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Review Article

# The Efficacy of Naringenin in Poisoning Cases Remediation

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There is a growing interest to use the alternative medicine and natural therapies in the treatment of toxicity. Flavonoids are one of these natural therapies. Naringenin is the most influential flavonoid wherein it is found in citrus fruits such as orange, grapefruit, and mandarin. Naringenin is considered a potent natural antioxidant both *in vitro* and *in vivo*. It can be hepatoprotective, renoprotective, cardioprotective, neuroprotective, and cytoprotective in many cases of toxicity besides its ability in ameliorating the testicular and developmental toxicity. Its efficacy depends on the capability to scavenge strongly free radicals and prevent the oxidative stress toxicity and lipid peroxidation.

**Keywords:** Naringenin, intoxication, antioxidant, protection

There is a growing interest for the use of bioactive compounds in the treatment of some intoxication cases. Flavonoids are one of these bioactive compounds that are plant-based dietary nutrients (1). Naringin and naringenin are the most influential flavonoids present in isolates from the citrus fruits that are a good source of flavonoids. The Family of citrus fruits consists of orange, grapefruit, mandarin, lemons, bergamots, and limes. Flavonoids possess potent antioxidant and anti-inflammatory effects both *in vitro* and *in vivo* (2).

Naringin is considered to have fewer efficacies in comparison with naringenin, but it is converted into naringenin in the intestine. Naringenin is usually absorbed from the gut and rapidly metabolized in the liver, and then it is converted into glucuronide intermediates (3).

Naringin and naringenin prevent the lipid peroxidation because they are strong scavengers of free radicals such as superoxide and hydroxyl radicals. The study of Sirovina et al. (4) confirmed this concept when it indicated the positive effect of naringenin on lipid peroxidation in the hepatic and renal tissues. Noteworthy, liver and kidney are the most sensitive organs to the oxidative stress. Moreover, the antioxidant role of naringenin is usually exerted through several mechanisms by directly or indirectly reacting with reactive oxygen species via a single electron transfer, hydrogen atom transfer, metal chelation or through activating the intercellular antioxidant enzymes (5).

The antioxidant activity of naringenin is based on its structural features, especially the existence of hydroxyl groups in the B chain wherein active 4' hydroxyl group in the B ring of naringenin is responsible for its antioxidant activity. Bioavail-ability of naringenin depends mainly on its source and form wherein the bioavailability of naringenin and naringenin-7-glucoside are similar while naringenin-7-rhamnoglucoside has slower absor-

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ption (6).

In the last years, more attention was paid toward naringenin to investigate its efficacy as a treatment in medicine. A number of studies were carried out to assess its efficacy in the treatment and prevention of toxicity. Therefore, this article will present an overall review about the available published literature that showed its preventive and therapeutic role in the poisoning cases

**Ameliorative effects of naringenin**

Recently, many studies were conducted to investigate the ameliorative role of naringenin in many cases of intoxication. Some of these studies focused on its overall therapeutic effect while others concentrated on its protective effect against the toxic manifestations in specific organs and systems such as the liver, kidney, testes, and neurological system.

**Hepato- and reno-protective effects of naringenin**

Taking into account the results of a large number of researches, we found that the outcomes of these studies confirmed the hepatoprotective and renoprotective effect of naringenin in different types of toxicity cases. For example but not limited to, the study of Al-harbi (7) concluded that co-administration of naringenin can protect the hepatic tissues against the arsenic toxicity-induced oxidative stress. Naringenin can ameliorate the efficacy of antioxidant enzymes and then the antioxidant capacity of hepatic tissues, improving the liver function. In the same context, Abdel-Ghaffar and his colleagues (8) proved also the efficacy of naringenin as a hepatoprotective agent against isoniazid-induced adverse reactions, especially on the liver wherein naringenin can restore the normal levels of all biochemical hepatic markers along with normalization of the other oxidant and antioxidants indicators. In the related context, Rashmi et al. (9) demonstrated the potent free radical scavenging activity of naringenin *in vitro* wherein it alleviates streptozotocin-induced hepatotoxicity via boosting the antioxidant defense enzyme activities and enhancing the glutathione levels. Naringenin significantly neutralized the hydroxyl radicals, hydrogen peroxide, superoxide, nitric oxide, and lipid peroxidation reflecting on a restoration of the normal hepatic structure. Moreover, Koyuncu and his colleagues (10) reported also that naringenin can prevent cisplatin-induced hepatotoxicity, nephrotoxicity, and genotoxicity by normalizing the biochemical and oxidative stress indicators in the serum, renal, and hepatic tissues along with decreasing 8-hydroxy-deoxyguanosine (8-OHdG) level that is the sign of oxidant-induced DNA damage. In addition to, El-Sayed et al. (11) concluded that the efficacy of naringenin as a hepatoprotective agent may extend to ameliorate iron oxide nanoparticles induced hepatotoxicity wherein the morphological and functional liver tissue damage was improved significantly via naringenin administration. As a result of this study, the consumption of fruit or vegetables enriched by naringenin is recommended to protect humans against liver toxicity.

