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Perspectives of the *Apiaceae* Hepatoprotective Effects – A Review

Milica G. Aćimović[a] and Nataša B. Milić[b*]

[a]*University of Novi Sad, Institute of Field and Vegetable Crops, Maksima Gorkog 30, 21000 Novi Sad, Serbia*
[b]*University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 3, 21000 Novi Sad, Serbia*

natasa.milic@mf.uns.ac.rs

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The liver has the crucial role in the regulation of various physiological processes and in the excretion of endogenous waste metabolites and xenobiotics. Liver structure impairment can be caused by various factors including microorganisms, autoimmune diseases, chemicals, alcohol and drugs. The plant kingdom is full of liver protective chemicals such as phenols, coumarins, lignans, essential oils, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenes. *Apiaceae* plants are usually used as a vegetable or as a spice, but their other functional properties are also very important. This review highlights the significance of caraway, dill, cumin, aniseed, fennel, coriander, celery, lovage, angelica, parsley and carrot, which are popular vegetables and spices, but possess hepatoprotective potential. These plants can be used for medicinal applications to patients who suffer from liver damage.

Keywords: Apiaceae, Liver, Hepatoprotective, Phytotherapy.

Introduction

The liver as a vital organ has a crucial role in the regulation of various physiological processes and in the excretion of endogenous waste metabolites and xenobiotics. It has a superior role in the maintenance, performance and regulation of body homeostasis: it is involved in carbohydrate and fat metabolism, bile secretion, vitamin storage and synthesis of useful biologically active compounds. Liver injury or dysfunction is a major health problem that challenges not only the health care professionals, but also the pharmaceutical industry and drug regulatory agencies [1]. Liver structure impairment can be caused by various factors including microorganisms, autoimmune diseases, chemicals, alcohol and drugs. Hence, the modern lifestyle, insufficient physical activity, environmental impact, medication and food additives cause a change in oxidative balance and consequently in oxidative stress and thus influence both life quality and disease development, including liver function impairment.

Despite the fact that the advances in modern medicine are significant, there is no drug which is completely effective and safe in the treatment of liver diseases and which regenerates the hepatic tissue, stimulates the renewal of the hepatic function or completely protects the liver from damage. Herbal drugs, which have been traditionally used in the treatment of various medical conditions for centuries, have gained popularity in recent years because of their safety, efficacy and cost effectiveness, cultural acceptability and minimal side effects [2, 3]. Herbal drugs are used worldwide, mainly in developing countries as the primary health care [2].

The use of natural remedies for the treatment of liver diseases has a long history. Medicinal plants are a significant source of hepatoprotective drugs. It has been claimed by Pharmacopeia Foundation that about 170 phytoconstituents isolated from 110 plants belonging to 55 families possess hepatoprotective activities [2]. Liver protective plants contain a variety of chemical constituents such as phenols, coumarins, lignans, essential oils, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenes [2].

Plants from the *Apiaceae* (or *Umbelliferae*) family are widespread throughout the world; however, they are most common in temperate regions. The representatives of this family are annual and perennial herbs characterized by a well-developed secretory system in all plant parts, such as schizogeneus secretory cavities in the root, phloem in the stem and leaves and clearly-delimited tissue known as vittae in the fruit [4]. These structures are important for depositing essential oils, which give the specific odor and flavor to each plant. Due to their flavor, a large number of plants from this family are used as vegetables or spices. Lately, the focus has been directed to the great potential of these plants as functional food [5, 6]. Their use in folk medicine, phytotherapy, as health-promoting agents, and homeopathy medicaments has also been on the rise.

