Journal of Biotechnology and Bioengineering
Volume 2, Issue 1, 2018, PP 8-23

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].

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 C*urcuma 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].

Figure1. *Curcumin (Curcuma longa L.)*

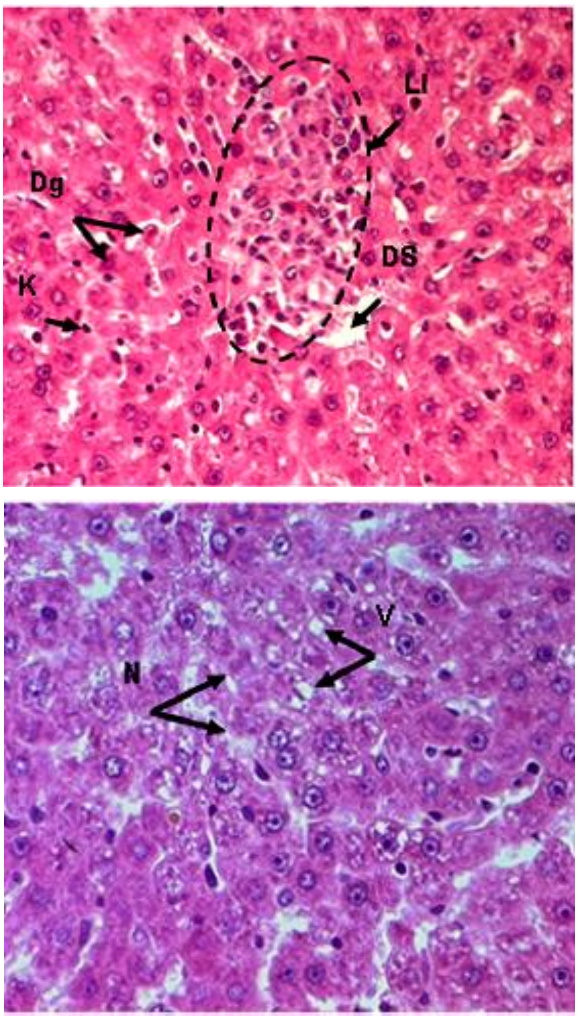
Curcumin could exert antioxidative effects either directly as a chemical antioxidant due to its ability to scavenge reactive oxygen and nitrogen free radicals or by modulating cellular defenses which themselves exert antioxidant effects [25, 26]. Previous studies mentioned that curcumin is a natural 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 streptotocin 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 C*urcuma longa* has antioxidant and anti-inflammatory properties for inhibiting reactive oxygen species formation. Also, Kadasa *et al.*, [29] found that C*urcuma 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 CCl_4 caused significantly reduced serum levels of ALT, AST and ALP activities, and significant elevations in serum total protein and albumin concentrations compared to CCl_4 intoxicated group. Treatment of curcumin reverted the serum protein and albumin levels back to normal in CCl_4-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].

Figure2. *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_4-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_4 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 $AlCl_3$ 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 $AlCl_3$ were showed improvement in changes induced by $AlCl_3$ 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 $AlCl_3$. The administration of fenugreek seed with $AlCl_3$ restored the normal level of plasmatic and hepatic ALT activity and succeeded to increase AST activity in liver and plasma. $AlCl_3$ decreased GGT activity but fenugreek seed supplementation ameliorated it.



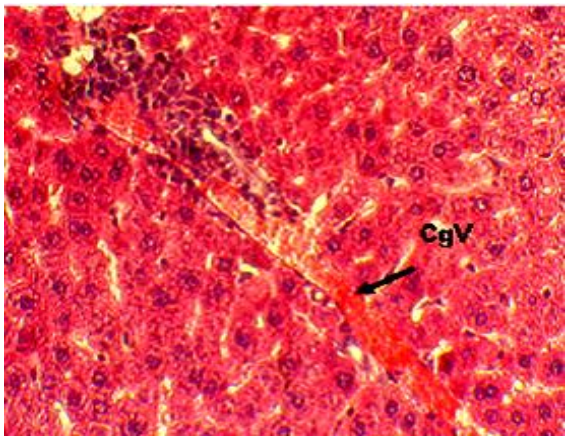


Figure3. *Light micrographs of rat liver tissue stained by hematoxylin-eosin (HE) in AlCl3-treated group (x320, x500, x500). Dg: degenerating cell, K: Kupffer cell, DS: dilated sinusoid, LI: lymphoid infiltrate, N: necrotic cells, V: vacuoles, CgV: congested vein [40].*

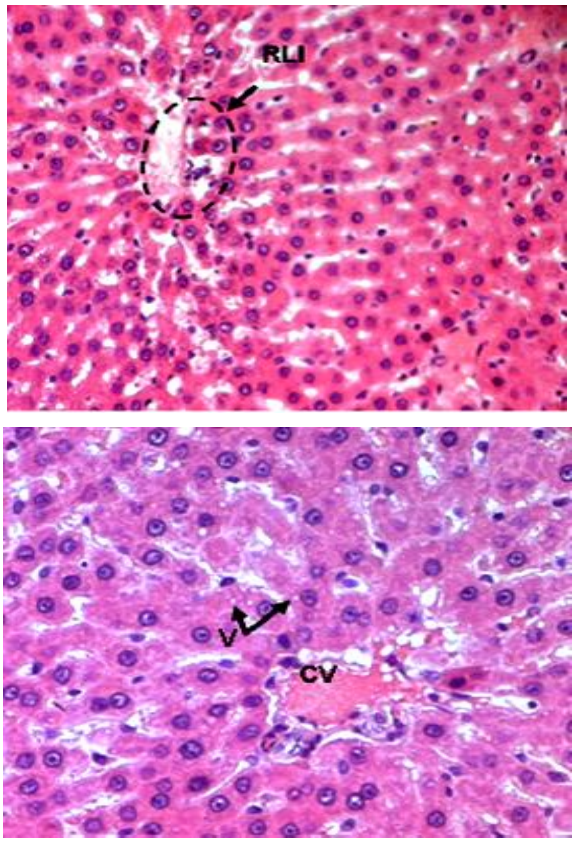


Figure4. *Light micrographs of rat liver tissue stained by hematoxylin-eosin (HE) in Fenugreek + AlCl3-treated group (x320, x500 respectively). LI: lymphoid infiltrate, V: vacuoles, CV: central vein [40].*

Garlic (*Allium sativum*)

Allium sativum (Figure.5) is has been used as food, a spice, and folklore 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].

