CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EFFECTS OF LEPIDIUM SATIVUM-A REVIEW

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ABSTRACT

Lepidium sativum contained many bioactive constituents included cardiac glycoside, alkaloids, phenolic, flavonoids, cardiotoxic glycosides, coumarins, glucosinolates, carbohydrates, proteins and amino-acids, mucilage, resins, saponins, sterols, tannins, volatile oils, triterpene, sinapic acid and uric acid. The pharmacological investigation revealed that Lepidium sativum possessed antimicrobial, antiabetic, antioxidant, anticancer, reproductive, gastrointestinal, respiratory, anti-inflammatory, analgesic, antipyretic, cardiovascular, hypolipidemic, diuretic, central nervous, fracture healing and protective effects. The current review discussed the chemical constituents and pharmacological effects of Lepidium sativum.

Keywords: Constituents, Pharmacology, Lepidium sativum

INTRODUCTION

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-6]. The phytochemical analysis of Lepidium sativum showed that it contained cardiac glycoside, alkaloids, phenolic, flavonoids, cardiotoxic glycosides, coumarins, glucosinolates, carbohydrates, proteins and amino-acids, mucilage, resins, saponins, sterols, tannins, volatile oils, triterpene, sinapic acid and uric acid. The pharmacological investigation revealed that Lepidium sativum possessed antimicrobial, antiabetic, antioxidant, anticancer, reproductive, gastrointestinal, respiratory, anti-inflammatory, analgesic, antipyretic, cardiovascular, hypolipidemic, diuretic, central nervous, fracture healing and protective effects. The current review will highlight the chemical constituents and pharmacological effects of Lepidium sativum.

Plant profile

Synonyms

Arabis chinesis, Cardamom sativum, Crucifera nasturtium, Lepia sativa, Lepidium hortense, Lepidium sativum var. crispum, Lepidium sativum subsp. sativum, Lepidium sativum var. spinescens, Lepidium spinescens, Nasturtium crispum, Nasturtium sativum, Nasturtium spinescens, Thlaspi nasturtium, Thlaspi sativum and Thlaspidium sativum [7].

Taxonomic classification

Kingdom: Plantae, Subkingdom: Viridiplantae, Infrakingdom: Streptophyta, Superdivision: Embryophyta, Division: Tracheophyta, Class: Magnoliopsida, Order: Brassicales, Family: Brassicaceae, Genus: Lepidium, Species: Lepidium sativum [8].

Common names

Arabic: habb al-rashad, rashad, thafa; Bengali: halim; Chinese: jia du xing cai; English: garden cress, peppercwort, tongue cress, town cress; French: cresson alénois; German: Gartenkresse; Hindi: chandrasur; Italian: agretto, Portuguese: agrião, mastruço; Swedish: smörgåskresse [9].

Distribution

It is distributed in Africa (Egypt, Ethiopia and Kenya), Asia (Kuwait, Oman, Saudi Arabia, United Arab Emirates, Yemen, Afghanistan, Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, Pakistan, China, Japan, India), Europe (Britain, France, Italy, Germany), Australasia (Australia and New Zealand), Northern America (Canada and United States) and Southern America (Argentina and Chile) [9].

Description

Lepidium sativum is an erect, branched, glabrous herb with 60 cm height. Leaves are entire or pinnately dissected, variously lobed often with linear segments; up to 5-6 cm long and lobes are 0.7-1.2 to 0.3-0.6 cm size, upper leaves usually entire and 2-3 cm long, oblaneolate, sessile. The basal leaves have long petioles and are lyrate Pinatipartite; the couliner leaves are lanceolate. The inflorescence is in dense racemes. The flowers have white or slightly pink petals, measuring 2 mm. The silique measure 5 to 6 mm, are elliptical elates from the upper half and glabrous. Racemes are 7 to 15 cm long axillary and terminal; flowers are white or pale pink; pedicels are 3-5 mm long. Pods are obovate or broadly elliptical, roundate, emarginated slightly but thickly winged above Fruit a round or ovate, flattened silique 4-6 mm × 3-5.5 mm, pale green to yellowish, margins wing-like, apex emarginate, dehiscing by 2 valves, usually 2-seeded [10-12].

Traditional uses

The seeds of Lepidium sativum were used as an aperient, diuretic, tonic, demulcent, carminative, galatogote, emmenagogue, to cure throat diseases, uterine tumour, nasal polyps and breast cancer. Seeds were supplemented in the diet of lactating women to increase the milk secretion during the postnatal period. Seeds also applied as a poultice to pains, hurts, sprains, in the treatment of bacterial and fungal infections [13-16].

The seeds were also used for the treatment of fracture healing in Saudi traditional medicine [17]. In Unani system of medicine, seeds and leaves were used as diuretics, aperient and aphrodisiac, and were recommended in inflammation, bronchitis, rheumatism and muscular pain [18]. In Turkish folk medicine, Lepidium sativum was used as to enhance digestion, as carminative and appetizer [19]. The plant was eaten and seed oil was used in treating dysentery, diarrhea and migraine [20].

The mucilage in the outer seed was used as a substitute for tragacanth and gum Arabic [21].

Parts used medicinally

Seeds, oils and leaves [15, 18, 20].

Physicochemical characteristics

Physicochemical characteristics of Lepidium sativum were total ash: 1.57%, acid insoluble ash: 0.74%, water soluble ash: 0.83%, successive...
extract (petroleum ether: 2.05%, chloroform: 2.67%, methanol: 9.09%: water: alcohol (5/50): 4.94%: water: 0.29%) [22].

