



Tunisian Hepatoprotective Plants

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Abstract Purpose: Liver diseases are an important health problem in Tunisia where the use of the medicinal plants in liver protection is very popular. Many previous studies showed that a wide range of Tunisian medicinal plants had hepatoprotective activity.

Methods: A comprehensive review was conducted to a mass data from scientific researches about Tunisian medicinal plants used for their hepatoprotective potential.

Results: Twenty-nine available Tunisian medicinal plants were found and described in this review for their potent liver protective potentials.

Conclusions: The elucidation of Tunisian medicinal plants having hepatoprotective potentials could be helpful for the development of new drugs used in the treatment of liver diseases.

Keywords hepatoprotective effect, liver, toxicity, medicinal plants, Tunisia

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAT: catalase; CCl₄: carbon tetrachloride; DDT: dichlorodiphenyltrichloroethane, DNA: deoxyribonucleic acid; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: reduced glutathione; GST: glutathione-S-transferase; H₂O₂: hydrogen peroxide; LDH: lactate dehydrogenase; LPO: lipid peroxidation; MDA: malondialdehyde; ROS: reactive oxygen species; SOD: superoxide dismutase; TBARS: Thiobarbituric acid.

Introduction

Liver is a vital organ having a primordial role in metabolism and excretion of xenobiotics from the body. The liver main function is to filter the blood coming from the digestive system, before going to the body rest area. The liver also detoxifies chemicals and metabolizes drugs. Additionally, it secretes bile that ends up back in the intestines as well as it makes proteins important for blood clotting and other acts [1]. Liver diseases are one of the most disastrous disorders disturbing human health with high levels of death in the worldwide [2]. About 250,000 new cases and 20,000 deaths are reported every year. The causative factors of liver disorders include viral infection, xenobiotics, hepatotoxins, environmental pollutants and alcohol ingestion. These factors can induce a rise of oxidative stress provoking changes in liver metabolic functions and leading to fibrosis, cirrhosis, tumors and liver cell necrosis [3]. The type of liver diseases differs according to country and may be influenced by local factors. In fact, excessive consumptions of alcohol and viral infections are the most common risk factors for liver diseases in developed countries while environmental pollution, hepatic viruses, parasitic infections and chemotherapeutics are the main factors known to cause hepatic damage in developing countries [4]. Several synthetic drugs have been known for the treatment of liver disorders but some of them accompanied by intolerable adverse effects and

undesirable drug interactions [5]. Scientists always turn to nature to find promising drugs for liver diseases without much side effects [3].

Living in harmony with the nature, all human societies have used plants not only as sources of nutrition but also as therapy against diseases [6]. Plants have long history with human healthcare owing to their medicinal properties. Several plants have currently gained more importance as source of new drugs. One quarter of all medicinal remedies are preparations made on natural or synthetic analogues of plant constituents [7]. Additionally, it is estimated that 70%-80% of universal population mainly rely on traditional herbal medicine to meet their primary remedies [8]. From 250,000 to 500,000 plants in the worldwide, a small percentage has been examined for its medicinal properties. Tunisia, a smallest Northern Africa country, has more than 500 species of medicinal and aromatic plants and a total of 2,163 varieties [9]. In earlier studies, we assayed to assemble Tunisian medicinal plants that have been experimentally tested and shown to be efficient against diabetes [10], ulcer [11] and cancer [6]. In the same way, the present research defines Tunisian medicinal plants that have been experimentally proved for their hepatoprotective potential.

Methodology

The search was done in electronic databases to collect data from scientific researches using the key words: hepatoprotective effect, liver, hepatotoxicity, medicinal plants and Tunisia.

Findings

Allium sativum

The hydromethanolic extract of *A. sativum* cloves (20 mg/Kg) was used to study the hepatoprotective effect on deltamethrin-induced hepatotoxicity in rats. Results indicated that *A. sativum* extract, given orally for 4 weeks, attenuated the extensive changes in hepatic AST, ALP, LDH and ALT in deltamethrin-treated rats. Additionally, the administration of *A. sativum* extract restored the hepatic SOD, CAT, GPx enzymes. Histological observation also revealed a good recovery of deltamethrin-induced hepatotoxicity by *A. sativum* extract [12]. The main part of therapeutic effect of *A. sativum* is associated with its phenolic compounds especially allicin [13]. Allicin, the main active constituent of *A. sativum* cloves, had a significant protective effect against galactosamine-made liver damage in rats [14].

Amaranthus spinosus

The hepatoprotective activity of methanolic extract from *A. spinosus* seeds was investigated against deltamethrin-caused liver damage in rats. The methanolic extract of *A. spinosus* seed (250 mg/Kg) was orally administered to the animals intoxicated by deltamethrin (15 mg/Kg). Results showed that methanolic extract of *A. spinosus* seed reversed hepatotoxicity in deltamethrin treated rats. Histological examination also showed a good recovery of deltamethrin-induced hepatotoxicity by *A. spinosus* seed extract. The chemical composition of *A. spinosus* seed extract was rich in caffeic acid with 33.42%, quercetin with 13.14%, isorhamnetin with 11.13%, cinnamic acid with 9.56%, epicatechin with 7.85% and gallic acid with 5.03% [15]. In fact, caffeic acid and quercetin, present with important proportions in *A. spinosus* seed extract, were explored for their protective activities against paracetamol and CCl₄-provoked liver injury in rats [16]. Additionally, the pretreatment with epicatechin also offered protection against CCl₄-caused liver alterations in mouse liver [17]. Kim *et al.* [18] showed that isorhamnetin derivatives ameliorated CCl₄-induced hepatic damage by enhancing the anti-oxidative defense system and reducing the inflammatory signaling pathways. Fernandez-Martinez *et al.* [19] also reported the hepatoprotective activity for 15 cinnamic acid derivatives in the CCl₄-induced acute liver damage model. It is also the case of gallic acid isolated from *Peltiphyllum peltatum* which had a liver protective effect against sodium fluoride-induced oxidative stress [20].

