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THE CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EFFECTS OF *CARUM CARVI*- A REVIEW

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ABSTRACT

Carum carvi was used traditionally in different populations for many medical complains. It contained a wide range of chemical constituents. Essential and volatile oils, flavonoids, proteins, carbohydrate and many vitamins and trace elements. The previous studies showed that the seeds of the plant and its constituents exerted antimicrobial, anticancer, antioxidant, hypolipidemic, antidiabetic, analgesic, diuretic, gastrointestinal, bronchial relaxant effects and many other pharmacological activities. This paper is a step ahead to open a new insight for the therapeutic efficacy of *Carum carvi*.

Keywords:

INTRODUCTION

Carum carvi belongs to the family Apiaceae, which originated in Europe, was cultivated nowadays in different parts of the world from Northern Europe to the Western Asia. It was used in folk medicine for the treatment of many complains. The previous studies showed that the plant contained many bioactive metabolites and exerted antimicrobial, anticancer, antioxidant, hypolipidemic, antidiabetic, analgesic, diuretic, gastrointestinal, bronchial relaxant effects and many other pharmacological activities.

Taxonomic classification
Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Apiales
Family: Apiaceae
Genus: *Carum* L.,
Species: *Carum carvi* L [1].

Common names

Arabic: KamunKirmani, Karawya; Deutsch: Kümmel; English: Black Caraway, Caraway; French: Carvi; Hindi: Kalajira; Italian: Carvi; Punjabi: Zira Siyah, Kalajira; Sanskrit: Asitajiraka, Krishna jeeraka; Tamil: Karamjiragam, Shimaishambu; Telugu :NallaJeelakarra; Unani: ZeeraaSiyaah, Kamoon, Kamoon-roomi; Urdu: Kala Zira and KaroJeero, ZiraSiyah [2-3].

Description

Leaves, Stem and Root

Carum carvi is usually a biennial, 30 to 100 cm high plant with a fleshy, fusiform tap root. The stem is erect, angular, grooved, filled with latex, glabrous and branched from the ground up. The rosette leaves and the cauline leaves are glabrous and in part tri-pinnate. The lower pinna are typically crossed. *Flower and Fruit*: The main trunk and the side branches each terminate in a compound flowering umbel of 8 to 16 umbel rays. The epicalyx and calyx are almost non-existent. The florets are white or reddish and very small. The fruit is a schizocarp that is glabrous, oblong and elliptoid. It consists of 2 mericarps that are 3 to 6 mm long, sickle-shaped, brownish with 5 lighter, angular main ribs (caraway seeds) [4].

Distribution

It is native to Europe and West Asia. Now

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cultivated in different parts of the world (from Northern Europe to the Mediterranean regions, Russia, Iran, Iraq, Indonesia and North America)[2,5].

Traditional uses

Caraway was used for gastrointestinal cramps and feelings of fullness, as well as nervous cardiac-gastric complaints, in spasmodic gastrointestinal complaints, flatulence, irritable stomach, indigestion, lack of appetite, dyspepsia in adults, and in relieving flatulent colic of infants. It was also used as tranquilizer, diuretic, emenagogue, and gastric stimulant, aphrodisiac, astringent, in the treatment of morning sickness, headache, to improve liver function, in bronchopulmonary disorders, cough and as an analgesic. Vapor of caraway seeds is used to relief lumbago and rheumatism. The seeds were also used for the treatment of scabies. Caraway was also used to improve lactation in nursing mothers. The essential oil is used as constituent in mouthwashes and bath additives [4, 6-14], and in perfumery, for scenting soap and as a parasiticide [15-17].

It was commonly used as a flavorant in ice cream, candy, meat, cheese, condiments, soft drinks, and alcoholic beverages [18].

Part used

The parts of the plant used medicinally are seeds and the oil obtained from the seeds [4].

Physiochemical parameter

Moisture: not more than10%, total ash on dry mass: not more than8%, acid insoluble ash on dry basis: not more than1.5%, volatile oil content on dry basis, ml/100g: not less than2.5, alcohol-soluble extractive: not less than 2%, water-soluble extractive: not less than 12 % [19-20].

Chemical constituents

Carum carvi seeds contain 1–9% essential oils consisting of more than 30 compounds. Carvone and limonene were account the main portions [21-24].

