Send Orders for Reprints to reprints@benthamscience.ae

Current Pharmaceutical Design, 2016, *22*, 1-19

REVIEW ARTICLE

Pharmacological Properties and Therapeutic Potential of Naringenin: A Citrus Flavonoid of Pharmaceutical Promise

Neha Rani[a], Saurabh Bharti[a], Bhaskar Krishnamurthy[a], Jagriti Bhatia[a], Charu Sharma[b], Mohammad Amjad Kamal[c,d], Shreesh Ojha[e]* and Dharamvir Singh Arya*[a]

[a]*Department of Pharmacology, All India Institute of Medical Sciences, New Delhi-110029, India;* [b]*Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE;* [c]*King Fahd Medical Research Center, King Abdulaziz University, P.O. Box 80216, Jeddah, Kingdom of Saudi Arabia;* [d]*Enzymoics and Novel Global Community Educational Foundation, 7 Peterlee Place, Hebersham, NSW 2770, Australia;* [e]*Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE*

ARTICLE HISTORY

Received: April 23, 2016
Accepted: May 27, 2016

DOI: 10.2174/1381612822666160530150936

Abstract: Naringenin chemically known as 5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one is a common dietary polyphenolic constituent of the citrus fruits. It has received considerable attention for pharmaceutical and nutritional development due to potent pharmacological activities and therapeutic potential. Accruing evidence from both *in vitro* and *in vivo* studies have unraveled numerous biological targets along with complex underlying mechanisms suggesting possible therapeutic applications of naringenin in various neurological, cardiovascular, gastrointestinal, rheumatological, metabolic and malignant disorders. Functionally, this ameliorative effect of naringenin is primarily attributed to its anti-inflammatory (via inhibiting recruitment of cytokines and inflammatory transcription factors) and anti-oxidant (via scavenging of free radicals, bolstering of endogenous anti-oxidant defense system and metal ion chelation) effects. The present article provides a comprehensive review of the various studies that have evaluated the therapeutic potential of naringenin and its actions at the molecular level. It also summarizes the pharmacokinetic data and issues and challenges involved in pharmaceutical development and suggest that it may be a potential agent for further exploration as well as may be useful as a dietary adjunct in treatment of various human ailments.

Shreesh Ojha

Keywords: Naringenin, animals, drug design, antioxidant, anti-inflammatory, phytochemicals, natural compounds, cancer.

1. INTRODUCTION

Extensive scientific research over the past few decades has indicated that an inverse relationship may exist between flavonoid intake by humans and disease occurrence; and that flavonoids can be considered safer than the allopathic medications. This has sparked a research interest in the identification and evaluation of various flavonoids obtained from human diet, such as naringenin.

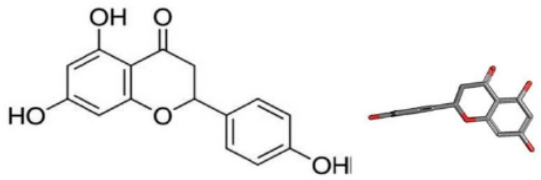
Naringenin (5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one) is a major natural flavonoid found in oranges, grapefruit and tomato skin. Naringenin is an aglycone, obtained by hydrolysis of naringenin-7-neohesperidoside (naringin) and naringenin-7-rutinoside (narirutin). It has a bitter taste and is soluble in alcohol and dimethyl sulfoxide and relatively insoluble in water [1]. The chemical structure and physicochemical properties of naringenin are represented in Fig. **1**. Owing to its anti-oxidant and anti-inflammatory properties, it has shown to exert therapeutic potential against various disorders such as neurodegenerative, cardiovascular, diabetes and malignancies.

This review focuses on pharmacokinetics and preclinical data emphasizing the multifaceted activities of naringenin and its potential therapeutic implication in human disorders.

*Address correspondence to these authors at the [e]Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE, Tel/Fax: +971 50 3125748; Fax: +971 3 7602033; E-mail: shreeshojha@uaeu.ac.ae and Department of Pharmacology, All India Institute of Medical Sciences, New Delhi-110029, India; E-mail: dsarya16@hotmail.com

Database searches using Medline/PubMed, EMBASE, Google Scholar, and Science Direct were conducted to include all the available published literature in the present review article. The search was limited to English language papers, however if the abstract was available in English, its included in present article. For literature search, the following MeSH words were used in the database search engines mentioned: naringenin AND allergies / Parkinsons's disease/Alzheimer's disease/neuronal diseases/ cardiovascular diseases/respiratory diseases/gastrointestinal diseases/cancer/cough/ dentistry/ hyperlipidemia/ hypertension/colitis/infection/ hyperglycemia / cough/ atherosclerosis/inflammation/oxidative stress/nitrosative stress/apoptosis/malignancies/tumor/carcinoma/pain/ diabetes/blood pressure/radiation/stroke/epilepsy/metabolic syndrome/arrhythmias/anxiety/antimicrobial/antifungal/antiviral/anticancer/antiparasiticidal/antimalarial/immunomodulator/infections/depression /schizophrenia/ arthritis/ musculoskeletal diseases / immune diseases/psychotic diseases/neuroprotection/nephroprotection/ cardioprotection/hepatoprotection/radioprotection, naringenin AND brain / heart / lung / kidney / skin / bone / liver / cholesterol / blood / insulin / hormones, naringenin AND anti-inflammatory / antioxidant, naringenin AND bioavailability / chromatography/ transporters / analysis / pharmacokinetics / safety / toxicity/ adverse effects / side effects / pregnancy / pharmacology/ pharmaceutics / dosage forms / pharmaceuticals / uses/ indications, naringenin AND in vitro / in vivo and articles all together on 'naringenin'. In almost all cases, the original articles were obtained and the relevant data was extracted. The further paragraphs briefly describe the pharmacological properties and therapeutic potential of naringenin in human diseases.

1381-6128/16 $58.00+.00



Chemical structure

3 D Conformer

Molecular Weight	272.25278 g/mol
Molecular Formula	$C_{15}H_{12}O_5$
XLogP3	2.4
H Bond Donor	3
H Bond Acceptor	5
Rotatable Bond	1

Physicochemical characters

Fig. (1). Chemical structure and physiocochemical properties of naringenin.

1.1. PHARMACOKINETICS OF NARINGENIN

1.1.1. Absorption

Naringenin has been absorbed through both active transport and passive diffusion. A study by Xu and group demonstrated that amount of naringenin absorbed was higher in colon (68%) followed by duodenum (47%), terminal ileum (42%) and jejunum (39%) [2]. Oral administration of naringenin (135mg/kg) to healthy volunteers resulted in C_{max} of 2009.51ng/ml, T_{max} of 3.67hours, $AUC_{0-\theta}$ of 9424.52ngh/ml, elimination half-life of 2.31hour and oral bioavailability of 5.81% [3].

1.1.2. Distribution

Naringenin is circulated as glucuronide and sulfated conjugated metabolites in the blood stream. Naringenin-o-β-D-glucuronides constituted 98% of plasma metabolites and naringenin aglycone retained in the tissues following 2hour and 18hour respectively post gavage treatment with 50mg/kg naringenin [4]. Recent study on tissue distribution of naringenin revealed that naringenin glucuronides were predominantly found in serum, while naringenin sulfates were detected in higher concentration in liver, spleen, heart and brain tissue [5]. Upon topical administration of 1% naringenin eye drops to rabbits, naringenin concentration was shown to be highest in cornea (67945.30–4109.34ng/g), followed by aqueous humor (1325.69–239.34ng/mL), retina (1927.08–660.77ng/g) and vitreous body (160.52–38.78ng/mL) [6].

1.1.3. Metabolism

Glucuronidation is the key metabolic step post-absorption mainly occurs at the 7- and 4'-hydroxyl groups of naringenin via UDP-glucuronyl-transferase enzyme and subsequent O-sulphation occur at 7-, 4'- or 5-hydroxyl groups of naringenin via sulfotransferases enzyme [7-9]. Naringenin is hydrolyzed in the small intestine by beta-glucosidases and then absorbed in the caecum [7, 10]. Furthermore, naringenin was also shown to be metabolized by intestinal microflora into p-coumaric acid (p-CA), p-hydroxybenzoic acid (p-HBA) and p-hydroxyphenylpropionic acid (p-HPPA), mainly identified in the urine and plasma [4].

1.1.4. Excretion

After single dose of naringenin (135mg/kg), maximum excretion rate occurs at 4.5hours with a urinary excretion of 66.2±3.1μmol/24hours [3]. Naringenin 7-glucuronide, naringenin 7-sulfate 4'-glucuronide and naringenin 7-glucuronide 4'-sulfate are excreted in the bile whereas naringenin 4'-glucuronide, naringenin 7-glucuronide and naringenin 7,4'-disulfate are excreted in the urine [11]. The metabolite conjugates which are excreted in bile further undergo enterohepatic circulation showed double peak phenomenon in plasma concentration–time curve; thus resulting in longer elimination half-life [12]. Naringenin exist into two chiral forms such as R-enantiomer and S-enantiomer and their lowest limits of quantitation in plasma is 0.05μg/mL [13]. In comparison to S-(-) enantiomer, R-(-) enantiomer has 40% higher cumulative urinary excretion [14].

2. PHARMACOLOGICAL PROPERTIES OF NARINGENIN

2.1. ANTIOXIDANT EFFECTS

The antioxidant potential of naringenin has been well studied in various cell lines and animal models. One of the best-studied effects of naringenin includes scavenging of free radicals, inhibiting the activities of pro-oxidant enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase, lipooxygenase and xanthine oxidase and metal ion chelation. Apart from that, naringenin amplifies several antioxidant enzymes levels viz. catalase, glutathione peroxidase and superoxide dismutase; suppresses protein nitration and peroxynitrite-induced protein oxidation [15]. A comparative study revealed that naringenin exhibited superior chelation of metallic ions, antioxidant capacity, hydroxyl and superoxide radical scavenger activity and protection against oxidative damage to lipids than its glycosidic form, naringin [16]. The various supportive evidences for the antioxidant activity of naringenin are as follows:

2.1.1. In Vitro

Naringenin (0.02mM) inhibited nitrite-induced oxidation of hemoglobin to methemoglobin via its ability to scavenge free radicals [17]. In mouse neuroblastoma cells, naringenin (100μM) prevented carbaryl induced neurotoxicity through its antioxidant and anti-apoptotic potential [18]. Naringenin (50mg/kg) has been shown to upregulate antioxidant enzyme activities and alleviate oxidative stress against iron-induced neurotoxicity in cerebral cortex [19]. Mechanistically, its property to activate nuclear factor E2-related factor 2 (Nrf2) signaling pathway may be an imperative rationale in preventing oxidative stress in human bronchial epithelial BEAS-2B cells at concentration of 100μM [20] and in H9c2 cardiomyoblast cells at 50μM [21].

2.1.2. In Vivo

Owing to its strong anti-oxidant potential, naringenin (50mg/kg) demonstrated protective effect in various models viz. arsenic [22], cadmium [23, 24] and lead-induced hepatic and renal dysfunction in rats [25], ethanol-induced hepatotoxicity in rats [26] and oxytetracycline-mediated liver damage in rats [27]. Naringenin (50mg/kg) attenuated carbon tetrachloride-induced hepatotoxicity and nephrotoxicity in mice [28, 29]. Moreover, naringenin (200mg/kg) ameliorated N-nitrosodiethylamine-induced hepatocarcinogenesis in rats via both free radical scavenging and augmenting antioxidant enzyme activities [30]. Naringenin (100mg/kg) has been shown to exhibit hypouricemic action in mice [31] and therefore could be developed for therapeutic use in the treatment of gout mediated by xanthine-oxidase inhibition [32].

2.2. ANTI-INFLAMMATORY EFFECTS

Similar to its antioxidant potential, various *in vitro* studies have demonstrated anti-inflammatory activity of naringenin. In macrophages exposed to lipopolysaccharide (LPS), naringenin (100μM) significantly inhibited Nuclear factor kappa B (NF-κB) activation, inducible nitric oxide synthase (iNOS) expression and nitric oxide

(NO) production [33]. In another study using the same model, naringenin (0-50μg/mL) suppressed pro-inflammatory cytokine response in whole blood as well as macrophages and markedly reduced phosphorylation of activator protein-1 (AP-1) [34]. In various studies on LPS-stimulated mouse macrophage cell line J774.1, naringenin (0.5-50μM) significantly impeded tumor necrosis factor-α (TNF-α) production [35], iNOS and cyclo-oxygenase-2 (COX-2) expression and prostaglandin E_2 (PGE_2) release [36]. Similar effects were also observed in glial cells at concentrations of 0.01-0.3μmol/l [37] and 30-200μM [38]; which were attributed to modulation of p38 mitogen-activated protein kinase (p38MAPK) phosphorylation and signal transducer and activator of transcription-1 (STAT-1) activity [37]. Furthermore, naringenin (0-70μM) has been shown to attenuate cytokine secretion in mouse primary splenocytes treated with LPS [39]. In another study, naringenin (200 and 400μM) significantly reduced LPS/interleukin-1β (IL-1β)-induced inflammatory and contractile pathways in human placenta, foetal membranes and myometrium [40].

Thus, the aforementioned examples outline the antioxidant and anti-inflammatory potential of naringenin which theoretically believed to be beneficial in various human disorders plagued by oxidative stress and inflammation as underlying pathophysiological events are depicted in Fig. **2**. Hence, researchers have evaluated naringenin in such human disorders, employing appropriate *in vitro* techniques and animal models. A brief list of such diseases and the possible role of naringenin in them is discussed in the next section of the present review.

3. THERAPEUTIC POTENTIAL OF NARINGENIN IN MODELS OF CNS DISEASES

As depicted in Table **1**, naringenin exhibited diverse neuropharmacological properties including neuroprotective, memory enhancer, antidepressant and analgesic. We discuss below the relevant studies in different areas of CNS research with regard to naringenin.

3.1. Alzheimer's Disease (AD)

One of the most frequently and magnificently elucidated CNS disorders involving oxidative stress and inflammation is AD; which is characterized by deposition of Amyloid beta (Aβ) proteins in CNS; culminating in the formation of amyloid plaques and neurofibrillary tangles. *In vitro*, naringenin (25-100μM) significantly attenuated Aβ-induced free radical-mediated neurotoxicity in PC12 cells [41]. In the same study, naringenin (4.5mg/kg) also augmented latency and retention time in male ICR mice. In intracerebroventricular streptozotocin-induced model of AD, naringenin (50mg/kg) significantly improved cognitive deficits and neuronal injury in rats; through modulation of oxidative stress [42, 43] and insulin signaling pathway [44]. At a dose of 4.5mg/kg, it significantly ameliorated scopolamine-induced amnesia in mice [45]. It also ameliorated type-2 diabetes-induced memory dysfunction at a dose of 50mg/kg in rats via inhibition of cholinesterase activity and improvement in anti-oxidant activity [46]. Therefore, naringenin could serve as a preventive/therapeutic agent in AD.

