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Ethnomedicinal uses, phytochemical, pharmacological and pharmacokinetics properties of Cumin (*Cuminum cyminum*)

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ABSTRACT

A well-known plant for its distinctive scent is cumin [*Cuminum cyminum* Linn.]. It is a herbaceous annual plant in the Umbellifereae family. Many traditional cuisines have been prepared with cumin seeds as a spice or a key component. In various cultural contexts in the Middle East, cumin has also been said to have significant culinary and therapeutic purposes. The chemical make-up, nutritional value, ethnomedical applications, and traditional usage of cumin seeds were all covered in this review. The review discussed the isolated and discovered bioactive components evaluated and validated therapeutic qualities in addition to describing the pharmacological properties of cumin based on publications that are currently accessible. The most current research on drug bioavailability, pharmacokinetics, and potential negative effects are also reported.

Keywords: *Cuminum cyminum* Linn., Umbellifereae, Ethnomedicinal, Pharmacological properties, Pharmacokinetics.

INTRODUCTION

An annual herb, Cumin (*Cuminum cyminum* Linn.), is a member of the Umbellifereae plant family. It is well renowned for its preventive, medicinal, and dazzling scent qualities. The plant is native to the Mediterranean region of the world, where it is widely planted [1], though it is primarily grown in Egypt. On fertile loam soil in warm, moderate climates, cumin grows and blooms beautifully. The plant is grown from seedlings. When fully grown, cumin can reach a height of around 0.5 metres and develop numerous branches and stem extensions. The plant's leaves have a dark green appearance. When the blossoms, which are typically white in colour, start to turn yellow and then start to fade and the seed colour changes to brown, the plant is ready for harvest [1].

Oblong in shape and brown in colour, cumin seeds have been used for a long time in the production of many traditional meals, either whole or ground. For instance, in India, the seeds are used as a spice and in the manufacture of soup mixes as well as other regional foods. Cumin is still a key ingredient in many Asian dishes, despite the fact that the majority of people classify the seed as a spice. In addition to the seeds' use as a culinary additive and spice, researchers have discovered specific uses for them in conventional and pharmaceutical medicine [2]. The plant's increasing relevance can be observed in its persistent demand and low production and supply levels [3]. Farmers incur crop losses every year as a result of insect and disease effects, with Fusarium wilt disease being the most common of these diseases [4]. There have been reports of the plant's use in the creation of traditional and indigenous medicine. For instance, the plant has long been used in India by the Ayurvedic medical system to cure a variety of illnesses, including dyspepsia, diarrhoea, and digestive abnormalities [5].

Oil from Egyptian cumin seeds has reportedly been found to have 39.2% cumin aldehyde [6]. Probably as a result of cumin aldehyde's presence, cumin oil possesses excellent antifungal capabilities. According to research, the seeds promote bile acid elimination and activity [7]. In addition, it has observed to stimulate pancreatic activity in laboratory rats and to increase the activity of digestive enzymes in the small intestine, including amylase, trypsin, and lipase [8]. Rats allegedly had a much shorter time for food to pass through their digestive tracts after ingesting roughly 1.25% of cumin seeds [9]. Broiler weight gain was dramatically accelerated by adding cumin seeds to the diet. Additionally, the presence of significant amounts of dietary fibre resulted in improved absorption of meals [10].

Although cumin was initially grown in Egypt, it is currently grown throughout much of Asia, including China, India, and other Middle Eastern nations. Cumin has reportedly had significant culinary and therapeutic purposes throughout history in a variety of Middle Eastern cultural contexts. The Christian

Holy Book includes historical references to cumin, primarily as a method of paying tithes required by the law to the Levitical Priesthood [11]. It was employed in ancient Egypt as an ingredient in the preservation and embalming of pharaohs. It is employed as a seasoning in the preparation of regional specialities in the ancient Greek and Roman kitchens. The reason for its popularity, pervasiveness, and wide acceptability was due to its peppery and spicy flavour, which has made it a suitable substitute for black pepper, which is typically expensive and hard to come by. Cumin has fantastic medicinal and aesthetic properties and can be used to fake pallor.

Chemical Constituents:

The region of growth and cultivation, also known as agronomic circumstances, the developmental stages of harvest, the extraction procedure, and the solvent, among many other factors, all have an impact on the chemical makeup of various plants. The main biological effects and aroma of cumin essential oils are caused by aldehyde, methane derivatives, terpinene, *p*-cymene, and pinene [12, 13]. Understanding the makeup of C. cyminum seeds and essential oil has been a major focus of numerous scholarly research projects [14, 15]. According to the reports, the seeds include fixed oil (about 10%), volatile oil (1–5%), protein, cellulose, sugar, and minerals. Very little is known about how climatic and agronomic factors affect the physiologically active chemicals found in *C. cyminum* L. [16]. The medicinal advantages of cumin bioactives have been the focus of intense research. Although cumin seeds' therapeutic processes and modes of action are yet unknown, there is undeniable proof of their prospective benefits as a workable therapy. In fact, further research should be done to determine whether there is a connection between the chemical makeup of cumin seeds and its historical use as a medicine. Cumin seeds are highly nutrient-dense; they include significant levels of fat (particularly monounsaturated fat), protein, and dietary fibre. Cumin seeds also contain significant amounts of iron, a number of nutritional elements, including vitamins B and E. Terpenoids, cymene, and cumin aldehyde are the principal volatile components of cumin [17]. The flavour of cumin is extremely pungent. Its essential oil content is what gives it a warm scent. Cumin aldehyde and cuminic alcohol are the primary aromachemicals in it. The substituted pyrazines 2-ethoxy-3-isopropylpyrazine, 2-methoxy-3-*sec*-butylpyrazine, and 2-methoxy-3-methylpyrazine are additional significant fragrance components of roasted cumin. Safranal, *p*-cymene, *α*-pinene, and *α*-terpinene are additional ingredients [18]. *Cuminum cyminum* included alkaloids, anthraquinones, coumarins, flavonoids, glycosides, proteins, resins, saponins, tannins, and steroids, according to phytochemical study. From the seeds of *C. cyminum*, organic acids including aspartic, citric, malic, tartaric, propionic, ascorbic, oxalic, maleic, and fumaric acids were extracted [19]. 10% fixed oil and 2.5 to 4.5% volatile oil were present in cumin fruits [20]. According to the region where the *C. cyminum* samples were collected, it seemed that the essential oil's chemical composition varied. Cumin aldehyde (19.25-27.02%), *p*-mentha-1,3-dien-7-al (4.29-12.26%), *p*-mentha-1,4-dien-7-al (24.48-44.91%), -terpinene (7.06-14.10%), *p*-cymene (4.61-12.01%), and -pinene (2.98-8.90%) were the main constituents in the Turkish cumin seed oil. The main components of Syrian cumin were found to be cumin aldehyde, *o*-cymene, limonene, and -pinene [21]. Cumin aldehyde (35.25%), tetradecene (12.25%), *α*-terpenene (12%), *α*-ocimene (9.72%), *p*-mentha-2-en-ol (9%), *α*-terpinyl acetate (5.32%), -terpinolene (3%), limonene (0.5%), myrcene (0.2%), *α*-pinene (0.9%), and -pinene Cumin aldehyde (39.48%), gamma-terpinene (15.21%), *O*-cymene (11.82%), *γ*-pinene (11.13%), 2-caren-10-al (7.93%), trans-carveol (4.49%), and myrtenal (3.5%) were the main components of the cumin variety from Tunisia [14]. Analysis of the *C. cyminum* fruit oil from Delhi revealed that transdihydrocarvone (31.11%), -terpinene (23.22%), *p*-cymene (15.8%), *α*-phellandrene (12.01%), and *p*-menth-2-en-7-ol (3.48%) were the main ingredients, with cumin aldehyde making up only 0.58% [22, 23]. 20 compounds were identified by Romeilah et al. [24, 25] from the *C. cyminum* seeds oil. Additionally, 14 free amino acids and steroidal constituents were extracted from the seeds. While apigenin-7-glucoside, luteolin-7-glucoside, luteolin-7-glcuronosyl glucoside, luteolin, and apigenin were among the flavonoid glycosides identified from the plant [26, 27]. From the seeds of *C. cyminum*, polyphenols [28], phenols (such as salicylic acid, gallic acid, cinnamic acid, hydroquinone, resorcinol, *p*-hydroxybenzoic acid, rutin, coumarin, and quercetin) were extracted [29]. However, the total phenolics, flavonoids, and tannin concentrations of *C. cyminum* roots, stems, leaves, and flowers were examined. Gallic acid equivalents per gramme of dry weight (mg of GAE/g of DW) for all organs ranged from 11.8 to 19.2 mg. Thirteen of the polyphenols under investigation were found in the roots, 17 in the stem and leaves, and 15 in the flowers. Quercetin (26%) was the primary phenolic constituent in the roots, whereas *p*-coumaric, rosmarinic, *trans*-2-dihydrocinnamic acids, and resorcinol predominated in the stems and leaves. Vanillic acid made up 51% of the compounds in the flowers [30]. During the ripening of cumin seeds, a total of 19 phenolic components were effectively identified. While p-coumaric acid predominated in half-ripe and fully-ripe seeds, rosmarinic acid was the dominant phenolic acid in unripe seeds [31].

Composition of volatile oil:

Cumin's essential oil composition is influenced by a variety of elements, including the maturity stage of the seeds from which oil is extracted, the extraction technique, the cultivars used, the region of origin, and the storage conditions [32]. Cumin seeds can be steam-distilled to produce 2.5–4.5% volatile oil, which is colourless or pale yellow when it is extracted and turns dark when stored in an ambient environment. The yield is influenced by the seed's age and quality because older seeds have less oil. It has been claimed that quantitative steam distillation of cumin oil [2.5% in 4 hours] is faster than liquid carbon dioxide extraction (4.5% for 2 hours at 58 bar pressure and 20°C), without losing the active flavour components [33]. Cumin aldehyde is present in 62.7% of the volatile oil from Mexico compared to 47.4% and 43% in samples from the Mediterranean and India, respectively [34]. The aldehyde found in cumin seeds, specifically cumin aldehyde, which makes up roughly 20–40% of the oil, is primarily responsible for the spice's distinctive aroma. Other substances include *p*-cymene, terpinene, sabinene, geraniol, citronellol, safranal, germacrene, *p*-mentha-1, 3-dien-7-al, and p-mentha-14-dien-7-al. The volatile oil must meet the following specifications: be colourless or pale yellow, have a specific gravity of 0.905-0.925 at 25°C, a specific rotation of 3 to 8 at 20°C, and have a cumin aldehyde content of 40-52% [35]. Several techniques, including SCFE, OS-SD, HD, SD, SWE, Sx Ex, and MWE, have been used to isolate the chemical makeup of cumin seed essential oil [36]. GC and GC-MS were used to characterise the volatile oils from cumin seeds that were extracted by HD [37]. In comparison to the oxygenated components, the essential oil produced by the SWE technique was more valuable [38]. Cumin fruits' essential oils had antibacterial efficacy against both gramme positive and gramme negative bacteria after being extracted by HD. The genera that cause plant and cultivated mushroom diseases, including *Clavibacter*, *Curtobacterium*, *Rhodococcus*, *Erwinia*, *Xanthomonas*, *Ralstonia*, and

Agrobacterium, showed very significant antibacterial activity. Lower activity was shown against bacteria from the genus *Pseudomonas*, though [39]. By using two distinct methods (namely, peroxide value and thiobarbituric acid value), the antioxidant activity of extracts from cumin seed from Gorakhpur (India) was assessed and shown to be efficient in linseed oil. *Curvularia lunata* and *Fusarium monoliforme* both showed 100% antifungal activity in response to the volatile oil. *Aspergillus ochraceus*, *Aspergillus flavus*, and *Pencillium citrinum mycelia* growth was found to be 85% controlled by the acetone extract [40]. Cumin volatile oil has the potential to be used in food preservation due to its radical scavenging and antioxidant characteristics, which have been examined using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay and the *β*-carotene bleaching test [37]. Following the separation of the essential oil, the wasted cumin was examined for a variety of enzymatic activities and antioxidant activity. The outcome suggests that used cumin may be used to make a variety of health food formulations that are more easily digestible and have a favourable nutritional profile [41].

Traditional and ethnomedical uses of *C. cyminum:*

Cumin is a multipurpose plant that is used both as medicine and food in many different parts of the world. In the creation of other cuisines, such as soup, bean dishes, pickles, cheese, and liquors, it is also employed as an additive and spice [42, 43]. For instance, cumin is a highly well-liked spice all across the world and is a key condiment spice in India [44]. After black pepper (Piper nigrum), cumin-based spices are thought to be the second most consumed spices worldwide [45]. *C. cyminum* seeds are traditionally used for the treatment of a wide range of illnesses, including toothaches, dyspepsia [44], diarrhoea, epilepsy, and jaundice [46]. Strong bioactives and biochemicals like terpenes, phenols, and flavonoids are what give them such a significant therapeutic potential. Cumin seeds are used in traditional medicine as a carminative and appetite stimulant, as well as a stomachic, astringent remedy for diarrhoea and to enhance taste [47].

The powder or decoction of cumin seeds has been used in many Maghreb nations, including Algeria, Morocco, and Tunisia, to cure digestive issues. As a stomachic, carminative, antispasmodic, and anthelmintic, it is advised. Additionally, cumin has frequently been applied externally as a poultice to treat acute viral inflammations like neck mumps [48]. Additionally, Indian herbalists frequently recommend cumin for the treatment of fever, colds, and sleeplessness. The fruit of the plant has been used extensively in ancient Iranian medicine to treat a variety of ailments, including treatment of toothaches and epilepsy [49]. Cumin has also reportedly been used frequently to cure dyspepsia, diarrhoea, and jaundice in Ayurvedic medicine (the traditional Indian medicine). Growing research suggests that the plant material has beneficial anti-inflammatory, diuretic, and hypoglycemic properties [50]. Colic, gas, and diarrhoea are also relieved by the tonic and stimulating effects of cumin [51]. It has been demonstrated to improve lactation, lessen morning sickness while pregnant, and can be used as a poultice to alleviate breast or testicular edoema [52].

Green cumin is a significant medicinal and aromatic plant with therapeutic properties, including antimicrobial [37, 53], antioxidant [37, 54], antitumor [55], anti-nociceptive, anti-inflammatory [55], epileptic activity [49], and hypoglycemic effect [44]. Cumin seeds (*C. cyminum* L.) are extensively used as a spice because of their characteristic aroma, but they are also frequently used in traditional medicine to cure a number of illnesses. The biological and medicinal effects of cumin are well documented in the literature, and are typically attributed to its bioactive ingredients such terpenes, phenols, and flavonoids [16]. Below, we describe the health benefits of cumin seeds that have been scientifically proven.

Pharmacological effects of *C. cyminum:*

Numerous pharmacological benefits of *C. cyminum* (Cumin), including anti-inflammatory, anti-diabetic, antioxidant, neuroprotective, and chemopreventive properties, have been identified (Figure 1).