However, the chemical groups isolated from the oils of the seeds of *Carum carvi* were included monoterpene hydrocarbons, oxygenated monoterpenes, oxygenated sesquiterpenes, saturated and unsaturated fatty acids, aldehydes, ketones and esters [25-33]. The essential oil compounds were included (%) α-Pinene 0.3, Camphene 0.2, β-Pinene 0.1, β-Myrcene 0.1, Limonene 5.1, γ-Terpinene 12.6, β-Ocimene 0.1, *p*-Cymene 0.1, Terpinolene 0.1, limonene oxide 0.1, Camphor 0.2, Linalool 0.7, Linalyl acetate 0.3, Terpinene-4-ol 0.1, β-Caryophyllene, Dihydrocarvone 0.2, α-Terpineol 0.1, Germacrene-D 0.1, Carvone 70.1, β- Selinene 0.2, α-Farnesene 0.4, Citronellol 0.1, δ-Cadinene 0.3, γ-Cadinene 0.5, Cuminaldhyde 0.1, Nerol 0.2, Trans-carveol 0.1, Nonadecane 0.1, Spathulenol 0.3, Eugenol 0.2, Thymol 0.5 and Carvacrol 0.2 [34]. However, the same compounds with fluctuated percentages were recorded by other studies [26, 35-38].

An aromatic compound, glucoside and a glucide were isolated from the water-soluble portion of the methanolic extract of caraway fruit (*Carum carvi* L.). Their structures were clarified as 2-methoxy-2-(4'-hydroxyphenyl)ethanol, junipediol A 2-O-beta-D-glucopyranoside and L-fucitol [39].

The flavonoid constituents of caraway were included quercetin-3-glucuronides, isoquercitrin, quercetin 3-0 caffeylglucoside, and kaempferol 3-glucoside[40].

The nutritional analysis of *Carum carvi* seeds (100g) showed that they contained water 9.87 g, energy 333 kcal, protein 19.77g, total lipids (fat) 14.59 g, carbohydrates, by difference 49.90g, fiber, total dietary 38.0g, sugars, total 0.64g, Calcium 689 mg, Iron 16.23mg, magnesium 258mg, phosphorus 568mg, potassium 1351mg, sodium 17mg, zinc 5.50mg, total ascorbic acid 21.0 mg, thiamine 0.3606mg, riboflavin 0.379mg, niacin 3.606mg, vitamin B6 0.360mg, folate 10µg, vitamin A (RAE) 18µg, vitamin A (IU) 363IU, vitamin E 2.50mg, vitamin, fatty acids, total saturated 0.620g, fatty acids , monounsaturated 7.125g and fatty acids polyunsaturated 3.272g[41].

PHARMACOLOGICAL EFFECTS

Antimicrobial effect

Antibacterial and antifungal effects

Carum carvi volatile oil showed weak antimicrobial activity against *Pseudomonas aeruginosa* and *Candida albicans* at 2% concentration. 1% concentration of the volatile oil was the minimum inhibitory concentration against *Escherichia coli* and 0.5% concentration against *Pseudomonas aeruginosa*. Against *Candida albicans*, caraway volatile oil exhibited antimicrobial activity at all tested dilution (0.5, 1 and 2%) [35].

The essential oil of *Carum carvi* L. seeds was screened for its antimicrobial activity against ten pathogenic bacteria and six phytopathogenic fungi. The essential oil showed promising inhibitory activity against all the test bacteria. The minimum inhibitory concentration was 100-300 ppm and minimum bactericidal concentration was 200-400 ppm. Diameter of zone of inhibition (mm) of 2, 3, 10 and 15 (µl/disc) of essential oil of *Carum carvi* seeds against Gram-positive organism were: *Bacillus cereus* 30, 35, 38 and 43; *Bacillus megaterium*38 42 47 52; *Bacillus subtilis*38, 40, 43 and 46 ; *Staphylococcus aureus*29, 34, 38 and 45 respectively, while , the diameter of zone of inhibition (mm) of the same concentrations against Gram-negative organism were: *Escheriachia coli* 31, 33, 36 and 40; *Pseudomonas species* 29, 32, 36 and 41 ; *Salmonella typhi*27, 32, 35 and 39; *Shigelladysenteriae*35, 39, 42 and 46 ; *Shigellasonnei*45, 48, 52 and 59 and *Vibrio cholerae*35, 38, 42 and 47.

The antifungal screening of the essential oil showed 100% inhibition of radial mycelial growth of all the test fungi at 100 ppm. The MIC and minimum fungicidal concentration (MFC) values were found to vary from 50-300 ppm and 200-400 ppm respectively [42].

Caraway essential oil also inhibited growth of *Salmonella typhi*, *Vibrio cholera* and *Mycobacterium tuberculosis*[43-44].

The microbiological activity of caraway oil obtained from different genotypes was studied in addition to the correlation between the activity and essential oil content. Caraway essential oil exhibited medium antimicrobial activity, the minimal inhibitory concentration of oil, which inhibited standard bacterial strain (*Staphylococcus aureus*ATCC 6538 P) was investigated. MIC value was recalculated to antibiotic units (AU). The microbiological activity of caraway oil of the tested objects was significantly different. The strongest activity was recorded for the oil of genotype Cluj (MIC=0.16 mg/ml; AU=8650), while the weakest activity was determined for oil of population from genotype Krakow (MIC=1.75 mg/ml; AU=582). A significant negative correlation was observed between MIC and carvone content, however positive correlation was observed between MIC and limonene content [45].