3.2. Parkinson's Disease (PD)

Another of the neurodegenerative disorders, PD is characterized by degeneration of the dopaminergic neurons in the nigrostriatal pathway. In primary rat mesencephalic cultures, naringenin (40μM) significantly protected dopaminergic neurons from N-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium hydrochloride (MPP+) induced oxidative stress [47]. Moreover, naringenin (50 mg/kg) augmented the number of tyrosine hydroxylase-positive cells in the substantia nigra and dopamine levels in the striatum [48]; as well as activated Nrf2/antioxidant response element (Nrf2/ARE) signaling pathway at a dose of 70mg/kg [49] in the 6-hydroxydopamine model of PD in mice. Thus naringenin may ameliorate the degeneration of dopaminergic neurons, thus, potentially proving of its preventive/ therapeutic benefit in PD.

3.3. Mood Disorders

Naringenin has been shown to exhibit antidepressant-like effect in various mouse behavioral models of depression, through mechanisms involving monoaminergic system [50], inhibition of monoamine oxidase (MAO-A and MAO-B) [51], regulation of hippocampal glucocorticoid receptor and serum corticosterone levels [52] and activation of brain-derived neurotrophic factor (BDNF) signaling [53]; suggesting a potential therapeutic role in depressive disorders. A study by Amer and colleagues demonstrated that naringenin (10nM-10μM) also exerts a strong estrogenic activity in a stably transduced rat serotonergic cell line; thus modulating serotonergic mood regulation [54].

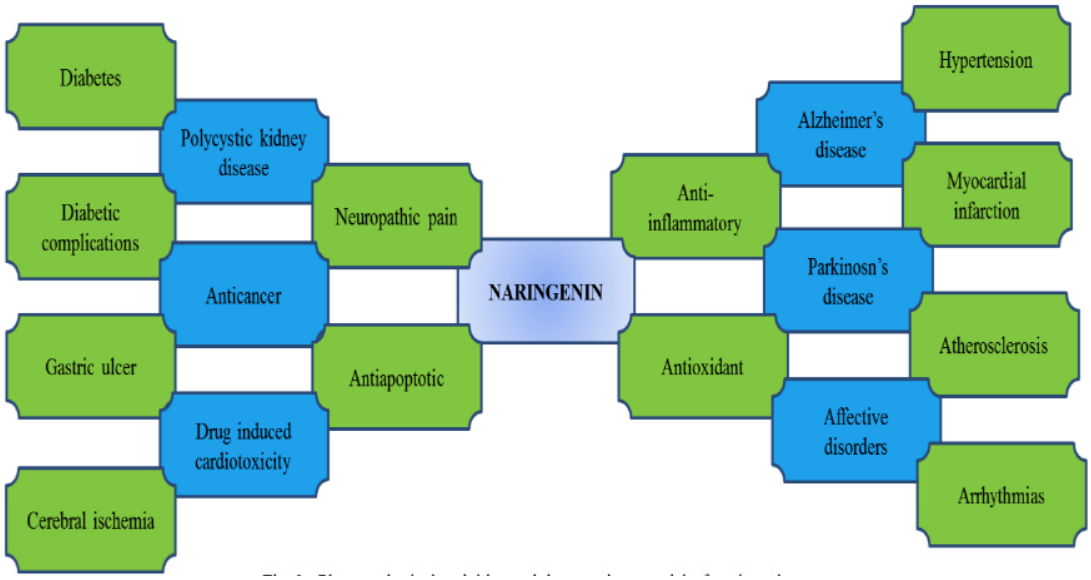


Fig. (2). Pharmacological activities and therapeutic potential of naringenin.

Table 1. Effect of naringenin on neurological diseases.

Dose	Model	Target/End points		Refer-ence
		Increase	Decrease	
Alzheimer's disease (AD)				
70-210 µg/ml	PC12 cells	–	Acetylcholinesterase activity	[41]
50 mg/kg	Male albino Wistar rats	GSH level; GPx, GR, GST, SOD and Na^+/K^+-ATPase activity; ChAT protein expression	4-HNE, TBARS, H_2O_2 and PC level	[42]
25, 50 and 100 mg/kg	Male Sprague-Dawley rats	PPAR-γ, insulin, insulin receptor and IDE mRNA expression; IDE protein expression	Phospho-Tau and Aβ42 level; GSK-3β activity	[44]
25, 50 and 100 µM and 1.5, 3.0 and 4.5 mg/kg	PC12 cells and male ICR mice	–	ROS level; LDH activity	[45]
25 and 50 mg/kg	Male Sprague-Dawley rats	GSH level	MDA and NO level; ChE activity	[46]
Parkinson's Disease				
40 µM	Primary rat mesen-cephalic cultures	–	TH-positive neurons and TUNEL positive neurons	[47]
50 mg/kg	Male Sprague-Dawley rats	DOPAC and HVA level	–	[48]
20, 40 and 80 µM and 70 mg/kg	Human neuroblastoma SH-SY5Y cells and male C57BL/6 mice	GSH, DA, DOPAC and HVA level; Nrf2,GCLC, GCLM and HO-1 protein expression	ROS and LDH level; p-JNK, p-p38 and caspase-3 protein expression	[49]
Depression				
IC_{50} = 342±33 µM, 955±129 µM and 288±18 µM respectively	Rat liver mitochondrial fraction	–	MAO, MAO-A and MAO-B activity	[51]
5, 10 and 20 mg/kg	Male ICR mice	5-HT and NE level; glucocorticoid receptor mRNA and protein level	Serum corticosterone level	[52]
5, 10 and 20 mg/kg	Male ICR mice	BDNF mRNA and protein expression	–	[53]
Stroke				
10, 25 and 50 mg/kg	Male Wistar rats	GSH level; SOD activity and protein ex-pression	TBARS, NO, TNF-α, IL-1β level; NF-κB and MPO activity; GFAP, Iba-1, NF-κB, iNOS and Cox-2 expres-sion	[55]
50 and 100 mg/kg	Male Sprague-Dawley rats	Claudin-5 mRNA and protein expression	NOD2, NF-κB and MMP-9 mRNA and protein expression; RIP2 protein expression	[56]
Neuropathic pain				
IC_{50} = 0.5±0.07µM	HEK293 cells and C57BL6/N mice DRG neurones and Wistar rat DRG neurones	–	TRPM3 channel	[57]
50, 100 and 200 mg/kg	Male Sprague-Dawley rats	–	TNF-α, IL-1β and MCP-1 level; GFAP and Mac-1 mRNA expression	[58]
25 and 50 mg/kg	Male Sprague-Dawley rats	GSH level	MDA and NO level	[59]

3.4. Stroke

Naringenin (50mg/kg) ameliorated cerebral ischemia-reperfusion injury in rats due to its anti-inflammatory effect [55]. It also decreased cerebral edema and infarct volume and improved neurological deficit at 100mg/kg following middle cerebral artery occlusion in rats [56].

3.5. Neuropathic Pain

Naringenin (IC_{50}=0.5±0.07μM) was shown to block melastatin-related transient receptor potential (TRPM3), a calcium-permeable cation channel involved in nociception [57]. In rat models of neuropathic pain, naringenin (200mg/kg) mitigated mechanical allodynia and thermal hyperalgesia following L_5 spinal nerve ligation [58] and chronic constriction injury at 50mg/kg [59]; thereby representing a potential analgesic action.

3.6. Other Neurodegenerative Disorders

Naringenin (0-100μM) suppressed polyglutamine protein aggregates via inducing glucose-regulated proteins 78 (GRP78), thereby conferring its potential in diseases caused by endoplasmic reticulum (ER) stress such as polyglutamine diseases, huntington disease, spinobulbar muscular atrophy, dentatorubral-pallidoluysian atrophy and several spinocerebellar ataxias [60]. In hypoxia-induced murine model, naringenin (10mg/kg) ameliorated behavioral impairment and neuronal damage [61]. Naringenin (100mg/kg) has been shown to decrease motor movements by pathway other than modulation of the gamma-aminobutyric acid A ($GABA_A$) receptor [62]. An *in vitro* (0-20μM) and *in vivo* (10 and 20mg/kg) study demonstrated that naringenin mitigates microglial-related neuroinflammation through inhibiting iNOS and COX-2 mediated by upregulation of suppressor of cytokine signaling 3 (SOCS-3) expression and AMP-activated protein kinase α/Protein kinase Cδ (AMPKα/PKCδ) activation [63].

4. THERAPEUTIC POTENTIAL OF NARINGENIN IN MODELS OF CARDIOMETABOLIC DISORDERS

Naringenin has been reported to be protective in atherosclerosis, hyperlipidemia and several other cardiovascular related disorders (Table **2**). The evidences available from different experimental studies in cardiometabolic disorders are represented below:

4.1 Myocardial Infarction

Naringenin (100mg/kg) was shown to significantly reduce the rat heart infarct size in Langendorff-perfused model of myocardial ischemia reperfusion injury through activation of mitochondrial BK potassium channels [64, 65].

4.2. Hypertension

In vascular smooth muscles, naringenin (1-100μM) was shown to activate large conductance BK_{Ca} channel and therefore exhibited vasorelaxant effect on endothelium-denuded vessels [66]. This effect is also mediated via inhibition of phosphodiesterase type 1, 4 and 5 (PDE1, PDE4 and PDE5) at concentration of 0.1mM [67]. Naringenin (30μM and 100μM) significantly induced vascular relaxation in porcine coronary artery [68]. Furthermore, naringenin (50mg/kg) prevented monocrotaline-induced pulmonary hypertension through inhibition of oxidative stress and inflammation [69]. In comparison to clonidine, naringenin ($2x10^{-6}$-$1x10^{-7}$M) was shown to be a better α_2 agonist in experiments on rat vas deferens, therefore can be used as an experimental drug to identify novel α-agonistic molecules [70]. Naringenin (10^{-9} to $3x10^{-4}$M with $IC_{50}=2.72\times10^{-7}$M) was shown to inhibit rat vas deferens contractions, thereby indicating its role as an investigational tool in hypertensive models [71].

4.3. Arrhythmias

Naringenin (100μM, IC_{50}=173.3±3.1μM) was shown to block human ether-a-go-go-related gene (hERG) current and exhibited synergistic effect when co-administered with other I(Kr)-blocking anti-arrhythmic drugs (azimilide, amiodarone, dofetilide and quinidine) [72]. Furthermore, naringenin (1mmol/l, with IC_{50}=102.3 μmol/L) blocked hERG potassium channels in *Xenopus oocytes* thereby acting as either a pro-arrhythmic and anti-arrhythmic agent [73, 74].

4.4. Drug Induced Cardiotoxicity

Naringenin (10^{-4}–10^{-6}mol/l) significantly ameliorated daunorubicin-induced toxicity in cultured adult rat cardiomyocytes [75] and in H9c2 cardiomyoblasts [76]. Naringenin (15mg/kg) was found to attenuate doxorubicin-induced cardiotoxicity in rats [77]. In a similar model, naringenin (25mg/kg) modulated oxidative and NO milieu to exert cardioprotection [78].

4.5. Atherosclerosis

In metabolic syndrome associated with atherogenic dyslipidemia and a pro-inflammatory and pro-thrombotic state, phytochemicals have been shown to be a promising candidate. The atherosclerosis retarding effects of naringenin have been widely evaluated in both *in vitro* and *in vivo* models (Table **3**) and are as follows:

4.5.1. In Vitro

Naringenin (20-160μM) was shown to exhibit anti-atherogenic effects via modulating peroxisome proliferator-activated receptor (PPAR) and adiponectin expression [79]. In adipocytes, naringenin (0-50μg/mL) dose-dependably suppressed adipogenesis and decreased adiponectin expression and insulin sensitivity [80]. Moreover, naringenin (10-200μM) decreased the cholesterol esterification and availability of lipids for assembly of apolipoprotein B (apoB)-containing lipoproteins, which might explain its usefulness in hypercholesterolemia [81]. Naringenin (100μM) also inhibited the secretion of apoB-100 in HepG2 cells by activation of phosphatidylinositol 3-kinase (PI3K) and MAPK pathway in a manner similar to insulin but not involving the insulin receptor [82-84]. In another *in vitro* study, naringenin (10μM, IC_{50}=10μM) was shown to inhibit the human serum paraoxonase 1 [major anti-atherosclerotic component of high-density lipoprotein (HDL)] [85]. In TNF-α-induced vascular smooth muscle cells, naringenin (10-25μM) inhibited invasion and migration of smooth muscle cells, and Protein kinase B (AKT) phosphorylation via PI3K/AKT/mTOR/p70S6K pathway and could be of value in atherosclerotic disease [86]. Besides, naringenin (25-100μM) was also shown to decrease the TNF-α induced vascular smooth muscle cell proliferation and migration via induction of hemeoxygenase-1 (HO-1) and thus, may improve the pathogenesis of atherosclerosis and restenosis [87].

A study by Xu and colleagues reported that naringenin reduces angiotensin II-stimulated migration and proliferation of vascular smooth muscle cells at concentration of 100μM as well as neointimal hyperplasia following balloon injured rat carotid artery at 25mg/kg [88]. In vascular endothelial cells, naringenin (100μM) has been shown to induce suppressor of cytokine signaling 3 (SOCS3) gene expression which led to inhibition of IL-6-activated STAT3 activation [89]. Not only naringenin but also its metabolites have been shown positive effects in *in vitro* model of atherosclerosis. For instance, naringenin-4'-glucuronide, a metabolite of naringenin, significantly inhibited the expression of genes involved in inflammation and cell adhesion via decreasing monocyte adhesion to TNF-α-activated endothelial cells at a concentration of 2μM [90].

Table 2. Effect of naringenin in cardiovascular diseases.

Dose	Model	Target/End points		Reference
		Increase	Decrease	
Myocardial Infarction				
1-100 μM and 100 mg/kg	Isolated rat cardiac mitochondria and male Wistar rats	BK potassium channels activation	Mitochondrial calcium uptake	[65]
Hypertension				
1-100 μM	Aortic ring preparations and tail artery myocytes	BK_{Ca} channels activation	–	[66]
0.1mM	Rat aortic myocytes	cGMP and cAMP level	Calcium influx	[67]
50 mg/kg	Male Wistar rats	Serum NO_x and GSH level; eNOS protein expression	NO_x, TBARS, TNF-α & TGF-β level; MPO & caspase-3 activity; iNOS expression	[69]
Arrhythmias				
100 μM (IC_{50} = 173.3±3.1 μM)	Xenopus oocytes	–	hERG current	[72]
1mmol/L (IC_{50} = 102.3 μmol/L and 36.5 μmol/L)	Xenopus oocytes and HEK cells	–	hERG current	[73]
Drug induced cardiotoxicity				
10^{-4}–10^{-6} mol/L	Male Wistar rat cardiac myocytes	–	LDH activity	[75]
10^{-4}–10^{-5}mol/L	H9c2 cardiomyoblasts	–	Apoptosis (Annexin V^+ cells)	[76]
15 mg/kg	Swiss albino rats	GSH level; SOD and CAT activity	TBARS level	[77]
25 mg/kg	Swiss albino rats	GSH level; SOD, GST and CAT activity	MDA and NO level; LDH and CPK activity	[78]

4.5.2. In Vivo

Naringenin (3%w/w) significantly prevented cholesterol-induced metabolic dysregulation and atherosclerosis in low density lipoprotein receptor-null ($Ldlr^{-/-}$) mice via attenuating hepatic macrophage infiltration, formation of foam cells and expression of inflammatory markers in peritoneal macrophages [91]. In high-fat-fed $Ldlr^{-/-}$mice, naringenin (1% or 3%w/w) also decreased progression of atherosclerosis and metabolic syndrome by ameliorating dyslipidemia, apoB overproduction and hyperinsulinemia [92, 93]. Moreover, rats fed with naringenin (0.003, 0.006 and 0.012%w/w) were found to exhibit reduced plasma and hepatic triglyceride and cholesterol levels which may contribute to its hypolipidemic and anti-adiposity effects [94].

