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EXPLORING THE POTENTIAL HEPATOPROTECTIVE EFFICACY OF LEPIDIUM SATIVUM SEEDS: A COMPREHENSIVE REVIEW

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***Background**: Chronic liver diseases are the leading cause of morbidity and mortality worldwide.Lepidium sativum (L. sativum) is a famous member of the Brassicaceae family that has been utilized for medicinal and culinary purposes for centuries. The hepatoprotective activity of various portions of the plant has been reported in several experimental and clinical trials. **Aim:** The current review study aimed to discuss the hepatoprotective effects of L. sativum seeds. **Methods:** The data of this review were collected from English-language in-vivo and in-vitro studies published in electronic databases; with no time limit; including Web of Science, Scopus, MEDLINE, Google Scholar and PubMed. The searched keywords were "Lepidium sativum" and/or "chemical composition", "Hepatoprotective", "liver diseases". **Results:** Lepidium sativum seeds significantly decreased the elevated inflammatory markers and oxidative stress in hepatic tissues. The seed extract significantly lowered serum levels of ASP, ALT, and bilirubin. The potential molecular mechanism may be through upregulating Bcl-2 protein expression and downregulating caspase-3. **Conclusion:** Lepidium sativum seeds are promising hepatoprotective natural remedy through their multi-targeted action on different pathophysiological mechanisms involved in liver diseases*

***Keywords:** Lepidium sativum, Secondary metabolites, Hepatoprotective*

INTRODUCTION

The liver is the most vital organ in our body owing to its crucial role in bile secretion and detoxification, along with fat, carbohydrate, and protein metabolism [1]. It also controls critical biological pathways that are involved in reproduction, energy production, and maintaining body homeostasis in a surprising manner **(Fig. 1)** [1]. Unfortunately, chronic liver diseases are the leading cause of morbidity and mortality worldwide. According

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to recent estimates, there are 1.5 billion people worldwide with chronic liver diseases, including any stage of severity, with a mortality rate of 2 million annually and accounting for 4% of all deaths **(Fig. 2)**; roughly two-thirds of all liver-related mortality occur in men [2]. The severity of chronic liver diseases, the price of medications, and the decline in treatment effectiveness have significant implications. Action must be taken right away in order to prevent, diagnose, manage, and treat hepatic diseases, especially when they are still in the early stages. For the prevention and treatment of liver disorders, numerous plant-based remedies have been used[1].

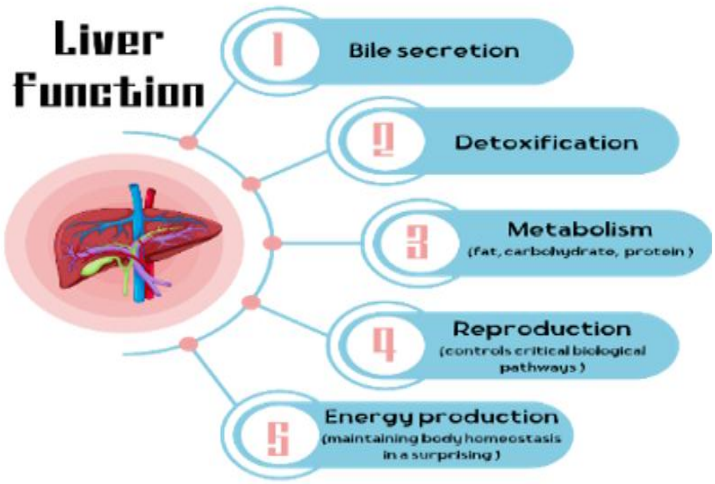

Fig. 1: Liver Functions.

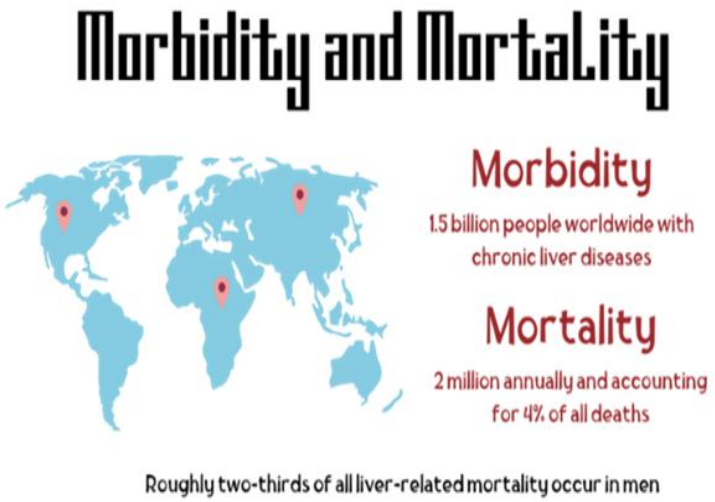

Fig. 2: Morbidity and Mortality of hepatic diseases.

Throughout history, *L. sativum*, had acquired great value in the ancient Egyptian and Roman populations for its diverse therapeutic properties such as asthma, urinary tract tumors, ulcers, hemorrhoids, coughs, wounds, fungal infections, painful menstruation, and nasal polyps. Moreover, it was traditionally used for gastrointestinal disorders, jaundice, liver problems, and spleen diseases **(Fig. 2)** [3–5].