Physicochemical characteristics of Lepidium sativum whole meal, endosperm and bran were moisture content 41.4±0.05, 25.8±0.01 and 4.27±0.01% protein: 22.47±0.78, 27.74±0.02 and 12.58±0.21; fat: 27.48±0.14, 33.06±0.16 and 6.34±0.19%; carbohydrates: 34.24±0.92, 28.45±0.21 and 50.31±0.08%; crude fiber: 7.01±0.08, 4.02±0.13 and 14.29±0.06%; ash: 4.65±0.09, 4.06±0.08 and 6.19±0.01%; insoluble dietary fiber: 25.49±0.38, 13.10±0.62 and 74.7±0.49%; soluble dietary fiber: 1.51±0.09, 0.50±0.10 and 0.93±0.01%; total dietary fiber: 30.4±0.47, 13.6±0.62 and 75.1±4.99% energy; 474±1.06, 523±0.82 and 363±0.87 Kcal [23].

The seed oil extracted by solvent extraction, supercritical CO₂, and cold expression were 21.54, 18.15, and 12.60 % dry weight, respectively. Physicochemical parameters of oils extracted by solvent extraction, supercritical CO₂, and cold expression were, respectively: refractive index (nD): 1.47±0.001, 1.47±0.003 and 1.47±0.002; specific gravity (g/ml): 0.91±0.001, 0.90±0.001 and 0.91±0.001, viscosity (η): 64.3±0.90, 55.5±0.37 and 53.8±0.6; peroxide value (mequiv peroxide/kg oil): 0.70±0.13, 4.09±0.09 and 2.63±0.81; free fatty acid (% oleic): 0.28±0.02, 0.39±0.04 and 1.52±0.28; saponification value (mg KOH/g): 178.85±0.46, 182.23±0.38 and 174±0.82; unsaponifiable matter (g %): 1.65±0.24, 1.39±0.10 and 1.16±0.30; iodine value (g of I2 per 100 g); and nonessential amino acids: (aspartic acid 9.76±0.03, methionine 0.97±0.02, phenylalanine+tyrosine 9.62, histidine 3.51±0.007%) and (non-essential amino acids: arginine 2.89±0.00, aspartic acid 11.47±0.014, glutamic acid 19.68±0.28, glycine 6.49±0.014, alanine 5.85±0.007, serine 5.30±0.007%), and mineral composition: (potassium 785.0±7.51, phosphorus 616.50±9.67, calcium 253±0.14, sodium 40.50±0.05, iron 5.38±0.04, copper 1.90±0.09, zinc 4.10±0.07%) [33].

The GC-MS spectrum of Lepidium sativum seed oil from Saudi Arabia revealed the presence of 16 components. The constituents included: β-amyris (31.33%), 9,12,15-octadecatrienoic acid (15.97%), 9-octadecenoic acid methyl ester (11.93%), α-amyris (9.32%), 11-eicosenoic acid (6.64%), 9,12-octadecadienoic acid methyl ester (6.03%), hexadecanoic acid (5.24%), 13-docosanoic acid (2.64%), Urs-12-en-24-oic acid, 3-oxo-, methyl ester (2.52%), 9-octadecenamide (2.2%), eicosanoic acid (1.98%), methyl stearate (1.75%), phenol, 2,2-methylenebis[6-(1,1-dimethyl (0.96%)], docosanoic acid, methyl ester (0.69%), butyldihydroxytoluene (0.42%) and 1s,7R,711R-1,3, 4, 7-tetramethylycricly (0.31%) [34].

Lepidium sativum seeds also contained heavy metal: cadmium: 0.24±0.02, lead: 0.42±0.14, arsenic: 0.48±0.06 and mercury: 0.38±0.06 ppm [22]. Analysis of methanolic seeds extract of Lepidium sativum, showed that the extract contained 46 compounds included desoperguinal, 6-oxa- bicyclo[3.1.0]hex-3-one-3, 2-furancarboxaldehyde, 5-methyl, 9-0xacycl[b]x[3.1.]lone-2,6-diol, glycol-dl-serine, 2-hydroxy-1,1,10- trimethyl-6-epidioxide, methyl nicotinate, 4-phenyl-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-thiocianic acid, octyl ester, maltose, benzofuran,2,3-dihydro, 5-hydroxymethylfuranyli, 2-methoxy-4-vinylphenol, ascaridole epoxide, phenol, 2-methoxy-5-(1-propenyl)- (E), α-D-gluco- pyranoside, α-D-gluco-pyrano[1.1f]an[1.2-d-fruc, 2h-inden[e][2]-bifuran-2-one,3a,4,5,6,7,8-8-hydroxy-8-dim, limonene-6-ol, pivalate, (50%)pregnane-3,20-diol, 14α, 18x-[4-methyl- 3-oxo-1-oxa-4-azabul, cinnamic acid, 4-hydroxymethoxy-3-butyloxy-2-hydroxyethyl, 9-oximino-2,7-dioxyhexane, Fluorone, Phorbol, Streptovitacin A, 4,25-seco-scevocrinear-4-0,16,7-diketohexadec-15,16-dimethyl, desulphosinigrin, d-mannose, methyl (1-0-retinyl-2,3,4-triacyl-h-6-d-glucopyran). Urnate, tetracetyl-d-saliclyl-nitric, dasycarpian-1-methanol, acetate (ester), octadecanoic acid, 1H-cyclopropa[a]x[3.4]benz[e][2]-alulene-5,7-b, 9a-tertol,1a,4,4a, 8o,octaneoic acid-3-octyl-cis, 9-octadecenamide, (Z), octadecanal, 2-bromo, tributyl acetylitate, pyrrolidine, 1-(1-oxy-7,10- hexadecadienyl), 8H-Azocin[5,4-b]nhdole-8-one, 5-ethylidene- 1,2,3,4,5,6,7,9-octacy, 16-Nitrobcycl[k][0.4]hexadecene-1-ol-13-one, 2β,benzox[0xieno[2.3-E]benzofuran-8(H)-one, 9β-[2-methylphenyl, 5-propen-5-ene-3,8,11,12,14-20, hexol, (38,11x,128,14R,20R), Y- tocopherol, vitamin E, 6,7-epoxypreg-4-ene-1,9,11,18-triol-3,20-dione, 11,18-diaceate, stigmasterol, 9,19-cyclolanostane-3,7-diol and ergosta-5,22-dien-3-olacetate. (38,22E) [35].