A large number of the members of this family are cultivated for various purposes. Some plants, such as celery, lovage, angelica, parsley and carrot include a taproot, which is used as a vegetable to flavor dishes or to prepare alcoholic and non-alcoholic drinks. Some of them, such as parsley, dill and coriander, having aromatic leaves, are used for flavoring food or as a garnish. Celery and fennel are used for their luscious leaf stalks. Also, the seeds from *Apiaceae* plants are used. Caraway, aniseed and cumin are used exclusively as seed spices. On the other hand, most of these plants are used for essential oil distillation, which has a wide range of application in food preparation and the food industry (Table 1). Apart from the essential oils, there are a lot of constituents determined in these plants, such as fatty oils, vitamins, flavonoids, carotenoids, chlorophylls, and polyphenols (Table 1). Their complex chemical composition has a high biological activity. *Apiaceae* plants are reported to possess a lot of nutraceutical properties, such as antioxidant, antimicrobial, antidiabetic, hypolipidemic, antispasmodic and carminative, anticarcinogenic/antimutagenic, anti-inflammatory, antistress, antiulcerogenic and many others [7-17].

This review highlights the significance of the *Apiaceae* family, the source of many popular vegetables and spices, and potential hepatoprotective sources and their possible medicinal applications.

Table 1: *Apiaceae* plants, their usage and chemical composition.

Herb	Used part	Chemical composition
Caraway	**Seed** is used in cakes, cheese, confections, fresh cabbage, meat dishes, rye bread, salads **Seed essential oil** is used to flavor chewing gum, candy, liqueurs.	essential oil, fatty oil, vitamins (A, B6, B12, C, D, E), flavonoids, proteins [18, 19]
Dill	**Seed** is used in pickled cucumbers, bread, processed meats, sausages, cheese, condiments **Leaf** is used in pickles, while fresh is used for garnish or to flavor salads, vegetable dishes, sea food, soups, yogurt, mayonnaise.	essential oil, fatty oil, vitamin C, carotenoids, flavonoids, coumarins, chlorophylls [6, 20]
Cumin	**Seed** is used as a flavor component in beverages, confectioneries, baked goods, meat and meat products, condiments and relishes, gravies, snack foods, gelatines and puddings.	essential oil, fatty oil, flavonoids, anthocyanins [21-23]
Aniseed	**Seed** is used in beverages, baked goods, condiments, relishes, oils and fats, frozen dairy, gravies, meat products, soft candy **Seed essential oil** is used in chewing gums, gelatines, puddings, soft and hard candies.	essential oil, fatty oil, flavonoids, coumarins [6, 24]
Fennel	**Seed** is used in meat dishes, in curries, spice blends, soups, vegetables, breads. **Leaf** fresh and chopped can be used as garnish for fish dishes, sauces, salads, stews and curries. **Leaf stalk (pseudobulb)** is used raw in salads, stuffing or blanched as vegetable, in soups and sauces and baked. **Seed and herb essential oil** is used in beverages, condiments, relishes, baked goods, frozen dairy, gelatines, puddings, meat products, candies.	essential oil, fatty oil, vitamin C, flavonoids, coumarins and minerals (K, Na, Ca, Mg), nitrates [6, 25-27]
Coriander	**Leaf** is used to make chutneys and sauces, green salsas, dips, snacks, soups **Seed** is used in couscous, stews and salads **Seed essential oil** is used in beverages, baked goods, condiments, relishes, meat products	essential oil, fatty oil, vitamins (A and C), flavonoids, coumarins [6, 28]
Celery	**Root, leaf and leaf stalk** are used as a vegetable, fresh for salads, for the preparation of juices, in meat dishes, snacks, gravies, sauces **Seed** is used in pickling vegetables, salad dressings, breads, biscuits, soups, celery salt, bouquet garni	essential oil, fatty oil, flavonoids, coumarins, minerals (Na, P, K, Ca, Mg, Fe, Cu, Mn, Zn) [6, 29, 30]
Lovage	**Leaf** is used for seasoning soups, sauces, meat dishes **Root** is used for producing soup seasonings, finished flavorings in liqueurs and tobacco **Seed** is used as spice, for flavoring cakes, soups, salads, for pickled vegetables (especially cabbage and cucumbers).	essential oil, flavonoids, coumarins, phenolic acids, saponins, alkaloids [31, 32]
Angelica	**Root** is used in herbal liqueurs and bitter spirits, in flavoring meat and canned vegetables. **Herb** is used for decorating cakes and pastry, and to flavor jams and jellies, confectionaries and liqueurs. **Leaf** chopped is added to fruit salads, fish dishes, and cottage cheese. **Seed** is used in alcoholic distillates.	essential oil, coumarins, phenolic compounds [*33]*
Parsley	**Leaf** is used as a garnish (for salads, soups, boiled potatoes and egg dishes), blended in dips, cooked sauces and stews **Root** is used as a vegetable to enhance soups flavor , stews and condiments **Essential oil** is used to flavor meat sauces, pickles, spice blends, baked goods, oils and fats, processed vegetables, soups, gelatines and puddings	essential oil, vitamin C, tocopherol, carotenoids, flavonoids, coumarins, sterols, triterpenes [6, 34, 35]
Carrot	**Root,** raw, is used for juices, salads, cakes, for pickling, while cooked it is used in casseroles, soups and stews **Seed essential oil** is used in beverages, baked goods, condiments, relishes, meat products	essential oil, carotenoids (β-carotene, α-carotene, γ-carotene, lycopene, cryptoxanthin, leutein, violaxanthin) [36-38]

