Hepatoprotective Effect of Some Medicinal Plants and Herbs against Hepatic Disorders Induced by Hepatotoxic Agents

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ABSTRACT

The liver is a vital organ in the body. It plays a major role in metabolism, including ridding the body of substances that would otherwise be injurious if allowed to accumulate, and excretion of xenobiotics from the body. The endogenous antioxidants defenses from reactive oxygen species are strengthened by natural antioxidants and restore the optimal balance by neutralizing reactive species. The present study aims to highlight on hepatotoxic agents, and prevention of hepatic disorders using Curcuma longa, Trigonella foenumgraecum, Allium sativum, Coffea arabica, Petroselinum crispum, Olea europaea leaves, and Mentha piperita. Curcuma longa showed that hepatoprotective effect against hepatotoxicity induced by paracetamol, diethyl nitrosamine, CCl4, and gentamicin. Also, the hepatoprotective effect of Trigonella foenumgraecum seeds has been elucidated against hepatic disorders induced by γ-radiation, monosodium glutamate, ethanol, CCl4, AlCl3, and diabetes. Allium sativum has been used in the treatment of hepatic disorders. The hepatoprotective effect of Allium sativum has been confirmed against oxidative damage and hepatic toxicity of D-galactosamine, lipopolysaccharide, ethanol, and CCl4, which may be due to the presence of organosulfur compounds. Coffea arabica intake has been inversely related to the incidence of liver diseases. Petroselinum crispum showed a hepatoprotective effect against hepatic disorders induced by CCl4 and diabetes, which may be due to their high content of antioxidants. The leaves of Mentha piperita showed a good hepatoprotection against hepatopathy induced arsenic, anti-tuberculosis drugs, and CCl4 which may be due to their high content of phenolics and flavonoids. Olea europaea leaves extract significantly ameliorated pathophysiological changes induced in the liver by diazinon, carbendazim, and γ-irradiation in rats. It can be concluded that administration of Curcuma longa, Trigonella foenumgraecum, Allium sativum, Coffea arabica, Petroselinum crispum, Olea europaea leaves, and Mentha piperita showed a remarkable hepatic protection against hepatotoxic agents, which may be due to its antioxidant properties of these medicinal plants and herbs. So, Human expose to hepatotoxic agents and the patients with hepatic disorders should be advised to take these medicinal plants and herbs.

Keywords: Hepatotoxicity, Hepatoprotective, Curcumin, Fenugreek, Coffee, Garlic, Parsley, Peppermint, Olive leaves;

INTRODUCTION

The liver is a vital organ in the body, essential for life because it plays a major role in metabolism, including ridding the body of substances that would otherwise be injurious if allowed to accumulate, and excretion of xenobiotics from the body [1-4]. Hepatotoxic agents can react with the basic cellular components and consequently induce almost all types of liver lesions [5, 6]. Liver cell injury caused by various toxic chemicals (antibiotics, cyclosporin A chemotherapeutic agents, carbon tetrachloride, Thioacetamide, excessive alcohol consumption, sodium nitrite, heavy metals, and microbes is well-studied [1-10]. Liver diseases are still a global health problem may be classified as inflammatory liver diseases (acute or chronic hepatitis), non-inflammatory diseases (hepatosis) and degenerative disorder resulting in liver fibrosis (cirrhosis). Unfortunately, treatments of choice for liver diseases are controversial because conventional or synthetic drugs for the treatment of these diseases are insufficient and sometimes cause serious side effects [11, 12]. Nowadays, the numbers of patients with liver dysfunction increase due to overwhelming usage of alcohol and drugs has paved the path for researchers in an interest in herbal medicine, because there are only a few universally effective and available options for the treatment of common liver diseases, such as cirrhosis, fatty liver and chronic hepatitis [13].
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Natural and herbal products have been used in traditional medicine to treat a variety of diseases including malignancies [14]. The anticancer activities of the extract from a number of herbal plants have been demonstrated. A number of previous studies concluded that herbal medicine might have anticancer effect by enhancing the immune system, including cell differentiation, inhibiting telomerase activities and inducing apoptosis of cancer cells [15]. Natural antioxidants strengthen the endogenous antioxidants defenses from reactive oxygen species and restore the optimal balance by neutralizing reactive species [5, 16-18]. The antioxidant activities of phenolics are related to a number of different mechanisms, such as free radical-scavenging, hydrogen-donation, singlet oxygen quenching, metal ion chelating, and acting as a substrate for radicals such as superoxide and hydroxyl [19]. Treatment with herbs has been used to attenuate hepatic disorders for many centuries [13]. So, the present study aims to highlight on hepatotoxic agents, and prevention of hepatic disorders using Curcuma longa, Trigonella foenumgraecum, Allium sativum, Coffea arabica, Petroselinum crispum, Olea europaea leaves, and Mentha piperita.

