Review article
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Evidence for health-promoting properties of *Lepidium sativum* L.: an updated comprehensive review

Lepidium sativum L.'nin sağlığı destekleyici özellikleri için kanıt: güncellenmiş kapsamlı bir derleme

SHORT TITLE: Health-promoting properties of Lepidium sativum L

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Abstract
Lepidium sativum L. (*L. sativum*) is a common herb distributed worldwide, used as food ingredient and therapeutic agent in traditional medicine for treating health related disorders. *L. sativum* and its extracts have been described to represent numerous biological activities including anti-microbial, anti-diabetic, anti-oxidant, antidiarrheal, anti-cancer and numerous health-promoting effects in animal and *in vitro* studies. The purpose of this review is to highlight the findings that describes important biological functions and therapeutic effects of *L. sativum* in different cell lines and animal models. In this review, the English-language articles were gathered from electronic databases including Web of Science, PubMed and Google Scholar with no time limit applied to any database. The search terms used in this review include, '*Lepidium sativum* L.' and/or 'chemical composition', 'health benefits', 'antimicrobial', 'antioxidant', 'anticancer', 'diuretic', 'nephro-protection', 'antidiarrheal', 'anti-diabetic', 'anti-asthmatic', 'neuroprotection', 'metabolic', 'bone fracture', and 'reproductive performance'. Additional and eligible studies were collected from reference lists of appropriate articles. The information presented will be helpful to attract more interest towards medicinal plants by defining as well as developing novel clinical applications and new drug formulations in the future. Pre-clinical studies exhibited that *L. sativum,* possess potent health-promoting effects involving various molecular mechanisms. Taken all together, data suggested that identified herbal plants such as *L. sativum*, can be exploited as nutritional and therapeutic agents to combat various ailments. Despite several research in this field, further comprehensive *in vitro*/*in vivo* studies and clinical trials are needed to identify the mechanisms underlying the biological and therapeutic activities of *L. sativum*.

Keywords: Ethnomedicine, Medicinal plants, *L. sativum*, Nutraceutical, Therapeutic agents.

Özet

Lepidium sativum L. (*L. sativum*), geleneksel tıpta hastalıkları tedavi etmek için gıda bileşeni ve terapötik ajan olarak dünya genelinde yaygın olarak kullanılan bir bitkidir. *L. sativum* ve ekstrelerinin, hayvan çalışmalarında ve *in vitro* çalışmalarda antimikrobiyal, antidiyabetik, antioksidan, antidiareik, antikanser ve çeşitli sağlığı destekleyici etkiler de dahil olmak üzere çok sayıda biyolojik aktivite gösterdiği ortaya konulmuştur. Bu derlemenin amacı, *L. sativum'*un farklı hücre serilerindeki ve hayvan modellerindeki önemli biyolojik fonksiyonlarını ve terapötik etkilerini gösteren bulgulara dikkat çekmektir. Bu derlemede İngilizce makaleler Web of Science, PubMed ve Google Scholar gibi elektronik veri tabanlarından, herhangi bir zaman sınırlaması uygulanmadan toplanmıştır. Bu derlemede kullanılan arama terimleri *'Lepidium sativum* L.' ve/veya 'kimyasal bileşim', 'sağlığa faydaları', 'antimikrobiyal', 'antioksidan', 'antikanser', 'idrar söktürücü', böbrek koruyucu', 'antidiareik', 'antidiyabetik', 'antiastım', 'sinir sistemini koruyucu', 'metabolik', 'kemik kırığı' ve 'üreme performansı' dır. İlave olarak makalelerin referans listelerinden de uygun çalışmalara ulaşılmıştır. Sunulan bilgiler, gelecekte yeni klinik uygulamaların ve ilaç formülasyonlarının tanımlanması ve geliştirilmesi için tıbbi bitkilere daha fazla ilginin çekilmesine yardımcı olacaktır. Klinik öncesi çalışmalar, *L. sativum*'un çeşitli moleküler mekanizmalarla güçlü bir şekilde sağlığı destekleyci etkilere sahip olduğunu göstermiştir. Bu çalışmalardan elde edilen veriler *L. sativum* gibi tanımlanmış tıbbi bitkilerin çeşitli hastalıklarla mücadelede terapötik ajan ve besin olarak kullanılabileceğini öne sürmektedir. Bu alanda yapılan çeşitli araştırmalara rağmen, *L. sativum*'un biyolojik ve terapötik aktivitelerinin altında yatan mekanizmaları belirlemek için daha kapsamlı *in vitro/in vivo* çalışmalara ve klinik denemelere ihtiyaç vardır.

Anahtar kelimeler: Etnomedicine, Tıbbi bitkiler, *L. sativum*, Nutrasötik, Terapötik ajanlar

1. Introduction

Many plants have been considered as a principal source of potent therapeutic drugs for centuries. *Lepidium sativum*, (alias Garden cress) is a fast-growing perennial herb with edible leaves which grows up to 50 cm height and belongs to the family *Brassicaceae* (*cruciferae*) [1-3]. It is widely dispersed throughout the world; Africa, Asia, Australasia, Europe, Northern and Southern America [4-6]. The leaves and seed oils are commonly applied in traditional medicine in treating various clinical complications including asthma, hypertension, hyperglycaemia, hepatitis, menstrual problems, sexual debility, arthritis, fracture, diarrhea, vitamin C deficiency, constipation, and migraine [2, 7, 8]. Additionally, they have been represented pharmacological properties such as immunity booster, anticancer, antioxidant, laxative, febrifuge, diuretic, and galactogogue activities (Figure 1) [1, 9-11].