Artemisia campestris

The essential oil of *A. campestris* aerial parts was evaluated for its liver protective potential against hepatic damage caused by deltamethrin. Before deltamethrin treatment, rats were intraperitoneally pre-treated with *A. campestris* essential oil (200 mg/Kg) during two weeks and then deltamethrin (7.20 mg/Kg) was applied along with *A.*



campestris essential oil for the second week. Administration of *A. campestris* essential oil showed hepatoprotective property on AST, ALP, ALT and MDA in deltamethrin-treated rats as well as restoration of SOD, CAT and GPx in liver. Histological examination also confirmed that *A. campestris* essential oil ameliorated alterations induced by deltamethrin [21]. Monoterpene hydrocarbons were shown to be the major fraction of *A. campestris* essential oil (87%) and mainly composed by β -pinene (32.95%), α -limonene (15.13%), α -pinene (12.25%), γ -terpinene (7.60%) and β -myrcene (5.51%) [22]. El-Sawi et al. [23] explained that the cytotoxicity effect of *Juniperus Phoenicia* essential oil against liver carcinoma cell lines could be due to the high content of monoterpenes, namely α -pinene and β -pinene. Myrcene, α -pinene and γ -terpinene were the main compounds of *Ferulago campestris* essential oil which had an interesting hepatoprotective effect against D-galactosamine/lipopolysacchride-induced liver injury in rats [24]. Concerning limonene compound, it helps combat cell mutations and increases glutathione levels in the liver which is the end-product of all antioxidants [25]. Glutathione and the enzyme glutathione reductase participate in the formation of the correct disulfide bonds of many proteins and polypeptide hormones and participate in the metabolism of xenobiotics [26].

Asparagus albus

The hot aqueous extract of *A. albus* leaves was studied against CCl₄ induced hepatic injury in rats. Results showed that intragastric administration of *A. albus* leaf extract (150 mg/Kg bw) twice a week for 28 days to rats intoxicated with CCl₄ (3 ml/Kg) had a significant protective effect by lowering the levels of hepatic marker enzymes (AST and ALT) and by improving the histological architecture of the rat liver. The hot aqueous extract from *A. albus* leaf attenuated oxidative stress by restoring the activities of SOD, CAT, and GPx [27]. The main phenolic compounds identified in the hot aqueous extract of *A. albus* leaves were vanillic acid (50.75%), gallic acid (28.51%) and catechin (9.93%) [27]. In fact, a potent hepatoprotective activity against CCl₄-induced hepatic injury was observed in the case of vanillic acid [28], gallic acid [29] and catechin [30].

Capparis spinosa

The hepatoprotective effect of methanolic extract from *C. spinosa* leaves was investigated against CCl₄-induced liver injury in rats. The CCl₄ was administered by gastric gavage twice a week (on every Tuesday and Thursday) for 8 weeks. Oral pretreatment with methanolic extract of *C. spinosa* leaves (200 mg/kg in olive oil) was realized 7 days before CCl₄ exposure and daily thereafter throughout the study. Results showed that methanolic extract of *C. spinosa* leaves significantly prevented the increase in serum ALT, AST and LDH levels in acute liver damage induced by CCl₄, decreased the amount of hepatic malondialdehyde (MDA) formation and elevated the activities of SOD, CAT and GPx, and restored liver injury. The histopathological observation demonstrated that methanolic extract of *C. spinosa* leaves regenerated the healthy liver with comparison to CCl₄-treated groups and confirmed the obtained results. The interesting hepatoprotective effect of the methanolic extract from *C. spinosa* leaves could fundamentally be attributed to its phenolic compounds which were rutin (35.78%), resveratrol (21.25%), coumarin (12.00%), epicatechin (11.57%), luteolin (7.01%), catechin (5.10%), kaempferol (3.63%), vanillic acid (2.41%) and gallic acid (1.23%) [31]. Hafez et al. [32] reported that rutin has a potent protective effects against CCl₄-induced liver damage. A potent hepatoprotective potential against CCl₄-induced hepatic injury was also observed in the case of coumarin [33], luteolin [34], vanillic acid [28] and gallic acid [29]. Wang et al. [35] have demonstrated the hepatoprotective effect of resveratrol against acetaminophen (APAP)-induced liver injury in mice. Epicatechin was found to ameliorate ionizing radiation-induced oxidative stress in mouse liver [17]. Catechin, isolated from the root of *Rosa rugosa*, was able to change the activities of hepatic drug metabolizing enzymes in rats treated with bromobenzene [36]. Wang et al. [37] showed the liver protective potential of kaempferol against alcohol-induced hepatotoxicity by reducing of CYP2E1 activity and by enforcing the protective role of antioxidative defense system.

Ceratonia siliqua

The ethyl acetate extract of *C. siliqua* leaves was evaluated against CCl₄-treated rats. The intraperitoneal administration of ethyl acetate extract from *C. siliqua* leaves (250 mg/kg b.w) for 8 days prevented CCl₄-induced



liver damage at a dose of 1 ml/kg. The biochemical changes were in accordance with histopathological examination signifying a potential liver protective effect of the ethyl acetate extract from *C. siliqua* leaves [38]. In this study, Ben Hsouna et al. [38] reported that the constituents of *C. siliqua* leaf extract mainly contained syringic acid, myricetin glycosides and gallic acid derivatives. In this way, Itoh et al. [28] had determined the hepatoprotective effect of syringic acid on CCl₄-induced liver injury. Guo et al. [39] mentioned that myricetin derived from *Hovenia dulcis* ameliorated liver injury in high choline fed mice. Gallic acid also possessed a potent hepatoprotective effect against paracetamol-induced liver injury in mice [40].

Citrus aurantium

The ethyl acetate extract of *C. aurantium* leaves was investigated against CCl₄-induced liver toxicity in rats. Animals were intraperitoneally treated with *C. aurantium* ethyl acetate extract (250 mg/kg b.w) for 14 days and intoxicated with CCl₄(1 ml/kg in olive oil) on the 14th day. The biochemical changes were in accordance with histopathological examination signifying a potential liver protective effect of the ethyl acetate extract from *C. aurantium* leaves. HPLC analysis of *C. aurantium* leaf extract showed the presence of quercetin (45.16%), epicatechin (17.70%), caffeic acid (16.83%), kaempferol (8.98%), gallic acid (7.25%), rutin (2.76%) and catechin (1.29%) [41]. In fact, a potent liver protective activity against CCl₄-induced hepatotoxicity in rats was observed for quercetin [16], epicatechin [17], caffeic acid [16], gallic acid [29], catechin [30] and rutin [32].