In parallel, previous experimental and preclinical studies reported a promising hepatoprotective effect of *L. sativum*, a commonly available annual plant related to the Brassicaceae family [6]. Additionally, the pharmacological investigation revealed that *L. sativum* possessed hypolipidemic, anti-inflammatory, antioxidant, reproductive, antimicrobial, gastrointestinal, antidiabetic, respiratory, analgesic, antipyretic, cardiovascular, diuretic, central nervous, anticancer, and fracture healing effects as indicated in **Fig. 3** [7,8]

Plants produce secondary metabolites as a result of different metabolic reactions that have a crucial role in their defense mechanisms and are also recognized for their biological and therapeutic properties[9–13]. Phytochemically, L. sativum seeds are considered a rich source of secondary metabolites such as flavonoids, alkaloids, terpenes, glucosinolates, and phenolics[14–17]. Additionally, preclinical trials reported promising hepatoprotective efficacy of these active constituents [6] .

Although several researches discussed different versatile activities of L. sativum, the reviews addressing its hepatoprotective efficacy are limited. So, the current review article aimed at collecting, summarizing and adding new insights to the studies describing hepatoprotective efficacy of L. sativum seeds and their active constituents in both in-vitro and in-vivo laboratory models. Also, this review investigated the feasible utilization of the secondary metabolites and their related molecular mechanisms that may ameliorate different liver toxicities.

So, the aim of the current review study is to investigate the hepatoprotective efficacy of L. sativum as primary outcome and its active constituent's in vitro and in vivo laboratory models. Also, the review investigated the feasible utilization of the secondary metabolites and its related molecular mechanisms that may ameliorate different liver toxicities as secondary outcome.

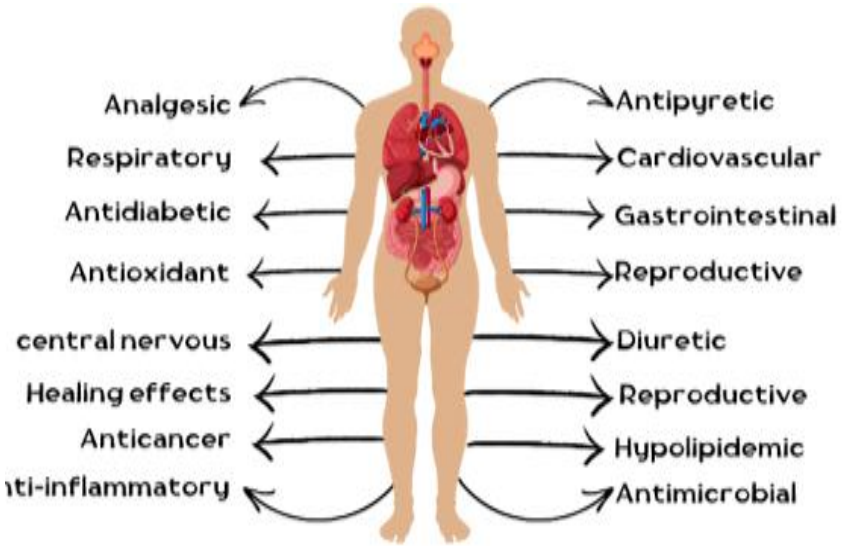

Fig. 3: Therapeutic effects of *L. sativum* in various physiological/pathological conditions.

METHODS

Numerous databases were utilized to gather the English language relevant articles with no time limit, such as Web of Science, MEDLINE, Scopus, Clinical key, Science Direct and PubMed. The searched keywords were "*Lepidium sativum* seeds" and/or "chemical composition", "Hepatoprotective", "liver diseases". The articles were collected from May 2023 to August 2023. All articles discussing the hepatoprotective effect of *Lepidium sativum* seeds and its explanations in English were included. Both experimental and clinical studies were enrolled. Also, the articles reporting the safety and toxicity of *Lepidium sativum* were involved. The articles in languages other than English, or reporting any protective effect for seeds other than *Lepidium sativum* were excluded.

CHEMISTRY OF *LEPIDIUM SATIVUM* SEEDS

The chemical composition of the active components in *L. sativum* can differ depending on various factors, such as the location where the plants were cultivated, the environmental conditions during the growing season, the genotype of the species, the plant's growth stage, the storage conditions between the time of harvest and analysis, and the method used for extraction [18].

A comparative study of *L. sativum* seeds collected from four different regions of Morocco using GC/MS analysis reported the existence of fatty acids, sterols, and tocopherols. Linolenic acid and oleic acid are the main fatty acids. And the major sterol is *β*-sitosterol, with a dominance of *γ*-tocopherol [19].

The GC/MS analysis of the ethanolic extract of L. sativum seeds revealed the presence of 12 major fatty acids, among them α-linolenic acid , Cis-13-eicosenoic acid (omega-7 fatty acid), palmitic acid, myristic acid , and palmitoleic acid [20].

In another trial, the GC/MS analysis of the seed oil of L. sativum showed the occurrence of two major omega fatty acids: 7,10-hexadecadienoic acid as an omega-6 fatty acid and 7,10,13-hexadecatrienoic acid as omega-3 fatty acid [21]. The chemical structure of active components in *L. sativum* is shown in **Fig. 4**.

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Regarding the polyphenolics, for instance, the ethanolic extract of *L. sativum* seeds was reported to have the greatest concentration of flavonoid and phenolic components (0.375%and 0.5%, respectively) when compared to an aqueous extract [18].

Another phytochemical analysis of *L. sativum* seeds methanolic extract revealed a high polyphenol content of 13:752 ± 0:96 mg GAE/g DW, flavonoid content of 1:516 ± 0:82 mg QE/g DW, and alkaloid content of 0:138 ± 0:56 mg/g DW [25]

Another phytochemical study revealed that the total phenolic and total flavonoid contents were 54.83 mg GAE/g and 10.01 mg RE/g, respectively of the ethanolic extract of *L. sativum* seeds. The HPLC analysis characterized the polyphenolics where the major phenolic acids are gallic acid and caffeic acid, while the major flavonoids are catechin and rutin. Moreover, isolation of eight compounds gallic acid, catechin, rutin, kaempferol-3-O-rutinoside, quercetin-3-O-rhamnoside , kaempferol-3-O-rhamnoside,

quercetin, and kaempferol. Also, the GC/MS analysis characterized the polysaccharides in the extract [26]. The flavonoid-rich extract of *L. sativum* was characterized using HPLC analysis and characterized the presence of flavonols, flavones, and flavanones namely, quercetin, kaempferol, luteolin, apigenin, naringin, and naringenin [27].