Figure5. *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, ajoene, 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.

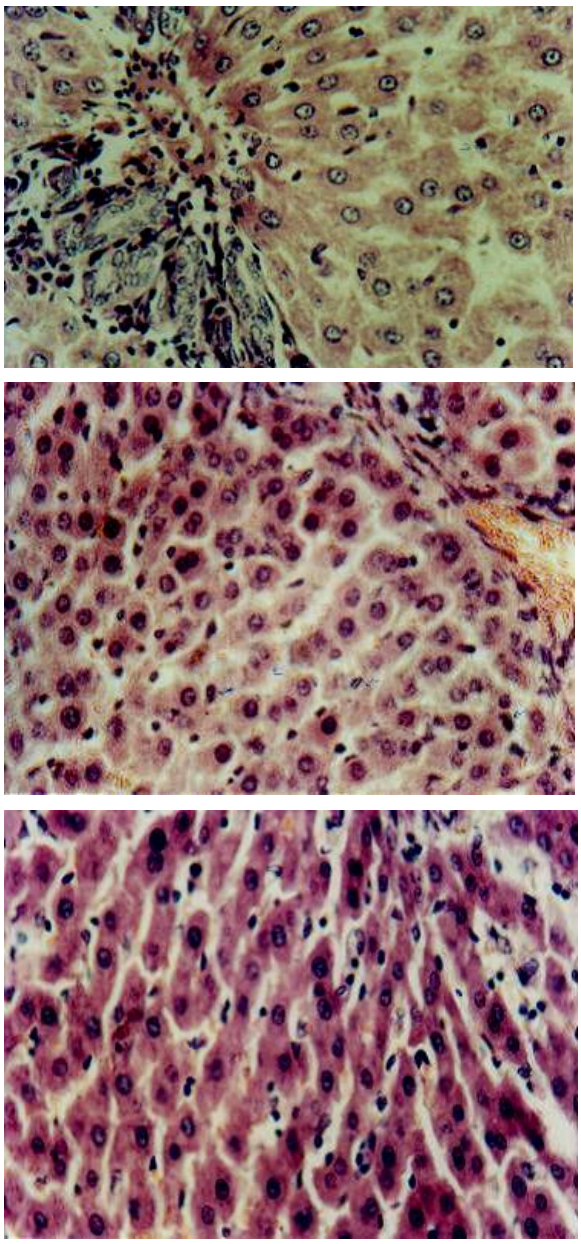


Figure6. *Photomicrographs of rat liver sections in A: liver of a rat given combined administration of ethanol and carbon tetrachloride; B and C: Liver of rats pretreated with 5 and 10 mg/kg GO respectively + ethanol and carbon tetrachloride; X 160 [61].*

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 garlic offers protection against oxidative stress and antioxidant activities in alcoholic liver disease patients. Hence, garlic plays a promising role in antioxidant and it can be considered as a potent drug for the treatment of alcoholic disorders. El-Khayat *et al.*, [59] reported that oral pre-treatment with garlic oil effectively protected the liver from the toxicity of D-galactosamine and lipopolysaccharide by decreasing the oxidation process proved by decreasing the levels of urinary F2-isoprostane, 8-hydroxyguanosine and serum Advanced oxidation protein products (AOPP) together with increasing the serum activity of SOD. Concomitantly, it partly prevented liver enzymes from elevation indicating the protection of the cell membrane from free radicals attack. The histopathological examination confirmed these results showing the improvement in the signs of fibrosis and cellular infiltration together with a marked increase in the protein content of hepatocytes cytoplasm as well as a noticeable increase in DNA content and in the percentage of proliferating cells. There is a possibility that orally administered garlic oil exerts a preventive effect on liver injury progression in D-galactosamine treated rats through its indirect antioxidant action to maintain antioxidant defense system in addition to its direct antioxidant action to scavenge ROS and to inhibit lipid peroxidation [59, 65]. The hepatoprotective property of garlic may be attributed to the presence of organosulfur compounds (such as diallyl disulfide and diallyl sulfide), which have antioxidant and detoxifying properties [59]. This detoxifying effect is explained by the induction of phase II antioxidant enzymes [59, 66]. Garlic contains certain compounds such as germanium and selenium that play an important role in normalizing the oxygen utilization in the cells [59, 67].

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

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].

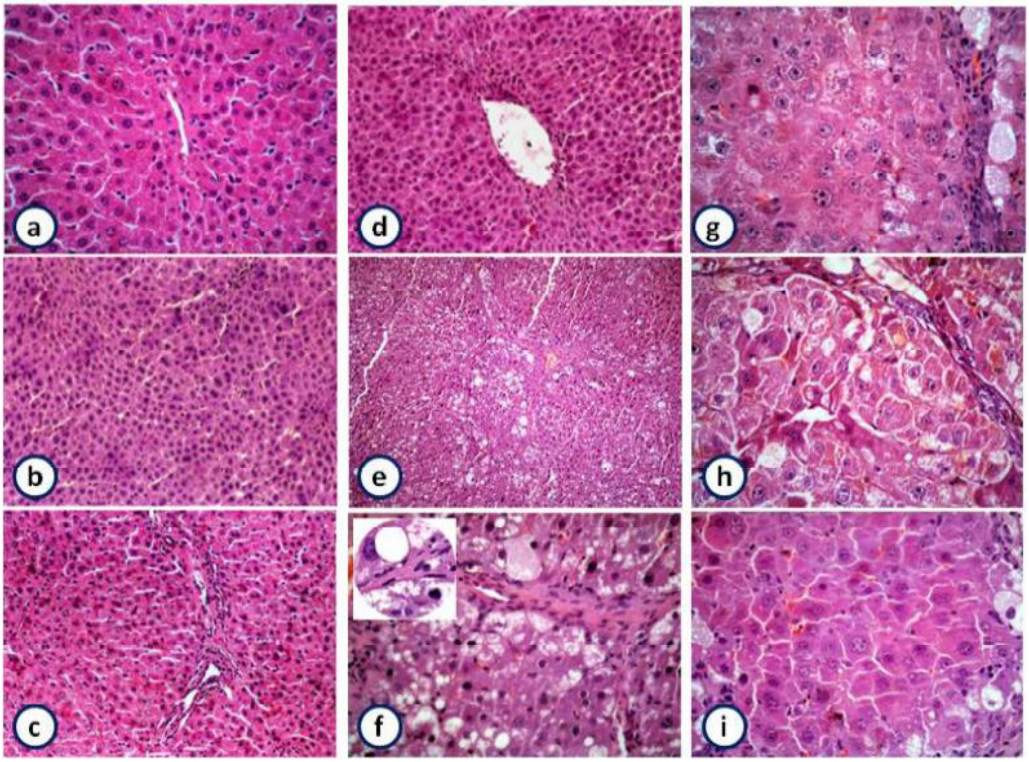


Figure7. *Histopathology of liver showing the normal architecture and cells with granulated cytoplasm and small uniform nuclei of control, garlic, silymarin or both of them, respectively liver (a-d) (HE X100). NDEA-treated rats show loss of architecture, fibrosis and fatty infiltration (e; X100 and f; 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].