Citrus limon

The hepatoprotective effect of *C. limon* essential oil was evaluated against aspirin-induced liver damage in female Wistar albino rats. The essential oil of *C. limon* aerial parts (1 ml/Kg) was orally administered to the animals for 56 days and then aspirin (600 mg/Kg) was given for 4 days. Results showed that the *C. limon* essential oil exhibited an excellent protective effect and may be considered as a useful source of cellular defense agent in liver against aspirin [42]. This protective effect of *C. limon* essential oil was shown by the decrease of levels of glucose, cholesterol AST, ALT, LDH and protein when compared to the untreated group. The decrease of the activities of liver enzymes in blood was due to its ability to reduce free radical-induced oxidative damage in the liver. The treatment of essential oil exerted a strong protective effect on aspirin-induced oxidative stress, as revealed by the decreased level of LPO (TBARS), and enhanced the enzymatic defense system (SOD, CAT and GPx). Histopathological liver of the rats treated with the *C. limon* essential oil showed improved hepatocellular architecture with signs of recovery, indicating the protective effect of *C. limon* essential oil [42]. The chemical composition of *C. limon* essential oil was characterized by the predominance of monoterpene hydrocarbons which mainly due to limonene with 78.92% in fruits [43], 44.20% in leaves [44] and 94.40% in peel [45]. This compound could interact with ROS produced by aspirin which induced aggressive oxidants. In fact, Reicks and Crankshaw [25] reported that limonene helps combat cell mutations and increases glutathione levels in the liver which is the end-product of all antioxidants.

Eryngium maritimum

The methanolic extract of *E. maritimum* seeds was evaluated against CCl₄-induced hepatotoxicity in rats. The CCl₄ (50 ml/kg in corn oil) was administered to rats by gastric gavage twice a week (on every Tuesday and Thursday) for 8 weeks. Pretreatment with methanolic extract of *E. maritimum* seeds (150 mg/kg in corn oil) was realized 7 days before CCl₄ exposure and daily thereafter throughout the study by gastric gavage. Results showed that methanolic *E. maritimum* extract restored the increased activities of AST, ALT, LDH and ALP levels induced by CCl₄. Methanolic *E. maritimum* extract also increased the activities of CAT, SOD and GPx while decreased the TBARS and protein carbonyl contents. The histopathological studies suggested that methanolic *E. maritimum* extract remarkably ameliorated the pathological changes in the liver tissues followed chronic intoxication by CCl₄. The methanolic extract of *E. maritimum* seeds was mainly rich in phenolic acids (74.38%) and flavonoids (20.15%). The main phenolic acids were caffeic acid (32.97%), gallic acid (19.04%) and protocatechuic acid (16.48%). Flavonoids were characterized by the predominance of kaempferol (8.25%) and luteolin (4.73%) [46]. In fact, caffeic acid showed a hepatic protection against oxidative hepatic damage [47]. Nabavi et al. [20] showed that gallic acid isolated from



Peltiphyllum peltatum had an hepatoprotective effect against sodium fluoride-induced liver damage. Protocatechuic acid isolated from *Hibiscus sabdariffa* L. was found to be protective against oxidative damage induced by tert-butylhydroperoxide [48]. Wang et al. [37] showed that kaempferol had a potent hepatoprotective potential against alcohol-induced liver injury. Luteolin was also found to be hepatoprotective CCl₄-induced liver injury in rats [34].

Ficus carica

The aqueous extract of *F. carica* stem extract was investigated against methanol-induced liver damage in rats. *F. carica* stem extract (10 g/l) was orally administered to animals for six weeks. Then, an intraperitoneal injection of methanol (2.37g/kg bw) was daily given for 30 days. Results showed that the treatment with methanol exhibited a significant increase of hepatic ALT, AST, ALP, LDHLPO while SOD, CAT, and GPx, significantly decreased. The treatment with *F. carica* stem extract had found to remove oxidative liver damage induced by methanol [49]. It was reviewed by Mawa et al. [50] that fifteen anthocyanins were isolated from *F. carica* fruit and bark which mainly were cyanidin, aglycone and some pelargonidin derivatives. Zaffer Ahmad et al. [51] had also isolated two new flavonols (caricaflavonol diester A and B) from *F. carica* stem bark which had an antidiabetic activity. Zhu et al. [52] demonstrated that the anthocyanin cyanidin-3-O- β -glucoside, a flavonoid, increased hepatic glutathione synthesis and protected hepatocytes against reactive oxygen species during hyperglycemia. In this way, several other flavonoids were reported for their hepatoprotective activities such as catechin, apigenin, quercetin, naringenin, rutin, silymarin and venoruton [53].

Hammada scoparia

The hepatoprotective effect of methanolic extract from *H. scoparia* leaves was evaluated against ethanol-induced liver injury in male rats. The animals were treated daily with 35 % ethanol solution (4g/kg) during 4 weeks. This treatment led to an increase in LPO, a decrease in antioxidative enzymes (CAT, SOD and GPx) in liver and a considerable increase in the serum levels of AST, ALT and ALP. However, the treatment with methanolic extract of *H. scoparia* leaves efficiently normalized various biochemical parameters and protected the liver against ethanol induced oxidative damage in rats. These biochemical changes were consistent with histopathological observations, suggesting marked hepatoprotective effect of methanolic *H. scoparia* extract. Phytochemical screening of methanolic *H. scoparia* leaf extract revealed its richness in alkaloids and flavonoids [54]. In earlier study, Saidi et al. [55] found that flavonoid-enriched fraction of *H. scoparia* leaves had a potent hepatoprotective effect on liver injury induced by warm ischemia/reperfusion. This flavonoid fraction of *H. scoparia* leaves was mainly rich in isorhamnetin triglycerides [56].

Hyparrhenia hirta

The methanolic extract of *H. hirta* aerial parts was evaluated against sodium nitrate-induced liver injury in male Wistar rats. Animals were treated with sodium nitrate (400 mg/kg) and methanolic *H. hirta* extract (200 mg/kg) during for 50 days. Results showed that the sodium nitrate treatment exhibited a significant increase of hepatic ALT, AST, ALP, LDH LPO while SOD, CAT, and GPx, significantly decreased. However, the treatment with methanolic extract of *H. hirta* aerial parts reversed hepatotoxicity in sodium nitrate intoxicated rats [57]. This reversal action of the altered antioxidant enzyme status and peroxidative damage in the liver by *H. hirta* extract confirmed its antioxidant, anti-peroxidative properties and its potential role in the defense against free radicals, which could be attributed to its richness in flavonoids, especially luteolin derivatives and apigenin derivatives. In fact, Azimova and Vinogradova [58] reported that luteolin derivatives had an antioxidant activity able to scavenge hydroxyl radicals and to eliminate ROS generated by hydrogen peroxide. Further, the antioxidant ability of quercetin and apigenin derivatives has been reported in several studies [58-59].