Antibacterial activity of the essential oil was recorded against Gram-positive and Gram-negative bacterial species in this study. The activity was particularly high against the genera Clavibacter, Curtobacterium, Rhodococcus, Erwinia, Xanthomonas, Ralstonia, and Agrobacterium, a lower activity was observed against bacteria belonging to the genus Pseudomonas [26].

The antimicrobial efficacy of pullulan films containing caraway essential oil (CEO) was evaluated. The films were prepared from a 10% of pullulan, containing 0.12% to 10.0% CEO. The composition of the CEO was analyzed with the use of gas chromatography. The antimicrobial activity of the CEO was evaluated with the method of serial microdilutions, and the films containing CEO-with the agar diffusion method against selected Gram-negative, Gram-positive bacteria, and fungi. The structure of the film surface and its cross-section were analyzed using a scanning electron microscope (SEM). Analyses were also carried out to determine the efficacy of a pullulan coating with 10% CEO on baby carrots experimentally inoculated with *Salmonella enteritidis, Staphylococcus aureus*, *Saccharomyces cerevisiae,* or *Aspergillusniger* and stored at a room temperature for 7 d. At a concentration of 0.12%, CEO inhibited the growth of all the tested microorganisms. Pullulan films containing 8% to 10% CEO were also active against all tested microorganisms. Populations of *S. aureus* on carrot samples were reduced by approximately 3 log CFU/g, while those of *A. niger* and *S. cerevisiae* by, 5 and 4 log CFU/g respectively, after 7 days of storage. *S. enteritidis* was the most resistant among the tested species, since it was not significantly reduced after 7 days of storage. At the end of storage, samples treated with pullulan-caraway oil coating maintained better visual acceptability than control samples [46].

The in vitro susceptibility of 15 *H. Pylori* strains to *Carum carvi* seed methanolic extract was studied. Methanol extracts of *Carum carvi* showed anti *H. pylori* effect with MIC of 100 microg/ml [47].

Effect on the pharmacokinetics of antibacterial drugs

The effect of *Carum carvi* on pharmacokinetics of rifampicin, isoniazid, and pyrazinamide in fixed dose combination was studied in 20 healthy human volunteers. Additions of *C. carvi* extract lead to increase in plasma levels of rifampicin, isoniazid, and pyrazinamide. The bioavailability indices showed that Cmax of rifampicin increased from 4.57 ± 0.19 to 5.95 ± 0.19 (P = 0.000) and AUC increased from 40.11 ± 1.69 to 53.01 ± 1.88 (P = 0.000). Similarly, Cmax of isoniazid increased from 2.66 ± 0.16 to 3.62 ± 0.16 (P = 0.000) and AUC from 17.72 ± 0.78 to 22.87 ± 0.94 (P = 0.000). The bioavailability indices of pyrazinamide also revealed an increase in Cmax from 18.81 ± 0.79 to 25.06 ± 1.14 (P = 0.000) and AUC from 107.65 ± 4.42 to 137.71 ± 5.92 (P = 0.000). These results revealed that *C. carvi* acts as a bioenhancer and modifies the kinetics of antitubercular treatment favorably [48].

Antiprotozoal effects

The anti-plasmodial activity of 47 plant essential oils and 10 of their constituents were screened for *in vitro* activity against *Plasmodium falciparum*. Five of these essential oils (sandalwood, caraway, monarda, nutmeg, and *Thujopsisdolabrata var. hondai*) and 2 constituents (thymoquinone and hinokitiol) were found to be active against *P. falciparumin vitro*, with 50% inhibitory concentration (IC_{50}) values equal to or less than 1.0 microg/ml. Furthermore, *in vivo* analysis using a rodent model confirmed the anti-plasmodial potential of percutaneously administered caraway oil against rodent *P. berghei*. Notably, caraway oils showed no efficacy when administered orally, intraperitoneally or intravenously. Caraway oil dissolved in carrier oil, applied to the skin of hairless mice caused high levels in the blood, with concentrations exceeding its IC_{50} values [49].

Insecticidal and molluscicidal effects

The essential oil of Caraway was found to possess strong contact toxicity against *Sitophiluszeamais* and *Triboliumcastaneum* adults, with LD_{50} values of 3.07 and 3.29 µg/adult respectively, and also showed strong fumigant toxicity against the two grain storage insects with LC_{50} values of 3.37 and 2.53 mg/l respectively. (R)-Carvone and D-limonene showed strong contact toxicity against *S. zeamais* (LD_{50}= 2.79 and 29.86 µg/adult) and *T. castaneum* (LD_{50} = 2.64 and 20.14 µg/adult). (R)-

Carvoneand D-limonene also possessed strong fumigant toxicity against *S. zeamais* (LC_{50} = 2.76 and 48.18 mg/l) and *T. castaneum* adults (LC_{50} = 1.96 and 19.10 mg/l) [38]. Plant essential oils from 26 plant species were tested for their insecticidal activities against the Japanese termite, *Reticulitermessperatus* Kolbe, using a fumigation bioassay. Responses varied with source, exposure time, and concentration. Among the essential oils which showed strong insecticidal activity were the essential oils of caraway (*Carum carvi*) [50].