Curcumin (Curcuma longa L.)

Curcumin (Curcuma longa L.) (Figure. 1) has been used since ancient times for promoting human health [20]. It represents a class of anti-inflammatory and anti-oxidant reported to be a potent inhibitor of reactive oxygen species (ROS) formation [21]. Traditional Indian medicine claims the use of curcumin powder against biliary disorders, anorexia, coryza, diabetic wounds, hepatic disorders, rheumatism, and sinusitis [22-24]. Curcumin could exert antioxidative effects either directly as a chemical antioxidant due to its ability to scavenge reactive oxygen and nitrogen free radicals or by modulating cellular defenses which themselves exert antioxidant effects [25, 26]. Previous studies mentioned that curcumin is a natural antioxidant hepatoprotective agent against hepatotoxicity induced by paracetamol, diethyl nitrosamine, CCl4 models, gentamicin [4, 27-29]. Curcumin administration has been reported to prevent hepatic lesions in streptococcal diabetic rats and to protect against oxidative stress in hepatic cell lines [30, 31]. Azab et al., [4] recorded that gentamicin induced hepatotoxicity was evidenced in Guinea pigs injected intraperitoneal with gentamicin at a dose of 100 mg/kg body weight/day by increase in serum levels of AST, ALT, ALP and γGT; a decrease in serum total proteins, albumin, and globulin concentrations; and a significant alteration in hepatic architecture. Co-administration of Curcumin at the doses of 200 mg/kg body weight / day orally by gavage with gentamicin for 10 days, prevented severe alterations of biochemical parameters and disruptions of liver structure, which may be due to its antioxidant property. Biswas et al., [32] reported that Curcuma longa has antioxidant and anti-inflammatory properties for inhibiting reactive oxygen species formation. Also, Kadasa et al., [29] found that Curcuma longa significantly lowered the serum levels of ALT, and AST activities in rats treated with diethyl nitrosamine. In addition, Ezz et al., [28] found that curcumin treatment to rats intoxicated with CCl4 caused significantly reduced serum levels of ALT, AST and ALP activities, and significant elevations in serum total protein and albumin concentrations compared to CCl4 intoxicated group. Treatment of curcumin reverted the serum protein and albumin levels back to normal in CCl4 intoxicated rats, which reflects the well functioning of hepatocytes in protein synthesis [28].

Fenugreek (Trigonella foenumgraecum)

Trigonella foenumgraecum (family: Legume) is an annual herb grown in Middle Eastern countries and India [33]. Trigonella foenumgraecum seeds (Figure.2) provide nutrients and natural food fibers required in the human body. Seeds are used as antioxidant, antibacterial, anticancer, hypocholesterolemic, and antidiabetic agent [34, 35].
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Figure 2. Fenugreek seeds (*Trigonella foenumgraecum* L.).

