PHYTO-PHARMACOLOGICAL PROFILE OF *CARUM COPTICUM*

Biren N. Shah[1], Mayank A. Panchal[2*], Dikshit C. Modi[1] and Hemal A. Bhuva[3]

[1]Department of Pharmacognosy, Vidybharti Trust College of Pharmacy, Umrakh, Gujarat, India.
[2*]P.G. Students, Department of Pharmacognosy, Vidybharti Trust College of Pharmacy, Umrakh, Gujarat, India.
[3]Department of Pharmaceutical Chemistry, Vidybharti Trust College of Pharmacy, Umrakh, Gujarat, India.

* For Correspondence
Mayank A. Panchal
mynk_1511@ymail.com
Mob: +919998666877

Summary

Ayurveda is an important system of medicine and drug therapy in India. Among traditional potential herbs, *Carum copticum* family Umbellifere commonly known as Ajwain is widely used for curing various diseases in both humans and animals. The active principle are extracted and purified for therapeutic utility for their selective and regulated activities. The quality control of herbal drug and their bio-constituents are of prime importance justifying their acceptability in modern system of medicine. *Carum copticum* is one of the most famous medicinal plants in the treatment of a large number of human ailments is mentioned in Ayurveda, Sushrita Samhita and Charaka Samhita. This review deals with the evidence-based information regarding the phytochemistry and pharmacological activity of *Carum copticum*.

Keywords: *Carum copticum,* Phytochemistry, Pharmacology.

Introduction

Ajwain (also known as ajowan, *Trachyspermum ammi* and *Carum copticum)* has a long history of use in Indian cooking. It is a very old and well known Ayurvedic spice that has medicinal effects. Ajwain originated in the Middle East, possibly in Egypt. It is now primarily grown and used in the Indian Subcontinent, but also in Iran, Egypt and Afghanistan. It is sometimes used as an ingredient in Berbere, an Eritrean and Ethiopian spice mixture. Its botanical name is *Carum ajowan* or *Carum copticum*, *Trachyspermum ammi, Ptychotis ajowan, Trachyspermum copticum*. It looks like cumin or caraway seeds; however, it has a bitter taste like thyme only stronger. The seeds are small, gray-green in color and quite peppery when raw, but milder when cooked. Ajwain is a small, erect, annual shrub with soft fine hairs. It has many branches of leafy stems, small feather like leaves, and 4 to 12 rays of flower heads, each bearing 6 to 16 flowers. The fruits are minute, egg shaped and grayish[1].

Figure: *Carum copticum*

PHYTOCHEMICAL STUDIES

Main constituents include an essential oil called thymol which constitutes 35-60% of The essential oil (2.5 to 5% in the dried fruits).There is also α-pinene, p-cymene, limonene and γ-terpinene found in the seed. Ajwain seeds consist of moisture, protein, fat, minerals, fiber, carbohydrates, calcium, phosphorus, iron, carotene, thiamin, riboflavin and niacin. Callus cultures of *Carum copticum* were established from cotyledons and healthy suspensions grown using Murashige and Skopg medium. The dichloromethane extract of cell suspension culture of *Carum copticum* was analysed by GC and GC-MS; 41 components were identified, of which the major constituents were found to be elemol (11.5%), cadinol (10.6%), cadinene (7.8%), caryophyllene (6.2%), muurolol (4.9%), eudesmol (3.1%), elemene (3.9%), muurolene (2.6%), limonene (2.4%) and humulene (2.0%) [2].

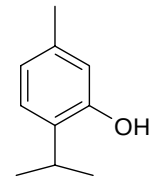
The investigation of flower scent represents an important field of modern biological research which is directed towards special theories of biological recognition. The headspace solid phase micro extraction coupled with gas chromatography-mass spectrometry was used to identify the volatile components of *Carum copticum* cultivated in Iran. The compounds were identified according to their retention indices and mass spectra (El, 70 eV). The effects of different parameters, such as the desorption time, the extraction temperature, the sample mass, the addition of salt, the pre-equilibration time and the extraction time, on the extraction efficiency were investigated.