Noteworthy, naringenin is not protecting the liver against iron toxicity only, but it can also protect the liver and kidney against zinc oxide nanoparticles toxicity. According to the study of Karnakar and his colleagues (12), naringenin may be beneficial in the treatment of zinc oxide nanoparticles toxicity, especially its toxic effects on the liver and kidney. Naringenin can alleviate the hepatic and renal toxicity of zinc oxide nanoparticles by decreasing the serum levels of creatinine, serum glutamic pyruvic transaminase (SGPT), and Creatine kinase-MB (CK-MB) expressions. Furthermore, Jayachitra and Nalini (13) identified the efficacy of naringenin against alcohol-induced hepatic disease indicating the prominent hepatoprotective effect of naringenin. Besides, it can significantly prevent the accumulation of plasma lipids and lipoproteins. This study showed the importance of the role of naringenin as a phytotherapeutic agent in the treatment of alcohol abuse and dependence that is one of the most challenging public health problems in Western countries. Likewise, Ahmed et al. (14)

reported that naringenin is also considered a potent nephroprotective agent wherein it can ameliorate the renal function and the histological integrity in cases of n-acetyl-p-aminophenol toxicity. The nephroprotective effects of naringenin may be mediated by the suppression of oxidative stress and the enhancement of the antioxidant defense system. According to the study of Adel et al. (15) naringenin successfully alleviates diethylnitrosamine/2-acetyl aminoflourene-induced nephrotoxicity, improving the renal histological perturbations and the serum renal markers in association with attenuation of the deteriorated renal oxidative stress and activation of the antioxidant defense system. In the same context, the study of Khan and his colleagues (16) proved the nephroprotective effect of naringenin on doxorubicin, another toxic agent inducing nephrotoxicity. Naringenin can normalize the renal levels of nitric oxide, tumor necrosis factor-α, and prostaglandin-E2 along with reversing all abnormal levels of malondialdehyde, renal biomarkers, and antioxidant enzymes. Furthermore, Rajappa et al. (17) indicated that naringenin has an ability to protect kidney against the complications of streptozotocin mitigating its nephrotoxicity via normalization of the levels of renal markers and antioxidants such as superoxide dismutase, catalase, glutathione-S-transferase, and glutathione peroxidase along with recovering the abnormal morphology of renal tissues. Another study was conducted by Elshama and his colleagues (18) to investigate the reno-protective role of naringenin in the cases of cyclosporine-induced nephrotoxicity. This study confirmed also the reno-protective effect of naringenin in amelioration of the renal toxic manifestations via normalization of renal function tests and improving the renal lesions in association with restoration of the efficacy of oxidant-antioxidant pathways.

**Neuroprotective effects of naringenin**

A number of studies were carried out to investigate the protective role of naringenin in attenuating the neurotoxic effects of some agents. Xu et al. (19) suggested that antioxidant and anti-inflammatory properties of naringenin can protect neurons via apoptosis prevention. This study reported that naringenin induced neuroprotective cytokines, improving the survival rates of the neurons in cases of monosodium glutamate toxicity wherein glutamate induces excitotoxicity in the central nervous system via hyperactivation of both ionotropic and metabotropic glutamate receptors leading to the neuronal cell death.

Another study was conducted by Muthaiah and his colleagues (20) who confirmed also the neuroprotective effect of naringenin against another toxicity that is carbaryl toxicity. Naringenin reduces the oxidative stress via decreasing the reactive oxygen species maintaining the integrity of mitochondrial membrane and causes a better survival of neuro 2A cells in association with down-regulation of pro-apoptotic genes and up-regulation of anti-apoptotic genes. Likewise, Peruru and Dodoala (21) showed that naringenin is significantly protecting against arsenic-induced neuronal damage wherein it is considered as a potent therapeutic option in the treatment of arsenic-induced neurotoxicity, reducing the lipid peroxidation and protein carbonyl formation along with an increase in the protective antioxidant enzyme levels.

