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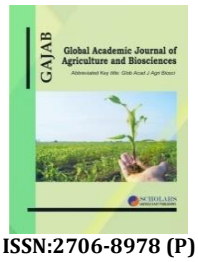

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Review Article

Phytochemical Profile of *Eruca sativa* and Its Therapeutic Potential in Disease Prevention and Treatment

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Abstract: *Eruca sativa (E. sativa)*, commonly known as arugula, salad arugula, or simply arugula, is an annual plant species belonging to the *Brassicaceae* family. This leafy vegetable is widely cultivated for its edible leaves, characterized by a distinctive peppery flavor. The seeds are used for their rich fatty acid oils. This botanical specimen has been incorporated into various forms of traditional medicinal practices such as anti-inflammatory, depurative, diuretic, digestive, aphrodisiac, and rubefacient effects. The plant contains various bioactive compounds, including antioxidants, vitamins, minerals, carotenoids, glucosinolates, and flavonoids. This vegetable's broad therapeutic potential and diverse components are under ongoing research, enhancing our understanding of its medicinal properties. This review explores the phytochemical components of *E. sativa* and its efficacy in treating various diseases, offering a summary of its medicinal properties. Furthermore, it emphasizes the plant's importance in human health and suggests potential directions for future research in natural medicine.
Keywords: *Eruca Sativa*, Arugula, Phytochemical Composition, Disease Prevention, Disease Treatment.

BACKGROUND

The nutraceutical contents of the *Brassicaceae* family members have led to a significant increase in their consumption over the past few decades. These nutraceutical compounds exert beneficial effects on human health, having potential in both disease treatment and prevention [1]. Historically it has been cultivated in countries and regions bordering the Mediterranean Sea, its use dates back to the Roman era when the herb was often employed as an aphrodisiac [2]. *E. sativa* seed oil is composed of constituents like fatty acids i.e. palmitic, stearic, oleic, linoleic, linolenic, eicosanoid, and erucic acids [3]. It has multiple purposes including the treatment of digestive problems, as a tonic for hair loss, and as an ointment for skin burns and eye infections [4]. *E. sativa* flowers have been shown to be a promising feedstock for bioactive compounds [5]. *E. sativa* is considered the main source of phenylethyl isothiocyanate, which is the compound that gives the plant its characteristic peppery flavor [6]. Traditional medicine has given *E. sativa* several medicinal qualities throughout more than 20 centuries, including antiphlogistic, depurative, diuretic, digestive, aphrodisiac, and rubefacient effects [7]. This plant is valued as oilseed, forage, fodder, condiments, and vegetable crops through the use of different parts of the plant such as buds, inflorescences, leaves, roots, seeds, and stems, *E. Sativa* extracts and oils contain a wide variety of health-promoting phytochemicals, vitamins, carotenoids, Fibers, minerals, glucosinolates, isothiocyanates, flavonoids such as kaempferol, quercetin, and isorhamnetin, flavonols, and phenolic compounds [7-9]. These compounds present antimicrobial, anti-secretory, anti-ulcer, cytoprotective, neuroprotective, anti-inflammatory,

and potent antioxidant properties [10]. Owing to its widespread consumption and diverse range of therapeutic constituents, this vegetable has stimulated ongoing research, advancing our understanding of its components and their potential to alleviate various ailments. This review systematically evaluates the phytochemical constituents of *E. sativa*, highlighting its therapeutic efficacy across diverse diseases.

Phytochemical Content

Eruca sativa possesses a diverse array of chemicals and minerals that exhibit both nutraceutical and organoleptic properties. This plant is recognized for harbouring a variety of phytochemicals, including flavonoids, phenolic acids, terpenes, carotenoids, tannins, glycosides, saponins, sterols, alkaloids, and other secondary metabolites [11].

Vitamins

Brassicaceae family members are recognized for their abundant content of vitamins, such as carotenes, tocopherols, vitamin C, and folic acid [12]. Arugula serves as a rich source of vitamins A, C, and K, as well as thiamine, riboflavin, niacin, vitamin B-6 (pyridoxine), and pantothenic acid [13].