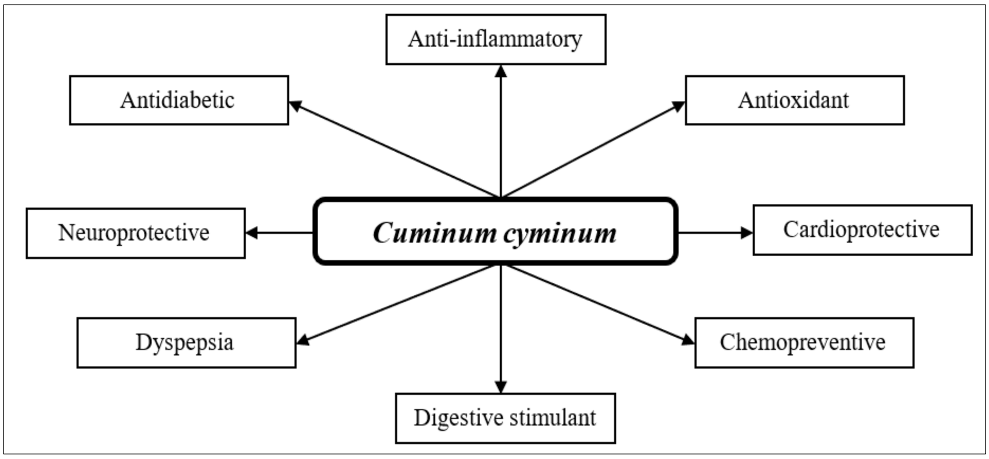

Figure 1: Schematic presentation of pharmacological potential of cumin

Antibacterial Activity

A drug that kills or prevents the growth of microorganisms like bacteria, fungus, or protozoa is known as an anti-microbial [56]. According to technical definitions, antibiotics are only those chemicals produced by one bacterium that may either kill or stop the growth of another [57]. Of fact, in modern parlance, the term "antibiotic" refers to practically any medication that aims to clear your body of bacterial infection. Antimicrobial substances include both synthetically created compounds and antibiotics [14]. Plant essential oils are renowned for their antibacterial properties and may be able to prevent plant illnesses brought on by bacteria, especially those that originate in seeds [58]. Due to their accessibility, lack of side effects or toxicity, and superior biodegradability in comparison to currently available antibiotics and preservatives, natural products have recently attracted increasing interest [59]. Due to public interest in natural food items and growing worries about microbe resistance to conventional preservatives, the study of naturally-occurring antimicrobials for food preservation is receiving more attention [60]. Besides having an antibacterial action, cumin includes fatty oils. There are many inhibitory effects of cumin in powder suspension [61]. A cumin seed oil extract improved cell shape, capsule expression, and reduced urease activity while inhibiting the development of *Klebsiella pneumoniae* and its clinical isolates [62]. In contrast, limonene, eugenol, α-pinene, and a few other minor elements have been proposed to contribute to the antibacterial action of cumin oil [63]. This feature was linked to cumin aldehyde, carvone, limonene, and linalool. Numerous antibacterial activities of cumin seed oil have been discovered [64]. According to reports, *Escherichia coli*, *Bacillus brevis*, and *Enterobacter aerogenes* are all susceptible to the cumin hydrosols. Additionally, rosemary essential oil was found to have weaker antibacterial properties than cumin essential oil against *Listeria monocytogenes*, *S. aureus*, and *E. coli* [37]. A natural resistance plasmid DNA from *K. pneumonia* as well as planktonic and biofilm cells have all been tested against the essential oil from cumin seeds [65]. The findings showed that the essential oil reduced biofilm formation, slowed strain development, and worked synergistically to increase ciprofloxacin's effectiveness against *K. pneumonia*.

Antifungal Activity

The in vitro examination of cumin hydrosols against a variety of phytopathogenic fungi revealed encouraging antifungal properties [66]. In contrast to other commercial items, commercial samples of cumin were uncontaminated by aflatoxin, a toxin made by *Aspergillus flavus*, according to O'Riordan and Wilkinson [67]. Cumin oil, which is notably high in *α*-pinene [29.2%], has been shown by Mnif et al. [16] to have positive inhibitory effects on the growth of *Aspergillus* strains from several species. Additionally, fluconazole-resistant fungi have been tested against using cumin essential oil.

Antiviral Activity

The MeOH extract of cumin seed shown a considerable antiviral activity when the effects of aqueous, methanolic, and hydroalcoholic extracts of cumin seed on HSV-1 development in a Vero cell line were examined in vitro. For Vero cells, it has a CC_{50} value of 0.45, an IC_{50} value of 0.18, and a therapeutic index of 2.5 mg/ml, respectively [68]. Cumin seed extracts in both aqueous and hydroalcoholic form had no inhibitory impact on HSV-1 [69].

Digestive stimulant

An animal study looked at whether cumin seeds had any stimulatory effects on the digestive enzymes in light of the fact that they are said to help with digestion in traditional medicine and home remedies. Particularly, the effects of continuous dietary consumption and one oral dosage of cumin seeds on the digestive enzymes of the rat pancreas and intestinal mucosa have been studied [7, 70]. Dietary cumin's ability to speed up food transit time is roughly related to the positive effects they have on bile secretion or digestive enzymes.