Lavandula stoechas

The hepatic protective effect of essential oil from *L. stoechas* aerial parts was determined against malathion-induced hepatotoxicity in rats. Malathion (200 mg/Kg b.w.) and *L. stoechas* essential oil (50mg/kg b.w.) were daily



administered by intragastric gavage during 30 days for rats. Results showed that malathion treatment revealed an increase of liver weight and a disorder of metabolic parameter. On the other hand, malathion treatment was escorted by an increase of LPO (MDA) and H₂O₂ levels as well as a depletion of antioxidant enzyme activities such as CAT, SOD and GPx. However, the treatment with *L. stoechas* essential oil eliminated all malathion liver perturbations [60]. The beneficial effect of *L. stoechas* essential oil might be related, in part, to its antioxidant properties which mainly due to the presence D-fenchone with 29.28%, α -pinene with 23.18%, camphor with 15.97% and camphene with 7.83% [60,61].

Lawsonia inermis

The liver protective potential of ethyl acetate fraction and its major purified compound, gallic acid, obtained from *L. inermis* fruits were investigated against CCl₄-treated rats. CCl₄ induced oxidative stress by a significant increase in serum marker enzymes. However, pretreatment of rats with ethyl acetate fraction of *L. inermis* fruits at a dose of 250 mg/kg b.w and gallic acid significantly lowered ALT, AST, ALP, LDH and TBARS in treated rats while an increase of SOD, CAT and GPx. Histopathological observation also showed a good recovery of CCl₄-induced hepatotoxicity by *L. inermis* extract. This hepatoprotective potential of *L. inermis* extract was comparable to that of the major purified antioxidant compound, gallic acid [62].

Lycium europaeum

The methanolic extract of *L. europaeum* leaves was evaluated against CCl₄-induced liver damage in male Wistar mice. Methanolic extract of *L. europaeum* leaves was orally administered (150 mg/kg in corn oil) to rats for 15 days and the CCl₄ (2 ml/kg in corn oil) was injected after the last day. CCl₄ administration induced hepatotoxicity by an increase of ALT, AST, ALP, LDH and LPO (MDA) in liver tissues. Pretreatment with methanolic extract of *L. europaeum* leaves significantly restored the majority of these biological parameters to normal levels, as well as an improvement of histopathological changes [63]. The methanolic extract of *L. europaeum* leaves was mainly rich in caffeic acid (31.53.48%), gallic acid (26.35%), naringenin (12.86%), epicatechin (7.45%), vanillic acid (5.96%), rutin (5.65%) and coumaric acid (0.31%). In fact, a potent hepatoprotective activity against CCl₄-induced liver injury was observed for caffeic acid [16], gallic acid [29], vanillic acid [28], naringenin [64] and rutin [32].

Marrubium vulgare

The liver protective potential of *M. vulgare* leaves was investigated against cyclophosphamide-induced hepatic damage in rats. The aqueous extract of *M. vulgare* leaves (500 mg/kg) was orally given to rats for 30 days then treated with cyclophosphamide (150 mg/kg) for 3 days. Cyclophosphamide administration was accompanied by an oxidative stress status assessed by alterations of hepatic biomarkers (ALT, AST, LDH and ALP) as well as a depletion of antioxidant enzyme activities such as CAT, SOD and GPx. The administration of *M. vulgare* extract was found to be beneficial by attenuating cyclophosphamide-induced liver damage. HPLC analysis showed the existence of phenolic acids (gallic acid, catechic acid, caffeic acid, epicatechic acid, vanillic acid and coumarin acid) and flavonoids (rutin, quercetin and kaempferol) [65]. A potent protective activity against cyclophosphamide-induced toxicity was observed in the case of gallic acid [66], caffeic acid [67], vanillic acid [68], quercetin [69] and rutin [70]. Coumaric acid was found to protect liver against cisplatin-induced toxicity [71]. Wang *et al.* [37] reported the hepatoprotective effect of kaempferol against alcoholic liver injury in mice.

Matricaria recutita

The decoction of *M. recutita* flower was used to study the hepatoprotective effect on ethanol-induced oxidative stress in rats. Results indicated that *M. recutita* decoction counteracted ethanol-induced liver damage, preserved thiol-SH groups and prevented the depletion of antioxidant enzyme activity of SOD, CAT and GPx. HPLC phenolic analysis allowed the detection of gallic acid, protocatechuic acid, chlorogenic acid, caffeic acid, cafeoylquinic acid, salicylic acid, quercetin, quinic acid derivative, hydroxybenzoic acid -O-hexoside and 5,7,4'-trihydroxy-6,3'-



dimethoxyflavone [72]. So, a potent hepatoprotective activity was observed in the case of gallic acid [66], chlorogenic acid [73], caffeic acid [67], quercetin [69] and quinic acid derivatives [74] and flavone derivatives [75].

Nitraria retusa

The aqueous extract of *N. retusa* fruit was studied for its hepatoprotective effect against penconazole induced hepatic injury in adult rats. Animals daily received by gavage 300 mg/kg bw of lyophilized *N. retusa* extract and they intraperitoneally received 67 mg/kg bw of penconazole every two days from day 7 until day 15. Results showed that penconazole exposure increased MDA, H₂O₂, and AOPP levels while CAT, SOD and GPx antioxidant status were altered. Treatment with *N. retusa* extract improved all these parameters which were also confirmed by liver histological studies [76]. *N. retusa* fruit was mainly rich in isorhamnetin derivatives [77] which found to ameliorate CCl₄-induced hepatotoxicity [18].