Carotenoids

β-carotene presence has been detected in arugula [14]. Total carotenoids in the *E. sativa* range vary with lutein as the main carotenoid component of the plant [15].

Minerals

The rich mineral and electrolyte components of *E. sativa* are attributed to its consumption as a low-calorie vegetable [14]. It contains Calcium, Copper, Iron, Magnesium, Manganese, Phosphorus, Selenium as well as Zinc [4].

Polyphenols

Arugula is recognized for its substantial concentration of phenolics, which are plant secondary metabolites renowned for their antioxidant properties. These compounds have undergone extensive research due to their potential positive impacts on human health. The exploration of their effectiveness in preventing and treating diseases induced by oxidative stress has been the subject of thorough investigation [16]. Flavonoids are one of the most common and widely distributed groups of plant phenolics [17].

Fatty Acid Composition

Erucic acid, a significant industrial compound, is notably abundant in Eruca sativa, positioning this species as a promising candidate for industrial cultivation. The substantial presence of erucic acid renders it unsuitable for use as a culinary oil due to its unpalatable flavor and its association with cardiac concerns. Notably, erucic acid is at times employed as an adulterant in rapeseed or mustard oils. Leveraging its biodegradable property, the crude oil from the plant serves as a feasible alternative to mineral oil in various industries. The overall oil content of the plant is 35%, and its fatty acid composition includes a notable concentration of erucic acid [18].

Glucosinolates

Glucosinolates (GSLs), alternatively referred to as (Z)-N-hydroximinosulfate esters, represent secondary metabolites found in *Brassicaceae* and plants belonging to the Brassicales order. These compounds consist of a shared glycone unit and a diverse aglycone side chain (R) originating from amino acids [19]. Glucosinolates can undergo hydrolysis, resulting in a diverse range of products. These products include isothiocyanates (ITC), nitriles, epithionitriles, hydroxynitriles, oxazolidine-2-thiones, thiocyanates, and indoles [20].

Medicinal and Biological Roles of *E. Sativa*

***E. Sativa* and Anti-Inflammatory**

Upon tissue damage by infective agents and/or toxins, the body's defensive responses are activated causing inflammation in the tissue to eliminate the causative agents and heal it. When inflammation persists longer than necessary, it may be destructive. Specifically, the nervous system when compared to other types of tissues is considered to be more sensitive to inflammation, given its limited regeneration capacity. Neuroinflammation has been linked with different disorders, including neurodegenerative diseases [21, 22]. Several distinct mechanisms contribute to neuronal degeneration and death following neuroinflammation, including the release of different cytokines by activated microglia and the infiltration of the central nervous system by immune cells from the periphery [21]. In a study exploring the anti-inflammatory potential of *E. sativa* seed extract on NSC 34 motor neurons exposed to the medium from lipopolysaccharide-stimulated RAW 264.7 macrophages, increased apoptosis and heightened expression of Toll-like receptor 4 and cyclooxygenase 2 (COX2) in treated NSC 34 motor neurons was observed. This stimulation also resulted in the upregulation of NLR family pyrin domain-containing 3 (NLRP3) inflammasome proteins and the production of pro-inflammatory cytokines. Consequently, this indicates that *E. sativa* seed extract may possess anti-inflammatory properties [23].

***E. Sativa* and Antibacterial**

The capacity of microorganisms to genetically transfer and acquire resistance to

antibiotics has emerged as a significant global health challenge. Consequently, there has been a scientific imperative to explore novel drug candidates derived from plant sources [24]. All the investigated extracts of *E. sativa* exhibit relevant antibacterial activity [24]. The extract derived from its flowers has demonstrated its effectiveness as an antibacterial agent, exhibiting inhibitory effects against both Gram-positive and Gram-negative bacteria. Remarkably, it displayed a higher growth inhibition compared to the antibiotic penicillin when tested against pathogenic strains [5]. The seed oil has demonstrated the highest growth inhibition against all considered antibiotic-resistant bacteria, with a maximum zone inhibition of 97% observed for Gram-positive bacteria, while Gram-negative bacteria exhibited inhibition ranging from 74% to 97%. Thus, it establishes that *E. sativa* seed oil holds significant promise in exerting antimicrobial effects against antibiotic-resistant strains of both Gram-negative and Gram-positive bacteria. The documented antimicrobial potential of the seed oil validates its traditional use in addressing skin infections, fever, urinary infections, and diarrhoea. The presence of bioactive isothiocyanates and a relevant quantity of free erucic acid justifies its antibacterial activity [24]. Furthermore, it clarified that this oil had an approximately equivalent activity concerning the broad-spectrum antibiotic Gentamicin [8]. Eruic acids, found in high concentrations, are accountable for antibacterial activity that could be applied in drug production [25].

