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Review Paper

Ameliorative nature of flavonoid naringin: A comprehensive review of antitoxic effects

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ABSTRACT

Naringin is a flavonoid abundantly found in *Citrus* L. spp. with diverse applications. The present review emphasizes on the ameliorative role of naringin against hepatotoxicity, neurotoxicity, renal toxicity and cardiotoxicity. Naringin has been found to be a strong antioxidant and beneficial in inflammation cases. Its supplementation revealed a drop in pathological changes in liver, brain and kidney tissues in hyperammonemia conditions. Naringin also regulates the expressions of glutamine synthetase, neuronal nitric oxide and soluble guanylate cyclase. It also inhibits some virus activities including herpes simplex. Treatment with naringin was found to be associated with controlled serum creatinine, blood urea nitrogen, bilirubin, aspartate transaminase, alanine transaminase and low-density lipoproteins. It has also been found to possess ameliorative properties against cardiac toxicity and hypertrophy. It improves myocardial fibrosis by modulating p38 and PKC-beta protein expressions. It also enhances oxidative enzyme activities and regulate the increase in malondialdehyde, protein carbonyls and tumour necrosis factor-alpha concentrations. Naringin, as one of the key flavonoids, possesses enormous potential to mitigate the effects of harmful drugs. It is a robust antitoxic agent revealing resilient action against hepato-, neuro-, renal and cardio-toxicity. Naringin may be used as a strong therapeutic agent to cure disease like herpes, diabetes, alcoholism and heart failure.

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1. Introduction

Flavonoids are widely distributed in plants having enormous benefits and diverse biologic activities (Singh, 2018). These activities may include antioxidant effect, modulation of the enzymatic activity and inhibition of cellular proliferation (Jucá et al., 2018). The extract of *Achillea* spp. is reported to have ethnopharmacological uses like treatment of stomachache, inflammation, hemorrhoid, hay fever, and wound healing (Mohammadhosseini et al., 2017). Phytochemical analysis on the total aerial parts of *Galeopsis ladanum* subsp. *angustifolia* revealed that it has enormous potential to be used in the ethnopharmacological field. Moreover, no potential toxic component was found (Frezza et al., 2017). The volatile fraction extracts obtained from *Ferula* spp. are found to have anti-proliferative, anti-inflammatory and neuroprotective properties (Mohammadhosseini et al., 2019). Arq Zeera is reported to have anti-hyperlipidemic action against high fat diet through lipid lowering action, reduction of intestinal absorption of dietary fat, and increased antioxidant defence (Haque and Ansari, 2018). Similarly, extracts obtained from *Ziziphora* spp. are reported to possess similar properties (Mohammadhosseini et al., 2017). Phytochemical analysis of *Styrax officinalis* L. (Styracaceae) fruit revealed that it might be a useful source of enantiopure 1,5-anhydro-D-mannitol which has ancient ethnopharmacological and medicinal uses (Venditti et al., 2018).

Bioactivity of eight newly synthesized acacetin-7-O-methyl ether Mannich based derivatives from naringin was examined and it was found that most of them exhibited moderate or potent acetylcholinesterase (AChE) inhibitory activity (Liu et al., 2018). Similarly, flowers of *Osmathus fragrans* were found to have numerous flavonoid compounds including quercetin, rutin, verbascoside, genistin, kaempferol, isorhamnetin

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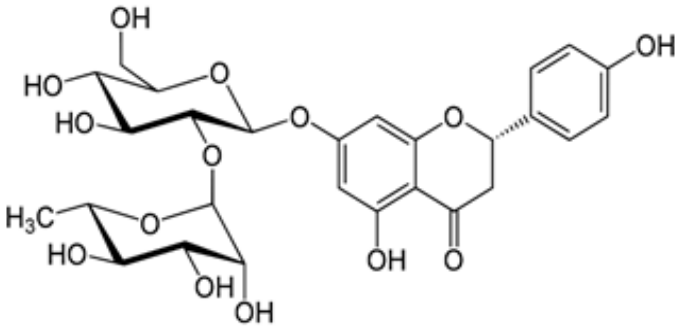

Fig. 1. Structure of naringin.