Olea europea

The protective effect of ethanolic extract from *O. europea* fruit and its phenolic compound, oleuropein, against hepatotoxicity induced by deltamethrin in Wistar rats. Animals were treated with *O. europea* extract (200 mg/kg bw) and others with oleuropein compound (50 mg/kg bw) one hour before deltamethrin administration (15 mg/kg bw) for 30 days. All treatments were given orally using stomach gavage. Results showed that deltamethrin administration made a highly significant elevation in the serum biomarkers as MDA. Additionally, a significant reduction in SOD and CAT activities was noted. This toxic effect was confirmed by histological studies and the expression levels of inflammatory (cox-2) and apoptotic genes (bcl-2 and p53). The treatment with ethanolic extract from *O. europea* fruit and oleuropein highlighted the efficacy of olive fruit phenolic compounds as hepatoprotectant in deltamethrin-induced hepatotoxicity through improving the oxidative status as well as suppressing inflammation and apoptosis. HPLC analysis showed that ethanolic extract from *O. europea* fruit was characterized by its richness in oleuropein (9.29 mg/g), verbascoside (5.70 mg/g), luteolin-7-glucoside (5.50 mg/g), apigenin-7-glucoside (2.76 mg/g) and hydroxytyrosol (2.08 mg/g) as mentioned by Maalej *et al.*[78]. Mahmoudi *et al.* [79] determined the hepatoprotective effect of oleuropein and hydroxytyrosol extracted from olive leaf extract against bisphenol A treatment in rats. Zhao *et al.* [80] reported the protective effect of verbacoside on immunological liver injury induced by *Bacillus Calmette-Guerin* plus lipopolysaccharide. Sà *et al.* [81] reclaimed that the dietary flavone luteolin-7-glucoside is capable of regulating liver lipid metabolism in rats. Additionally, the potent hepatoprotective effect of apigenin-7-glucoside, isolated from *Ixeris chinesis*, against CCl₄-induced liver injury was determined by Zheng *et al.* [82].

Opuntia ficus-indica

The hepatoprotective effect of aqueous extract from *O. ficus-indica* cladodes was investigated against lithium carbonate-induced liver injury in rats. The animals received *O. ficus-indica* cladode extract (100 mg/kg bw) for 60 days and then intraperitoneally injected with lithium carbonate (25 mg/kg bw) during the last 30 days of cladode extract treatment. Results showed that the treatment with lithium carbonate caused significant increases in the levels of AST, ALT, ALP and LDH activities in the blood of lithium carbonate-treated rats. Furthermore, exposure to lithium carbonate significantly increased LPO level and decreased SOD, CAT and GPx activities in the hepatic tissues. The administration of *O. ficus-indica* cladode extract possessed a significant hepatoprotective effect as revealed by a significant increase in hepatic CAT, SOD and GPx activities. Histological examination also showed a good recovery of lithium carbonate-induced hepatotoxicity [83]. HPLC analysis revealed the presence of rutin, isorhamnetin, quercetin, kampferol, gallic acid, catechin, caffeic acid, epicatechin, vanillic acid and coumarin [83] which are known to have beneficial effects as their responsibility in preventing the formation of reactive oxygen species [83,84].

Peganum harmala



The hepatoprotective effect of chloroform extract from *P. harmala* seeds was studied against chronic ethanol treatment. The chloroform extract from *P. harmala* (10 mg/kg/day) was co-administered with ethanol 35% (4 g/kg/day) to animals, by intraperitoneal injection for 6 weeks. Chronic ethanol administration strengthened LPO(TBARS) in liver. Ethanol treatment caused a decrease in antioxidant defense system; namely hepatic SOD, CAT and GPx activities. A co-administration of *P. harmala* extract during ethanol treatment inhibited LPO and improved antioxidants activities. However, treatment with *P. harmala* extract protects efficiently the hepatic function of alcoholic rats by the considerable decrease of aminotransferase contents in serum of ethanol-treated rats [85]. In earlier study, Hamden et al. [86] had also determined the potent hepatoprotective effect of ethanol and chloroform extracts from *P. harmala* seeds against thiourea in rats. Additionally, Hamden et al. [87] had proved the potent protective effect of *P. harmala* aqueous extract against oxidative stress and hepatic toxicity in aged rats. The main bioactive molecules of this plant are β -carboline alkaloids. Phytochemical studies on *P. harmala* showed the presence of harmaline, harmine, harmalol, harman and tetrahydroharmine [86,88].

Periploca augustifolia

The methanolic extract of *P. augustifolia* leaves was evaluated against cadmium-induced oxidative damage in rats. Methanolic extract of *P. augustifolia* leaves (250 mg/kg) and cadmium chloride (1 mg/kg) were taken by rats for 5 weeks. Cadmium-intoxication increased ALT, AST and bilirubin contents. SOD, CAT and GPx were decreased in cadmium-intoxicated rats with concomitant enhancement of LPO. *P. augustifolia* leaf extract can exert beneficial effects for cadmium-treated rats according to histopathological changes. *P. augustifolia* leaf extract was characterized by the presence of catechin, caffeic acid, ferulic acid, rosmarinic acid and amentoflavone [89]. Sharma and Goyal [90] reported that green tea catechin treatment found to reduce cadmium-induced sickness, mortality and oxidative stress in mice. So, a potent hepatoprotective activity was observed in the case of ferulic acid [91], amentoflavone [92], caffeic and rosmarinic acids [47].

Phoenix dactylifera

The aqueous extract of *P. dactylifera* fruit was studied against dimethoate induced oxidative damage and hepatotoxicity in rat liver. 30 min before the daily oral administration of dimethoate (20 mg/Kg), *P. dactylifera* fruit extract (4 ml/Kg) was given to the animals for two months. Oral administration of dimethoate caused hepatotoxicity as monitored by the increase of ALT, GGT and LDH. The activities of SOD and GPx were also increased by dimethoate while CAT activity was significantly reduced. The pretreatment with *P. dactylifera* fruit extract restored the liver damage induced by dimethoate, as revealed by inhibition of hepatic LPO, amelioration of SOD, GPx and CAT activities and improvement of histopathology changes [93]. In recent study, El Arem et al. [94] had determined the hepatoprotective effect of aqueous extract from *P. dactylifera* fruit on dichloroacetic acid induced liver damage in rats. The aqueous extract of *P. dactylifera* fruit (4 ml/kg) was orally administered to the animals intoxicated with dichloroacetic acid at 0.5 and 2 g/l as drinking water for 2 months. Results showed that *P. dactylifera* fruit extract had a significant protective effect by lowering AST, ALT, LDH and GGT by improving the histological architecture of the rat liver. *P. dactylifera* fruit extract attenuated oxidative stress by decreasing the extent of hepatic TBARS formation, restoring the activities of SOD, CAT and GPx. The interesting hepatoprotective effect of the aqueous extract from *P. dactylifera* fruit could basically due to its phenolic compounds which were gallic, chlorogenic, protocatechuic, caffeic, ferulic, m-hydroxybenzoic, syringic, phenylacetic, p-coumaric, m-coumaric and o-coumaric acids and catechin [94]. The Several studies had determined potent hepatoprotective effects of these phenolic acids as the case of gallic acid [95], chlorogenic acid [96], protocatechuic acid [97], caffeic acid [98], ferulic acid [99], syringic acid [100], p-coumaric acid [71] and catechin [36].