The molluscicidal activity of the seed powder of *Carum carvi* was studied against the snail *Lymnaeaacuminata*. The molluscicidal activity was found to be both time and concentration dependent. The toxicity of *C. carvi* (96 h LC_{50}) was 140.58 mg/l. Ethanol extract was more toxic than other organic extracts. The toxicity of the ethanol extract of *C. carvi* (24h LC_{50} was 130.61 mg/l). The 96 h LC_{50} of column purified fraction of seed powder of *C. carvi* was 5.40 mg/l [51].

Anticancer effects

Four different derivatives of carvone were prepared in order to evaluate the anticancer potential. Only (1E)-1-[2-methyl-5-(prop-1-en-2-yl) cyclohex-2-en-1-ylidene]-2-phenyl hydrazine showed anticancer activity on MCF7 (breast), HeLa (cervix) and SK-OV3 (ovary) cell lines. Other derivatives were shown to have poor anticancer activity [52].

The effect of dietary caraway (*Carum carvi*) oils was studied on the progression of cancer, with emphasis on β-catenin expression in the colon during DMH-induced colonic carcinogenesis. For this purpose, colon cancer was induced by DMH in rats (20 mg/kg body weight for 5 weeks), groups of animals were given dietary caraway essential oils at two levels (0.01 and 0.1%) for 16 weeks. After 16 weeks and at the end of the experimental period the colon tissue biopsies were processed for histopathological examination and the expression of β-catenin at mRNA and protein levels was estimated by polymerase chain reaction and enzyme-linked immunosorbent assay. The formation of premalignant lesions based on aberrant crypt foci (ACF) in DMH-treated rats was greatly inhibited (72-87%) in rats given dietary essential oils when compared to respective controls. There was a correlation between the number of colonic ACF formation and the expression levels of β-catenin [53].

The effect of different doses of caraway (CC) on the formation of aberrant crypt foci (ACF) and the levels of fecal bile acids, neutral sterols, and alkaline phosphatase (ALP) activities were studied in 1,2-dimethylhydrazine (DMH)-induced colon cancer in rats. Animals were received caraway at 30, 60, and 90 mg/kg body weight orally every day until the end of whole experimental period of 15 weeks. Caraway supplementation significantly reduced ACF development and also decreased the levels of fecal bile acids, neutral sterols, and tissue ALP activities. The histological alterations induced by DMH were also significantly improved. The results showed that all 3 doses of caraway inhibited tumorigenesis, the effect of the intermediary dose of 60 mg/kg body weight was more pronounced [54].

The effect of caraway on the development of aberrant crypt foci (ACF) and modulation of fecal bacterial enzyme activities was studied in 1,2-dimethylhydrazine (DMH)-induced experimental rat colon carcinogenesis. Caraway was administered at the dose of 30, 60 and 90 mg/kg body weight everyday orally for the entire period of 15 weeks. The ACF number (incidence), multiplicity and its distribution along the colon and the fecal bacterial enzyme activities were assayed in all experimental groups at the end of 15 weeks. Caraway supplementation at three different doses significantly suppressed ACF development, bacterial enzyme activities and modulated oxidative stress significantly as compared to the unsupplemented DMH-treated group. According to the results, the dietary caraway markedly inhibited DMH-induced colon carcinogenesis and the optimal dose was 60 mg/kg body weight, it was more effective than the other two doses [55].

To elucidate the mechanism of antimutagenicity of caraway, the effects of caraway seed extract was examined on N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced mutagenesis in DNA methyltransferase-deficient *Salmonella typhimurium* strains, O6-methylguanine DNA adduct formation, and thiol content in S. *typhimurium* cells. MNNG was highly mutagenic for ogt- strains YG7104 (ogt- ada+) and YG7108 (ogt- ada-), and it showed slightly higher mutagenicity in strain YG7100 (ogt+ ada-) than in strains TA100 and TA1535. Hot water extract of caraway seeds inhibited MNNG-induced mutation only in the ogt+ strains. O6-methylguanine DNA adducts in strain YG7100 were decreased in proportion to the decrease of MNNG-induced mutagenesis. Although MNNG is known to degrade in the presence of thiols to produce methyl cation which can react with DNA, caraway had no effect on cellular concentrations of acid-soluble thiols [56].

