Ameliorative effect of naringenin in intoxication cases recovery

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***Abstract*—The use of bioactive compounds as alternative medicine in the treatment of some intoxication cases is growing in the last years. Flavonoids are one of these bioactive compounds that are plant-based dietary nutrients. Naringenin is the most influential flavonoid wherein it is found in citrus fruits such as orange, grapefruit, and mandarin. A lot of studies showed the ability of naringenin to scavenge free radicals in different body tissues preventing oxidative stress toxicity and lipid peroxidation. Therefore, naringenin can protect many body organs and systems against toxic manifestations of many drugs and toxic agents. So, it prevents the liver, kidney, heart, testes, and neurological system from toxic effects of a wide range of toxicants. Moreover, it can also ameliorate manifestations of cytotoxicity and developmental toxicity based on its efficacy as an antioxidant.**

***Key words*—Naringenin, Antioxidant, Amelioration, Intoxication**

INTRODUCTION

Recently, there is a growing interest by toxicologists 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 wherein it 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 wherein it is rich with flavonoids that possess potent antioxidant and anti-inflammatory effects in vitro and in vivo [2].

Naringin is considered less in efficacy in comparison to 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 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 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 the active 4' hydroxyl group in the B ring of naringenin is responsible for its antioxidant activity [6]. The bioavailability of naringenin depends mainly on its source and form wherein the bioavailability of naringenin and naringenin-7-glucoside are similar while naringenin-7-rhamnoglucoside is slower in absorption [7].

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

AMELIORATIVE EFFECT OF NARINGENIN

In the last years, a lot of 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 [8].

Considering the results of a large number of studies, we find that the outcomes of these studies confirmed the hepatoprotective and renoprotective effects of naringenin in different types of toxicity cases. For example, but not limited to, the study of Al-harbi [9] concluded that co-administration of naringenin can protect the hepatic tissues against the arsenic toxicity-induced oxidative stress depending on its antioxidant effect. So, naringenin can ameliorate the efficacy of antioxidant enzymes and then the antioxidant capacity of hepatic tissues improving liver functions.

In the same context, Abdel-Ghaffar and his colleagues also proved the efficacy of naringenin as a hepatoprotective agent against isoniazid-induced adverse reactions, especially on the liver wherein naringenin can restore normal levels of all biochemical hepatic markers along with normalization of other oxidant and antioxidants indicators [10]. Moreover, naringenin also possesses a protective role against other antituberculosis drugs such as rifampicin, pyrazinamide, and ethambutol that induce hepato-renal injury. It is effective in reversing all serological, biochemical, and histological indices in the liver and kidney. So. naringenin supplementation as food may reduce hepato-renal injury caused during antituberculosis drugs treatment [11].

In the related context, Rashmi et al. [12] demonstrated the potent free radical scavenging activity of naringenin in vitro wherein it alleviates streptozotocin-induced hepatotoxicity via boosting antioxidant defense enzyme activities and enhancing glutathione levels. Naringenin

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significantly neutralized hydroxyl radicals, hydrogen peroxide, superoxide, nitric oxide, and lipid peroxidation reflecting restoring the normal hepatic structure.

Moreover, Koyuncu and his colleagues [13] reported also that naringenin can prevent cisplatin-induced hepatotoxicity, nephrotoxicity, and genotoxicity by normalizing biochemical and oxidative stress indicators in serum, renal, and hepatic tissues along with decreasing 8-OHdG level that is a sign of oxidant-induced DNA damage.

In addition, El-Sayed et al. [14] concluded that the efficacy of naringenin as a hepatoprotective agent may extend to ameliorate iron oxide nanoparticles induced hepatotoxicity wherein 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 with 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 [15], 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 via decreasing serum levels of creatinine, SGPT, and CK-MB expressions.

Furthermore, Jayachitra and Nalini [16] identified the efficacy of naringenin against alcohol-induced hepatic disease indicating the prominent hepatoprotective effect of naringenin besides it can significantly prevent accumulation of plasma lipids and lipoproteins. This study showed the importance of naringenin role as a phytotherapeutic approach 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. [17] reported that naringenin is also considered a potent nephroprotective agent wherein it can ameliorate renal function and histological integrity in cases of n-acetyl-p-aminophenol toxicity. The nephroprotective effects of naringenin may be mediated via suppressing oxidative stress and enhancing the antioxidant defense system.

