

Cuminum cyminum and *Carum carvi*: An update

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ABSTRACT

Cuminum cyminum and *Carum carvi* are the sources of cumin and caraway seeds respectively, which have been used since antiquity for the treatment of various indications in traditional healing systems in wide geographical areas. Cumin and caraway seeds are rich sources of essential oils and have been actively researched for their chemical composition and biological activities. In recent times (especially during the last 3 years) considerable progress has been made regarding validation of their acclaimed medicinal attributes by extensive experimental studies. In this attempt many novel bioactivities have been revealed. This review highlights the significance of cumin and caraway as potential source of diverse natural products and their medicinal applications.

Key words: Caraway, *Carum carvi*, cumin, *Cuminum cyminum* chemistry, pharmacology

INTRODUCTION

Cuminum cyminum and *Carum carvi*, belonging to the family Apiaceae, are one of the earliest cultivated herbs in Asia, Africa and Europe. Cumin and caraway seeds from *Cu. cyminum* and *Ca. carvi*, respectively, have remained popular as culinary spices and are also overwhelmingly used in folklore therapy since antiquity in diverse geographical areas [Figure 1a, b]. The aromatic substances present in these herbs have attracted enormous attention of researchers worldwide to experimentally validate the therapeutic uses of cumin and caraway seeds, which are documented in several indigenous healing systems. This review attempts to highlight the recent investigations in which diverse pharmacodynamic actions of cumin and caraway seeds overwhelmingly support their acclaimed medicinal attributes in traditional medicines.

ETHNOMEDICAL/FOLKLORE USAGE

Ayurveda is an ancient Indian therapeutic system, which is based on the curative properties of plants and plant derived products. A very large number of medicinal herbs of various taxonomic genera are included in many forms in this traditional therapy, which are also relied upon in other indigenous systems of medicine practiced in Southeast Asia, such as Siddha and Unani systems. In these traditional therapies, cumin as well as caraway seeds are prominently considered carminative, eupeptic, antispasmodic, astringent and used in the treatment of mild digestive disorders, diarrhea, dyspepsia, flatulence, morning sickness, colic, dyspeptic headache and bloating, and are said to promote the assimilation of other herbs and to improve liver function. They have also been used in bronchopulmonary disorders and as a cough remedy, as well as an analgesic. Vapors from caraway seeds are reported to give relief in patients suffering from lumbago and rheumatism. Caraway water finds use as a vehicle for pediatric medicines. As a mixture with alcohol and castor oil, it has been used for the treatment of scabies.^[1-4]

In fact, medicinal usage of cumin and caraway seeds has also been immensely widespread in diverse ethnomedical systems from Northern Europe to the Mediterranean regions, Russia, Iran, Indonesia and North America, where these have remained as an integral part of their folk medicines. In Iranian traditional medicine, cumin is considered stimulant, carminative and astringent and its therapeutic effects have been described on gastrointestinal, gynecological and respiratory disorders, and also for the treatment of toothache, diarrhea and epilepsy.^[5] In the Moroccan traditional medicine, caraway seeds are used as diuretics^[6] and given to treat diabetes and hypertension.^[7]

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Figure 1a: *Cuminum cyminum*

In traditional medicine of Tunisia, cumin is considered abortive, galactagogue, antiseptic, antihypertensive herb, while in Italy, it is used as bitter tonic, carminative, and purgative.^[8] In indigenous Arabic medicines, the seeds are documented as stimulant, carminative, and attributed with cooling affect and therefore form an ingredient of most prescriptions for gonorrhoea, chronic diarrhea and dyspepsia; externally, they are applied in the form of poultice to allay pain and irritation of worms in the abdomen. Seeds reduced to powder, mixed with honey, salt and butter are applied to scorpion bites.^[9] In Poland, caraway is recommended as a remedy to cure indigestion, flatulence, lack of appetite, and as a galactagogue. In Russia, it is also used to treat pneumonia. In Great Britain and USA, it is regarded a stomachic and carminative. In Malay Peninsula, caraway is one important medicinal herb, and in Indonesia, it is used in the treatment of inflamed eczema.^[10]