β-sitosterol and some phytosterogens were isolated from Lepidium sativum. The amount of β-sitosterol was estimated to be about 0.20% w/w for seed powder and 0.024% w/w for callus powder of Lepidium sativum. Daidzein and formononetin were also isolated from the samples of Lepidium sativum [36].

Lepidium sativum ethanolic extract contained total phenolics 4.46±0.14 to 11.03±0.75 mg GAEE/g dw plant material and flavonoids of 3.57±1.2 to 4.79±0.24 mg QE/100 g dw plant material. Phenolics identified in the ethanolic extract of Lepidium sativum were kaempferol, coumaroyquinic acid, p-coumaroy glycolic acid and cafic acid [37-38]. The isoflavonoids: 5,6-dimethoxy-2',3'-methyleneoxy-7'-β-D-glucopyranoside, 5,6-dimethoxy-2',3'-methyleneoxy-lsosfalone were isolated from Lepidium sativum [39].

The seeds of Lepidium sativum also contained dimeric imidazole alkaloids, lepine B, C, D, E and F and in semipaludosine A and B [40]. Fractionation of the glucosinolate contents of the seeds of Lepidium sativum revealed the isolation of glucotropaeolin and 2-Phenyl ethyl glucosinolate, while, fractionation of the glucosinolate contents of the fresh herb revealed the presence of 2-ethyl butyl glucosinolate, methyl glucosinolate, butyl glucosinolate and glucotropaeolin [41].
The percentage yield of total alkaloid in the Lepidium sativum seeds was 0.23% w/w. GC-MS analysis revealed identification of 15 compounds in total alkaloidal extract of Lepidium sativum seeds. The compounds were: 3-hydroxy-1-propene-1,1,2-trimethylhydrazine (0.3%), 1-(1-adamantyl)-3-(1-piperidinyl)-1-propanone (6%), 1-hydroxy-2,2-dimethylhydrazine (0.3%), and 1-(2-ethyl-2-methylhydrazinyl)-2-methylhydrazine (0.3%). The petroleum ether extracts of Lepidium sativum showed the highest zone of inhibition against Streptococcus mutans (31 mm) followed by Pseudomonas aeruginosa (17 mm), Candida albicans (15.5 mm), Staphylococcus aureus (15 mm) and Escherichia coli (12.5 mm). The ethanol extract showed greater zone of inhibition against Pseudomonas aeruginosa (18 mm). Hexane extract showed the greatest zone of inhibition against Candida albicans (16 mm).

The antimicrobial activity of the petroleum ether, methanol and water extracts (2.5, 5 and 10%) of Lepidium sativum seed extracts was tested against Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa and Candida albicans. The petroleum ether extracts of Lepidium sativum seeds in different concentrations showed antimicrobial activity against all the tested microorganisms with strong anti-Candida activity at the concentration of 2.5 and 10%. Staphylococcus aureus and Candida albicans were resistant to 2.5 and 5% water extracts, whereas Candida albicans was also resistant to 5% methanolic extract.

Lepidium sativum seed oil extracted by soxhlet and maceration was evaluated against Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Candida albicans and Aspergillus flavus. Lepidium sativum seed oil extracted by soxhlet showed no activity at these concentrations. At 15 μg/ml both samples were partially active against Klebsiella pneumoniae. The soxhlet sample also exhibited partial activity against Bacillus subtilis at a concentration of 10 and 50 μg/ml, while the oil extracted by soxhlet showed no activity at these concentrations. At 50 μg/ml both samples were partially active against Klebsiella pneumoniae. The soxhlet sample also exhibited partial activity against Bacillus subtilis at a concentration of 10 and 50μg/ml, while the macerated sample was inactive at these concentrations. Both samples were inactive against Staphylococcus aureus.

Methanol and ethyl acetate extract of the seeds of Lepidium sativum showed significant antibacterial activity against Rhodococcus equi [27].

The methanolic extract of Lepidium sativum seed was studied at different concentrations (10, 30, 60 and 90 μg/ml) against human pathogenic and opportunistic fungi (Aspergillus flavus, Aspergillus fumigatus, Candida albicans, Staphylococcus aureus, Bacillus subtilis, Candida albicans and Aspergillus flavus). The Aspergillus fumigatus was the most sensitive fungi, it inhibited at 30 μg/ml. Rhizopus sp. showed slow and weak growth on 30 μg/ml and 60 μg/ml slant and was completely inhibited at 90 μg/ml. At a concentration of 90 μg/ml, Aspergillus fumigatus, Candida albicans, Fusarium sp. and Penicillium sp. were completely inhibited.

The antifungal activity of the ethanolic extract of Lepidium sativum seeds (2-8 μg/ml) was evaluated against Fusarium equisetum, Aspergillus flavus and Alternaria alternata. The diameter of the inhibition zone ranged from 4 to 22 mm against the tested fungi [19].

**Hypoglycemic effects**

The hypoglycemic effect of the aqueous extract of Lepidium sativum seeds (20 mg/kg, orally for 16 d) was investigated in normal and streptozotocin-induced diabetic rats. Administration of the aqueous extract of Lepidium sativum seeds caused a significant reduction in glucose, creatinine, and alkaline phosphatase levels. Elevated cholesterol level was restored approximately to normal and a significant decrease in malondialdehyde levels was also observed compared to diabetic controls.

The hypoglycemic activity of the methanol extract (three concentrations for four weeks) of Lepidium sativum seeds was tested.
in alloxan-induced diabetic male rats. Treating of diabetic rats with *Lepidium sativum* methanol extract decreased blood sugar and restored all biochemical and histological changes to the normal [48]. The antidiabetic effect of *Lepidium sativum* seed alkaloid (50, 150 and 250 mg/kg, ip for 21 d) was studied in alloxan-induced diabetic rats. *Lepidium sativum* seed total alkaloid at 250 mg/kg showed 1.94% body weight gain on 21st day relative to 6.14 and 8.93% of control and diabetic group. *Lepidium sativum* seed total alkaloid at the same dose significantly (<0.001) suppressed blood glucose, cholesterol, triglyceride and urea level in diabetic rats [49].