According to the study of Adel et al. [18] naringenin successfully alleviate diethylnitrosamine (DEN)/2-acetylaminoflourene (2AAF)-induced nephrotoxicity improving renal histological perturbations and serum renal markers in association with attenuation of deteriorated renal oxidative stress and activation of the antioxidant defense system. In the same context, the study of Khan and his colleagues [19] was undertaken and proved the nephroprotective effect of naringenin on another toxic agent-induced nephrotoxicity that is doxorubicin. Naringenin can normalize 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. [20] indicated that naringenin can protect kidney against complications of streptozotocin mitigating its nephrotoxicity via normalization of renal functions and antioxidants markers such as superoxide dismutase, catalase, glutathione-S-transferase, and glutathione peroxidase along with recovering abnormal morphology of renal tissues. Another study was conducted by Elshama and his colleagues [21] to investigate the renoprotective role of naringenin in cases of cyclosporine-induced nephrotoxicity. This study confirmed also the renoprotective effect of naringenin in ameliorating renal toxic manifestations via normalization of renal function tests and improving the renal lesions in association with restoring the efficacy of oxidant-antioxidant pathways.

In addition, several studies were carried out to investigate the neuroprotective role of naringenin in attenuating neurotoxic effects of some agents. Xu et al. [22] suggested that antioxidant and anti-inflammatory properties of naringenin can protect neurons via apoptosis prevention. This study reported that naringenin-induced neuroprotective cytokines improve the survival rates of 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 neuronal cell death.

Another study was conducted by Muthaiah and his colleagues who also confirmed the neuroprotective effect of naringenin against another toxicity that is carbaryl toxicity. Naringenin reduces oxidative stress via decreasing reactive oxygen species maintaining the integrity of mitochondrial membrane causing the better survival of neuro 2A cells in association with downregulation of pro-apoptotic genes and upregulation of anti-apoptotic genes [23]. Likewise, Peruru and Dodoala showed that naringenin is significantly doing against arsenic-induced neuronal damage wherein it is considered as a potent therapeutic option in the treatment of arsenic-induced neurotoxicity reducing lipid peroxidation and protein carbonyl formation along with an increase in protective antioxidant enzyme levels [24]. In a related context, administration of naringenin leads to a significant neuroprotective effect in toxicity cases of the anesthetic propofol. Naringenin can prevent neurodegeneration and restore long-term neurocognitive functions via suppressing apoptosis and preventing cellular inflammation [25].

On another hand, Arafa et al. concluded that naringenin also is a cardioprotective agent; it can prevent and abate cardiac toxicity manifestations of doxorubicin. Thus, naringenin abates biochemical abnormalities of cardiac toxicity such as rising levels of serum lactate dehydrogenase and creatine phosphokinase in concomitant with 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 [26].

Furthermore, Daneshgar et al. suggested that administration of naringenin may ameliorate mitochondria toxicity in cases of paraquat intoxication restoring mitochondrial antioxidant status and improving mitochondrial functions, but in a concentration-dependent manner [27]. The study of Podder and his colleagues also indicated the cytoprotective effect of naringenin against paraquat-induced toxicity in human bronchial epithelial BEAS-2B cells through NRF2-regulated antioxidant defense pathway. So, naringenin may be a good therapeutic option in cases of oxidative stress related to paraquat toxicity [28].

Every day and with the scientific research development, a new role for naringenin is discovered. According to Mazhar et al. [29] Co-administration of naringenin with methyl mercuric chloride can diminish its developmental toxicity. Naringenin can reduce fetal morphological and skeletal abnormalities, the incidence of growth retardation, percentage of fragmented DNA in the fetal brain and alleviate histopathological changes in the cerebral cortex of the fetus.

Finally, some studies proved the efficacy of naringenin in modulating testicular toxicity that is resulted from the toxicity of cisplatin, doxorubicin, and permethrin. Mostafa et al. [30] reported that naringenin in cases of permethrin intoxication demonstrated an overall improvement in epididymal sperm count and serum testosterone level in association with modulating in structural and ultrastructural testicular abnormalities that were confirmed by light and electron microscopic examination. Another study was undertaken by Fouad and his colleagues [31] concluded that naringenin can also impede testicular toxicity of cisplatin and doxorubicin via mitigating oxidative stress, nitrosative stress, inflammation, and apoptosis.

CONCLUSION

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

RECOMMENDATION

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

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