Figure8. *Coffee (Coffea arabica)*

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

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, antidiabetic, cytoprotective, 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].

Figure9. *Parsley leaves (Petroselinum crispum)*

The active compounds in *Petroselinum crispum* are apiin, apigenin, 6"-Acetylapiin, apiol, 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, ficusin, bergapten, majudin, heraclin and antimicrobial furocoumarins namely 8-methoxypsoralen, 5-methoxypsoralen, oxypeucedanin, isopimpinellin, 6'-acetylopin, and a new monoterpene 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 CCl_4. 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 CCl_4 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

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.

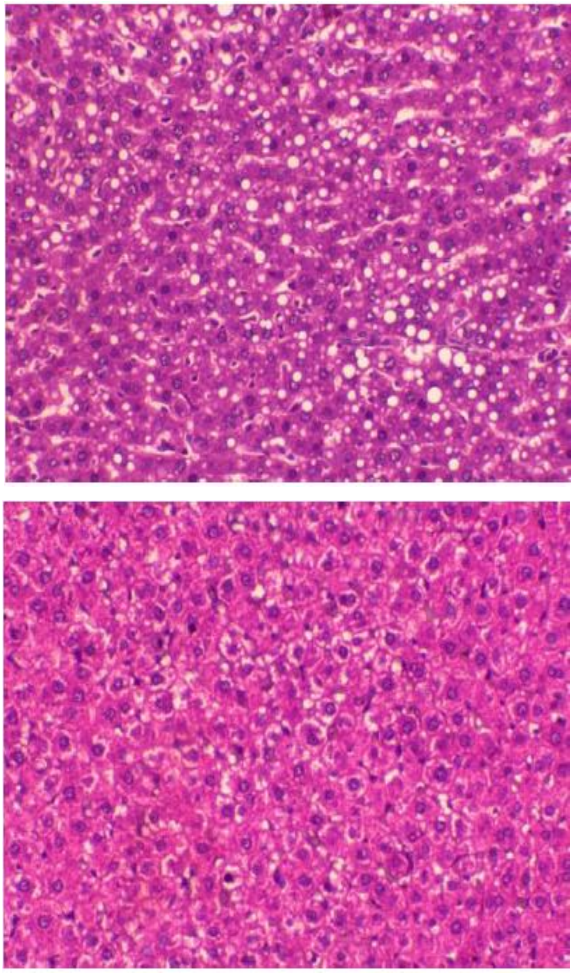


Figure10. *H & E staining for liver tissue of albino rat. (A) CCl4 treated albino rat; (B) parsley treated albino rat.*

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].

Figure11. *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 hepato-protection 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).

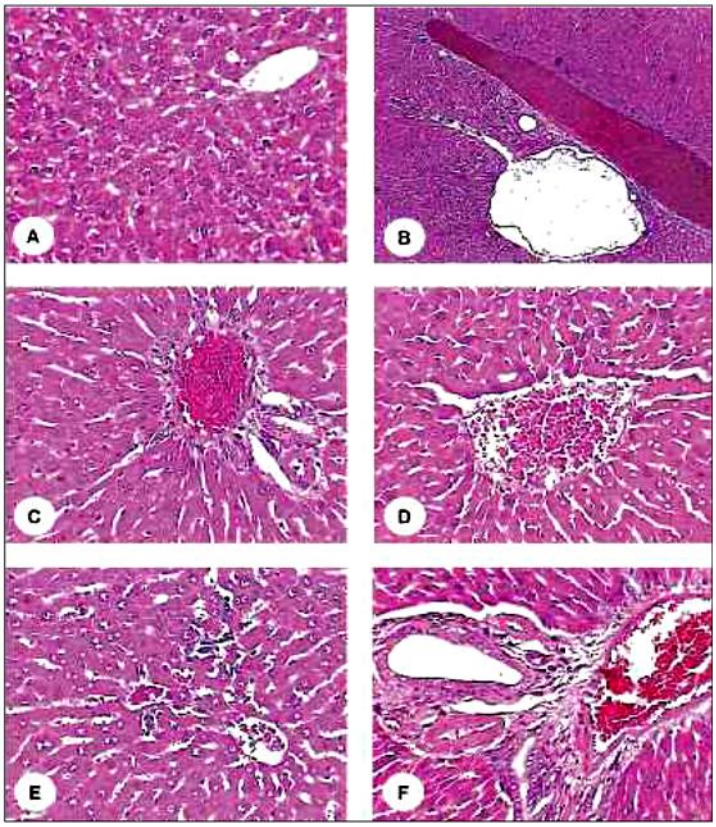


Figure13. *(A-F) Representative microscopic photographs. Normal liver structure of control rats (A, X 400). Carbendazim treated rats (B, X100; C-F, X 400) [133].*

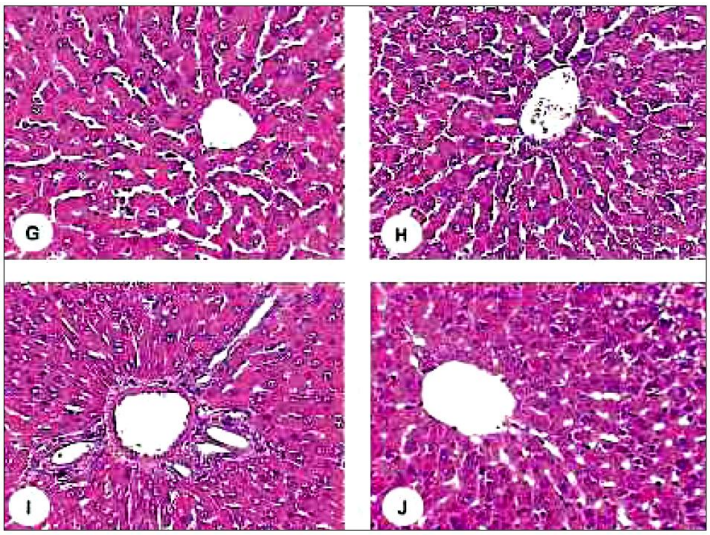


Figure14. *Representative microscopic photographs. Olive leaves extract plus carbendazim treated rats (G-I, ×400). Olive leaves extract treated rats (J, ×400) [133].*

CONCLUSION

It can be concluded that administration of C*urcuma 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, $AlCl_3$, CCl_4, monosodium glutamate, ɣ-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.

