Phytopharmacology of unani drug Zeerah Siyah  
(Carum Carvi Linn)-A review

Mohd Akram, Misbahuddin Azhar, Nighat Anjum and Neelam Quddusi

Abstract
The objective is to report Zeerah siyah in Unani Classical literature, phytochemistry, pharmacology and Unani formulations and to make an effort to prove the strengths of Zeerah siyah mentioned in Unani classical literature. This review gives research questions to young researchers of Unani and other traditional system of medicine. All the information on the plant available in Urdu, Persian, Arabic language in classical Unani literature available in different libraries of India from recent to past were searched, for phyto-chemical and pharmacological activities and computerized databases such as Medline, Pubmed, Ovid SP, Google Scholar and Science-direct were searched. The temperament of Zeerah siyah is Hot and Dry in third degree, therefore Unani scholars have recommended to detoxify it before use. Almost all phyto-chemical, experimental and clinical trials carried out on Zeerah siyah were collected. It has been used for several centuries to treat gastrointestinal disorders and obesity in Unani system of medicine. It is Muhazzil (Anti-obesity); Daf-i Nafakh (Anti-Flatulent); Fad-i Zahar (Antidote) Hazim (Digestive); Mudammil-i Qurooh (Cicatrizant); Mudir-i Bawl (Diuretic); Mudir-i Shir (Galactogogue); Mudir-i Tams (Emmenagogue); Mufatti-i Hasaat (Lithotriptic); Kasir-i Riyah (Carminative) etc. as per Unani classical literature. Phytochemical studies reveals that it contains limonene, carvacrol, carvone, carvenone, -terpinene, [-pinene, linalool, and p-cymene etc. Total of twenty seven Unani classical books were referred. Thirty one different experimental and clinical studies were recognised. These studies prove the effect of Zeerah siyah (Carum carvi Linn).

Keywords: Zeera Siyah, Kamoon, Carum Carvi, Unani System of Medicine, Phytochemistry, Pharmacology

1. Introduction
Kamoon is derived from a Unani word Khamoon. It has been used for several centuries to treat gastrointestinal disorders e.g. Fuwaaq (hiccup), Maghas (gastrointestinal cramps) etc. [1-4]. Kamoon or Zeera Siyah are fruits of Carum carvi Linn. It is an annual or perennial herbs found in temperate and subtropical regions [5-6]. It is native to Europe and west Asia. It is found in Egypt, Morocco, Australia, and China. In India, it is found in Himalaya, Kashmir, Garhwal, Himachal Pradesh and North India [5-10]. It is biennial or annual glabrous herb, 30-100 cm in height, have taste and an aromatic smell. Root is fleshy tapering brown, often branched, stem is an erect angular grooved filled with latex; flowers are small whitish or reddish in colour. Fruits which is used for medicinal purpose is nearly 1/6 inch long, oblong oval, yellowish brown angular main ribs [5, 9, 11]. According to Unani literature, it is found as Jungli/Barri (Wild) and Bustani (Cultivated) variety and each has four varieties (i) Kirmani, which is black in colour and bitter in taste, its shelf life is 7 years, (ii) Kamoon farsi, which is pale in colour, (iii) Zeera Nibti, which is white in colour (iv) Zeera Shami [2-4,12-16].

2. Material and Methods
The books on Unani classical and ethnobotanical literature available in libraries of Central Council for Research in Unani Medicine, Headquarters, New Delhi, Regional Research Institute, Aligarh, Seminar Department of Ilmul Advia, Ajmal Khan Tibbiya College Library, AMU Aligarh were thoroughly searched. Apart from that online and offline review included research papers and review articles published by reputed were also referred to collect the data on Kamoon (Zeera Siyah).

