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Debate

Antidotal or protective effects of honey and chrysin, its major polyphenols, against natural and chemical toxicities

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Summary. *Objective:* Honey and its polyphenolic compounds are of main natural antioxidants that have been used in traditional medicine. The aim of this review was to identify the protective effects of honey and chrysin (a polyphenol available in honey) against the chemical and natural toxic agents. *Method:* The scientific databases such as MEDLINE, PubMed, Scopus, Web of Science and Google Scholar were searched to identify studies on the antidotal effects of honey and chrysin against toxic agents. *Results:* This study found that honey had protective activity against toxic agents-induced organ damages by modulating oxidative stress, inflammation, and apoptosis pathways. However, clinical trial studies are needed to confirm the efficacy of honey and chrysin as antidote agents in human intoxication. *Conclusion:* Honey and chrysin may be effective against toxic agents. (www.actabiomedica.it)

Key words: honey, chrysin, natural toxic agent, chemical toxic agent

1. Introduction

Nowadays, antioxidants are used for reducing risk of various diseases such as cancer, cardiovascular, neurodegenerative, renal failure, gastrointestinal, and respiratory diseases (1-3). Honey is one of the main natural antioxidants which is used as a nutritional product and an alternative treatment in traditional medicine (4). Honey is a natural liquid consisting of at least 181 ingredients including proteins, amino acids, minerals, vitamins, and organic acids (5). Honey also contains polyphenols, flavonoids, glycosides, quinone, alkaloids, cardiac glycosides, and volatile substances (6). The honey composition is related to the plant source, seasonal and environmental properties as well as honeybee species. Honey is also comprised of different impurity (7). Honey contains less fructose and glucose when compared to sugar, but contains more calories. Honey and sugar are both carbohydrates, consisting of the two types of sugar: glucose and fructose. Refined fructose, which is found in sweeteners, is metabolized by the liver and has been associated with: obesity. Although, Sugar is sugar, however, honey is (mostly) sugar. On the other hand, sugar is higher on the glycemic index (GI) than honey, meaning it raises blood sugar levels more quickly. This is due to its higher fructose content, and the absence of trace minerals. The difference between the digestion of honey compared to the digestion of sugar lies in the composition of enzymes in each of these products. Sucrose (table sugar) passes through the stomach without any digestion happening because of its disaccharide (a sugar composed of two monosaccharides) composition. This means, honey also has trace elements in it. These will depend on region, so depending on the source of your honey, it could have varying small amounts of minerals like zinc and selenium, as well as some vitamins. Where honey shines is in its content of bioactive plant compounds

and antioxidants. Various constituents of honey are found to have antioxidant activities. Flavonoids and polyphenols such as chrysin in honey indicated the strong antioxidants properties (7). The pharmacological properties of honey are associated with the presence of polyphenols in honey. Although, honey may be low in vitamins and minerals but is high in some plant compoundsincluding chrysin (7). According to the recent scientific literature, honey and chrysin may be effective against a wide range of diseases from a wound to cancer (9-13). Various studies have also reported protective effects of honey and chrysin against natural and chemical toxic agents in different tissues (14). Thus, the present study was designed to review the protective effects of honey and chrysin against tissue injuries induced by natural and chemical agents.

2. Methods

We searched the literature for basic and clinical studies concerned with the antidote and protective effects of honey and chrysin against toxic agents. The electronic databases including PubMed-Medline, Embase, Google Scholar, and Scopus were searched from 1990 to 2018. Keywords were Honey, chrysin, natural toxic agent, toxic chemical agent, and protective effects combined in different ways to retrieve related articles. After reading the abstracts, the full texts of 58 articles were critically scrutinized.

3. Neuroprotection

3.1 Honey and neurotoxic agents

Lead

Lead (Pb) is one of the major toxic heavy metals causing severe tissue injury in both human and animal. Oxidative stress has been found as an essential mechanism involved in lead-induced neurodegenerative diseases such as memory impairment and locomotor disability. Lead exposure reduces locomotor and exploratory activities and also increases anxiety and memory impairment via disrupting the oxidant-antioxidant system in animal models. The study has indicated that administration of honey (1 and 1.5 ml/kg, PO) inhibited lead induced-neurotoxicity as seen through improvement of memory and locomotor functions in animals. The study suggested that honey protected brain against lead via enhancing antioxidant activities as evidenced by increasing superoxide dismutase (SOD), glutathione-S-transferase (GST), and glutathione peroxidase (GPx) activities and glutathione (GSH) level as well as decreasing brain level of lipid peroxidation (15).

Aluminum

Aluminum (Al) is one of the most abundant heavy metals in the Earth's crust. It exists in the water, air, natural and commercial food, and medicinal agents such as drugs. Aluminum has been recognized as a neurotoxic agent inducing neurodegenerative diseases. Aluminum induces oxidative stress and increases amyloid beta level in the brain of animal models. Sub-chronic exposure to aluminum elevates lipid peroxidation and decreases GSH levels as well as catalase (CAT), SOD, and GST activities in brain. Aluminum also increases serum levels of tumor indices including arginase and a-l-fucosidase by modifying glutamate GABA system. It was reported that co-administration of $AlCl_3$ with honey syrup (500 mg/kg, PO) increased antioxidant enzymes activities and decreased lipid peroxidation level in mouse brain. Honey administration also reduced serum tumor indices levels by modulating expression of BCL-W gene which is an anticancer gene in brain cells (16).

Lipopolysaccharide

Lipopolysaccharide (LPS) causes neurodegenerative diseases by inducing inflammatory mediators in the brain of experimental models (17, 18). It is suggested that inhibition of microglia-mediated neuroinflammation is an effective strategy for treatment of neurodegenerative diseases. In this regards, Candiracci et al., 2012 (19) indicated that honey extract (0.5 and 1 μg/ml) decreased secretion of pro-inflammatory mediators such as interleukin (IL-1β) and tumor necrotic factor (TNF-α) induced by LPS in N13 microglia.

Honey decreased the inducible nitric oxide synthetize (iNOS) expressions and production of reactive oxygen species (ROS) (20). The study indicated honey may act as a potent inhibitor of microglial activation and prevent the neurodegenerative diseases (19) (Fig. 1).

3.2 Chrysin and Neurotoxic agents

Formalin

Formalin is used for inducing neuropathic pain in the animal models. Chrysin (50, 100 and 150 mg/kg, IP, 60 min before formalin injection) was effective against formalin-induced pain in rats by modulating corticosterone and noradrenaline levels in serum (21). Chrysin (5 and 10 mg/kg, IP) have indicated analgesic and anti-inflammatory effects via modulating COX-2 activity (22).