The hypoglycaemic effect of an aqueous extract of *Lepidium sativum* seeds was investigated in normal and streptozotocin-induced diabetic rats. After a acute (single dose, 20 mg/kg) or chronic (20 mg/kg, 15 daily repeated administration) orally, the extract significantly decreased blood glucose levels in STZ diabetic rats (p<0.001); and normalised the blood glucose levels after 2 w daily oral administration of the extract (p<0.001). A significant reduction on blood glucose levels was noticed in normal rats after both acute (p<0.001) and chronic treatment (p<0.001) [50].

The mechanism underlying the hypoglycaemic activity of the aqueous extract perfusion of *Lepidium sativum* was studied in normal and streptozotocin-induced diabetic rats. The aqueous extract at a dose of 10 mg/kg/h reduced blood glucose levels and increased glycosuria in normal (p<0.001) and diabetic rats (p<0.001). Oral administration of aqueous extract for 15 d normalized glycaemia (p<0.001), enhanced glycosuria (p<0.05) and decreased the amount of urinary TGF-beta (p<0.01) in diabetic rats [51].

**Reproductive effects**

The effect of tocopherol extracted from *Lepidium sativum* seeds on the fertility was studied in the adult male rabbit. The results showed a significant increase (p<0.05) in testicular sperm concentration, epididymus sperm concentration and in the sperm count per ml of the tests, sperm motility percent, grade activity, sperm viability percent, with a decrease in abnormal sperm morphology percent [52].

The possible protective effects of *Lepidium sativum* seed extract (200 and 400 mg/kg, orally) on fasting blood sugar and on the histopathological change of epididymis were studied in streptozotocin-induced diabetic rats. Administration of 200 and 400 mg/ml doses of *Lepidium sativum* seed extract increased epithelium height and decreased interstitial volume density and fibromuscular thickness significantly. Tubular and lumen diameter did not change significantly in different groups [53].

The effect of *Lepidium sativum* seed ethanol extract (200 and 400 mg/kg, orally) on fasting blood sugar and its protective effect on histopathological changes in the ventral prostate gland were studied in streptozotocin-induced diabetic rats. Administration of the 200 and 400 mg/kg doses of *Lepidium sativum* seed extract increased epithelium height and decreased interstitial volume density and fibromuscular thickness of the prostate significantly [54].

The effect of *Lepidium sativum* aqueous extract on the fertility criteria in males was studied in mice. The aqueous extract was given alone for 2 w, or after sulpiride for 6 w and then with the aqueous extract for 2 w. The results showed that the weight does not change over the first three weeks, but there was a significant increase in body weight at the fourth week. The group treated with both, sulpiride and *Lepidium sativum* aqueous extract showed the higher level of LH, while the group which was treated with *Lepidium sativum* aqueous extract only showed a higher level of FSH. Prolactin showed its lowest level in the group treated only with *Lepidium sativum* aqueous extract. Testosterone showed a higher level in the group treated only with *Lepidium sativum* aqueous extract. Histological sections for the testes in the group treated with *Lepidium sativum* aqueous extract only showed normal appearance of seminiferous tubule with presence of high number of sperms, sulpiride hyperprolactinemic mice testis showed partial degeneration and damage of dispersed spermatogonia cells with still presence of sperms inside the lumen with certain morphological abnormality in the shape of the sperms. Sections of treated mice testis showed a look like normal shape and structure of seminiferous tubules with the presence of normal morphology shape sperms in the lumen [55].

However, the effects of aqueous extract of *Lepidium sativum* seed on the development and magnitude of surge releases of GnRH, LH, FSH, testosterone secretion and spermatogenesis were studied in rat. Rats that received *Lepidium sativum* extract showed no changes in hormonal status and reproductive organs histology. The author concluded that there was no conclusive data for the aphrodisiac claims. There is a paucity of information on of *Lepidium sativum* seed effects on female reproductive function. *Lepidium sativum* seed has been shown in females to act as a galactagogue, abortifacient and contraceptive [56].

The effect of methanolic extract (200 and 400 mg/kg for 21 d) of seeds of *Lepidium sativum* was studied on preoptic and receptive behaviors of ovariectomized female Wistar rats. On 11th and 21st day, each female was tested in estrous phase for their sexual behavior in the copulatory test. Behavioral estrus was induced by subcutaneous administration of 25 μg estradiol benzoate 48 h prior to behavioral testing and 500 μg of progesterone 5 h before testing. As a measure of proceptivity, the number of hops, darts, ear wiggling and solicitations made by methanolic extract treated female rats were significantly increased when compared against control estrus females. Lordosis quotient, as a measure of receptivity, was unaffected by doses of methanolic extract [57].

However, the effects of dietary supplementation of *Lepidium sativum* seed powder (0%, 5%, 7% and 10% w/w) on growth performance and gonadotropins secretion were studied in ovariectomized, estradiol implanted rats. Feed intake was significantly (p<0.05) increased in *Lepidium sativum* seed powder supplemented group, but its didn't increase body weight gain. *Lepidium sativum* seed powder supplementation significantly (p<0.001) increased mean plasma LH, dose-dependent from low to the mid-*Lepidium sativum* seed powder level and then decreased LH at the high-*Lepidium sativum* seed powder level. *Lepidium sativum* seed powder supplementation increased (p<0.001) plasma FSH secretion [58].

**Gastrointestinal effects**

The aqueous-methanolic extract of *Lepidium sativum* seeds (30 and 100 mg/kg possessed atropine-sensitive prokinetic and laxative activities in mice, which were partially sensitive to atropine. In isolated gut preparations of mouse and guinea-pig, aqueous-methanolic extract (0.1-1 mg/ml) caused a concentration-dependent stimulatory effects both in jejunum and ileum, which was blocked by atropine. In rabbit jejunum, the stimulant effect of aqueous-methanolic extract remained unchanged in the presence of atropine, pyrilamine or SB203186, while in rabbit ileum, the stimulatory effect was partially blocked by atropine. The aqueous-methanolic extract was more efficacious in gut preparations of a rabbit than in guinea-pig or mouse. The physicochemical analysis of the plant extract revealed that it consisted of alkaloids [59].