Cytochrome P450 1A1 (CYP1A1) is among the cytochrome P450 classes known to convert xenobiotics and endogenous compounds to toxic and/or carcinogenic metabolites. Suppression of CYP1A1 over expression by certain compounds is implicated in prevention of cancer caused by chemical carcinogens. The genomic and proteomic effects of *Carum carvi* extracts containing high levels of both flavonoids and steroid-like substances was studied on ethoxyresorufindealkylation (EROD) activity and CYP1A1 at mRNA levels. Rat hepatoma cells co-treated with a CYP1A1 inducer i.e. TCDD (2, 3, 7, 8-tetrachlorodibenzo-p-dioxin) and different preparations of caraway extracts at concentrations of 0, 0.13, 1.3, and 13 microM in culture medium. The results show that caraway seed extract prepared in three different organic solvents suppressed the enzyme activity in hepatoma cells in a

dose-dependent manner. The extracts added above 0.13 microM could significantly inhibit EROD activity and higher levels of each extract (1.3 and 13 microM) caused approximately 10-fold suppression in the enzyme activity [57].

After the liver cancer was induced by single intraperitoneal injection of N-nitrosodiethylamine (NDEA) at a dose of 200 mg/kg body weight in saline, ethanolic fruit extract of *Carum carvi* (EECC) was given at the dose of 10 mg/kg /bw/orally to animals for up to 28 days. The results showed that EECC was able to prevent the cancer progression by modulating the antioxidant system and also regulatory role in the proteins of anti-apoptotic flow against the NDEA induced oxidative stress mediated ailments [58].

The apoptotic activities were recorded for ethanol extracts from fruits *Carum carvi* when evaluated against ML-1-human acute myeloblastic leukaemia, J-45.01-human acute T cell leukaemia, EOL-human eosinophilicleukaemia, HL-60-human Caucasian promyelocyticleukaemia, 1301-human T cell leukaemia lymphoblast, C-8166-human T cell leukaemia, U-266B1-human myeloma, WICL-human Caucasian normal B cell, and H-9-human T cell[59].

Effect on gastrointestinal system:

Pretreatment with oral doses of 250 and 500 mg/kg was found to provide a dose dependent protection against ulcerogenic effect of different necrotizing agents in rats, ethanol induced histopathological lesions, depletion of stomach wall mucus and nonprotein sulfhydryl groups (NP-SH) and pylorous ligated accumulation of gastric acid secretion. The mechanism of action might be due to flavonoids related suppression of cytochrome P450 IAI (CYPIAI) which known to convert xenobiotics and endogenous compounds to toxic metabolites [60].

The antiulcerogenic activity was also evaluated by the HCl/ethanol method, which causes injury to the gastric mucosa. The results showed that *C. carvi* essential oil enhanced a significant inhibition of 47%, 81% and 88%, respectively, for three doses (100, 200 and 300 mg/kg) of essential oil used, which was similar to that induced by omeprazole (95%) ($p < 0.005$) [37].

Extracts from the *Carum carvi* was investigated for a potential anti-ulcerogenic activity against indometacin induced gastric ulcers in rat as well as for their antisecretory and cytoprotective activities. The extracts produced a dose dependent anti-ulcerogenic activity associated with a reduced acid output and an increased mucin secretion, an increase in prostaglandin E2 and a decrease in leukotrienes release [61]. In addition, methanol extracts of *Carum carvi* showed anti *H. pylori* effect with MIC of 100 microg/ml [47].

The direct effects of *Carum carvi* ethanol extract was tested in dispersed intestinal smooth muscle cells (SMC) of guinea pigs. Effects of the plant extract on SMC and of acetylcholine (Ach) pretreated SMC were measured by micrometric scanning technique. Ethanol extract of *C. carvi* (2.5 mg/ml, 250 mug/ml, and 25 mug/ml) reduced significantly the response of dispersed SMC to Ach. Pretreatment of SMC with the highest concentration of *C. carvi* ethanol extract (2.5 mg/ml) has significantly inhibited the response of SMC to Ach. The result showed a dose-dependent inhibition of the contraction induced by Ach. This response may explain, in part, the beneficial effect of caraway in relieving gastrointestinal symptoms associated with dyspepsia [(62)]. It was efficient aromatic carminative and gentle stomachic; both the fruit and the oil are of value in flatulent colic [63].

