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Role of Natural Antioxidants in Treatment of Toxicity

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Abstract

Oxidative stress is the generation of reactive oxygen species that lead to a depletion in the antioxidant defense mechanism of the body inducing a lipid peroxidation along with a cell membrane disruption and nucleic acids oxidation and then cell damage. Many studies proved that the mechanism of the toxicity of drugs as well as some other chemicals compounds may be attributed to oxidative stress in the different body organs and systems such as kidney, liver, nervous and cardiovascular system. So, there is growing desire for searching in the use of the natural antioxidants agents in the treatment of toxicity and investigating its mechanism and efficacy. Recently, a lot of natural plants and food supplements have been used as antioxidant agents in the different studies to prevent or treat toxicities in the various body systems that are induced by diverse toxicants. The safety, efficacy and the low price of the natural antioxidant agents in comparison with other therapeutic agents make them an excellent choice in the prevention and treatment of toxicities.

Keywords: Toxicity; Antioxidant; Treatment; Prevention

Introduction

Free radicals are highly reactive unstable compounds that are generated inside the body or it may be introduced from the environment. The cellular systems such as NADPH oxidase, xanthine oxidase, and cytochrome P450 enzymes can generate free radicals, but mitochondria are considered the main source of reactive oxygen species production in the most mammalian cells. They cause a loss of the cellular structures and functions leading to different pathological processes as a result of their reaction to cellular proteins, lipids, and carbohydrates [1]. Oxidative stress is the generation of reactive oxygen species such as hydrogen peroxide and hydroperoxides that lead to a depletion in the antioxidant defense mechanism of the body inducing a lipid peroxidation along with a cell membrane disruption and nucleic acids oxidation (DNA and RNA), and then a cell damage. The oxidants are produced via the cells as a consequence of normal aerobic metabolism or oxidative burst from phagocytes such as white blood cells during the bacteria and viruses attack, or xenobiotic metabolism such as toxic substances detoxification. Thus, infection, allergy, and drug or toxin exposure such as pesticides, insecticides and cigarette smoke may increase the body's oxidant load [2].

The antioxidant defense mechanism of the body encompasses enzymatic and non-enzymatic antioxidants wherein the glutathione (GSH) represents the most important endogenous antioxidant. Glutathione has a major role in xenobiotic metabolism because it helps the liver in the detoxification process. So, when the body is exposed to the high levels of xenobiotics, glutathione is utilized extensively, and then it becomes unavailable as an antioxidant [3]. Glutathione has two types; reduced GSH and oxidized glutathione (GSSG). The reduced glutathione acts as an important antioxidant that overcomes the free radicals while the oxidized glutathione is formed due to a combination of GSH with another molecule of GSH in the presence of the glutathione peroxidase enzyme. Normally, 90% of total glutathione in the cells is a reduced form while the oxidized form represents 10% only that may convert into a reduced glutathione by the enzyme glutathione reductase. Conversely, the oxidized glutathione concentration is much higher than the reduced glutathione concentration under the oxidative stress [4].

Antioxidant enzymes can deactivate the free radicals via reducing the energy of the free radicals to become stable minimizing the cellular damage and the risk of free radical related-health problems; they include superoxide dismutase, catalase, glutathione peroxidase and superoxide reductase [5]. Furthermore, there are many different types of antioxidants such as dietary antioxidants (vitamin C and E), metal binding proteins (ferritin, lactoferrin, and albumin) and other plant foods antioxidants (flavonoids). Therefore, one of the

therapeutic approaches that protect the body from the oxidative injury and prevent many disorders is to increase the body levels of antioxidant enzymes by increasing the dietary intake of supplements rich in antioxidant enzymes [6].

Many studies proved that the mechanism of the toxicity of drugs as well as some other chemical compounds may be attributed to oxidative stress in different body organs and systems such as kidney, liver, nervous and cardiovascular system. Non-steroidal anti-inflammatory drugs (NSAID), chemotherapy for cancer and antipsychotics are common examples of drug-induced oxidative stress associated with toxicity. Mechanism of drug-induced oxidative stress has been varied; some drugs produce a reactive intermediate which reduces the molecular oxygen to generate reactive oxygen species such as singlet oxygen and superoxide species while the other drugs cause directly a rise in the cellular reactive oxygen species [7].