Raphanus sativus

The role of *R. sativus* extract (5 mg/kg) in protection against hepatotoxicity induced by zearalenone (40 mg/kg) in rats was studied. Results showed that zearalenone administration provoked a significant decrease in the levels of ALP, LDH, ALT and AST in the liver, suggesting hepatic damage. Moreover, a marked increase in the level of LPO



and concomitant decrease of hepatic GPx, GR, SOD, CAT and GST were also observed. The co-treatment with *R. sativus* extract plus zearalenone succeeded in reversing the condition back to the normal condition for all studied parameters. HPLC analysis showed that *R. sativus* extract was characterized by the presence of gallic acid, ferulic acid, isoferulic acid, sinapic acid, methyl ferulate and methyl sinapate [101]. Among these bioactive components, a potent hepatoprotective effect was detected in gallic [95], ferulic [99] and sinapic [102] acids.

Rhus oxyacantha

The hepatoprotective effect of ethyl acetate extract from *R. oxyacantha* root cortex was investigated against DDT-induced liver injury in male rats. At the 7th day of treatment by *R. oxyacantha* extract in drinking water with either 150 or 300 mg/kg/day, the animals received an intraperitoneal injection of DDT (100 mg/kg). Results showed that DDT administration enhanced levels of hepatic serum markers (ALT, AST and LDH). It also increased the oxidative stress markers resulting in increased of LPO with a significant induction of SOD, GPx and MTsin liver. In the other hand, pretreatment with *R. oxyacantha* extract regulated these biochemical changes which consistent with histopathological observations. The ethyl acetate extract of *R. oxyacantha* extract was particularly rich in catechol and gallic acid [103]. De La Cruz et al. [104] demonstrated that the antioxidant effect of olive oil phenolic compounds is related to the presence of the catechol in their chemical structure. Moreover, gallic acid is well known for its antioxidant and hepatoprotective activity [105].

Rhus tripartitum

the hepatoprotective effect of methanol extract from *R. tripartitum* fruit was evaluated against CCl₄-induced hepatotoxicity in Wistar rats. The daily pretreatment with methanolic extract of *R. tripartitum* (200 mg/kg in olive oil; gastric gavage) was done 7 days before intraperitoneal CCl₄ administration (50 µL/kg in olive oil) twice per week for 8 weeks. The increased of MDA and protein carbonyls were attenuated by methanolic *R. tripartitum* extract pretreatment. The pretreatment with methanolic extract of *R. tripartitum* significantly reduced the increase of hepatic ALT, AST, LDH and GGT caused by CCl₄ treatment improving by histopathologic examination. The observed results could be due to the high phenolic content of methanolic *R. tripartitum* extract and its important antioxidant potential. The methanolic extract of *R. tripartitum* fruit was mainly rich in betulinic acid having a level of 79.71% [106] and this phenolic acid had been found to prevent alcohol-induced liver damage by improving the antioxidant system in mice [107].

Taraxacum officinale

the hepatoprotective effect of *T. officinale* leaf extract in treating sodium dichromate hazards by inducing liver injury in rats was studied. Oral administration of *T. officinale* leaf extract (500 mg/kg b.w) daily for 30 days was followed by intraperitoneal injection of sodium dichromate (10 mg/kg) for 10 days. Results showed that sodium dichromate significantly increased serum biochemical parameters (ALT, AST and ALP). In the liver, it was found to induce an oxidative stress, evidenced from increase in LPO and changes in antioxidative activities (CAT, SOD and GPx) improving by histopathological observations. Pretreatment with *T. officinale* leaf extract, prior to sodium dichromate administration revealed by a significant reduction of sodium dichromate-induced oxidative damage [108]. HPLC phenolic analysis of *T. officinale* leaf extract showed the predominance of cichoric (≥ 90%) acid [109,110]. The potent hepatocyte protective and anti-hepatitis-B virus effects of cichoric acid isolated from *cichorium intybus* leaves was determined by Zhang et al. [111].

Teucrium polium

The protective effect of aqueous extract from *T. Polium* arial parts was evaluated against CCl₄-induced toxicity in male albino Wistar rats. The animals received CCl₄ in olive oil (0.5 ml/ kg) by gavage after three days of orally receiving *T. Polium* extract (5 g/l) for seven days. Results showed that CCl₄ administration caused hepatotoxicity as monitored by the significant increase in the levels of hepatic markers enzymes (LDH, PAL, TB and gGT).



Treatment with *T. Polium* extract appeared to be effective against hematotoxic and the liver changes induced by CCl_4 , as evidenced by the improvement of the parameters cited above. The CCl_4 treated rats demonstrated a significant increase of MDA levels in erythrocytes thus causing a reduction in antioxidant defense system. Pretreatment with *T. Polium* extract improved the biochemical analyses and antioxidant defense system [112]. *T. Polium* extract was mainly rich in fumaric acid and luteolin derivatives [113]. A potent hepatoprotective effect of fumaric acid isolated from *Moringa pterygosperma* stem bark against CCl_4 -induced toxicity was determined by Kurma and Mishra [114]. Bigoniya and Singh [34] had also determined the role of luteolin isolated from *Achillea Millefolium* flower in protection against CCl_4 -induced toxicity.

Thymus algeriensis

The essential oil of *T. algeriensis* aerial parts was studied for its protective effect on H_2O_2 -induced oxidative stress in liver of rats. The animals were exposed for 2 weeks to low (100 $\mu\text{mol/L}$) and high doses (1 mmol/L) of H_2O_2 in the presence of *T. algeriensis* essential oil (180 mg/kg). Results showed that H_2O_2 induced liver atrophy, as evinced by the rise of ALT and AST. However, *T. algeriensis* essential oil treatment alleviated oxidative stress in the H_2O_2 -induced liver toxicity by reducing the levels of MDA concomitantly with marked elevations in SOD, CAT, GPx and GST, as well as decrease in GSH activity. In fact, *T. algeriensis* essential oil protected against H_2O_2 toxicity by decreasing oxidant stress [115]. The major compounds of *T. algeriensis* essential oil were α -pinene (7.41-13.94%), 1,8-cineole (7.55-22.07%), cis-sabinene hydrate (0.10-12.95%), camphor (6.8-19.93%), 4-terpineol (1.55-11.86%), terpenyl acetate (0-14.92%) and viridiflorol (0-11.49%) as reported by Zouari et al. [116]. Among these volatile compounds, α -pinene had a potent anti-cancer activity on human hepatoma cell lines [117]. Santos et al. [118] found that 1,8-cineole protected against hepatotoxicity. Johari et al. [119] determined that camphor has a stimulating effect on rat liver enzyme.