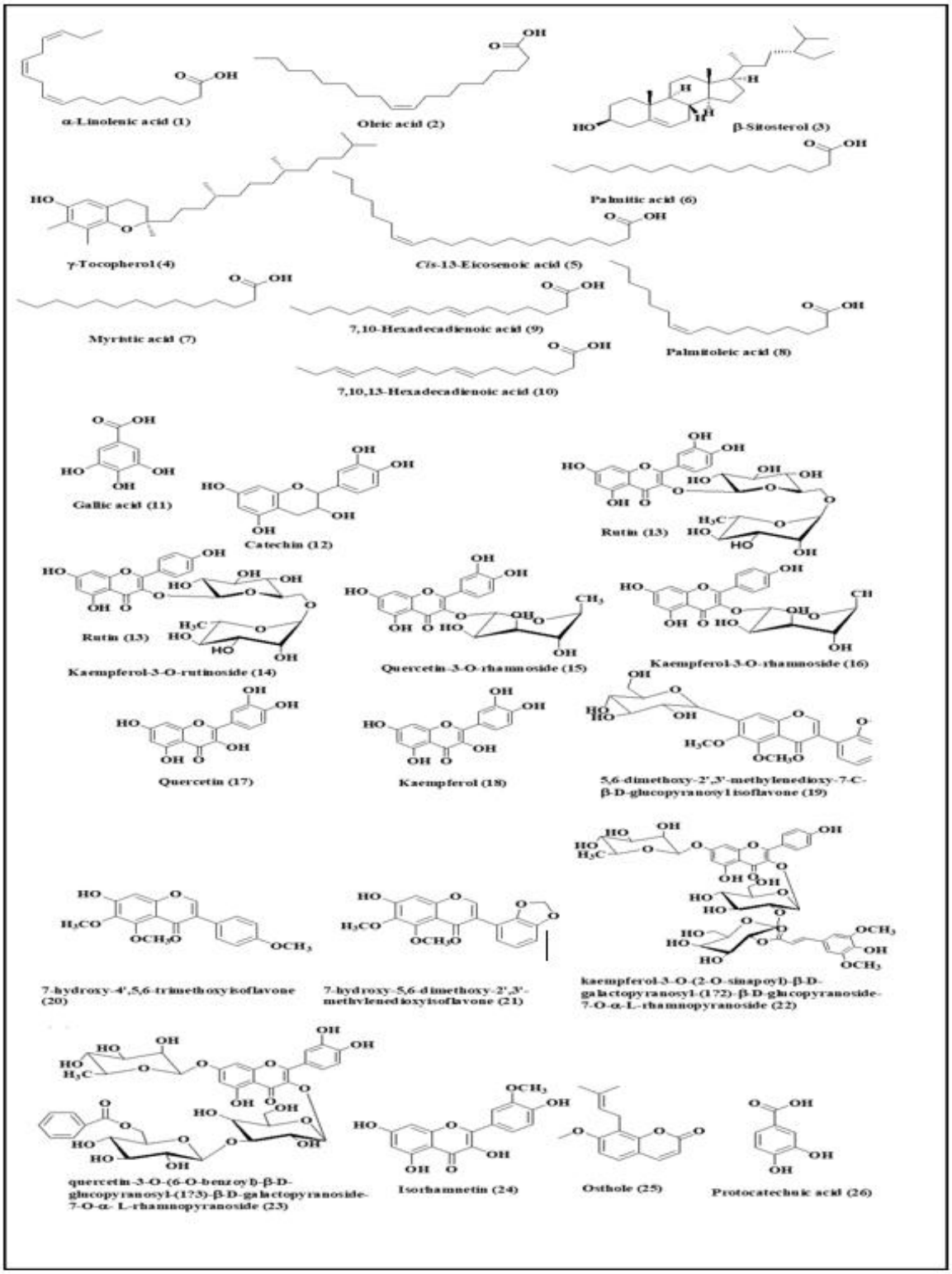

Fig. 4: Chemical structure of the major identified compounds in *Lepidium sativum* seeds .

A new isoflavonoid namely, 5,6-dimethoxy-2′,3′-methylenedioxy-7-C-β-D-glucopyranosyl isoflavone was isolated from the seeds of L. sativum and showed hepatoprotective activity. Along with two previously identified compounds, 7-hydroxy-4',5,6-trimethoxyisoflavone and 7-hydroxy-5,6-dimethoxy-2',3'-methylenedioxyisoflavone[6].

Two new acylated flavonol glycosides were isolated from the seeds of L. sativum, named kaempferol-3-O-(2-O-sinapoyl)- β-D-galactopyranosyl-(1→2)-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside and quercetin-3-O-(6-O-benzoyl)-β-D-glucopyranosyl-(1→3)-β-D-galactopyranoside-7-O-α L-rhamnopyranoside along with six previously identified compounds isorhamnetin, quercetin, kaempferol, osthole, protocatechuic acid, and staphylionosides A [28].