E. Sativa and Antioxidant

Antioxidants obtained from plants constitute a diverse range of natural products known for their ability to reduce or scavenge radicals. Given their powerful preventive and therapeutic properties, these compounds acquire significant interest from scientists, pharmacologists, and physicians alike [26]. Glucoerucin, along with its metabolite erucin found in the plant is capable of efficiently breaking down hydrogen peroxide and alkyl hydroperoxides, serving as a preventive antioxidant that scavenges peroxides [27]. The leaf extract of *Eruca sativa Mill*. Demonstrated antioxidant activity across various *in vitro* systems, while the glucosinolate fraction specifically exhibited the ability to chelate Fe2+. Both the extract and glucosinolate fraction displayed a notable cytoprotective effect, along with the suppression of intracellular reactive oxygen species production, in human peripheral blood mononuclear cells [28]. The extract from *E. sativa* flowers demonstrates potent antioxidant properties. The assessment of its antioxidant activities involved conducting tests such as the DPPH free radical scavenging assay, total antioxidant activity evaluation, and the β-carotene bleaching test [5]. The seed extract is rich in phenolics, which are recognized as natural antioxidants due to their ability to scavenge free radicals or exert a quenching effect [29].

E. Sativa and Anticancer

Research has been conducted to establish supporting evidence indicating that increased consumption of cruciferous vegetables is linked to a reduced risk of cancer in humans [30]. *E. sativa* possesses effective active constituents that could be useful in enhancing human well-being and serving as a preventive measure against cancer [31]. Isothiocyanates, one of the many compounds in arugula is classified as organosulfur compounds, it exhibits anticarcinogenic, anti-inflammatory, and antiproliferative activities [32]. An experiment exploring the role of arugula showed that seed oil enriched with isothiocyanates stood out as the sole *E. sativa* preparation capable of significantly reducing melanoma in vivo, requiring a dosage only twice as large as the effective dose of the reference drug doxorubicin [24]. Isothiocyanate inhibits tumour growth either by generating reactive oxygen species or by inducing cell cycle arrest, ultimately leading to apoptosis [33].

E. Sativa and Antiulcer

E. sativa extract has demonstrated anti-secretory, cytoprotective, and anti-ulcer activities against experimentally induced gastric lesions, the traditional uses of this salad herb introduced a novel therapeutic approach for addressing gastric ailments [34]. The traditional use of *E. sativa* for its antiulcer effect finds scientific support in its ability to significantly reduce urease activity. Helicobacter pylori, implicated in ulcer pathogenesis, relies on high urease activity for metabolism and colonization in gastric mucosa. The observed reduction in urease activity upon *E. sativa* extract application provides scientific validation for its utilization as an antiulcer agent [35]. The precise mechanism(s) responsible for this antiulcerogenic effect are still not fully elucidated, but the extract comprises substances that could potentially enhance endogenous prostaglandins thus, it most probably results from prostaglandin-mediated activity and/or through the combination of anti-secretory and antioxidant properties (34). The crude extract and fractions of *E. sativa* exhibited a significant reduction in urease activity in vitro. This study offers scientific validation for the traditional uses of the plant in the treatment of ulcers, confirming its efficacy in addressing this medical condition [36].