The effect of the *Carum carvi* plant on resumption of bowel motility after Cesarean section was investigated by a randomized controlled pilot study conducted on 20 women undergoing elective Caesarean section under general anesthesia. The patients were randomly divided into two groups. The intervention group drank 10 ml of *Carum carvi* syrup containing 2 g of *Carum carvi* in 20 ml of syrup at 8 to $8_{1/2}$ hours after surgery. The control group was given 10 ml of the placebo syrup at 8 to $8_{1/2}$ hours after surgery. Demographic characteristics, time of first peristaltic, first gas passage, first bowel movement, and time until hospital discharge were compared for the two groups. The results showed that compared to the control group, the intervention group had significantly shorter mean interval of the first intestinal sounds (10.0 ± 2.03 h vs. 19.28 ± 3.95 h); mean time to first passage of flatus (15.91 ± 3.73 h vs. 26.82 ± 5.83 h), mean time to first bowel movement (20.31 ± 4.63 h vs. 31.7 ± 10.2 h) and mean length of hospitalization (31.71 ± 7.57 h vs. 50.6 ± 16.49 h) ($p < 0.05$). There were no serious side effects associated with consumption of the syrup. Accordingly, the use of *Carum carvi* after caesarean section can speed the resumption of post-operative bowel motility [64].

The effects of caraway hydroalcoholic extract (CHE) and its essential oil (CEO) were investigated in an immunological model of colitis in rats induced by trinitrobenzene sulfonic acid (TNBS). Different doses of CHE (100, 200, 400 mg/kg) and CEO (100, 200, 400 µl/kg) were administered orally and also doses of CHE (100, 400 mg/kg) and CEO (100, 400 µl/kg) were given intraperitoneally. Administration of the doses started 6 h after induction of colitis and continued daily for 5 consecutive days. CHE and CEO at all tested doses were effective in reducing colon tissue lesions and colitis indices and the efficacy was nearly the same when different doses of plant fractions were administered orally or intraperitoneally [65].

Antioxidant and hypolipidemic effects

The efficacy of different doses of dietary *Carum carvi* on tissue lipid peroxidation (LPO) and antioxidant profile in rat colon carcinogenesis was studied. To induce

colon cancer, rats were given a weekly subcutaneous injection of 1,2-dimethylhydrazine (DMH) at a dose of 20 mg/kg bw for the first 15 weeks. Caraway was supplemented every day orally at doses of 30, 60 and 90 mg/ kg for the total period of 30 weeks. The results showed diminished levels of intestinal, colonic and caecal LPO products, such as conjugated dienes (CD), lipid hydroperoxides (LOOH) and thiobarbituric acid reactive substances (TBARS) and also the antioxidants superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and glutathione reductase (GR) in DMH treated rats, which were significantly reversed ($P<0.05$) on caraway supplementation. Moreover, enhanced activity of intestinal, colonic and caecal glutathione peroxidase (GPx), glutathione S-transferase (GST) and colonic ascorbic acid and alpha-tocopherol levels were observed in carcinogen-treated rats, which were significantly ($P<0.05$) reduced on caraway supplementation [66].

The Methanolic and acetonic seed extracts of *Carum carvi* were able to neutralize free radicals and carried antioxidant properties. Both seed extracts were able to protect erythrocytes from hemolysis [67].

The antioxidant activity of essential oils of *Carum carvi* was studied in different model systems. Antioxidant activity was evaluated as a free radical scavenging capacity (RSC), together with the effect on lipid peroxidation (LP). The essential oils reduced the DPPH radical formation (IC50=4.1µl/ml) and H_2O_2 (IC50=5.77µl/ml), in dose dependent manner. Strong inhibition of LP in both systems of induction was observed for the caraway essential oil [68].

The effects of caraway extracts on preventing sepsis induced by oxidative tissue injuries have been investigated by measuring heart and kidney oxidative stress parameters. Sepsis was induced in rats by experimental cecal ligation and puncture (CLP) model. Then, either hydroalcoholic extract or essential oils (50 and 100 mg/kg body weight) were injected intraperitonially immediately after CLP operation. Twenty-four hours after CLP, the rats were anesthetized, kidney and heart tissues were removed to analyze the tissue oxidative stress parameters, [glutathione (GSH) and lipid peroxidation (LP)]. Sepsis induction caused a significant increase in kidney but not heart LP, indicating that kidney was more affected by sepsis induction than heart. Kidney LP and plasma urea/creatinine ratio levels were readily reversed in rats treated with essential oils but not in those treated with hydroalcoholic extract. Unlike LP, the heart and kidney GSH levels were not affected in all treated groups [69].

Essential oils of *Carum carvi* fruits were assayed for their *in vitro* and *in vivo* antioxidant activity and hepatoprotective effect against carbon tetrachloride (CCl_4) damage. The *in vitro* antioxidant activity was evaluated as a free radical scavenging capacity (RSC), measured as scavenging activity of the essential oils on 2,2-diphenyl-1-picrylhydrazyl (DPPH), OH radicals and effects on lipid peroxidation (LP) in two systems of induction. The tested essential oils were able to reduce the stable DPPH in a dose-dependent manner and to neutralize H_2O_2, reaching 50% neutralization with IC_{50} values of <2.5 microL/ml Caraway essential oil strongly inhibited LP in both systems of induction [70].