Recently, a lot of natural plants and its active constituents have been used in the different studies to prevent or treat toxicities in the various body systems that are induced by diverse toxicants. The safety, efficacy and the low price of the natural antioxidant agents in comparison to other therapeutic agents make them an excellent choice in the prevention and treatment of toxicities in accordance with World Health Organization (WHO) wherein 70-80 % of the world population become users of the natural agents such as herbs and some plants as therapeutic agents. So, there is an inevitable desire for searching in the use of the natural antioxidant agents in treatment of toxicity and investigating its mechanism and efficacy [8].

In this article, we present a review about the use of natural antioxidants in modulating the toxicity of some drugs and chemical compounds that are based on inducing an oxidative stress along with a discussion about the role of antioxidants as an alternative or adjuvant therapy in the treatment of drug intoxication and some commonly used chemical compounds.

Nigella Sativa

Nigella Sativa (black seed) is one of the natural dietary antioxidants wherein thymoquinone is an active component of its oil that has a radical scavenger activity (antioxidant effect) [9]. The potent antioxidant properties of thymoquinone may attribute to the redox properties of the quinine structure and its unlimited ability to cross the morphological barriers to the subcellular compartments facilitating the reactive oxygen species scavenging and inducing its antioxidant effect at a low concentration [10]. *Nigella Sativa* is a spontaneous growth plant; its seeds are a bit spicy and used in cooking curries, pastries, and Mediterranean cheeses. *Nigella Sativa* seeds are used extensively as a treatment for many diseases in the traditional and popular medicine wherein it has over 100 different chemical constituents such as the essential fatty acids [11].

Many previous studies demonstrated the role of *Nigella Sativa* as an antioxidant in modulation the toxicity manifestations of some drugs. Alenzi et al. [12] showed the protective effect of *Nigella Sativa* against toxicity that is induced by cyclophosphamide which is considered one of the common anticancer drugs while Badary et al. reported that *Nigella Sativa* can ameliorate hyperlipidemic nephropathy of doxorubicin because of the potent effect of thymoquinone. Antioxidant properties of *Nigella Sativa* can also modulate gentamicin-induced nephrotoxicity and improve cyclosporine A-induced cardiotoxicity via improving the antioxidant enzyme status and the cellular protein oxidation through the antioxidant mechanism [13-16].

According to Nagi and Almakki *Nigella Sativa* has also a protective role against chemical toxicity such as carbon tetrachloride and mercuric chloride whereas it can alleviate hepatotoxicity of carbon tetrachloride and renal toxicity of mercuric chloride as shown in studies of Mansour [17,18]. In the same context, *Nigella Sativa* seeds can improve manifestations of testicular toxicity induced by repeated use colchicine including normalization of plasma testosterone level with a reduction in the number of abnormal-shaped sperms and improvement in the sperm motility and liveability [19].

Furthermore, thymoquinone of *Nigella Sativa* is considered as an antidote or protective agent against natural toxicities such as mycotoxins (aflatoxin B1), lipopolysaccharides and D-galactosamine. It shows a protective effect against aflatoxin B1-induced hepatotoxicity preventing malondialdehyde production that is an indicator of lipid peroxidation leading to amelioration all histopathological, hematological and biochemical changes that may result from ingestion of aflatoxin-contaminated diet [20,21].

Curcumin

Curcumin is a yellow-colored hydrophobic polyphenol natural food spice and is used also as a promising natural food additive; it is a dried powder derived from turmeric roots of *Curcuma longa*. It is a safe nutritional antioxidant and has also a wide spectrum of biological functions, so it has detoxification effects and becomes used as a prophylactic and therapeutic agent in many toxicities [22,23].

Sudjarwo et al .[24] reported that curcumin has a protective effect on lead acetate-induced testicular toxicity showing an improvement in all manifestations of intoxication such as testicular histopathological changes, motility and viability of sperm along with a significant increase in the levels of superoxide dismutase and glutathione peroxidase in testicular tissue associated with a decrease in the level of malondialdehyde. Furthermore, Curcumin is an effective agent in inhibiting the harmful effects of nicotine on the testes reducing the reproductive toxicity that is caused by nicotine addiction [24]. Moreover, curcumin proved that it has also protective efficacy against testicular toxicity that is induced by cisplatin wherein it increases the level of endogenous antioxidants preventing lipid peroxidation in the testicular tissues and the testicular damage [25].