Naringenin (0.1%w/w) also reduced cholesterol concentrations in liver and plasma via inhibiting 3-hyroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and acyl-CoA: cholesterolacyl transferase activity (ACAT) in high-cholesterol diet fed-rats [95]. In a similar model, naringenin (0.02%wt/wt) has been shown to decrease hepatic cholesterol, plasma total-cholesterol, triglyceride, HMG-CoA, ACAT activity and atherogenic index, with concomitant increase in HDL-c [96]. Besides, naringenin (50mg/kg) was shown to mitigate high cholesterol diet-associated myocardial oxidative stress and necroptosis in rats [97]. In high cholesterol fed rabbits, naringenin (0.05%wt/wt) also decreased aortic fatty streak formation thereby exhibiting anti-atherogenic effect [98]. Of note, naringenin (0.6%w/w) supplementation attenuated levels of hepatic neutral and polar lipids in rats fed a high coconut oil diet, but not in the corn starch-fed rats [99]. Naringenin (1%wt/wt) was shown to increase the gene expression of enzymes involved in hepatic fatty acid oxidation, peroxisomal β-oxidation and ω-oxidation of fatty acids and may be useful in lowering serum lipid level [100]. Recent research has demonstrated that naringenin (3%w/w) attenuates ovariectomy-associated metabolic disturbances in mice [101]. Naringenin (100mg/kg) also inhibited neointimal hyperplasia following vascular injury through downregulation of smooth muscle cell migration and proliferation in rats [102].

4.6. Diabetes

4.6.1. In Vitro

Naringenin administration inhibited intestinal and renal Na^+-glucose cotransporter and reduced D-glucose uptake in different *in vitro* systems viz. rabbit intestinal BBMV (10-500μM with IC_{50}=205.9μmol/l), rat everted intestinal sleeves (0.1-100μM with IC_{50}=2.4μmol/l), normal rat renal BBMV (50-1000μM with IC_{50}=323.9μmol/l) and diabetic rat renal BBMV (50–1000μM with IC_{50}=166.1μmol/l) [103]. In L6 rat myotubes and skeletal muscle cells, naringenin (10-150μM) stimulated glucose uptake via AMPK activation [104]. Naringenin (6-100μM) suppressed hepatic glucose

Table 3. Effect of naringenin on metabolic disorders.

Dose	Model	Target/End points		Reference
		Increase	Decrease	
Atherosclerosis				
20-160 μM	3T3-L1 mouse preadipocytes and HU-2OS osteosarcoma cells	Adiponectin, PPAR-α and PPAR-γ mRNA expression	–	[79]
0-50 μg/mL	Murine 3T3-L1 preadipocytes	–	aP2, PPAR-γ, STAT5A and IRS-1 tyrosine^{896} phosphorylation protein expression	[80]
10-200 μM	HepG2 cells	LDL receptor activity and mRNA expression	ACAT1, ACAT2 and MTP activity; ACAT2 and MTP mRNA expression	[81]
10-25 μM	VSMC	–	IL-6 and IL-8 level; NF-κB and AP-1 activity; MMP-9, p-AKT, p- mTOR and p-p70S6K protein expression	[86]
25-100 μM	VSMC	HO-1 activity, mRNA and protein expression	ROS generation; OPN and PAI-1 mRNA expression; ERK1/2 and p-Akt protein expression	[87]
100 μM 25mg/kg	VSMC Male Sprague-Dawley rats	SOD activity; IκB protein expression	ROS production; NADPH oxidase activity; p-ERK1/2 and p38MAPK and NF-κBp65 protein expression 8-iso-PGF2α level; PCNA and NF-κB protein	[88]
100 μM	COS- 1 cells HUVECs cells	SOCS3 promoter activity SOCS3 mRNA and protein expression	pSTAT3 protein expression	[89]
Diet 1 or 3% w/w	Male C57BL/6J and Ldlr$^{-/-}$ mice	Mitochondrial DNA content; Pgc1α, Cpt1α and Aco mRNA expression	Srebp1c mRNA expression	[92]
3% w/w	Male C57BL/6J Ldlr$^{-/-}$ mice	MOMA-2 protein expression	Collagen and SMC α-actin expression	[93]
In diet (0.003-0.012% w/w)	Male Long-Evans hooded rats	PPAR-α, CPT-1 and UCP2 protein expression	–	[94]
0.1% w/w	Male Sprague-Dawley rats	–	Total neutral sterol, coprostanol and coprostanone excretion level	[95]
0.02% w/w	Male Sprague-Dawley rats	SOD and GSH-Px activity	Total neutral sterol and TBARS level; CAT activity	[96]
50mg/kg	Male Wistar rats	GSH level	TC, TG, HDL-C, LDL-C, MDA, LOOH, NO_2^- and protein carbonyl level; MMP-2 & 9 activity; TNF-α, IL-1β, IL-6, iNOS, Emr1 and NF-κB mRNA expression	[97]
0.05% w/w	Male New Zealand white rabbits	–	Hepatic ACAT activity; VCAM-1 and MCP-1 mRNA expression	[98]
1% w/w	Male ICR mice	Acyl-CoA oxidase, carnitine octanoyl transferase, peroxisomal bifunctional, peroxisomal 3-ketoacyl-CoA thiolase, Cyt P-450 IVA1 mRNA level	–	[100]
3% w/w	Ovariectomized C57BL/6J mice	Srebf1,Cpt1α, PGC1α PEPCK and Fasn mRNA expression	TC, lipids and TG level; Leptin, MCP-1, IL-6, Scd1 & Acyl-CoA oxidase1 mRNA expression	[101]
100 mg/kg	Male Sprague-Dawley rats	–	PDGF-BB and TNF-α level ; Ki-67 protein expression	[102]

production and decreased cellular adenosine triphosphate (ATP) level without increasing cell cytotoxicity in Fao hepatoma cells and played a significant role in the attenuation of hyperglycemia [105]. Moreover, naringenin (50-300μM, with IC_{50}=85.5μM) impeded hepatic gluconeogenic pathway similar to metformin [106], thus indicating its role in type 2 DM. Importantly, naringenin (50μM) has also been shown to prevent pancreatic β-cell damage from cytokine-mediated apoptosis and enhanced cell survival via activation of PI3K pathway and recovering of mitochondria membrane potential [107].

Naringenin (100μM) has been shown to directly inhibit TNF-α-stimulated free fatty acid secretion in mouse adipocytes through NF-κB and extracellular signal-regulated kinase (ERK) pathways and may be useful in improving free fatty acid-induced insulin resistance [108]. On the contrary, naringenin (6μM) significantly inhibited insulin-stimulated glucose uptake through inhibiting PI3K in 3T3-L1 adipocytes and may aggravate insulin resistance [109].

4.6.2. *In Vivo*

An *in silico*, *in vitro* (IC_{50}=384μM) and *in vivo* (25mg/kg) study, naringenin improves postprandial glycemic response via suppression of α-glucosidase activity [110]. Besides, this group further revealed the hypoglycemic and insulin sensitizing potential of naringenin (25mg/kg) through modulating glucose transporter-4 (GLUT4) and TNF-α expression [111]. In streptozotocin (STZ)-nicotinamide rat model of diabetes, intragastrically administered naringenin (50mg/kg) was found to reduce hyperglycemia and triglyceride levels not via inhibiting alpha-glucosidase activity but through repression of carbohydrate absorption from intestine [112]. In a similar model, naringenin (50mg/kg) exhibited anti-hyperglycemic and antioxidant effect which was similar to the standard anti-diabetic drug Gliclazide [113] and also decreased hyperglycemia-mediated inflammation [114].

In a high fructose diet-induced model of insulin resistance, naringenin (50mg/kg) improved insulin sensitivity and enhanced tyrosine phosphorylation [115] as well as reduced nitro-oxidative stress [116] and thereby indicating its beneficial role in insulin resistance and metabolic syndrome. Antithetically, low doses of naringenin acutely impaired glucose homoeostasis in HT-22 neuronal cells at 25-100μM, Djungarian hamsters and female C57BL/6JRj-mice at 10mg/kg possibly through inhibition of hypothalamic insulin/PI3K signaling [117].

4.7. Diabetic complications

Naringenin (10mg/kg) was found to improve aortic reactivity to contractile stimuli (phenylephrine and potassium chloride) in STZ induced-diabetic rats via modulation of NO and oxidative stress [118]. Naringenin (0.5-2%w/w) has been shown to attenuate diabetic nephropathy in mice owing to its anti-inflammatory and anti-fibrotic activity [119]. Naringenin (50 and 100mg/kg) was shown to mitigate diabetic neuropathy in rats through NOS inhibition and PPAR-γ activation [120]. In an *in vitro* (5μg) and *in vivo* (50mg/kg) study, naringenin prevented high glucose-induced apoptosis through alteration of mitochondria-mediated apoptotic pathways and scavenging of reactive oxygen species (ROS), thereby implicating its favorable role in diabetes associated liver complications [121, 122].

5. THERAPEUTIC POTENTIAL OF NARINGENIN IN MODELS OF LIVER DISEASES

5.1 *In vitro*

In the activated hepatic stellate cells, naringenin (0-50μM) exhibited anti-fibrogenic property through decreased expression of extracellular matrix and downregulated small mothers against decapentaplegic homolog 3 (smad3) protein expression induced by transforming growth factor beta 1(TGF-1β) [123]. Naringenin (0-400μM) has been reported to transcriptionaly regulate human and rat hepatic lipid metabolism via activating PPARα and PPAR-γ and inhibiting liver X receptor alpha (LXRα) as well as reduced insulin dependence and regulate dyslipidemia. Therefore, it may be useful in hepatosteatosis and other metabolic conditions [124].

5.2. *In vivo*

In metallothionein-null mice, naringenin (400 and 800mg/kg) has shown to prevent acetaminophen-mediated hepatotoxicity [125]. Naringenin (50mg/kg) significantly attenuated ethanol induced liver injury in rats via modulating phase-1 and phase-2 metabolizing enzymes [126] and inhibiting pro-inflammatory cytokines [127] and was reportedly useful in alcoholic liver disease. Naringenin (20 and 50mg/kg) inhibited dimethylnitrosamine-mediated rat hepatic injury and could also be useful agent for hepatic fibrosis [128]. In another study, naringenin (50mg/kg) significantly attenuated carbon tetrachloride (CCl4)-induced hepatic inflammation through activating Nrf2 and inhibiting TNF-α pathway [129].

6. THERAPEUTIC POTENTIAL OF NARINGENIN IN MODELS OF LUNG DISEASES

6.1. *In vitro*

In human airway epithelial cells, naringenin (100μM) was shown to minimize mucous production via decreasing ROS production and inhibiting the NF-κB activity via EGFR-PI3K-Akt/ERK MAPK signaling pathway [130]. Besides, naringenin (10-40μmol/L) reduced LPS-induced cytokine and chemokine secretion in normal human bronchial epithelial (NHBE) cells and thus, may have promising value in prevention and treatment of asthma [131].

6.2. *In Vivo*

Naringenin (100mg/kg) significantly attenuated the symptoms of lung injury and inflammation in a mouse model of *Staphylococcus aureus* pneumonia [132]. In both acute (25-100mg/kg) and chronic (50mg/kg) mice model of ovalbumin-induced asthma, naringenin alleviated airway inflammation and airway responsiveness via inhibiting inflammatory cytokines and NF-κB activity [133, 134]. Naringenin was shown to possess expectorant activity via augmenting tracheal mucociliary velocity (90mg/kg), basal lysozyme secretion (100μM), secretion of phenol red from mouse tracheas (30-67mg/kg) and inhibiting LPS-induced mucin increase (10μmol/l). Findings reveal that naringenin can be used alone or as an adjuvant to the other expectorants available [135].

7. THERAPEUTIC POTENTIAL OF NARINGENIN IN MODELS OF KIDNEY DISEASES

Naringenin has been shown to inhibit gentamicin (50mg/kg) [136], cisplatin (20mg/kg) [137] and oxytetracycline-induced (50mg/kg) [138] kidney damage in rats via bolstering anti-oxidant defense system. In addition, naringenin suppressed *Dictyostelium* cell growth (EC_{50}=50-100μM), MDCK C7 cell growth (EC_{50}= 28.5±1μM) and cyst proliferation (EC_{50}=10μM) through TRPP2 (polycystin-2)-dependent mechanism, therefore might be of therapeutic value in autosomal dominant polycystic kidney disease [139].

8. THERAPEUTIC POTENTIAL OF NARINGENIN IN MODELS OF GASTROINTESTINAL DISEASES

8.1. Gastric Ulcers

Naringenin has been shown to exert vasorelaxant effect on rat colonic smooth muscle. It reduced colonic spontaneous contractions both *in vitro* (100μM) and *in vivo* (25 and 50mg/kg) through direct activation of BK_{Ca} channels and decreased calcium influx, thus suggesting its beneficial role in treatment of GI motility disorders [140]. A study by Amira and colleagues reported that, naringenin (0.1-100μM) exhibits gastric relaxant activity in mouse isolated stomach at pEC_{50}=5.09±0.17 and E_{max}=72.84±6.2 [141]. In a rat

model of ethanol-induced gastric lesions, naringenin (200mg/kg) has also been reported to possess cytoprotective effect through a mechanism involving prostaglandins [142].