Lipopolysaccharide

Chrysin (1, 5 and 10 μM) prevented LPS-stimulated microglia cells by decreasing NO, TNF-α, IL-1β productions and expressions of iNOS and COX-2. The findings indicated chrysin ameliorated neuroinflammation through modulating c-Jun N-terminal kinase and Nuclear factor-κB (NF-κB) signaling molecules (23). Chrysin inhibited LPS-induced vascular cell adhesion molecule-1 (VCAM-1) expression in cerebral vascular endothelial (bEnd.3) mouse cells by preventing NF-κB translocation and p38 mitogen-activated protein kinase (MAPK) signaling. It seems, the neuroprotective effects of chrysin is related to its anti-inflammatory activities (24).

Streptozotocin

Streptozotocin (STZ, 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose) is produced by Streptomycetes achromogenes inducing diabetes mellitus in the animal models. Brain is susceptible to hyperglycemia induced by STZ. Oxidative stress has a vital role in developing neurovascular complications in diabetes. Natural antioxidants such as chrysin can penetrate to blood-brain barrier that may be effective against diabetic neuropathy. In this context, it was reported chrysin (30 and 100 mg/kg for 26 days) combated against STZ-induced diabetes-associated cognitive decline in rats by modulating oxidative stress indices (MDA, CAT, SOD, and GSH), NF-κB, TNF-α, IL-6, IL-1β, as well as caspase-3 in cerebral cortex and hippocampus (25). Chrysin (20, 40, 80 mg/kg/day) prevented STZ-induced brain toxicity by modulating oxidative stress and decreasing MDA levels as well as an increase in total protein, SOD, CAT, and GST in rats' brain (26).

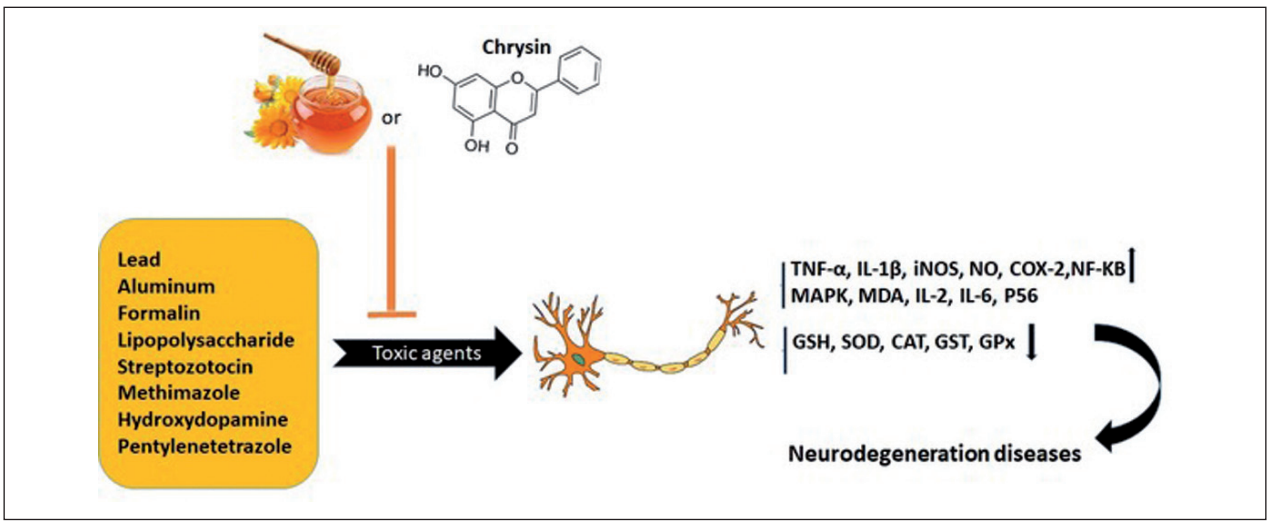

Figure 1. The protective effect of honey and chrysin against neurotoxic agents

Methimazole

Methimazole (MTZ) is useful for treatment of overactive thyroid patients. In animal models, MTZ is used for inducing hypothyroidism. Hypothyroidism usually causes depression. Chrysin (20 mg/kg, IP) represented protective effects against MTZ-induced depressive-like behavior in female mice. Chrysin modulated serotonin (5HT) in the prefrontal cortex, hippocampus as well as dopamine in hippocampus of theanimals (27).

Hydroxydopamine

6-hydroxydopamine (6-OHDA) is a neurotoxic catecholaminergic agent which is used for inducing Parkinson's disease in animal models. 6-OHDA affects inflammatory responses and neurotrophic factors in Parkinson's disease. Chrysin (10 mg/kg, PO) showed a protective effects against 6-OHDA-induced Parkinson's disease in rats. Chrysin decreased TNF-α, IL-1β, IL-2, IL-6, and NFKB levels and increased IL-10 level, total antioxidant capacity in the striatum, as well as brain-derived neurotrophic factor, nerve growth factor, and glial cell line-derived neurotrophic factor levels. Chrysin also increased dopamine, 3,4-dihydroxyphenylacetic acid, tyrosine hydroxylase, and homovanylic acid levels. Chrysin improved Parkinson's disease through modulating inflammatory cytokines and neurotrophic factors in the brain of rats with Parkinson's diseases (28).

Ammonium chloride

Hyperammonemia changes ammonia metabolism and increases inflammatory cytokines production in brain. Chrysin (100mg/kg, PO) showed protective effects on ammonium chloride (NH_4Cl)-induced neuroinflammation in rats. Chrysin up-regulated glutamine synthetase (GS) activity and glial fibrillar acidic protein (GFAP) expression as well as down-regulated TNF-α, IL-1β, IL-6, p65 NF-κB, iNOS, and COX-2 expression in hyperammonemic rats brain (29).

Pentylenetetrazole

Pentylenetetrazole (PTZ) is a selective blocker of chloride channel coupled to ɣ-aminobutyric acid type A (GABAA) receptor complex. PTZ has been used as a circulatory and respiratory stimulant drug and in convulsive therapy. However, the side effects such as uncontrolled seizure limited its use. Recently, PTZ is applied for inducting seizure in animal models. Chrysin (2.5, 5, and 10 mg/kg) representes anticonvulsant properties against PTZ-induced convulsions in rats (30) (Fig. 1).