The diarrheal activity of the methanolic extract of *Lepidium sativum* was investigated in three experimentally induced diarrhoea models (castor oil-induced diarrhoea; prostaglandin E2; induced enteropooling in rats and charcoal meal test in mice). In castor oil induced model, the methanolic extract (50, 100 and 200 mg/kg, po) showed the significant dose-dependent reduction of cumulative wet fecal mass. In PG-E2 induced enteropooling model, the methanolic extract (50, 100 and 200 mg/kg, po) inhibited PG-E2 induced secretions. In charcoal meal test, the methanolic extract (50, 100 and 200 mg/kg, po) decreased the movement of charcoal, indicating its antimotility activity [60].

The seed extract of *Lepidium sativum* at 100 and 200 mg/kg inhibited castor oil-induced diarrhea in rats. In isolated rat ileum, the seed extract (0.01-5 mg/ml) reversed carbachol (1 μM) and K+ (80 mM)-induced contractions with higher potency against carbachol. Preincubation of rat ileum with a lower concentration of seed extract (0.03 mg/ml) caused a rightward parallel shift in the concentration-response curves of carbachol without suppression of the maximum response, while at the next higher concentration (0.1 mg/ml) it produced a non-parallel rightward shift with suppression of the maximum response. The seed extract shifted the
concentration-response curves of Ca⁺⁺ to the right with suppression of the maximum response. Accordingly, *Lepidium sativum* seed extract possessed antidiarrheal and spasmodic activities mediated through dual blockade of muscarinic receptors and Ca⁺⁺ channels [61].

The antidiarrheal and antispasmodic activities of the crude extract of *Lepidium sativum* were further studied using in vivo and in vitro experiments. The crude extract inhibited castor oil-induced diarrhea in mice at 500 and 1000 mg/kg (three times higher dose than for rats). In isolated rat ileum and jejunum, crude extract completely inhibited carbachol, low K⁺ (25 mmol) and high K⁺ (80 mmol)-induced contractions while in Guinea-pig tissues, crude extract caused complete inhibition of only carbachol-induced contraction. In rabbit tissues, crude extract completely inhibited carbachol and low K⁺-induced contractions sensitive to K⁺ channel antagonists. Pretreatment of Guinea-pig and rat tissues with crude extract caused a rightward shift in carbachol-induced contractions, while in rabbit and rat tissues, crude extract shifted isoprenaline curves. The results indicated that the antidiarrheal and antispasmodic activities of *Lepidium sativum* mediated through activation of K⁺ channels, and inhibition of muscarinic receptors, Ca⁺⁺ channels and PDE enzyme [62].

Clinical isolates of *H. pylori* were tested in vitro for susceptibility to ethanolic extract of *Lepidium sativum*. The ethanol extract exerted antibacterial activity against *H. pylori* isolates. MIC value was 15-29 mm for concentrations of 100,000, 50,000 and 25,000 µg/ml respectively [63].

**Respiratory effects**

The ethanolic extract of seeds of *Lepidium sativum* and its fractions (ethyl acetate, n-butanol and methanol) were tested for bronchodilatory effect against histamine and acetylcholine-induced acute bronchospasm in Guinea pigs. The ethanolic extract and its fractions exhibited significant protection against bronchospasm induced by histamine and acetylcholine, while, n-butanol fraction induced significant (p<0.001) protection comparable to ketotifen (1 mg/kg) and atropine sulphate (2 mg/kg) [64].

The anti-asthmatic effect of *Lepidium sativum* seed powder (1 gm thrice a day orally) was investigated in patients of mild to moderate bronchial asthma. The respiratory functions (FVC, FEV1, FEF25-75% and MVV) were assessed using a spirometer prior to, and after 4 w of treatment. Efficacy of the drug in improving clinical symptoms and severity of asthmatic attacks was evaluated by interviewing the patient and by physical and hematological examination at the end of the treatment. For 4 w of treatment with the drug showed significant improvement in pulmonary functions and in clinical symptoms and severity of asthmatic attacks. None of the patients showed any adverse effect with *Lepidium sativum* [65].

The crude extract of *Lepidium sativum* inhibited carbachol (1 µM) and K⁺ (80 mmol) induced contractions in Guinea pig tracheal ring strips, in a pattern similar to that of dicyclocline. The crude extract at 0.03 mg/ml produced a rightward parallel shift of carbachol curves, followed by a nonparallel shift at higher concentration (0.1 mg/ml), suppressing maximum response, similar to that caused by dicyclocline. Pretreatment of tissues with crude extract [0.1-0.3 mg/ml] shifted Ca⁺⁺-concentration-response curves to right, as produced by verapamil. The crude extract at low concentrations (0.03-0.1 mg/ml) caused a leftward shift of isoprenaline-induced inhibitory Ca⁺⁺-concentration-response curves, like that caused by rolipram, a phosphodiesterase inhibitor. Accordingly, the results indicated that the bronchodilatory effect of *Lepidium sativum* was mediated by anticholinergic, Ca⁺⁺-antagonist and phosphodiesterase inhibitory pathways [66].

**Anti-inflammatory, analgesic and antipyretic effects**

The activities of the optimized LSP extract of *Lepidium sativum* were tested in an in vivo endotoxin shock induced in mice with a single E. coli ip injection. Septic mice showed a substantial rise in the levels of TNF-α in plasma, whereas mice treated with *Lepidium sativum* polysaccharides (LSP) after E. coli injection showed considerable lower plasma levels of TNF-α (p<0.05), which indicated the beneficial effects of LSP when administered to mice with endotoxin shock by diminishing the pro-inflammatory response [67].

Modulatory effects on lipid composition, spleen lymphocyte proliferation and inflammatory mediators (such as nitric oxide and leukotriene B4) were possessed by α-linolenic acid-rich *Lepidium sativum* seed oil (2.5, 5 and 10 %, w/w, for 8 w) in rats [68].