The chemical composition of the *L. sativum* seeds illustrated that they contain high levels of proteins, fatty acids (oleic and linolenic acids), crude fiber (lignans, etc), essential minerals (potassium, phosphorus, calcium, and iron), phytosterols (sitosterol, campesterol, and avenasterol), carotenoids, alkaloids (glucotropaeolin, lepidine, N, N'-dibenzylthiourea, N, N'-dibenzyl urea, sinapine and sinapic acid) [12], glucosinolates (glucotropaeolin and 2-phenyl ethyl glucosinolates)[13] riboflavin, ascorbic acid and tocopherols [1, 2, 14-16].

Toxicological studies state that *L. sativum* seeds are considered to be practically non-toxic and safe [17]. Nowadays, ethnomedicinal studies gained great attention due to their beneficial roles against various ailments, though proper identification and documentation of medicinal plants seems indispensable [18, 19]. Herein, we aimed to provide an updated comprehensive overview of the chemical composition of *L. sativum* with focusing on its beneficial impacts, medicinal utilities and underlying mechanisms.

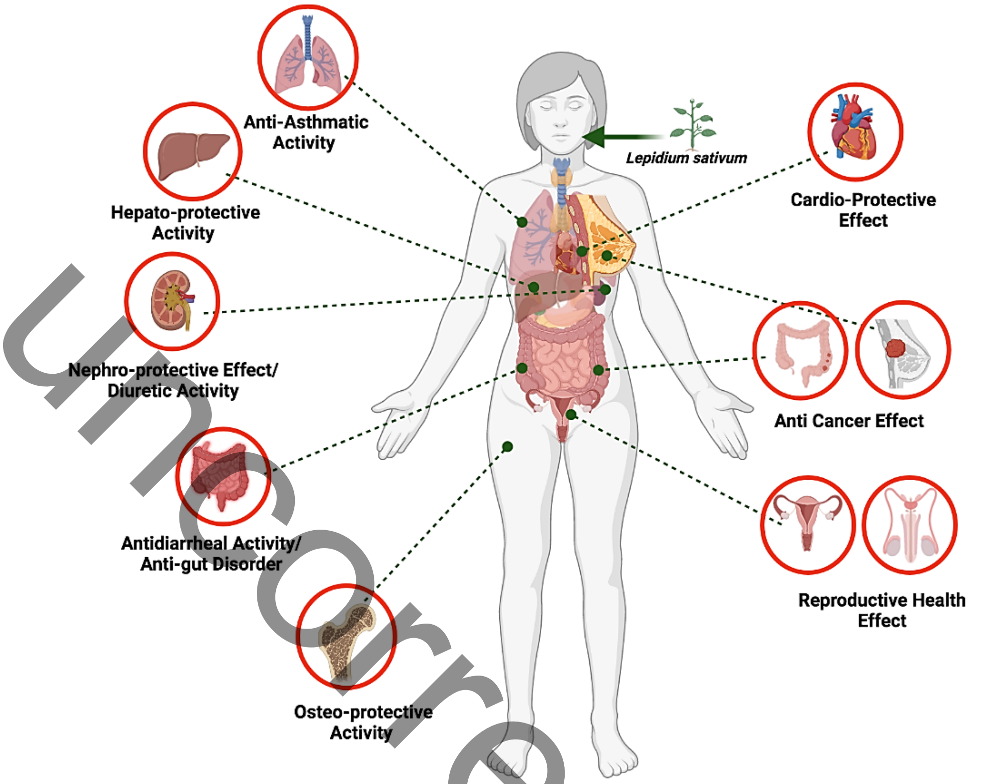

Figure 1. Therapeutic effects of *L. sativum* in various physiological/pathological conditions.

2. Chemical Composition of *L. sativum*

Various factors (including variety, plant agronomic practices, seed collection stage and geological conditions) contribute to the differences of the chemical composition of *L. sativum* seeds [20]. *L. sativum* seeds consist of carbohydrates, protein, lipids, and fiber [21]. *L. sativum* seeds also contain mucilaginous substances (cellulose and uronic acid containing polysaccharides). Additionally, seeds have high protein and lipid contents, minerals as well as vitamins (i. e. Vitamin A, C, D, B-6, and cobalamin) [22]. The presence of numerous components has been reported in *L. sativum* seeds including alkaloids, phenolic compounds, anthraquinone and cardiac glycosides, flavonoids, tannins, benzoic, dihydroxybenzoic, gallic, chlorogenic, 4-hydroxycoumaric, vanillic and salicylic acids, pyrogallol, catechin, catechol, caffeine, isoleucine, as well as different imidazole alkaloids alias lepidine and semilepidine [20]. Essential (Leucine, Valine, Lysine, Phenyl alanine, Isoleucine, Arginine, Histidine, Threonine, and Methionine) and non-essential (Glutamic acid, Aspartic acid, Glycine, Proline, Serine, Alanine, and Tyrosine) amino acids are present in *L. sativum* seeds. The majority of fatty acids in *L. sativum* seeds is α-linolenic acid (ALA), however, oleic, palmitic, stearic, arachidic, linoleic, lignoceric acids, behenic, and β-sitosterol are found in different concentrations. *L. sativum* seed oils comprise high amounts of γ-tocopherol as well as α-tocopherol. Benzyl cyanide and Benzyl isothiocyanate are detected as significant volatile components of the seeds [20, 23]. In a recent research, the results of the liquid chromatography/mass spectroscopy (LC/MS) of the *L. sativum* extracts demonstrated various secondary metabolites (including kaempferol, apigenin, luteolin, quercetin, and 7-hydroxy-40,5,6-trimethoxyisoflavone, chlorogenic acid, sinapic acid, ascorbic acid, p-coumaric acid, , 6-prenylnaringenin and α-tocopherol) in different concentrations [24].