**Cardioprotective effects of naringenin**

Arafa et al. (22) concluded that naringenin is a cardioprotective agent that can prevent and abate the cardiac toxicity manifestations of doxorubicin. Thus, naringenin abates the biochemical abnormalities of cardiac toxicity such as the rising level of serum lactate dehydrogenase and creatine phosphokinase in concomitant with the reduction of lipid peroxidation and malondialdehyde. Besides, naringenin increases the activities of superoxide dismutase, catalase, and glutathione-S-transferase in cardiac tissues in association with a significant increase of glutathione.

**Effects of naringenin on mitochondrial toxicity**

Daneshgar et al. (23) suggested that the administration of naringenin may ameliorate the

mitochondria toxicity in the cases of paraquat intoxication, restoring the mitochondrial antioxidant status and improving the mitochondrial functions, but in a concentration-dependent manner. The study of Podder and his colleagues (24) indicated also the cytoprotective effect of naringenin against paraquat-induced toxicity in human bronchial epithelial BEAS-2B cells through nuclear factor erythroid 2-related factor 2 (NRF2)-regulated antioxidant defense pathway. So, naringenin may be a good therapeutic option in the cases of oxidative stress-related to paraquat toxicity.

**Attenuation of developmental and testicular toxicities**

Every day and with the scientific research development, a new role for naringenin is discovered. According to Mazhar et al. (25) co-administration of naringenin with methylmercuric chloride can diminish its developmental toxicity. Naringenin can reduce the fetal morphological and skeletal abnormalities, the incidence of growth retardation, the percentage of fragmented DNA in the fetal brain, and alleviate also the histopathological changes in the cerebral cortex of fetus.

Finally, some studies proved the efficacy of naringenin in modulating the testicular toxicity that is resulted from the toxicity of cisplatin, doxorubicin, and permethrin. Mostafa et al. (26) reported that naringenin in cases of permethrin intoxication demonstrated an overall improvement in the epididymal sperm count and serum testosterone level in association with structural and ultrastructural testicular abnormalities modulation that were confirmed by light and electron microscopic examination. Another study was undertaken by Fouad and his colleagues (27) and concluded that naringenin can also impede the testicular toxicity of cisplatin and doxorubicin via mitigating the oxidative stress, nitrosative stress, inflammation, and apoptosis.

**Conclusion**

Naringenin plays an important ameliorative role in many cases of intoxication as a hepatoprotective, renoprotective, cardioprotective, neuroprotective, and cytoprotective agent, besides its ability in modulating the testicular and developmental toxicity. Naringenin is a strong scavenger of free radicals such as superoxide and hydroxyl radicals leading to prevention of the oxidative stress toxicity and lipid peroxidation.

The role of naringenin is still elusive in medical practice because of the shortage of clinical evidence. Therefore, further human researches should be carried out in the future to investigate its role as a preventive and therapeutic agent in different types of toxicity.

**Conflict of interest**

The authors declared no conflict of interest.

## References

1. Martin K R and Appel C L. Polyphenols as dietary supplements: a double-edged sword. Nutr Diet Suppl. 2009 ;2:1-12.

2. Tripoli E, La Guardia M, Giammanco S, et al. Citrus flavonoids: Molecular structure, biological activity and nutritional properties: A review. Food chem. 2007;104:466-79.

3. Wang M J, Chao P D L, Hou Y C, et al. Pharmacokinetics and conjugation metabolism of naringin and naringenin in rats after single dose and multiple dose administrations. J Food Drug Anal . 2006;14:247-53.

4. Sirovina D, Oršolić N, Gregorović G, et al. Naringenin ameliorates pathological changes in liver and kidney of diabetic mice: a preliminary study. Arh Hig Rada Toksikol. 2016 ;67:19-24.

5. Cavia-Saiz M, Busto M D, Pilar-Izquierdo M C, 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.

6. Orhan I E, Nabavi S F, Daglia M, et al. Naringenin and atherosclerosis: a review of literature. Curr Pharm Biotechnol. 2015;16:245-51.

7. Al-Harbi M S. Hepatoprotective effect and antioxidant capacity of naringenin on arsenic induced liver injury in rats. Int J Pharm Pharm Sci. 2016;8:103-8.