Four different derivatives of carvone were prepared in order to evaluate the antioxidant potential. All the derivatives have show good antioxidant activity as compared to standard carvone [52].

The hypolipidemic effect of aqueous extract of *Carum carvi* seeds (60 mg/kg of body weight for eight weeks) was investigated in diet induced hyperlipidemia in rats. *Carum carvi* and simvastatin significantly decreased lipids levels in rats. *Carum carvi* extract reduced lipid levels more effectively than the simvastatin. *Carum carvi* constituents, especially flavonoids and carvone have strong anti-oxidant activity which might be involved in hypolipidemia [71].

Oral administration of caraway to rats,1g/kg body weight, daily caused a significant decrease in blood glucose level ($p=0.001$) and alleviated their body weight loss ($p = 0.037$). Furthermore, it caused significant decrease in total cholesterol ($p = 0.036$), and low-density lipoprotein cholesterol levels ($p = 0.001$) compared with the diabetic control rats, and with no significant changes in triglyceride and high-density lipoprotein cholesterol levels were recorded [72].

The effect of single and repeated oral administration of the aqueous extract of *Carum carvi* fruits at a dose of (20mg/kg) on lipid metabolism was studied in normal and streptozotocin-induced diabetic rats (STZ). After a single oral administration, *Carum carvi* extract produced a significant decrease on triglycerides levels in normal rats ($p<0.05$). In STZ diabetic rats, cholesterol levels were decreased significantly 6h after *Carum carvi* treatment ($p<0.05$). On the other hand, repeated oral administration of *Carum carvi* extract exhibited a significant hypo-triglyceridemic and hypo-cholesterolemic activities in both normal ($p<0.01$) and STZ diabetic rats ($p<0.001$), 15 days after *Carum carvi* treatment [73].

Antidiabetic effect

The hypoglycemic effect of caraway ethanolicextract was investigated in normal and streptozotocin-induced diabetic rats. The results showed that the caraway ethanolic extract seeds at doses 0.2, 0.4 and 0.6 g/kg body weight significantly decreased serum glucose in diabetic rats in 3 and 5 h, but not in healthy rats [74].

To evaluate the effect of oral administration of caraway on the blood glucose level and the weight of diabetic rats. Diabetes was induced by intraperitoneal injection of 60 mg/kg body weight streptozotocin. Caraway was given orally at a dose of 1g/kg body weight daily. The results showed that oral administration of caraway caused a

significant decrease in blood glucose level (p=0.001) and alleviated their body weight loss (p=0.037) [72].

The hypoglycaemic effect of aqueous extracts of *Carum carvi* was investigated in normal and streptozotocin (STZ) diabetic rats. Single dose or 14 days oral administration of the aqueous extracts (20 mg/kg) produced significant decrease in blood glucose levels in STZ diabetic rats (P<0.001); the blood glucose levels were nearly normalized 2 weeks after daily repeated oral administration of aqueous extracts (20 mg/kg) (P<0.001). No highly significant changes on blood glucose levels were noticed in normal rats after both acute and chronic treatments with extract. In addition, no changes were observed in basal plasma insulin concentrations after treatment with aqueous extract in either normal or STZ diabetic rats, which indicate that the underlying mechanism was doesn't depend of insulin secretion [75].

Endocrine effect

The effects of aqueous and ethanolic extract of the seeds of *Carum carvi* were investigated on hormone and reproductive parameter of female rat. Aqueous and ethanolic extracts of the seeds of the plant were administered orally to female rat for 30 consecutive days. Estrous cycle, reproductive hormones (LH, FSH and estrogen) and weight of reproductive organ were studied. After oral administration of different doses of aqueous and ethanolic extracts of *Carum carvi*, a significant antifertility activity was recorded. FSH and LH levels were significantly decreased, while amount of estrogen in ethanolic extract was found to be increased. The estrus phase was blocked by treatment with aqueous and ethanolic extract. It also increase the weight of ovary, uterus and body weights, while uterine weight in immature rats increased in extract treated group. Accordingly, the study showed that *Carum carvi* exerted a significant antifertility activity [76].

Carum carvi elevated TSH level, high TSH levels was recorded in few patients with thyroid cancer who receiving *Carum carvi* despite being on suppressive dose of levothyroxin. TSH level returned to normal after discontinuation of the *Carum carvi* [77].