Antidiabetic effects

It has been observed that giving diabetic rats treated with alloxan an aqueous extract of cumin for six weeks prevented body weight loss and significantly decreased blood glucose and glycosylated haemoglobin. Additionally, it has been noted that the treatment lowers the levels of triglycerides, free fatty acids, cholesterol, and phospholipids in the plasma and tissues of the experimental rats [50]. Cumin has also shown a promising potential for usage as a dietary supplement to guard against diabetic DNA damage and reduce diabetes complications, according to Mnif and Aifa [16]. Human diabetics have claimed that cumin seeds have an anti-diabetic effect [71] In alloxan-diabetic rabbits, *Cuminum nigrum* seeds or their water or methanol extracts have been found to be hypoglycemic [72]. The flavonoid chemicals found in *C. nigrum* seeds have been suggested to have an antihyperglycemic effect [73, 74] When compared to quercetin as an aldose reductase inhibitor and acarbose as *α*-glucosidase inhibitor, cumin aldehyde, an isolated component of *C. cyminum* seeds, exhibits more inhibitory efficacy against Sprague-Dawley rat lens aldose reductase and *α*-glucosidase [75].

Anti-inflammatory and Antioxidant Activity

The anti-inflammatory properties of cumin essential oil in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells and the underlying processes were examined [76]. By employing Gas Chromatography-Mass Spectrometry (GC-MS), volatile components in essential oils were discovered, with cumin aldehyde (48.8%) being the most prevalent. Cumin oil's ability to reduce inflammation was demonstrated in LPS-stimulated RAW cells through its inhibition of NF-B and nitogen activated protein kinases. Numerous studies have been done on the antiradical and antioxidant properties of cumin essential oils. Results from -carotene bleaching tests outperformed those from free radical scan experiments using 2,2-diphenyl-1-picrylhydrazyl (DPPH) [37].

Hypotensive Effect

In renal hypertensive rats, the standardized aqueous extract of *C. cyminum* seeds was tested for its ability to lower blood pressure as well as its effects on inflammation, the production of arterial endothelial nitric oxide synthase, and oxidative stress. Rats were subjected to the two-kidney, one-clip (2K/1C) technique to produce renal hypertension [77].

Hypolipidemic and weight reduction effects

Rats with removed ovaries [OVX] were used to assess the hypocholesterolemic effect of the methanolic extract of *C. cyminum* (MCC). OVX rats received 10 weeks of oral administration of MCC 1000 mg/kg and estradiol benzoate equivalent to 0.15 mg/kg of estradiol. The findings showed that whereas MCC was superior to estradiol in protecting OVX mice from elevated LDL levels brought on by ovariectomy [78]. Taghizadeh et. al [79] studied the effects of *C. cyminum* intake on weight loss and metabolic profiles among overweight subjects by a randomized double-blind placebo-controlled clinical trial.

Cardio-protective influence through hypolipidemic

It was investigated how cumin seed aqueous extract affected arterial-endothelial nitric oxide synthase and its potential anti-hypertensive effects. In renal hypertension rats, expression, inflammation, and oxidative stress have been studied [77]. Cumin seeds contain flavonoids, which are known to have antioxidant action and strengthen the antioxidant system. According to a study, cumin extract boosted the activities of paraoxonase and arylesterase in serum while considerably lowering the amount of oxidised low-density lipoprotein (OxLDL) [80]. Rats' liver and serum cholesterol levels were examined after cumin was introduced to diets that were both normal and hypercholesterolemia-inducing [81]. When dietary cumin was consumed at a level that was about five times the average amount (1.25%), no cholesterol-lowering effects were observed.

Chemopreventive effects

When 2.5 and 5.0 percent dietary cumin were tested against benzo[a]pyrene-induced carcinogenesis in the stomach and 3-methylcholanthrene (MCA)-induced tumorigenesis in the uterine cervix in mice, it showed a substantial effect against the tumour [82]. Cumin exhibits chemopreventive properties. Cumin prevented lipid peroxidation, indicating that its capacity to modify may be responsible for its ability to prevent cancer.