In addition, we can use curcumin as a natural food additive to counteract the oxidative stress and hepatotoxicity that are caused by the dietary artificial color dye such as tatrazine due

to its potent protective antioxidant activity [26,27]. In the same context, Singh [28] explored the therapeutic role of curcumin in the treatment of acetaminophen-induced hepatotoxicity wherein curcumin increased hepatocytes viability, calcium ATPase activity and reduced the elevated malondialdehyde level along with stimulation in a glutathione synthesis. Curcumin can also prevent hepatotoxicity induced by acetaminophen based on its ability to eliminate the hydroxyl radical, singlet oxygen, superoxide radical and nitrogen dioxide.

Curcumin can modulate heavy metal toxicity where it has a protective efficacy against cadmium chloride induced colon toxicity in accordance with Preeti et al. [29] while nanocurcumin has also a preventive efficacy against oxidative stress induced by arsenic and fluoride toxicity lowering the reactive oxygen species along with the restoration of the blood glutathione level in agreement with Yadav et al. [30]. It can be used as a therapeutic agent in mercury intoxication as well as a protective against mercury exposure through its routine dietary intake [31].

Effects of curcumin on modulation of toxicity extend to include different organs and drugs such as anticancer drugs and its toxic effects on the heart; it can alleviate morphological and biochemical manifestations of cardiotoxicity that are caused by cyclophosphamide and doxorubicin restoring the oxidant and antioxidant balance. Curcumin can induce nitric oxide synthase inhibitor where nitric oxide synthase enzyme is involved in nitric oxide formation which has a role in cardiotoxicity. Nitric oxide reacts with superoxide producing a peroxynitrite that is a powerful oxidant converting tyrosine in the myocardium to nitrotyrosine leading to myocardial damage [32,33]

Elshama et al. [34] showed that curcumin has chemoprotection and cytoprotection effects against endogenous and exogenous noxious stimuli and then co-administration of curcumin with subchronic use of atorvastatin can improve myotoxicity manifestations such as histopathological, ultrastructural and biochemical changes in the different types of the muscles.

Latter, Poapolathep et al. [35] reported that curcumin can reduce the toxic and carcinogenic effect of aflatoxin B1 via modulating the hepatic drug metabolizing enzymes that are responsible for aflatoxin B1 metabolism leading to amelioration in hepatotoxicity and hepatocarcinogenicity which are produced by Aflatoxin B1.

Gum arabic

Gum Arabic is a mixture of polysaccharides, oligosaccharides, and glycoproteins; its composition is different according to the source, climate, and soil. It is extracted from exudates of *Acacia Senegal* or *Acacia seyal* trees in Sudan and many African countries wherein it dissolves in water forming a low viscosity solution. Gum Arabic is used as an emulsifier and flavor stabilizer in both pharmaceutical and food industries as well as in other different industries such as textile, pottery, and cosmetics. It has a wide range of possible health benefits; it causes a significant increase in Bifidobacteria, Lactobacteria, and Bacteriode, so it has a prebiotic effect. It has also anticarcinogenic and antioxidant effect along with a protective role against hepatic and cardiac toxicities. There is an acceptable daily intake of gum Arabic for human that was determined via the Joint FAO/WHO Expert Committee on Food Additives since 1969 [36].

The study of Elshama et al. [37] investigated the antioxidant effect of gum Arabic on modulation the systemic toxicity of indomethacin via assessment the oxidants and antioxidants parameters, liver and renal function tests, complete blood picture, coagulation profile, and morphological changes of liver, kidney, and retina. This study proved that co-administration of gum Arabic with the high dose of indomethacin induced a significant improvement in its systemic toxicity manifestations.

There are many previous studies that focused on the protective and antioxidant effect of gum Arabic attenuating the nephrotoxicity of gentamicin, cisplatin, and gamma-radiation [38-40], and the cardiotoxicity of doxorubicin [41], and the hepatotoxicity of acetaminophen [42]. These studies showed the ability of gum Arabic to overcome the generation of free radicals that is considered the main mechanism for the induction of these toxicities. Najla et al. demonstrated that gum Arabic supplementation in trichloroacetate-induced toxicity profited the hepatic antioxidant status and then improved the liver damage preventing hepatotoxicity [43].