8.2. Colon

In a rat constipation model, naringenin (150mg/kg) significantly restored the levels of fecal output, water content and mucus secretion probably due to stimulation of Cl- secretion in colonic epithelium via modulating cyclic adenosine monophosphate (cAMP), protein kinase A (PKA) and basolateral K^+ channels, thereby conferring its beneficial role in constipation [143]. Naringenin (100μM) inhibited chloride secretion in isolated rat and human colonic epithelia through a mechanism involving inhibition of basolateral Na^+-K^+-Cl^- co-transporter 1 [144]. Naringenin (10-300μmol/l) was shown to reduce guinea pig intestinal peristalsis through a decrease in distension sensitivity without changing in peristaltic performance [145]. In an experimental model of colitis, mice fed with naringenin (0.3%w/w) have been shown to ameliorate dextran sulfate sodium-induced severe colon damage [146]. In a similar model, naringenin (50mg/kg) also abrogated colitis through inhibiting toll-like receptor 4 (TLR-4)/NF-κB signaling [147]. In acetic acid-induced ulcerative colitis model, naringenin (25-100mg/kg) augmented colonic mucus content via its antioxidant and anti-inflammatory effect and thus could be useful in inflammatory bowel disease [148]. Furthermore, naringenin (0.1-1.0mM) has been shown to induce cholecystokinin secretion via activation of transient receptor potential channels (TRP channels) in enteroendocrine STC-1 cells, thus could act as a potential candidate for appetite regulation and satiety [149].

9. THERAPEUTIC POTENTIAL OF NARINGENIN IN CANCER MODELS

Naringenin has been shown to exert suppressive effect on TGF-β ligand-receptor interaction, the initial step of TGF-β signaling, therefore could be of significance in condition such as cancer where TGF-β plays a direct role [150]. In addition, naringenin has inhibitory effect on tumor growth [151]. Naringenin exerted cytotoxicity in different cell lines of leukemia, pancreas, breast, stomach, liver, cervix and colon [152]. The specific effects in various cancer experiments are described in Table **4** and as follows:

9.1. Pancreatic Cancer

Naringenin (100μM) decreased invasiveness and metastasis in pancreatic cancer cells by inhibiting TGF-β-induced epithelial to mesenchymal transition and reversed resistance to gemcitabine [153].

9.2. Glioma

Naringenin (50mg/kg) has been shown to exert ameliorative effect against cerebrally implanted C6 glioma cells in rats via promoting apoptosis and inhibition of proliferation and PI3K [154-156].

9.3. Breast Cancer

In MCF-7 human breast cancer cells (1-1000nM) and female rat uterus (30mg/rat), naringenin was found to possess weak estrogen activity along with partial antiestrogenic activity [157]. It (IC_{50}=18.0μg/ml) also inhibited proliferation of estrogen receptor-positive MCF-7 human breast cancer cells [158]. Naringenin (10μM) mitigated insulin stimulated glucose uptake in MCF-7 breast cancer cells and has the potential to act as an anti-proliferative agent, thereby highlighting its therapeutic potential in the treatment of breast cancer [159]. Furthermore, naringenin has been shown to inhibit proliferation (250μM) and viability (<200μM) of MCF-7 breast cancer cells by localizing ERα to the cytoplasm and by suppressing both PI3K and MAPK pathways [160]. Contrary, naringenin (6.25-100μM) was found to promote growth of MCF-7 cells via a pathway independent of NO and dependent on estrogen receptors (ER-α and ER-β) [161]. In another study, naringenin (1-10μM) has also been shown to exert cell proliferation (EC_{50}=287nM), inhibit aromatase activity (IC_{50}=2.2μM) and have anti-estrogenic effects in human primary mammary fibroblasts, MCF-7 breast tumor cells and their co-culture [162]. In T47D-KBluc breast cancer cells, naringenin (0.01 to 10μM) was shown to act as selective estrogen receptor modulator via activation of pS2 mRNA expression and inhibition of TGFβ3 expression [163]. Naringenin ($1.0x10^{-9}$ to $1.0x10^{-4}$M) has been shown to exhibit chemopreventive effect in breast cancer cell lines in the presence and absence of bisphenol A owing to its proapoptotic effect [164]. Moreover, naringenin (100mg/kg) also reduced the number of metastatic breast cancer cells to the lung and extended the life span of tumor resected mice via stimulation of regulatory T cells [165]. Naringenin (3-100μM with IC_{50}=2.6μM) inhibited 20α-hydroxysteroid dehydrogenase, an enzyme which inactivates human progesterone and thus can be useful in breast and endometrium cancer [166]. Furthermore, naringenin (Ki=0.3μM) has been shown to inhibit human recombinant aromatase activity, thereby conferring its therapeutic potential in endometriosis [167].

9.4. Hepatocellular Carcinoma

9.4.1. In Vitro

In human hepatocellular carcinoma HepG2 cells, naringenin (100-200μM) has been reported to possess anti-proliferative and apoptosis-inducing effects and thus could be of interest in liver cancer [168]. In the same cell line, naringenin (25-100μM) decreased invasiveness and metastasis via downregulation of matrix metalloproteinase-9 (MMP-9), NF-κB and AP-1 expressions [169].

9.4.2. In Vivo

In Ehrlich ascites carcinoma tumor model of mice, naringenin (50mg/kg) has been reported to exhibit anti-angiogenic and anti-proliferative effects with significantly reduced number of cells, accumulation of ascitic fluid, no noticeable neoplastic lesions and ameliorated hepatocellular architecture [170, 172]. Naringenin (200mg/kg) inhibited the N-nitrosodiethylamine induced hepatocarcinogenesis in rats via bolstering antioxidant status and inhibiting inflammatory pathway [30, 172].

9.5. Neuroblastoma

Naringenin augmented transamidation activity and cytotoxicity of suberoylanilidehydroxamic acid (SAHA), a histone deacetylase inhibitor, in neuroblastoma cell lines (240μM) and also reduced tumor progression through activating caspase-3, in N-Myc transgenic mice (100mg/kg) [173].

9.6. Melanoma

In murine B16-F10 melanoma cells, naringenin (3-50μM) enhanced melanogenesis through the activation of Wnt/β-catenin signaling [174]; augmented melanin content, tyrosinase activity and the expression of melanogenic enzymes (100μM) [175]; and reduced cell proliferation and intracellular levels of polyamine, spermidine and spermine with an increase in transglutaminase activity (10μM) [176]. In mice inoculated with B16-F10 melanoma cells, naringenin (200nmol/kg) also significantly decreased the lung metastases of the malignant cells [177].

9.7. Lung Cancer

Naringenin (100μM) was shown to accelerate TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in human lung cancer A549 cells via up-regulation of death receptor 5 (DR-5) expression and hence, could be a safe strategy for treatment of resistant non-small cell lung cancers [178]. Naringenin (100mg/kg) when administered to C57BL/6 and BALB/c mice subjected to bleomycin-induced pulmonary fibrosis and challenged using tumors; led to significantly suppressed pulmonary fibrosis, lung

Table 4. Effect of naringenin on different types of cancer.

Dose	Model	Target/End points		Reference
		Increase	Decrease	
Pancreatic cancer				
0-100 μM	Aspc-1 and Panc-1 cells	E-cadherin protein expression	Smad3, vimentin, N-cadherin, MMP2 and MMP9 mRNA and protein expression	[153]
50 mg/kg	Cerebrally implanted C6 glioma cells in rats	Bax, caspase-3, caspase-9, Cx43 and Cytochrome c protein expression	Bcl-2 protein expression	[154]
50 mg/kg	Cerebrally implanted C6 glioma cells in rats	GSH, vitamin E and vitamin C level; GPx and GR activity	LPO and AgNORs level; PKC, NF-κB, cyclin D1, cyclin dependent kinase 4, PCNA and VEGF protein expression	[155]
50 mg/kg	Cerebrally implanted C6 glioma cells in rats	–	PGE_2 level; PI3K, Akt and Cox-2 mRNA and protein expression	[156]
Breast cancer				
100 μM	Serum starved MCF-7 cells	–	p-Akt (Ser473) and p-p44/p42 MAPK protein expression	[159]
200 μM	MCF-7 cells	cleaved PARP protein expression	Caspase-7, ERK and Akt protein expression	[160]
$1.0x10^{-9}$ to $1.0x10^{-4}$ M	MCF-7 and T47D cells	caspase-3, PARP and p38-P protein expression	Bcl-2 and Akt-P protein expression	[164]
Hepatocellular carcinoma				
200 mg/kg	Male albino Wistar rats	GSH, Billirubin and AFP level; SOD, CAT, GPx, AST, ALT, ALP, LDH, GGT and GST activity	TBARS and LPO level; Cytochrome P450 activity	[30]
100-200 μM	Human hepatocellular carcinoma HepG2 cells	p53, Bax, cytochrome C and caspase-3 protein expression	Bcl-2 protein expression	[168]
0-100 μM	HepG2 cells	–	MMP-9, NF-κB and AP-1 mRNA expression; MMP-9,EGFR, PI3k-p, AKT-p, IκB-p, JNK-p, p38-p, ERK-p, PKC-α, PKC-β and PKC- γ protein expression	[169]
50 mg/kg	Ehrlich ascites carcinoma tumor model of mice	–	VEGF, Hif1α, HSP90 and p-Akt protein expression	[171]
200 mg/kg	Male albino Wistar rats	Bax and capsase-3 protein expression	NF-κBp65, VEGF, MMP-2, Cox-2 and MMP-9 mRNA and protein expression; PCNA and Bcl-2 protein expression	[172]
Melanoma				
3-50 μM	B16-F10 murine melanoma cells	Tyrosinase, MITF, β-catenin, p-GSK-3β and Akt protein expression	–	[174]
100 μM	B16mouse melanoma cells	Tyrp1, Dct and Mitf protein expression	–	[175]

(Table 4) Contd….

Dose	Model	Target/End points		Reference
		Increase	Decrease	
Lung cancer				
100mg/kg	C57BL/6 mice and BALB/c mice	IFN-γ and IL-2 level	TGF-β1 and IL-4 level	[179]
Prostate cancer				
10-100 μM	PC3-AP1 cells	p-JNK and p-ERK protein expression	–	[180]
10–80 μmol/L	LNCaP prostate cancer Cells	hOGG1, APE/Ref-1 and DNA polyβ mRNA expression	8-OH-dG to 10^6dG ratio	[181]
Benign Prostatic Hyperplasia				
6 μg/ml	LNCaP prostate cancer Cells	ERα and ERβ activity	AR activity	[183]
Gastric cancer				
200mg/kg	Male Wistar albino rats	GSH, vitamin C and vitamin E level; GPx, SOD and CAT activity	hydroxyl radical, superoxide radical and LPO level	[186]
Leukemia				
50–200 μM	Human myeloid leukemia THP-1 cells	Bax protein expression; caspase-3, caspase-8 and caspase-9 activity	Bcl-2 and p-Akt protein expression	[187]
0.1-1mM	Human promyeloleuke-mia HL-60 cells	caspase-3 and caspase-9 activity; cleaved caspase-3 protein expression	IκBα protein expression	[188]
Oral Cancer				
50 mg/kg	Male golden Syrian hamsters	TBARS level; CAT and SOD activity	Vit E and GSH level; GPx activity; PCNA and p53 protein expression	[191]
17β-estradiol dependent cancers				
1.0X 10^{-8}M to 1.0X 10^{-4}M	HeLa and HepG2 cells	p38-P, caspase-3 and PARP protein expression in both HeLa and HepG2 cells	PD1 promoter activity; ERK1/2-P and AKT-P protein expression only in HeLa cells	[196]

metastases and increased survival via modulating $CD4^+CD25^+Foxp3^+$ regulatory T cells, suggesting a potential immunomodulatory role in lung carcinoma [179].

9.8. Prostate Cancer

Naringenin (10-100μM) has been shown to exert chemopreventive effect in PC3 human prostate cancer cells through modulation of AP-1 and MAPK pathway [180]; as well as LNCaP human prostate cancer cells through activation of DNA repair at 10–80μmol/L [181]. Naringenin (15mg/kg) significantly decreased 17β-hydroxysteroid dehydrogenase and glucose-6-phosphate dehydrogenase (G6PDH) activity in male rats, thereby, could be a novel therapeutic approach in prostate cancer [182]. Naringenin (100μg/mL, IC_{50}=48.5μM) has also been shown to inhibit the prostate specific antigen secretion in LNCaP cells with no cytotoxicity and therefore could be used to treat benign prostatic hyperplasia [183].

9.9. Colon Cancer

Naringenin (0.02%w/w) was shown to suppress colon carcinogenesis in azoxymethane-treated rats through a pro-apoptotic effect [184] and cell proliferation at a dose range of 0.02 to 2.85mmol in HT29 colon cancer cells [185]. Thus, it can serve as a chemoprotective agent in colon cancer.

9.10. Gastric Cancer

In N-methyl-N'-nitro-N-nitrosoguanidine-induced gastric carcinogenesis in rats, naringenin (200mg/kg) significantly decreased tumor size and weight loss by modifying the redox status of the tumor cells [186].

9.11. Leukemia

In human leukemia THP-1 cell line, naringenin (0-200μM) was shown to induce apoptosis through activation of caspase-3 and

poly(ADP-ribose) polymerase (PARP) cleavage as well as suppression of PI3K [187]. Naringenin (0.1-1mM) also induced apoptosis in human promyelocytic leukemia HL-60 cells via activation of NF-κB, necrosis, intracellular ATP depletion and mitochondrial dysfunction, thus exerting a chemopreventive effect [188]. Naringenin has been shown to exert anti-cancer effect in K562 leukemia cells through apoptosis and regulating the expression of FAS, Fas ligand (FasL), caspase-3 and caspase-8 [189]. In addition, other mechanisms related to its (0-800μmol/L) anti-leukemic effect are cell cycle arrest and apoptosis via upregulation of p53-independent p21/WAF1 [190].

9.12. Oral Cancer

In 7,12-dimethylbenz(a)anthracene (DMBA)-mediated experimental model of oral squamous cell carcinoma, naringenin (50mg/kg) has been shown to possess chemopreventive efficacy in Syrian hamsters [191]. In the same model, Raman spectroscopic investigation further revealed that naringenin-loaded nanoparticles (50mg/kg) exhibit more potent antitumor effect than naringenin (50mg/kg) [192]. In hamster cheek pouch model of oral carcinogenesis, naringenin (2.5%) significantly attenuated the tumor cell number [193].

9.13. Adrenal cancer

In human adrenocortical carcinoma H295R cell line, naringenin (100μM with IC_{50}=85±12μM) significantly mitigated aromatase activity [194].

9.14. Soft Tissue Tumors

Naringenin (30-300mg/kg) was found to inhibit tumor growth in sarcoma S-180-implanted mice [152].

9.15. Other Tumors

Naringenin (10μM) has been shown to exhibit antiproliferative and antiestrogenic effects by activation of p38 kinase and regulation of estrogen receptor alpha-palmitoylation respectively [195]. Furthermore, naringenin (1.0X 10^{-8}M to 1.0X 10^{-4}M) suppressed 17β-estradiol-induced human cancer cell growth and could be a valuable chemo-preventive agent in 17β-estradiol dependent cancers such as breast, ovarian, colorectal, prostate and endometrial [196]. Naringenin (100-500μM) has been shown to induce apoptosis and antiproliferative activity in human epidermoid carcinoma cells through ROS generation and cell cycle arrest [197]. In another study, naringenin (100μM) amplified antitumor effect of doxorubicin through modulating the function of multi-drug resistance proteins and could be a useful adjunct to other chemotherapeutic agents [198]. In Human bladder carcinoma TSGH‐8301 cells, naringenin (25-300μm) mitigated cell migration via inhibiting AKT, NF-κB and MMP-2 pathways [199].