Anticarcinogenic Effect

The protective mucins colon and glucuronide conjugates are hydrolyzed as a result of the activity of -mucinases and glucuronidase being significantly elevated in the presence of the colon carcinogen 1,2-dimethylhydrazine (DMH). Toxins that are released by glucuronide hydrolysis increase the risk of colon cancer. Cumin can protect the colon by reducing mucinase and *α*-glucuronidase activities in the presence or absence of DMH, according to a prior rat model study [83]. A black cumin hexane extract was also shown by Bourgou et al. [84] to be effective against the colon cancer cell line DLD-1 and the tongue cancer cell line A-549, with IC_{50} values of 31.0 and 63.0 mg/ml, respectively. Two-ethyl-6-heptylphenol (EHP), a physiologically active substance isolated with benzene from Egyptian *C. cyminum* seeds, was shown to have good anticancer activity against six different tumour cell lines by Goodarzi et al. in 2009 [85] (HEPG2, HELA, HCT116, MCF7, HEP2, and $CACO_2$). EHP had no cytotoxic effects when its action on the common fibroblast cell lines [BHK] was examined [85]. More recently, Daneshmandi et al. [86] showed that *C. cyminum* essential oil displayed appealing immuno-modulatory capabilities and might therefore be employed as a therapeutic or complementary drug in the treatment of tumours. In fact, it was found that *C. cyminum* essential oils strongly suppressed tumor-cell development when applied at dosages of 50 and 500 mg/ml [86]. The ability of different cumin seed dosages in diets to prevent cancer has also been confirmed. For example, the effects of such diets have been examined in relation to 3-methylcholanthrene [MCA] and benzo[a]pyrene (BaP)-induced uterine cervix and stomach carcinogenesis, respectively [82]. The findings showed that cumin significantly inhibited stomach tumour growth. The nutraceutical potential of spent cumin produced by the Ayurvedic industry was assessed and compared to that of raw cumin in terms of antioxidant (in terms of scavenging DPPH radical), antidiabetic [in terms of better *α*-amylase inhibition and glucose uptake activity in L6 cells), and anticancer properties [87]. The findings indicated that cumin waste-derived nutraceutical food formulations might have a significant impact on the management or prevention of degenerative illnesses.

Ovicidal [Insecticidal] Activity

Cumin essential oil was proven to be an ovicidal agent by having the greatest impact on the destruction of Tribolium confusum and Ephestia kuehniella eggs. The Ephestia kuehniella TL99 (median lethal time) value was 127.0 h at a concentration of 98.5 ml cumin essential oil/lair [88]. In adult male and female *Blattella germanica*, assessed the insecticidal and acetylcholine esterase (AChE) inhibitory activity of cumin and Apicaceae plant essential oils. At a dosage of 5 mg/filter-paper, cumin demonstrated > 90% fumigant toxicity against German adult male cockroaches [89].

4.12 Miscellaneous nutraceutical effects

The seeds of cumin have historically and traditionally been used to alleviate diarrhoea. For instance, castor oil-induced diarrhoea in albino rats was tested against the aqueous extract of cumin seeds (100, 250, and 500 mg/kg) [90].

According to research on the inhibitory effects of *C. cyminum* essential oil on the fibrillation of -SN, cuminaldehyde contained in cumin essential oils can control -SN fibrillation, demonstrating the potential therapeutic uses of such naturally occurring bioactive aldehydes in cumin [20]. Fibrilliation of -SN is a crucial process in the pathogenesis of various neurodegenerative illnesses, including Parkinson's disease.

Protective effects

The impact of cumin on kidney exposure to profenofos was assessed in female swiss albino mice. According to the study's findings, cumin has a moderating influence on both the amount of creatine and uric acid. Rats given 500 mg/kg of paracetamol orally for 4 weeks showed growth retardation, hepatotoxicity, and nephrotoxicity [91]. The impact of cumin on sperm quality and testicular tissue was investigated in mice after experimentally induced copper poisoning (copper sulphate 100 mg/kg). The dosage of *C. cyminum* used was 1 mg/kg. The findings revealed that, in contrast to the control group, the copper group's sperm concentration, motility, and viability dramatically declined at weeks 4 and 6, and severe degenerative alterations were found in the testicular tissues. When compared to the copper group, the cumin-treated group showed a significant improvement in sperm count, motility, and viability as well as normal architecture in the majority of seminiferous tubules with ordered epithelium [92].

Bronchodilatory and Wound-Healing activity

Because previous studies have demonstrated the relaxing effects of 2-stimulatory [93, 94], histamine H1 receptor inhibitory [95], and anticholinergic drugs [96], it is possible that the relaxing effects of various extracts from *C. cyminum* on the tracheal chains of guinea pigs result from a variety of different mechanisms, including stimulation of -adrenergic receptors, inhibition of histamine H1 receptors, or an anticholine. The effects of KCl on calcium channels have been demonstrated [97], and calcium channel blockers have been found to have bronchodilatory effects [98].

Acute inflammation precedes the production of collagen and other intracellular macromolecules, which are then remodelled to form scars during the healing process of a wound [99]. On the wound models of granuloma, incision, and excision in albino rats, extracts and various fractions derived from cumin seeds were tested for their ability to heal wounds [99]. Triterpenes were found to be the primary ingredient in wound healing, according to other investigations [100]. The wound healing activity of cumin seeds can therefore be extrapolated to have been caused by terpenoids in the alcoholic extract and petroleum-ether fraction [101].

Immunological and Anti-amyloidogenic effect

Using flow cytometry and ELISA in healthy and immune-suppressed mice, *C. cyminum*'s health-modifying impacts and immunomodulatory capabilities were assessed. In healthy mice, *C. cyminum* induced the production of Th1 cytokines and T cells. The findings indicated that treatment dramatically raised the number of T cells (CD4 and CD8) and the Th1-dominant immune response in a dose-dependent manner, indicating immunomodulatory activity through modulation of T lymphocyte expression [102]. The active amyloidogenic inhibitors in cumin oil were investigated. Two substances that had extremely similar chemical structures, terpinolene and limonene, prevented fibrillation. HEWL fibrils had an adverse effect on PC12 cells (derived from a transplantable rat pheochromocytoma), whereas inhibited forms of HEWL fibrils in the presence of terpinolene led to higher levels of viability, as shown by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT), lactate dehydrogenase (LDH), and flow Terpinolene was predicted to interact with the protein's flexible cleft via molecular local docking studies. In the hot spot sections of the protein, this contact site was around the tryptophan residues 62 and 63 as well as two additional hydrophobic residues [103].