REFERENCES

[1] Al-Kenanny ER, Al-Hayaly LK, and Al-Badrany AG. (2012). Protective effect of arabic gum on liver injury experimentally induced by gentamycin in mice. J Kufa Vet Med Sci 3: 174-89.

[2] Ademiluyi AO, Oboh G, and Owoloye TR, Agbebi OJ. (2013). Modulatory effects of dietary inclusion of garlic (*Allium sativum*) on gentamycin-induced hepatotoxicity and oxidative stress in rats. Asian Pac. J Trop Biomed; 3: 470-5.

[3] Galaly SR, Ahmed OM, and Mahmoud AM. (2014). Thymoquinone and curcumin prevent gentamicin-induced liver injury by attenuating oxidative stress, inflammation and apoptosis. J Physiol Pharmacol, 65(6): 823-32.

[4] Azab AE, Albasha MO and Elsayed ASI. (2016). Prevention of hepatotoxicity with curcuma longa and rosmarinus officinalis in gentamicin treated guinea pigs. Indo Amer J Pharm Res, 6(03): 4791-4802.

[5] Albasha M O, and Azab AE. (2014). Effect of cadmium on the liver and amelioration by aqueous extracts of fenugreek seeds, rosemary, and cinnamon in Guinea pigs: Histological and biochemical study. Cell Biol, 2(2): 34-44.

[6] Azab AE. (2014) Hepatoprotective effect of sesame oil against lead induced liver damage in albino mice: Histological and biochemical studies Amer J BioSc, 2(2): 1-11.

[7] Jaya Sankar Reddy V, Deval Rao G, and Mallikajuna K. (2014) A Review on Hepatoprotective Activity of Some Medicinal Plants. Inter J Inn Pharm Res, 5(2): 395-404.

[8] Azab AE, and Albasha MO. (2015) Simultaneous administration of aqueous extract of *Rosmarinus officinal* with ncotine resulted in prevention of induced hepatorenal toxicity in Guinea pigs. Amer J Biosci Bioeng, 3(5): 80-86.

[9] Aboulgasem GJA, Azab AE and Almaky MM. (2015) Sodium nitrite induced biochemical alterations in the blood serum and its amelioration by aqueous extract of Libyan propolis in Guinea pigs. Inter J Sci Res 4(8): 1040-1048.

[10] Elsayed ASI, Bayomy MFF, and Azab AE. (2016) Effect of acute and chronic treatment of Cyclosporin A on liver and kidney functions in rats. J Appl Pharm Sci, 6(3): 116-119.

[11] Kumar CH, Ramesh A, Kumar JNS, and Ishaq BM.(2011) A review on hepatoprotective activity of medicinal plants. Int J Pharm Sci Res 2: 501-515.

[12] Asadi-Samani M, Kafash-Farkhad N, Azimi N, Fasihi A, Alinia-Ahandani E, and Rafieian-Kopaei M. (2015) Medicinal plants with hepatoprotective activity in Iranian folk medicine. Asian Pac J Trop Biomed ,5(2): 146-157

[13] Rajaratnam M, Prystupa A, Lachowska-Kotowska P, Załuska W, (2014) and Filip R. Herbal medicine for treatment and prevention of liver diseases. JPCCR 8(2): 55–60.

[14] Yin X, Zhou J, Jie C, Xing D, and Zhang Y. (2004). Anticancer activity and mechanism of Scutellaria barbata extract on human lung cancer cell line. Life Sci. 75: 2233–2244.

[15] Gill CL, Boyed A, McDermott E, McConn M, Servili M, Selvaggini R, et al., 2005. Potential anticancer effects of virgin olive oil phenols on colorectal carcinogenesis models in vitro, Int. J. Cancer 117 (1): 1–7.

[16] Al-Mamary M, Al-Meeri A, Al-Habori M. (2002). Antioxidant activities and total phenolics of different types of honey. Nutr Res 22: 1041–1047.

[17] Ho C., Ferrara T., Chen Q., Rosen R. and Huang M.(1994). Phytochemicals in teas and rosemary and their cancer preventive properties in food phytochemicals for cancer prevention. Amer. Chem. Soci., Washington: 2-19.

[18] Fetouh FA, and Azab, AE. (2014) ameliorating effects of curcumin and propolis against the reproductive toxicity of gentamicin in adult male Guinea pigs: Quantitative analysis and morphological study. Amer J Life Sci, 2(3): 138-149.

[19] Marquele FD, Di Mambro VM, Georgetti SR, Casagrande R, Valim YML and Fonseca MJV. (2005) Assessment of the antioxidant activities of Brazilian extracts of propolis alone and in topical pharmaceutical formulation. J Pharmacol Biomed Anal 39: 455-462.

[20] Joe B, Vijaykumar M, and Lokesh BR. Biological properties of curcumin-cellular and molecular mechanisms of action. Crit Rev Food Sci Nutr, 2004; 44: 97-111.

[21] Venkatesan N, Punithavathi D, and Arumugan V. (2000) Curcumin prevent adriamycin nephrotoxicity in rats. Br J Pharmacol, 12: 231-234.

[22] Ammon, H.P.T. Anazodo, M.I. Safayhi, H. Dhawan, B.N. and Srimal RC.(1992) Curcumin: a potent inhibitor of Leukotriene B4 formation in rat peritoneal polymorphonuclear neutrophils. Planta Med, 58: 26-30.

[23] Araujo CAC and Leon LL. (2001). Biological activities of *Curcuma longa* L. Mem Inst Oswaldo Cruz, Rio de Janeiro, 96(5): 723-728.

[24] Elsayed AS. (2016). The curcumin as an antioxidant natural herb, with emphasize on its effects against some diseases. Inter J Appl Biol Pharm Tech, 7(1): 26-40.