Six alkaloids and proto-alkaloids were identified and characterized in the alkaloid extract of seeds of *L. sativum* namely, benzyl isothiocyanate, 2- ethoxy-4H-3,1-benzoxazin-4-one, (4R)-2-(2-aminophenyl)-4-phenyloxazoline, 5-acetyl-1,2-dihydro-6-methyl-2-oxo-4-phenyl-3-pyridinecarbonitrile, benzo[b][1,8]-naphthyridin-5(10H)-one,2,4,7-trimethyl and 1,4-diaminoanthraquinone [29].

The above mentioned characteristic chemical composition of L. sativum seeds could explain their effective anti-oxidant properties that can reduce inflammation and suggest a potential hepatoprotective activity. In the following section, we will address both in-vivo and in-vitro studies that reported hepatoprotective properties of L. sativum seeds either as powder, extract or oil and these studies will be summarized in **Table (1)**.

Hepatoprotective activity of *Lepidium sativum* seeds

Hepatoprotective Activity of *Lepidium sativum* Whole Seed or Powder

Lepidium. sativum seeds ameliorated the hepatotoxicity induced by CCl4 in New Zealand rabbits. In comparison to rabbits injected with CCl4, biochemical investigations of 200 and 400 mg/kg body weight of rabbits protected by *L. sativum* seeds for 5 and 10 weeks revealed significant decreases in the serum levels of cholesterol, total bilirubin, ALP, γ-GT, triglycerides, and transaminases, along with significant increases in the serum levels of albumin and T protein. The liver tissues of the CCl4-treated group displayed inflammation, oxidative stress and a suppressed antioxidant system in a pronounced manner [30].

The liver's histoarchitectural changes caused by CCl4 in protected rabbits with *L. sativum* seeds had returned to their normal state, as evidenced by the presence of regenerating hepatocytes without steatosis or isolated inflammatory chronic venous congestion[30]. This reported anti-inflammatory activity of *L. sativum* seeds is in agree with Ahmad et al. who evaluated the potential impact of *L. sativum* seed powder (at 250 or 500 mg/kg doses) on the production of TNF-α in mice treated with Escherichia coli. The polysaccharides present in this plant had significantly inhibited the E. coli-induced inflammation by lowering the levels of TNF-α in the blood.[31].

In a more recent study, El-Gendy et al. evaluated the hepatoprotective, antihyperlipidemic, and anti-oxidant efficacy of L. sativum whole seeds (60 g/kg b.w.) against Monosodium glutamate (MSG) induced hepatotoxicity in rats for 30 days. L. sativum seeds significantly decreased LDL-c, VLDL-c, and triglycerides while increasing HDL-c. Lipidum sativum seeds inhibited the hepatic cells' glutathione reductase and superoxide dismutase enzymes as well as lower the peroxide content of serum lipids. Through improvement of the hepatic histological architecture and reduction of apoptotic cells, this supplementation in the diet exerted hepatoprotection due to anti-apoptotic and antioxidant properties [32].

This anti-oxidant action of *L. Sativum* seeds were previously demonstrated by Fan et al. who extracted two novel acylated flavonol glycosides from L. sativum seeds that could prevent a macrophage cell line from producing NO. These glycosides are: "quercetin-3-O-(6-O-benzoyl)-β D-glucopyranosyl-(1⟶3)-β-D-galactopyranoside-7-O-α L-rhamnopyranoside" and "kaempferol-3-O-(2-O-sinapoyl)-β-D galactopyranosyl-(1⟶2)-β-D-glucopyranoside-7-O-α-L rhamnopyranoside" [28].

Hepatoprotective Activity of *Lepidium sativum* Seed Oil

Umesha et al. examined the effect of *L. sativum* seed oil and its mixtures with n-6 PUFA-rich edible vegetable oils such as sunflower oil (SFO), rice bran oil (RBO), and sesame oil (SESO) on the antioxidant status of the oils and antioxidative enzymes in Wistar rats. *Lepidium sativum* seed oil was physically blended with n-6 PUFA-rich vegetable oils (SFO, RBO, and SESO) to increase the content of natural antioxidants like tocopherols, oryzanol, and lignans, lower the n-6/n-3 PUFA ratio, and enhance the blend's capacity to scavenge free radicals. Sixty days of dietary consumption of *L. sativum* seed oil and its blended oils increased the tocopherol levels (12.2-21.6%) and the liver activity of antioxidant enzymes such as catalase and glutathione peroxidase (GPx) compared to rats given native oil. On the other hand, glutathione reductase (GR), superoxide dismutase (SOD), and glutathione S-transferase (GST) were unaffected. As a result, combining *L. sativum* seed oil with other vegetable oils reduced the n-6/n-3 PUFA ratio (>2.0) and increased the antioxidant activity of GPx and catalase enzymes through dietary ingestion of its blended oils[33].

These anti-inflammatory and free radical (DPPH) scavenging properties of L. sativum seed oil were also reported by Alqahtani et al. For concentrations of 300, 200, and 100 µg/mL of this oil, the percentage of inhibition of DPPH of L. sativum seeds oil was 21%, 11%, and 7% respectively [21]. Moreover, the modulatory effect of linolenic acid-rich L. sativum seed oil (2·5, 5·0, and 10%, w/w) on the lipid compositions, spleen lymphocyte proliferation, and peritoneal macrophage production of inflammatory mediators in female Wistar rats was demonstrated by Diwakar etal. This oil may be useful in the treatment of inflammatory diseases by modifying inflammatory markers like NO and LTB4 [22,34].

In parallel, Reddy et al. had demonstrated that 10% w/w L. sativum seed oil ameliorated the ulcerative colitis in Wistar rats caused by dextran sulfate sodium. The rats treated with L. sativum seed oil showed a significant decrease in TNF-α, IL-1β, and leukotriene B4. They concluded that in rats with ulcerative colitis, L. sativum seed oil could lessen oxidative stress, lower inflammatory mediators, and lessen colon damage[35].