3. Beneficial effects of the *L. sativum*

3.1. Antimicrobial activity

The growth of antibiotic resistance in bacterial strains and adverse effects of synthetic antibiotics, provide a rout to exploiting plants with strong medical potential in treating bacterial infections [2]. A number of studies have reported that the *L. sativum* extract was effective against bacterial strains and pathogens. It has been proposed that the anti-bacterial potency of *L. sativum* depends on benzyl isothiocyanate presence [25]. An increasing number of studies, confirmed *L. sativum*'s antimicrobial properties (Table 1), however, exact mechanism of action which elucidates how they could perform such activities has not fully understood. Recently, Al-Otaibi et al. revealed the probable therapeutic potential of the methanolic extract of *L. sativum* seeds in *Trypanosoma evansi* (a parasitic protozoan) infected-Swiss albino mice. Their findings showed that the methanolic extract treatment results in restoring the haematology analysis (haemoglobin content, HCT, erythrocyte count, leucocyte count and percentage of lymphocytes) to the pre-infection values. Besides, the study discovered that the intraperitoneal injection of the extract exerts more efficacy rather than oral administration [26]. In another research it has been shown that the leaf extract of *L. sativum* could inhibit the viability of the protoscolices *Echinococcus granulosus* [27]. Al-Marzoqi and colleagues examined the antimicrobial potential of the crude alkaloid, phenolic and terpenoid compounds of *L. sativum* extract. Their findings demonstrated that both Gram positive and Gram negative pathogens (*S. aureus, S. epidermedis, S. saprophyticus, Klebsilla, Serratia, Proteus, Escherichia coli, Pseudomonas*, and *Provedenatia*) were resistant to phenolic compounds, whereas the alkaloid and terpenoid compounds exerted extensive antimicrobial activity against Gram positive and Gram negative bacteria. Over all, they suggested that the hydrophobicity of components of the plant extracts, leads to disruption of bacterial cell membrane lipids and mitochondria which in turn causes microbial death [28]. They also showed that different concentrations of active components of the aforementioned plant demonstrated diverse effects on various pathogenic organisms (25).

Table 1. Antimicrobial activity of various extracts of *L. sativum.*

L. sativum	**Antimicrobial activity**	**Reference**
Seed Petroleum ether, methanol, and water extracts	*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonae*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Candida albicans*	2
Seed extract	*K. pneumonia*, *E. coli*, *S. aureus* and *Bacillus cereus*	7
Seed extract	*S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *S. enterica*, *K. pneumoniae*, and *C. albicans*	29
Chloroform, methanol extract	*E. coli*, *S. typhi, S. aureus*, *B. subtillis, Aspargillus niger, Fusarium oxysporum* and *Fusarium solani*	30
Ethanol, methanol and chloroform extract	*E. coli, K. pneumoniae, P. aeruginosa, S. aureus* and *Shigella sonnie*	31
Seed Methanol and ethyl acetate extract	*Rhodococcus equi*	32
Whole plant water, methanol and ethanol extract	Multi drug resistant *E. coli*	33

Crude extract of seeds	*P. aeruginosa, E. coli, S. aureus, B. subtilis,* and two fungi species *(Aspergillus niger* and *C. albicans)*	34

3.2. Antioxidant activity

Reactive oxygen species (ROS) formation are provoked through normal metabolism, however, excessive amounts are detrimental and should be scavenged to avoid any damage [35]. Oxidative stress is implicated in the pathogenesis of several chronic ailments such as cancer, cardiovascular disease, and etc. [36]. Intake of nutraceuticals (rich in antioxidants) from different herbs possibly protect human body against free radicals thus alleviate oxidative damage and degenerative diseases [36]. In a study conducted by Aydemir and colleagues, *L. sativum* seed extract exhibited antioxidant activity [36]. In another study, antioxidant activity of *L. sativum* seeds oil (petroleum ether) were evaluated employing free radical scavenging activity (DPPH) method. The petroleum ether extract exerted antioxidant activity dose-dependently [29]. Omer et al. reported that the ethyl acetate fractions of the *L. sativium* seeds had highest antioxidant activity [34]. Another study conducted by Malar and coworkers revealed the substantial antioxidant activity of the ethanolic extract of *L. sativum* plant parts (shoot, leaf, stem and seed) [37]. Further, it has been shown that the presence of flavonoid and tannin in the methanolic extract of *L. sativum* leads to the significant antioxidant activity [32]. The cyanobacterial toxins and crude extract provoke oxidative stress response in *L. sativum* seedlings through lipid peroxidation, elevation of the levels of tocopherol and antioxidant enzymes (including glutathione peroxidase, glutathione S-transferase and glutathione reductase) [35]. Furthermore, in a study performed by Kasabe et al. it has been elucidated that the seeds of *L. sativum* possess antioxidant activities due to total phenolic content of the seeds [38]. In the recent study, it was reported that methanolic extract of *L. sativum* exerted potent radical scavenger activity comparing to the ethanolic extract [23].

