AZT is effective to treat trachoma, topical formulation is difficult to develop because of the hydrophobicity nature. The aim of present work is to formulate in the form of ocular films to treat ocular infections. AZT ocular films are formulated by using hydrophilic polymers HPMC E15, L-HPC, PG or PEG 400, gelatin and sodium alginate in different concentrations eight formulations (F1-F8) are formulated. The prepared formulations are evaluated for its thickness, folding endurance, surface texture, surface pH, moisture absorption, moisture loss, swelling index, content uniformity, in vitro and ex vivo drug release studies. Among eight formulations (F1-F8) F1 is the best formulation, which releases 71.57 % in 6hrs and it can be used to prolong the release.

Keywords: Macrolide Antibiotic, Hydrophilic, ocular films, In-Vitro and Ex-Vivo

INTRODUCTION

Ocular inserts (OC) are sterile preparations, in which a slender, profound, drug-impregnated, solid or semisolid constancy devices positioned into cul-de-sac or conjunctiva sac ready up of polymeric vehicle containing drug (Heller, 1980). The anatomy, physiology and biochemistry of the eye render it exquisitely impervious to foreign materials (Sahane *et al.*, 2010). One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. Ocular drug delivery is one of the most fascinating and challenging tasks facing the Pharmaceutical researchers (Di Colo *et al.*, 2001).The therapeutic efficacy of an ocular drug can be greatly improved by prolonging its contact with the corneal surface (Gurtler and Gurny, 1995). Polymeric film ocular drug delivery systems/ocular inserts, which are gaining worldwide accolade, release drugs at a pre-programmed rate for a longer period by increasing the pre-corneal residence time.

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and whose size and shape are especially designed for ophthalmic application. The inserts are placed in the lower fornix and less frequently, in the upper fornix or on the cornea. Ocular inserts release drug by controlled, sustained and continuous rate.

The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment composing of polymeric support with or without drugs, the latter being incorporated as dispersion or a solution in the polymeric support. AZT is a bacteriostatic drug acts by inhibiting protein synthesis. It binds reversibly to 50S ribosomal subunits of sensitive microorganism. AZT interferes with transpeptidation and translocation thus there is inhibition of protein synthesis and thus inhibition of cell growth.

Materials and Methods

Materials

Pure drug gift sample of Azithromycinwas from *Pvs Laboratories Ltd.*, Vijayawada. All other ingredients HPMC E15, PEG 400, Gelatin, L-HPC, Starch,Sodium Alginate used were of pharmaceutical grade.

Manufacturing Procedures

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Protective effect of *Fragarria ananassa* and *Vaccinium corymbosum* fruit extracts against L-arginine induced acute pancreatitis in rats

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ABSTRACT

The study was aimed to evaluate the protective effects of alcoholic extracts of *Strawberry* and *Blueberry* fruits [AESF and AEBF] in acute pancreatitis in rats. Treatment groups received AESF and AEBF at doses of 200 and 400 mg/kg for 7 days with prior injections of L-arginine on 5th day. Biochemical parameters were estimated in serum and pancreatic tissue samples. Histopathological studies and DNA fragmentation assay were carried out in isolated pancreatic tissue. The results of the study indicated that treatment of AESF and AEBF exhibited a significant dose dependent protective effect. Upon the treatment, anti-oxidant enzymes were significantly (*$p<0.05$) increased. Biochemical results were correlated with the histopathological findings. In addition, the DNA fragmentation assay showed an intact DNA in pancreatic cells of treated groups. In conclusion, berry fruit extracts exerted a potential protective effect against L-arginine induced damage in rat pancreas, at least in part, due to its antioxidant properties.

Key words: Amylase, *Blueberry*, L-Arginine, Lipase, Oxygen free radicals, Pancreatitis, *Strawberry*.

INTRODUCTION

Acute pancreatitis (AP) is a critical self limiting gastrointestinal condition with wide clinical variation. Although 80% of the cases are mild 20% may lead to severe necrotizing pancreatitis causing high mortality rates in spite of the availability of advanced treatment modalities (Kui *et al.*, 2015). The incidence of acute pancreatitis is increasing by 13 to 45 cases per 100,000 persons (Yadav *et al.*, 2013). Many etiological factors have been derived for the occurrence of the disease of which alcohol and biliary tract abnormalities are the most common. The risk of AP ranges from 2 to 5 % among patients who are chronic alcoholics (Lankisch *et al.*, 2002). In 10% of the cases, the cause is unknown and may be secondary to microlithiasis of gall bladder. Although many pathogenic mechanisms have been derived; auto digestion, generation of oxygen free radical and lipid peroxidation is broadly accepted theory leading to rapid activation of inflammatory responses at the site of activation with the involvement of systemic organs (Abdin *et al.*, 2010). The systemic complications are implied by the activation of inflammatory cytokines like TNF α, IL-6 which are macrophage derived factors involved in the progression of the disease (Czako *et al.*, 1998). It has been suggested that trypsinogen, play a key role in the progression of severe acute pancreatitis. The balance of trypsinogen conversion to trypsin is mediated by a negative feedback loop and excessive activation of trypsinogen adds to the disturbance of the homeostasis leading to severe acute pancreatitis (Ning *et al.*, 2013). Lack of conventional therapy opens a novel approach for the use of antioxidants obtained from many resources for the development of new drugs.