10. NARINGENIN FOR DRUG DESIGN, DELIVERY AND DEVELOPMENT

To effectively utilize the therapeutic potential of naringenin, researchers are now focusing on the formulation of naringenin-based drugs for human ailments. Naringenin physiochemical and pharmacokinetic properties including, minimal water solubility, absorption, bioavailability, dissolution rate and faster elimination rate are the main hurdles in the drug design of naringenin. Several techniques such as structural modification [200, 201], β-cyclodextrins and phospholipid complexation [202], solid dispersion and nanoparticles formulation could be few areas which could be taken into consideration for the improvement of naringenin drug delivery system and they are mentioned as below:

10.1. Structural Modification

Structural alteration at C-7 and C-4 position of naringenin augmented anti-tumor efficacy against colon cancer; thus signifying the role of naringenin derivative in the drug design of naringenin-based anti-cancer therapeutics [201]. For instance, narigenin-6-C-glucoside has shown increased bioavailability as compared to naringenin following oral administration of similar dose (5mg/kg) [200].

10.2. Complexation

In order to achieve the therapeutic plasma concentration of naringenin, naringenin phospholipid complex was synthesized and has longer half-life and enhanced antioxidant potential than naringenin [203]. Naringenin dissolution rate and water solubility was shown to increase following complex formation with β-cyclodextrin [202] and its derivative 2-hydroxypropyl-β-cyclodextrin [204] respectively, which could be of importance in designing water soluble naringenin dosage form. Furthermore, naringenin β-cyclodextrin complex has shown preventive effect in experimental rat model of choroidal neovascularization [205].

10.3. Solid Dispersion

The dissolution rate and absorption of naringenin was reported to augment owing to the conversion of its crystalline form to amorphorus via solid dispersion with soluplus [206]. Another study by Kanaze and group revealed that drug delivery of nanodispersions containing naringenin and polyvinylpyrrolidone (PVP) has been reported to increase the dissolution rate and gastric stability of naringenin [207].

10.4. Naringenin-Encapsulated Nanoparticles

In comparison to naringenin, its self nanoemulsifying formulation resulted in the fastest and complete release of drug and enhanced absorption rate and bioavailability [208]. Recently, more research is conducting on the formulation of naringenin-encapsulated nanoparticles in the field of cancer chemoprevention, liver failure and ulcerative colitis. In human cervical (HeLa) cancer cells, naringenin-loaded nanoparticles are designed to maximize the bioavailability, anticancer potential and also for the sustained release of naringenin to target site [209]. Furthermore, these nanoparticles containing naringenin has shown higher antitumor efficacy than naringenin in experimental model of oral carcinogenesis [191]. Beside cancer, naringenin-loaded nanoparticles have shown to enhance hepatoprotective effect via augmenting the solubility and release of naringenin in rats treated with carbon tetrachloride [210]. In a recent study, naringenin has been loaded into the polymeric nanoparticles (monomethoxy poly(ethylene glycol)-poly(3-caprolactone) to improve drug delivery options by developing buccal tablet. This process augmented encapsulation efficiency, anti-inflammatory effect and more than 80% of rapid release of naringenin to targeted disease site; thus indicative of an competent drug delivery progress in the treatment of oral inflammatory and ulcerative disease [211].

11. ISSUE AND PROSPECTS FOR PHARMACEUTICAL DEVELOPMENT

Considering pharmacokinetics data, enterohepatic circulation of naringenin is an important feature for determining its safety and efficacy [12]. Secondly, low bioavailability of naringenin is major constraint in lowering its therapeutic efficacy [3]. Thirdly, naringenin stereospecific nature demands more research in this area for evaluating the biological activity of individual enantiomers [13, 14]. In the serum, naringenin exist as glucuronides and sulfoconjugated metabolites, therefore further studies should be conducted to evaluate the biological activity of these conjugated metabolites rather than naringenin pure form [10]. A study by Lin and group have demonstrated that naringenin sulfate retained in the tissues including, liver, spleen, heart and brain as compared to naringenin glucuronide, therefore further research should be done for evaluation of biological activity of these sulfate metabolites in these tissues [5]. Being a substrate of drug efflux carriers such as drug resis-

tance-associated proteins (MRP1 and MRP2) and P-glycoprotein, naringenin play an important role in drug interaction [212].

CONCLUSION

The data published so far have suggested naringenin to be efficacious, safe, well tolerated, orally available and exerted multifaceted effect ranging from antioxidant to anti-carcinogenic and might meet few, if not all, of the aforementioned indications. Additionally naringin being abundantly and ubiquitously present in dietary substances, the administration of naringin can also be achieved in a simplified manner as a part of normal daily diet, thus offering another significant advantage. Moreover, many researches are still underway which might enlighten newer areas hitherto unexplored, where naringin might emerge as an efficient therapeutic modality or alternative; as the submerged portion of the iceberg is yet to be unearthed. Thus, naringenin joins the list of curcumin and hesperidin in being one of the most widely explored and observed efficacious phytopharmaceutical compounds. Considering its efficacy and safety, naringenin might be regarded as the forebearer of the phytopharmaceutical revolution to, if not replace, then at least could use as an adjuvant with the allopathic medications. Perhaps clinical effectiveness of naringenin based therapies both alone or in combination with other drugs has been just initiated and could be area worth further research where it can benefit human health.

LIST OF ABBREVIATIONS

ACAT	=	cholesterol acyl transferase
Acyl CoA	=	Aco: Acyl-CoA oxidase
AP-1	=	Activator protein-1
aP2	=	Adipocyte protein 2
apoB	=	Apolipoprotein B
Aβ	=	Amyloid β peptide
BDNF	=	Brain-derived neurotrophic factor
BK_{Ca}	=	Large conductance calcium-activated potassium channels
cAMP	=	Cyclic adenosine monophosphate
CAT	=	Catalase
VCAM-1	=	Vascular cell adhesion molecule-1
CcL2	=	Chemokine (C-C motFif) ligand 2;
cGMP	=	Cyclic guanosine monophosphate
ChAT	=	Choline acetyltransferase
ChE	=	Cholinesterase
COX-2	=	Cyclooxygenase-2
CPK	=	Creatine phosphokinase
CPT-1	=	Carnitine-palmitoyl transferase-1
CYP7A1	=	Cholesterol 7alpha-hydroxylase
DA	=	Dopamine
DOPAC	=	Dihydroxyphenylacetic acid
Emr1 (or F4/80)	=	EGF-like module-containing mucin-like hormone receptor-like1
eNOS	=	Endothelial nitric oxide synthase
ERK1/2	=	Extracellular signal-regulated kinase 1 and 2
Fasn	=	Fatty acid synthase
FGF21	=	Fibroblast growth factor 21
GCLC	=	Glutathione cysteine ligase regulatory subunit
GCLM	=	Glutathione cysteine ligase modulatory subunit
GFAP	=	Glial fibrillary acidic protein
GPx	=	Glutathione peroxidase
GR	=	Glutathione reductase
GSH	=	Reduced glutathione
GSH-Px	=	Glutathione peroxidase
GSK-3β	=	Glycogen synthase kinase-3β
GST	=	Glutathione S-transferase
4-HNE	=	4-Hydroxynonenal
5-HT	=	5-Hydroxytryptamine
H_2O_2	=	Hydrogen peroxide
HDL-C	=	High-density lipoprotein cholesterol
hERG	=	Human ether-a-go-go-related gene
HO-1	=	Hemeoxygenase-1
HVA	=	Homovanilic acid
8-iso-PGF2α	=	8-iso-ProstaglandinF2α
Iba-1	=	Ionized calcium binding adaptor molecule-1
IDE	=	Insulin degrading enzyme
IL	=	Interleukin
iNOS	=	inducible Nitric oxide synthase
IRS-1	=	Insulin receptor substrate-1
IκB	=	Inhibitor of κB
LDH	=	Lactate dehydrogenase
LDL	=	Low density lipoprotein
LDL-C	=	Low-density lipoprotein cholesterol
LOOH	=	Lipid hydroperoxide
Mac-1	=	Macrophage antigen-1
MAC-2	=	Macrophage marker-2
MAO	=	Monoamine oxidase
MAPK	=	Mitogen-activated protein kinases
MCP-1	=	Monocyte chemoattractant protein-1
MDA	=	Malondialdehyde
MMP-9	=	Matrix metalloproteinase-9
MOMA-2	=	Monocyte/macrophage antibody-2
MPO	=	Myeloperoxidase
MTP	=	Microsomal triglyceride transfer protein
NADPH	=	Nicotinamide adenine dinucleotide phosphate
NE	=	Norepinephrine
NF-κB	=	Nuclear factor kappa B
NO	=	Nitric oxide
NO_2^-	=	Nitrite
NOD2	=	Nucleotide oligomerization domain-like receptors 2
NOx	=	Total nitrate/nitrite
Nrf2	=	Nuclear factor E2-related factor 2
OPN	=	Osteopontin
PAI-1	=	Plasminogen activator inhibitor-1
p-Akt	=	Phospho-protein kinase B
PC	=	Protein carbonyl
PCNA	=	Proliferating cell nuclear antigen
PDGF-BB	=	Platelet derived growth factor-BB
PEPCK	=	Phosphoenol pyruvate carboxykinase

PGC-1α	=	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
p-JNK	=	Phospho-c-Jun NH2-terminal kinase
p-mTOR	=	Phospho-mammalian target of rapamycin
p-p70S6K	=	Phospho-p70 ribosomal protein S6 kinase
PPAR-γ	=	Peroxisome proliferator-activated receptor-γ
pSTAT3	=	Signal transducer and activator of transcription 3
RIP2	=	Receptor-interacting protein 2
ROS	=	Reactive oxygen species
Saa1/2	=	Serum amyloid a
Scd1	=	Stearoyl-CoA desaturase 1
SMC α-actin	=	Smooth muscle cell alpha actin
SOCS3	=	Suppressor of cytokine signalling 3
SOD	=	Superoxide dismutase
SREBF-1c	=	Sterol regulatory element binding factor-1c
SREBP-1c	=	Sterol regulatory element binding protein-1c
STAT5A	=	Signal transducer and activator of transcription 5A
TBARS	=	Thiobarbituric acid reactive substances
TC	=	Total cholesterol
TG	=	Triglyceride
TGF-β	=	Transforming growth factor-beta
TH	=	Tyrosine hydroxylase
TNF-α	=	Tumor necrosis factor-α
TRPM3	=	Melastatin-related transient receptor potential
TUNELvTerminal		deoxynucleotidyl transferase dUTP nick end labeling
UCP2	=	Uncoupling protein 2

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ACKNOWLEDGEMENTS

All individuals listed as authors must have contributed substantially to the design, performance, analysis, or reporting of the work and are required to indicate their specific contribution. Anyone (individual/company/institution) who has substantially contributed to the study for important intellectual content, or who was involved in the article's drafting the manuscript or revising must also be acknowledged.

Guest or honorary authorship based solely on position (e.g. research supervisor, departmental head) is discouraged.

REFERENCES

[1] Erlund I. Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. Nutr Res 2004; 24: 851-874.

[2] Xu H, Kulkarni KH, Singh R, *et al.* Disposition of naringenin via glucuronidation pathway is affected by compensating efflux transporters of hydrophilic glucuronides. Mol Pharm 2009; 6: 1703-15.

[3] Kanaze FI, Bounartzi MI, Georgarakis M, *et al.* Pharmacokinetics of the citrus flavanone aglycones hesperetin and naringenin after single oral administration in human subjects. Eur J Clin Nutr 2007; 61: 472-7.

[4] El Mohsen MA, Marks J, Kuhnle G, *et al.* The differential tissue distribution of the citrus flavanone naringenin following gastric instillation. Free Radic Res 2004; 38: 1329-40.

[5] Lin SP, Hou YC, Tsai SY, *et al.* Tissue distribution of naringenin conjugated metabolites following repeated dosing of naringin to rats. Biomedicine (Taipei) 2014; 4: 16.

[6] Lin J, Sun J, Wang Y, *et al.* Ocular pharmacokinetics of naringenin eye drops following topical administration to rabbits. J Ocul Pharmacol Ther 2015; 31: 51-6.

[7] Felgines C, Texier O, Morand C, *et al.* Bioavailability of the flavanone naringenin and its glycosides in rats. Am J PhysiolGastrointest Liver Physiol 2000; 279: G1148-54.

[8] Bredsdorff L, Nielsen IL, Rasmussen SE, *et al.* Absorption, conjugation and excretion of the flavanones, naringenin and hesperetin from alpha-rhamnosidase-treated orange juice in human subjects. Br J Nutr 2010; 103: 1602-9.

[9] Zhang J, Brodbelt JS. Screening flavonoid metabolites of naringin and narirutin in urine after human consumption of grapefruit juice by LC-MS and LC-MS/MS. Analyst 2004; 129: 1227-33.

[10] Hsiu SL, Huang TY, Hou YC, *et al.* Comparison of metabolic pharmacokinetics of naringin and naringenin in rabbits. Life Sci 2002; 70: 1481-9.

[11] Abe K, Katayama H, Suzuki A, *et al.* Biological fate of orally administered naringin and naringenin in rats. Shoyakugaku Zasshi 1993; 47: 402-7.

[12] Ma Y, Li P, Chen D, *et al.* LC/MS/MS quantitation assay for pharmacokinetics of naringenin and double peaks phenomenon in rats plasma. Int J Pharm 2006; 307: 292-9.

[13] Wan L, Sun X, Wang X, *et al.* A stereospecific HPLC method and its application in determination of pharmacokinetics profile of two enantiomers of naringenin in rats. J Chromatogr Sci 2011; 49: 316-20.

[14] Yáñez JA, Davies NM. Stereospecific high-performance liquid chromatographic analysis of naringenin in urine. J Pharm Biomed Anal 2005; 39: 164-9.

[15] Wang N, Li D, Lu NH, *et al.* Peroxynitrite and hemoglobin-mediated nitrative/oxidative modification of human plasma protein: effects of some flavonoids. J Asian Nat Prod Res 2010; 12: 257-64.

[16] Cavia-Saiz M, Busto MD, Pilar-Izquierdo MC, *et al.* Antioxidant properties, radical scavenging activity and biomolecule protection capacity of flavonoid naringenin and its glycoside naringin: a comparative study. J Sci Food Agric 2010; 90: 1238-44.

[17] Kumar MS, Unnikrishnan MK, Patra S, *et al.* Naringin and naringenin inhibit nitrite-induced methemoglobin formation. Pharmazie 2003; 58: 564-6.