[25] Awasthi S, Pandya U, Singhal SS, Lin JT, Thiviyanathan V, Seifert WE, et al. (2000) Curcumin glutathione interactions and the role of human glutathione S- transferase P1-1. Chem Biol Interact 128(1): 19-38.

[26] Priyadarsini KI, Maity DK, Naik GH, Kumar MS, Unnikrishnan MK, Satav JG, et al. (2003) Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. Free Rad Biol Med 35(5): 475-84.

[27] Farghaly HS, and Hussein MA. (2010). Protective effect of curcumin against paracetamol-induced liver damage. Australian J Bas Appl Sci 4(9): 4266-4274.

[28] Ezz MK, Hamdy GM, and Abd El Atti RM. (2015) The synergistic hepatoprotective effect of curcumin and ginger against carbon tetrachloride induced- liver fibrosis in rats. Australian J Bas Appl Sci (9): 1962 -1971.

[29] Kadasa NM, Abdallah H, Afifi M, Gowayed S. (2015) Hepatoprotective effects of curcumin against diethyl nitrosamine induced hepatotoxicity in albino rats. Asian Pac J Cancer Prev 16(1):103-108.

[30] Suresh Babu P, and Srinivasan K. (1998) Amelioration of renal lesions associated with diabetes by dietary curcumin in streptozotocin diabetic rats, Mol Cell Biochem 181: 87–96.

[31] Balogun E, Foresti R, Green CJ, and Motterlini R. (2003) Changes in temperature modulate heme oxygenase-1 induction by curcumin in renal epithelial cells. Biochem Biophys Res Commun , 308: 950–5.

[32] Biswas S.K., Mc Clure D., Jimenez L.A., Megson I.L., and Rahman I.(2005). Curcumin induces glutathione biosynthesis and inhibit NF-kappa B activation and interleukin-8 release in alveolar epithelial cells. Mechanism of free radical scavenging activity. Anti. Red. Sign, 7: 32-41.

[33] Flammang A.M., Cifone M.A., Ereson G.L. and Stankowskci L.F. (2004). Genotoxicity testing of fenugreek extract. J Food Chem Toxicol, 42: 205-208.

[34] Meghwal M, Goswami TKA. (2012) review on the functional properties, nutritional content, medicinal utilization and potential application of fenugreek. J Food Processing Technol, 3(9): 1-10.

[35] Shitaw, KN (2015). Studies on the levels of fluoride in selected spices cultivated and consumed in Ethiopia. Master of science in analytical chemistry, department of chemistry, college of natural sciences, Addis Ababa universtiy.

[36] Thakran S, Siddiqui MR, and Baquer NZ. (2004). *Trigonella foenum graecum* seed powder protects against histopathological abnormalities in tissues of diabetic rats. Mol Cell Biochem, 266:151–159.

[37] Eidi A, Eidi M, and Sokhteh M (2007). Effect of fenugreek (*Trigonella foenum-graecum* L) seeds on serum parameters in normal and streptozotocin-induced diabetic rats. Nutr Res, 27: 728–733.

[38] Kaviarasan S, Sundarapandiyan R, and Anuradha CV. (2008). Protective action of fenugreek (*Trigonella foenum graecum*) seed polyphenols against alcohol-induced protein and lipid damage in rat liver. Cell Biol Toxicol, 24: 391–400

[39] Sushma N, and Devasena T. (2010). Aqueous extract of *Trigonella foenum graecum* (fenugreek) prevents cypermethrin-induced hepatotoxicity and nephrotoxicity. Hum Exp Toxicol, 29:311–319.

[40] Belaid-Nouira Y, Bakhta H, Haouas Z, Flehi-Slim I, Neffati F, Najjar MF and Ben Cheikh H. (2013). Fenugreek seeds, a hepatoprotector forage crop against chronic AlCl3 toxicity. BMC Veterinary Research 2013, 9(22): 1-9.

[41] Botsoglou N, Taitzoglou I, Zervos I, Botsoglou E, Tsantarliotou M,and Chatzopoulou PS. (2010) Potential of long-term dietary administration of rosemary in improving the antioxidant status of rat tissues following carbon tetrachloride intoxication. Food Chem Toxicol, 48: 944-950.

[42] Das, S. (2014). Hepatoprotective activity of methanol extract of fenugreek seeds on rats. Int. J. Pharmacol. Sci. Res., 5(4): 1506-1513.

[43] Kumar P, and Bhandari U. (2013). Protective effect of *Trigonella foenum-graecum* Linn. on monosodium glutamate-induced dyslipidemia and oxidative stress in rats. Indian J. Pharmacol., 45:136-140.

[44] Kaviarasan S., Ramamurti N., Gunasekaran P., Varalaksmi E., Anuradha C.V.(2006). Fenugreek (*Trigonella foenum-graecum*) seed extract prevents etanol-induced toxicity and apoptosis in changed liver cells, Alcohol Alcohol, 41(3): 267-273.

[45] El-Tawil GA. (2009). Effect of Fenugreek (*Trigonella Foenum-Graecum*) Supplementation on Radiation-Induced Oxidative Stress in Liver

and Kidney of Rats. J Rad Res Appl Sci, 2(1): 19-30.

[46] Mirunalini S, Arulmozhi V, and Arulmozhi T. (2010). Curative Effect of Garlic on Alcoholic Liver Diseased Patients. Jordan J Bio Sci. 3(4): 147 – 152.

[47] Bongiorno, P. B.; Fratellone, P. M.; Fratellone, P. (2008) Potential health benefits of garlic (Allium sativum): A narrative review. Journal of Complementary and Integrative Medicine, 5(1): 1-24.

[48] Agarwal KC. 1996. Therapeutic actions of garlic constituents. Med Res Rev. 16: 111-125.

[49] Pushpendran CK Devasagayam TPA and Eapan J. (1982). Age related hyperglycemic effect of diallyl disulphide's in rats. Ind J Exp Biol. 20: 428-429.

[50] Yoshida S Kasuga S Hayashi N Ushiroguchi T Matsumura H and Nakagawa S. (1987). Antifungal activity of ajoene derived from garlic. Appl Env Microbiol. 53: 615-617.

[51] Bordia A. (1981). Effect of garlic on blood lipids in patients with coronary heart disease. Am J Clin Nutr. 34: 2100-2103.

[52] Josling PA. (2005). the heart of garlic Nature's aid to healing the human body, HEC Publishing, Chicago Illinois. pp 20.