3.3. Anticancer activity

Cancer has remained the leading cause of death worldwide. Nowadays, applying natural remedies to overcome the side effects of conventional methods in cancer treatment have received growing attention [39, 40]. *L. sativum* demonstrated anticancer, anti-proliferative and cytotoxic effects through different mechanisms such as induction of apoptosis and necrosis in various cancer cells. An *in vitro* study carried out on breast cancer cell line (MCF-7), reported the apoptosis induction capability of the aqueous extract of *L. sativum* seeds. However, high concentrations of the extract results in necrosis [41]. Recently, El Sayed et al. reported the antioxidant and anti-mutagenic effects of *L. sativum* against *in vivo* Ehrlich ascites carcinoma (EAC) in Swiss albino mice. Their findings demonstrated anticancer effect of *L. sativum* in EAC tumor-bearing mice lifespan. Additionally, increased levels of liver enzymes and glutathione peroxidase activity as well as decreased levels of malondialdehyde (MDA) were observed which in turn indicated the antioxidant properties of the extract. Besides, *L. sativum* extract decreased chromosomal aberration and DNA fragmentation [42]. In another study conducted by Selek et al. *L. sativum* methanolic extract substantially induced apoptosis in human peripheral lymphocyte cells, colon cancer (DLD-1) and endometrium cancer cell lines (ECC-1) in a dose-dependent pattern, besides, the extract presented significant antioxidant activity. Taken all together, they suggested that high levels of phenolic and flavonoid compounds of the extract may be considered as the underlying mechanism for the anticancer activity of the *L. sativum* [43]. The anti-proliferative effects of the leaf aqueous extracts of *L. sativum* were explored on human tongue squamous carcinoma (CAL-27). The aqueous extract inhibited the growth of CAL-27 cells concentration-dependently. Apoptosis induction and DNA damage was observed in *L. sativum* extract-treated cancer cells. ROS generation in the mitochondria of the treated cells seems the cause of apoptosis induction [44]. According to the recent study, the hydroalcoholic extract of *L. sativum* showed cytotoxicity on HeLa cell line [45]. Further, Aslani et al. evaluated cytotoxic effects of hydro-alcoholic extracts of *L. sativum* shoots on K562 cell line as a model of CML. MTT assay results depicted that the extract exerted cytotoxic effect on K562 cell line in a dose and time dependently [46].

3.4. Effects on urinary system

3.4.1. Diuretic Activity

There are different studies suggested that the plants' diuretic effects may depend on presence of phytochemicals such as flavonoids, saponins, steroids, or organic acids [47]. In line with this, Patel et al. illustrated that the aqueous and methanolic extract of *L. sativum* dose dependently augments urine secretion in rat models. They suggested that the *L. sativum* extracts diuretic activity possibly induced by individual or synergistic effects of flavonoids and steroids which in turn leads to increased local blood flow and vasodilation or inhibition of water and anions tubular reabsorption [47]. In addition to excessive urine production, increased sodium and water excretion, contributes to *L. sativum*'s anti-hypertensive effect [47]. Maghrani et al. investigated diuretic and antihypertensive properties of the aqueous extract of *L. sativum* in normotensive and spontaneously hypertensive rats (SHR). Oral administration of the extract caused substantial drop in blood pressure as well as increase of urinary exertion of sodium, potassium and chlorides in SHR rats [48].

3.4.2. Nephro-protective effect

Numerous evidence elucidates some medications have potential to induce nephrotoxicity and acute renal failure which causes loss of renal functions. Phytochemicals of the *L. sativum* may have antioxidant activity thus overcome the drug-induced nephrontoxicity [49]. In this regard, Yadav et al. depicted that the ethanolic extract of *L. sativum* exerts nephro-protective and curative activity against cisplatin-induced nephrotoxicity in Wistar rats. The administration of the extract markedly declined the levels of urea, creatinine, as well as lipid peroxidation, and enhanced GSH levels [49]. Recently, it has been presented that *L. sativum* seed aquatic extract could ameliorate oxidative stress induced by dexamethasone in rats. Dexamethasone administration led to the elevation of thiobarbituric acid reactive substances (TBARS), hydrogen peroxide (H_2O_2), and liver function biomarkers level, and lactate dehydrogenase activity. However, enzymatic and non-enzymatic antioxidants, protein content, and alkaline phosphatase activity were markedly reduced. The aquatic extract administration in rats received dexamethasone, could alleviate lipid peroxidation, antioxidant status and biochemical indices when compared to the dexamethasone treated group [50]. Furthermore, administration of *L. sativum* powder to the gentamicin-induced nephropathy in diabetic albino rats, caused a substantial reduction of the serum levels of glucose, malondialdehyde (MDA) and augmentation of the glutathione transferase (GST), superoxide dismutase (SOD), total antioxidant capacity (TAC), glutathione pyroxidase (GPX) and catalase (CAT) activity as well as serum insulin levels, though exerted nepho-protective effect by enhancing renal damage [51].