CHEMICAL COMPOSITION

In the recent past, exploration of chemical composition of cumin and caraway seeds (which are also rich sources of essential oils) has remarkably captured enormous attention of researchers. In the quest to identify the constituents, a diverse array of compounds have been revealed in essential oils, oleoresins and seeds of carum and caraway that have grown in diverse agro-climate locations. Majority of such compounds are monoterpene hydrocarbons, oxygenated monoterpenes, oxygenated sesquiterpenes, saturated and unsaturated fatty acids, aldehydes, ketones and esters.^[11-40] The other components which occur in caraway seed are fatty acids, triacylglycerols, polysaccharides, and lignin.^[41-46] From these studies, it has emerged that the major compounds occurring in caraway are carvacrol, carvone, α -pinene, limonene, γ -terpinene, linalool, carvenone, and *p*-cymene, whereas the major compounds occurring in cumin are cuminaldehyde, limonene, α - and β -pinene, 1,8-cineole, *o*- and *p*-cymene, α - and γ -terpinene, safranal and linalool.

In aqueous and solvent derived seed extracts, diverse flavonoids, isoflavonoids, flavonoid glycosides, monoterpenoid glucosides, lignins and alkaloids and other phenolic compounds have been found.^[24,47-52] Roots of caraway have also been found to contain



Figure 1b: *Carum carvi*

flavonoids.^[53] The seed and root of caraway showed the presence of polyacetylenic compounds.^[54] In a recent study, a nonspecific lipid transfer protein has been isolated from the cumin seed.^[55] Several nutrients (vitamins, amino acids, protein, and minerals), starch, sugars and other carbohydrates, tannins, phytic acid and dietary fiber components have also been found in cumin seeds.^[19,56-60]

The surge for investigating chemical constituents in cumin and caraway has remained equally matched with the attempts to evaluate their biological activities in many collateral studies. About 30 independent experimental investigations on the chemistry and biology of cumin and caraway seeds were documented in 2009–2010.

BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY

Antioxidant

Cumin and caraway products (oils as well as their aqueous and solvent derived extracts) have shown significant antioxidant activity in several test methods. These effects are documented as their ability to prominently quench hydroxyl radicals, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and lipid peroxides. The other assays employed were ferric thiocyanate method in linoleic acid system, Fe^{2+} ascorbate-induced rat liver microsomal lipid peroxidation (LPO), soybean lipoxygenase dependent lipid peroxidation and ferric reducing ability.^[13,16,18,20,39,53,58,61-70] A caraway root extract has also shown significant anti-DPPH radical activity.^[53] The cumin and caraway oils exhibited high antioxidant activity which has been attributed largely to the presence of monoterpene alcohols, linalool, carvacrol, anethole and estragol, flavonoids and other polyphenolic compounds.^[16,53,67,71,72] The antiradical profile of cumin and caraway has been proposed as the underlying mechanism for their multifaceted pharmacological properties such as antimicrobial, antidiabetic, anticarcinogenic/antimutagenic, antistress, antiulcerogenic, etc. as outlined in the succeeding sections.

Antimicrobial

Numerous investigations have revealed a potential antimicrobial activity of cumin and caraway products (oils as well as their

aqueous and solvent derived extracts). This antibacterial action was assessed against a range of useful and pathogenic gram-positive and gram-negative bacterial strains.^[16,20,21,23,26,38,69,73-79] Cumin seed oil and alcoholic extract inhibited the growth of *Klebsiella pneumoniae* and its clinical isolates and caused improvement in cell morphology, capsule expression and decreased urease activity. This property was attributed to cuminaldehyde [Figure 2a].^[80,81] Biofilm-formation preventive properties were found against *Streptococcus mutans* and *Streptococcus pyogenes*.^[81,82]

The ability of caraway oils to inhibit the growth of fungi and bacteria is attributed to carvone, limonene and linalool, whereas limonene, eugenol, -pinene and some other minor constituents have been suggested to contribute to the antimicrobial activity of cumin oil.^[83-86] The antibacterial activity of carvacrol (5-isopropyl-2-methylphenol) [Figure 2b] is amply documented in various experimental studies and is suggested to be in synergism with its precursor *p*-cymene.^[87]

Antifungal activity of cumin and caraway oil is recorded against soil, food, animal and human pathogens, including dermatophytes, *Vibrio* spp., yeasts, aflatoxins and mycotoxin producers.^[16,21,31,88-94] Carvacrol (from caraway oil) proved most active against *Penicillium citrinum*.^[88]