The hepatoprotective effect of *Trigonella foenumgraecum* seeds has been elucidated against hepatic disorders induced by ethanol, aluminum chloride, and diabetes [36, 40]. The livers of rats treated with an extract of fenugreek seeds showed a significant attenuation from CCl<sub>4</sub>-induced liver damage as evident from normal hepatocytes with well-defined nuclei. The improvement of histological changes in the liver is well correlating with the biochemical estimations. These results suggest that the extract of fenugreek seeds has potential clinical applications for treating liver disorders [41, 42]. Kumar and Bhandari, [43] demonstrated that the activities of serum ALT and AST were increased in rats treated with monosodium glutamate. Administration of aqueous *Trigonella foenum-graecum* seeds significantly reduced the elevated ALT and AST levels, which could be attributed to the protective effect on hepatic tissues. Das, [42] reported that administration of an extract of fenugreek seeds in CCl<sub>4</sub> treated rats caused a reduction in serum ALT, AST, ALP levels. A water extract of Fenugreek seeds concurrently during 60 days of alcohol ingestion was associated with a reduction in the risk of oxidation and liver enzymes noted in the serum of rats given ethanol alone, suggesting protective effects [44]. El-Tawil [45] determine the possible protective effect of *Trigonella foenumgraecum*, against hepatic oxidative stress induced by γ-radiation in rats. *Trigonella foenumgraecum*-treated irradiated rats received 1g *Trigonella foenumgraecum* seed powder/kg body weight/day by gavages for 7 days before irradiation. *Trigonella foenumgraecum* treatment has significantly alleviated hepatic oxidative stress induced by radiation, which was substantiated by the significant amelioration of serum aminotransferases enzymes and ALP activities. Belaid-Nouira *et al.*, [40] found that administration of rats to AlCl<sub>3</sub> induced a moderate hepatocellular necrosis, increased in inflammatory cell infiltration, vascular congestion, dilated sinusoids, pyknotic nuclei, a granulous aspect of cytoplasm, and moderate cytoplasmic vacuolation (Fig.3). Treatment of rats with fenugreek after exposure to AlCl<sub>3</sub> were showed improvement in changes induced by AlCl<sub>3</sub> which exhibited areas of normal liver architecture, sinusoidal spaces, and reduced cytoplasmic vacuolation, centrilobular necrosis, a granulous aspect of cytoplasm, and increased number of binucleated cells (Fig.4). Also, the activities of ALT and AST in both liver and plasma were significantly decreased in rats treated with AlCl<sub>3</sub>. The administration of fenugreek seed with AlCl<sub>3</sub> restored the normal level of plasmatic and hepatic ALT activity and succeeded to increase AST activity in liver and plasma. AlCl<sub>3</sub> decreased GGT activity but fenugreek seed supplementation ameliorated it.
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**Figure 3.** Light micrographs of rat liver tissue stained by hematoxylin-eosin (HE) in AlCl3-treated group (x320, x500, x500). Dg: degenerating cell, K: Kupffer cell, DS: dilated sinusoid, LI: lymphoid infiltrate, N: necrotic cells, V: vacuoles, CgV: congested vein [40].

**Figure 4.** Light micrographs of rat liver tissue stained by hematoxylin-eosin (HE) in Fenugreek + AlCl3-treated group (x320, x500 respectively). LI: lymphoid infiltrate, V: vacuoles, CV: central vein [40].

**Garlic (Allium sativum)**

*Allium sativum* (Figure 5) is has been used as food, a spice, and folkloric medicine [46]. *Allium sativum* has been exhibited antioxidant, anticancer, antibacterial, antiviral, and hypocholesterolemic which may be due to sulfur-containing compounds, enzymes, and high trace minerals [35,47]. It has been reported to possess antioxidant, antimutagenic, immune modulation, hepatoprotection, anticarcinogenic effects [48], hypolipidemic [49], hypoglycemic [50], and anti-atherosclerotic properties [51].