The optimized conditions were: the desorption time, 2 min; the extraction temperature, 58 degrees Celsius; the sample mass, 1.000 g in 4.0 ml 2.0 M NaCI solution; the pre-equilibration time, 25 min; the extraction time, 20 min. Finally, ten components were identified in the volatile components of *C. copticum*. The major components of *C. copticum* were thymol (68.2%), γ-terpinene (13.9%), p-cymene (11.6%), myrcene (1.0%) and β-pinene (0.6%). Precision of the proposed method is good and %RSD less than 14 was obtained [3].

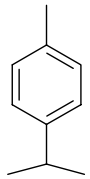
From the water-soluble portion of the methanol extract of the fruit of *Carum ajowan* (ajowan), which has been used as a spice and medicine, 25 compounds, including five new monoterpenoid glucosides, a new monoterpenoid, two new aromatic compound glucosides, and two new glucides, were obtained. Their structures were clarified by spectral investigation[4].

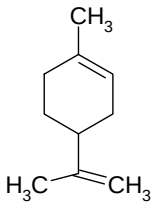
Essential oil of *Carum copticum* cultivated in Iran was obtained by hydro-distillation and supercritical (CO_2) extraction (SFE) methods. The oils were analysed by capillary gas chromatography, using flame ionization and mass spectrometric detection. The compounds were identified according to their retention indices and mass spectra (El, 70 eV). The effects of different parameters, such as pressure, temperature, modifier volume and extraction time, on the supercritical fluid extraction of *C. copticum* oil were investigated. The results showed that, under pressure of 30.4 mpa, temperature 35°C, methanol 0% and dynamic extraction time of 30 min, the method was most selective for the extraction of thymol. Eight compounds were identified in the hydrodistilled oil. The major components of *C. copticum* were thymol (49.0%), γ-terpinene (30.8%), p-cymene (15.7), β-pinene (2.1%), myrcene (0.8%) and limonene (0.7%). However, by using supercritical carbon dioxide under optimum conditions, only three components constituted more than 99% of the oil. The extraction yield, based on hydrodistillation was 2.8% (v/w). Extraction yield based on the SFE varied in the range of 1.0-5.8% (w/w) under different conditions. The results show that, in Iranian *C. copticum* oil, thymol is a major component[5].

From South Indian ajwain fruits, almost pure thymol has been isolated (98%), but the leaf oil was found to be composed of monoterpenoids and sesquiterpenoids: 43% cadinene, 11% longifolene, 5% thymol, 3% camphor and others[6].

