

Cardioprotective and Hepatoprotective Potential of Citrus Flavonoid Naringin: Current Status and Future Perspectives for Health Benefits

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ABSTRACT

Flavonoids are natural phenolic compounds having wide range of biological activities and have great potential to be used in functional foods. Naringin (C₂₇H₃₂O₁₄) is a well known flavonoid. Citrus fruits are naturally rich in this flavonoid. Naringin exhibit various pharmacological activities with immense therapeutic potential. Researchers all over the world have reported the effect of naringin on diabetes, cancer, obesity, hypertension, bone regeneration, osteogenesis and osteoporosis. It has also been reported for its cardioprotective, renoprotective and hepatoprotective role. Cardiac and hepatic diseases are of major concern worldwide. Role of naringin as cardioprotective and hepatoprotective are under significant investigations. The results are also promising with firm future perspectives. This article reviews the research on cardioprotective and hepatoprotective role of naringin and its future perspectives to be used as phytomedicine or in form of functional food for possible cure of these diseases.

Key words: Naringin, Citrus fruit, Therapeutic potential, Cardioprotective, Hepatoprotective, Phytomedicine, Functional foods.

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INTRODUCTION

Flavonoids are important bioactive natural compounds having diverse properties. Flavonoids are extensively used in functional foods due to various health benefits. Various therapeutic effects of different flavonoids have been reported. Flavonoids are known for strong antioxidant and anti-inflammatory activities *in vitro* as well as *in vivo*.^[1,2] Flavonoids cannot be produced by the human body and generally taken through the daily diet.^[2] Citrus flavonoids constitute an important group of flavonoids. Citrus fruits, peels and seeds are good sources of flavonoids but the use of citrus flavonoids is still limited. More extensive research is required for exploration of health benefits of citrus flavonoids.

Naringin is one of the important flavonoid reported from various citrus fruits.^[1,2] Naringin gives a characteristic bitter flavor to grapefruit. Naringin has been reported to have antibacterial,^[3] anti-inflammatory,^[4-6] and antioxidant properties.^[6-8] It is chiefly used for its antioxidant properties in various industries including perfumes, beverages, sweeteners, stabilizers and vegetable oils in bakery products.^[9,10] Along with broad and general usage in terms of antioxidant and antimicrobial substance, naringin has also been reported for its different therapeutic properties (Figure 1). It has been found to be effective as hepatoprotective,^[5] cardioprotective^[11] and renoprotective.^[12] Effect of naringin on bone regeneration,^[13] controlled drug release,^[14,15] osteogenesis,^[13] osteoporosis,^[16,17] osteoblasts,^[18] chromosomal damage,^[19] metabolic syndrome, oxidative damage^[20] and nervous system disorder^[6,21,22] have been reported. Its various pharmacological activities have been reviewed recently by Chen *et al.*^[23]

Cardiac, cancer, diabetes and liver diseases have high-economic impact on human life. Epidemiologic evidence suggests that people with diabetes are at

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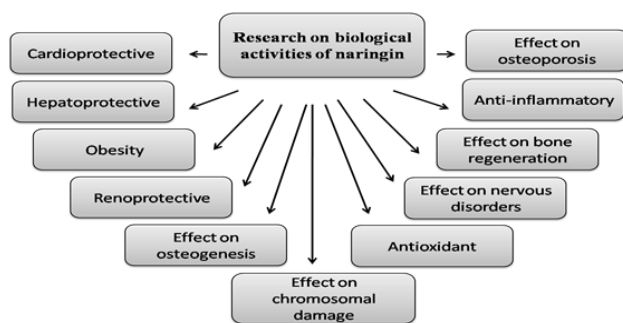


Figure 1: Various therapeutic properties and health benefits of citrus flavonoid naringin.

significantly higher risk for many forms of cancer.^[24] Naringin has been reported for its anti-cancerous, cardioprotective, hepatoprotective and anti-diabetic properties. Recently, effect of naringin on diabetes and cancer has been reviewed by Sehrawat *et al.*^[25] In this review article, the cardioprotective and hepatoprotective role of naringin has been discussed with current status of research and future perspectives.

Cardioprotective effect of naringin

Naringin is a flavanone glycoside known for its therapeutic and biological activities. It has the ability to act against oxidative stress and it has been found to increase the levels of enzymes that counteract oxidative stress.^[26] It has also been investigated for its cardioprotective role by various researchers. The experimental results revealed the significant positive effects of naringin.