**Figure 5.** Garlic (Allium sativum)

*Allium sativum* contains sulfur compounds, 17 amino acids, several enzymes, magnesium, selenium, iron, calcium, copper, germanium, zinc, potassium, vitamins A, B1, C, and fiber [52, 53]. *Allium sativum* contains fatty acids, proteins, carbohydrates, fiber, glycolipids, phospholipids, glycosides lectins, saponins, ajene, allicin, diallyl trisulfide, diallyl disulfide, SAC sulfoxide, B, E, and C vitamins [54-56], which may be responsible for protection from various disorders and tissue damage. Aged *Allium sativum* extract has a high antioxidant content. However, free radical scavenging activity has been suggested as a possible mechanism of hepatoprotective action [46]. Garlic suppresses the incidence of tumors in rodent models [57, 58]. Garlic oil seems to be a highly promising compound in protecting the hepatic tissue against oxidative damage and in preventing hepatic dysfunction due to DGa1N / LPS – induced hepatitis in rats [59]. Garlic oil contains numerous organosulfur compounds with potential hepatoprotective effects [60, 61], which is responsible for the bioactivation of a wide variety of hepatotoxins and for generation of deleterious oxyradicals [61, 62], and enhance phase II enzymes such as UDP-glucuronyl transferase, microsomal epoxide hydrolase activities and glutathione S-transferases, which are essential for hepatic detoxification processes [61, 63]. Furthermore, The activity of superoxide dismutase and glutathione peroxidase were found to be enhanced by organosulfur compounds [61, 64].

Abdel-Naim et al., [61] reported that pretreatment of rats with garlic oil protected the liver from
the toxicity of ethanol and carbon tetrachloride by decreasing the levels of ALT, ALP and AST activities, and prevented liver histopathological changes (Fig.6). Hepato protection might be due to garlic oil effects against cellular leakage and protection of the integrity of the cell membrane in the liver.

Mirunalini et al., [46] found that oral supplementation of garlic to alcoholic patients for 45 days, significantly lowered the activities of liver marker enzymes, decreased the levels of lipid peroxidation and enhanced the antioxidant status to near normal. These data suggest that the hepatoprotective effect of garlic oil might be due to garlic oil effects against cellular leakage and protection of the integrity of the cell membrane in the liver.

Figure6. Photomicrographs of rat liver sections in A: liver of a rat given combined administration of ethanol and carbon tetrachloride; B and C: Liver of rats pretreated with 5 and 10 mg/kg GO respectively + ethanol and carbon tetrachloride; X 160 [61].

Shaarawy et al., [68] reported that administration of garlic significantly reduced the liver toxicity induced in rats by N-nitrosodiethylamine and carbon tetrachloride (Fig.7). Nasr, [69] reported that aged garlic extract (250 mg/kg once for 21 days), pretreated rats revealed a significant reduction in serum levels of AST, ALT induced by cisplatin (7.5 mg/kg, once intraperitoneal) administration. Additionally, histopathological revealed markedly ameliorated cisplatin-induced toxicity on the liver structure. Aged garlic extract has antioxidant and protective effects against cisplatin-induced oxidative stress and...
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liver structure in rats. Thus, it could be used as a dietary supplementation to reduce toxic side effects of anticancer drugs. Zaidi, et al., [70] found that the intragastric administration of the crude extract of garlic significantly decreased the circulating activities of AST, ALT, ALP. 

Allium sativum extract was found to prevent oxidative stress induced by immobilization stress, which may be due to high contents of SAC, alliin, S-allylmercaptocysteine, and allicin, which are potent free radical scavengers [54].

Figure 7. Histopathology of liver showing the normal architecture and cells with granulated cytoplasm and small uniform nuclei of control, garlic, silymarin or both of them, respectively liver (a-d) (HE X100). NDEA-treated rats show loss of architecture, fibrosis and fatty infiltration (e; X100 and f; X400) and magnified part shows malignant nuclei (X1000). Rats pretreated with garlic (g) or silymarin (h) or both (i) before injection of NDEA showing minimal pleomorphism, vaculation, fibrosis, less disarrangement and degeneration of hepatocytes (HE X 400) [68].

Coffee (Coffea arabica)

Coffee (Coffea arabica) (Figure 8) intake has been inversely related to the incidence of liver diseases, although there are controversies on whether these beneficial effects on human health are because of caffeine or other specific components in this popular beverage [71].