8. Abdel-Ghaffar O, Ali A A M, Soliman S A M. Protective effect of Naringenin against isoniazid-induced adverse reactions in rats. Int J Pharmacol. 2018;14:667-80.

9. Rashmi R, Bojan Magesh S, Mohanram Ramkumar K, et al. Antioxidant Potential of Naringenin Helps to Protect Liver Tissue from Streptozotocin-Induced Damage. Rep Biochem Mol Biol. 2018;7:76-84.

10. Koyuncu I, Kocyigit A, Gonel A, et al. The Protective Effect of Naringenin-Oxime on Cisplatin-Induced Toxicity in Rats. Biochem Res Int. 2017;2017:1-9

11. El-Sayeda A, Hussein M, Solimana A. Naringenin and hesperidin ameliorate iron oxide nanoparticles toxicity in rat liver. AJMS. 2018;1:26-30.

12. Karnakar R Y, Saritha CH, Sridhar Y, et al. Naringenin Prevents the Zinc Oxide Nanoparticles Induced Toxicity in Swiss Albino Mice. J Pharmacol Clin Toxicol. 2014;2:1-6

13. Jayachitra J and Nalini N. Effect of naringenin (citrus flavanone) on lipid profile in ethanol-induced toxicity in rats. J Food Biochem. 2012;36:502-11.

14. Ahmed O, Fahim H, Ahmed H, et al. The nephropreventive and antioxidant effects of navel orange peel hydroethanolic extract, naringin and naringenin in n-acetyl-p-aminophenol-administered wistar rats. Adv Anim Vet Sci. 2019;7:96-105.

15. Yassin M. Ameliorative Effects of Quercetin and Naringenin on Diethylnitrosamine/2-acetyl aminoflourene-Induced Nephrotoxicity in Male Wistar Rats. Am J Biochem. 2016;6:113-21.

16. Khan T H, Ganaie M A, Alharthy K M, et al. Naringenin prevents doxorubicin-induced toxicity in kidney tissues by regulating the oxidative and inflammatory insult in Wistar rats. Arch Physiol Biochem. 2018;8:1-8.

17. Rajappa R, Magesh S B, Sarvajayakesavulu S, et al. Nephroprotective Effect of Naringenin Against Multiple Low Dose Streptozotocin (MLDSTZ) Induced Renal Damage in Mice. Biomed Pharmacol J. 2017;10:583-93.

18. Said Elshama S, Osman H E H, El-Kenawy A E M. Renoprotective Effects of Naringenin and Olive Oil against Cyclosporine-Induced Nephrotoxicity in Rats. Iranian Journal of Toxicology. 2016;10:27-37.

19. Xu X-H, Ma C-M, Han Y-Z, et al. Protective effect of naringenin on glutamate-induced neurotoxicity in cultured hippocampal cells. Arch Biol Sci. 2015;67:639-46.

20. Muthaiah V P, Venkitasamy L, Michael F M, et al. Neuroprotective role of naringenin on carbaryl induced neurotoxicity in mouse neuroblastoma cells. J Pharmacol Pharmacother. 2013;4:192-7.

21. Peruru R S and Dodoala S. Protective effect of Naringenin against Arsenic trioxide induced oxidative stress. The FASEB J. 2017;31:1b577.

22. Arafa H M, Abd-Ellah M F, Hafez H F. Abatement by naringenin of doxorubicin-induced cardiac toxicity in rats. J Egypt Natl Canc Inst. 2005;17:291-300.

23. Daneshgar N, Rezaei M, Goudarzi M, et al. The Ameliorative Effect of Naringenin on Paraquat-Induced Toxicity in Mitochondria Isolated from Rats. J Nat Pharm Prod. 2016;11:e32968.

24. Podder B, Song H Y, Kim Y S. 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.

25. Mazhar F, Moawad K, El-Dakdoky M H. Evaluation of the potential interaction between methylmercuric chloride and naringenin on pre-and postnatal rat development. World J Pharm Res. 2015;3:2328-39.

26. Mostafa Hel S, Abd El-Baset S A, Kattaia A A, et al. Efficacy of naringenin against permethrin-induced testicular toxicity in rats. Int J Exp Pathol. 2016;97:37-49.

27. Fouad A A, Refaie M M M, Abdelghany M I. Naringenin palliates cisplatin and doxorubicin gonadal toxicity in male rats. Toxicol Mech Methods. 2019;29:67-73.