Doxorubicin is an active chemotherapeutic agent used to treat various types of cancers but its clinical utility is compromised due to fatal cardiac toxicity characterized by an irreversible cardiomyopathy.^[27] Naringin treatment has been reported to reduce doxorubicin (DOX) induced cardiac toxicity and it has been found that naringin do not interfere with the DOX antineoplastic activity.^[11,28] According to researchers,^[11] application of naringin before DOX administration resulted in significant reduction in serum levels of glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), creatine kinase (CK-MB) and lactate dehydrogenase (LDH). Moreover, the naringin pretreatment also reduced the level of several enzymes (CK-MB, LDH, GOT, GPI), 8-OHdG DNA adducts and PARP activity, significantly (Jagetia and Reddy, 2014). But it has been reported that treatment with naringin increased the glutathione concentration, activities of catalase and superoxide dismutase in specific organs.^[11]

The cardioprotective potential of naringin (NR) against DOX-induced acute cardiac toxicity in rats has been evaluated by Kwatra *et al.*^[27] Naringin has been revealed

to play a protective role against doxorubicin-induced acute cardiac toxicity in rats. The study was carried out on male Wistar rats. Authors reported that naringin administration resulted in significant decrease in MDA level, raised GSH level, SOD and CAT activities. Also it resulted in increased mitochondrial complexes I, II, III and IV activities. The findings showed cardioprotection by naringin.

The cardioprotective activity of naringin against the doxorubicin-induced cardiotoxicity in mice has also been reported by Reddy *et al.*^[29] To investigate the cardioprotective role, naringin was administered orally to mice for five days in increasing concentrations before intraperitoneal injection of 15 mg/kg doxorubicin (DOX). Authors estimated serum lactate dehydrogenase (LDH), creatine kinase isoenzyme (CK-MB), glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT). The excised livers and hearts were used for the estimation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), Poly (ADP-ribose) polymerase (PARP), antioxidant and histopathology analysis. Treatment with DOX induced a significant elevation in the serum levels of GPT, GOT, CK-MB and LDH, in mice indicating acute cardiotoxicity. Prior exposure of mice to naringin (before administration of DOX) resulted in significant reduction in serum levels of GPT, GOT, CK-MB and LDH which indicated the naringin mediated protection against the DOX-induced cardiotoxicity. Oral administration of naringin to mice before DOX administration also significantly reduced the levels of 8-OHdG and the activity of PARP in the heart and liver. Further, it was found that pretreatment of mice with naringin inhibited the DOX-induced decline in the antioxidant status of heart and liver. With help of further experimentation, authors concluded the protective role of naringin in mice against the DOX-induced cardiotoxicity, without altering the antineoplastic activity of DOX.

Papasani *et al.*^[26] have also evaluated the cardioprotective activity of naringin. The cardioprotective role of naringin has been studied by estimation of both serum and oxidative biomarkers of cardiomyopathy including, Troponin I, Creatine Kinase, LDH, SGPT, SGOT, LDH, SOD, CAT, GSH, MDA, Iron and Calcium against doxorubicin induced cardiomyopathy in rats.^[26] Authors conducted the experiments on Male albino rats. Naringin (100 and 200 mg/kg dose) administration was started one week prior to Doxorubicin and was continued with daily dose of 100 and 200 mg/kg body weight. Results revealed that naringin treatment significantly decreased the serum biomarkers levels Troponin I, Creatine Kinase, SGPT, SGOT, Iron and Calcium. It

also decreased oxidative biomarkers LDH and MDA while it increased SOD and CAT levels. Further, it was observed that higher dose of naringin (200 mg/kg) was more significant as compared to lower dose (100 mg/kg) which showed the dose dependent cardioprotective role of naringin.

Cardioprotective role of naringin against isoproterenol-induced cardiotoxicity has been investigated and reported by Rajadurai and Prince.^[30] For their study, authors pretreated the Male albino Wistar rats with naringin (10, 20 and 40 mg/kg, respectively) for a period of 56 days and isoproterenol was used to induce cardiotoxicity. Pre-treatment with naringin exhibited a significant positive effect on investigated biochemical parameters in ISO-induced rats. The investigated parameters included heart weight, blood glucose, serum uric acid, serum iron, levels of total proteins, A/G ratio, iron binding capacity, activity of Na(+)/K(+) ATPase, activities of Ca(2+) and Mg(2+) ATPase and other parameters.