4. Respiratory protection

4.1 Honey and respiratory toxic agents

Ovalbumin

Ovalbumin (OVA) is the main protein of egg white applying for induction of allergic reaction such as airway hyper-responsiveness in experimental models. It was reported that the aerosolized honey at a dose of (25% (v/v) and 50% (v/v) inhibited of ovalbumin (OVA)-induced asthma on airway tissues in a rabbit model. The findings indicated aerosolized honey ameliorated OVA-induced structural changes in epithelium, mucosa, and submucosal regions of airway. Honey decreased the number of airway inflammatory cells in bronchoalveolar lavage fluid and also inhibited the goblet cell hyperplasia (31). Shamshuddin et al. 2016 (32) indicated honey at a dose of 10% (v/v), 40% (v/v) and 80% (v/v) inhibited OVA-induced allergic asthma in mice model by decreasing inflammatory cell infiltration and beta-hexosaminidase level in bronchoalveolar lavage fluid. All histopathological evaluations confirmed the preventive effects of honey against OVA-induced allergic asthma. It evidenced through improving epithelium thickness, number of mast cell and mucus expression in the treated animals (32) (Fig. 2).

4.2 Chrysin and respiratory toxic agents

Ovalbumin

OVA induces lung inflammation and airway hyperresponsiveness via shifting immune response toward a T-helper type 2 (Th2) profile in mice airway. Chrysin (50 mg/kg, PO) had protective effects against

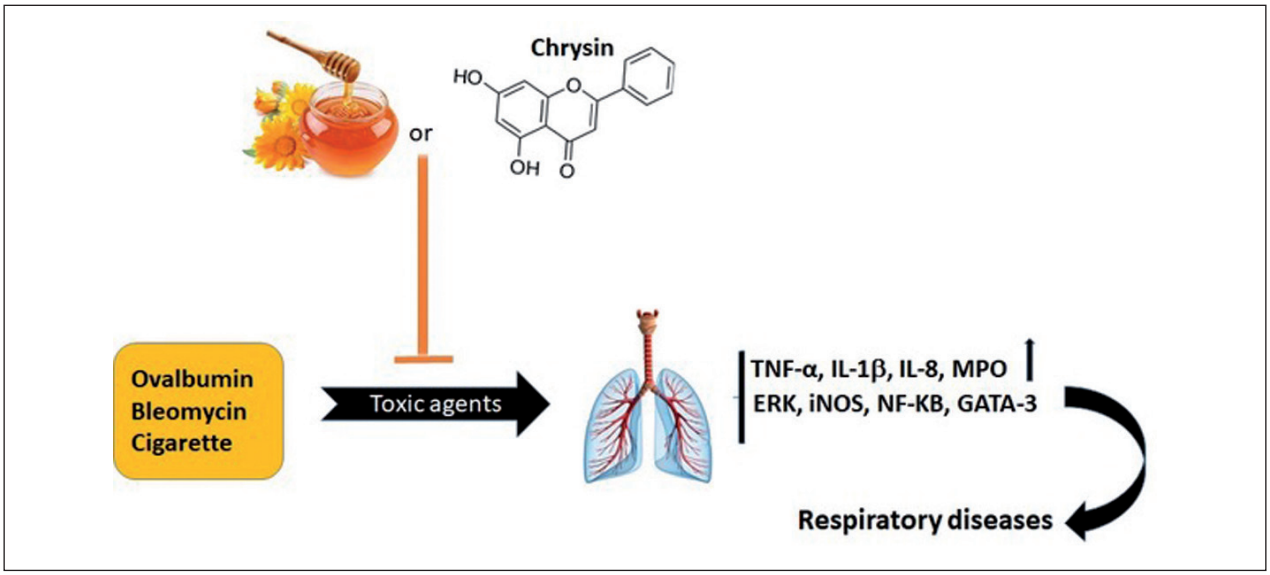

Figure 2. The protective effects of honey and chrysin against respiratory agents

ovalbumin-induced inflammation by regulating transcription factors T-bet and GATA-3 in mice (33). Chrysin (3, 10, and 30 mg/kg, PO) also ameliorated histopathological lung injury in the rats exposed to ovalbumin. It was suggested that anti-asthmatic effects of chrysin might be associated with its protective effects on Th1/Th2, iNOS and NF-κB expressions (34).

Bleomycin

Bleomycin is an anti-cancer drug inducing pulmonary inflammation and fibrosis. Bleomycin induces lung injury through producing inflammatory cytokines such as IL-18 and IL-1β in and oxidative stress (35). Chrysin (50 mg/kg, PO) indicated protective effects against bleomycin-induced lung inflammation and fibrosis in rats by modulating oxidant-antioxidant system (36).

Cigarette smoke

Cigarette smoke induces airway inflammation through increasing inflammatory cytokine in serum levels such as TNF-α, IL-1β, IL-8, and MPO. Chrysin pretreatment (10 and 20 mg/kg, IP) inhibited cigarette smoke-induced airway inflammation via modulating ERK and p38 phosphorylation (37) (Fig. 2).

5. Cardiovascular protection

5.1 Honey and cardiovascular toxic agents

Cadmium

Cadmium (Cd) is one of the major heavy metals that is associated with various diseases by inducing cellular toxicity (12). Cd produces cardiovascular abnormalities via modifying oxidative and inflammatory responses. Cd elevated mean corpuscular volume and reduced white and red blood cells counts, lymphocytes, platelets, hemoglobin, and hematocrit. However, it was reported honey (50% concentration, PO) increased hemoglobin and white blood cell count in rats exposed $CdCl_2$ (38). Abdelaziz et al. 2013 (39), also reported orally administration of honey (9 mg/kg, 1 h before a single dose of $CdCl_2$ injection) decreased in hematotoxic effects of Cd by ameliorating the changed blood parameters (39).

Lead

Some studies have indicated the hematotoxic effects of lead in animal models. It was indicated that honey (1 mg/kg, o) improved lead-induced anemia in rabbits. The study suggested the protective effects of honey against lead-induced blood toxic effects (40).

Copper sulfate

Copper sulfate ($CuSo_4$), an inorganic compound, is used as a pesticide and herbicide that its toxicity is related to copper content. Copper is an "essential mineral" that is very toxic at high concentrations. Copper causes oxidative stress by inducting Fenton-type redox reactions. However, copper toxicity usually occurs following disruption of absorption, distribution, and excretion of this metal. Copper toxicity might be associated with cardiovascular diseases. In vitro study conducted by Makedou et al., 2012 (41) have indicated that Greek pine tree honey (100, 200 and 400 µg/ml diluted serum, and 10, 20 and 40 µg/ml diluted LDL, respectively) prevented cardiotoxicity of copper sulfate by decreasing susceptibility of human LDL-c to oxidation. The study indicated Greek honey could delay LDL oxidation induced by copper sulfate, and may be useful for treating cardiovascular diseases (41).