Contraceptive and Anti-osteoporotic effect

Male albino rats were used to test the effectiveness of *C. cyminum* isolated fractions (CcFr) as a contraceptive. No significant changes in body weight were seen after oral administration of CcFr 50 mg/rat/day for 60 days, but there were clear anomalies in spermatogenesis, as seen by lower numbers in round spermatids, preleptotene spermatocytes, and secondary spermatocytes. A 100% negative fertility result was produced by sperm motility, density, and morphology. Significant declines were observed in testosterone levels. According to the authors' findings, *C. cyminum* can operate as a natural male contraceptive by inhibiting spermatogenesis in rats [104]. Rats were used to test *C. cyminum*'s anti-osteoporotic effectiveness. After receiving bilateral ovariectomies (OVX), adult Sprague-Dawley rats were randomised into 3 groups. More sham operations involved animals. The other two OVX groups received 0.15 mg/kg of estradiol and 1 g/kg of the methanolic extract of *C. cyminum* fruits (MCC) over the course of 10 weeks, whereas OVX and sham control groups received oral administration of vehicle. Animal bones, uteri, and blood were gathered at the conclusion of the study. In compared to OVX control, MCC (1 g/kg, po) considerably raised calcium content and mechanical strength of bones while dramatically reducing urine calcium excretion. In SEM examination, it revealed higher bone and ash densities and enhanced bone microarchitecture. It had no effect on body weight gain or the weight of the atrophic uterus in OVX animals, in contrast to estradiol. MCC had no anabolic impact on an atrophic uterus, but it reversed ovariectomy-induced bone loss in rats [105].

Drug Bioavailability-Enhancing Activity:

Recently, interest in herbal drug interactions has grown. The research offers compelling evidence that these interactions could result in positive outcomes, with drug bioavailability standing out as the most significant one. An approach known as herbal drug synergism has shown cumin to increase the bioavailability of rifampicin, which is very intriguing. In fact, Sachin et al. [106, 107] researched the pharmacological approach in which a drug's bioavailability may be influenced by the synergism of herbal drugs. A pure component isolated from *C. cyminum* and some herbal items were shown to interact pharmacokinetically with RIF in the investigation. The flavonoid glycoside 3',5-dihydroxyflavone 7-*O*-D-galacturonide 4'-*O*-D-glucopyranoside, present in aqueous cumin seed extract, was responsible for significant increase in rat plasma levels of RIF action (CC-I). The C_{max} and AUC [area under the curve] of RIF were found to be improved by 35 and 53%, respectively, by CC-I. The changed bioavailability profile of RIF was determined to be due to the glycoside's capacity to increase permeability [106, 107]. Recent research has demonstrated the critical functions that drug efflux pumps, including P-gp, play in preventing drug entry into the systemic circulation [108]. P-gp is an energy-dependent trans-membrane drug efflux pump that is an ATPase and a member of the ABC transporter family. Its molecular weight is around 170 kDa and it contains 1,280 amino acid residues [16, 109]. Given that it is distributed at the drug absorption site and has a selectivity for substrates, P-gp is becoming increasingly important in the improvement of absorption; however, additional work needs to be done to examine its modulation. Additionally, it has been shown that the bioactive fraction of *C. cyminum* increases the bioavailability of drugs like erythromycin, cephalexin, amoxicillin, fluconazole, ketoconazole, zidovudine, and 5-fluorouracil [110]. Various volatile oils, luteolin, and other compounds have been implicated in *C. cyminum*'s bioavailability and bioefficacy. Luteolin proved to be a potent P-gp inhibitor [16, 111].

Pharmacokinetics:

The investigation of enzymatic hydrolysis of fats and oils as a potential alternative to the current use of high temperature and pressure for the industrial synthesis of fatty acids has been attempted on numerous occasions [112, 113]. Previous research has also shown that cumin seeds are a great source of secondary metabolites, such as polyphenols, which have a wide range of uses in the food industry [114]. Cuminoside A and B [115], 1-*O*-*β*-D-glucopyranoside [115], (1*S*,5*S*,6*S*,10*S*)-10-hydroxyguaia-3,7(11)-dien-12,6-olide *β*-d-glucopyranoside, (1*R*,5*R*,6*S*,7*S*,9*S*,10*R*,11*R*)-1,9-dihydroxyeudesm-3-en-12,6-olide 9-*O*-*β*-D-glucopyranoside, methyl *β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside and ethane-1,2-diol 1-*O*-*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside [116] are among the major secondary metabolites identified from cumin seed.