Hepatoprotective role of naringin

Among the various therapeutic properties of naringin, its hepatoprotective role has also been investigated. Mahmoud *et al.*^[5] reported hepatoprotective properties of naringin against the d-galactosamine (d-GalN) induced hepatic injury in rats. The potential hepatic injury induced by a d-GalN injection was assessed by measuring the serum transferase activities (AST, ALT and GGT) as markers of necrosis and total bilirubin. After 24 h of d-GalN administration, AST, ALT, GGT activities and total bilirubin were found to increase dramatically as compared to non-treated controls. Pretreatment of rats with naringin attenuated the increase in AST and ALT activities and total bilirubin level but had no effect on serum GGT activity. Hepatic TNF- α levels were markedly reduced in naringin treated animals. Naringin also reduced the neutrophils infiltration.^[5]

Alam *et al.*^[2] have reviewed various properties of naringin. Authors also discussed the hepatoprotective role of naringin and naringenin. Naringenin is also common flavonoid in citrus plants. Similar to naringin, it is also important as therapeutic agent. A hepatoprotective action of naringin was reported by several investigators.^[2,31-33] Hepatoprotective role of naringin on nickel-induced toxicity in male Wistar rats has been reported by Pari and Amudha.^[33] Nickel sulfate was used to induce toxicity and naringin was administered orally (20, 40 and 80mg/kg body weight) with intraperitoneal administration of nickel sulfate.^[33] Naringin at a dose of 80mg/kg body weight significantly reversed the activities of hepatic marker enzymes, decreased the

lipid peroxidative markers, increased the antioxidant cascade and decreased the nickel concentration in the liver. Naringin at a dose of 80mg/kg body weight was more effective as compared to lower doses. The obtained results were also supported by histopathological observations. The results demonstrated potential of naringin in alleviating the toxic effects of nickel in rat liver.^[33] The related flavonoid naringenin has also been shown to provide protective role against the cadmium induced liver toxicity in rats.^[32] Also, it was reported that naringenin significantly reduced lipid peroxidation and restored the levels of antioxidant defense in the liver. Naringenin (50mg/kg) was found to significantly reduce the toxicity of cadmium and preserved the normal histological architecture of the tissue. The effects of naringin on metabolic syndrome in mice have been investigated by Pu *et al.*^[34] Naringin attenuated the changes induced by high-fat diet in C57BL/6 mice which included obesity, dyslipidemia, fatty liver, liver dysfunction and insulin resistance.^[34] The hepatoprotective nature of naringin in a high-fat-diet-fed rat model was partially mediated by activating the AMPK, which restored the antioxidant enzymes and prevented inflammation.^[34] Effect of naringin on LPS-induced TNF release followed by liver injury was investigated by Kawaguchi *et al.*^[35] The naringin supplementation was found effective in decreasing the release of TNF and improved liver injury.^[35] Naringin has also been reported to ameliorate the hepatic steatosis.^[36] Also, naringin was found to increase PPAR γ expression in liver and kidney; phosphorylated tyrosine insulin receptor substrate 1 in liver; and stress proteins heat shock protein (HSP)-27 and HSP-72 in pancreas, liver and kidney.^[36] In other study, naringin inhibited steatosis, necrosis and fibrosis in a rat model of alcoholic liver disease.^[37] Naringin was found to prevent the increase in hepatic marker enzyme activities (AST, ALT and ALP) and reduced the accumulation of lipid deposition and fibrosis in the liver of high-carbohydrate, high-fat-diet-fed obese rats.^[38] Naringin also improved the mitochondrial respiration in the rats which suggested an improvement in mitochondrial compartment dysfunction and rapid energy expenditure by liver tissues.^[38] It has been reported that naringin alleviates the adverse effects of ethanol ingestion in rats by increasing ethanol and lipid metabolism.^[39] Bharti *et al.*^[40] have reviewed the the hepatoprotective role of naringin. Naringin has been found to have a protective effect against naturally occurring genotoxins in food like PhIP and other cooked food mutagens.^[41] Besides this, naringin also reported to have good potential in protecting rat hepatocytes from environmental toxins.^[42]

Naringin significantly prevented the okadaic acid-induced inhibition of hepatocyte autophagy and endocytosis.^[43]

CONCLUSION

Naringin (4',5,7-trihydroxy flavanone) is an important and major flavanone glycoside naturally present in grape fruit and other citrus fruits. Naringin has been investigated for its various therapeutic properties. It has been found to be biological active compound with immense potential in health industry. The number of peoples with hepatic and cardiac diseases is increasing continuously due to various reasons. Naringin has been studied for its cardioprotective and hepatoprotective properties. The results are positively significant and promise the possible usage of naringin for its cardioprotective and hepatoprotective role. Being a flavonoid, it is beneficial as comparison to the chemical drugs and can be afforded by large population because it can be extracted from waste citrus peel also. Recent findings need to be supported with further investigations (pre-clinical and clinical) for possible usage of naringin for its cardioprotective and hepatoprotective role.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUMMARY

Naringin is an important flavonoid. It is naturally present in citrus fruits. It can be extracted from waste citrus fruit peels. Various therapeutic properties of naringin are already reported. In current review, potent cardioprotective & hepatoprotective role of naringin has been reviewed.

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