Cigarette

Cigarette smoking plays a principal role in initiating and progression of cardiovascular diseases by inducing inflammation. Honey consumption (20 g/day, PO) ameliorated inflammatory indices including high sensitive C-reactive protein (h-CRP), IL-6, and TNF-α among chronic smokers from Quit Smoking Clinic and Health Campus, Universiti Sains Malaysia. The study suggested that honey inhibited the development of cardiovascular problems by ameliorating inflammatory response (42).

Isoproterenol

Isoproterenol is one of the non-selective β agonist drugs that are effective for treatment of bradycardia, heart block, and asthma. However, several studies have indicated the cardiotoxicity effects of isoproterenol in the animal models (43-45). Isoproterenol increased the cardiac enzymes activity including lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), aspartate transaminase (AST), alanine transaminase (ALT), as well as the cardiac troponin I (cTnI) triglycerides (TG), total cholesterol (36), low-density lipoprotein-cholesterol (LDL-C), and lipid peroxidation levels. Isoproterenol also decreased the activities of antioxidants enzymes and GSH levels in heart as well as high-density lipoprotein-cholesterol (HDL-C) serum levels. Pretreatment of Tualang honey (3 g/kg, PO) and Sundarban honey (5 g/kg, PO) in the ischemic rats inhibited isoproterenol-induced myocardial infarction through modulating oxidative stress and dyslipidemia (46, 47).

Ethanol

Clinical observation in a patient presenting with a history of alcohol abuse and experimental studies indicated the association between ethanol consumption and cardiovascular diseases. The protective effect of Anzer honey against ethanol- increased vascular permeability in rats has been studied. The results indicated that Anzer honey (0.275 g/kg, PO) with 25.44 mg/g ascorbic acid inhibited vascular permeability after ethanol exposure. It was suggested that the vascular protective effects of Anzer honey against ethanol might be related to the antioxidant content including a high amount of the ascorbic acid (48).

Lipopolysaccharide

LPS induces innate immune responses leading to the release of cellular NO and other inflammatory mediators as well as macrophage migration which causes sepsis (12). High doses of LPS is associated with organ failure and induces a systemic inflammatory response and septic shock. The effect of honey against a lethal dose of LPS-induced organ failure in rabbit has been studied. Honey (1 mL of 500 mg/kg in saline, IV) protected cardiac and lipid profiles against a lethal dose of LPS as evidenced by ameliorating red blood cell (RBC), white blood cell (WBC) and thrombocyte counts, blood pH, neutrophil infiltration and MPO activity. The study suggested that honey may be protected organs failure during inflammatory disorders (49).

High-Fat Diet

A high-fat diet is one of the leading risk factors for obesity and cardiovascular diseases distributing lipid profile. Several studies indicated that honey

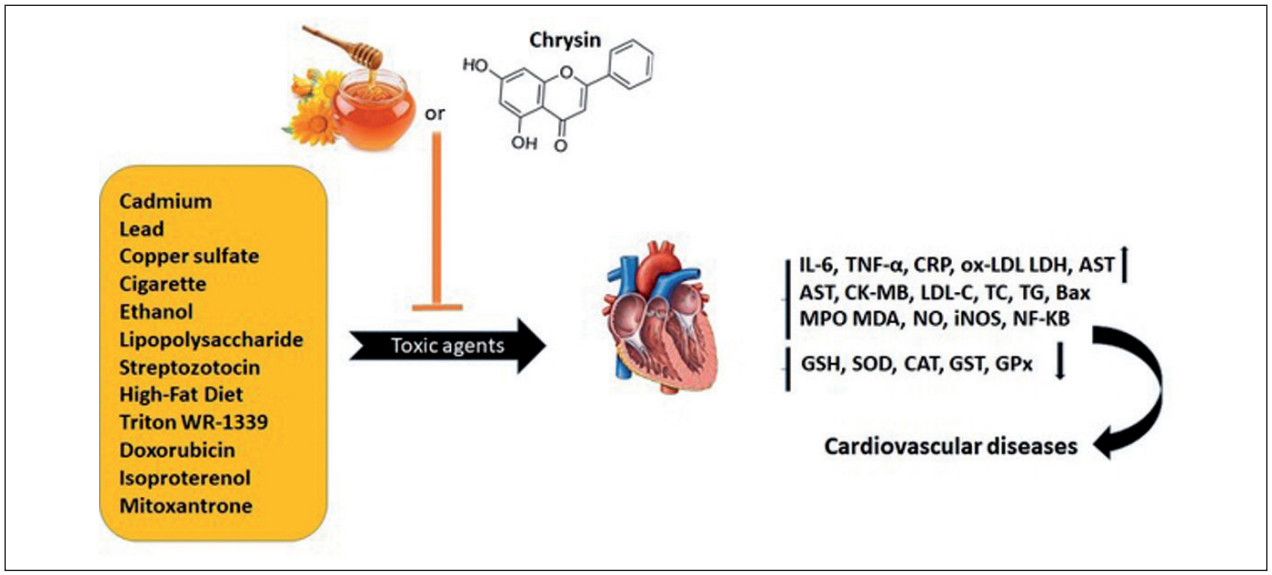

Figure 3. The protective effects of honey and chrysin against cardiotoxic agents

consumption is useful for controlling lipid hemostasis. Gelam honey decreased the percentage of adiposity index including body mass index (BMI) and the TC, TG, leptin, and resistin plasma levels in rats fed high-fat diet. The study suggested honey consumption decreased the risk of obesity and cardiovascular diseases by modulating lipid metabolism (50) (Fig. 3).

5.2 Chrysin and cardiovascular toxic agents

Triton WR-1339

Triton WR-1339 is used for inducting hypercholesterolemia in the animal models. Triton WR-1339 causes hypercholesterolemia by inhibiting lipoprotein lipase activity. Hypercholesterolemia is one the main risk factors for progressing coronary artery disease such as atherosclerosis. Chrysin (200 mg/kg, PO) improved Triton WR-1339-induced hypercholesterolemia by increasing the enzymatic and nonenzymatic antioxidants in rats (51).

Doxorubicin

Doxorubicin (DOX) is one of the anticancer chemotherapeutic drugs with severe side effects including cardiotoxicity (52). Chrysin (25 and 50 mg/kg, PO) indicated protective effects against DOX-induced acute cardiotoxicity via modulating oxidative stress indices (GSH,CAT, SOD and MDA), inflammatory markers (NF-κB, iNOS, COX-2 ,TNF-α and NO) as well as apoptotic components (Bax, Bcl-2, cytochrome c , caspase-3) (53).

Streptozotocin

Chrysin (20, 40 and 80 mg/kg, IP) inhibited hyperlipidemia induced by STZ trough modulating oxidative stress in rats liver (26).