and naringin which exhibited good free radical scavenging activity (Zhou et al., 2018). The methanolic extracts of *Adonidia merrillii* fruits exhibited higher antioxidant activity as compared to the ethyl acetate and water extracts in 2,2'-diphenyl-1-picryl-hydrazyl-hydrate (DPPH), nitric Oxide (NO_2) and 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS) scavenging assays (Vafaei et al., 2018). The red wines were found to have more total phenolic content (TPC) and radial scavenging activity (RSA) when quantified with ultra high-performance liquid chromatography (UHPLC) (Pantelić et al., 2017). Methanol extract of *Indigofera hirsuta* was used to derive ethyl acetate fraction which showed the greatest antioxidant capacity and butanol was found to be the strongest inhibitor of lipoxygenase enzyme (Karakousi et al., 2018). Extracts (water, ethanol, and methanol) of *Rheum ribes* stems were found to possess effective antiradical and cytotoxic properties in PC-3, A2780, HCT-116 and MCF-7 cancer cell lines (Keser et al., 2018). High resolution mass spectrometric analysis of *Ovale calabrese* revealed high contents of phytochemical compounds which confirmed the potential use of the *Ovale calabrese* as a rich source of nutraceutical compounds (Celano et al., 2018). Commonly the flavonoids have a property of protective effects against free radicals by stimulating the production of a strong antioxidant glutathione. Naringin has numerous benefits and it is gaining popularity day by day. Vitamin C is a proved antioxidant and naringin can even enhance its antioxidative properties (Punithavathi et al., 2008).

1.1. Chemistry and structure of naringin

A basic flavonoid has about 15 carbon atoms arranged in 3 rings, 2 of which are benzene. Naringin has the basic flavonoid structure and two rhamnose units attached to its aglycone portion at 7 carbon position. Naringin has chemical formula $C_{27}H_{32}O_{14}$ and molar mass of 580.54 g/mol and it is a conjugate product of naringenin and sugar molecule. It has two more alternative names as 4,5,7-trihydroxyflavanone 7-rhamnoglucoside and naringenin-7-neohesperidoside. The structure of naringin is shown in Fig. 1.

1.2. Pharmacological properties of naringin

Flavonoids recovered from *Citrus* L. spp. constitute an important series of flavonoids due to enormous associated health benefits (Alam et al., 2014; Viswanatha et al., 2017). Naringin has been reported to show broad spectrum of pharmacological properties including lipid-lowering, anti-inflammatory (Kawaguchi et al., 2011), free radical-scavenging, anti-fibrosis and anti-obesity effects (Singh et al., 2018). Naringin was found to display strong anti-inflammatory and antioxidant activities (Alam et al., 2014). A number of molecular mechanisms underlying its beneficial activities have also been elucidated in different studies. Recently, the ability of naringin to prevent neuro-degeneration in a neurotoxin model of Parkinson's disease was reported (Jung and Kim, 2014). Intraperitoneal injection of naringin was found to protect the nigrostriatal dopaminergic projection by increasing glial cell line-derived neurotrophic factor expression. Similarly, another study investigated the protective effects of naringin against the colchicine-induced cognitive impairment and oxidative damage in rats. Naringin caused significant improvement in the cognitive performance and attenuated oxidative damage which was evident by lowering of malondialdehyde level and nitrite concentration; restoration of superoxide dismutase, catalase, glutathione S-transferase, reduced glutathione levels and acetylcholinesterase activity compared to control (Kumar et al., 2010).

Naringin is most commonly used in supplements to reduce the effect of free radicals in the body and to enhance the availability of nutrients in the body. It can also inhibit some virus activities like in case of herpes simplex (Kaul et al., 1985). Naringin, when administered orally, prevents some of the digestive enzyme actions so that nutrients are not broken down and are directly absorbed in blood stream, ultimately increasing the nutrient absorption in the body. It also enhances the drug absorption in the blood.

2. Action against neurotoxicity

Naringin has been found effective in reducing neurotoxicity by mitigating hyperammonemia.