Anticarcinogenic/antimutagenic

In independent studies, dietary supplementation of both cumin and caraway was found to prevent the occurrence of rat colon cancer induced by a colon-specific carcinogen, 1,2-dimethylhydrazine (DMH). In cumin receiving animals, no colon tumors were observed. The excretion of fecal bile acids and neutral sterols was significantly increased, and cumin was shown to protect the colon and to decrease the activity of β -glucuronidase and mucinase enzymes. β -glucuronidase increases the hydrolysis of glucuronide conjugates and liberates the toxins, while the increase in mucinase activity may enhance the hydrolysis of the protective mucins in the colon. Histopathological studies also showed lesser infiltration into the submucosa, fewer papillae and lesser changes in the cytoplasm of the cells in the cumin-treated colon. In cumin-treated rats, the levels of cholesterol, cholesterol/phospholipid ratio and 3-methylglutaryl COA-reductase activity were reduced.^[95-96] Dietary supplementation of caraway also showed similar preventing action. It attenuated

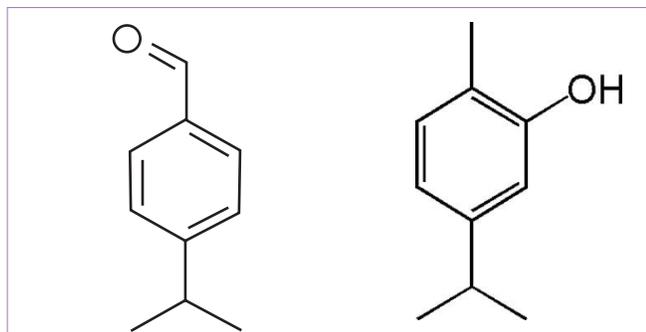


Figure 2: (a) Cuminaldehyde, (b) Carvacrol

DMH-induced histopathological lesions and suppressed aberrant crypt foci development, while decreasing the levels of fecal bile acids, neutral sterols, and tissue alkaline phosphatase activities.^[97-98] Dietary cumin inhibited benzopyrene-induced forestomach tumorigenesis, 3-methylcholanthrene induced uterine cervix tumorigenesis, and 3-methyl-4-dimethylaminoazobenzene induced hepatomas in mice. This was attributed to the ability of cumin in modulating carcinogen metabolism via carcinogen/xenobiotic metabolizing phase I and phase II enzymes. Activities of cytochrome (CYP) P-450 reductase and CYP b5 reductase were augmented, whereas phase II enzymes GST and DT-diaphorase were increased.^[99-100] Solvent derived seed extract of caraway reversed 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) induced mutagenicity. It inhibited TCDD induced CYP 1A2 activity and CYP 1A1 activities and expression in rat hepatoma cells in a dose-dependent manner.^[101] CYP P-450 1A1 is considered to convert xenobiotics and endogenous compounds to toxic and/or carcinogenic metabolites, and its suppression is implicated in the prevention of cancer caused by chemical carcinogens.

In these studies, the attenuation of carcinogenicity by cumin and caraway has been attributed to their potential antioxidative action in the target tissues.^[98,100] After caraway treatment along with carcinogens like DMH, 3-methylcholanthrene, and benzopyrene, the levels of intestinal, colonic and cecal lipid peroxidation products (conjugated dienes, lipid hydroperoxides and thiobarbituric acid reactive substances) were decreased, while the activity of superoxide dismutase (SOD), catalase, GSH-reductase, and the level of reduced glutathione (GSH) were augmented. Monoterpenes like anethofuran, carvone, and limonene occurring in cumin and caraway oil have specifically been highlighted for anticarcinogenic action.^[40,98,102-105]

Many studies have related the anticarcinogenic actions of cumin and caraway to their potential apoptotic, antimutagenic and antiproliferative properties. The apoptotic activities of caraway ethanol extract are reported against several human cancer leukemia cell lines.^[106] Methanol extracts of caraway showed antiproliferative activity in tumor cell lines MK-1, HeLa and B16F10. These chemopreventive and antiproliferative actions have been suggested to be due to bioactive polyacetylenic compounds and other monoterpenes, anethofuran, carvone, and limonene.^[40,54] Aqueous and solvent derived caraway extracts have shown protective effect against several mutagens such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), dimethylnitrosamine, nitrosodimethylamine, methylazoxymethanol acetate, methylated/ethylated nitrosourea, and methyl and ethylmethane sulfonates, in *Salmonella typhimurium* and other test strains.^[107,108] This activity was attributed to carvone content which was found to inhibit the development of diethylsitosamine-induced stomach cancers in mice.^[40,104,105] The cumin and caraway were devoid of any inherent mutagenic potential.^[56]