Caraway (*Carum carvi* L.): Caraway seed (Carvi fructus) and its essential oil (Carvi aetheroleum) are official drugs in the European Pharmacopoeia (Ph.Eur.2011). Caraway is traditionally used as a remedy for a range of health problems, especially stomach ache, flatulence, intestinal spasms and for treating obesity [43].Caraway seed contains 2-7% essential oil with carvone and limonene constituting more than 90% [39-41]. Caraway seed essential oil has been reported to have potential therapeutic effects, mainly due to its high antioxidant activity [18]. Considering the radical scavenging [42] and good antioxidant profile of caraway essential oil, it has been proposed for its multifaceted pharmacological properties [14].

Examination of the antioxidant properties of Carvi aetheroleum conducted *in vitro* by both free radical scavenging capacity (RSC) and protective effect on lipid peroxidation (LP) showed that it could be used as a safe antioxidant and antiseptic supplement. Further research conducted *in vivo* with carbon tetrachloride (CCl_4) induced hepatotoxicity in mice showed that Carvi aetheroleum was able to reduce the 2.2-diphenyl-1-picrylhydrazyl (DPPH) levels in a dose-dependent manner and neutralize H_2O_2 [44]. Other *in vivo* assays also showed the potent hepatoprotective properties of Carvi aetheroleum, which modulated the antioxidant defense system by changing the oxidative stress parameters, namely LP, myeloperoxidase (MPO) and glutathione (GSH) [45].

Dill (*Anethum graveolens* L.): Dill, also known as European dill, is a native of the Mediterranean region, but it is also cultivated across Europe and America. Seed and leaf, named dill weed, are the mainly used parts. Dill seed essential oil has similar composition to caraway seed, with carvone and limonene as the dominant compounds [46], while the main compounds in the essential oil are α-phellandrene, apiole, dill ether, limonene, geraniol and *p*-cymene [47]. Both oils possess a high antioxidant capacity [48, 49]. There is also Indian dill (*A. sowa*), which has a slightly different chemical composition in comparison with European dill, and is mainly grown in Africa [50]. Even though these plants are not official drugs, they are widely used in traditional medicine, as well as in modern phytotherapy and in everyday nutrition as a spice [51, 52]. Their stimulant, carminative, antibacterial, antispasmodic, antiulcer, and antidiabetic activities, as well as their antioxidant, hypolipidemic, and diuretic effects have been reported [11, 13].

The hepatoprotective effect of dill seed oil against CCl_4 induced hepatotoxicity in rats was found as it decreased the serum aspartate transaminase (AST) and alanine aminotransferase (ALT) levels and significantly increased the level of serum total protein and albumin. Furthermore, by supplementing dill oil, suppression of the increased alkaline phosphatase (ALP) activity was achieved with the simultaneous decrease of raised bilirubin. This fact suggests that this oil could have the ability to stabilize biliary dysfunction in rat liver during the hepatic injury caused by CCl_4. Additionally, dill seed oil treatment significantly reversed CCl_4 induced effects like enhanced LP. Consequently, it is plausible that the hepatoprotection mechanism of dill seed oil is due to its antioxidant effect [53]. Hepatoprotective and antioxidant efficacy of dill herb ethanol extract was performed in CCl_4 induced hepatotoxicity in rats where the results were comparable with the normal and standard hepatoprotective drug silymarin [54]. The powder of dill herb and its hydro-alcoholic extract significantly increased the activity of antioxidant and liver function enzymes in paracetamol induced liver injury [55].