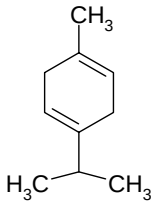


Thymol

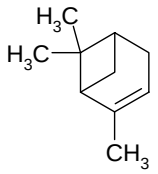

p-Cymene



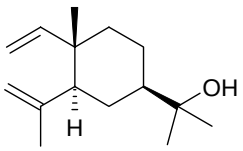
Limonene



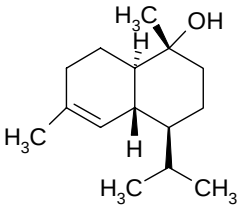
γ-Terpinene



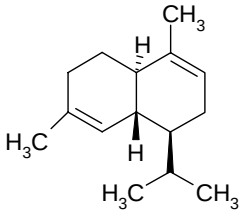
α-Pinene



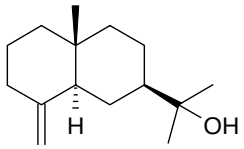
Elemol



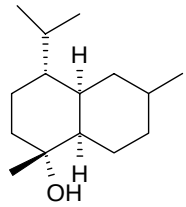
Cadinol



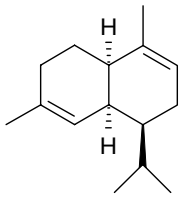
Cadinene



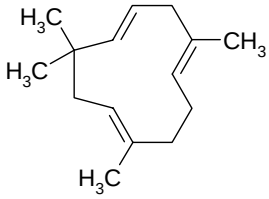
Eudesmol



Muurolol



Muurolene



Humulene

PHARMACOLOGICAL STUDIES

Analgesic effect

Pain is a universal complaint, which needs further investigations for new pain relieving agents. *Carum copticum* (L.) Sprague ex Turrill is a plant in Umbelliferae family, which is mentioned to have some therapeutic effects on headache and joint pains in Iranian traditional literature, but there are not enough scientific reports to prove its effects on pain. So, it conducted to design an experimental clinical trial study to assess and compare the analgesic effect of ethanolic extract of *Carum copticum* fruit with morphine by using a tail-flick analgesiometer device. The results indicate that the test drug produced significant increase in tail-flick latency (TFL) during 2h post-drug administration ($p<0.05$). The peak of the effect was observed at 45min after drug injection, which was comparable to that of 1mg/kg morphine (i.p.). Positive results in this type of analgesiometric test indicate that the antinociceptive action may be of the opoid type. The present study supports the claims of Iranian traditional medicine showing that *Carum copticum* extract possesses a clear-cut analgesic effect. However, further investigations are required to evaluate the efficacy and safety of this herbal medication in man[7].

Antiaggregatory effects

An ethereal extract of omum (*Trachyspermum ammi*; Hindustani: ajwan)-a frequently consumed spice-was found to inhibit platelet aggregation induced by arachidonic acid (AA), epinephrine and collagen; in this respect it was most effective against AA-induced aggregation. Inhibition of aggregation by omum could be explained by its effect on platelet thromboxane production as suggested by the following experimental observation, (i) Omum reduced TxB2 formation in intact platelet preparations from added arachidonate, and (ii) it reduced the formation of TxB2 from AA-labeled platelets after stimulation with Ca^{2+}-ionophore A23187 by a direct action on cyclooxygenase as it did not affect the release of AA from labeled platelets. An increased formation of lipoxygenase-derived products from exogenous AA in omum-treated platelets was apparently due to redirection of AA from cyclooxygenase to the lipoxygenase pathway[8].

Antibacterial activity

The essential oils extracted from the seeds of seven spices, *Anethum graveolens, Carum capticum, Coriandrum sativum, Cuminum cyminum, Foeniculum vulgare, Pimpinella anisum* and *Seseli indicum* have been studied for antibacterial activity against eight pathogenic bacteria, causing infections in the human body. It has been found that the oil of *C. capticum* is very effective against all tested bacteria. The oil of *C. cyminum* and *A. graveolens* also gave similar results. These oils are equally or more effective when compared with standard antibiotics, at a very low concentration[9].

Antifungal activity

GC and GC-MS analysis of ajwain essential oil showed the presence of 26 identified components which account for 96.3% of the total amount. Thymol (39.1%) was found as a major component along with p-cymene (30.8%), γ-terpinene (23.2%), β-pinene (1.7%), terpinene-4-ol (0.8%) whereas acetone extract of ajwain showed the presence of 18 identified components which account for 68.8% of the total amount. The major component was thymol (39.1%) followed by oleic acid (10.4%), linoleic acid (9.6%), γ-terpinene (2.6%), p-cymene (1.6%), palmitic acid (1.6%), and xylene (0.1 %}. Moreover, the oil exhibited a broad spectrum of fungitoxic behavior against all tested fungi such as *Aspergillus niger, Aspergillus flavus, Aspergillus oryzae, Aspergillus ochraceus, Fusarium monoliforme, Fusarium graminearum, Pencillium citrium, Penicillium viridicatum, Pencillium madriti,* and *Curvularia lunata* as absolute mycelial zone inhibition was obtained at a 6 μL dose of the oil[10].

Anti-inflammatory activity

Anti-inflammatory potential was evaluated using acute rat model (carrageenan induced rat paw oedema) and a sub acute rat model (cotton pellet induced granuloma). Aspirin (ASA) (150 mg/ kg) and anti-inflammatory drug phenyl butazone (PBZ) (150 mg/kg) were used as standard positive controls. Total alcoholic extract (TAE) and total aqueous extract (TAQ) in 100 mg/kg doses exhibited significant ($P<0.001$) anti-inflammatory activity in both the animal models. In carragenan induced rat paw oedema, ASA and PBZ showed an inhibition of 45.23% and 43.83% respectively, while TAE and TAQ extracts showed an inhibition of 38.32% and 41.11%.

In cotton pellet induced granuloma studies also TAE and TAQ produced 38.05% and 43.87% inhibition of the pellets weight respectively whereas ASA and PBS produced 44.69% and 42.04% inhibition. The weights of the adrenal glands were found to be significantly increased in TAE and TAQ treated animals {25.53% and 32.2%) where as ASA and PBS showed an increase of 18.86% and 10.00% respectively. TAE and TAQ extracts from the seeds of *Carum copticum* Linn, exhibit significant anti-inflammatory potential[11].