Tanaka et al., [72] investigated the potential relationship between coffee consumption and alanine (ALT) and aspartate (AST) aminotransferase. As with GGT, coffee intake was significantly related to decreased serum concentrations of both enzymes among males. Also, eleven observational studies demonstrated a significant inverse association between coffee intake and serum ALT [73]. A cross-sectional study conducted in about 6000 adults at high risk of liver damages from various etiologies, found that coffee and caffeine consumption reduces the risk of elevated serum alanine aminotransferase activity [74]. Previous researches indicate that coffee consumption is inversely related to hepatic cirrhosis. Animal models and cell culture studies indicate that kahweol, diterpenes, and cafestol (some coffee compounds) can function as blocking agents by modulating multiple enzymes involved in

Figure 8. Coffee (Coffea arabica)
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carcinogenic detoxification, kahweol, diterpenes, and cafestol alter the xenotoxic metabolism by inhibiting N-acetyltransferase and inducing the enzymes glutathione-S-transferase [75]. Caffeine is the significant player in hepatoprotection, and necessary to some extent in order for coffee’s protective effects to be manifest in the liver [76].

Parsley (Petroselinum crispum)

Petroselinum crispum has been employed in the cosmetic industries, perfume, and pharmaceutical [77], and used as a food additive and herbal remedies for many ailments [78]. It has been exhibited immunosuppressant, antioxidant, anti-diabetic, cytotoxic, and hepatoprotective [79].

Parsley leaves (Figure 9) were used for the treatment of colic, jaundice, constipation,flatulence edema, and rheumatism. It was used to treat as impotence, a blood pressure regulator, lumbago and nose bleed [80], knee, ache, eczema, and bleeding [80, 81]. Parsley has been used as the antidote and anti-inflammatory [79].

The active compounds in Petroselinum crispum are apin, apigenin, 6′-acetylapiin, apiole, coumarins, and myristicin [79]. Petroselinum crispum is rich in vitamin A and tocopherol [82-84]. Also, Petroselinum crispum contains zinc, β-carotene, vitamins C, B, and starch [85], calcium, iron, phosphorous, and luteolin, which may likely account for its hepatoprotective effect [86, 87]. Phytochemically, the leaves, and seeds of P. crispum has been shown to contain high levels of essential oil known as apiole, while the tender buds contain psoralen and related compounds that can induce photosensitivity and these include xanthotoxin, fucsin, bergapten, majudin, heraclin and antimicrobial furocoumarins namely 8-methoxypsoralen, 5-methoxypsoralen, oxyypeucedanin, isopimpinellin, 6′-acetyllopin, and a new monoterpen glycoside [80, 88, 89]. Besides having significant nutritional value, parsley also exhibits antioxidant and neutralizing properties [78, 90]. The constituents of parsley which include ascorbic acid, carotenoids, flavonoids, coumarins, apiole, various terpenoic compounds, phenylpropanoids, phthalides, furanocoumarins, and tocopherol, have been chemically investigated [91]. Petroselinum crispum contains several classes of flavonoids [92] such as quercetin, apigenin, luteolin, and Kaempferol [93]. Kaempferol and quercetin have been recommended as chemopreventive agents [94, 95], which may inhibit enzyme antioxidant activity, and the capacity to scavenge free radicals [94, 96, 97].

Petroselinum crispum is rich in luteolin that searches out and eradicates free radicals in the body that cause oxidative stress in cells [84, 98]. Fresh Petroselinum crispum leaves scavenge superoxide anion [99], and methanol extracts scavenge hydroxyl radical [92]. Supplementation of diets with a fresh leaf can increase the antioxidant capacity of rat blood plasma [100] and decrease the oxidative stress in humans [101]. Jassim [102] found that alcoholic extract of Petroselinum crispum has a protective effect against sodium valproate toxicity in male rats. Petroselinum crispum leaves are rich in Apigenin and Apigenin glucosidal flavonoids which possess anticancer, anti-inflammatory, and antioxidant activities [103, 104].