Denaturation of tissue proteins is one of the well-documented causes of inflammatory and arthritis diseases. The protein denaturation bioassay was used for in vitro assessment of the anti-inflammatory property of methanol extract of *Lepidium sativum* seeds. The methanol extract of *Lepidium sativum* seeds exhibited a concentration-dependent inhibition of protein (albumin) denaturation throughout the concentration range from 25 to 1000 µg/ml [69].

The ethanolic extract of *Lepidium sativum* seeds was studied for anti-inflammatory, antipyretic, and analgesic activities. The extract significantly inhibited carrageenan-induced paw edema in rats. It also significantly inhibited the yeast-induced hyperpyrexia in mice. The mean predrug rectal temperature in yeast-induced fevered mice was 37.13±0.05 °C. The administration of extract reduced the temperature to 36.60±0.04, 36.66±0.05 and 36.52±0.07 °C at 30, 90 and 150 min following the treatment respectively. Administration of *Lepidium sativum* extract (500 mg/kg) also significantly prolonged the hot plate reaction time. The ethanolic extract of *Lepidium sativum* seeds which possessed anti-inflammatory, antipyretic and analgesic activities also exacerbated indomethacin-induced gastric mucosal damage. The coagulation studies showed a significant increase in fibrinogen level and an insignificant decrease in prothrombin time, confirming its coagulating property [15].

The antinociceptive effect of the aqueous extract of *Lepidium sativum* (20 mg/kg orally) was investigated using acetic acid-induced writhing test and hot plate test in mice. The aqueous extract showed significantly (p<0.05) analgesic activity evidenced by an increase in the reaction time by hot plate method and significant (p<0.05) reduction in acetic acid-induced writhings in mice with a maximum effect of 27% reduction [70].

In a clinical trial, the seeds (6 gm divided in two doses daily, orally) were evaluated for the management of osteoarthritis. The patients were subjected to the evaluation of cardinal signs and symptoms on the basis of scores according to their severity, frequency and duration before and after treatment. Seeds showed considerable improvements in cardinal signs and symptoms like pain in joints, swelling, stiffness, crepitus, tenderness and difficulty in movement (30% complete remission, 57.5% marked improvement, 25% moderate improvement, and only 7.5% didn’t improve)[71].

**Cardiovascular and diuretic effect**

The ethanolic extract of the seeds of *Lepidium sativum* (10-20 mg/kg, iv) caused marked rise in blood pressure of anesthetized cats and dogs, with slight transient (0.5-1 min) respiratory stimulation. The extract was not potentiated or depress the pressor responses of adrenaline and carotid occlusion. The extract caused marked increase in the rate and force of auricular and ventricular movements of open chest cat heart preparation. The cardiac stimulatory effect was also observed on isolated rabbit aortae [72, 73].

The antihypertensive effect of the aqueous extract of *Lepidium sativum* was studied in normotensive and spontaneously hypertensive rats. Daily oral administration of the aqueous extract (20 mg/kg for 3 w) caused a significant decrease in blood pressure (p<0.01) in hypertensive rats, which no significant change in normotensive rats during the period of treatment. The systolic blood pressure was decreased significantly from the 7th day (p<0.05) to the end of treatment (p<0.01) in hypertensive rats. No significant changes were recorded on heart rate after the aqueous extract treatment in hypertensive and normotensive rats. The diuretic effect of the aqueous extract of *Lepidium sativum* was studied in normotensive and spontaneously hypertensive rats. The aqueous extract enhanced significantly the water excretion in normotensive rats (p<0.001) but not in hypertensive rats. Furthermore, oral administration of the aqueous extract at a dose of 20 mg/kg produced significant increase of urinary excretion of sodium.
Antioxidant activities with IC\textsubscript{50} of 6.25 mg/ml [78].

The diuretic effect of aqueous and methanol extracts of the dried seeds of \textit{Lepidium sativum} (orally, 50 and 100 mg/kg) was investigated in normal rats. Urine volume and the excretion of sodium were significantly increased by the two doses of aqueous and methanol extracts, while, potassium excretion was only increased by the aqueous extract at a dose of 100 mg/kg. The extracts caused no significant change in the conductivity and pH of urine [75].

Antioxidant activity

The antioxidant content and activity of the methanol extract of \textit{Lepidium sativum} subsp. \textit{spinenses} was investigated in vitro. The extract contained high amounts of phenolic and flavonoid compounds and showed significant antioxidant activity [76].

The antioxidative effects of the ethanolic extract of \textit{Lepidium sativum} shoot, leaf, and stem were studied against DPPH, total glutathione S-transferase, and reduced glutathione activities. The extract had a significant ability to reduce the activity of the total glutathione S-transferase enzyme, which was more in seed (9600±56.3 μg/ml) than other plant parts. The reduced glutathione content of the ethanolic extracts of \textit{Lepidium sativum} was more in leaf (950.2 μg/ml). In the reducing power assay, ethanolic extracts showed the most potent reducing ability [77].

The antioxidant activity was also correlated to the total phenolic content of the seed [79].

The protective effects

The hepatoprotective effect of \textit{Lepidium sativum} ethanol extract (150 and 300 mg/kg) was assessed by \textit{D}-galactosamine-induced/lipopolysaccharide liver damage model in rats. The extract possessed marked amelioration of hepatic injuries by attenuation of serum and lipid peroxidation. The extract also significantly down-regulated the D-GalN/IPS induced pro-inflammatory cytokines TNFα and IL-6 mRNA expression in a dose-dependent fashion and up-regulated the IL-10. It also possessed hepatoprotective activity by down-regulating mRNA expression of iNOS and HO-1. MPO activity and NF-κB DNA-binding effect were mitigated by the extract dose-dependently [84].