Mitoxantrone

Methotrexate (MTX) belongs to the chemotherapeutic drugs; however, its toxic effects including cardiotoxicity limited its clinical uses. MTX causes cardiomyopathy with a reduction in left ventricular ejection fraction and heart failure (54). Chrysin inhibited MTX-induced cardiotoxicity by modulating apoptosis indices such as an increase in the Bcl-2 and also a reduction in Bax and caspase-3 expressions (55) (Fig. 3).

6. Hepatoprotective effects

6.1 Honey and hepatotoxic agents

Lead

Lead is recognized as a potent hepatotoxic agent. Several underlying mechanisms, including oxidative stress, inflammation, and apoptosis are involved in hepatotoxicity induced by lead. Lead disturbs liver metabolism, decreases liver antioxidant content and increases serum levels of liver enzymes. Carob honey (1 g/kg, PO) inhibited lead-induced hepatotoxicity in rabbits as noted by decreasing the liver enzymes serum levels (40).

Aluminum

Aluminum exposure disturbs mitochondrial energy metabolism by inducing mitochondrial oxidative stress, which leads to liver dysfunction. Honey (500 mg/kg, PO) inhibited hepatotoxicity induced by aluminum chloride ($AlCl_3$) in mice as evidenced through decreasing liver enzymes, total bilirubin, and lipid peroxidation activities. The study suggested that honey decreased the hepatotoxic effects of $AlCl_3$ by modulating oxidative stress (56).

Carbon tetrachloride

Carbon tetrachloride (CCl_4) is a hepatotoxic agent that causes liver injury by induction of ROS generation, inflammation, apoptosis and cell death. CCl_4 increases the liver enzymes serum levels including ALT, AST, ALP, and GGT. Slow or rapid intravenous injection of honey (40 and 80 mg/kg, PO) was effective against CCl_4-induced liver injury in sheep (57). It was also indicated that total food restriction with 50% honey decreased the ALT and AST serum levels in rats exposed to CCl_4 (38). Sider honey (5 g/kg, PO) ameliorated CCl_4-induced hepatotoxicity in rats as noted by decreasing in the ALT, AST, ALP, and bilirubin serum levels as well as the MDA content. Honey increased liver weight, GSH content while CCl_4 decreased these parameters. Honey improved pathological damages such as cell necrosis, vacuolar degeneration, mononuclear cellular infiltration pyknotic nuclei, and apoptotic bodies in the liver of animal exposed to CCl_4 (58). The protective effects of Saudi Sider honey (SSH) against CCl_4 induced oxidative stress and liver injury have been investigated in the rat. Administration of SSH (0.5 and 1.0 g/kg/day, PO) prior exposure to CCl_4 decreased the enzyme markers serum levels including ALT, AST, ALP, GGT and also bilirubin**.** SSH also increased total protein content and reduced malondialdehyde (MDA) levels in the rats liver exposed to CCl_4. The histopathological study of liver confirmed the hepatoprotective effects of honey which is seen by a reduction in liver lesions (59). Cheng et al., 2015 (60) have investigated the impact of buckwheat honey on CCl_4-induced liver injury in mice. Administration of buckwheat (0.22 g/10 g, PO) decreased serum lipoprotein oxidation and elevated serum oxygen radical absorbance capacity. Additionally, buckwheat honey ameliorated the ALT and AST activities that are induced by CCl_4. The hepatic levels of MDA were reduced and the antioxidant enzymes (SOD and GST) activities elevated following honey administration. The findings indicated that the hepatoprotective effects of buckwheat honey might be related to its antioxidant activity (60). Sadek et al., 2016 (61) also reported that honey inhibited CCl_4-induced liver injury via increasing phosphorylase activity in liver and decreasing carbohydrate intolerance and insulin resistance index (HOMA-IR). Moreover, the modulatory effects of honey on cytokine genes such as TNF-α and transducing growth factor beta (TGF-β) have been involved in the hepatoprotective effects of honey (61).

Acetaminophen

Acetaminophen (paracetamol or N-acetyl-p-aminophenol; APAP) belongs to analgesic drugs that its overdose is accompanied with hepatotoxicity. The hepatotoxicity of acetaminophen is initially associated with over-production of N-acetyl-p-benzoquinone imine (NAPQI) by cytochrome p450. NAPQI is eliminated by binding to GSH following exposure to therapeutic doses of acetaminophen. Overdosing of APAP decreases the cellular GSH content, permitting NAPQI to attach to the cellular proteins and cause li-

pid peroxidation (LPO), which can lead to hepatotoxicity. Acetaminophen increases the ALT, AST, ALP, GGT, total bilirubin and MDA serum levels as well as proinflammatory cytokines such as TNF-α and IL-1β levels in liver tissue. Acetaminophen overdose causes liver failure in experimental animals and humans. Pretreatment with honey inhibited acetaminophen-induced hepatotoxicity by modulating oxidative stress and inflammatory responses in rats liver. Honey (5, 10 and 20 g/kg, PO) inhibited liver injury as evidenced by a decrease in the AST and ALT activities serum as well as the Il-1β levels in the animals exposed to acetaminophen. Honey increased the GSH content and GPx activity as well as decreased MDA levels in liver. The histopathological study indicated that honey improved the liver lesions induced by acetaminophen (62). Afroz et al., 2014 (63) has shown that Sundarban honey from Bangladesh (5 g/kg, PO) inhibited acetaminophen-induced liver injury by modulating oxidative stress. A hepatic histopathological evaluation conducted by Galal et al., 2012 (62) and Gupta et al., 2016 (64) indicated the protective effects of honey against acetaminophen, noted by decreasing in congestion, necrosis, hemorrhage, distorted hepatic architecture and nuclear inclusion in the rat and mice models.

Bromobenzene

Bromobenzene is an industrial chemical that used for producing pesticides and dyes. This agent causes hepatotoxicity by converting into bromobenzene 3, 4-oxide, which produces oxidative stress and liver injury. Apis cerana honey (5, 10 and 20 g/kg, twice a day, PO) had protective effects against bromobenzene-induced hepatotoxicity in mice. Honey decreased MDA level and transforming growth factor β1 (TGF-β) expression and increased the SOD and GPx activities in the liver of mice exposed to bromobenzene (65).

Metanil-yellow

Metanil yellow is one of the mono azo dyes with high water solubility. The use of metanil yellow as a colorant agent is banded, However, in developing countries, it is still used as a colorant in several food industries such as ice-creams, sweet meat, beverages, and soft drinks. Metanil yellow causes hepatotoxicity in animal models as evidenced by an increase in the enzymes levels liver including ALT, AST, ALP and gamma-glutamyl transpeptidase (GGT). It also induces the NF-κB signaling pathways and increases the inflammatory mediators expression such as TNF-α and IL-1 β in liver. Honey (2.5 mg/kg, PO) suppressed metanil yellow-induced the NF-κB expression and TNF- α and IL-1 β levels in rats liver. The study suggested that honey has hepatoprotective activity against metanil-yellow-induced liver injuries due to its anti-inflammatory properties (66) (Table 1).