Kamal et al., [105] reported that carbon tetrachloride-induced acute hepatotoxicity in rats by increasing the serum activities of AST, ALT, and GGT. It was found a significant decrease in AST, ALT, and GGT after parsley treatment. In addition parsley reduced fatty degeneration, cytoplasmic vascularization and necrosis of liver in CCl4 treated group (Fig.10). This study indicated that parsley has a hepatoprotective effect on acute liver injury induced by CCl4. Khalil et al., [106] found that pretreatment of rats with Petroselinum crispum leaves oils caused significant increases in activity of antioxidant enzymes when compared with CCl4 treated rats. Bolkent et al., [107] reported that degenerative changes were observed in the hepatocytes of diabetic rats. These changes were significantly reduced in the
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hepatocytes of diabetic rats treated with parsley. Blood alanine aminotransferase and alkaline phosphatase activities were observed to be raised in diabetic rats. Diabetic rats treated with parsley demonstrated significantly lower levels of blood alanine transaminase and alkaline phosphatase activities. The study suggests that parsley demonstrates a significant hepatoprotective effect in diabetic rats.

Figure 10. H & E staining for liver tissue of albino rat. (A) CCl4 treated albino rat; (B) parsley treated albino rat.

Peppermint (Mentha piperita)

*Mentha piperita* (family: Labiatae) (Figure 11) is nutrient-rich native to the Mediterranean region [108, 109]. Methyl acetate, menthol, and menthone are the main essential oils in *Mentha piperita* [110]. *Mentha piperita* has antiperoxidant and antioxidant properties [109, 111]. Peppermint is usually used in treatment for disorders of the biliary system, liver problems, irritable bowel syndrome, and inflammatory bowel disease [112, 113]. The effects of peppermint are related to its effect on bile flow and liver function [112].

Figure 11. Peppermint (*Mentha piperita*)

Antioxidant and anti-peroxidant traits of α-tocopherol shaping, eugenol, flavonoids, rosmarinic acid, and caffeic acid were documented [114]. The antioxidant function of peppermint may be due to scavenge free radicals and neutralize ferryl ion-induced peroxidation [115, 116]. *Mentha piperita* has numerous pharmacological, cosmetic, and alimental applications due to its ability to produce terpene and terpenoid compounds.

Sharma *et al.*, [115] studied that the protective role of leaves of *Mentha piperita* in adult Swiss albino mice against arsenic-induced hepatopathy. In the arsenic-treated group, there was a significant increase in ALP, AST, and ALT activities, whereas a significant decrease was recorded in body weight, liver weight and LDH activity in the liver. Pre- and post-treatment of *Mentha* with arsenic significantly alters the biochemical parameters in the liver. A significant decline in ALP, AST, and ALT activities were observed. However, a significant increase in body weight, liver weight, and LDH activity in liver was estimated. The results indicate that the *Mentha* extract may be useful in reducing the side effects of arsenic-induced hepatopathy. Barbalho *et al.*, [117] studied that the effects of administration of peppermint juice twice daily for 30 days on some biochemical parameters in human. The results showed that a reduction 41.5% in blood glucose, 58.5% in triacylglycerides, 66.9% in total cholesterol levels, 52.3% in LDL-c indices, 70% in AST levels, 74.5% in ALT levels, and that 52% presented an increase in HDL-c indices. The use of peppermint by humans can be considered beneficial in the prevention and treatment of risk factors for chronic degenerative diseases.
Marjani et al., [118] determined that the influences of various doses of peppermint oil on the hepatic enzymes, alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma-glutamyl transferase in the serum of mice with and without immobility stress. The mice exposed to drink water, 0.9, 27 and 60 mg/kg peppermint oil from the days 1 to 5 for a period of 4 h before and after immobility stress. There was a significant decrease in ALT in treatment group III and IV after immobility stress. There were also significant decreases in ALP and GGT in treatment group IV after immobility stress. Ali, [109] confirmed that the protective effects of the hydroethanolic extract of mint against toxicity induced during treatment with anti-tuberculosis drugs compared with silymarin in rats.

Administration of combined anti-TB drugs induced hepatotoxicity as evidenced by a significant elevation in the serum, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase activities, total bilirubin, and a decrease in total protein. However, co-administration of mint extract with anti-TB drugs showed good hepatoprotection as evidence from maintenance of the aforementioned biochemical changes near normal. This improvement may be due to their high content of phenolics and flavonoids.