[18] Muthaiah VP, Venkitasamy L, Michael FM, *et al.* Neuroprotective role of naringenin on carbaryl induced neurotoxicity in mouse neuroblastoma cells. J Pharmacol Pharmacother 2013; 4: 192-7.

[19] Chtourou Y, Fetoui H, Gdoura R. Protective effects of naringenin on iron-overload-induced cerebral cortex neurotoxicity correlated with oxidative stress. Biol Trace Elem Res 2014; 158: 376-83.

[20] Podder B, Song HY, Kim YS. Naringenin exerts cytoprotective effect against paraquat-induced toxicity in human bronchial epithelial BEAS-2B cells through NRF2 activation. J Microbiol Biotechnol 2014; 24: 605-13.

[21] Ramprasath T, Senthamizharasi M, Vasudevan V, *et al.* Naringenin confers protection against oxidative stress through upregulation of Nrf2 target genes in cardiomyoblast cells. J Physiol Biochem 2014; 70: 407-15.

[22] Mershiba SD, Dassprakash MV, Saraswathy SD. Protective effect of naringenin on hepatic and renal dysfunction and oxidative stress in arsenic intoxicated rats. Mol Biol Rep 2013; 40: 3681-91.

[23] Renugadevi J, Prabu SM. Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. Toxicology 2009; 256: 128-34.

[24] Renugadevi J, Prabu SM. Cadmium-induced hepatotoxicity in rats and the protective effect of naringenin. Exp Toxicol Pathol 2010; 62: 171-81.

[25] Jayaraman J, Veerappan M, Namasivayam N. Potential beneficial effect of naringenin on lipid peroxidation and antioxidant status in rats with ethanol-induced hepatotoxicity. J Pharm Pharmacol 2009; 61: 1383-90.

[26] Wang J, Yang Z, Lin L, *et al.* Protective effect of naringenin against lead-induced oxidative stress in rats. Biol Trace Elem Res 2012; 146: 354-59.

[27] Pari L, Gnanasoundari M. Influence of naringenin on oxytetracycline mediated oxidative damage in rat liver. Basic Clin Pharmacol Toxicol 2006; 98: 456-61.

[28] Hermenean A, Ardelean A, Stan M, *et al.* Antioxidant and Hepatoprotective Effects of Naringenin and Its β-Cyclodextrin Formulation in Mice Intoxicated with Carbon Tetrachloride: A Comparative Study. J Med Food 2014; 17: 670-7.

[29] Hermenean A, Ardelean A, Stan M, *et al.* Protective effects of naringenin on carbon tetrachloride-induced acute nephrotoxicity in mouse kidney. Chem Biol Interact 2013; 205: 138-47.

[30] Arul D, Subramanian P. Inhibitory effect of naringenin (citrus flavonone) on N-nitrosodiethylamine induced hepatocarcinogenesis in rats. Biochem Biophys Res Commun 2013; 434: 203-9.

[31] Mo SF, Zhou F, Lv YZ, *et al.* Hypouricemic action of selected flavonoids in mice: structure-activity relationships. Biol Pharm Bull 2007; 30: 1551-6.

[32] Naoghare PK, Kwon HT, Song JM. On-chip assay for determining the inhibitory effects and modes of action of drugs against xanthine oxidase. J Pharm Biomed Anal 2010; 51: 1-6.

[33] Hämäläinen M, Nieminen R, Vuorela P, *et al.* Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. Mediators Inflamm 2007; 2007: 45673.

[34] Bodet C, La VD, Epifano F, *et al.* Naringenin has anti-inflammatory properties in macrophage and ex vivo human whole-blood models. J Periodontal Res 2008; 43: 400-7.

[35] Herath HM, Takano-Ishikawa Y, Yamaki K. Inhibitory effect of some flavonoids on tumor necrosis factor-alpha production in lipopolysaccharide-stimulated mouse macrophage cell line J774.1. J Med Food 2003; 6: 365-70.

[36] Raso GM, Meli R, Di Carlo G, *et al.* Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1. Life Sci 2001; 68: 921-31.

[37] Vafeiadou K, Vauzour D, Lee HY, *et al.* The citrus flavanone naringenin inhibits inflammatory signalling in glial cells and protects against neuroinflammatory injury. Arch Biochem Biophys 2009; 484: 100-9.

[38] Chao CL, Weng CS, Chang NC, *et al.* Naringenin more effectively inhibits inducible nitric oxide synthase and cyclooxygenase-2 expression in macrophages than in microglia. Nutr Res 2010; 30: 858-64.

[39] Lin WC, Lin JY. Five bitter compounds display different anti-inflammatory effects through modulating cytokine secretion using mouse primary splenocytes in vitro. J Agric Food Chem 2011; 59: 184-92.

[40] Lim R, Barker G, Wall CA, *et al.* Dietary phytophenols curcumin, naringenin and apigenin reduce infection-induced inflammatory and contractile pathways in human placenta, foetal membranes and myometrium. Mol Hum Reprod 2013; 19: 451-62.

[41] Heo HJ, Kim MJ, Lee JM, *et al.* Naringenin from Citrus junos has an inhibitory effect on acetylcholinesterase and a mitigating effect on amnesia. Dement Geriatr Cogn Disord 2004; 17: 151-7.

[42] Khan MB, Khan MM, Khan A, *et al.* Naringenin ameliorates Alzheimer's disease (AD)-type neurodegeneration with cognitive impairment (AD-TNDCI) caused by the intracerebroventricular-streptozotocin in rat model. Neurochem Int 2012; 61: 1081-93.

[43] Baluchnejadmojarad T, Roghani M. Effect of naringenin on intracerebroventricular streptozotocin-induced cognitive deficits in rat: a behavioral analysis. Pharmacology 2006; 78: 193-7.

[44] Yang W, Ma J, Liu Z, *et al.* Effect of naringenin on brain insulin signaling and cognitive functions in ICV-STZ induced dementia model of rats. Neurol Sci 2014; 35: 741-51.

[45] Heo HJ, Kim DO, Shin SC, *et al.* Effect of antioxidant flavanone, naringenin, from Citrus junos on neuroprotection. J Agric Food Chem 2004; 52: 1520-5.

[46] Rahigude A, Bhutada P, Kaulaskar S, *et al.* Participation of antioxidant and cholinergic system in protective effect of naringenin against type-2 diabetes-induced memory dysfunction in rats. Neuroscience 2012; 226: 62-72.

[47] Mercer LD, Kelly BL, Horne MK, *et al.* Dietary polyphenols protect dopamine neurons from oxidative insults and apoptosis: investigations in primary rat mesencephalic cultures. Biochem Pharmacol 2005; 69: 339-45.

[48] Zbarsky V, Datla KP, Parkar S, *et al.* Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. Free Radic Res 2005; 39: 1119-25.

[49] Lou H, Jing X, Wei X, *et al.* Naringenin protects against 6-OHDA-induced neurotoxicity via activation of the Nrf2/ARE signaling pathway. Neuropharmacology 2014; 79: 380-8.

[50] Yi LT, Li CF, Zhan X, *et al.* Involvement of monoaminergic system in the antidepressant-like effect of the flavonoid naringenin in mice. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34: 1223-8.

[51] Olsen HT, Stafford GI, van Staden J, *et al.* Isolation of the MAO-inhibitor naringenin from Mentha aquatica L. J Ethnopharmacol 2008; 117: 500-2.

[52] Yi LT, Li J, Li HC, *et al.* Antidepressant-like behavioral, neurochemical and neuroendocrine effects of naringenin in the mouse repeated tail suspension test. Prog Neuropsychopharmacol Biol Psychiatry 2012; 39: 175-81.

[53] Yi LT, Liu BB, Li J, *et al.* BDNF signaling is necessary for the antidepressant-like effect of naringenin. Prog Neuropsychopharmacol Biol Psychiatry 2014; 48: 135-41.

[54] Amer DA, Kretzschmar G, Müller N, *et al.* Activation of transgenic estrogen receptor-beta by selected phytoestrogens in a stably transduced rat serotonergic cell line. J Steroid Biochem Mol Biol 2010; 120: 208-17.

[55] Raza SS, Khan MM, Ahmad A, *et al.* Neuroprotective effect of naringenin is mediated through suppression of NF-κB signaling pathway in experimental stroke. Neuroscience 2013; 230: 157-71.

[56] Bai X, Zhang X, Chen L, *et al.* Protective Effect of Naringenin in Experimental Ischemic Stroke: Down-Regulated NOD2, RIP2, NF-κB, MMP-9 and Up-Regulated Claudin-5 Expression. Neurochem Res 2014; 39: 1405-15.

[57] Straub I, Mohr F, Stab J, *et al.* Citrus fruit and fabacea secondary metabolites potently and selectively block TRPM3. Br J Pharmacol 2013; 168: 1835-1850.

[58] Hu CY, Zhao YT. Analgesic effects of naringenin in rats with spinal nerve ligation-induced neuropathic pain. Biomed Rep 2014; 2: 569-73.

[59] Kaulaskar S, Bhutada P, Rahigude A, *et al.* Effects of naringenin on allodynia and hyperalgesia in rats with chronic constriction injury-induced neuropathic pain. Zhong Xi Yi Jie He Xue Bao 2012; 10: 1482-9.

[60] Yamagishi N, Yamamoto Y, Noda C, *et al.* Naringenin inhibits the aggregation of expanded polyglutamine tract-containing protein through the induction of endoplasmic reticulum chaperone GRP78. Biol Pharm Bull 2012; 35: 1836-40.

[61] Sarkar A, Angeline MS, Anand K, *et al.* Naringenin and quercetin reverse the effect of hypobaric hypoxia and elicit neuroprotective response in the murine model. Brain Res 2012; 1481: 59-70.

[62] Anderson W, Barrows M, Lopez F, *et al.* Investigation of the anxiolytic effects of naringenin, a component of Mentha aquatica, in the male Sprague-Dawley rat. Holist Nurs Pract 2012; 26: 52-7.

[63] Wu LH, Lin C, Lin HY, *et al.* Naringenin Suppresses Neuroinflammatory Responses Through Inducing Suppressor of Cytokine Signaling 3 Expression. Mol Neurobiol 2015. [Epub ahead of print].

[64] Testai L, Martelli A, Cristofaro M, *et al.* Cardioprotective effects of different flavonoids against myocardial ischaemia/reperfusion injury in Langendorff-perfused rat hearts. J Pharm Pharmacol 2013; 65: 750-6.

[65] Testai L, Martelli A, Marino A, *et al.* The activation of mitochondrial BK potassium channels contributes to the protective effects of naringenin against myocardial ischemia/reperfusion injury. Biochem Pharmacol 2013; 85: 1634-43.

[66] Saponara S, Testai L, Iozzi D, *et al.* (+/-)-Naringenin as large conductance Ca(2+)-activated K+ (BK_{Ca}) channel opener in vascular smooth muscle cells. Br J Pharmacol 2006; 149: 1013-21.

[67] Orallo F, Camiña M, Alvarez E, *et al.* Implication of cyclic nucleotide phosphodiesterase inhibition in the vasorelaxant activity of the citrus-fruits flavonoid (+/-)-naringenin. Planta Med 2005; 71: 99-107.

[68] Xu YC, Leung SW, Yeung DK, *et al.* Structure-activity relationships of flavonoids for vascular relaxation in porcine coronary artery. Phytochemistry 2007; 68: 1179-88.

[69] Ahmed LA, Obaid AA, Zaki HF, *et al.* Naringenin adds to the protective effect of l-arginine in monocrotaline-induced pulmonary hypertension in rats: Favorable modulation of oxidative stress, inflammation and nitric oxide. Eur J Pharm Sci 2014; 62: 161-70.

[70] Herrera MD, Marhuenda E. Effect of naringin and naringenin on contractions induced by noradrenaline in rat vas deferens--I. Evidence for postsynaptic alpha-2 adrenergic receptor. Gen Pharmacol 1993; 24: 739-42.

[71] Capasso R, Fiorino F, Ascione V, *et al.* Inhibition of rat vas deferens contractions by flavonoids in-vitro. J Pharm Pharmacol 2006; 58: 381-4.

[72] Lin C, Ke X, Ranade V, *et al.* The additive effects of the active component of grapefruit juice (naringenin) and antiarrhythmic drugs on HERG inhibition. Cardiology 2008; 110: 145-52.

[73] Zitron E, Scholz E, Owen RW, *et al.* QTc prolongation by grapefruit juice and its potential pharmacological basis: HERG channel blockade by flavonoids. Circulation 2005; 111: 835-8.

[74] Scholz EP, Zitron E, Kiesecker C, *et al.* QS Inhibition of cardiac HERG channels by grapefruit flavonoid naringenin: implications for the influence of dietary compounds on cardiac repolarisation. Naunyn Schmiedebergs Arch Pharmacol 2005; 371: 516-25.

[75] Mojzisová G, Mirossay L, Kucerová D, *et al.* Protective effect of selected flavonoids on in vitro daunorubicin-induced cardiotoxicity. Phytother Res 2006; 20: 110-4.

[76] Mojzisová G, Sarisský M, Mirossay L, *et al.* Effect of flavonoids on daunorubicin-induced toxicity in H9c2 Cardiomyoblasts. Phytother Res 2009; 23: 136-9.

[77] Shiromwar SS, Chidrawar VR. Combined effects of p-coumaric acid and naringenin against doxorubicin-induced cardiotoxicity in rats. Pharmacognosy Res 2011; 3: 214-9.

[78] Arafa HM, Abd-Ellah MF, Hafez HF. Abatement by naringenin of doxorubicin-induced cardiac toxicity in rats. J Egypt Natl Canc Inst 2005; 17: 291-300.

[79] Liu L, Shan S, Zhang K, *et al.* Naringenin and hesperetin, two flavonoids derived from Citrus aurantium up-regulate transcription of adiponectin. Phytother Res 2008; 22: 1400-3.

[80] Richard AJ, Amini-Vaughan Z, Ribnicky DM, *et al.* Naringenin inhibits adipogenesis and reduces insulin sensitivity and adiponectin expression in adipocytes. Evid Based Complement Alternat Med 2013; 2013: 549750.

[81] Wilcox LJ, Borradaile NM, de Dreu LE, *et al.* Secretion of hepatocyte apoB is inhibited by the flavonoids, naringenin and hesperetin, via reduced activity and expression of ACAT2 and MTP. J Lipid Res 2001; 42: 725-34.

[82] Allister EM, Borradaile NM, Edwards JY, *et al.* Inhibition of microsomal triglyceride transfer protein expression and apolipoprotein B100 secretion by the citrus flavonoid naringenin and by insulin involves activation of the mitogen-activated protein kinase pathway in hepatocytes. Diabetes 2005; 54: 1676-83.

[83] Allister EM, Mulvihill EE, Barrett PH, *et al.* Inhibition of apoB secretion from HepG2 cells by insulin is amplified by naringenin, independent of the insulin receptor. J Lipid Res 2008; 49: 2218-29.