6.2 Chrysin and hepatotoxic agents

Methotrexate

MTX causes hepatotoxicity via inducing oxidative stress. Chrysin (40 and 80 mg/kg, PO) showed a protective effect against MTX-induced hepatotoxicity via increasing hepatic glutathione GSH, GPx, GR, SOD, and CAT levels and decreasing lipid peroxidation in rats (67).

Acetaminophen

Chrysin (25 and 50 mg/kg, IP) ameliorated hepatotoxicity induced by acetaminophen in rats. Chrysin decreased lipid peroxidation which led to an elevation in the antioxidant enzymes activities. Chrysin modulated inflammatory responses via elevating the TNF-α and IL-1β levels. Chrysin inhibited apoptosis and autophagy through decreasing caspase-3 activity and LC3B level. Chrysin indicated a protective effect on acetaminophen-induced hepatotoxicity by reducing oxidative stress, inflammation, apoptotic and autophagic pathways (68).

Tert-butyl hydroperoxide

Tert-butyl hydroperoxide (tBHP) causes hepatotoxicity via increasing generation of cellular ROS (69). Chrysin (5, 10 and 25 μM) improved the hepatotoxicity of tBHP by modulating ERK2/Nrf2/ARE signaling pathways in rat primary hepatocytes (70).

Table 1. Hepatoprotective effects of honey and chrysin against chemical or natural toxic agents

Results	Constituents	In vitro/ In vivo	Toxic agents	References
Decreased the serum levels of liver enzymes	Honey	Rabbit	Pb	[40]
Decreased the serum levels of liver enzymes, total bilirubin, and lipid peroxidation	Honey	Mice	Al	[56]
Decreased the serum levels of liver enzymes	Honey	Sheep	CCl4	[57]
Decreased the serum levels of ALT and AST.	Honey	Rat		[38]
Decreased the elevated serum levels ALT, AST, ALP, and bilirubin Decreased the liver levels of MDA Increased liver weight , GSH content AND total protein t Improved cell necrosis, vacuolar degeneration, mononuclear cellular infiltration pyknotic nuclei and apoptotic bodies in the liver Increased the phosphorylase activity Decreased the carbohydrate intolerance and insulin resistance index (HOMA-IR) Modulated the expression of TNF-α and TGF-β.				[58, 59, 61]
Decreased serum lipoprotein oxidation, MDA content Increased the activities of ALT , AST SOD and GST Decreased inflammatory cascade via Blockage of TNF-α-converting enzyme activity and TNF-α production	Honey Chrysin	Mice	CCL4	[60, 75]
Decreased the activities of serum AST, ALT, Il-1β and MDA content; Increased the GSH content and GPx activity; Improved the liver lesions Inhibited apoptosis and autophagy via decreasing the activity of caspase-3 and LC3B level. Decreased congestion, necrosis, hemorrhage, distorted hepatic architecture and nuclear inclusion	Honey Chrysin	Rat	Acetaminophen	[62, 63, 64] [68]
Decreased MDA level and expression of TGF-β Increased the activities of SOD and GPx	Honey	Rat	Bromobenzene	[65]
Decraesed NF- κ B expression, the liver levels of TNF- α and IL-1 β.	Honey	Rat	Metanil-yellow	[66]
Modulated the (ERK2)/Nrf2/ARE signaling pathways in hepatocytes.	Chrysin	Rat	tBHP	[70]
Decreased lipid peroxidation, XO activity; Increased GSH content, CAT, GR, SOD, GPx, GST, G6PDD and QR enzyme activities; Ameliorated expression of COX-2, iNOS, levels of NF-κB, and TNF-α.	Chrysin	Rat	Cisplatin	[72]
Modulated the activities of ADH, XO and CYP 2E1 a Decreased the levels of TBARS, lipid hydroperoxides, and conjugated dienes Increased the activity of SOD, CAT, GPx, GR, GST, levels of GSH, vitamin C, and vitamin E.	Chrysin	Rat	Ethanol	[73, 74]
Ameliorated hepatic enzyme activities, lipid peroxidation, activities of SOD, CAT, GPx, GR, GST and the levels of GSH, vitamin C, and vitamin E.	Chrysin	Rat	GalN	[76]
Modulated the oxidative stress.	Chrysin	Rat	STZ	[92]
Increasing hepatic glutathione GSH, GPx, GR, SOD, and CAT Decreased lipid peroxidation.	Chrysin	Rat	MTX	[67]

Pb: Lead; SOD: superoxide dismutase; GST: glutathione-S-transferase; GSH-Px: glutathione peroxidase; GSH: glutathione; Al: Aluminum; CAT: Catalase; IL-1β: interleukin-1β; TNF-α: tumor necrotic factorNF-κB: Nuclear factor-κB; STZ: Streptozotocin; MTX: Methotrexate; CCl4: Carbon tetrachloride; tBHP: Tert-butyl hydroperoxide; GalN: D-galactosamine

Cisplatin

Cisplatin causes hepatotoxicity through inducing oxidative stress and inflammation (71). Chrysin (25 and 50 mg/kg, PO) can improve cisplatin-caused hepatotoxicity via inhibiting oxidative stress and inflammatory responses. Chrysin decreased lipid peroxidation, xanthine oxidase (XO) activities and increased

GSH, CAT, GR, SOD, GPx, GSTlevels as well as glucose-6 phosphate dehydrogenase (G6PDD) and quinone reductase (QR) enzyme activities. Chrysin ameliorated the cyclooxygenase-2 (COX-2), iNOS expressions and NF-κB, and TNF-α levels in the liver of cisplatin-treated rats (72).

Ethanol

Excessive ethanol consumption damages to the various organs including the liver. Ethanol induces hepatotoxicity in three stages including fatty liver, alcoholic hepatitis, and cirrhosis-fibrous. Chrysin (20 and 40 mg/kg, IV) indicated the hepatoprotective effects during ethanol consumption via modulating ADH, XO, CYP 2E1 and CAT activities in rats (73). Chrysin (20 mg/kg) ameliorated ethanol-induced hepatotoxicity through decreasing the thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides levels, and conjugated dienes. Chrysin increased the SOD, CAT, GPx, GR, GST activities, and even the GSH, vitamin C, and vitamin E levels in rats liver (74).

Carbon tetrachloride

Chrysin (50mg/kg, PO) ameliorated CCl_4-induced acute liver by blocking TNF-α-converting enzyme activity and TNF-α production that leads to suppressing the inflammatory cascade (75).