[53] Gebreyohannes G, and Gebreyohannes M. (2013). Medicinal values of garlic: A review. Inter J Med Med Sci 5(9): 401-408.

[54] Asdaq SM, and Inamdar MN. (2010). Potential of garlic and its active constituent, S-allyl cysteine, as antihypertensive and cardioprotective in presence of captopril. Phytomed 17: 1016-26.

[55] Rai SK, Sharma M, Tiwari M. (2009). Inhibitory effect of novel diallyldisulfide analogs on HMG-CoA reductase expression in hypercholesterolemic rats: CREB as a potential upstream target. Life Sci. 85: 211-219.

[56] Ried K, Toben C, Fakler P. (2013). Effect of garlic on serum lipids: an updated meta-analysis. Nutr Rev. 71: 282-99.

[57] Liu J, Lin RI, Milner JA. 1992. Inhibition of 7, 12-dimethylbenz[a]anthracene-induced mammary tumors and DNA adducts by garlic powder. Carcinogen. 13:1847-1851.

[58] Song K, Milner JA. (1999). Heating garlic inhibits its ability to suppress 7, 12-dimethylbenz (a) anthracene-induced DNA adduct formation in rat mammary tissue. J Nutr. 129:657-661.

[59] El-Khayat Z, Rasheed W, Ramzy T, Hussein J, Agaiby M, Morsy S, Morsy F and Shaffie N. (2010). Protective effect of garlic oil against liver injury in experimental animals. J Med Plants Res. 4(22): 2359-2369.

[60] Sheen LY, Chen HW, Kung YL, Liu CT, and Lii CK (1999). Effects of garlic oil and its organosulfur compounds on the activities of hepatic drug-metabolizing and antioxidant enzymes in rats fed high-and low-fat diets. Nutr Cancer 35: 160-166.

[61] Abdel-Naim AB, Khalifaa AE, and Ahmed SH. (2002) Protective effects of garlic oil against liver damage induced by combined administration of ethanol and carbon tetrachloride in rats. Egypt J Hosp Med. 6 : 27-36.

[62] Kwak MK, Kim SG, Kim ND . (1995) Effects of garlic oil on rat hepatic P4502E1 expression. Xenobiotica, 25: 1021-1029.

[63] Siess MH, Le Bon AM, Canivenc-Lavier MC, and Suschetet M (1997). Modification of hepatic drug-metabolizing enzymes in rats treated with alkyl sulfides. Cancer Lett 120: 195-201.

[64] Banerjee SK, Maulik M, Manchanda SC, Dinda AK, Das TK, and Maulik SK (2001). Garlic-induced alteration in rat liver and kidney morphology and associated changes in endogenous antioxidant status. Food Chem Toxicol 39: 793-797.

[65] El-Beshbishy HA (2008). Aqueous garlic extract attenuates hepatitis and oxidative stress induced by galactosamine/lipopolysaccharide in rats. Phytother Res. 22: 1372-1379.

[66] Munday R, Munday CM (2004). Induction of phase II enzymes by aliphatic sulfides derived from garlic and onions: An overview. Methods Enzymol. 382: 449-456.

[67] Hussein JS, Oraby FS, El-Shafey N (2007). Antihepatotoxic effect of garlic and onion oils on ethanol –induced liver injury in rats. J Appl Sci Res. 3(11): 1527-1533.

[68] Shaarawy SM, Tohamy AA, Elgendy SM, Abd Elmageed ZY, Bahnasy A, Mohamed MS, Kandil E, and Matrougui K (2009). Protective effects of garlic and silymarin on NDEA-induced rats hepatotoxicity. Int J Biol Sci. 5(6): 549-557.

[69] Nasr AY. (2014). Protective effect of aged garlic extract against the oxidative stress induced by cisplatin on blood cells parameters and hepatic antioxidant enzymes in rats. Toxicol Reports 1:682–691

[70] Zaidi SK, Ansari SA, Ashraf GM, Jafri MA, Tabrez S, and Banu N. (2015). Reno-protective effect of garlic extract against immobilization stress induced changes in rats. Asian Pac J Trop Biomed. 5(5): 364-369.

[71] Furtado KS, Prado MG, Silva MAA, Dias MC, Rivelli DP, Rodrigues MAM and Barbisan LF. (2012) Coffee and caffeine protect against liver injuryi by thioacetamide in male Wistar rats. Basic Clin Pharm Toxicol, 111:339–347

[72] Tanaka K, Tokunaga S, Kono S, et al. (1998). Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase

activities among male alcohol drinkers. Int J Epidemiol 27: 438–443.

[73] Walker N. (2016). Daily coffee: Safeguard against liver injury? Nutr Bytes 20(1): 1-11.

[74] Ruhl CE, and Everhart JE. (2005) Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterol 128: 24-32.

[75] Muriel P, and Arauz J. (2010) Coffee and liver diseases. Fitoterapia 81: 297–305.

[76] Feld JJ, Lavoie ÉG, Michel F, and Dranoff JA. (2015) I drink for my liver, Doc: emerging evidence that coffee prevents cirrhosis. Referee Status: (0):1-11.

[77] Lopez MG, Sanchez-Mendoza IR and Ochoa-Alejo N. (1999). Compartive study of volatile components and fatty acids of plants and in-vitro cultures of parsley Petroselinum crispum (Mill) nym ex hill. J Agric Food Chem, 47: 3292–3296.

[78] Awe EO, and Banjoko SO. (2013) Biochemical and haematological assessment of toxic effects of the leaf ethanol extract of *Petroselinum crispum* (Mill) Nyman ex A.W. Hill (Parsley) in rats. BMC Complementary and Alternative Medicine 13:75

[79] Farzaei, M. H., Abbasabadi, Z., Ardekani, M. R. S., Rahimi, R., and Farzaei, F. (2013). Parsley: a review of ethnopharmacology, phytochemistry and biological activities. Journal of Traditional Chinese Medicine, 33(6), 815-826.

[80] Manderfeld MM, Schafer HW, Davidson PM, Zottola EA. (1997). Isolation and identification of antimicrobial furocoumarins from parsley. J Food Prot, 60:72–77.