The cytotoxic activity of \textit{Lepidium sativum} seed (100, 200, and 400 mg/kg, once daily for 7 consecutive days) was studied against colon tetrachloride-induced acute liver injury in rats. Pretreatment with the ethanolic seed extracts significantly reduced the level of serum alanine transaminase, aspartate transaminase, alkaline phosphatase and bilirubin, which was increased significantly in colon tetrachloride intoxicated group. Histological analysis of liver tissues in groups pretreated with the ethanolic seed extracts showed mild necrosis and inflammation of the hepatocytes compared to the intoxicated group [85].

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Three isoflavonoids (5,6-dihydroxy-2',3'-methyleneoxy-7-6-d-gluc-pyranosyl isoflavone, 7-hydroxy-4',5,6-trimethoxyisoflavone and 7-hydroxy-5,6-dimethoxy-2',3'-methylenediisoflavone) isolated from \textit{Lepidium sativum} were evaluated for their ability to reduce the hepatotoxicity induced by paracetamol in male rats. Isoflavonoids possessed hepatoprotective effects by reducing the damage and toxicity with a significant improvement of total antioxidant capacity and normalizing the levels of liver enzymes GSH, SOD, GPX, CAT and GST compared to control group [39].

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chloroform extract at 25 μg/ml concentration significantly inhibited the induction of reactive oxygen species generation (45%) and lipid peroxidation (56%), and increases the mitochondrial membrane potential (55%) and reduced glutathione levels (46%) [87].

The effects of aqueous extract of Lepidium sativum (200 and 400 mg/kg, po) against nephrotoxicity induced by doxorubicin was investigated in rats. The serum urea and creatinine levels in the doxorubicin treated group was significantly elevated (P<0.001), while it was significantly reduced in the Lepidium sativum aqueous extract treated groups. The renal antioxidant enzymes such as superoxide dismutase, catalase activities and level of reduced glutathione were declined and the level of malondialdehyde was elevated in the doxorubicin treated group. The activities of superoxide dismutase, catalase and level of reduced glutathione were elevated and level of malondialdehyde declined significantly in the Lepidium sativum plus doxorubicin. Histopathologically, Lepidium sativum markedly ameliorated doxorubicin-induced renal tubular necrosis [88].

The nephroprotective and nephroprotective activity of 200 mg/kg ethanolic extract of Lepidium sativum seed was investigated against cisplatin-induced nephrotoxicity. A single dose of cisplatin-induced loss in body weight, increase urine excretion and increased serum urea and creatinine. These effects were significantly reduced by 200 mg/kg in curative and protective groups. The malondialdehyde, superoxide dismutase, catalase and reduced glutathione level were significantly elevated by 200 mg/kg in curative and protective groups. The level of brush border enzymes like Na+/K+ATPase were significantly reduced after single dose cisplatin injection and significantly elevated by treatment in curative and protective groups [89].

The protective effect of 5% and 10% of Lepidium sativum seeds powder was studied in acute renal failure in male albino rats. The results showed that feeding acute renal failure with seeds powder at 5% and 10% in curative and protective groups improved the body weight gain, feed intake and feed efficiency ratio. The diet fortified at 5% and 10% seeds powder helped to improve blood lipid levels as well as reducing hazards on kidney and liver function compared with positive control groups (injected with cisplatin, which were considered as a major risk factor for renal failure disease). Histopathologically, kidney of rats in curative and protective groups fed on basal diet containing seeds powder at 10% showed mild proximal tubules cell necrosis and minimal interstitial inflammation [90].

The chemoprotective effect of Lepidium sativum and its constituents, glucotropaeolin and benzylisothiocyanate (a breakdown product of Lepidium sativum), towards 2-amino-3-methyl-imidazo[4,5-f] quinoline-induced genotoxic effects and colonic preneoplastic lesions was investigated in single cell gel electrophoresis (SCGE) assays and in aberrant crypt foci (ACF) experiments. Pretreatment of F344 rats with either fresh Lepidium sativum juice (0.8 ml), glucotropaeolin (150 mg/kg) or benzylisothiocyanate (70 mg/kg) for three consecutive days caused significant (p<0.05) reduction in 2-amino-3-methyl-imidazo[4,5-f] quinoline (90 mg/kg, 0.2 ml corn oil/animal)-induced DNA damage in colon and liver cells in the range of 75-92%. Chemical analysis of Lepidium sativum juice showed that benzyl isothiocyanate didn’t account for the effects of the juice, as its concentration in the juice was found to be 1000-fold lower than the dose required to cause a chemoprotective effect. Lepidium sativum juice and benzylisothiocyanate did not affect the activity of cytochrome P450A12, glutathione-S-transferase significantly, Lepidium sativum juice caused significant (p<0.05) increase in the activity of hepatic UDPGT-2. In the aberrant crypt foci assay, 2-amino-3-methylimidazo[4,5-f] quinoline was administered by gavage to 10 alternating days in corn oil (dose 100 mg/kg). Five days before and during 2-amino-3-methylimidazo[4,5-f] quinoline treatment, subgroups received drinking water which contained 5% Lepidium sativum juice. The total number of 2-amino-3-methylimidazo[4,5-f] quinoline-induced aberrant crypts and ACF as well as ACF with crypt multiplicity of >or =4 were reduced significantly (p<0.05) in the group that received 2-amino-3-methyl-imidazo[4,5-f] quinoline plus Lepidium sativum juice compared with the group that was fed with 2-amino-3-methyl-imidazo[4,5-f] quinoline only [91].

### CNS activity

The effect of total alkaloid from seeds of Lepidium sativum (50, 150 and 250 mg/kg, ip) on body weight, food intake and feed efficiency ratio. The diet fortified at 5% and 10% seeds powder helped to improve blood lipid levels as well as reducing hazards on kidney and liver function compared with positive control groups [89].

#### Hypolipidemic effects

The total cholesterol, triacylglycerol and alanine transaminase (ALT) activity were increased significantly in the rats fed with high cholesterol diet as compared to the control group. Lepidium sativum reduced total cholesterol and ALT; however, higher dose (6 g/kg diet) was found better than lower dose (3 g/kg diet) in reducing serum triacylglycerol. Histopathological findings revealed that liver of cholesterol-fed rats showed varying degrees of vacuolar degeneration, fatty changes, fatty cysts, and lobular disarray. Livers of the Lepidium sativum-treated rats showed mild to moderate degree of recovery [93].