D-galactosamine

D-galactosamine (GalN) is a hepatotoxic agent increasing serum hepatic enzyme activities and lipid peroxidation level in the liver. Chrysin (20, 50 and 100 mg/kg, PO) ameliorated the hepatic enzyme activities, lipid peroxidation, the antioxidant enzymes (SOD, CAT, GPx, GR, GST) activities as well as GSH, vitamin C and vitamin E levels in liver (76).

Streptozotocin

STZ causes liver toxicity by inducing oxidative stress synthesized. Chrysin (20, 40 and 80, IP) showed the hepatoprotective effects against STZ via modulating oxidative stress (26) (Table 1).

7. Nephroprotective effects

7.1 Honey and nephrotoxic agents

Acetaminophen

The overdose of acetaminophen induces kidney toxicity by disturbing oxidase isoenzymes function in kidney. Acetaminophen increases creatinine, urea, BUN levels, inflammatory mediators, and oxidative stress indices in kidney tissues. Sundarban honey (5 g/kg, PO) from Bangladesh indicated nephroprotective effects on acetaminophen via decreasing BUN, creatinine, and MDA serum levels in rats. Histopathological evaluation in kidneys also confirmed protective effects of honey against acetaminophen. The protective effect of honey may be caused by binding to acetaminophen metabolites and reducing of their affnity to cellular GSH. Thus, honey increased the GSH level and excretion of acetaminophen metabolites (63).

Cisplatin

Cisplatin causes severe nephrotoxicity in humans via inducing inflammation and oxidative stress (77). Cisplatin-induced inflammation and oxidative stress in kidney through activation of NF-κB pathways. Oxidants including hydrogen peroxide superoxide and hydroxyl radicals activate the NF-κB pathways. The nephrotoxicity of cisplatin is determined by an increase in urea, creatinine and uric acid levels in serum. Cisplatin causes significant tubulointerstitial injuries, increases α-smooth muscle actin (α-SMA), fibrogenic factors, TGF-β1, and reduces the cell proliferation index, bromodeoxyuridine (Brdu). Pretreatment with honey (500 mg/kg, PO) decreased cisplatin-induced tubular epithelial cell necrosis, infiltration of the immune component into kidney and also inflammatory cytokine and adhesion molecule expression (TNFα, IL-6, ICAM-1, MCP-1) in kidney of cisplatin-treated animals. The findings indicated that cisplatin-enhanced the expression of NF-κB that has been decreased with honey. The study has suggested that honey inhibited cisplatin-induced nephrotoxicity via suppressing the NF-κB pathway (78). Orally honey administration (100 mg/kg) reversed the increased se-

rum levels of urea, creatinine, and uric acid, and also ameliorated the histopathologic alteration. Honey showed a decrease in the α-SMA and TGF-β1 expressions and an increase in the expression of Brdu (79).

The consumption of honey (3 days before the onset of cisplatin administration) decreased cisplatin-induced nephrotoxicity in cancer patients as noted by creatinine and urea serum levels (80).

Carbon tetrachloride

Carbon tetrachloride (**CCl_4**) is recognized as a potent nephrotoxic agent inducing acute and chronic renal damage. CCl_4 increases creatinine, ALP, BUN, Uric acid and NO serum levels as an index of kidney damage. Oxidative stress has a main role in nephrotoxicity induced by CCl_4.

Sider honey (5 g/kg, PO) ameliorated CCl_4-induced nephrotoxicity in the rats as noted by a decrease in ALP, urea, uric acid, creatinine and NO serum levels and also in the MDA content in kidney. Honey increased kidney weight, GSH content while CCl_4 decreased these parameters. Honey also improved the pathological damages such as cell necrosis, intertubular infiltration and cloudy swelling in kidney of rats exposed to CCl_4 (58).

The protective effects of Saudi Sider honey (SSH) against CCl_4 induced oxidative stress, and kidney injury have been investigated in rats. Administration of SSH (0.5 and 1.0 g/kg, PO) prior exposure to CCl_4 decreased creatinine, urea, and uric acid serum levels**.** SSH increased total protein content and reduced MDA levels in kidney of rats exposed to CCl_4. The histopathological study of kidney indicated that honey reversed glomeruli, interstitial tubules, and blood vessels to the normal condition (59) (Table 2).

7.2 Chrysin and Nephrotoxic agents

Acetaminophen

Chrysin (25 and 50 mg/kg, PO) prevented nephrotoxicity in rats due to its antioxidant, anti-apoptotic and anti-inflammatory activities. Chrysin modulated acetaminophen-induced oxidative stress in the kidney by increasing the GSH level and activities of antioxidant enzymes (SOD, CAT, and GPx). Chrysin additionally decreased the levels of inflammatory markers including TNF-α, IL-1β, and IL-33. Furthermore, chrysin inhibited apoptotic tissue damage through increasing caspase-3 activity. Chrysin also ameliorated autophagic tissue injury by elevating the light chain 3B (LC3B) expression (81).

Glucose

Excess of glucose consumption causes diabetes and its complications including podocyte damage and dysfunction in human and animals. Glomerular epithelial podocytes play a leading role in modulating the glomerular filtration barrier function through their foot processes. Chrysin indicated the renoprotective effects against glucose in podocytes and mouse kidneys. Chrysin (1-20 μmol/L) inhibited glomerular podocyte apoptosis through reduction of DNA fragmentation. Chrysin decreased the Bax/Bcl-2 ratio, Apaf-1 activations and cytochrome c in renal podocytes exposed to high glucose. Chrysin (10 mg/kg, PO) ameliorated proteinuria and the abnormal alterations in glomerular ultrastructure. Chrysin showed the protective effects against glucose-induced podocyte injury by regulating ER stress (82).

Adenine

Adenine is an organic compound of purine family inducing nephrotoxicity in animal models (20). Adenine increases creatinine, urea, neutrophil gelatinase-associated lipocalin serum levels as well as *N*-Acetyl-β-D glucosaminidase activity, uremic toxin 3-indoxyl sulfate, inflammatory cytokines, and urinary albumin concentration. Adenine also increases the antioxidant content and decreases lipid peroxidation in kidney. Chrysin (10, 50 and 250 mg/kg, PO) indicated the protective effects against adenine-induced renal failure in rats via regulating peroxisome proliferator-activated receptor γ and the NF-κB signaling pathways (83).