Pre-treatment with a dill ethanol extract showed an antioxidant activity and hepatoprotective effect (decreased the AST and ALT levels) on paracetamol-induced hepatic damage in rats by

decreasing hepatic steatosis and hepatic necrosis [56]. The investigations showed that the dill leaf water extract could either increase glutathione biosynthesis or reduce the extent of oxidative stress leading to less glutathione degradation or that it could have both effects [57].

Nowadays a commercial medicinal form of this plant formulated as dill tablet (DT) is available. DTs contain mainly dill (68%), and other herbs such as chicory, fine leaf fumitory and lime that display a potential hepatoprotective effect against CCl_4 induced liver damage based on both biochemical markers and antioxidant status [58].

Cumin (*Cuminum cyminum* L.): Cumin is a native of Egypt and is extensively cultivated for seed in Asia. The distinctive flavor and aroma are due to essential oil, the dominant compounds of which are γ-terpinene-7-al, cumin-aldehyde, β-pinene and γ-terpinene [21-23, 59, 60]. This plant, as well as dill, is not an official drug; it is widely used in Indian traditional medicine and as a spice [14]. In medicine, cumin is important as an antispasmodic agent, carminative and as an appetizer. It also has good antimicrobial and antioxidative properties [9, 61, 62].

Normal serum glutamic-pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) levels were restored when cumin was administered in low doses to profenofos intoxicated mice. This fact suggests that cumin has a vital role in reducing hepatotoxicity at the cellular and biochemical levels [63]. The aqueous ethanol extract of cumin seeds, in a dose-dependent manner, significantly reduced the SGPT, SGOT, ALP and serum total bilirubin (STB) levels in nimesulide induced hepatotoxicity in rats. Additionally, histopathological examination of the rat liver tissue showed a reduction in ballooning degeneration, fibrosis, inflammation and apoptosis of the hepatocytes, which all supported hepatoprotection [64].

Cumin seed powder demonstrated strong hepatoprotective activity upon CCl_4 induced hepatic damage in rats. The levels of urea, bilirubin and creatinine were normalized in cumin powder treated rats and a significant reduction of ALP and STB confirmed the hepatoprotective effect. Additionally, the significantly lower LP suggests that cumin seed powder is efficient against free radical injury [65].

Aniseed (*Pimpinella anisum* L.): Aniseed (Anisi fructus), as well as its essential oil (Anisi aetheroleum), are official drugs in the European Pharmacopoeia (Ph.Eur.2011). Aniseed contains 1.5-6% essential oil with *trans*-anethole as the major compound, which comprises more than 90% [66, 67]. Anise has been traditionally used as an analgesic, anti-inflammatory, appetizer, hypnotic, expectorant, antibacterial and hepatoprotective agent and to increase milk secretion [7, 8, 68].

Recent investigations have shown a potential protective effect of Anisi aetheroleum against CCl_4 induced fibrosis in rats. It was demonstrated that the rats treated with Anisi aetheroleum orally for 7 successive weeks showed a significant protection against the induced increase in serum liver enzymes (AST, ALT, ALP), restored the total protein level and improved the increased triglycerides (TG), total cholesterol, and low density lipoprotein cholesterol (LDL-C), and decreased the high density lipoprotein cholesterol (HDL-C). A significant curative effect of Anisi aetheroleum on biochemical parameters was supported by histopathological examination [69].

The protective properties against CCl_4 was confirmed with *n*-hexane aniseed extract both *in vitro* and *in vivo* as revealed by reduction in cell death, serum transaminase levels, LDH activity, and liver histopathological changes. Moreover, liver hepatocellular carcinoma (HepG2 cells) and rat liver treated with *n*-hexane aniseed extract showed higher levels of glutathione (GSH) and lower levels of thiobarbituric acid reactive substances (TBARs). In this study, hydroalcoholic aniseed extract and Anisi aetheroleum showed no significant protective properties against CCl_4 induced injury, presuming that hydrophobic substances, such as anethole, were the major components for the hepatoprotective effect of aniseed, but further investigations are necessary for confirmation [70]. An aniseed extract decreased serum AST and ALT levels compared with those in the CCl_4 group, although these were not as low as those in the silibinin control group [29].