3. Results:
3.1 Taxonomic hierarchy:

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Plantae</th>
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<tr>
<td>Division</td>
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3.2 Origin and Distribution

Carum carvi (Caraway) is a member of a family Umbelliferae due to flowers head are umbrella shaped. It is Erect, branched, glabrous and biennial herb. Aroma of Leaf and flowers are similar to parsnip, powerful when dried; crushed seed strong smelling. The Root are Tap, thick, fusiform, while Stems are Striate, smooth, hollow the average height of plant are 25-60 cm or 1.5 to 2 feet. Umbels are 2-4 cm in diameter compound, irregular; Leaves have soft fern with thread-like divisions. Flowers are White, pink or red. The Root are Tap, thick, fusiform, while Stems are similar to parsnip, powerful when dried; crushed seed strong smelling. The Root are Tap, thick, fusiform, while Stems are Striate, smooth, hollow the average height of plant are 25-60 cm or 1.5 to 2 feet. Umbels are 2-4 cm in diameter compound, irregular; Leaves have soft fern with thread-like divisions. Flowers are White, pink or red. The Outer petals are radiating. Irregular; Leaves have soft fern with thread-like divisions.

3.3 Mizaj (Temperament)

There is controversy between the Unani physicians for its temperament; some says it is Hot & Dry temperament, some says it is Hot & Dry in second degree of temperament [22] and some says it is Hot & Dry in third degree of temperament [1, 3, 13-14, 18-21, 34], while some says it is Hot & Dry temperament, some says it is Hot & Dry in second degree of temperament [22].

3.4 Part used

Most of the scholars have mentioned that fruits of C. carvi are used for medicinal purpose; however, its essential oil is also used for therapeutic. Action of Zeera siyah mentioned in Unani classical literature alphabetically arranged here followed by the indication of the uses.

3.5 Actions as per Unani classics

- Daf-e-Nafak (Anti-Flatulent) [4, 25, 34]
- Fad-i Zahar (Antidote) [20, 14-15, 16, 26]
- Habis-e-Dam (Hemostyptic) [31]
- Hazim (Digestive) [1, 13, 15-16, 26-27, 32]
- Jal (Detergent) [53]
- Kasir-i Raiyah (Carminative) [2-4, 12, 14-16, 20-23, 25-27, 32-34]
- Mane’Arq (Anti-Perspiration) [1-3]
- Mudammil-i Qurooh (Cicatrizant) [2-4, 12, 14, 31]
- Mudir-i Bawl (Diuretic) [1-3, 14, 21, 22, 26-27, 33, 34]
- Mudir-i Shir (Galactogogue) [16, 26, 32-33]
- Mudir-i Tams (Emmenogogue) [1-3, 14, 21, 32-33, 34]
- Mufti-i Hassat (Lithotriptic) [9, 13-14, 18, 28]
- Mulahili (Resolvent) [1, 3, 19, 22, 29, 31, 33]
- Mulahili-i Waram (Anti-inflammatory) [1, 10, 28]
- Muazzil (Anti-obesity) [23, 24]
- Mufajfiz (Desiccant) [1-4, 12-13, 19, 21-22, 25, 27-29, 33]
- Mufatteh (Deobstruant) [31]
- Mukhriji-i Balgham (Expectorant) [21-22, 33]
- Mulattif (Demulcent) [1-3, 14, 16, 19, 21, 25-26, 29, 31]
- Muqawwi-i Aam (General Tonic) [1-3, 14, 25]
- Muqawwi-i Basr (Strengthens the vision) [1, 4]
- Muqawwi-i Kabid (Liver Tonic) [1-3, 14, 25, 27]
- Muqawwi-i Me’da (Stomachic) [1-3, 14, 22, 23, 25, 33]
- Muqawwi-i Kuliya (Renal tonic) [1, 3, 14, 25]
- Musakakhin (Calorific) [2, 3, 19, 27, 29]
- Mushtahi (Appetizer) [1-3, 15, 21, 27]
- Muwallid-i Hararat (Thermogenic) [1, 21]
- Qabiz (Astringent) [1-4, 12, 14, 19, 22, 25-29, 33]
- Qutil-i Kirm (Vermicidal) [1, 3, 14, 22]