Ammonium chloride (NH_4Cl) induced hyperammonemic rats were treated with naringin (80mg/kg b.w.) via oral gavages. Its supplementation retrogressed the pathological changes in liver, brain and kidney tissues. The expressions of glutamine synthetase (GS), neuronal nitric oxide (nNOS) and soluble guanylate cyclase (sGC) in hyperammonemic rats were also found to be regulated (Ramakrishnan et al., 2016). Naringin was found to ameliorate HIV-1 nucleoside reverse transcriptase inhibitors (NRTI)-induced mitochondrial toxicity (Oluwafeyisetan et al., 2016). Rats were randomly distributed into four groups viz. Zidovudine (AZT)-only (100 mg/kg body weight- BW), AZT+Naringin (100+50 mg/kg BW), Stavudine (d4T)-only (50 mg/kg BW), d4T+Naringin (50+50 mg/kg BW) and were exposed for 56 days. Naringin alleviated mitochondrial malondialdehyde (MDA) and blood lactate concentrations, increased liver manganese superoxide dismutase (MnSOD) and upregulated ETC complex IV protein (Oluwafeyisetan et al., 2016). Similarly, naringin was also found to significantly increase ($p<0.05$) myocardial mitochondrial enzymes (I-IV) activity (Adil et al., 2016a). Thus, naringin was reported to mitigate mitochondrial damage observed in AZT- or d4T-only treated rats.

3. Action against hepatic and renal toxicity

Naringin has been found beneficial in both hepatic and renal toxicity conditions. In two different studies by Adil et al. (Adil et al., 2016b; Adil et al., 2015), naringin was found to attenuate acetaminophen (APAP) and arsenic-induce hepatic and renal toxicities in rats. APAP is a common analgesic and antipyretic agent which may cause hepatic and renal toxicities at a higher doses. Naringin (20, 40 and 80 mg/kg, p.o.) was administered to rats 2 h before APAP (700 mg/kg, p.o., 14 days). Naringin pre-treatment, substantially decreased ($p<0.05$) serum creatinine, blood urea nitrogen, bilirubin, aspartate transaminase, alanine transaminase, low-density lipoprotein, very low-density lipoprotein, cholesterol, triglycerides and restored mRNA expression of hepatic farnesoid X receptor and renal injury molecule-1 (KIM-1) as compared to control rats (Adil et al., 2016b). Similarly, in the second study, treatment with naringin (40 and 80 mg/kg) substantially and dose-dependently ($p<0.01$ and $p<0.001$) restored level of kidney and liver by down-regulation of elevated oxido-nitrosative stress, KIM-1, Caspase-3, TGF-beta, and TNF-alpha levels, thus reducing the arsenic induced toxicity. Naringin restored the parameters of liver function (AST and ALT) induced by sodium arsenite (Adil et al., 2015).

4. Action against cardiac toxicity

Naringin has been found to play a vital role in protective effects against cardiac toxicities (Adebiyi et al., 2016a; Adebiyi et al., 2016b). It has been found to possess ameliorative effects against doxorubicin and arsenic-induced cardiac toxicity (Adil et al., 2016a; Kwatra et al., 2016). Naringin (40 and 80 mg/kg, p.o.) appreciably inhibited ($p<0.05$) arsenite-induced cardiac markers including LDH, CK-MB, AST, ALT, and ALP. It also altered the lipid metabolism including total cholesterol, triglyceride, LDL, HDL, and VLDL. Alteration in heart Nrf-2, HO-1, Smad-3, and TGF-beta mRNA expression was also restored (Adil et al., 2016a). In the same line, Kwatra et al. (2016) showed Naringin (100 mg/kg) to be cardio-protective against Dox-induced acute cardiac toxicity in rats. Naringin has also been reported for preventive effect on lipid peroxides and antioxidants in isoproterenol-induced cardio-toxicity in Wistar rats (Rajadurai and Stanely Mainzen, 2006). In a study by Adebiyi et al. (2016a), the effects of naringin on hyperglycemia-associated activation of c-Jun Nuclear Kinase (JNK-1) and cardiac hypertrophy (CH) were investigated in Sprague-Dawley rats. Naringin treatment of diabetic rats significantly reversed the CH indices. In another study, naringin has been shown to ameliorate myocardial fibrosis by modulating p38 and PKC-beta protein expression (Adebiyi et al., 2016b).

5. Action against nephrotoxicity

Various common drugs including aspirin and ibuprofen, when taken in higher amounts may result in serious side-effects on kidney. Naringin has proved to reduce the nephrotoxic effects of several drugs like cisplatin, cyclosporine and metals including nickel (Amudha and Pari, 2011). In a study by Chandramohan and Parameswari (2013), naringin was reported to reduce cyclosporine A-induced nephrotoxicity in rats. Co-treatment of naringin with cyclosporine-A reduced the levels of lipid peroxides, hydroxyl radicals and restored the levels of heme oxygenase-1. Levels of enzymic and non-enzymic antioxidants were also reinstated in renal tissues (Chandramohan and Parameswari, 2013). In another study, naringin alleviated the nickel induced nephrotoxicity. Here, naringin was administered orally (20, 40 and 80mg/kg b.w.) which attenuated lipid peroxidation and reduced nickel concentration in blood and kidney (Amudha and Pari, 2011).