Tetrachlorodibenzo-p-dioxin

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a polychlorinated dibenzo-p-dioxin that causes ne-

Table 2. Nephroprotective effects of honey and chrysin against chemical or natural toxic agents

Results	Constituents	In vitro/ In vivo	Toxic agents	References
Decreased the serum levels of BUN, Cr, MDA,TNF-α, IL-1β, and IL-33 Increased the serum levels of GSH, the activities of SOD, CAT, and GPx and excretion of acetaminophen metabolites.	Honey Chrysin	Rat	Acetaminophen	[63, 81]
Increasing GSH level,; Decreased; Inhibited apoptotic tissue damage by increasing caspase-3 activity and autophagic tissue injury by elevating the expression of LC3B				
Decreased the expression of NFkB.	Honey	Mice	Cisplatin	[78]
Decreased the serum levels of urea, Cr and uric acid Inhibited oxidative stress	Honey Chrysin	Rat		[79, 88]
Ameliorated the histopathologic alteration Decreased the expression of α-SMA and TGF-β1	Honey	Human		[80]
Decreased the serum levels of ALP, urea, uric acid, Cr, NO Decreased the kidney levels of MDA Increased the kidney levels of GSH Improved cell necrosis, intertubular infiltration and cloudy swelling in the kidney	Honey Chrysin	Rat	CCl4	[59, 89]
Inhibited glomerular podocyte apoptosis via reduction of DNA fragmentation, decreased the Bax/Bcl-2 ratio, Apaf-1 activation and cytochrome c in renal podocytes; Ameliorated proteinuria and abnormal alterations in glomerular Protected podocyte injury via regulating ER stress.	Chrysin	Mice	Glucose	[82]
Regulated the PPAR-γ and NF-κB signaling pathway	Chrysin	Rat	Adenine	[83]
Increased the serum levels of GSH, CAT, GPx, and SOD Decreased lipid peroxidation	Chrysin	Rat	TCDD	[85]
Increased antioxidant content in kidney tissue	Chrysin	Rat	DOX	[86]
Alleviated oxidative stress and apoptotic damage.	Chrysin	Rat	5-FU	[87]
Decreased MDA, CYP 2E1, ADH, and XO Increased GSH, Gpx, CAT, and GR Modulated the ROS production	Chrysin	Rat	Ethanol	[73]

SOD: superoxide dismutase; GST: glutathione-S-transferase; GSH-Px: glutathione peroxidase; GSH: glutathione; CAT: Catalase; IL-1β: interleukin-1β; TNF-α: tumor necrotic factor; NF-κB: Nuclear factor-κB; DOX: Doxorubicin; MTX: Methotrexate; CCl4: Carbon tetrachloride;TCDD: Tetrachlorodibenzo-p-dioxin; 5-FU: 5-Fluorouracil.

phrotoxicity (84). Chrysin (2, 20 and 50 mg/kg, PO) prevented TCDD-induced nephrotoxicity through elevating the GSH, CAT, GPx, and SOD levels and reducing lipid peroxidation (85).

Doxorubicin

Doxorubicin is associated with nephrotoxicity. This drug causes nephrotoxicity via inducing oxidative stress. Chrysin (40 and 80 mg/kg, PO) treatment attenuated nephrotoxicity induced by doxorubicin through increasing antioxidant content in kidney tissues (86).

5-Fluorouracil

5-Fluorouracil (5-FU) is an antineoplastic drug that its clinical use is limited due to its toxic effects

including renal toxicity. 5-Fluorouracil causes renal toxicity via inducing oxidative stress, activating p53, Bax, and caspase-3 and down-regulation of Bcl-$_2$ expression. Chrysin (50 and 100 mg/kg, PO) showed the protective effects against 5-FU-induced renal toxicity via ameliorating oxidative stress and apoptotic damage in rat kidney (87).

Cisplatin

Renal toxicity is one of the main side effects of cisplatin that leads to limit its usage in treatment of various cancers. Cisplatin causes renal injury via inducing ROS generation. Chrysin ameliorated cisplatin-induced renal toxicity as noted by a decrease in serotonin and BUN, lipid peroxidation serum levels and XO activity which is accompanied by an increase in antioxidant enzyme (CAT, GPx, GR, and GST) and GSH levels. Chrysin showed the protective effects against cisplatin-induced renal injury by ameliorating oxidative stress (88).

Ethanol

Chronic ethanol consumption disturbs renal functions through inducing oxidative stress. Chrysin (20 and 40 mg/kg, IP) represented the protective effects against ethanol-induced renal toxicity. Chrysin administration decreased MDA, CYP 2E1, ADH, and XO levels in kidney. Chrysin also increased GSH, Gpx, CAT, and GR levels in kidney of ethanol-treated rats. Chrysin reduced renal toxicity by modulating ROS production (73).

Carbon tetrachloride

CCl_4 disturbs renal function through increasing the iNOS expression and MDA level as well as decreasing GSH and CAT, SOD, and Gpx levels in kidney. Chrysin (200mg/kg, IP) inhibited CCL_4-induced renal toxicity by inhibiting oxidative damage in rat kidney (89) (Table 2).

8. Reproductive system protection

8.1. Honey and reproductive toxic agents

Nicotine

Nicotine is one of the major components of tobacco and cigarette. Nicotine exposure disturbs the cellular oxidant-antioxidant balance and induces organ toxicities. The reproductive system is one of the targets for nicotine toxicity. Nicotine decreases percentage of sperm motility, viability and counts as well as follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels in serum. Honey administration (1g/kg, PO) improved sperm motility, viability, counts, morphology as well as FSH, LH, and testosterone levels in rats exposed to nicotine. Additionally, honey ameliorated histopathological changes including the degenerative seminiferous tubule architecture induced by nicotine (90).

Cigarette

Cigarette smoking causes sexual dysfunctions and decreases the fertility in males. Honey (1.2 g/kg, PO) markedly elevated the percentages of achieving intromission and ejaculation and raised mating and fertility markers in the male rats exposed to cigarette (91).

Conclusion

Recent years, natural products are considered as the new strategy in treatment of various diseases due to their main activities such as antioxidant. Chemical and natural toxic agents cause toxicity in human and animal specially following chronic exposure or high doses. These toxic agents lead to toxicity in the various organs such as nervous, respiratory, cardiovascular, gastrointestinal, renal and reproductive systems. The studies have indicated natural products may be effective against toxic agents in vitro and animal experiments . One of the natural products with more pharmacological protective effects is honey. Several studies have suggested that honey and its polyphenol such as chrysin decreased neurotoxicity, lung toxicity, cardio-

toxicity, hepatotoxicity, nephrotoxicity, reproductive toxicity, genotoxicity and immunotoxicity via modulating oxidative stress, inflammation, and apoptosis in the various organs. The above findings confirmed *in vitro* and animal studies. Therefore, clinical trial studies should be done to confirm the efficacy and safety of honey and chrysin for treating intoxication in humans.

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