Discussion

In the world, at least one quarter of patients use medicinal plants in treating liver diseases [120]. Several plant derived drugs were approved last decades as the case of daphnoretin, dicoumarin drug, extracted from the Chinese herb *Wilkstroemia indica*. As well, Glycyrrhizin, a group of related sulfated saponins and lectins, obtained from *Glycyrrhiza glabra* root, has been used for over 20 years to treat chronic viral hepatitis in Japan. Silymarin, derived from ancient European medicinal practices, is a standardized extract from the milk thistle *Silybum marianum*, included flavonoids silybinin, silydianin, and silychristin. Picroliv, orally used in India, is an alcoholic extract from *Picrorhiza kurroa* root having iridoid glycosides, namely kutkoside and picroside [121]. In Tunisia, 29 medicinal plants were studied for their hepatoprotective effects against liver toxicity caused by hepatotoxins which were reported in this review (Table 1). Liver toxicity is generally caused by several hepatotoxins such as drugs, alcohols, pesticides and chemical additives (Table 2). More than 1000 hepatotoxins have been reported to cause liver injury. Drug-provoked liver failure is one of the flagrant complications in therapeutic system [122]. In this review, most studies have focussed on industrial chemicals, particularly CCl_4 -caused hepatotoxicity (Figure 1). CCl_4 has been widely used for experimental induction of liver injury [123]. The principal causes of CCl_4 -induced liver injury are LPO and decreased activities of antioxidant enzymes and generation of free radicals [124]. Many intracellular enzymes are involved in scavenging peroxide free radicals like CAT, GPx, GST, GR and SOD, which have recently received much attention in connection with antioxidant property. LPO leads to the generation of free radicals which cause cell damage and leads to the release of marker enzymes as ALP, ACP, AST, ALT, LDH and γ -GT. So, the reversal of increased serum enzymes (ALP, ACP, AST, ALT, LDH and γ -GT) in intoxicated liver by plant extracts may be due to the prevention of the leakage of intracellular enzymes (CAT, GPx, GST, GR and SOD) by the stabilisation of membrane activity [125]. Several phytochemicals are known to protect liver like phenols, coumarins, monoterpenes, glycosides, alkaloids and xanthenes [126]. From table 1, phenolic and terpene compounds were the most highlighted to have hepatoprotective effects against liver injuries in most studies. Phenolic and terpene compounds exhibited a strong antioxidant activity exerting their hepatoprotective effects by neutralising free radicals.



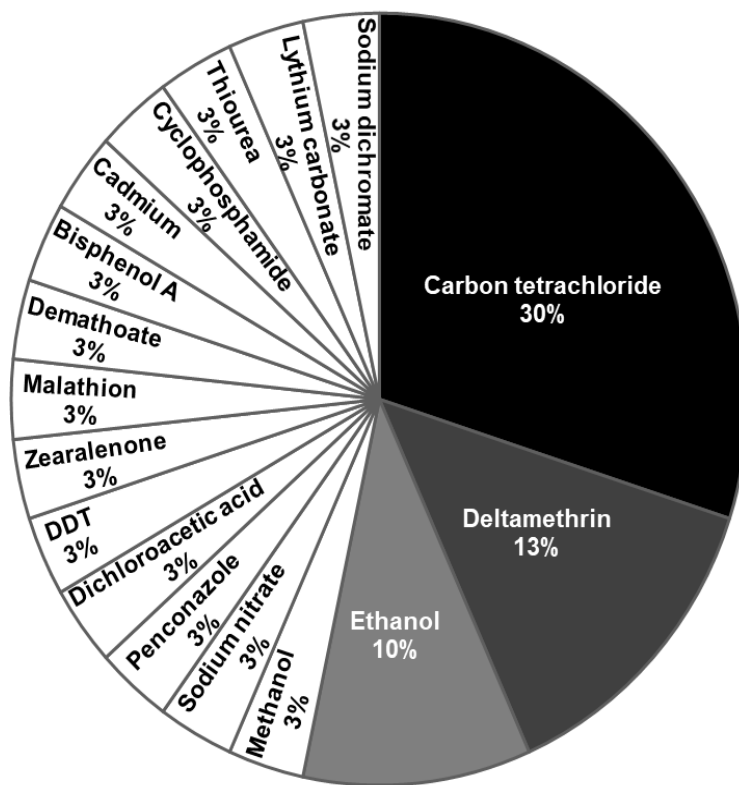


Figure 1: Distribution of Tunisian hepatoprotective plant studies according to different hepatotoxin used

Table 1: Tunisian medicinal plants with hepatoprotective activity

Botanical name	Part used	Extract	Bioactive compounds	Hepatotoxin used	References
<i>Allium sativum</i>	Cloves	Aqueous methanol	Organosulfur compound (Allicin)	Deltamethrin	[12]
<i>Amaranthus spinosus</i>	Seeds	Methanol	Phenolic compounds (caffeic acid, cinnamic acid, gallic acid, epicatechin, isorhamnetin and quercetin)	Deltamethrin	[15]
<i>Artemisia campestris</i>	Aerial parts	Essential oil	Monoterpene hydrocarbons (β -pinene, α -limonene, α -pinene, γ -terpinene and β -myrcene)	Deltamethrin	[21]
<i>Asparagus albus</i>	Leaves	Aqueous	Phenolic compounds (vanillic acid, gallic acid, catechin, rutin and quercetin)	CCl ₄	[27]
<i>Capparis spinosa</i>	Leaves	Methanol	Phenolic compounds (rutin, resveratol, coumarin, epicatechin, luteolin, catechin, kaempferol, vanillic acid and gallic acid)	CCl ₄	[31]
<i>Ceratonia siliqua</i>	Leaves	Ethyl acetate	Phenolic compounds (syringic acid, myricetin glycosides and gallic acid derivatives)	CCl ₄	[38]
<i>Citrus aurantium</i>	Leaves	Ethyl acetate	Phenolic compounds (quercetin, epicatechin, caffeic acid, kaempferol, gallic acid, rutin and catechin)	CCl ₄	[41]
<i>Citrus limon</i>	Aerial parts	Essential oil	Monoterpene hydrocarbon (Limonene)	Aspirin	[42]
<i>Eryngium maritimum</i>	Seeds	Methanol	Phenolic compounds (caffeic acid, gallic acid, protocatechuic acid, kaempferol and luteolin)	CCl ₄	[46]
<i>Ficus carica</i>	Stem	Aqueous	Anthocyanin pigments (especially cyanidins)	Methanol	[49]
<i>Hammada scoparia</i>	Leaves	Methanol	Flavonoids (especially isorhamnetin triglycerides)	Ethanol	[54]
<i>Hyparrhenia hirta</i>	Aerial parts	Methanol	Flavonoids (luteolin derivatives, apigenin derivatives and 3-O-methylquercetin)	Sodium nitrate	[57]
<i>Lavandula stoechas</i>	Aerial parts	Essential oil	Terpenes (D-fenchone, α -pinene, camphor and camphene)	Malathion	[60]