Antidiabetic

The antidiabetic effects of cumin and caraway products are

amply documented.^[109] In a glucose tolerance test conducted in rabbits, cumin significantly increased the area under the glucose tolerance curve and hyperglycemic peak.^[110] A methanolic extract of cumin seeds reduced the blood glucose and inhibited glycosylated hemoglobin, creatinine, blood urea nitrogen and improved serum insulin and glycogen (liver and skeletal muscle) content in alloxan and streptozotocin (STZ) diabetic rats.^[111,112] The collateral benefits included decreased creatinine, urea nitrogen and improved insulin and glycogen in tissue and skeletal muscles, accompanied by a reduction in rat tail tendon collagen-linked fluorescence and pepsin digestion which are implicated in the pathogenesis of diabetic microvascular complications.^[112] In another study, an aqueous extract of cumin prevented *in vitro* glycation of total soluble protein, α -crystallin, and delayed the progression and maturation of STZ-induced cataract in rats. Cumin prevented loss of chaperone activity in diabetic rats and also attenuated the structural changes of α -crystallin in lens, which is a long-lived protein and is susceptible to several post-translational modifications in certain diabetic conditions.^[113] Eight-week sub-acute administration of cumin to STZ-diabetic rats reduced hyperglycemia and glucosuria accompanied by an improvement in body weight, blood urea and reduced excretion of urea and creatinine.^[114] Oral administration of cumin also showed hypoglycemic effect in normal rabbit, resulting in significant decrease in the area under the glucose tolerance curve.^[110] Caraway oil exhibited anti-hyperglycemic activity in alloxan-induced diabetic rats and increased the body weight.^[115] A similar effect was recorded in STZ diabetic rats, while no changes were observed in basal plasma insulin concentrations, indicating that the underlying mechanism of this pharmacological activity seems to be independent of insulin secretion.^[116] The biologically active constituent of cumin seed oil was characterized as cuminaldehyde which inhibited aldose reductase and alpha-glucosidase isolated from rat.^[29] In hyperglycemia associated with diabetes, the use of aldose reductase inhibitors has shown efficacy in attenuating diabetic complications.

Hyperlipidemia is an associated complication of diabetes mellitus. Oral administration of cumin to alloxan diabetic rats reduced body weight, plasma and tissue cholesterol, phospholipids, free fatty acids and triglycerides. Histological observations demonstrated significant decrease in fatty changes and inflammatory cell infiltrates in diabetic rat pancreas.^[111] Cumin suppressed alcohol and thermally oxidized oil induced hyperlipidemia. It decreased aspartate transaminase (AST), alkaline phosphatase (ALP) and γ -glutamyl transferase (GGT) activities and decreased the tissue (liver and kidney) levels of cholesterol, triglycerides and phospholipids and prevented the changes in the composition of fatty acids in the plasma of rats administered with alcohol and/or thermally oxidized oil. The activity of phospholipase A and C decreased significantly.^[102,117] Hypocholesterolemic effect of methanolic extract of *cumin* is also documented in ovariectomized rat in relation to its anti-osteoporotic effect.^[118] Aqueous extract of caraway showed potent lipid lowering activity (hypotriglyceridemic and hypocholesterolemic) in both normal and STZ-diabetic rats after single and repeated oral

administration.^[119] Cumin added to a hypercholesterolemic diet decreased serum and liver cholesterol in rats.^[120]

Diuretic

The traditional use of caraway as a diuretic was confirmed in an experimental study in which peroral treatment of an aqueous extract of caraway (in acute and sub-chronic mode) was shown to increase the urine output during and after 24 hours in rat. The urinary levels of sodium and potassium were found to be increased, while in plasma these were not affected. Carum extract did not produce any renal toxicity or any other adverse effects during the study period.^[6]

Immunomodulatory

In a recent study, oral treatment with cumin showed immunomodulatory properties in normal and immune-suppressed animals via modulation of T lymphocytes' expression in a dose-dependent manner. It stimulated the T cells' (CD4 and CD8) and Th1 cytokines' expression in normal and cyclosporine-A induced immune-suppressed mice. In restraint stress-induced immune-suppressed animals, the active compound of cumin countered the depleted T lymphocytes, decreased the elevated corticosterone levels and size of adrenal glands and increased the weight of thymus and spleen.^[121]