Fennel (*Foeniculum vulgare* Mill.): Fennel seed (Foeniculi fructus) and essential oil (Foeniculi aethroleum), obtained from seed or from herb, are official drugs in the European Pharmacopoeia (Ph.Eur.2011). Both essential oils have a similar chemical composition to aniseed with *trans*-anethole as the main compound, but at a lower range [25, 71-73]. Fennel oil, like aniseed, possesses a good antioxidative activity and could contribute to the daily antioxidative diet [15]. Antibacterial, antiviral, antifungal, insecticidal, anti-inflamatory and antidiabetic activities of fennel essential oil, along with vasorelaxant, antiplatelet and antithrombotic properties were established [72, 74-77].

Decreased levels of serum AST, ALT, ALP and bilirubin were registered after administration of Foeniculi aetheroleum to CCl_4 induced liver injury model rats [78]. Histopathological findings also suggested that Foeniculi aetheroleum prevented the development of chronic liver injuries and acted as a strong hepatoprotective agent against hepatic induced fibrosis [79, 80].

It was reported that fennel essential oil increased the activity of superoxide dismutase (SOD) and catalase (CAT) [81]. Conversely, diglucoside stilbene trimers and a benzoisofuranone derivative present in fennel did not show strong antioxidant activity [82]. Another study showed that the administration of Foeniculi aetheroleum significantly decreased the levels of serum AST and ALT and significantly increased the level of serum total protein and albumin in rats with induced CCl_4 hepatotoxicity [53]. Furthermore, Foeniculi aetheroleum supplementation induced significant reverse changes in alkaline phosphatase (ALP), raised bilirubin, malondialdehyde (MDA), and SOD values, improving the antioxidant defense mechanism and preventing the formation of excessive free radicals. In addition, rats with CCl_4 induced fibrosis treated orally with Foeniculi aetheroleum showed significant protection against induced increase in serum liver enzyme (AST, ALT, ALP), and the improvement of other biochemical parameters of liver function [69].

The co-administration of Foeniculi aetheroleum with emamectin benzoate (EB) mitigated the hemotoxicity, immunotoxicity and hepatotoxicity induced by sub-chronic treatment of EB in male rats. This may be attributed to antioxidant, anti-inflammatory and hepatoprotective activities of Foeniculi aetheroleum. Therefore, this study indicates that supplementation of this oil may ameliorate toxic effects in individuals who are at risk of prolonged EB exposure [83]. The findings with *trans*-anethole, a major component of *F. vulgare*, suggest that it protects the liver against ischemia /reperfusion (I/R) injury by suppressing interferon regulatory factor

(IRF-1) and by high mobility group box (HMGB1) release and subsequent toll-like receptor (TLR) activation [84].

Coriander (*Coriandrum sativum* L.): Coriander seed (Coriandri fructus), as well as its essential oil (Coriandri aetheroleum), are official drugs in the European Pharmacopoeia (Ph.Eur.2011). Coriandri aetheroleum contains mainly linalool [85], while coriander herb oil has a significantly different composition with decanal, *trans*-2-decenal, 2-decen-1-ol, cyclodecane and *cis*-2-dodecenal as the main compounds [86]. However, both oils possess a good antioxidative activity [87, 88]. The seed is mainly used for medicinal purposes and has been used as a drug for indigestion, against worms, rheumatism, and pain in the joints, showing a potent antioxidant effect [89]. Coriander seed oil extract showed antibacterial and antifungal properties, a cardiovascular protective effect as well as gut modulation activities. Additionally, it lowers blood pressure and has a diuretic effect [90-96].