The effects of Lepidium sativum extract (20 mg/kg, orally for 4 w) on the blood glucose and lipid profile were studied in hypercholesterolemic rats. Lepidium sativum treated group showed a significant lower value of plasma glucose 30%, cholesterol 22%, triglycerides 25%, LDL 23% and increase in HDL 32% [94].

### Effect on fracture healing

The effect of Lepidium sativum seeds on fracture healing was investigated in fractures induced in the midshaft of the left femur of adult New Zealand White rabbits. The rabbits were fed soon after surgery with Lepidium sativum seeds mixed with their normal diet, whereas no seeds were given to the control group. X-rays of the induced fractures were taken at 6 and 12 w postoperatively to assess the healing of the fractures; furthermore the callus formation in millimeters at the longitudinal medial, longitudinal lateral and circumferential areas were also investigated. The test group had a statistically significant increase in the healing of fractures compared with the control group (p<0.001 for longitudinal medial/6 w; p<0.004 for circumferential, and p<0.043 for longitudinal medial/12 w) [95].

### Side effects and toxicity

The administration of the ethanolic extract of Lepidium sativum seeds in single doses of 0.5 to 3.0 g/kg did not produce any adverse effects or mortality in mice. The acute and subchronic toxicity of Lepidium sativum seeds was studied in adult Wistar rats. The acute toxicity study, 0.5–5.0 g/kg bw of the seed powder was administered through diet to rats, and obvious symptoms of toxicity and mortality were monitored for 72 h. Acute doses of seed powder did not induce any symptoms of toxicity or mortality in rats. In subchronic toxicity study, 1.0–10.0% of the seed powder was administered to rats through diet for 14 w. Dietary feeding of seed powder did not produce any mortality, no significant changes in food intake, gain in body weight, the relative weight of organs and hematological parameters, microscopic, and microscopic changes in vital organs, were observed between experimental and control groups. Enzymes (LDH and SGPT) were within normal levels; however, the serum ALP and SGOT were significantly increased in male rats receiving 5.0 and 10 % of seed powder [96].

Lepidium sativum seed fed to Wistar albino rats at 2% (w/w) was non-toxic, 10% (w/w) was toxic but not fatal and 50% (w/w) of the diet for 6 w was lethal and caused depression in growth rate and enterohepato-nephrotoxicity. Organ lesions were accompanied by anemia and leukopenia and were correlated with alterations in
serum AST and ALT activities and concentrations of total protein, cholesterol, urea, and other serum constituents [97].

Water suspension of seed powder of Lepidium sativum (2, 4, 8 g/100/ml) in male rats for 3 and 6 w increased total serum protein, albumin was increased at the high dose group, and AST and GGT were within normal levels. ALT and ALK were significantly increased after 3 w in males receiving 2 and 4 g/kg, respectively. Liver parenchyma showed vascular dilation with congestion of central and portal veins in low doses (2 and 4 mg/ml) for 3 w, high doses given for 3 w showed perportal fibrosis and perivascular edema. Bile duct proliferation was a prominent feature in the specimens of Lepidium sativum treated animals [98].

The possible adverse effect of alcoholic extract of seeds of Lepidium sativum and Lepidium sativum seed oil on HepG2 cells, a human liver cell line was studied. Cells were exposed to 25 to 1000 μg/ml of alcoholic extract of seeds of Lepidium sativum and Lepidium sativum seed oil for 24 h. The results show that the extracts reduced cell viability and altered the cellular morphology in dose-dependent manner. They were also induced oxidative stress in dose-dependent manner indicated by decrease in glutathione level, catalase activity, and SOD activity and an increase in lipid peroxidation [99].

In the study of the acute and chronic effects of 15% of Lepidium sativum seed supplementation on gross organ morphology and histomorphometric indices in rats, it appeared that Lepidium sativum seed increased renal weight in the treated group. Histological analysis showed a significant change in the diameter of the Bowman’s capsule, glomerulus and Bowman’s space in the treated group. There was also an increase in glomerulosclerosis, metaplasia and hyperplasia in rats fed 15% of Lepidium sativum seed. In the proximal and distal tubules, there was a significant increase in tubular degeneration throughout the experiment. These results paired together show a significant toxic effect for rats fed 15% Lepidium sativum seed [56].

The effects of an aqueous Lepidium sativum seeds extract on the immune system and general health was studied in mice. An aqueous extract of ground Lepidium sativum seeds was orally gavaged to young adult male Swiss albino mice at a low dose (0.5 ml) and a high dose (1 ml) daily for 19-21 d. The results show that Lepidium sativum seeds extract caused statistically significant increases in the mean white blood cell count and mean spleen weight in low dose group; however, for the high dose group, the increases tended to be more significant. The mean body weight for the high dose group showed clear increases compared to the control. The mean of white blood cell types; red blood cell, and platelet counts; mean hemoglobin concentration; mean total body gases; and weights of the organs (except for the spleen) were not significantly different for the low dose and high dose groups compared to the control [100].

One gram of Lepidium sativum seed powder/thrice a day for four weeks in asthmatic patients produced no adverse effect in all treated patients [65].

The oil extracted from the plant was edible and was used as a cooking medium, some people may experience symptoms of indigestion due to its use. However, consuming of large quantities of the plant caused digestive difficulties in some people. Furthermore, it contained goitrogens that prevent iodine absorption in thyroid and can lead to hypothyroidism. It should be avoided by patients of hypothyroidism.

It was an abortifacient; pregnant women should avoid taking the plant in any form because it induce uterine contractions and triggered spontaneous abortion [24-25].

CONCLUSION

The current review discussed the chemical constituents, pharmacological effects and therapeutic importance of Lepidium sativum as a promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

There is no conflicts of interest. I am, alone responsible for the content and writing of this article.

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