Side effects and toxicity:

Fleming [117] said that when therapeutic quantities are correctly delivered, there are no known health hazards, toxicity, or side effects related to them. Essential oil LD_{50} in mice was calculated to be 0.59 ml/kg [11]. Male Wistar rats were given *C. cyminum* fruits for six weeks at 2% or 10% of their regular diet. Rats were also given a mixture (5% *C. cyminum* fruits + 5% T. vulgaris leaves) for a comparable amount of time. Rats were not poisoned by diets containing 2% of *C. cyminum* fruits. Rats fed a diet containing 10% of *C. cyminum* fruits showed signs of enterohepatonephropathy and development impairment. The rats fed a combination of the two plants also showed these changes, which were accompanied by leukopenia, anaemia, increases in serum AST activity and urea, as well as decreased levels of total protein and albumin. In a 30-day oral toxicity study in rats, the acute and subchronic toxicity of cumin essential oil was investigated. WBC count decreased by 17.38%, whereas haemoglobin concentration, hematocrit, and platelet count all increased, respectively, by 25.77%, 14.24%, and 108.81%. The LDL/HDL ratio was halved [118].

Modern analytical methods like SIRA, SIM, and measuring optical rotation can be used to detect adulteration of cumin essential oil with synthetic cumin aldehyde [35]. Cumin has not yet been found to have any negative side effects when used whole, processed, or as its essential oil. It is used as a food additive and a medication for aches, fever, worm infestation, diarrhoea, skin conditions, vomiting, inflammation and nausea [119].

Some results demonstrated that the serum level of insulin significantly increased after treatment by green cumin [120]. It was observed that the increased serum levels of insulin depended on the used dose of the green cumin [121].

Dose:

Daily dosage: Typically, a single dose of medication contains 300–600 mg [equivalent to 5-10 fruits]. Yet cumin was utilised both internally and externally, both as a pressed oil and in pulverised form [117]. Cumin oil at a dose of 50 µl/g diet was administered to Swiss mice. A dose of more than 50 µl/g diet was toxic to mice [2]. Özbek et al., [19] examined lethal doses of *C. cyminum* essential oil and fixed oil Lethal doses [ml/kg]. [EO] LD_1 is 0.162, LD_{10} 0.440, LD_{50} 0.780, LD_{90} 1.121, LD_{99} 1.399 [FO] LD_1 is 0.449, LD_{10} 0.655, LD_{50} 1.039, LD_{90} 1.650, LD_{99} 2.404.

CONCLUSION

Cumin (*Cuminum cyminum* Linn.), a herb with a heady aroma, is well-known for its preventative and medicinal uses. Cumin seeds are a common element in cooking or are used as a spice. Cumin has reportedly had vital culinary and therapeutic purposes throughout history in a variety of cultural contexts. Around the world, cumin has been used frequently. Cumin seeds have long been used to alleviate digestive issues in several Maghreb nations. Stomachic, carminative, antispasmodic, and anthelmintic characteristics support this historic use. While in India, cumin has been used to treat fever, colds, and sleeplessness. Cumin seeds are highly nutritious and have a high nutritional value. They offer significant levels of protein, dietary fibre, and fat, particularly monounsaturated fat. Cumin seeds also include a number of minerals, particularly iron, as well as other vitamins like vitamins B and E. Aldehyde, derivatives of methane, terpinene, p-cymene, and pinene make up cumin essential oil. The scent and biological effects of cumin are primarily caused by the elements listed. Numerous studies have demonstrated cumin's antibacterial properties. Against a variety of helpful and harmful microorganisms, the studied extracts and extracted chemicals displayed antibacterial, antifungal, and antiviral activity. Studies on animals have shown that cumin improves digestion. The activity of pancreatic enzymes was discovered to be increased. Additionally, it was discovered that dietary cumin consumption significantly stimulated bile flow rate. Cumin was said to significantly lower blood sugar and glycosylated haemoglobin when taken orally, and it also stopped the body from losing weight. Additionally, it has been noted that the medication lowers the levels of triglycerides, free fatty acids, cholesterol, and phospholipids in the plasma and tissues of the experimental rats. Cumin oil's ability to reduce inflammation was demonstrated in LPS-stimulated RAW cells through its inhibition of NF-B and nitogen activated protein kinases. They also have intriguing antioxidant capabilities. In the current review, additional pharmacological activities including anti-hypertensive, hypocholesterolemic, wound healing, and chemo prevention have been reported. The effectiveness of contraceptives and immune-modulating medications was also covered. The current analysis offers compelling evidence of cumin's positive effects and reports and discusses experimental studies that confirm the results that have been claimed. Finally, cumin has a place in supplementary medicine. As a phytoconstituent in the cosmetic business, it can also be used due to its broad spectrum of biological qualities. But in order to make greater use of this plant, mechanisms and modes of action of cumin still need to be clarified.

Declarations

Ethical Approval

Not applicable.

Competing interests

No potential conflict of interest was reported by the authors.

Authors' contributions

HMS was involved in conceptualization and Methodology; SMLKBB and JNN contributed to investigation and writing—original draft; JNN was involved in project Administration, validation and Writing - review & editing; JPA, JG, VRP and NS contributed to writing - review & editing and GE-S B was involved in methodology, validation and supervision. All authors read and approved the final manuscript.

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