The oral administration of both aqueous and ethanol coriander seed extracts attenuated, to some extent, the histopathological changes to lead treated mice and significantly reduced the adverse effects related to most of the altered biochemical parameters and hepatic and renal oxidative stress [97]. Treatment with an aqueous extract of coriander leaf normalized enzymatic and nonenzymatic parameters in cadmium treated animals [98]. In addition, both coriander leaf and seed helped improve the adverse effects of thioacetamide induced hepatotoxicity which was confirmed by the histological study [99].

The ethanol-water extract of coriander leaf in a dose dependent manner protected the liver from the oxidative stress induced by CCl_4, significantly lowering serum transaminases (SGOT, SGPT), and TBARs levels. Hepatic enzymes like SOD, CAT, and glutathione peroxidase (GPx) were significantly increased with the plant extract treatment against CCl_4 treated rats. The activity of the leaf extract was comparable with that of the standard drug, silymarin [100].

Significant improvement in all biochemical parameters, which were close to the control, was found in rat liver supplemented with aqueous coriander seed extract and then administrated with paracetamol. The results were confirmed by histopathological examination of the liver tissue [101]. Another study pointed out that ethanolic extract of *C. sativum* displays a hepatoprotective effect by reducing liver weight, activities of SGOT, SGPT, and ALP, and direct bilirubin in CCl_4 intoxicated animals. Administration of coriander extract resulted in the fatty deposit disappearing, ballooning degeneration and necrosis, which all indicated antihepatotoxic activity [102].

A study which aimed to investigate the antioxidant activity of *C. sativum* leaf extract on CCl_4 treated Wistar albino rats showed that the serum from pre-treated animals had significant increases in SOD, CAT, and GPx activity, when compared with CCl_4 treated rats. Oral administration of the leaf extract significantly reduced the toxic effects of CCl_4 and, at a dose of 200 mg/kg, was comparable with the standard drug, silymarin. Based on these results, it was observed that *C. sativum* extract protected the liver from oxidative stress induced by CCl_4 and thus helped in the evaluation of the traditional claim for this plant [103].

Celery (*Apium graveolens* L.): Celery is not an official drug, but is among the favorite vegetables. It has a characteristic flavor similar to that of fennel and aniseed. The flavor is grassy and hay like, rather bitter [104] which originates from essential oil with limonene as the dominant compound, while phthalides are present in small amounts that give the characteristic fragrance [105, 106]. Celery is used in the pharmaceutical industry and traditional medicine because of its numerous beneficial properties important for preventing cardiovascular diseases, lowering blood glucose and serum lipid levels, decreasing blood pressure and strengthening the heart. This herb has antimicrobial, anti-inflammatory and antioxidant effects [107].

A significant hepatoprotective activity of the celery seed methanol extract was reported on rat liver damage induced by a single dose of paracetamol or thioacetamide [108]. Several liver function tests, such as SGOT and SGPT, ALP, sorbitol dehydrogenase (SDH), glutamate dehydrogenase (GLDH) and SBR were performed which showed a global ameliorated hepatic status.

The pre-treatment of celery seed extract to rats with induced hepatocarcinogenesis resulted in the elevation of quinonereductase (QR), glutathione-S-transferase (GST) and serum gamma glutamyl transferase (GGT) activities and the reduction of GSH in tissues after i.p. injection of 2-acetylaminofluorine [109].

Juices from celery root and leaf influenced the biochemical parameters and showed antioxidative effects when applied with doxorubicine to Wistar laboratory rats. The serum lipid peroxidases (LPx) activity was decreased only by administering celery leaf juice (alone or with doxorubicin), while the activities of xanthine oxidase (XOD), CAT, and GPx were increased with celery root and leaf juices [110].

The potential of celery juice in the prevention of oxidative stress and hepatotoxic effects induced by lead-acetate and an exposure to gamma-radiation (4Gy) was examined on an animal model. The results showed that celery juice normalized the levels of SBR, total protein and albumin. The intake of celery juice promoted a significant decrease in TBARs and protein carbonyl content (PCC), as well as an increase of GSH, CAT and SOD activitie, which confirmed the enhancement of the antioxidant defense mechanisms in rats [16]. The supplemented diet with a dry powder of celery leaf lowered the elevated serum level of liver enzymes and blood lipids in hypercholesterolemic rats. The histopathological lesions seen in the liver of these rats were also ameliorated. This study suggests that the dietary intake of celery can be beneficial to patients suffering from hypercholesterolemia and liver diseases [111].