E. Sativa and Cardiovascular System

The intake of green leafy vegetables has been linked to a diminished risk of cardiovascular diseases [37, 38]. *E. sativa* extract demonstrates anti-ischemic effects, consistent with other Brassica extracts

known for their protective effects against oxidative stress on cardiomyocytes [39]. The aerial parts extract of *E. sativa* induced endothelium-mediated vasorelaxation under normotensive conditions, likely attributed to the activation of muscarinic receptors. Conversely, in hypertensive conditions, an endothelium-independent vasorelaxation was observed [40]. The cardiovascular benefits observed, aside from isothiocyanates derived from glucosinolates (GSL), may be attributed to the presence of flavonoids and phenolic acids in the *E. sativa* defatted seed meal extract. Markedly, luteolin and sinapic acid are particularly relevant among these components. Recent research has shown that luteolin can induce cardioprotective effects both *in vitro* and *in vivo* by activating Nrf2 and inhibiting the NF-kβ pathways [41]. Luteolin has additionally been documented as cardioprotective through the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt pathway. It is capable of enhancing the phosphorylation of phospholamban (PLB) and sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), thereby safeguarding the heart against acute myocardial ischemia–reperfusion injury [42]. Sinapic acid has been accredited in vitro and in vivo as an antioxidant and cardioprotective agent, particularly exhibiting protective effects against ischemia–reperfusion injury [43]. In a cell-free model, the defatted seed meal extract of *E. sativa* gradually released hydrogen sulfide (H_2S) [38].

E. Sativa and Hepatoprotective

Liver diseases persist as a significant health challenge. Despite considerable advancements in conventional medicine, there are currently no efficient remedies that can enhance liver functions, provide safeguarding against damage, and promote the regeneration of hepatic cells [44]. A diverse number of vegetables, herbs, and medicinal plants are often suggested for addressing liver disorders [45]. Liver toxicity is associated with free radicals, which can either bind to proteins or abstract hydrogen atoms from unsaturated lipid molecules. This process accelerates lipid peroxidation, leading to a toxic effect. It has been noted that the administration of *E. sativa* in male rabbits enhances the activities of alanine aminotransferase and aspartate aminotransferase, possibly due to the high sulfur content in it, aiding in the expulsion of body wastes. *E. sativa* leaves and seeds have been found to significantly restore non-protein sulfhydryl levels in liver tissue. This restoration may play a supportive role in liver and immune function. The potential hepatoprotective activity of ethanolic arugula extract may be attributed to the suppression of the cytochrome P450 oxygenase enzyme system. Additionally, glucoerucin, the major glucosinolate in arugula, exhibits both direct and indirect antioxidant actions. These actions, coupled with the properties of hydroperoxide and H2O2 decomposition, contribute to the potential protective effects on the liver [46, 47].

E. Sativa and Nephroprotective action

Given the significant role of oxidative stress in mercury chloride ($HgCl_2$) induced nephrotoxicity, substances possessing antioxidant properties are anticipated to protect against it [48, 49]. The ethanolic extract derived from *E. sativa* seeds has demonstrated significant capabilities in scavenging free radicals and providing protection against renal toxicity induced by $HgCl_2$. The study indicates that $HgCl_2$-induced nephrotoxicity involves oxidative stress in its mechanism. Seed extract exhibited robust free radical scavenging, antioxidant, and nephroprotective properties. It effectively maintains and enhances the levels of antioxidant molecules and enzymes in the kidney, protecting kidney tissues from oxidative damage. The observed free radical scavenging ability of the *E. sativa* seed extract is likely responsible for its nephroprotective effects modulated through the presence of various polyphenols, including glucoerucin and flavonoids, in the alcoholic extracts [50]. Correspondingly, another study indicates that *E. sativa* seed extract and rutin have beneficial effects on health by reducing gentamicin, an antibiotic, induced nephrotoxicity in rats. These natural substances exhibit potential in alleviating the negative consequences linked to gentamicin usage, suggesting their possible use as therapeutic agents or supplements for the prevention and treatment of nephrotoxicity [51]. Additionally, the aqueous extract of *E. sativa* has been shown to effectively prevent nephrocalcinosis in rabbits by inhibiting the formation and deposition of calcium oxalate crystals in renal tissues. This preventive action is attributed to the diuretic effect of arugula, which promotes the alkalization of urine. The enhanced deposition of calcium oxalate crystals in acidic urine is counteracted by the alkalizing effect of *E. sativa*. Moreover, it is rich in magnesium, which may play a role in reducing free oxalate levels in the intestine and urine. This reduction in free oxalate availability diminishes its capacity to bind to cations in renal tubules, thereby suppressing the formation of calcium oxalate crystals. In summary, the multifaceted properties of *E. sativa*, including its diuretic effect, urine alkalization, and magnesium content, collectively contribute to the prevention of nephrocalcinosis by impeding the formation and deposition of calcium oxalate crystals in the kidneys [50-53].