3.5. Effects on digestive tract

3.5.1. Antidiarrheal activity

A few studies reported the antidiarrheal and antispasmodic properties of *L. sativum* [9, 52]. In a study performed in rat model, the administration of extract can inhibit castor oil-induced diarrhea like dicyclomine. Data from the study proposed that dual suppression of muscarinic receptors and Ca^{2+} channels were responsible for the antidiarrheal/antispasmodic activities of the *L. sativum.* Moreover, presence of gut relaxant compounds and phytochemicals such as alkaloids and β-sitosterol , play an important role in *L. sativum* antidiarrheal/antispasmodic effect [9]. Additionally, they examined the antidiarrheal/antispasmodic properties of the crude extract of *L. sativum* seeds in multiple species (mice, Sprague–Dawley rats, guinea-pigs, and local breed rabbits). They also depicted the antidiarrheal/antispasmodic mechanisms specific to each species as below: 1) in rabbit model: activation of K^+ channels and blockade of PDE enzyme, 2) in guinea-pig model: anti-muscarinic and weak Ca^{2+} antagonist-like pathways and 3) in rat model: a combination of anti-muscarinic, Ca^{2+} antagonist and PDE-inhibitory-like mechanisms [53].

3.5.2. Effect on gut disorders

The aqueous-methanolic extract of *L. sativum* seeds were also reported to be potent contributors to indigestion and constipation (as digestive disorders). Rehman et al. described an *in vivo* experiment conducted in mice model displaying the atropine-sensitive pro-kinetic and laxative properties which were relatively mediated through muscarinic receptors [54].

3.6. Metabolic activity

Findings of a recent study depicted that ethanolic and aqueous extracts of *L. sativum* significantly exerted hepato-protective, hypolipidemic, hypoglycemic, hypoinsulinemic, anti-obesity, antioxidant, and anti-inflammatory properties in high fat diet (HFD)-fed rats. Moreover, the hepatic tissues of ethanolic/aqueous extracts-treated rats demonstrated upregulation of the intracellular phosphorylation of common markers of insulin signaling cascade (p-IR/p-AKT/pmTOR/p-p70S6K). Both extracts mitigated lipid peroxidation and restored the amounts of antioxidant enzymes [55]. Al-Asmari et al. designed a study to assess the hepato-protective effect of ethanolic extract of *L. sativum* against carbon tetrachloride (CCl4)-induced toxicity in rat model. Their findings demonstrated that the level of serum alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST) and bilirubin, were significantly decreased in ethanolic extract-treated rats. Additionally, histological analysis of liver tissues exhibited mild necrosis and inflammation in extract-treated group in comparison to the CCl4-treated group [56].

Similar findings were obtained by Zamzami and collaborators for hepato-protective effects of *L. sativum* seeds against CCl4-induced hepatic injury in New-Zealand rabbits. The extract-treated rabbits showed significant reduction in serum levels of liver biomarkers (transaminases, γ-GT, and ALP), total bilirubin, cholesterol, triglycerides and elevated levels of total protein and albumin. Moreover, *L. sativum* extract reduced oxidative stress in liver tissues. Overall, biochemical analysis as well as histopathological examination revealed that the *L. sativum* extract effectively could reverse the hepatotoxicity of CCl4 *in vivo* [57]. In another study, potential protective and therapeutic effects of *L. sativum* against aluminum-induced injury of liver and kidney in albino rat were investigated. Data from this experiment exhibited that administration of the extract led to a marked reduction in levels of serum biomarkers of liver (e. g. AST, ALT, ALP, bilirubin, urea, and creatinine) and kidney functions. It is also significantly augmented the total protein and albumin. Besides, rats fed with the extract reversed necrosis of hepatocytes, glomeruli, and renal tubules. It has been suggested that the antioxidant properties of *L. sativum* seeds exerted the aforementioned beneficial effects [58].

L. sativum seed powder exhibited the potent cardio-protective effect against 5-FU-induced cardiotoxicity and oxidative stress in albino rats. The *L. sativum* seed powder significantly reduced the inflammatory markers (myocardial IL-1β and myeloperoxidase activity), concentration of serum cardiac biomarkers (CK-MB and cTnI), whereas it increased glutathione (GSH) concentration. Moreover, in the *L. sativum*-treated group, the hypertriglyceridemia and hypercholesterolemia factors were returned to the normal status compared to the 5-FU-induced cardiotoxicity group [59]. In another research, the hypolipidemic activity of *L. sativum* seed extract against Triton x-100 and high cholesterol diet (HCD)-induced hyperlipidemia was investigated on rats. Their results showed that the extracts significantly protected against all parameters [total cholesterol, triglyceride, low density lipoprotein cholesterol (LDLc), very low density lipoprotein cholesterol (VLDLc)] of HCD