The hepatoprotective potential of celery was also examined on fish. The study on *Pangasius sutchi* revealed that a short-term treatment with celery leaf powder could protect the liver from paracetamol induced liver injury [112].

Horse celery (*Smyrnium olusatrum* L.): Horse celery is a wild culinary plant all parts of which are edible. Its use was diminished after the domestication of celery. The essential oils of the root, herb and flower are characterized by a high content of oxygenated sesquiterpenoids, most of them furanosesquiterpenoids, while the green and ripe fruit are dominated by monoterpene hydrocarbons with β-phellandrene and α-pinene as major constituents [113]. The main component of the aboveground parts and the root is isofuranodiene, which possesses cytotoxic activity against the human colon cancer cell line and has hepatoprotective activity [114, 115]. It was proven that isofuranodiene protected the liver against D-galactosamine/lipopolysacchride (GalN/LPS)-induced injury in rats. According to the obtained results, it can be suggested that this plant may be a potential functional food ingredient for the prevention and treatment of liver diseases [115].

Lovage (*Levisticum officinale* Koch.): Lovage root (Levistici radix) is an official drug in the European Pharmacopoeia (Ph.Eur.2011). However, leaf, herb and seed are also used. The lovage flavor, like the celery one, originates from essential oil where the dominant compound is β–phellandrene, while phthalides are present in small amounts and give the characteristic fragrance [105]. Although lovage is used in traditional medicine as an emmenagogue, carminative, diuretic and remedy for various skin ailments, it possesses proven anti-inflammatory, antioxidant and anticancer properties [116].

The results of biochemical tests, in which rats were treated with lovage essential oil, a lovage fruit infusion and lovage herb infusion after subacute intoxication with acrylamide (hepatic cytolysis and proteosynthesis indicators) highlighted the high antitoxic potential of the lovage volatile oil [117]. Moreover, the essential oil of *L. officinale* showed antiproliferative activity *in vitro* [31].

Angelica (*Angelica archangelica* L.)*:* Angelica root (Angelicae radix) is an official drug in the European Pharmacopoeia (Ph.Eur.2011). However, the leaf and the seed are also used. The whole plant contains essential oil with α-and β-phellandrenes, as well as phthalides that considerably influence the oil flavor [118]. Angelica has traditionally been used as a carminative, diaphoretic and diuretic [119]. However, angelica also possesses antianxiety, antimicrobial and antioxidant properties [120-122].

The dietary supplementation of New Zealand albino rabbits with angelica improved the body burden of lead and therefore protected liver function against lead toxicity. However, the exact mechanism of the angelica protection effect was unclear [123].

Treating mice with angelica ameliorated the chronic ethanol induced hepatotoxicity effects. It was found that angelica inhibited malondialdehyde formation in mouse liver homogenates both *in vitro* and *in vivo*. Angelica is a cytoprotective agent efficient against chronic ethanol induced hepatotoxicity, possibly by inhibiting the production of oxygen free radicals that cause LP, and therefore, indirectly protecting the liver from oxidative stress [124].

Parsley (*Petroselinum crispum* L.): Parsley is not an official drug, but it is among the favorite vegetables. The root and leaf are used as well as seed, which are usually used for essential oil extraction. All parts contain essential oil rich in myristicin, apiol, and α- and β-pinene that give its characteristic fragrance [125]. Parsley leaf is used for treating various problems such as constipation, colic, edema, rheumatism, and prostate and liver diseases. Parsley is mostly used because of its antimicrobial, anti-anemic, hemorrhagic, antiplatelet, anticoagulant, antihyperlipidemic and laxative properties [126-129].