3.6 Indications as per unani classics:

- Auram (Inflammation) [3, 4, 26]
- Bussoor-i Labaniyah (Acne) [3, 4]
- Bawaseer (Haemorrhoids) [1]
- Bawal al Dam (Heamaturia) [4]
- Bayaz al Ain (Corneal opacity) [22]
- Ehtibas-e-Haiz (Amenorrhoea) [2, 3, 13-15, 26, 27, 32]
- Fuwwaq (Hiccups) [1-3, 12-14, 16, 22, 26]
- Ishaal (Diarrhoea) [1, 3, 16, 21, 22, 26]
- Jarab (Trachoma) [3, 13, 14, 16, 20, 26, 27]
- Kasrat-i Luaab (Excessive salivation) [13, 13, 14, 27]
- Khafaqan (Palpitation) [2-4, 14]
- Maghas-i Reehi (Tenesmus due to flatulence) [3, 14, 16, 20, 26-27]
- Maghas (Gastrointestinal cramps) [1, 4, 22]
- Nafakh (Flatulence) [1-3, 16, 23, 26-27, 32, 34]
- Qillat-e Laban (pressed lactation.) [32]
- Qurooh al Ain (Corneal ulcers) [1, 3, 14, 16, 20, 26]
- Ramad-i Haar (Conjunctivitis) [2, 3, 14, 16, 20, 26]
- Ruaf (Epistaxis) [2-4, 16-18, 19-26, 34]
- Sue Hazm (Indigestion) [20, 22, 32, 34]
- Sabal (Vascular keratitis) [2-4, 14, 16, 20, 26, 27]
- Taqtir al Baul (Dribbling of urine) [1, 3, 4-4, 13-14, 27]
- Usr-i Baul (Dysuria) [28]
- Usr-i Tannahis (Dyspnoea) [2-4, 14-16, 20, 26-27]
- Waja al Asnaan (Odontalgia) [1-3, 14, 16, 20, 34]
- Waram-i Rahim (Metritis) [22]
- Waram-i Tihaal (inflammation of spleen) [2, 3, 14, 16, 26]
- Waram-i Unsiyain (Orchitis) [3, 13-14, 16, 18, 26]
- Zufrah (Pterygium) [2-4, 16, 14, 20, 22, 26, 27]

3.7 Dose

Various Unani Physicians have recommended that the therapeutic dose of Zeera Siyah may be 1 gm [32]; 2-7 gm [1-2, 13, 14, 16, 19, 25, 29, 33]; and some are of the opinion that its dose may be 7-10.5 gm [30].

3.8 Substitute

The substitutes mentioned in different classic of Unani system of medicine are Kalonji (Nigella sativa) [1]; Kishneez-e-Sehra (Cuminum cyminum) [1]; Nankhaw (Trachyspermum ammi (Linn.) Spragne) [14, 25]; Zeera Safaid (Cuminum cyminum) [1, 3, 13-16, 25, 33].

3.9 Corrective

The drugs which have been recommended to be used along with Zeera Siyah so as to avoid its adverse effects are Kateera (Sterculia urens) [1, 4, 13, 14, 19, 21, 25, 26, 30, 33], Sirka (vinegar) [1, 2, 16], and Khanpur (Cuminum cyminum) [1].

3.10 Chemical constituents

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, α- and p-cymene, α- and γ-terpinene, safaranal 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 [35-40]. Roots of caraway have also been found to contain flavonoids [41]. The seed and root of caraway showed the presence of polyacytlenic compounds [42]. In a recent study, a nonspecific lipid transfer protein has been isolated from the cumin seed [43]. 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 [44-48]. 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 [49]. The flavonoid constituents of caraway were included quercetin-3-glucuronides, isouqueretin, quercetin 3-0 caffeylglucoside, and kaempferol 3-glucoside [50].

3.11 Pharmacological studies
The scientific experimental and clinical studies conducted on Zeerah siyah (Carum carvi linn.) are arranged alphabetically.

3.11.1 Anti Cholinesterase activity
Fruit extract of Carum carvi effectively inhibited AChE (acetylcholinesterase) and BChE (butyrylcholinesterase) and exert a beneficial therapeutic role in the treatment of Alzheimer’s disease by restoring of cognitive function and improving the memory [51-54].