Anti-stress effect

The aqueous extract of *Carum carvi* was evaluated for antistress activity in normal and stress induced rats. The extract was studied for nootropic activity in rats and *in vitro* antioxidant potential to be correlated with its antistress activity. For the evaluation of antistress activity groups of rats were subjected to forced swim stress one hour after daily treatment of *Carum carvi* extract. Urinary vanillylmandelic acid (VMA) and ascorbic acid were selected as non invasive biomarkers to assess the antistress activity. The 24 h urinary excretion of vanillylmandelic acid (VMA) and ascorbic acid was determined in all groups under normal and stressed conditions. The nootropic activity of the extract as determined from acquisition, retention and retrieval in rats was studied by conditioned avoidance response using Cook's pole climbing apparatus. Daily administration of *Carum carvi* at doses of 100, 200 and 300 mg/kg body weight one hour prior to induction of stress inhibited the stress induced urinary biochemical changes in a dose dependent manner. However no change in the urinary excretion of VMA and ascorbic acid was observed in normal animals. The cognition, as determined by the acquisition, retention and recovery in rats was observed to be dose dependent. The *in vitro* antioxidant activity was determined based on the ability of *Carum carvi* to inhibit lipid peroxidation in liver and brain homogenates. The extract produced significant inhibition of lipid peroxide formation in comparison with ascorbic acid in a dose dependent manner in both liver and brain [78].

Bronchodilatory effects

The bronchodilatory effects of the aqueous extract (AE), macerated extract (ME), essential oil (EO) of caraway, and 4/μM theophylline (T) in comparison with saline (S) were examined by their relaxant effects on precontracted [by 10 /μM methacholine (M)] of the isolated tracheal chains of guinea pigs. The bronchodilatory effect of AE, ME, and EO was lower than that of T (p<0.00l for all cases), but it was significantly higher than the effect of S (p<0.05 for AE, p<0.01 for ME, and p<0.005 for EO). The results indicated that the bronchodilatory effect was mainly due to the non-competitive antagonistic property of this plant at muscarinic receptors. The β- stimulatory effect and/or anti-histaminic effect of EO might be contributed to its non-competitive property [79].

Diuretic effect

The diuretic activity of *Carum carvi* was investigated in rats. Water extracts of *Carum carvi* (100 mg/kg) were administrated orally to male Wistar rats and their urine output was quantitated at several intervals of time after the dose. After single doses of the extracts of caraway seeds, urine output was significantly increased at all time points, and at 24 h after the dose, the total volume of urine excreted was similar for the plant extracts and furosemide. *Carum carvi* extracts increased urinary levels of Na^+ and $K^{+.}$, while furosemide increased urinary levels of only Na^+ and decreased urinary K^+. In the 8-day sub-chronic study, *Carum carvi* extract induced significant diuresis and natriuresis. The plant extracts did not appear to have renal toxicity or any other adverse effects during the study period [80].

Analgesic effect

The analgesic effect of *Carum carvi* (CC) (100 and 500 mg/kg) was tested in acute and chronic pain in formalin test in mice. The results indicated that CC has

analgesic effect in both doses in acute and chronic phases and the higher dose of the drug was more effective ($P<0.01$) [81].

Renoprotective and hepatoprotective effects

The renoprotective effect of aqueous extract of *Carum carvi* seeds was evaluated in experimentally induced diabetic nephropathy (DN) in rodents. The diabetic rats showed a variable increase in the serum levels of glucose, urea, creatinine, total urinary protein and microalbuminuric levels. Body weight decreased and urine volume increased in the diabetic groups. 30 and 60 mg/kg body weight of *Carum carvi* significantly decreased the levels of the biochemical parameters. High dose of *Carum carvi* aqueous seeds extract (60 mg/kg) showed renoprotection against STZ induced diabetic nephropathy in rats [82].

The renoprotective effect of *Carum carvi* essential oil (10 mg/kg of body weights orally) was also studied in diabetic rats. Diabetic rats showed an increase in the serum level of glucose, and decrease in glutathione peroxidase. 10 mg/kg body weight of *Carum carvi* oil significantly corrected these parameters. The morphological examination of untreated diabetic rats kidneys showed glomerular and tubular degeneration with massive cellular infiltration, hemorrhage in interstitial tissue and deformed renal tissue architecture. Whereas the kidney of *Carum carvi* essential oil treated rats showed marked improvement with minor pathological changes [34].

Essential oils of *Carum carvi* fruits were assayed for their hepatoprotective effect against carbon tetrachloride (CCl_4) damage. It exerted hepatoprotective effect and decreasing oxidative damage [70].

Contraindications and side effects

Hazards and/or side effects were not known for proper therapeutic dosages [4, 57, 83]. The plant is contraindicated in inflammation of the kidneys. Overdoses for long periods can lead to kidney and/or liver damage [83].

Dose

1.5-6 g fruit; 1–2 tsp crushed seed/cup water 2-4 /day, between meals; chew 1 tsp seed 3-4 ×/day; 0.5–2 g powdered seed; 0.05–0.2 ml concentrated seed water; 0.5–1 tsp tincture up to 3 /day; 3–4 ml liquid extract 3–4 /day; 3-6 drops oil; 0.05–0.2 ml caraway oil [2,4,63,83].

CONCLUSION

The paper reviewed *Carum carvi* as 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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