Parsley showed a hepatoprotective effect against an acute liver injury induced by CCl_4, significantly decreasing AST, ALT and GGT. Also, SOD and CAT were decreased in the group treated with parsley. The expression of tumor necrosis factor-alpha (TNF-α) was improved in the group treated with CCl_4 and parsley when compared with the group treated with CCl_4 only. Moreover, parsley reduced fatty degeneration, cytoplasmic vascularization and necrosis of the liver in the CCl_4 treated group. Although CCl_4 caused a decrease in non-protein sulfhydryl (NP-SH) level, the extract of parsley significantly renewed the NP-SH concentration [34, 130]. The hepatoprotective effect of parsley leaf was proven in a few studies made on liver injury caused by either paracetamol [131] or sodium valproate [132], as well as injuries due to the complication of diabetes [133]. Vitamin C and flavonoids are probably responsible for the hepatoprotective role of parsley [134]. Additionally, myristicin from the essential oil induced the activity of GST enzyme in the liver [135].

P. crispum extract administrated to rats fed with a fructose-enriched diet, which caused dyslipidemia, hepatic steatosis and infiltration of inflammatory cells in the liver and higher plasma hepatic markers, reversed the metabolic changes, and attenuated the chronic changes induced in non-alcoholic fatty liver disease (NAFLD) [136].

Carrot (*Daucus carota* L.): The cultivated carrot (*D. carota* ssp. *sativus*) is mainly consumed as a root vegetable, while its seed oil is sometimes used as a flavoring agent in food products and in the cosmetics industry [36, 137]. Wild carrot seed (*D carota* ssp. *carota*) has been used for medicinal purposes since ancient times. Nowadays, it is established that the oil of this seed possesses antinociceptive, anti-inflammatory, hypoglycemic, antidiabetic, antioxidative and anticancer activities [138].

Pre-treatment with a cultivated carrot seed extract significantly decreased the SGPT, SGOT and ALP levels in animals with thioacetamide induced oxidative stress. There was also a significant increase observed in SOD, CAT, GRD, GPx and GST, while the levels of LPO were significantly reduced, which showed a great antioxidant potential of the carrot extract [139]. The carrot extract could provide a significant protection against paracetamol, isoniazid and alcohol induced hepatocellular injury in animal models [140].

It was reported that a carrot seed extract could lower the plasma levels of AST, ALT and bilirubin in a dose-dependent manner in CCl_4 induced hepatotoxicity [141] and lindane induced hepatotoxicity [142] where the carrot extract also restored the depressed antioxidant and HDL cholesterol levels to near normal values. Another study showed that oral treatment with kaempferol isolated from carrot seed reversed all the serum and liver parameters in the paracetamol treated rats [143].

Methanol-acetone extract of wild carrot umbels demonstrated significant DPPH activity and high ferric reducing antioxidant power (FRAP) values. The sesquiterpene-rich fraction had the highest ferrous ion chelating (FIC) ability. Pretreatment with this extract reversed the CCl_4 decrease in SOD, CAT, and GST levels and significantly reduced the hepatic damage. The current results suggest that wild carrot oil fractions exhibit a unique chemical composition and possess significant antioxidant activities as well as hepatoprotective effects against CCl_4-induced hepatotoxicity [144].

Conclusion: Medicinal plants can serve as a vital source of potentially useful new compounds for the development of effective therapies to combat a variety of liver problems. The members of the *Apiaceae* family have demonstrated their heptatoprotective effects by both ameliorating hepatic functions and regenerating hepatic tissue on animal studies. The possible mechanism of their activities against chemically induced hepatotoxicity is their rich natural antioxidant content which inhibits undesirable oxidation processes occurring in the liver. The hepatoprotective potential of the *Apiaceae* family herbs should not be underestimated, and in the light of the presented evidence of their efficacy in animal studies, further detailed research is required. The reported studies have used various extracts of the same plant which were obtained from different parts of the given plant, or if the same parts were used, different extraction methods have been applied and the extracts differed in the composition and content of the active compounds. Even if the same extracts have been used in various studies, the doses applied were inconsistent. Well-designed human studies with

standardized extracts of the defined plant parts where the hepatoprotective activity of the *Apiaceae* herbs should be monitored are urgent and welcomed. Further studies should define the parts of the herbs which are the most potent in liver damage protection, as well as the safest and the most effective applied dose.

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