[81] Maodaa SN, Allam AA, Ajarem J, Abdel-Maksoud MA, Al-Basher GI, and Wang ZY. (2016). Effect of parsley (Petroselinum crispum, Apiaceae) juice against cadmium neurotoxicity in albino mice (Mus Musculus). Behavioral and Brain Functions, 12(1): 6

[82] Ozsoy-Sacan O, Yanardag R, Orak H, Ozgey Y, Yarat A, and Tunali T. (2006). Effects of parsley (*Petroselinum crispum*) extract versus glibornuride on the liver of streptozotocin induced diabetic rats. J Ethnopharmacol, 104:175-181.

[83] Vora SR, Patil RB, and Pillai M. (2012). Oxidative stress associated alterations in lysosomal enzymes and modulatory effect of *Petroselinum crispum* (Mill) Nyman Ex. A.W. Hill leaf extract on mouse brain. American-Eurasian Journal of Scientific Res, 7(2): 64-68.

[84] Soliman HA, Eltablawy NA, and Hamed MS. (2015). The ameliorative effect of *Petroselinum crispum* (parsley) on some diabetes complications. J Med Plants Stud, 3(4): 92-100

[85] Caunii A, Cuciureanu R, Miklósné AZ, Tonea E, Giuchici C.(2010) Chemical composition of common leafy vegetables. Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii 20(2):45-48.

[86] Yoshikawa M, Uemura T, Shimoda H, Kishi A, Kawahara Y, and Mastuda H (2000). Medicinal food stuff XVIII. Phytoestrogens from aerial part of *Petroselinium crispum* Mill, and structures of 6"-acetylopin and a new monoterpene glycoside. Chem Pharm Bull, 48: 1039–1044.

[87] Popovic D, Kaurinovic B, Jakovljvic V, Mimica-Dukic N, Bursac M. (2007). Effect of *Petroselinium crispum* extracts on some biochemical parameters of oxidase stress in mice treated with carbon tetrachloride. Phytothera Res, 7: 531–537.

[88] Zaynoun S, Abi-Ali L, Tenekjian K, and Karban A. (1985). The bergapten content of garden parsley and its significance in causing cutaneous photosenstization. Clin Exp Dermatol, 10: 328–331.

[89] Zhang H, Chen F, Wang X, and Yao HY. (2006). Evaluation of antioxidant activity of parsley (*Petroselinum crispum*) essential oil and identification of its antioxidant constituents. Food Res Int, 39: 833–839.

[90] Mahmood S, Hussain S, and Malik F. (2014). Critique of medicinal conspicuousness of parsley (*Petroselinum crispum*): A culinary herb of Mediterranean region. Pak. J. Pharm. Sci, 27(1):193-202

[91] Tunali T, Yarat A, Yanardag R, Ozçelik F, Ozsoy O, Ergenekon G, and Emekli N. (1999). Effect of parsley (*Petroselinum crispum*) on the skin of STZ induced diabetic rats. Phytotherapy Res, 13(2), 138-141.

[92] Fejes SZ, Blazovics A, Lemberkovics E, Petri G, Szoke E and Kery A. (2000). Free radical scavenging and membrane protective effects of methanol extracts from *Anthriscus cerefolium* (Hoffm) L. and *Petroselinum crispum* (Mill) Nym. Ex A. W. Hill. Phytother Res, 14: 362–365.

[93] Peterson S, Lampe JW, Bammler TK, Gross-Steinmeyer K and Eaton DL. Apiaceous vegetable constituents inhibit human cytochrome P-450 1A2 (hCYP1A2) activity and hCYP1A2-mediated mutagenicity of aflatoxin B1. Food Chem. Toxicol. (2006) 44: 1474–1484.

[94] Potapovich AI and Kostyuk VA. (2003). Comparative study of antioxidant properties and cytoprotective activity of flavonoids. Biochem, 68: 514-519.

[95] Kinoshita T, Lepp Z, Kawai Y, Terao J and Chuman H. (2006). An integrated database of flavonoids. Biofactors, 26: 179-188.

[96] Lin CM, Chen CS, Chen CT, Liang YC and Lin JK. (2002). Molecular modeling of flavonoids that inhibits XO. Biochem Biophys Res Commun, 294: 167–172.

[97] Hall IH, Scoville JP, Reynolds DJ, Simlot R and Duncan P. (1990). Substituted cyclic imides as potential anti-gout agents. Life Sci, 46: 1923-1927.

[98] Rashwan NM. (2012). Biological study on the effect of arginine and parsley on renal toxicity in rats. World J Med Sci, 7 (4): 264-269.

[99] Campanella, L., Bonanni, A., Favero, G., and Tomassetti, M. (2003). Determination of antioxidant properties of aromatic herbs, olives and fresh fruit using an enzymatic sensor. Analytical and Bioanalytical Chemistry, 375(8), 1011-1016.

[100] Hempel, J., Pforte, H., Raab, B., Engst, W., Böhm, H., & Jacobasch, G. (1999). Flavonols and flavones of parsley cell suspension culture change the antioxidative capacity of plasma in rats. Molecular Nutrition & Food Research, 43(3), 201-204.

[101] Nielsen, S., et al. (1999). Effect of parsley (*Petroselinum crispum*) intake on urinary apigenin excretion, blood antioxidant enzymes and biomarkers for oxidative stress in human subjects. British J Nutrition, 81(06): 447-455.

[102] Jassim AM. (2013). Protective effect of *Petroselinum crispum* (parsley) extract on histopathological changes in liver, kidney and pancreas induced by sodium valproate-in male rats. Kufa J Vet Med Sci, 4(1): 20 - 27.

[103] Dorman HJ, Lantto TA, Raasmaja A and Hiltunen R. (2011). Antioxidant, pro-oxidant and cytotoxic properties of parsley. Food Func, 2(6): 328-337.

[104] Papay ZF, Kosa A, Boldizsar I, Ruszkai A, Balogh E and Antal I. (2012). Pharmaceutical and formulation aspects of Petroselinum crispum extract. Acta Pharmaceut Hung, 82(1): 3-14.

[105] Kamal T, Abd-Elhady E, Sadek K, and Shukry M (2014). Effect of parsley (*Petroselium Crispum*) on carbon tetrachloride-induced acute hepatotoxicity in rats. Res J Pharm Biol Chem Sci, 5(6): 1524-1534.

[106] Khalil, A. F., Elkatry, H. O., and El Mehairy, H. F. (2015). Protective effect of peppermint and parsley leaves oils against hepatotoxicity on experimental rats. Annals of Agricultural Sciences, 60(2), 353-359.