[84] Borradaile NM, de Dreu LE, Huff MW. Inhibition of net HepG2 cell apolipoprotein B secretion by the citrus flavonoid naringenin involves activation of phosphatidylinositol 3-kinase, independent of insulin receptor substrate-1 phosphorylation. Diabetes 2003; 52: 2554-61.

[85] Mahrooz A, Rashidi MR, Nouri M. Naringenin is an inhibitor of human serum paraoxonase (PON1): an in vitro study. J Clin Lab Anal 2011; 25: 395-401.

[86] Lee EJ, Kim DI, Kim WJ, *et al.* Naringin inhibits matrix metalloproteinase-9 expression and AKT phosphorylation in tumor necrosis factor-alpha-induced vascular smooth muscle cells. Mol Nutr Food Res 2009; 53: 1582-91.

[87] Chen S, Ding Y, Tao W, *et al.* Naringenin inhibits TNF-α induced VSMC proliferation and migration via induction of HO-1. Food Chem Toxicol 2012; 50: 3025-31.

[88] Xu C, Chen J, Zhang J, *et al.* Naringenin inhibits angiotensin II-induced vascular smooth muscle cells proliferation and migration and decreases neointimal hyperplasia in balloon injured rat carotid arteries through suppressing oxidative stress. Biol Pharm Bull 2013; 36: 1549-55.

[89] Wiejak J, Dunlop J, Mackay SP, *et al.* Flavanoids induce expression of the suppressor of cytokine signalling 3 (SOCS3) gene and suppress IL-6-activated signal transducer and activator of transcription 3 (STAT3) activation in vascular endothelial cells. Biochem J 2013; 454: 283-93.

[90] Chanet A, Milenkovic D, Claude S, *et al.* Flavanone metabolites decrease monocyte adhesion to TNF-α-activated endothelial cells by modulating expression of atherosclerosis-related genes. Br J Nutr 2013; 110: 587-98.

[91] Assini JM, Mulvihill EE, Sutherland BG, *et al.* Naringenin prevents cholesterol-induced systemic inflammation, metabolic dysregulation, and atherosclerosis in $Ldlr^{-/-}$ mice. J Lipid Res 2013; 54: 711-24.

[92] Mulvihill EE, Allister EM, Sutherland BG, *et al.* Naringenin prevents dyslipidemia, apolipoprotein B overproduction, and hyperinsulinemia in LDL receptor-null mice with diet-induced insulin resistance. Diabetes 2009; 58: 2198-210.

[93] Mulvihill EE, Assini JM, Sutherland BG, *et al.* Naringenin decreases progression of atherosclerosis by improving dyslipidemia in high-fat-fed low-density lipoprotein receptor-null mice. Arterioscler Thromb Vasc Biol 2010; 30: 742-8.

[94] Cho KW, Kim YO, Andrade JE, *et al.* Dietary naringenin increases hepatic peroxisome proliferators-activated receptor α protein expression and decreases plasma triglyceride and adiposity in rats. Eur J Nutr 2011; 50: 81-8.

[95] Lee SH, Park YB, Bae KH, *et al.* Cholesterol-lowering activity of naringenin via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and acyl coenzyme A: cholesterol acyltransferase in rats. Ann Nutr Metab 1999; 43: 173-80.

[96] Jeon SM, Kim HK, Kim HJ, *et al.* Hypocholesterolemic and antioxidative effects of naringenin and its two metabolites in high-cholesterol fed rats. Transl Res 2007; 149: 15-21.

[97] Chtourou Y, Slima BA, Makni M, *et al.* Naringenin protects cardiac hypercholesterolemia-induced oxidative stress and subsequent necroptosis in rats. Pharmacol Rep 2015; 67: 1090-7.

[98] Lee CH, Jeong TS, Choi YK, *et al.* Anti-atherogenic effect of citrus flavonoids, naringin and naringenin, associated with hepatic ACAT and aortic VCAM-1 and MCP-1 in high cholesterol-fed rabbits. Biochem Biophys Res Commun 2001; 284: 681-8.

[99] Wood N. Hepatolipidemic effects of naringenin in high cornstarch- versus high coconut oil-fed rats. J Med Food 2004; 7: 315-9.

[100] Huong DT, Takahashi Y, Ide T. Activity and mRNA levels of enzymes involved in hepatic fatty acid oxidation in mice fed citrus flavonoids. Nutrition 2006; 22: 546-52.

[101] Ke JY, Kliewer KL, Hamad EM, *et al.* The flavonoid, naringenin, decreases adipose tissue mass and attenuates ovariectomy-associated metabolic disturbances in mice. Nutr Metab (Lond) 2015; 12: 1.

[102] Cayci C, Wahlquist TC, Seckin SI, *et al.* Naringenin inhibits neointimal hyperplasia following arterial reconstruction with interpositional vein graft. Ann Plast Surg 2010; 64: 105-13.

[103] Li JM, Che CT, Lau CB, *et al.* Inhibition of intestinal and renal Na+-glucose cotransporter by naringenin. Int J Biochem Cell Biol 2006; 38: 985-95.

[104] Zygmunt K, Faubert B, MacNeil J, *et al.* Naringenin, a citrus flavonoid, increases muscle cell glucose uptake via AMPK. Biochem Biophys Res Commun 2010; 398: 178-83.

[105] Purushotham A, Tian M, Belury MA. The citrus fruit flavonoid naringenin suppresses hepatic glucose production from Fao hepatoma cells. Mol Nutr Food Res 2009; 53: 300-7.

[106] Constantin RP, Constantin RP, Bracht A, *et al.* Molecular mechanisms of citrus flavanones on hepatic gluconeogenesis. Fitoterapia 2014; 92: 148-62.

[107] Lin CY, Ni CC, Yin MC, *et al.* Flavonoids protect pancreatic beta-cells from cytokines mediated apoptosis through the activation of PI3-kinase pathway. Cytokine 2012; 59: 65-71.

[108] Yoshida H, Takamura N, Shuto T, *et al.* The citrus flavonoids hesperetin and naringenin block the lipolytic actions of TNF-alpha in mouse adipocytes. Biochem Biophys Res Commun 2010; 394: 728-32.

[109] Harmon AW, Patel YM. Naringenin inhibits phosphoinositide 3-kinase activity and glucose uptake in 3T3-L1 adipocytes. Biochem Biophys Res Commun 2003; 305: 229-34.

[110] Priscilla DH, Roy D, Suresh A, *et al.* Naringenin inhibits α-glucosidase activity: a promising strategy for the regulation of postprandial hyperglycemia in high fat diet fed streptozotocin induced diabetic rats. Chem Biol Interact 2014; 210: 77-85.

[111] Priscilla DH, Jayakumar M, Thirumurugan K. Flavanone naringenin: An effective antihyperglycemic and antihyperlipidemic nutraceutical agent on high fat diet fed streptozotocin induced type 2 diabetic rats. J Funct Foods 2015; 14: 363-73.

[112] Ortiz-Andrade RR, Sánchez-Salgado JC, Navarrete-Vázquez G, *et al.* Antidiabetic and toxicological evaluations of naringenin in normoglycaemic and NIDDM rat models and its implications on

moglycaemic and NIDDM rat models and its implications on extra-pancreatic glucose regulation. Diabetes Obes Metab 2008; 10: 1097-104.

[113] Annadurai T, Muralidharan AR, Joseph T, *et al.* Antihyperglycemic and antioxidant effects of a flavanone, naringenin, in streptozotocin-nicotinamide-induced experimental diabetic rats. J Physiol Biochem 2012; 68: 307-18.

[114] Annadurai T, Thomas PA, Geraldine P. Ameliorative effect of naringenin on hyperglycemia-mediated inflammation in hepatic and pancreatic tissues of Wistar rats with streptozotocin- nicotinamide-induced experimental diabetes mellitus. Free Radic Res 2013; 47: 793-803.

[115] Kannappan S, Anuradha CV. Naringenin enhances insulin-stimulated tyrosine phosphorylation and improves the cellular actions of insulin in a dietary model of metabolic syndrome. Eur J Nutr 2010; 49: 101-9.

[116] Kannappan S, Palanisamy N, Anuradha CV. Suppression of hepatic oxidative events and regulation of eNOS expression in the liver by naringenin in fructose-administered rats. Eur J Pharmacol 2010; 645: 177-84.

[117] Koch CE, Ganjam GK, Steger J, *et al.* The dietary flavonoids naringenin and quercetin acutely impair glucose metabolism in rodents possibly via inhibition of hypothalamic insulin signalling. Br J Nutr 2013; 109: 1040-51.

[118] Fallahi F, Roghani M, Moghadami S. Citrus flavonoid naringenin improves aortic reactivity in streptozotocin-diabetic rats. Indian J Pharmacol 2012; 44: 382-6.

[119] Tsai SJ, Huang CS, Mong MC, *et al.* Anti-inflammatory and antifibrotic effects of naringenin in diabetic mice. J Agric Food Chem 2012; 60: 514-21.

[120] Hasanein P, Fazeli F. Role of naringenin in protection against diabetic hyperalgesia and tactile allodynia in male Wistar rats. J Physiol Biochem 2014; 70: 997-1006.

[121] Kapoor R, Kakkar P. Naringenin accords hepatoprotection from streptozotocin induced diabetes in vivo by modulating mitochondrial dysfunction and apoptotic signaling cascade. Toxicol Rep 2014; 1: 569-81.

[122] Kapoor R, Rizvi F, Kakkar P. Naringenin prevents high glucose-induced mitochondria-mediated apoptosis involving AIF, Endo-G and caspases. Apoptosis 2013; 18: 9-27.

[123] Liu X, Wang W, Hu H, *et al.* Smad3 specific inhibitor, naringenin, decreases the expression of extracellular matrix induced by TGF-beta1 in cultured rat hepatic stellate cells. Pharm Res 2006; 23: 82-9.

[124] Goldwasser J, Cohen PY, Yang E, *et al.* Transcriptional regulation of human and rat hepatic lipid metabolism by the grapefruit flavonoid naringenin: role of PPAR alpha, PPAR gamma and LXR alpha. PLoS One 2010; 5: e12399.

[125] Lv Y, Zhang B, Xing G, *et al.* Protective effect of naringenin against acetaminophen-induced acute liver injury in metallothionein (MT)-null mice. Food Funct 2013; 4: 297-302.

[126] Jayaraman J, Namasivayam N. Naringenin modulates circulatory lipid peroxidation, anti-oxidant status and hepatic alcohol metabolizing enzymes in rats with ethanol induced liver injury. Fundam Clin Pharmacol 2011; 25: 682-9.

[127] Jayaraman J, Jesudoss VA, Menon VP, *et al.* Anti-inflammatory role of naringenin in rats with ethanol induced liver injury. Toxicol Mech Methods 2012; 22: 568-76.

[128] Lee MH, Yoon S, Moon JO. The flavonoid naringenin inhibits dimethylnitrosamine-induced liver damage in rats. Biol Pharm Bull 2004; 27: 72-6.

[129] Esmaeili MA, Alilou M. Naringenin attenuates CCl4-induced hepatic inflammation by the activation of an Nrf2-mediated pathway in rats. Clin Exp Pharmacol Physiol 2014; 41: 416-22.

[130] Yang J, Li Q, Zhou XD, *et al.* Naringenin attenuates mucous hypersecretion by modulating reactive oxygen species production and inhibiting NF-κB activity via EGFR-PI3K-Akt/ERK MAPKinase signaling in human airway epithelial cells. Mol Cell Biochem 2011; 351: 29-40.

[131] Yu DH, Ma CH, Yue ZQ, *et al.* Protective effect of naringenin against lipopolysaccharide-induced injury in normal human bronchial epithelium via suppression of MAPK signaling. Inflammation 2015; 38: 195-204.

[132] Zhang Y, Wang JF, Dong J, *et al.* Inhibition of α-toxin production by subinhibitory concentrations of naringenin controls Staphylococcus aureus pneumonia. Fitoterapia 2013; 86: 92-9.

[133] Shi Y, Dai J, Liu H, *et al.* Naringenin inhibits allergen-induced airway inflammation and airway responsiveness and inhibits NF-kappaB activity in a murine model of asthma. Can J Physiol Pharmacol 2009; 87: 729-35.

[134] Shi Y, Tan Y, Mao S, *et al.* Naringenin inhibits allergen-induced airway remodeling in a murine model of asthma. Mol Med Rep 2014; 9: 1204-1208.

[135] Lin BQ, Li PB, Wang YG, *et al.* The expectorant activity of naringenin. Pulm Pharmacol Ther 2008; 21: 259-63.

[136] Fouad AA, Albuali WH, Zahran A, *et al.* Protective effect of naringenin against gentamicin-induced nephrotoxicity in rats. Environ Toxicol Pharmacol 2014; 38: 420-9.

[137] Badary OA, Abdel-Maksoud S, Ahmed WA, *et al.* Naringenin attenuates cisplatin nephrotoxicity in rats. Life Sci 2005; 76: 2125-35.

[138] Gnanasoundari M, Pari L. Impact of naringenin on oxytetracycline-mediated oxidative damage in kidney of rats. Ren Fail 2006; 28: 599-605.

[139] Waheed A, Ludtmann MH, Pakes N, *et al.* Naringenin inhibits the growth of Dictyostelium and MDCK-derived cysts in a TRPP2 (polycystin-2)-dependent manner. Br J Pharmacol 2014; 171: 2659-70.

[140] Yang ZH, Pan A, Zuo WL, *et al.* Relaxant effect of flavonoid naringenin on contractile activity of rat colonic smooth muscle. J Ethnopharmacol 2014; 155: 1177-83.

[141] Amira S, Rotondo A, Mulè F. Relaxant effects of flavonoids on the mouse isolated stomach: structure-activity relationships. Eur J Pharmacol 2008; 599: 126-30.

[142] Motilva V, Alarcón de la Lastra C, Martín MJ. Ulcer-protecting effects of naringenin on gastric lesions induced by ethanol in rat: role of endogenous prostaglandins. J Pharm Pharmacol 1994; 46: 91-4.

[143] Yang ZH, Yu HJ, Pan A, *et al.* Cellular mechanisms underlying the laxative effect of flavonol naringenin on rat constipation model. PLoS One 2008; 3: e3348.

[144] Collins D, Kopic S, Geibel JP, *et al.* The flavonone naringenin inhibits chloride secretion in isolated colonic epithelia. Eur J Pharmacol 2011; 668: 271-7.

[145] Gharzouli K, Holzer P. Inhibition of guinea pig intestinal peristalsis by the flavonoids quercetin, naringenin, apigenin and genistein. Pharmacology 2004; 70: 5-14.

[146] Azuma T, Shigeshiro M, Kodama M, *et al.* Supplemental Naringenin Prevents Intestinal Barrier Defects and Inflammation in Colitic Mice. J Nutr 2013; 143: 827-34.