6. Action against oxidative stress and inflammation

Naringin has been shown to affect oxidative stress levels by regulating many enzymes involved in lipid peroxidation. A number of studies report the role of naringin in reducing the oxidative stress levels (Kwatra et al., 2016; Oluwafeyisetan et al., 2016; Punithavathi et al., 2008) including the levels of malondialdehyde (MDA) (Adebiyi et al., 2016b; Chtourou et al., 2015; Kwatra et al., 2016; Oluwafeyisetan et al., 2016), SOD (Chandramohan and Parameswari, 2013; Chtourou et al., 2015; Jain and Parmar, 2011; Kwatra et al., 2016; Oluwafeyisetan et al.,

2016) and catalase (Chandramohan and Parameswari, 2013; Chtourou et al., 2015; Jain and Parmar, 2011; Kwatra et al., 2016; Pari and Amudha, 2011; Rajadurai and Stanely Mainzen, 2006). A study by Chtourou et al. (2015) reported the protective role of naringin against cisplatin induced oxidative stress and inflammatory response. Administration of Naringin (25, 50 and 100mg/kg) attenuated the deterioration in striatum tissue, abrogate oxidative enzyme activities and suppressed the increase in MDA, protein carbonyls, nitrite concentration and tumour necrosis factor -alpha concentrations (Chtourou et al., 2015). Naringin shows a preventive effect on lipid peroxides and antioxidants in isoproterenol-induced toxicity in Wistar rats. Oral administration of naringin (10, 20 and 40 mg/kg) to isoproterenol exposed rats showed a considerable decrease in the levels of lipid peroxidative products including superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in the heart; reduced glutathione, vitamin C and vitamin E in plasma and heart (Rajadurai and Stanely Mainzen, 2006). Naringin mitigates cardiac hypertrophy by inhibiting oxidative stress leading to inactivation of JNK-1 (Adebiyi et al., 2016a). Mitochondrial reactive oxygen species (ROS) generation and defective oxidative phosphorylation (OXPHOS) have been proposed as possible mechanisms underlying the development of nucleoside reverse transcriptase inhibitors (NRTIs)-induced mitochondrial toxicities. Naringin administration reversed the indices of mitochondrial dysfunction as revealed by significantly reduced mitochondrial malondialdehyde (MDA) and blood lactate concentrations; and increased liver manganese superoxide dismutase (MnSOD) activity (Oluwafeyisetan et al., 2016).

Naringin has been found to be anti-inflammatory and anti-oxidative in rat air pouch model of inflammation. Carrageenan and naringin treatment normalized lipid peroxidation, TNF-alpha, activity of CAT, number of total leukocytes and neutrophils along with increase in lymphocytes and nitrite concentration (Jain and Parmar, 2011). Arsenic-induced hepatic and renal toxicity was also reported to be reduced via anti-oxidative nature of Naringin (Adil et al., 2015). Amelioration of myocardial fibrosis possibly through its known antioxidant actions is also described for naringin (Adebiyi et al., 2016b).

7. Action against metal or metalloid induced toxicity

Metals are known for their toxic nature in different biological systems (Singh and Chadha, 2012; Singh and Chadha, 2013; Singh and Chadha, 2014; Singh and Chadha, 2015a; Su et al., 2017; Yin et al., 2018). Different metals have also been reported to have a positive effect on oxidative stress levels (Singh and Chadha, 2013). Naringin has been presented to have hepato-protective effects on nickel induced toxicity in liver of male Wistar rats (Pari and Amudha, 2011). Naringin administered orally (20, 40 and 80mg/kg b.w.) reversed the activities of hepatic marker enzymes, increasing the antioxidant cascade and decreasing the nickel concentration and decreasing lipid peroxidation markers in liver in rats. In another study, Naringin abated the adverse effects of cadmium-mediated hepatotoxicity (Rathi et al., 2017). Here an optimal concentration of Naringin (5 μM) was potent enough to confer cyto-protection against $CdCl_2$ (50 μM) as observed by MTT assay. Similarly, another study revealed nephron-protective nature of naringin. Naringin alleviated the nickel induced nephrotoxicity in rats where Naringin was administered orally (20, 40 and 80 mg/kg b.w.) with i.p. administration of Ni (Amudha and Pari, 2011). Treatment with naringin attenuated the alterations in the renal and urine markers, decreasing lipid peroxidation markers, increasing the antioxidant cascade and decreasing the nickel concentration in blood and kidney. Yilmaz et al. (2012) also reported naringin to reduce the genomic damage induced by cadmium.