3.11.2 Antidiabetic activity
Methanolic and Aqueous extracts of cumin seeds reduced the blood glucose and inhibited glycosylated hemoglobin, creatinine, blood urea nitrogen and improved serum insulin and glycogen content in alloxan [55, 56] and streptozotocin (STZ) diabetic rats [57-62].

3.11.3 Anti-amylodigenic
Ethanolic extract possess acetylcholinesterase inhibitory activity as well as anti-amylodigenic activity in order to address multiple facets of Alzheimer’s disease [63].

3.11.4 Antibacterial
Essential oil of Carum carvi showed antibacterial property against isolated lactic acid bacteria in sliced vacuum-packed cooked sausage and against Clostridium genus [64-68].

In a clinical trial hydroalcoholic extract reduced intensity of oral mucositis in 5-fluorouracil induced oral mucositis in golden hamsters [69].

3.11.5 Anticarcinogenic
Caraway was found to prevent the occurrence of rat colon cancer induced by a colon-specific carcinogen, 1, 2-dimethylhydrazine (DMH) [70-73]. Solvent derived seed extract of caraway reversed 2,3,7,8-tetrachlorodibenzo- p-dioxin (TCDD) induced mutagenicity [71-74]. Caraway oil has specifically been highlighted for anticarcinogenic action [71, 75-77]. Ethanol extracts of showed anticancer activity against several human cancer leukemia cell lines [78]. Methanol extracts showed antiproliferative activity in tumor cell lines MK-1, HeLa and B1 6F10 [75, 79]. An essential oil component of leaves and fruits of caraway 4,7-dimethoxy-5-(2-propen-1 - yl)- 1, 3-benzodioxole, also named apiole, apio or parsley apio, showed anticancer activity [80]. SY-1 analogue “apiole” decreased the proliferation of COLO 205 cells, The G0/G1 phase cell cycle arrest induced by apiole (75-225 μM) was associated with significantly increased levels of p53, p21 and p27 and decreased levels of cyclin D1. Aqueous and solvent derived caraway extracts have shown protective effect against several mutagens such as N-methyl-N-nitro-N-nitrosoguanidine (MNNG), dimethyleneosamine [81-83]

3.11.6 Anti-colitic activity
Hydroalcoholic extract and essential oil of caraway possess anti-colitic activity irrespective of the dose and route of administration in an immunological model of colitis in rats induced by trinitrobenzene sulfonic [89].

3.11.7 Anticonvulsant
Aqueous extract and essential oil of caraway showed anticonvulsant activity against pentylenetetrazol induced convulsions. The findings support the acclaimed antiepileptic effect of caraway in folk medicine and propose its potential use in petit mal seizure in humans [90].

3.11.8 Antifertility activity
Aqueous and ethanolic extract significantly decreases FSH (follicle stimulating hormones) and LH (luteinizing hormone) in animals. The drug also increases the weight of ovary, uterus and body weights, while uterine weight in immature rats increased in extract treated group [91].

3.11.9 Antifungal
Essential oil exhibited a potential inhibition activity against toxic fungi of the genus Aspergillus parasiticus, A. parasiticus and A. flavus [66, 92-94].

3.11.10 Anti hyperlipidemic Activity
The aqueous extract of Carum carvi exhibited a potent lipid lowering activity in both normal and streptozotocin-diabetic rats after single and repeated oral administration and diet induced hyperlipidemic rats. It also found that the hyperlipidemic positive control group rats showed variable increase in serum triglycerides, LDL (low density lipoproteins) and total cholesterol levels [95-99].

3.11.11 Antimanic
Carvone is a monoterpene present in Carum carvi essential oil showed antimanic activity against methylphenidate-induced hyperactivity in mice [100].

3.11.12 Antimicrobial activity
Oils as well as their aqueous and solvent derived extracts showed potential antimicrobial activity against a range of useful and pathogenic gram-positive and gram-negative bacterial strains e.g. S. aureus, S. aureus, S. aureus, E. coli, Salmonella enterica serovar Enteritidis Bacillus cereus, Candida albicans, Aspergillus niger, Penicillium spp. etc [101-111].