Phytochemicals from plant origin are responsible for antioxidant property and are principally contributed by phenolics, anthocyanins and flavonoid compounds (Wang *et al.*, 2000). The consumption of fruits has been associated with decreased incidence of diseases. Berry fruits have been widely described for their antioxidant activity (Jaime Guerrero *et al.*, 2010). Wang *et al.*, (2000) has described notable antioxidant property of extracts of *Blueberry*, *Raspberry* and *Strawberry* against chemically generated superoxide radical species (Wang *et al.*, 2000). *Strawberry* fruit has been recommended in prevention of obesity, dermatitis, skin rejuvenation, and well documented evidence is available for its *in-vivo* and *in-vitro* antioxidant property (Wang *et al.*, 2000; Scalzo *et al.*, 2005; Tulipani *et al.*, 2009). It has been reported that fruit and leaves of *Strawberry*

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Original Article

Assessment of Success Rate of Directly Observed Treatment Short-Course (DOTS) in Tuberculosis Patients of South India

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ABSTRACT

Objective: To assess the success rate of DOTS for tuberculosis patients and the secondary objective was to identify the factors associated with unsuccessful treatment outcome. **Methods:** A retrospective study was conducted to review the medical records of patients (n = 1113) registered at the Directly Observed Treatment Short-Course (DOTS) clinic of Government Infectious Disease (Govt. ID) Hospital, Guntur, India. Multivariate logistic regression model was used to determine the factors associated with the treatment success rate. **Results:** The overall mean success rate of TB patients was found to be 82.8%. Treatment success rate (TSR) was steadily increased across the years from 73.9% in 2015 to 84.3% in 2016 and 88.9% in 2017 while the death rate was steadily decreased from 11.2% in 2015 to 6.25% in 2016 and 4.33% in 2017. Risk factors significantly associated with unsuccessful treatment outcome were found to be HIV positive ($P<0.001$), smear negative ($P<0.001$), all retreatment cases ($P<0.001$), smoking ($P=0.008$), and alcoholism ($P=0.019$). Smear positive patients had lower death rate (3.9% vs. 10.1%; $P < 0.001$) and failure rate ((2.6% vs. 8.7%; $P < 0.001$) compared to smear negative patients. Patients tested HIV positive had seen significantly unfavorable outcomes in death rate (OR= 9.17, 95% CI=5.31-15.83; $P < 0.001$) and treatment failure (OR=13.3, 95% CI= 7.31-24.17; $P < 0.001$). **Conclusion:** Implementing the DOTS strategy proved the satisfactory success rate in the South Indian hospital across three years. The unsuccessful treatment outcome was significantly associated with gender, HIV status, re-treatment, smear negative, smoking and alcoholism.

Key words: Directly observed treatment short-course, Retrospective study, Risk factors, Treatment success rate, Tuberculosis.

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INTRODUCTION

Tuberculosis (TB) has existed for millennia and remains a major global health problem. It causes ill-health in millions of people each year. In 2015, it was one of the top ten causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease. Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa.[1]

In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people and an additional 374 000 deaths among HIV-positive people. India accounted for 33% of global TB deaths among HIV-negative people. Globally, the TB mortality rate is falling at about 3% per year. TB incidence is falling at about 2% per year and 16% of TB cases die from the disease; by 2020, these figures need to improve to 4–5% per year and 10%, respectively to reach the first (2020) milestones of the End TB Strategy.[2]

In India, 29% of adults but 72% of HIV-positive adults live in four large states in the south where, even with the RNTCP, mortality is expected to fall by only 15% between 1990 and 2015.[3] There are more challenges for controlling TB worldwide by adopting the medication adherence. There was a high level of adherence to anti-TB treatment and also a high TB treatment success rate.[4]

Countries implementing DOT to ensure treatment adherence have shown impressive results with increasing treatment success and low default rates.[1,5,6] India has had an ongoing National TB Program (NTP) since 1962.[7] Large-scale implementation of the RNTCP began in late 1998.[8] Though the Indian government has made several announcements to eliminate TB by 2025, the WHO report showed that up to 27.9 lakh patients were estimated to be infected in the country in 2016. Out of the 27.9 lakh estimated patients, only 1,938,158 TB cases were notified in the public and private sector in India, which means over 8.5 lakh cases were missing the treatment options.

In order to overcome these lacunae, the Government decided to give a new thrust to TB control activities by revitalizing the NTP, with assistance from international agencies, in 1993. The Revised National Tuberculosis Control Programme (RNTCP) thus formulated, adopted the internationally recommended Directly Observed Treatment Short-course (DOTS) strategy, as the most systematic and cost-effective approach to revitalize the TB control programme in India.

Directly observed alternate day treatment (DOTS) for TB under RNTCP in India has shown to be effective in TB patients with or without HIV infection.[9,10] Furthermore, World Health Organization (WHO) has