diet-induced hyperlipidemia, thus, may exert anti-hyperlipidemic effect [60]. Additionally, Raish and colleagues evaluated the hepato-protective effect of the *L. sativum* ethanolic extract in rat model with liver damage induced by D-galactosamine/lipopolysaccharide. Data from their study revealed that the extract significantly down-regulated the pro-inflammatory cytokines (e. g. TNFα and IL-6 mRNA), stress genes (iNOS and HO-1) and up-regulated the IL-10 expression dose-dependently. Furthermore, the extract pretreatment leads to down-regulation of nuclear NF-κB (p65), NF-κB-DNA binding activity, myeloperoxidase (MPO) activity, and nitric oxide level. Additionally, it can down regulate the caspase 3 and up-regulate the Bcl-2 protein expression which overall indicated that *L. sativum* markedly alleviates hepatic damage through reduction of oxidative stress, inflammation, and apoptosis in the liver [61]. Administration of the *L. sativum* seeds ethanolic extract effectively could ameliorate triacylglycerol, LDLc, total cholesterol, as well as downregulation of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), and VEGF expression in rat NAFLD model thus in turn impedes obesity, NAFLD, NASH, and fibrosis. Additionally, the extract administration exerted antioxidant activity via increasing GSH, superoxide dismutase (SOD), and catalase (CAT) activities, as well as reduction of malondialdehyde (MDA) and nitric oxide level [62].
In another study, Sakran et al. isolated 5,6-dimethoxy-2',3'-methylenedioxy-7-C-β-D-gluco-pyranosyl isoflavone (a new isoflavonoid) from *L. sativum* seeds. They showed that this new isoflavonoid have a potential to diminish the hepatotoxicity induced by paracetamol in Adult Sprague Dawley male rats. They proposed that the hepato-protective effect depends on enhancing total antioxidant capacity and normalizing liver enzymes' level (including GSH, SOD, GPX, CAT and GST) [63].

3.7. Anti-diabetic activity

Hyperglycemia (high blood sugar) causes long-term complications in affected people. Untreated hyperglycemia results in renal failure, diabetic cataract, elevated risk of cardiovascular diseases, and excessive generation of free radicals. Numerous lines of evidence suggested ethnomedicinal plants in order to ameliorate the disease and lessen the side effects of synthetic drugs [64]. In line with this, Attia et al. demonstrated that the *L. sativum* seeds methanolic extract, reduced blood sugar and reversed all biochemical and histological complication of alloxan-induced diabetes in rat model [64]. In another study the hypoglycaemic activity of aqueous extract of *L. sativum* seeds was examined in streptozotocin (STZ)-induced diabetic rat model. Their results displayed significant blood glucose level reduction without any substantial alternation in basal plasma insulin concentration which supports the concept that its hypoglycaemic activity may act independent of insulin secretion [65]. Another study performed in hyper-cholesterolemic albino male rats revealed that the *L. sativum* seeds extract improved lipid profile (decrease in cholesterol, triglycerides, LDL and increase in HDL) and markedly diminished blood glucose in comparison to the control group [66]. Furthermore, Eddouks and colleagues designed a study to investigate the mechanisms underlying the hypoglycaemic activity of the *L. sativum* in streptozotocin-induced diabetic rats. Their results showed that the aqueous extract administration, decreased blood glucose, increased glycosuria and normalized glycaemia through prevention of renal glucose reabsorption that is independent of any alternations in insulin secretion [67]. *L. sativum* seed powder administration in alloxan-induced diabetic male Wistar rats, decreased fasting blood glucose levels (FBG), glycosylated haemoglobin (Hb A1C %), triglycerides (TG), lipid profile [total cholesterol (TC) and lipoprotein fractions (LDLc and VLDLc). The extract treatment also elevated the high density lipoprotein cholesterol levels (HDLc) significantly. Additionally, a marked decrease in thiobarbituric acid reactive substances (TBARS) levels and increase in GSH and antioxidant enzyme activity was detected in extract treated rats [68]. In a more recent study, Ullah and colleagues revealed that light (as great abiotic elicitor) play a critical role in biosynthesis of herbal metabolites. Data from their research illustrated that, callus cultures of *L. sativum* under white light exerted maximum level of phenolic profile, anti-diabetic and antioxidant properties compared to other conditions *in vitro* [69]. It is also marked by L'Hadj et al. that the dried *L. sativum* flavonoid-rich extract had potential hypoglycemic, hypolipidemic, anti-inflammatory, cytoprotective, and antidiabetic properties in Wistar rats via enhancing dyslipidemia, insulin sensitivity, inflammation, and pancreas β cell integrity [70].