E. Sativa and Antidiabetic

Clinical studies have confirmed the effectiveness of certain plant extracts in addressing oxidative stress associated with diabetes mellitus (DM). In research investigating the potential of *E. sativa* seed oil (ESS) in preventing and treating

experimentally induced DM using alloxan injection. Alloxan administration resulted in reduced insulin levels, hyperglycaemia, elevated lipid levels, and increased markers of oxidative stress in the liver. This oxidative stress was associated with decreased glutathione (GSH) content and superoxide dismutase activity in the liver of alloxan-diabetic rats. ESS oil, administered alone, significantly increased hepatic GSH levels. Daily oral administration of ESS oil, either before or after diabetes induction, mitigated hyperglycaemia, improved lipid profiles, and reduced oxidative stress markers in the liver of alloxan-treated rats. Thus, the findings suggest that ESS oil could be a potential complementary treatment for diabetes, attributed to its antioxidative properties and its ability to increase hepatic GSH levels [54]. Additional studies investigating the role of *E. sativa* seed oil on diabetic rats induced by streptozotocin exhibit potent antihyperglycemic and antihyperlipidemic effects. Elevated glucose levels lead to the generation of reactive oxygen species (ROS) through processes like autoxidation, glucose metabolism, and advanced glycosylation end-product formation [55, 56].

CONCLUSION

E. sativa emerges as a powerhouse of diverse medicinal properties with significant implications for human health. The vegetable exhibits anti-inflammatory and neuroprotective effects, offering potential interventions in conditions associated with prolonged inflammation, particularly within the sensitive nervous system. Its antibacterial activities, demonstrated against both Gram-positive and Gram-negative bacteria, underscore its role as a promising natural alternative in combating antibiotic resistance. Its antioxidant capabilities, attributed to compounds like glucoerucin and isothiocyanates, position it as a valuable resource for mitigating oxidative stress and preventing related disorders. Its anticancer properties, especially in inhibiting tumour growth through isothiocyanates, contribute to the growing body of evidence linking cruciferous vegetables to a reduced risk of cancer. Furthermore, arugula demonstrates antiulcer effects, providing a novel approach to addressing gastric ailments and validating its traditional use. The cardiovascular benefits of *E. sativa*, supported by its anti-ischemic effects and vasorelaxation properties, align with the broader association between green leafy vegetables and a reduced risk of cardiovascular diseases. Its antiplatelet and antithrombotic activities contribute to preventing thrombus formation without an increased risk of bleeding. The hepatoprotective effects of *E. sativa*, attributed to its antioxidant actions and impact on the cytochrome P450 enzyme system, suggest potential applications in liver health. Additionally, it exhibits nephroprotective actions, guarding against renal toxicity induced by oxidative stress, highlighting its multi-faceted role in safeguarding various organ systems extracts. In the realm of diabetes, *E. sativa* shows promise as an adjunctive treatment, with studies indicating its ability to mitigate hyperglycaemia, improve lipid profiles, and counteract oxidative stress associated with diabetes mellitus. These findings collectively emphasize the potential of *E. sativa* as a versatile medicinal resource, offering a holistic approach to address a spectrum of health issues. As research in this field continues, further exploration of its medicinal attributes may unveil additional therapeutic applications, reinforcing its status as a valuable component of natural medicine.

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Authors Contribution:

All writers participated in the composition, with Dilveen Ahmed responsible for the Background and References section. Rondik Naif, Evan Omer, and Payman Saleem collaborated on the Biological Roles and Conclusion. Basim Ahmed conducted a thorough review of the manuscript before its submission.

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