Arsenic is a metalloid and its chronic exposure may lead to renal and hepatic diseases. In a study by Adil et al. (2016b), naringin was reported to ameliorate sodium arsenite-induced renal and hepatic toxicity in rats. Reason of this protective effect may be attributed to its antioxidant and anti-inflammatory properties via down-regulation of elevated oxido-nitrosative stress, KIM-1, Caspase-3, TGF-beta, and TNF-alpha levels (Adil et al., 2015). The antioxidant activity of flavonoids is believed to increase when they are coordinated with transition metal ions (Pereira et al., 2007). To understand the contribution of the metal coordination and the type of interaction between a flavonoid and the metal ion, a metal complex of Cu (II) with naringin was synthesized. The Naringin-Cu (II) complex 1 showed higher antioxidant, anti-inflammatory and tumor cell cytotoxicity activities than free naringin without reducing cell viability (Pereira et al., 2007).

8. Effect on diabetes mellitus

Naringin has been explored in various studies for its control over carbohydrate metabolism (Punithavathi et al., 2008; Sharma et al., 2011; Xulu and Oroma Owira, 2012). Naringin has been shown to possess anti-hyperglycemic and antioxidant effects on Streptozotocin -induced type II diabetes mellitus in rats (Punithavathi et al., 2008). Naringin administered orally (30 mg kg^{-1}) and vitamin C (50 mg kg^{-1}) regulated the increase in blood glucose, water intake, food intake, glycated haemoglobin, decrease in plasma insulin and body weight. It also regulated increased glycoprotein components including hexose, hexosamine, fucose and sialic acid (Punithavathi et al., 2008). Naringin has also been shown to prevent bone loss in a rat model of type 1 Diabetes mellitus (Rivoira et al., 2018). In another study, modulatory effects of naringin on hepatic key enzymes of carbohydrate metabolism have been presented in

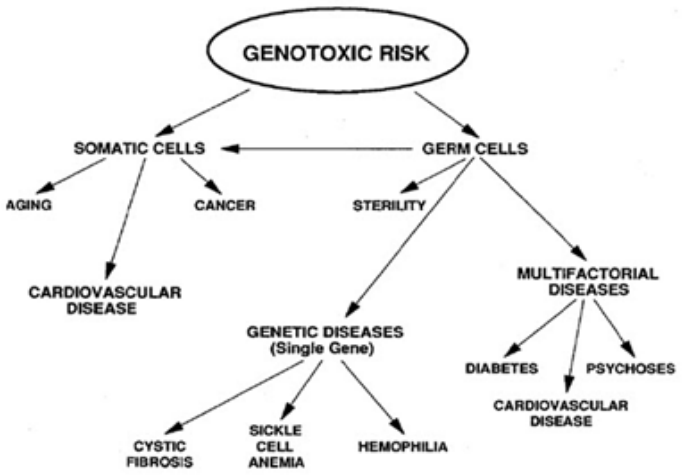

Fig. 2. Genotoxic risk posed by genotoxins on somatic and germ cells (Reddenna et al., 2017).

diabetic rat model (Pari and Chandramohan, 2017). Similarly, naringin have been shown to improve ketoacidosis and lipid peroxidation in Type 1 Diabetes Rat Model (Murunga et al., 2016). Another study reported the mitigation of cardiac hypertrophy by reduction in oxidative stress and inactivation of c-Jun Nuclear Kinase-1 protein in type I diabetes (Adebiyi et al., 2016a). Naringin was reported to ameliorate insulin resistance, dyslipidemia, beta-cell dysfunction, hepatic steatosis and kidney damage in type 2 diabetic rats. Naringin showed this effect by partly regulating oxidative stress, inflammation and dysregulated adipocytokines production through up-regulation of PPARgamma, HSP-27 and HSP-72 (Sharma et al., 2011).