Hepatoprotective Activity of *Lepidium sativum* Seed Extract

Sakran et al. investigated three isolated isoflavonoids (a new isoflavonoid, 5,6-dimethoxy-2',3'-methylenedioxy-7-C-β-D-gluco-pyranosyl isoflavone, along with two known isoflavonoids, 7-hydroxy-4',5,6-trimethoxyisoflavone, and 7-hydroxy-5,6-dimethoxy-2',3'-methylenedioxyisoflavone) from *L. sativum* seed extract in male rats for their potential to alleviate the hepatotoxicity generated by paracetamol at a dose of 100 mg/kg b. wt. The three compounds demonstrated a capacity to protect DNA from damage caused by free radicals and protect liver cells against various toxins, leading to a significant enhancement in the total antioxidant capacity. Additionally, they were found to normalize levels of superoxide dismutase (SOD), glutathione (GSH), catalase (CAT), glutathione *S*-transferase (GST), glutathione peroxidase (GPx), and liver enzymes in comparison to the control group [6]. These results are in concordance with Fan et al [28].

In an experimental study on human liver cells (HepG2), Al-Sheddi et al. demonstrated that phytoconstituents, including riboflavin, niacin, flavonoids, and others, significantly restored the cells' original morphology in a concentration-dependent manner when HepG2 cells were exposed to increasing concentrations of *L. sativum* seed extract (LSE) for 24 hours before H_2O_2 exposure. In HepG2, pre-treating cells with LSE at concentrations of 5, 10, and 25 mg/ml significantly decreased the levels of H_2O_2-induced ROS production, significantly increased the mitochondrial membrane potential, prevented the depletion of GSH levels brought on by H2O2, and reduced lipid peroxidation. It is therefore possible to conclude that liver cells exposed to *L. sativum* quench intracellular corrosive peroxide and restore the concentration of decreased GSH [36]. This finding agrees with previous investigations showing that L. sativum seed extract contains significant flavonoids like naringenin, naringin, kaempferol, apigenin,

and luteolin. These substances contain antioxidant and antiradical properties that shield cell membranes from harm caused by radicals, whether they are combined or used alone[22,34].

Al-Asmari et al. reported that the ethanol extracts of *L. sativum* seeds in different doses (100, 200, and 400 mg/kg b.w.) against carbon tetrachloride (CCl4)-induced acute liver injury in rats showed potent hepatoprotective effects through reduction of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and bilirubin (BIL). Also, the histological analysis of liver tissues in groups pre-treated with *L. sativum* showed mild inflammation and necrosis in hepatocytes compared to the toxic group. The hepatoprotective potential was comparable to the reference drug silymarin [37].

In another study, the ethanolic extracts of *L. sativum* seeds (400 mg/kg) were investigated in a D-galactosamine-induced lipopolysaccharide (D-GalN/LPS) (30 μg/kg) liver damage model in rats. The observations had shown a comparable and significant improvement in hepatic injuries with silymarin (25 mg/kg) through down-regulating IL-6 mRNA expression and TNFα in a dose-related manner. Interestingly, *L. sativum* assists hepatoprotective action by down-regulating HO-1 and iNOS expression. Similar to silymarin, *L. sativum* significantly reduced MPO activity and NF-B DNA-binding capacity in a dose-related manner. The suggested molecular mechanisms were up-regulation of BCl2 protein expression and down-regulation of caspase 3 [38].

Furthermore, the hepatoprotective properties of *L. sativum* seed methanolic extract are attributed to alkaloids, coumarin, flavonoids, tannins, and triterpenes [39]. These outcomes were recently augmented by Tounsi et al who conducted an in vitro study using peritoneal neutrophils isolated from BALB/c mice. Tounsi et al demonstrated that L. sativum extract (0.016 and 0.16 mg/mL) could, in a dose-dependent manner, inhibit the production of superoxide anion. It was proposed that flavonoids could function as an antioxidant to stop the synthesis of reactive oxygen species (ROS), scavenge free radicals and ROS, maintain the reduced levels of GSH, and shield biomolecules from oxidative damage [18].

In another similar experimental study, Hatem and Rajab, 2019 estimated the hepatoprotective impact of *L. sativum* seed extract at a dose of 200 mg/kg per day for twelve weeks against carbon tetrachloride-induced liver damage in white rats. Biochemical analysis revealed that the administration of CCl4 caused liver injury, as evidenced by a noticeable elevation in the serum levels of oxidative substances like CAT and MDA as well as liver enzymes like sGOT, sGPT, and ALP. However, administering the *L. sativum* seed extract caused a noticeable drop in the sGOT, sGPT, and ALP levels as well as an increase in the antioxidants glutathione peroxidase and catalase as compared to the control group. Additionally, histopathological investigation of the control group's livers reported degeneration, thickening in the walls of the central vein, and inflammation in the central veins and portal tracts. However, these alterations, which were significantly enhanced in the *L. sativum-treated* group, reported significant protection against the nuclear degeneration effect of CCl4 injection [40].

In a recent study, Ibrahim et al. investigated the ameliorative impact of an ethanolic extract of garden cress seeds in a rat model of NAFLD. In this study, rats that were fed a high-fat diet plus EEGS 400 mg/kg b.w. daily for six weeks revealed lower TAG, LDL-C, and TC, downregulation of hepatic HMGCR and VEGF expression, and hindered weight gain, NAFLD, NASH, and fibrosis as compared to the group fed a high-fat diet only. Moreover, treating this group with this extract elevated CAT activities, SOD, GSH, and diminished nitric oxide and MDA level [41].