3.11.13 Antiobesity
Arg-e-Zeera is a distillate product significantly showed more potential antiobesity effect than orlistat on high fat diet induced obese rats via hypolipidemic, hypoglycemic,
hypoinsulinemic, hypoleptinemic and pancreatic lipase inhibition action [122]. Aqueous extract of *Carum carvi* suppress appetite and anthropometric indices in aerobically trained, overweight, and obese women were in a triple-blind, placebo-controlled, clinical study [115-119].

3.11.14 Antioxidant Activity
Hot water extract, Essential oil isolated by hydrodistillation from dried caraway fruits showed dose dependent antioxidant activity [66, 116-123].

3.11.15 Anti-plasmodial
In a in-vitro study essential oil found active against P. falciparum [126].

3.11.16 Anti-stress (Adaptogenic) and nootropic activities
Aqueous extract of *Carum carvi* showed anti-stress activity in normal and forced swim stress induced in rats [127].

3.11.17 Antileucogenic activity
The extracts obtained from caraway showed dose-dependent antileucogenic effect against indomethacin-induced gastric ulcers, accompanied by reduction in acid and leukotrienes/output, and increased release of mucin and prostaglandin E2 [128]. *C. carvi* essential oil showed antileucogenic activity in HCl/ethanol causes injury to the gastric mucosa [130].

3.11.18 Bio-enhancer
*Carum carvi* extract acts as a bioenhancer and modifies the kinetics of antibacterial treatment by increasing plasma levels included C max, area under curve, time to reach maximum plasma concentration, clearance, volume of distribution, and half-life (t ½) when given in healthy male volunteers along with FDC (rifampicin, isoniazid, and pyrazinamide) [130-131].

3.11.19 Bronchodilator activity
Fraction of Carum carvi showed relaxant effect on tracheal smooth muscle with a stimulatory effect on β2-adrenoceptors mechanism for treatment of obstructive pulmonary diseases [132].

3.11.20 CNS Activity
Its oil reversed morphine dependence in a dose-dependent manner as evaluated by decreased conditioning scores in mice [133].

3.11.21 Diuretic effect
An aqueous extract of caraway in peroral treatment, increase the urine output during and after 24 hours in rat [134].

3.11.22 Estrogenic/Antiosteoporotic activity
An aqueous and an ethanolic extract of Cumin seeds produced significant antifertility effect via modulation of follicle stimulating hormone and leutinizing hormone levels, while the estrogen levels were increased. It also increase in the weight of ovary, uterus and also body weight. It oil effective in inhibiting tonic and phasic rhythmic contractions of isolated uterine preparations [135].

3.11.23 Gastrointestinal effect
Caraway oil displayed high degree of inhibition in the growth of potential pathogens associated with a number of gastrointestinal and systemic disorders [136, 137].

3.11.24 Hepatoprotective Activity
Caraway oil showed hepatoprotective effect in cadmium chloride and carbon tetrachloride induced hepatotoxicity in rat and mice [138, 139].

3.11.25 Hypothyroidism
Continuous use of *Carum carvi* by a papillary thyroid carcinoma patient increases the TSH level [140].

3.11.26 Immunomodulator Activity
Cumin showed immuno-modulatory properties in normal and immunesuppressed animals via modulation of T lymphocytes expression in a dose-dependent manner by stimulating the T cells (CD4 and CD8) and Th1 cytokines expression in normal and cyclosporine-induced immune-suppressed mice [141].

3.11.27 Improve female fertility
Aqueous extract improved female fertility against cadmium chloride intoxication in rats [138].

3.11.28 Insecticidal activity
Essential oil of *C. carvi* fruits and its major components were possessing strong insecticidal activity against *Sitophilus zeamais* and *Tribolium castaneum* adults as well as repellency against several insects and mites, e.g. Japanese termite (*Reticulitermes speratus*), rice weevil (*S. oryzae*), scarid fly *Lycoriel*, lesser grain borer (*R. dominica*), red flour beetle (*T. castaneum*) and flat grain beetle (*Cryptolestes pusillus*) and stored food mite *Tyrophagus putrescentiae* and against adult male and female German cockroaches [142-157].