9. Effect on osteogenic differentiation of human bone marrow

Naringin promoted the proliferation of hBMSCs in dose-dependent manner, enhanced the osteogenic differentiation of hBMSCs, and increased the protein and mRNA expression levels of osteogenic markers including Runx-2, OXS, OCN, and Col1 without any obvious toxicity on hBMSCs. Increase in osteogenic differentiation is related to activation of phosphor-ERK. Thus, naringin can be used as potential therapeutic agent for treating or preventing osteoporosis also (Wang et al., 2017).

10. Antigenotoxic nature

In everyday life a person gets exposed to a number of compounds or materials which cause damage to the DNA and that may ultimately lead to cancer after prolonged exposures. This simply means that genotoxins affect the integrity of the DNA. Genotoxins are compounds which have destructive properties on the genetic material of the cell i.e. DNA and RNA and their effects may be carcinogenic, mutagenic or teratogenic. Every cell has the ability of DNA repair but sometimes, cell fails to repair the genetic material. Generally, by the process of DNA repair, genotoxic mutations are escaped by all the cells but mutations can get expressed when exposure to the genotoxic compound is frequent or continuous. It is not sure that a damage caused by the mutagens will always be fixed. Genotoxicity can be seen in both somatic as well as germ cells. If genotoxins affect somatic cells then it may lead to cancer or cardiovascular diseases but if genotoxins affect germ cells then they can cause genetic diseases like cystic fibrosis, sickle cell anaemia or haemophilia, and multifactorial diseases like psychosis, cardiovascular diseases and diabetes (Reddenna et al., 2017). The genetic diseases are inheritable to next generations.

A number of techniques have been developed to check out the potential of a particular chemical compound to cause genotoxicity. These tests include Ames test, Comet test and micronucleus test. Ames test is a very commonly used test to determine the genotoxicity of a compound using *Escherichia coli* (PQ37) and S*almonella typhimurium*. It is very popular test because of its quick results while many old standard carcinogenic tests on rats and mice take a long time to complete and are very expensive. Ames test is a quick alternative for these conventional tests. Comet assay or SCGE (Single cell gel electrophoresis) assay detects the DNA damage at individual eukaryotic cell level. It is a very simple and quick detection method for genetic toxicity testing (Singh and Chadha, 2014; Singh and Chadha, 2015a; Singh et al., 2013; Singh and Randhawa, 2014). Micronucleus test is another reliable test for genotoxicity which can be done *in-vivo* or *in-vitro* (Chadha et al., 2012; Singh and Chadha, 2015b; Singh et al., 2015).

Antigenotoxins are those compounds which act against the genotoxins. They simply inhibit the actions of genotoxins. Recent studies suggested many compounds showing antigenotoxic behaviour. Some of these chemicals are naturally occurring in plants.

Table 1
Studies revealing the antitoxic effects of naringin.