Khodadust et al., [119] investigated that the effects of peppermint alcoholic extract on liver injury caused by carbon tetrachloride. Peppermint extract significantly increased blood serum concentrations of total protein, albumin, triglyceride, and HDL-C, while CCl4 decreased those concentrations. Blood serum concentrations of glucose, total cholesterol, LDL-C, and VLDL-C were decreased by peppermint extract, whereas those concentrations were increased by CCl4. Generally, this study indicated that in vivo administration of peppermint alcoholic extract attenuated the adverse effects of CCl4 on liver function, therefore it might be useful for the prevention of oxidative stress-induced hepatotoxicity in broilers.

**Olive (Olea europaea)**

Since ancient times, *Olea europaea* (family: Oleaceae), and its leaves (Figure.12) were used for a treatment of atherosclerosis, hypertension, diabetes, gout, wounds, and fever [120].

Figure12. Olive leaves (*Olea europaea*). Phenolics compounds in *Olea europaea* leaves similar to it's in the olive oil but in much higher concentration [121]. *Olea europaea* leaves contain maslinic acid, ursolic, oleanolic, quercetin, apigenin, luteolin, tannins, and caffeic acid [122]. Treatment of experimental animals with *Olea europaea* leaves extract caused a reduction in blood glucose [123], and blood pressure [124], prevention of hepatotoxicity [125, 126], prevention of tumor formation [127] and suppressed inflammatory reactions [128]. Eidi et al., [129] reported that treatment of diabetic rats with *Olea europaea* leaf extract caused a reduction in the serum levels liver enzymes [129]. The antioxidant activity of phenolic compounds could be a result of the presence of hydroxyl groups in their structure [130].

Al-Attar and Abu Zeid, [131] found that exposure of mice to 6.5mg/kg body weight of diazinon for seven weeks resulted in statistical increases of serum alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkaline phosphatase, and creatinine, while the value of serum total protein was declined. Treatment of diazinon intoxicated mice with *Olea europaea* leaves extracts caused marked improvement in serum liver and kidney parameters.

Ashour [132] recorded that a significant decrease in serum total protein, and albumin levels and a remarkable increased in serum AST, ALT and ALP activities after 2 weeks of exposure of rats to γ-radiation when compared with controls. Treatment of rats exposed to γ-radiation with ethanolic extract of *Olea europaea* leaves caused an increment of total protein, albumin levels and a significant decrease in AST, ALT, and ALP activities. Zari and Al-Attar, [133] found that treatment of rats with carbendazim caused statistically declines in the values of the level of plasma total protein.
and albumin, while the value of the levels of plasma alanine aminotransferase, and aspartate aminotransferase were elevated. Moreover, after one month of carbendazim exposure, there were severe changes in the structures of the liver. The liver of carbendazim-treated rats showed disarrangement of hepatic strands, an enlargement of the sinusoids, vacuoles formation, dilation and congestion of blood vessels with hemorrhage (Fig.13). Pretreatment of carbendazim- exposed rats with olive leaves extract showed marked improvement in both physiological and histopathological alterations (Fig.14).

**Figure 13.** (A-F) Representative microscopic photographs. Normal liver structure of control rats (A, X 400). Carbendazim treated rats (B, X100; C-F, X 400) [133].

**Figure 14.** Representative microscopic photographs. Olive leaves extract plus carbendazim treated rats (G-I, ×400). Olive leaves extract treated rats (J, ×400) [133].
CONCLUSION

It can be concluded that administration of Curcuma longa, Trigonella foenumgraecum, Allium sativum, Coffea arabica,  Petroselinum crispum, Olea europaea leaves, and Mentha piperita showed a remarkable hepatic protection against hepatotoxic agents such as antibiotics, ethanol, diazinon, carbendazim, arsenic, AlCl₃, CCl₄, monosodium glutamate, γ-radiation, and drugs, which may be due to its antioxidant properties of these medicinal plants and herbs. So, Human expose to hepatotoxic agents and the patients with hepatic disorders should be advised to take these medicinal plants and herbs.

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