<i>Lawsonia inermis</i>	Fruits	Ethyl acetate	Phenolic acid (Gallic acid)	CCl ₄	[62]
<i>Lycium europaeum</i>	Leaves	Methanol	Phenolic compounds (caffeic acid, gallic acid, vanillic acid, coumaric acid, naringenin, epicatechin and rutin)	CCl ₄	[63]
<i>Marrubium vulgare</i>	Leaves	Aqueous	Phenolic compounds (gallic acid, catechic acid, caffeic acid, vanillic acid, coumarin, rutin, quercetin and kaempferol)	Cyclophosphamide	[65]
<i>Matricaria recutita</i>	Flower	Aqueous	Phenolic compounds (gallic acid, protocatechuic acid, chlorogenic acid, caffeic acid, cafeoylquinic acid, salicylic acid, quercetin and quinic acid derivative)	Ethanol	[72]
<i>Nitraria retusa</i>	Fruits	Aqueous	Flavonoids (isorhamnetin derivatives)	Penconazole	[76]
<i>Olea europea</i>	Fruits	Ethanol	Oleuropein	Deltamethrin	[78]
	Leaves	Aqueous methanol	Oleuropein and hydroxytyrosol	Bisphenol A	[79]
<i>Opuntia ficus-indica</i>	Cladodes	Aqueous	Phenolic compounds (rutin, isorhamnetin, quercetin, kampferol, gallic acid, catechin caffeic acid, epicatechin, vanillic acid and coumarin)	Lithium carbonate	[83]
<i>Peganum harmala</i>	Seeds	Chloroform, ethanol	Alkaloids (β -carboline, harmaline, harmine, harmalol and harman)	Thiourea	[86]
		Chloroform		Ethanol	[85]
<i>Periploca augustifolia</i>	Leaves	Methanol	Phenolic compounds (catechin, caffeic acid, ferulic acid, rosmarinic acid and amentoflavone)	Cadmium	[89]
<i>Phoenix dactylifera</i>	Fruits	Aqueous	Phenolic compounds (gallic acid, chlorogenic acid, protocatechuic acid, caffeic acid, ferulic acid, syringic acid, coumaric acid and catechin)	Dimethoate	[93]
				Dichloroacetic acid	[94]
<i>Raphanus sativus</i>	Whole plant (Shoot+root)	Aqueous methanol	Phenolic compounds (gallic acid, ferulic acid and sinapic acid)	Zearalenone	[101]
<i>Rhus oxyacantha</i>	Root cortex	Ethyl acetate	Phenolic compounds (catechol and gallic acid)	DDT	[103]
<i>Rhus tripartitum</i>	Fruit	Methanol	Phenolic acids (especially betulinic acid)	CCl ₄	[106]
<i>Rumex tingitanus</i>	Leaves	Aqueous ethanol	Phenolic compounds (luteolin derivatives)	CCl ₄	[108]
<i>Taraxacum officinale</i>	Leaves	Aqueous	Phenolic acids (especially cichoric acid)	Sodium dichromate	[109]
<i>Teucrium polium</i>	Aerial parts	Aqueous	Phenolic compounds (fumaric acid and luteolin derivatives)	CCl ₄	[113]
<i>Thymus algeriensis</i>	Aerial parts	Essential oil	Terpenes (especially α -pinene, 1,8-cineole and camphor)	H ₂ O ₂	[116]

Table 2: Effect of Tunisian medicinal plants on different hepatoxins

Hepatotoxicity factors	Model used	hepatotoxin	Scientific plant name
Pesticides	Deltamethrin		<i>Allium sativum</i> [12]; <i>Amaranthus spinosus</i> [15]; <i>Artemisia campestris</i> [21]; <i>Olea europea</i> [78]
	DDT		<i>Rhus oxyacantha</i> [103]
	Dimethoate		<i>Phoenix dactylifera</i> [93]
	Malathion		<i>Lavandula stoechas</i> [60]
	Penconazole		<i>Nitraria retusa</i> [76]
	Zearalenone		<i>Raphanus sativus</i> [101]
Industrial additives	CCl ₄		<i>Asparagus albus</i> [27]; <i>Capparis spinosa</i> [31]; <i>Ceratonia siliqua</i> [38]; <i>Citrus aurantium</i> [41]; <i>Eryngium maritimum</i> [46]; <i>Lawsonia inermis</i> [62]; <i>Lycium europaeum</i> [63]; <i>Rhus tripartitum</i> [106]; <i>Teucrium polium</i> [111]
	Bisphenol A		<i>Olea europea</i> [79]
	H ₂ O ₂		<i>Thymus algeriensis</i> [115]
	Cadmium		<i>Periploca augustifolia</i> [89]
	Sodium dichromate		<i>Taraxacum officinale</i> [108]
	Sodium nitrate		<i>Hyparrhenia hirta</i> [57]
	Thiourea		<i>Peganum harmala</i> [86]
	Dichloroacetic acid		<i>Phoenix dactylifera</i> [94]
Drugs	Aspirin		<i>Citrus limon</i> [42]
	Cyclophosphamide		<i>Marrubium vulgare</i> [65]
	Lythium carbonate		<i>Opuntia ficus-indica</i> [83]
Alcohols	Ethanol		<i>Hammada scoparia</i> [54]; <i>Matricaria recutita</i> [72]; <i>Peganum harmala</i> [85]
	Methanol		<i>Ficus carica</i> [49]

Conclusion



To the best of our knowledge, this is the first review that summarizes several reports on Tunisian hepatoprotective plants. There is no doubt that these plants contain bioactive compounds able to treat liver diseases. These active molecules could be also isolated and served as suitable primary compounds for effective and targeted hepatotropic drugs. Such data may be valuable to the health professionals, scientists and scholars working in the field of pharmacology and therapeutics to produce new safety drug formulations to treat liver diseases.

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