CNS

Administration of cumin oil suppressed the development and expression of morphine tolerance (as measured by tail-flick method). The morphine dependence was also reversed in a dose-dependent manner as evaluated by decreased conditioning scores (the acquisition and expression of morphine-induced conditioned place preference) in mice.^[122,123] Anti-epileptic activity of cumin oil is documented. It decreased the frequency of spontaneous activity induced by pentylenetetrazol (PTZ). This protection was measured in a time- and concentration-dependent manner as increased duration, decreased amplitude of hyperpolarization potential, the peak and firing rate of action potential and excitability of nerve cells.^[124] Cumin oil was found to attenuate seizures induced by maximal electroshock and PTZ in mice.^[125] Cumin oil has also been found to possess significant analgesic action in a chemical model (formalin test) of nociception in rat.^[126] Cuminaldehyde [Figure 2b] was found to be a tyrosinase inhibitor and prevented the oxidation of L-3,5-dihydroxyphenylalanine (L-DOPA).^[127] The adaptogenic and antistress activity of an aqueous extract of caraway is documented in normal and stress induced rats (forced swim stress test) which was related to its antioxidant property.^[128]

Estrogenic/anti-osteoporotic

Cumin and caraway seeds are reported to be estrogenic.^[129] Potential effects of caraway on hormone and reproductive parameters of female ovariectomized rats are demonstrated due possibly to the presence of estrogenic isoflavonoids, luteolin and apigenin. An aqueous and an ethanolic extract of caraway

seeds produced significant antifertility effect via modulation of follicle stimulating hormone (FSH) and leutinizing hormone (LH) levels, while the estrogen levels were increased. This was accompanied by an increase in the weight of ovary, uterus and also body weight.^[130] Caraway oil was effective in inhibiting tonic and phasic rhythmic contractions of isolated uterine preparations.^[135] The presence of phytoestrogens in cumin has been shown and also related to its anti-osteoporotic effects. In the animals receiving a methanolic extract of cumin, a significant reduction in urinary calcium excretion and augmentation of calcium content and mechanical strength of bones was found. Animals showed greater bone and ash densities and improved microarchitecture, with no adverse effects like body weight gain and weight of atrophic uterus.^[131]

Gastrointestinal

In human trial studies, some herbal preparations consisting predominantly caraway have shown efficacy in relieving dyspeptic symptoms.^[132] The antispasmodic effect of an alcoholic extract of caraway has shown inhibitory effects on smooth muscle contractions induced by the spasmogens, acetylcholine and histamine.^[133,134] This response has been evaluated to explain the beneficial effect of caraway in relieving gastrointestinal symptoms associated with dyspepsia. In a study done on 12 intestinal bacteria, caraway oil displayed high degree of selectivity, inhibiting the growth of potential pathogens at concentrations that had no effect on the beneficial bacteria examined. This effect was related to the efficacy and usefulness of caraway oil in traditional medicine for treating dysbiosis which is associated with a number of gastrointestinal and systemic disorders.^[135] Solvent derived extracts of caraway seed showed antibacterial activity against gram-negative bacterium *Helicobacter pylori* and its clinical isolates. *H. pylori* is recognized as the primary etiological factor associated with the development of gastritis and peptic ulcer diseases along with chronic gastritis, gastric carcinoma and primary gastric B-cell lymphoma.^[136-138] Extracts from caraway produced dose-dependent antiulcerogenic effect against indomethacin-induced gastric ulcers, accompanied by reduction in acid and leukotrienes' output, and increased mucin secretion and prostaglandin E2 release. The antiulcerogenic activity was also confirmed histologically and was attributed to its flavonoid content and free radical scavenging properties.^[139] Perfusion of an aqueous extract of cumin via the stomach of pentobarbitone-anesthetized rats under the aspirin-induced gastric mucosal injury showed an increased acid secretion by a cholinergic mechanism.^[140] Aqueous and solvent derived extracts of cumin increased amylase, protease, lipase and phytase activities.^[58]