Consequently, they appreciated the hepatoprotective activity of garden cress seeds in addition to their hypolipidemic, anti-obesity, antioxidant, anti-steatosis, and anti-angiogenic properties in NAFLD induced by a high-fat diet in rats [41] .I Abdulmalek et al investigated the ameliorative effect of both ethanolic and aqueous *L. sativum* seed extracts on insulin response and hepatic inflammation in rats fed a high-fat diet. They demonstrated that high glucose levels, leptin, lipid profiles, liver enzymes, and body weight were all

significantly reduced by both extracts. By controlling AKT/mTOR signaling, these extracts markedly reduced oxidative stress and hepatic tissue inflammation in rats on a high-fat diet. In an experimental investigation, rats given *L. sativum* seed extracts had decreased levels of advanced glycation end products in their liver tissue and serum. *L. sativum* decreased the rise in hepatic proinflammatory mediators, such as TNF, IL-1, IL-6, and iNOS, in rats fed a high-fat diet [42]. Additionally, both extracts significantly reduced peroxidation of lipids and returned antioxidant enzyme levels to baseline. In parallel, the hepatic tissues of the *L. sativum-treated* groups showed an increase in the phosphorylation of the traditional markers of insulin signaling, p-IR, p-AKT, p-mTOR/p-p70S6K [42].

In addition, Tofik Ahmed et al. evaluated the effect of hydro-methanolic seed extract of *L. sativum* on nonalcoholic fatty liver disease induced by a deep-fried palm oil diet ingested by male Swiss albino mice using a dose of 200 and 400 mg/kg/day for 28 days. Blood samples were drawn for evaluating liver function tests, and liver tissues were used for histopathology analysis. They reported a significant decrease in serum levels of ALT and total bilirubin. Furthermore, the mice's liver sections in this group demonstrated a better response to the extract in terms of bringing the injured liver's histopathology nearly back to normal. However, both doses showed a significant decline in serum AST and ALP levels [43].

In a most recent trial, L. sativum seeds, extract (20 mg/kg/day), protected against hepato-nephrotoxic effects of dexamethasone in rats. *L. sativum* reported significant protective effects against oxidative stress induced by Dexamethasone in Rats. Lipid peroxidation was reduced in rats given *L. sativum* seeds extract improved in addition to increasing alkaline phosphatase activity and the level of antioxidants such as SOD, GSH, GPx, and CAT. And improved liver and kidney function biomarkers, and activity the activity of lactate dehydrogenase [44]. This finding is in concordance with some previous researches illustrating that the phenolic and flavonoid components in the seeds may be responsible for the antioxidant action seen in aqueous and alcoholic extracts [24,34].

Clinical trials

Although no clinical trials have been applied to test the hepatoprotective efficacy of *L. sativum* in humans, limited clinical studies have addressed the impact of *L. sativum* on some diseases. For instance, Maghrani et al. proposed that *L. sativum* seeds could be beneficial to patients with hypertension. They demonstrated that the oral administration of *L. sativum*. aqueous seed extract at a dose of 20 mg/kg daily for three weeks improved the blood pressure from the 7th day to the end of the treatment through enhanced electrolyte and water excretion [45].

Moreover, Paranjape and Mehta investigated the efficacy of *L. sativum* in treating bronchial asthma. This was a non-comparative open-label clinical trial carried out on patients with mild to moderate bronchial asthma of either sex [46]. In this clinical trial, powdered dried seeds of *L. sativum* at an oral dose of 1 gram three times daily were administered with water for one month. As a result, *L. sativum* significantly reduced the symptom score of all common symptoms of bronchial asthma and improved lung function parameters in asthmatic patients. In this study, *L. sativum* exhibited a highly significant ($p< 0.01$) increase in PEFR and Forced Vital Capacity (FVC) of the patients. Forced Expiratory Flow between 25% and 75% was also significantly increased by *L. sativum.* Moreover, they reported good tolerability of this drug, as all the asthmatic patients who received one gram of *L. sativum* seed powder three times per day for four weeks experienced no side effects. Additionally, no patients reported changes in physical or hematological parameters. Consequently, Paranjape and Mehta suggested *L. sativum* as a promising drug for treating asthma, considering its wide availability, accepted efficacy, and ease of oral administration [46]. In another recent clinical study, El Kilani et al. assessed the efficacy of *L. sativum* alone or in combination with Alendronate in treating chronic periodontitis in postmenopausal women with osteoporosis [47].

In treating chronic periodontitis in postmenopausal osteoporotic women, the combination of *L. sativum* and alendronate showed a synergistic action that increased

bone mass more favorably than alendronate alone. This combination showed the largest percentage change in the clinical attachment level at p = 0.001, the highest reduction in the mean gingival index (p = 0.01), and the highest elevation in the MI index compared to baseline after six months at p = 0.000 [47].

Toxicity and Safety

Al-Yahya et al. investigated the anti-inflammatory, antipyretic, and analgesic effects of an ethanolic extract of cress seed (*L. sativum*) in rodents, as well as the safety of acute and chronic use. The extract significantly reduced yeast-induced hyperthermia and prevented paw edema caused by carrageenan. The mouse on the hotplate now reacts more quickly as well. However, due to its anti-inflammatory activity, this extract aggravated the damage indomethacin caused to the gastric mucosa. This effect might be due to inhibiting prostaglandin biosynthesis, which is one of the main mechanisms by which NSAIDs have anti-inflammatory effects. Additionally, the extract reported coagulation properties confirmed by a significant rise in fibrinogen levels and a slight decline in prothrombin time[48] .