Physalis peruviana L

Physalis peruviana L is a fruit that is called Cape gooseberry or Harankash; it is considered one of the plants that have many health benefits because it contains high antioxidants, vitamins, minerals, polyunsaturated fatty acids, carbohydrates and fibers [44] El-Kenawy et al. referred to the use of *Physalis peruviana L* by heavy smokers can alleviate nicotine derived nitrosamine ketone (NNK) toxicity induced-lung cancer using pulmonary histopathological, immunohistochemical and DNA flow cytometric analysis where NNK is considered one of the tobacco smoke components that causes a pulmonary tumor. This previous study showed that antioxidant and antiproliferative effects of *Physalis peruviana L* caused an improvement in the DNA content along with protection against carcinogenesis of NNK and then it may be an applicable use as a therapeutic option for pulmonary cancer [45].

In addition, *Physalis peruviana L* Juice prevents the testicular toxicity that is attributed to intoxication of carbon tetrachloride as well as Cadmium because *Physalis peruviana L* Juice increases the levels of sex hormones and the testicular activity of antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, and glutathione-S-transferase leading to an increase in the testicular glutathione and a decrease in the lipid peroxidation as well as the nitric oxide production. Moreover, *Physalis peruviana L* Juice inhibits the activity of caspase-3 attenuating apoptosis in the testicular tissues that is caused by carbon tetrachloride. Thus, *Physalis peruviana L* can play an important therapeutic role in infertility and free radical-mediated

diseases [46]. In a similar context, *Physalis peruviana L* prevents the testicular toxicity of Cadmium along with a reduction in the testicular levels of malondialdehyde and nitric oxide [47].

In another context, Chang et al. showed that *Physalis peruviana* has potent antioxidative and hepatoprotective effects against acetaminophen-induced liver injury via enhancing the concentrations of antioxidants enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [48].

Propolis

Propolis consists of a mixture of beeswax and resins which is collected from the different parts of the plant via honeybees where its chemical composition depends on the type of accessible plant by honeybees and the local flora specificity at the collection site. It contains more than 300 constituents such as essential oils, plant resins, wax, pollen, balm, minerals, vitamins, proteins and a large number of other unknown components. Propolis is considered as a popular medicine in the different regions of the world since ancient times because it has a lot of beneficial biological effects based on its antioxidant activity [49].

Antioxidant properties of propolis have an ability to ameliorate the toxic effect of subchronic use of phenol on the lymphatic system and the count of the blood cells that is manifested by hematological and serum immunoglobulin abnormalities along with histopathological changes in the lymph nodes, spleen, and thymus gland [50].

Propolis can also counteract the toxic effect of Ochratoxin A on the kidney and liver due to the contaminated food via *Aspergillus ochraceus* that produces this toxic metabolite (Ochratoxin A). Propolis enhances the tissue antioxidant defense capacity preventing lipid peroxidation and then hepatoxicity and nephrotoxicity that results from oxidative stress of Ochratoxin A in the different body tissue [51].

A lot of studies were conducted to address the antioxidant effect of propolis and its efficacy in treatment or prevention the toxic effect of different toxicants on the different body organs or systems. Propolis can play an important role in modulation the toxic effects of different chemotherapy drugs on different body systems wherein Badr [52] indicates the ameliorative effect of propolis on hepatotoxicity that is induced by methotrexate while Rizk et al. showed that propolis can attenuate the testicular toxicity [53] which induced by doxorubicin as well as El-Naggar et al. [54] referred to the ameliorative effect of propolis against cyclophosphamide-induced toxicity.

In other context, many studies showed the protective effect of propolis against the toxic adverse effects of some antibiotics where Aldahmash et al. [55] demonstrated the renoprotective effect of propolis on gentamicin-induced renal toxicity while Bharti et al. proved the protective effect of propolis against hematological toxicity [56] that induced by anti-tuberculosis drugs (rifampicin and Isoniazid).

The studies that conducted on the toxicity of chemical elements led to the useful results related to the protective role of the antioxidant effect of propolis against the toxicity of these elements; Wen et al. showed the possible protective effect [57] of propolis against Aluminum-induced toxicity while El Masry et al. demonstrated the same effect but [58] against lead-induced neurotoxicity. El Sheikh reported the concurrent administration of propolis with chlorinated organophosphate insecticide (Chlorpyrifos) can overcome its oxidative stress which produces thyroid toxicity [59].