Other biodynamic actions

Aqueous extract of cumin was found to be antitussive and produced relaxant effect on guinea pig isolated tracheal chain via its stimulatory effect on beta-adrenoreceptors and/or histamine H1 receptors.^[141,142] An ethereal extract of cumin showed antiaggregatory activity and inhibited eicosanoid synthesis. It inhibited arachidonic acid (AA)-induced platelet aggregation and also thromboxane B2 production from exogenous AA; a

simultaneous increase in the formation of lipoxygenase-derived products was also observed. Cumin extract also inhibited collagen and adrenaline-induced aggregation.^[143,144] Acute and subchronic administration of cumin oil decreased WBC count and increased the hemoglobin concentration, hematocrit, and platelet counts. LDL/HDL ratio was reduced to half.^[61] Caraway oil has been evaluated for its possible hepatoprotective effect. In mice treated with carbontetrachloride, a hepatotoxin, caraway oil maintained the activities of xenobiotics detoxifying enzymes, glutathione S-transferase (GST) and glutathione peroxidase (GSH-Px) and the levels of reduced glutathione (GSH), in preventing lipid peroxidation which is the main consequence of the action of this hepatotoxin.^[62] An aqueous extract of cumin seeds showed protective action against gentamycin-induced nephrotoxicity. It decreased the gentamycin-induced elevated levels of serum urea, creatinine, lipid peroxidation and enhanced the clearance of the drug.^[145]

Drug bioavailability enhancing activity

In recent studies carried out in the author's laboratory,^[146,147] a significant pharmacokinetic interaction of some herbal products from cumin and caraway with anti-tubercular drugs has been revealed. An aqueous extract derived from cumin seeds produced a significant enhancement of rifampicin levels in rat plasma. This bioenhancer activity was found to be due to a novel flavonoid glycoside isolated from cumin. This was identified as 3',5'-dihydroxyflavone 7-O- β -D-galacturonide-4'-O- β -D-glucopyranoside [Figure 3], which enhanced the peak concentration (C_{max}) and area under the curve (AUC) of rifampicin by 35 and 53%, respectively, when co-dosed with this molecule. On the other hand, a chemically standardized butanolic fraction of caraway seed enhanced the plasma levels of three anti-TB drugs: rifampicin (RIF), pyrazinamide (PZA), and isoniazid (INH), when co-dosed in combination in rat. In the presence of the herbal fraction of caraway, C_{max} and AUC of RIF were enhanced by 63% and 53% respectively; for PZA, this increase was 57 and 35%, respectively; and for INH, this increase was 40 and 25%, respectively. The altered bioavailability profile of anti-TB drugs could be attributed to a permeation enhancing effect of cumin and caraway.^[146,147]

CONCLUSION

Although advances in chemical and pharmacological evaluation

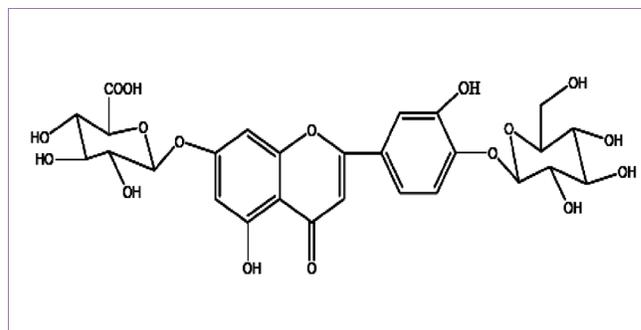


Figure 3: Flavonoid glycoside

of cumin and caraway have occurred in the recent past, they have always remained a hallmark of traditional drugs in diverse cultures. The chemical constituents of carum and caraway seem to be a bewildering array of compounds and to ascribe certain biological activity to a particular compound has remained a formidable task. Although individually some identified compounds have been associated with a bioactivity, it cannot be said about any particular mixture of compounds. It seems reasonable to assume that the “synergy” between and within a particular class of compound might be responsible for the remarkable bioactivity profile of this herb. Nonetheless, the pharmacological activities found in cumin and caraway overwhelmingly substantiate their preferred use in traditional medicaments.

In recent times, considerable information has also become available with respect to herb–drug interactions. Numerous evidences exist for many documented medicinal herbs, which suggest that such interactions could produce potential effects *in vivo*.^[148] Prominent among the many effects of these herb–drug interactions is the drug bioavailability. In this context, natural products which could facilitate the bioavailability of poorly bioavailable drugs offer great promise. Besides understanding of the natural products as an alternative to conventional treatment, cumin and caraway seem well positioned as a source of new entities to boost the bioavailability and bioefficacy of the existing medicines by virtue of their newly revealed bioenhancer action profile and need further exploration.

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