Regarding acute and chronic toxicity studies, a single dose of 0.5–3.0 g/kg of the extract did not result in any negative side effects or mouse deaths. However, other than a statistically non-significant increase in mortality rate, animals given the extract (100 mg/kg/day) for three months in drinking water exhibited no toxic effects. These findings imply that the seeds of watercress (*L. sativum*) have significant analgesic, antipyretic, anti-inflammatory, and coagulant properties without producing any acute or long-term harmful side effects or toxic effects [48].

Lepidium sativum seed was non-toxic when fed to Wistar albino rats at 2% (w/w), toxic when fed at 10% (w/w), but not fatal, and lethal when fed at 50% (w/w), causing entero-hepato-nephrotoxicity and a slowing of growth. Anemia and leukopenia were also present alongside organ lesions and changes in total protein, cholesterol, urea, and other serum constituent concentrations, as well as the serum's AST and ALT activities [49].

As mentioned above, all the asthmatic patients who received one gram of Lepidium sativum seed powder three times per day for four weeks experienced no side effects [46].

In adult Wistar rats, the sub chronic and acute toxicity of *L. sativum* seeds were investigated. Rats were fed between 0.5 and 5.0 g/kg bw of the seed powder for the acute toxicity study, and for 72 hours, visible toxicity symptoms and mortality were tracked. Rats receiving acute doses of seed powder did not exhibit any toxic effects or die. Rats were fed diets containing 1.0–10.0% of the seed powder during a 14-day subchronic toxicity study. No mortality was caused by the dietary administration of seed powder, and neither the experimental nor control groups showed any appreciable differences in food intake, weight gain, the relative weight of organs, haematological parameters, or macroscopic or microscopic changes in vital organs. LDH and SGPT enzyme levels were normal, but serum levels of ALP and SGOT were significantly elevated in male rats given 5.0 and 10% seed powder [50].

Male rats were given water suspensions of *L. sativum* seed powder (2, 4, 8 g/100 ml) for 3 and 6 days. This increased total serum protein, increased albumin in the high-dose group, and maintained normal levels of AST and GGT. The levels of ALT and ALK in males receiving 2 and 4 g/kg, respectively, significantly increased after 3 weeks. Low doses (2 and 4 mg/ml) for 3 weeks caused congestion of the central and portal veins, while high doses for 3 weeks caused periportal fibrosis and perivascular edema in the liver parenchyma. In the samples from the animals treated with *L. sativum*, bile duct proliferation was a noticeable characteristic [51].

It appeared that L. sativum seed increased renal weight in the treated group in the study of the acute and chronic effects of 15% L. sativum seed supplementation on gross organ morphology and histomorphometry indices in rats. According to histological analysis, the treated group's Bowman's space, glomerulus, and Bowman's capsule diameter all significantly changed. Rats fed 15% L. sativum seed also developed more glomerulosclerosis, metaplasia, and hyperplasia. Throughout the experiment, there was a noticeable rise in tubular degeneration

in the proximal and distal tubules. When these findings are combined, they demonstrate that rats fed 15% L. sativum seed were significantly toxic [52].

Mice were used in the study to examine the impact of an aqueous extract of L. sativum seeds on the immune system and general health. Young adult male Swiss albino mice were orally gavaged with an aqueous extract of ground L. sativum seeds at low doses (0.5 ml) and high doses (1 ml) every day for 19–21 days. The mean white blood cell counts and mean spleen weight increased significantly in the low-dose group treated with L. sativum seed extract, but the increases tended to be more pronounced in the high-dose group. Comparing the high-dose group to the control, there were obvious increases in the mean body weight. mean haemoglobin concentration, white blood cell types, red blood cell counts, and platelet counts. In comparison to the control group, the mean total body weight gains and the weights of the organs (aside from the spleen) were not significantly different between the low- and high-dose groups [53].

Because it causes uterine contractions and causes spontaneous abortion, it is an abortifacient that pregnant women should avoid ingesting in any form [54,55].

Another recent study evaluated and contrasted the in vivo toxicity of solid lipid nanoparticles (SLN) and ethanol extracts (EELS) from L. sativum seeds. To evaluate acute and subacute toxicity, Swiss albino mice were given EELS and SLN orally. In acute toxicity studies, animals given doses of 2000 mg/kg and 5000 mg/kg did not exhibit any toxic effects in terms of gross pathology, body weight, or behavior. Lethal doses (LD50) for SLN and EELS have been determined to exceed 400 mg/kg and 5000 mg/kg, respectively, in studies on acute toxicity [56].

In subacute toxicity studies, animals given oral doses of SLN (50 and 100 mg/kg) and EELS (250, 500, and 1000 mg/kg) for 28 days exhibited no clinical changes. Histological examination of the treated animals' organs (liver, heart, kidney, and spleen) revealed no abnormalities. In comparison to the control group, there were no differences in weight, biochemical parameters, or hematological parameters ($p > 0.05$). As a result, Ahmad et al. concluded that mice treated with acute and subacute doses of ethanolic extracts from L. sativum seeds and their SLNs did not experience any negative effects [56]

Table 1: Hepatoprotective effects of various parts of *L. sativum.*

Extract/Part used	Dose	Model	Effects	Ref.
Lepidium sativum seeds	200 and 400 mg/kg	CCl4 induced hepatotoxicity in New Zealand rabbits	The extract decreased levels of free radicals, TNF-, IL-6, iNOS, and HO-1; increased levels of IL-10 and antioxidant activity .	43
Lepidium sativum seeds	30 g/kg BW and 60 g/kg BW	MSG induced hepatotoxicity in rats.	*Lepidium sativum* seeds in diet (60 mg/kg/day) decreased LDL-c, TG, VLDL-c, NO serum levels and the activity of SOD, CAT, and GPx enzymes.	44
***Lepidium sativum* seed oil rich diet**	AIN-76 diet containing native oils or *Lepidium sativum* blended oils	Male Wistar rats	Dietary feeding of *L. sativum* seed oil and its blended oils for 60 days, increased the level of tocopherols (12.2–21.6 %) and antioxidant enzymes' activity (glutathione peroxidase and catalase)	1
Ethanolic extract/seeds	100, 200, and 400 mg/kg, administered once daily for seven days	CCl_4-induced acute liver injury in rats.	Groups that had been pretreated with the ethanolic seed extracts showed mild hepatocyte necrosis and inflammation.	27

Table 1: Continued.