Naringenin

Naringenin is active natural bioflavonoids which are found in citrus fruits, tomatoes, grapefruit and coca; it has many pharmacological actions such as anti-inflammatory and antioxidant [60].

Majority of the studies concluded that the antioxidant effect of naringenin can protect the different body tissues from the effects of oxidative stress that are produced via the toxic effect of different drugs and agents. Elshama et al. proved the renoprotective properties of naringenin against cyclosporine-induced nephrotoxicity via restoration the efficacy of oxidant-antioxidant pathways and then normalization [61] of renal function tests, and amelioration the renal lesions while Al-Harbi confirmed the hepatoprotective effect of naringenin on arsenic-induced liver damage via improving the antioxidant capacity of hepatic tissues, and then normalization of liver function tests [62].

Xiao-Hui et al. concluded that naringenin has a neuroprotective effect based on its antioxidant effect where it can induce neuroprotective cytokines preventing neurons apoptosis, and then improving the survival rates of the neurons after the glutamate exposure [63]. On the other hand, naringenin can also exert a cytoprotective effect against toxicity in human bronchial epithelial BEAS-2B cells that is induced by paraquat exposure through NRF2 activation which regulate the pathway of antioxidant defense in accordance with Podder et al. [64].

Adana et al. establish that naringenin as a potential complementary adjuvant can modulate the deleterious effects of highly active antiretroviral on the testes and the reproductive capacity that induce sperm DNA fragmentations and testicular toxicity, and then be impairing the fertility [65].

Vitamins

In last years, there are many articles concentrate on the use of nutritional supplementation such as vitamin as an adjuvant, complementary or protective antioxidant agent to treat and prevent the toxicity that is induced by multiple drugs and chemicals. For example but not limited to, the studies that were performed on both vitamins E and C showed its antioxidant effects whereas it suppresses the oxidative stress and decreases the lipid peroxidation, and augments the activity of antioxidant enzymes.

Therefore, vitamin C can modulate amiodarone (antiarrhythmic drug)-induced toxicity in thymocytes via restoring cellular glutathione content Cekic et al. while vitamin E has a protective effect on cisplatin-induced nephrotoxicity [66]. In addition, Osman et al. confirmed the role of antioxidant effect of vitamin C on modulation the hepatotoxicity of chronic use of monosodium glutamate [67].

In the same context, Combination of vitamins C and E exert a protective effect on metal-induced toxicity such as cadmium-induced oxidative liver damage [68] while the concurrent use of vitamins E and D can ameliorate the fluoride-induced reproductive toxicity [69].

Furthermore, many published articles showed a strong evidence about the ability of vitamins C and E in improving the resulting toxicity from insecticides exposure; the administration of vitamins C and E can also attenuate the polycyclic chlorinated hydrocarbon insecticide (endosulfan)-induced oxidative stress and toxic alteration in the spermatogenesis by reducing the lipid peroxidation [70]. Antioxidant vitamins (C and E) have also an ability to improve hepatic and renal functions, and testis via amelioration of oxidative stress during the exposure to macrocyclic lactone insecticide (abamectin) [71].

In the contrasting context, Elshama et al. showed that vitamin A has a protective effect in the modulation of hypervitaminosis D3 short-term toxicity but not depending on its antioxidant effect [72].

Conclusion

Mechanism of many drugs and chemicals toxicity is attributed to the oxidative stress leading to the generation of reactive oxygen species and depletion in the antioxidant defense mechanism in the different body systems. The antioxidant defense mechanism of the body consists of enzymatic and non-enzymatic antioxidants wherein the glutathione is the most important endogenous antioxidant which is cooperated with antioxidant enzymes to deactivate the free radicals minimizing the cellular damage and the risk of free radical related-health problems. A large number of different studies used some natural plants and the other food supplements as antioxidant agents in to prevent or treat toxicities in the various body systems that are induced by diverse toxicants.

Recommendation

Further studies should be conducted on the human in the future to verify the reliability of the results and confirm the efficacy of natural antioxidants as curative and protective agents in the various toxicities of drugs and chemicals because of the scarcity of studies on the human.

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