S. No.	Authors	Year	Animal/Cell Model used	Inference
1	Maatouk et al.	2017	Mice	Heated naringin mitigated the genotoxic effect of Mitomycin-C in BALB/c mice through enhancing the antioxidant activity
2	Wang et al.	2017	Human bone marrow	Naringin enhanced osteogenic differentiation through the activation of ERK signalling
3	Ramakrishnan et al.	2016	Rats	Naringin effectively reduced neurotoxicity by attenuating hyperammonemia; regulated glutamate-nitric oxide cGMP pathway in ammonium chloride induced neurotoxicity
4	Oluwafeyisetan et al.	2016	Wistar rat	Ameliorated oxidative stress and NRTI-induced mitochondrial damage
5	Adil et al.	2016a	Rats	Ameliorated arsenite-induced cardiotoxicity via modulation of TGF-beta/Smad-3 and Nrf-2/HO-1 pathways along with a reduction in myocardial apoptosis
6	Adil et al.	2016b	Rats	Naringin exerted its hepato- and nephro-protective effect via modulation of oxido-nitrosative stress, FXR and KIM-1 mRNA expression
7	Kwatra et al.	2016	Rats	Naringin showed high cardio-protective effect against Doxorubicin -induced cardiomyopathy when used in combination with Doxorubicin
8	Adil et al.	2015	Rats	Naringin ameliorated sodium arsenite-induced renal and hepatic toxicity
9	Chtourou et al.	2015	Wistar aged rats	Naringin showed a protective role against cisplatin induced oxidative stress, inflammatory response and apoptosis in rat striatum via suppressing ROS-mediated NF-kappaB and P53 signalling pathways
10	Yilmaz et al.	2016	Human blood lymphocytes	Naringin could prevent bleomycin induced genotoxicity
11	Takumi et al.	2015	Human hepatocytes	Attenuated the cytotoxicity of hepatotoxin microcystin-LR
12	Xie et al.	2014	Freshwater snail *Sinotaia histrica*	Naringin treatment revealed a strong inhibitory effect against microcystin-LR
13	Li et al.	2014	Sprague-Dawley rats	No-observed-adverse-effect-level (NOAEL) of naringin in rats is greater than 1250 mg/kg/day when administered orally even for 6 consecutive months
14	Chandramohan and Parameswari	2013	Rats	Naringin can act as effective reno-protective drug against cyclosporine-A induced toxicity
15	Li et al.	2013	Sprague-Dawley rats	No mortality, adverse clinical signs, abnormal changes in body weights or food consumption, toxicologically relevant changes in hematology, clinical biochemistry or macroscopic findings during 14 days of the acute toxicity study with naringin
16	Amudha and Pari	2011	Rats	Naringin exerts a protective effect against nickel toxicity
17	Jain and Parmar	2011	Rats	Hesperidin proved to be a better anti-inflammatory and anti-oxidative agent than indomethacin and naringin because of more pronounced pharmacological actions without any tissue toxicity
18	Pari and Amudha	2011	Wistar rats	Naringin attenuated the alterations in the renal and urine markers, decreasing lipid peroxidation markers, increasing the antioxidant cascade and decreasing the nickel concentration in blood and kidney
19	Ding et al.	2009	MC3T3-E1 cells	Cytotoxicity percentages in naringin treated groups decreased; capability of MC3T3-E1 cell to synthesize osteocalcin increased
20	Punithavathi et al.	2008	Wistar rats	Antihyperglycemic effect exerted by naringin (30 mg/ kg) and vitamin C (50 mg/kg) found similar to the effect of insulin (6 units/kg) in STZ-induced type II diabetes mellitus in rats
21	Rajadurai and Stanely Mainzen	2006	Wistar rats	Naringin showed anti-lipoperoxidative and antioxidant activity over experimentally induced cardiac toxicity

Naringin is one of naturally occurring compounds and is gaining importance due to its protective effects against genotoxicity (Alvarez-Gonzalez et al., 2001; Attia, 2008; Bacanli et al., 2015; Jagetia et al., 2007; Maatouk et al., 2017; Yilmaz et al., 2016).

11. Action against Microcystin-LR and Mitomycin-C

Naringin inhibited both uptake of microcystin-LR into HEK293-OATP1B3 liver cells in a dose dependent manner as well as microcystin-LR induced phosphorylation of p53 thus attenuating its toxicity (Takumi et al., 2015). Inhibitory effect of naringin on microcystin-LR uptake in the freshwater snail *Sinotaia histrica* has also been reported. On a continuous treatment of 10mM naringin, microcystin-LR uptake prevention rate was found to be 100% (Xie et al., 2014). Heat treated naringin has shown to possess protective effect against mitomycin C induced genotoxicity (Maatouk et al., 2017). Remarkable decrease in DNA damage was observed at the tested doses of naringin (20 mg/kg b.w. and 40 mg/kg b.w.). It also reduced mitomycin C -induced lipid peroxidation which confirmed the mitigating role of naringin (Maatouk et al., 2017).

12. Concluding remarks

Naringin is one of the important flavonoids possessing enormous potential to mitigate toxicities induced by different harmful chemicals. It is a strong antitoxic agent revealing resilient action against hepato-, neuro-, renal and cardio-toxicity. Naringin may be used as a potent therapeutic agent to cure diseases including herpes, diabetes, alcoholism and cardiac failure. Naringin has been found to be a strong antioxidant agent and its supplementation revealed a regulatory effect on the expressions of glutamine synthetase, neuronal nitric oxide and soluble guanylate cyclase. It also showed potency to control serum creatinine, blood urea nitrogen, bilirubin, aspartate transaminase, alanine transaminase and low-density lipoproteins. Conclusively, naringin may be used as a strong therapeutic agent to control a number of different disease pathologies.

Conflict of interest

The authors declare that there is no conflict of interest.

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Availability of data and materials

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Competing interest

None declared.

Ethics approval and consent to participate

Not applicable.

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