3.8. Impacts on reproductive health

Cumulative evidence proposed the capability of the herbal medicine in improving reproductive dysfunction or fertility due to their phytochemicals [71]. In a recent study in doe rabbit model, the *L. sativum* oil increased the level of the reproductive hormones and improved antioxidant status and reproductive performance (receptivity, conception rate and litter size) [71]. Moreover, Kamani et al. experimented the efficacy of ethanolic extract of *L. sativum* seed on histopathological alternations of epididymis in streptozotocine (STZ)-induced diabetic adult male Wistar rats. Their findings exhibited the improved epithelium height as well as reduction of interstitial volume density, fibro muscular thickness, volume density of epithelium through preventing oxidative stress which in turn demonstrated the extracts protective effect on reproductive system [72]. Recently, Rahimi Asl et al. revealed that the co-administration of coenzyme Q10 (CoQ10) and *L. sativum* markedly enhanced the hypothalamic-pituitary-gonadal axis activity and ameliorated the reproductive functions in adult male mice. Co-administration of CoQ10 and *L. sativum* resulted in elevation of all features of sexual behaviors and serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels, as well as sperm viability and motility [73]. Another animal study was performed to examine the impact of aqueous extract of *L. sativum* on fertility criteria in male mice. Findings of this study showed that extract-treated mice displayed higher levels of FSH and testosterone. Overall, all the infertility parameters improved in the hyper-prolactenimic animals treated with the extract. Histological analysis of the testis in extract treated mice exhibited normal status of seminiferous tubule with high number of sperms [74]. Imade and colleagues investigated the effects of *L. sativum* seeds on the male reproductive functions in rabbit bucks. Rabbits fed with *L. sativum* seeds significantly elevated plasma LH concentrations without any significant difference in testosterone levels. Motility and live sperm percentage were significantly decreased in *L. sativum* seed-treated rabbits. Besides, sperm abnormality percent was increased significantly in *L. sativum* seed-treated rabbits dose-dependently. Taken all together, in case of high amount consumption, toxic effects of *L. sativum* seed on sperm quality and testis in rabbit bucks were observed [75]. In another study, *L. sativum* elevated the concentrations of estrogen, progesterone, LH, FSH, and free testosterone hormones in female rabbits. Besides, significant augmentation of sexual receptivity, conception rate, gestation length, litter size and body weight at birth in extract treated groups were detected. Overall, *L. sativum* elevated reproductive hormones level and performance *in vivo* [76].

3.9. Osteo-protective Activity

Osteoporosis is a progressive "skeletal disorder characterized via low bone mass, micro-architectural deterioration of bone tissue leading to increased risk of bone fragility and fracture risk" [53]. In traditional medicine, *L. sativum* seeds have been proposed to have potential in healing bone fractures [53]. In light of this, recently, the fracture healing potential of the methanolic and aqueous extract of *L. sativum* seeds in rats was experimented by Giri and colleagues. Biochemical and radiological analysis revealed that the methanolic extract markedly led to callus formation [77]. It has been reported that Ibuprofen exerted toxic effects on the osteocytes in bone tissue whereas various concentrations of the aqueous extract of *L. sativum* seeds inhibited the effects of Ibuprofen in Male albino rats [78]. Administration of teriparatide (a recombinant parathyroid hormone utilized as antiosteoporotic therapy) and *L. sativum* (LS) seeds ameliorates biochemical, histological and morphometric bone alternations induced by glucocorticoids in male guinea pigs through osteocytes apoptosis reduction as well as osteoclasts elevation [79]. Abdallah and colleagues examined osteo-protective effect of *L. sativum* extract in an ovariectomized rat model. Their findings demonstrated that the extract improved bone weight, bone formation biomarkers (lactate dehydrogenase (LDH) and osteocalcin) levels, and free radicle scavenging activity (through enhancing SOD and glutathione peroxidase (GPx) activities). Furthermore, oral administration of the extract results in increase of the bone resorption markers (e.g. carboxyterminal telopeptide, type I (CTXI) and tartrate-resistant acid phosphatase (TRAP)) and regulation of receptor activator of nuclear factor kappa-B ligand (RANKL)/ osteoprotegerin (OPG) expression. Taken all together, they suggested that presence of glucosinolates, lignans, coumarins, phenolic acids, and alkaloids leads to the aforementioned anti-osteoporotic effects synergistically [80]. In another research, the synergistic anti-osteoporotic activity of *L. sativum* and alendronate in glucocorticoid-induced osteoporosis was evaluated by methylprednisolone injection in adult female rats. Their findings revealed that *L. sativum* alone and/or in combination with alendronate treatments, markedly diminished serum tartrate-resistant acid phosphatase (TRAP) and improved bone-specific alkaline phosphatase (b-ALP), phosphorus, calcium, and bone architecture (through increasing trabecular area or bone marrow area (PTB) percentage in the proximal femoral epiphysis) [81]. Further, Juma and colleagues revealed that *L. sativum* seeds significantly improved fractures healing in New Zealand white rabbits which documented via direct measurements of callus formation in millimeters at the longitudinal medial (LM) and longitudinal lateral (LL) and circumferential (CM) areas [82]. Administration of *L. sativum* seeds powder to the rabbits with bone fractures demonstrated significant increase in bone markers (osteopontin and Vitamin D), parathormone and lactoferrin levels as well as reduction in serum levels of osteocalcin when compared to the untreated group [83].

3.10. Anti-Asthmatic activity

Bronchial asthma is a chronic inflammatory disease of airways of the lung, that characterized by hyper-reactivity of the airways to various stimuli. Its clinical manifestations include paroxysmal dyspnea, wheezing cough, and a sense of thoracic constriction. From ancient times, the efficacy of the natural remedies in healing various diseases including bronchial asthma, hiccups, cough and etc. has been elucidated [84]. Nevertheless, there is lack of scientific studies which investigate the efficacy of *L. sativum* in bronchial asthma treatment. For that reason, Paranjape et al. carried out a clinical trial to assess the efficiency and safety of *L. sativum* in bronchial asthma affected patients. After 4 weeks of treatment with *L. sativum* seed powder, substantial improvement in several parameters of pulmonary functions, clinical symptoms and severity of asthmatic attacks without any adverse reaction were observed in asthmatic subjects [84]. In another study carried out on guinea pigs, the bronchodilatory effect of the ethanolic extract of *L. sativum* seeds was investigated in histamine and acetylcholine induced acute bronchospasm. Data from their study showed that the extract, markedly protected guinea pigs against bronchospasm in comparison to the Ketotifen and Atropine sulphate (as standard drugs) [85]. Additionally, Rehman et al. indicated that a combination of anticholinergic, Ca^{2+} antagonist and PDE inhibitory pathways were responsible for *L. sativum's* bronchodilatory activity of [86].