Chloroform extract/seeds	5, 10, and 25 mg/mL	H202 induced Hepatotoxicity in HepG2 cell lines	LSE significantly reduced the loss of cell viability caused by H2O2 (LD50 value ¼ 2.5 mM) by up to 48%, prevented the production of ROS (45%) and lipid peroxidation (56%), and increased glutathione levels (46%) as well as the mitochondrial membrane potential (55%).	46
Ethanolic extract/seeds	(150 and 300 mg/kg) and silymarin	D-GalN/LPS induced FHF in rat	L. sativum caused significant down-regulation in mRNA expression of TNF, IL-6, iNOS and HO-1 and upregulated the mRNA expression of IL-10. L. sativum significantly increased MPO activity and the NF-B DNA-binding effect.	19
Methanolic seeds extract of *L. sativum*	100 mg/kg	Paracetamol-induced hepatotoxicity in Sprague Dawley male rats	L. sativum significantly increased the total antioxidant capacity and normalized the levels of liver enzymes, which reduced the harm and toxicity.	3
Ethanolic seed extract of *L. sativum*	(LSS) (200 mg/kg) daily for twelve weeks	CCl4 (0.1) ml \100 gram body weight injected in white rats	AST, ALT, and ALP levels were all significantly reduced by the (LSS) extract and increased the antioxidant parameters GSH, GPx, SOD, and catalase levels significantly.	50
Ethanolic extract of garden cress seeds (EEGS)	400mg/kg b.w/day	High-fat diet rats	The extract reduced TAG, LDL-C, TC, hepatic HMGCR expression, and VEGF expression while preventing obesity, NAFLD, NASH, and fibrosis. GSH, SOD, and CAT activities increased while MDA and nitric oxide levels decreased.	51
Alcoholic and aqueous extract / seeds	200 and 400 mg/kg	High-fat diet rats	Increased antioxidant activity in hepatic tissue; decreased levels of free radicals, IL-6, TNF-α, , IL-1β, iNOS and AGES Antioxidant activity has increased in liver tissue	52
Hydromethanolic seed extract of *L. sativum* (HMSELS)	200 and 400 mg/kg/day	deep-fried palm oil diet induced NAFLD in male Swiss Albino mice.	Total bilirubin, ALT, AST, and ALP levels were all reduced by HMSELS. The damaged liver's histopathology was nearly restored to normal thanks to HMSELS.	53
***L. sativum* aqueous extract**	20mg/kg, daily) intraperitoneal injection)	Oxidative stress induced by dexamethasone (1 mg/kg/day intraperitoneal injection) for 14 days in rats	Administration of ***L. sativum*** decreased H2O2, TBARS, and liver function biomarkers levels. ***L. sativum*** increased the levels of alkaline phosphatase activity SOD, GST, GPx, CAT, GR and GSH.	54

Conclusion

The collective findings of numerous studies indicated a prevailing agreement that L. sativum possesses a wide range of hepatoprotective properties. Garden cress, with its diverse array of components, has garnered significant attention in the field of liver health research. Its remarkable ability to combat radicals and boost antioxidant properties highlights its status as a promising candidate for therapeutic interventions. As several esteemed researchers delve deeper into their investigations, the advantageous properties of L. sativum are being increasingly elucidated. Consequently, L. sativum is not merely regarded as a botanical entity, but rather as a prospective fundamental element in the field of hepatic therapy. Future clinical trials assessing the hepatoprotective efficacy of L. Sativum are recommended.

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الهدف : تهدف المراجعة الحالية إلى مناقشة التأثيرات الواقية للكبد لبذور حب الرشاد.

الطريقه: تم جمع بيانات من الأوراق المنشورة حتى يناير ٢٠٢٤ في قواعد البيانات بما في ذلك Web of Science و MEDLINE و Scopus و PubMed. كانت الكلمات الرئيسية التي تم البحث عنها هي حب الرشاد ، أمراض الكبد ، الكبد الدهني.

النتائج: ذكرت العديد من الدراسات أن بذور حب الرشاد قللت بشكل كبير من علامات الالتهاب المرتفعة والإجهاد الأوكسي في انسجة الكبد. علاوة على ذلك ، خفض مستخلص بذورحب الرشاد بشكل كبير مستويات انزيم(الأسبارتات أمينوترانسفيراز) ، وانزيم (ناقلات ألانين أمينية) والبيليروبين. قد تكون الآلية الجزيئية المحتملة من خلال تنظيم بروتين Bcl-2 expres-sion وتقليل تنظيم caspase-3.

الاستنتاج: اقترحت دراسة المراجعة الحالية أن بذور حب الرشاد لها نشاط وقائي كبدي واعد من خلال عملها متعدد الأهداف على الآليات الفيسولوجية المرضية المختلفة المشاركة في المرض. ومع ذلك ، يوصى بإجراء مزيد من الدراسات السريرية لإثبات فعاليتها وسلامتها في المرضى الذين يعانون من أمراض الكبد.