[107] Bolkent S, Yanardag R, Ozsoy-Sacan O, and Karabulut-Bulan O.(2004) Effects of parsley (*Petroselinum crispum*) on the liver of diabetic rats: a morphological and biochemical study. Phytotherap Res, 18(12): 996-999

[108] Unver A, Arslan D, Ozcan M and Akbulut M. (2009). Phenolic content and antioxidant activity of some spices. World App Sci J, 6(3): 373-377.

[109] Ali ZY. (2012). Biochemical evaluation of some natural products against toxicity induced by anti-tubercular drugs in rats. New York Sci J, 5(10): 69-80.

[110] Murray MT. The healing power of herbs . (1995) the enlightened person's guide to the wonders of medicinal plants. Rocklin, CA: Prima Pub., xiv, 410.

[111] Rita P, and Animesh DK. (2011). An updated overview on peppermint (*Mentha piperita* L). IRJP, 2(8): 1-10.

[112] Taylor B. (1984). The mechanism of the inhibitory action of menthol on gut smooth muscle. British Journal of Surgery, 71: 902-908.

[113] Bouchra C, Achouri M, Idrissi Hassani LM & Hmamouchi M. (2003). Chemical composition and antifungal activity of essential oils of seven Moroccan Labiatae against Botrytis cinerea. Journal of Ethnopharmacolgy, 89: 165-169.

[114] Rastogi, R.P., Mehrotra, B.N., (1993). Compendium of Indian Medicinal Plants. CDRI, Lucknow and Publications and Information Directorate, New Delhi.

[115] Sharma A, Sharma MK and Kumar M. (2007). Protective effect of *Mentha piperita* against arsenic-induced toxicity in liver of swiss albino mice. Bas Clin Pharmacol Toxicol, 100: 249–257.

[116] Singh D and Gupta RS. (2011). Hepatoprotective activity of methanol extract of Tecomella undulate against alcohol and paracetamol induced hepatotoxicity in rats. Life Science Medicine Research, 26:1-6.

[117] Barbalho SM, Machado FMVF, Oshiiwa M, Abreu M, Guiger EL, Tomazela P, and Goulart RA. (2011). Investigation of the effects of peppermint (Mentha piperita) on the biochemical and anthropometric profile of university students. Cienc Tecnol Aliment Campinas, 31(3): 584-588.

[118] Marjani A, Rahmati R, Mansourian AR and Veghary G. (2012). Effect of peppermint oil on serum lipid peroxidation and hepatic enzymes after immobility stress in mice. Open Biochem J, 6: 51-55.

[119] Khodadust MR, Samadi F, Ganji F, Jafari Ahangari Y and Asadi GH. (2015). Effects of peppermint (Mentha piperita L.) alcoholic extract on carbon tetrachloride-induced hepatotoxicity in broiler chickens under heat stress condition. Poult Sci J, 3 (1): 1-16.

[120] Al-Attar A.M; Alrobai A.A. and Almalki D.A. (2017) : Protective effect of olive and juniper leaves extracts on nephrotoxicity induced by thioacetamide in male mice. Saudi J. Biol. Sci. ; 24(1): 15-22.

[121] Silva S; Gomes L. ; Leitao F. ; Coelho A.V. ; and Boas L.V. (2006): Phenolic compounds and antioxidant activity of Olea europaea L. Fruits and Leaves. Food Sci. Technol. Inter; 12 (5): 385-395.

[122] Dekanski D. ; Janicijevic-Hudomal S. ; Tadic V. ; Markovic G. ; Arsic I. ; and Mitrovic D.M. (2009) : Phytochemical analysis and gastroprotective

activity of an olive leaf extract. J. Serbian Chem. Soc. ; 74 (4): 367-377.

[123] Jemai H.; El Feki A. and Sayadi S. (2009): Antidiabetic and antioxidant effects of hydroxytyrosol and oleuropein from olive leaves in alloxan-diabetic rats. J. Agric. Food Chem.; 57: 8798-8804.

[124] Khayyal M.T. ; El-Ghazaly M.A. ; Abdallah D.M. ; Nassar N.N. ; Okpanyi S.N. And Kreuter M.H. (2002): Blood pressure lowering effect of an olive leaf extract (Olea europaea) in L-NAME induced hypertension in rats. Arzne. Forsch. ; 52: 797-802.

[125] Abdel-Hamid N.M.; Fawzy M.A. and El-Moselhy M.A. (2011): Evaluation of Hepatoprotective and Anticancer Properties of Aqueous olive leaf Extract in Chemically Induced Hepatocellular Carcinoma in Rats. Amer. J. Med. Sci.; 1 (1): 15-22.

[126] Alirezaei M.; Dezfoulian O.; Kheradmand A.; Neamati S. ; Khonsari A. and Pirzadeh A. (2012) : Hepatoprotective effects of purified oleuropein from olive leaf extract against ethanol-induced damages in the rat. Iranian J. Veter. Res. Shiraz Univ.; 13 (3): 218-226.

[127] Hamdi H.k. and Castellon R. (2005) : Oleuropein, a non-toxic olive iridoid, is an anti-tumor agent and cytoskeleton disruptor. Biochem Biophys Res. Commun ; 334: 769-778.

[128] Pieroni A.; Heimler D.; Pieters L.; Van Poel B. and Vlietinck A.J. (1996) : In vitro anti complementary activity of flavonoids from olive (*Olea europaea* L.) leaves. Pharmazie ; 51: 765-768.

[129] Eidi A., Eidi M, and Darzi R. (2009). Antidiabetic effect of *Olea europaea* L. in normal and diabetic rats. Phytother Res, 23(3): 347-350.

[130] Benavente-Garcia O.; Castillo J.; Lorente J.; Ortuno A. and DelRio J.A. (2000): Antioxidant activity of phenolics extracted from Olea europaea L. leaves. Food Chem. ; 68: 457-62.

[131] Al-Attar AM and Abu Zeid IM. (2013) Effect of tea (*Camellia sinensis*) and olive (*Olea europaea* L.) leaves extracts on male mice exposed to diazinon. BioMed Res Inter Article ID 461415: 1-6.

[132] Ashour SES.(2011)Hematological and biochemical studies on the effect of some natural antioxidants pre-injection in irradiated rats. Ph.D. Thesis. Fac. Agri., Benha Univ.

[133] Zari TA and Al-Attar AM. (2011) Therapeutic effects of olive leaves extract on rats treated with a sublethal concentration of carbendazim. Europe Rev Med Pharmacol Sci 15: 413-426