[147] Dou W, Zhang J, Sun A, *et al.* Protective effect of naringenin against experimental colitis via suppression of Toll-like receptor 4/NF-κB signalling. Br J Nutr 2013; 110: 599-608.

[148] Al-Rejaie SS, Abuohashish HM, Al-Enazi MM, *et al.* Protective effect of naringenin on acetic acid-induced ulcerative colitis in rats. World J Gastroenterol 2013; 19: 5633-44.

[149] Park M, Kim K, Lee YM, *et al.* Naringenin stimulates cholecystokinin secretion in STC-1 cells. Nutr Res Pract 2014; 8: 146-50.

[150] Yang Y, Xu Y, Xia T, *et al.* A single-molecule study of the inhibition effect of Naringenin on transforming growth factor-β ligand-receptor binding. Chem Commun (Camb) 2011; 47: 5440-2.

[151] Kapoor S. Tumor Growth Attenuating Effects of Naringenin. Pathol Oncol Res 2014; 20: 483.

[152] Kanno S, Tomizawa A, Hiura T, *et al.* Inhibitory effects of naringenin on tumor growth in human cancer cell lines and sarcoma S-180-implanted mice. Biol Pharm Bull 2005; 28: 527-30.

[153] Lou C, Zhang F, Yang M, *et al.* Naringenin decreases invasiveness and metastasis by inhibiting TGF-β-induced epithelial to mesenchymal transition in pancreatic cancer cells. PLoS One 2012; 7: e50956.

[154] Sabarinathan D, Mahalakshmi P, Vanisree AJ. Naringenin promote apoptosis in cerebrally implanted C6 glioma cells. Mol Cell Biochem 2010; 345: 215-22.

[155] Sabarinathan D, Mahalakshmi P, Vanisree AJ. Naringenin, a flavanone inhibits the proliferation of cerebrally implanted C6 glioma cells in rats. Chem Biol Interact 2011; 189: 26-36.

[156] Sabarinathan D, Vanisree AJ. Plausible role of naringenin against cerebrally implanted C6 glioma cells in rats. Mol Cell Biochem 2013; 375: 171-8.

[157] Ruh MF, Zacharewski T, Connor K, *et al.* Naringenin: a weakly estrogenic bioflavonoid that exhibits antiestrogenic activity. Biochem Pharmacol 1995; 50: 1485-93.

[158] So FV, Guthrie N, Chambers AF, *et al.* Inhibition of proliferation of estrogen receptor-positive MCF-7 human breast cancer cells by flavonoids in the presence and absence of excess estrogen. Cancer Lett 1997; 112: 127-33.

[159] Harmon AW, Patel YM. Naringenin inhibits glucose uptake in MCF-7 breast cancer cells: a mechanism for impaired cellular proliferation. Breast Cancer Res Treat 2004; 85: 103-10.

[160] Hatkevich T, Ramos J, Santos-Sanchez I, *et al.* A naringenin-tamoxifen combination impairs cell proliferation and survival of MCF-7 breast cancer cells. Exp Cell Res 2014; 327: 331-9.

[161] Liu L, Xu DM, Cheng YY. Distinct effects of naringenin and hesperetin on nitric oxide production from endothelial cells. J Agric Food Chem 2008; 56: 824-9.

[162] van Meeuwen JA, Korthagen N, de Jong PC, *et al.* (Anti)estrogenic effects of phytochemicals on human primary mammary fibroblasts, MCF-7 cells and their co-culture. Toxicol Appl Pharmacol 2007; 221: 372-83.

[163] Kim S, Park TI. Naringenin: a partial agonist on estrogen receptor in T47D-KBluc breast cancer cells. Int J Clin Exp Med 2013; 6: 890-9.

[164] Bulzomi P, Bolli A, Galluzzo P, *et al.* The naringenin-induced proapoptotic effect in breast cancer cell lines holds out against a high bisphenol a background. IUBMB Life 2012; 64: 690-6.

[165] Qin L, Jin L, Lu L, *et al.* Naringenin reduces lung metastasis in a breast cancer resection model. Protein Cell 2011; 2: 507-16.

[166] Brozic P, Smuc T, Gobec S, *et al.* Phytoestrogens as inhibitors of the human progesterone metabolizing enzyme AKR1C1. Mol Cell Endocrinol 2006; 259: 30-42.

[167] Edmunds KM, Holloway AC, Crankshaw DJ, *et al.* The effects of dietary phytoestrogens on aromatase activity in human endometrial stromal cells. Reprod Nutr Dev 2005; 45: 709-20.

[168] Arul D, Subramanian P. Naringenin (Citrus Flavonone) Induces Growth Inhibition, Cell Cycle Arrest and Apoptosis in Human Hepatocellular Carcinoma Cells. Pathol Oncol Res 2013; 19: 763-70.

[169] Yen HR, Liu CJ, Yeh CC. Naringenin suppresses TPA-induced tumor invasion by suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells. Chem Biol Interact 2015; 235: 1-9.

[170] Orsolić N, Kosalec I, Basić I. Synergistic antitumor effect of polyphenolic components of water soluble derivative of propolis against Ehrlich ascites tumour. Biol Pharm Bull 2005; 28: 694-700.

[171] Anand K, Sarkar A, Kumar A, *et al.* Combinatorial antitumor effect of naringenin and curcumin elicit angioinhibitory activities in vivo. Nutr Cancer 2012; 64: 714-24.

[172] Subramanian P, Arul D. Attenuation of NDEA-induced hepatocarcinogenesis by naringenin in rats. Cell Biochem Funct 2013; 31: 511-7.

[173] Ling D, Marshall GM, Liu PY, *et al.* Enhancing the anticancer effect of the histone deacetylase inhibitor by activating transglutaminase. Eur J Cancer 2012; 48: 3278-87.

[174] Huang YC, Yang CH, Chiou YL. Citrus flavanone naringenin enhances melanogenesis through the activation of Wnt/β-catenin signalling in mouse melanoma cells. Phytomedicine 2011; 18: 1244-9.

[175] Ogiwara K, Akao Y, Nozawa Y. Stimulation of melanogenesis by the citrus flavonoid naringenin in mouse B16 melanoma cells. Biosci Biotechnol Biochem 2006; 70: 1499-501.

[176] Lentini A, Forni C, Provenzano B, *et al.* Enhancement of transglutaminase activity and polyamine depletion in B16-F10 melanoma cells by flavonoids naringenin and hesperitin correlate to reduction of the in vivo metastatic potential. Amino Acids 2007; 32: 95-100.

[177] Menon LG, Kuttan R, Kuttan G. Inhibition of lung metastasis in mice induced by B16F10 melanoma cells by polyphenolic compounds. Cancer Lett 1995; 95: 221-5.

[178] Jin CY, Park C, Hwang HJ, *et al.* Naringenin up-regulates the expression of death receptor 5 and enhances TRAIL-induced apoptosis in human lung cancer A549 cells. Mol Nutr Food Res 2011; 55: 300-9.

[179] Du G, Jin L, Han X, *et al.* Naringenin: a potential immunomodulator for inhibiting lung fibrosis and metastasis. Cancer Res 2009; 69: 3205-12.

[180] Gopalakrishnan A, Xu CJ, Nair SS, *et al.* Modulation of activator protein-1 (AP-1) and MAPK pathway by flavonoids in human prostate cancer PC3 cells. Arch Pharm Res 2006; 29: 633-44.

[181] Gao K, Henning SM, Niu Y, *et al.* The citrus flavonoid naringenin stimulates DNA repair in prostate cancer cells. J Nutr Biochem 2006; 17: 89-95.

[182] Papiez MA. Influence of naringenin on the activity of enzymes participating in steroidogenesis in male rats. Rocz Akad Med Bialymst 2004; 49: 120-2.

[183] Han HY, Shan S, Zhang X, *et al.* Down-regulation of prostate specific antigen in LNCaP cells by flavonoids from the pollen of Brassica napus L. Phytomedicine 2007; 14: 338-43.

[184] Leonardi T, Vanamala J, Taddeo SS, *et al.* Apigenin and naringenin suppress colon carcinogenesis through the aberrant crypt stage in azoxymethane-treated rats. Exp Biol Med (Maywood) 2010; 235: 710-7.

[185] Frydoonfar HR, McGrath DR, Spigelman AD. The variable effect on proliferation of a colon cancer cell line by the citrus fruit flavonoid Naringenin. Colorectal Dis 2003; 5: 149-52.

[186] Ekambaram G, Rajendran P, Magesh V, *et al.* Naringenin reduces tumor size and weight lost in N-methyl-N'-nitro-N-nitrosoguanidine-induced gastric carcinogenesis in rats. Nutr Res 2008; 28: 106-12.

[187] Park JH, Jin CY, Lee BK, *et al.* Naringenin induces apoptosis through downregulation of Akt and caspase-3 activation in human leukemia THP-1 cells. Food Chem Toxicol 2008; 46: 3684-90.

[188] Kanno S, Tomizawa A, Ohtake T, *et al.* Naringenin-induced apoptosis via activation of NF-kappaB and necrosis involving the loss of ATP in human promyeloleukemia HL-60 cells. Toxicol Lett 2006; 166: 131-9.

[189] Zuo XL, Zhou Y, Li RF, *et al.* Relation of apoptosis of K562 cells induced by naringenin in vitro to enzyme activity changes of caspase-3 and caspase-8 and expression of FAS/FASL proteins. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2008; 16: 286-9.

[190] Li RF, Feng YQ, Chen JH, *et al.* Naringenin suppresses K562 human leukemia cell proliferation and ameliorates Adriamycin-induced oxidative damage in polymorphonuclear leukocytes. Exp Ther Med 2015; 9: 697-706.

[191] Sulfikkarali N, Krishnakumar N, Manoharan S, *et al.* Chemopreventive Efficacy of Naringenin-Loaded Nanoparticles in 7,12-dimethylbenz(a)anthracene Induced Experimental Oral Carcinogenesis. Pathol Oncol Res 2013; 19: 287-96.

[192] Krishnakumar N, Sulfikkarali NK, Manoharan S, *et al.* Raman spectroscopic investigation of the chemopreventive response of naringenin and its nanoparticles in DMBA-induced oral carcinogenesis. Mol Biomol Spectrosc 2013; 115: 648-53.

[193] Miller EG, Peacock JJ, Bourland TC, *et al.* Inhibition of oral carcinogenesis by citrus flavonoids. Nutr Cancer 2008; 60: 69-74.

[194] Sanderson JT, Hordijk J, Denison MS, *et al.* Induction and inhibition of aromatase (CYP19) activity by natural and synthetic flavonoid compounds in H295R human adrenocortical carcinoma cells. Toxicol Sci 2004; 82: 70-9.

[195] Galluzzo P, Ascenzi P, Bulzomi P, *et al.* The nutritional flavanone naringenin triggers antiestrogenic effects by regulating estrogen receptor alpha-palmitoylation. Endocrinology 2008; 149: 2567-75.

[196] Bulzomi P, Bolli A, Galluzzo P, *et al.* Naringenin and 17 beta-estradiol coadministration prevents hormone-induced human cancer cell growth. IUBMB Life 2010; 62: 51-60.

[197] Ahamad MS, Siddiqui S, Jafri A, *et al.* Induction of apoptosis and antiproliferative activity of naringenin in human epidermoid carcinoma cell through ROS generation and cell cycle arrest. PLoS One 2014; 9: e110003.

[198] Zhang FY, Du GJ, Zhang L, *et al.* Naringenin enhances the anti-tumor effect of doxorubicin through selectively inhibiting the activity of multidrug resistance-associated proteins but not P-glycoprotein. Pharm Res 2009; 26: 914-25.

[199] Liao AC, Kuo CC, Huang YC, *et al.* Naringenin inhibits migration of bladder cancer cells through downregulation of AKT and MMP 2. Mol Med Rep 2014; 10: 1531-6.

[200] Gupta V, Srivastava M, Maurya R, *et al.* HPLC Method Development for Naringenin and its Glucoside in Rat Serum and their Bioavailibilty Studies. J Bioequiv Availab 2012; S14: 10.

[201] Yoon H, Kim TW, Shin SY, *et al.* Design, synthesis and inhibitory activities of naringenin derivatives on human colon cancer cells. Bioorg Med Chem Lett 2013; 23: 232-8.

[202] Yang LJ, Ma SX, Zhou SY, *et al.* Preparation and characterization of inclusion complexes of naringenin with β-cyclodextrin or its derivative. Carbohydr Polym 2013; 98: 861-9.

[203] Maiti K, Mukherjee K, Gantait A, *et al.* Enhanced therapeutic potential of naringenin-phospholipid complex in rats. J Pharm Pharmacol 2006; 58: 1227-33.

[204] Shulman M, Cohen M, Soto-Gutierrez A, *et al.* Enhancement of naringenin bioavailability by complexation with hydroxypropyl-β-cyclodextrin. PLoS One 2011; 6: e18033.

[205] Xin-rong Xu, Hai-tao Yu, Li Hang, *et al.* Preparation of naringenin/β-cyclodextrin complex and its more potent alleviative effect on choroidal neovascularization in rats. BioMed Research International 2014; 2014: 9.

[206] Khan AW, Kotta S, Ansari SH, *et al.* Enhanced dissolution and bioavailability of grapefruit flavonoid Naringenin by solid dispersion utilizing fourth generation carrier. Drug Dev Ind Pharm 2015; 41: 772-9.

[207] Kanaze FI, Kokkalou E, Niopas I, *et al.* Dissolution rate and stability study of flavanoneaglycones, naringenin and hesperetin, by drug delivery systems based on polyvinylpyrrolidone (PVP) nanodispersions. Drug Dev Ind Pharm 2010; 36: 292-301.

[208] Khan AW, Kotta S, Ansari SH, *et al.* Self-nanoemulsifying drug delivery system (SNEDDS) of the poorly water-soluble grapefruit flavonoid naringenin: design, characterization, in vitro and in vivo evaluation. Drug Deliv 2015; 22: 552-61.

[209] Krishnakumar N, Sulfikkarali N, RajendraPrasad N, *et al.* Enhanced anticancer activity of naringenin-loaded nanoparticles in human cervical (HeLa) cancer cells. Biomedicine & Preventive Nutrition 2011; 1: 223-31.

[210] Yen FL, Wu TH, Lin LT, *et al.* Naringenin-loaded nanoparticles improve the physicochemical properties and the hepatoprotective effects of naringenin in orally-administered rats with CCl(4)-induced acute liver failure. Pharm Res 2009; 26: 893-902.

[211] Wang K, Liu T, Lin R, *et al.* Preparation and in vitro release of buccal tablets of naringenin-loaded MPEG-PCL nanoparticles. RSC Advances 2014; 4: 33672.

[212] NaitChabane M, Al Ahmad A, Peluso J, *et al.* Quercetin and naringenin transport across human intestinal Caco-2 cells. J Pharm Pharmacol 2009; 61: 1473-83.

.