3.11.29 Larvicidal Activity
Essential oil has been reported for its larvicidal activity against the Asian tiger mosquito, *Aedes albopictus*, and the inhibition of acetylcholine esterase with their components [158-160].

3.11.30 Molluscicidal activity
Crude powder of *Carum carvi* showed molluscicidal activity against *Lymnaea acuminate*. These snails are the intermediate host of liver fluke *Fasciola gigantica*, which causes 94% fascioliasis in the buffalo population of northern India [161-169].

3.11.31 Muscle relaxant
Ethanol extract significantly inhibited the response to smooth muscle cells of guinea pigs to of SMC to acetylcholine, relieving gastrointestinal symptoms associated with dyspepsia [170].

3.11.32 Nephroprotective
Plant extracts significantly decreased the AGES formation and amyloid aggregation in glyciated BSA and reversed many modifications in albumin glycation, cellular dysfunction indicating that dietary sources with antiglucating and antioxidant potential for the effective management of streptozotocin induced diabetic nephropathy [171-173]. Aqueous extract showed nephroprotective activity against cadmium chloride intoxication in rats [138]. Hydroalcoholic extract or essential oils of caraway probably have a protective role in kidney tissue against oxidative injury in advanced stages of sepsis by experimental cecal ligation and puncture model [173].
3.12 Contraindicated and adverse effect
According to Unani classical literature Zeera siyah produces some side effects when used in excess or for a long time. Weakness [2, 14-16, 20], Adverse effect on Intestine [1, 14, 19, 30], Adverse effects on Lungs [1-2, 14-16/9, 21, 20], Yellow colouration of skin [1, 3, 14, 16, 20, 26], and scientific community have proved the claims of Unani scholars by conducting different studies on animal models. Different photochemical constituents isolated from the plant have the ability to cure and manage many diseases. Many more researches may be done to prove the claims of Unani scholars. Pharmacodynamic studies may also be conducted in future for further exploration of the drug for benefit of mankind. This review is a step to provide a direction of new researches for therapeutic efficacy of this important plant of Unani medicine.

Conflict of Interest: None

5. Acknowledgment
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4. Conclusion
Earlier two reviews on Zeerah Siyan (Carum carvi Linn) are available only covers its phytochemistry and pharmacology [176-180]. Zeerah siyah is mentioned in Unani Classical literature and have third degree of Hot and Dry temperament. It is advised to be used after detoxifying in vinegar by soaking for Teen Shabana Roz (two days and three nights). A number of studies based on the actions mentioned in Unani Classics have proved the efficacy of this drug in different ailments like cancer, gastrointestinal disorders, diabetes, hypolipidemia. After reviewing the pharmacological actions of the drug e.g Immunomodulator Activity; CNS Activity; Estrogenic/Antiosteoporotic activity; Antimicrobial activity; Antidiabetic activity; Hypolipidemic Activity; Antioxidant Activity; Anti-stress; (adaptogenic) and nootropic activities; Antifertility activity; Anti-colic activity; Molluscicidal activity; Insecticidal activity; Anti Cholinesterase activity; Anticarcinogenic; Hepatoprotective Activity; Antilucreogenic activity; Gastrointestinal effect; Diuretic effect etc. it was observed that most of them were mentioned in Unani classics and scientific community have proved the claims of Unani scholars by conducting different studies on animal models. Different photochemical constituents isolated from the plant have the ability to cure and manage many diseases. Many more researches may be done to prove the claims of Unani scholars. Pharmacodynamic studies may also be conducted in future for further exploration of the drug for benefit of mankind. This review is a step to provide a direction of new researches for therapeutic efficacy of this important plant of Unani medicine.

Fig 1: Kamooni (Zeerah Siyah) (Carum Carvi Linn)


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