3.11. Neuroprotective effects

A few studies stated potential neuroprotective activity of the *L. sativum*. In this regard, El-ghazouly et al. assessed neuroprotective effects of the *L. sativum* aqueous extract on the cerebellum of adult male albino rats. Methotrexate exerted adverse effects on cerebellum by reducing the number of Purkinje cells with significant reduction of Nissl's granules. However, in methotrexate and *L. Sativum* aqueous extract administrated rats approximately normal histological appearance of Purkinje cells with less vacuolated cytoplasm was observed which was validated by a substantial rise in the Purkinje cells number, significant diminution in caspase-3 positive cells and in GFAP immunostaining [87]. Moreover, the neuro-pharmacological impact of the alkaloid of *L. sativum* was evaluated in Swiss Albino mice and Wistar albino rats. The results of this study elucidated sedative, anxiolytic, myo-relaxant and analgesic effects of *L. sativum* alkaloid through diminished locomotor activity and motor coordination, and increased preference to plus maze open arm [88]. Al-Dbass et al. examined the potential beneficial impact of *L. sativum* seed extract against glutamate excitotoxicity induced retinal ganglion cell degeneration which results in severe blindness. The extract enhanced the cell viability in retinal ganglion cells after exposure to the high concentrations of the glutamate. Thus they deduced that the *L. sativum* seed extracts might exert effective anti-excitotoxic and antioxidant activity in various neurological disorders [89].

3.12. Other beneficial effects

There are also several studies evaluating various beneficial effects of *L. sativum* extract in animal models. The ethanolic extract of *L. sativum* seeds significantly prohibited carrageenan-induced paw edema and reduced the yeast-induced hyperpyrexia in mice models and exert anti-inflammatory, antipyretic effects, respectively. The coagulation studies demonstrated elevated levels of fibrinogen and negligible reduction in prothrombin time, which in turn validated the coagulant activity of the extract [90]. The ethanolic extract of the *L. sativum* seeds exerted significant anti-inflammatory activity in carrageenan-induced paw edema in mice through improving biomarkers of inflammation (serum albumin, C-reactive protein (CRP) and plasma fibrinogen) in comparison to the control group [91].

Alkharfy et al. examined drug–herb interactions and proposed that simultaneous consumption of herbs significantly changed the phenytoin (an anticonvulsant drug) disposition in a dog model [92]. In a follow-up study, the methanolic extract of *L. sativum* seed exerted genoprotective effect by inhibition of DNA aberrations in somatic and germ cells of mice dose-dependently. They proposed that the flavonoidal content and antioxidant activity may be responsible for this beneficial properties [93]. Another *in vivo* study performed to evaluate the safety of *L. sativum* seeds powder in adult Wistar rats. Administration of the *L. sativum* powder considered non-toxic and safe because of insignificant changes in food intake, gain in body weight, relative weight of organs (e. g. liver, lungs, kidney, spleen, brain, adrenals, gonads and heart), hematological parameters (including: red blood cells (RBC), white blood cells (WBC), hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)), macroscopic and microscopic changes in vital organs, in experimental group in comparison to the control group [94].

In the recent study, for the first time, the effects of the aqueous *L. sativum* seeds extract on the immune system and general health were reported in mice model. Their results demonstrated that the extract results in immune system boost (WBC types, RBC, and platelet counts as well as mean hemoglobin concentration, mean total body weight gains and weights of the organs) [95]. Moreover, addition of *L. sativum* seeds to the diet of rats for the first three weeks, results in elevated mean body weights and body weight gains [96]. In a study performed by Kaur et al., it has been elucidated that the supplementation of *L. sativum* seeds (for 2 months) moderately increased the haemoglobin (g/dl) levels among anemic adolescent girls possibly because of iron content [97].

Diwakar et al. investigated the modulatory effect of α-linolenic acid (ALA)-rich *L. sativum* seed oil on lipid composition, spleen lymphocyte (SL) proliferation and inflammatory mediator production in rat model. Data from their research illustrated that the extract modulates inflammatory mediators (NO, leukotriene B4 (LTB4)), consequently alleviates inflammatory responses [98].

4. Conclusions

Various herbs and their extracts have gained substantial interest since they encompass diverse phytochemicals which represents numerous health-promoting activities. Using different parts of the *L. sativum,* several pre-clinical studies demonstrated their potential in alleviating different disorders and improving health (e. g. antimicrobial, antioxidant, anticancer, anti-diabetic, anti-asthmatic, and many other protective activities). Hence, *L. sativum* have been considered as an attractive alternative over the conventional therapeutics due to their nutritional values, and less or no adverse effects. However, further comprehensive studies are required to define molecular mechanisms underlying certain health-promoting properties and provide more convincing evidence for the efficacy of *L. sativum*.

Authors' contribution

Y.H. and Y.R.S. conceived and designed the study. Y.H. and T. O. extracted the data. All authors co-wrote the manuscript, critically reviewed and approved the final version.

Conflict of interest

None.

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