Antimicrobial activity

The fruit oil of *Carum copticum* showed the presence of eleven components with carvacrol (45.20%) and cymene (41.98%) as the major constituents by GC-MS analysis. The essential oil exhibited considerable in vitro antimicrobial activity with most of the gram-positive and gram-negative bacteria tested and the results are comparable with the standard bactericide. The pure oil inhibited the growth of *Phomopsis destructum Aspergilius niger* and *A. flavus*[12].

Antioxidant activity

An inexpensive, natural antioxidant was developed for stabilizing flaxseed and bahera oils, which are readily available and consumed in large quantities for their EFA in India, Asia, and also parts of the Western world. With the incorporation of soluble ajowan *(Carum copticum)* extract, as ajowan powder, into the oils, their oxidation could be prevented. After storage of the oils for a year in the presence of antioxidant, the odour, taste and chemical properties of the oil were the same[13].

Antitussive effect

Several therapeutic effects including anti-asthma and dyspnea have been described for the seeds of *Carum copticum* In previous studies the relaxant and anticholinergic (functional antagonism) effects, histamine [H(1)] inhibitory effect of *Carum copticum* have been demonstrated on guinea pig tracheal chains. In the present study the antitussive effect of this plant was evaluated. The antitussive effects of aerosols of two different concentrations of aqueous and macerated extracts and carvacrol, codeine, and saline were tested by counting the number of coughs produced due to aerosol of citric acid 10 min after exposing animals to aerosols of different solutions (for carvacrol n=5 and for other solutions n=6). The results showed significant reduction of cough number obtained in the presence of both concentrations of aqueous and macerated extracts and codeine ($p<0.001$ for extracts and $p<0.01$ for codeine). The cough number obtained in the presence of higher concentration of aqueous and macerated extracts was significantly less than those of lower concentrations ($p<0.05$ for both extracts). In addition the cough number obtained in the presence of both concentrations of aqueous and macerated extracts was significantly lower than that of codeine ($p<0.05$ to 0.001). However, carvacrol did not show any antitussive effect. These results indicated an antitussive effect of *Carum copticum* which was even greater than that of codeine at concentrations used. In addition the antitussive effect of *Carum copticum* was not due to its main constituent, carvacrol[14].

Anti-vomiting effects

The fruits of *C. copticum* have several therapeutic effects including carminative, diuretic and anti-vomiting effects. There are some reports on the chemical composition of *C. copticum* fruits essential oil. In the research the results of GC-MS analyses of the essential oil from *C. copticum* fruits and differences among various reports were described. Major constitutes of the oil were thymol (54.50%), γ-terpinene (26.10%) and p-cymene (22.10%). Comparison of the result from this study with other reports indicates that *C. copticum* have thymol and carvacrol chemotypes[15].

Bronchodilatory effect

Several therapeutic effects including anti-asthma and dyspnea have been described for the seeds of *Carum copticum*. In previous studies the relaxant and anticholinergic (functional antagonism) effects, histamine H(1) inhibitory and beta (2) stimulatory effects of *Carum copticum* have been demonstrated on guinea pig tracheal chains. In the present study, the bronchodilatory effect of boiled extract from *Carum copticum* in the airways of asthmatic patients was examined. The bronchodilatory effects of 0.125 and 0.25 ml/kg of 10 g boiled extract in comparison with 6 mg/kg theophylline and placebo were studied by measuring pulmonary function tests (PFTs) and specific airway conductance (sGaw). Pulmonary function tests were measured before administration and repeated 30, 60, 90, 120, 150 and 180 min after administration of the oral extract and theophylline. The results showed that the boiled extract of *Carum copticum* caused significant increases in all PFT values, in most time intervals, ($p<0.05$ to $p<0,001$). However, the increase in most PFT values due to the both doses of boiled extract were significantly lower than those of theophylline in most time intervals ($p<0.05$ to $p<0.001$). The onset of brochodilatory effect of extract was similar to that of theophylline beginning 30 min, its maximum effect on PFTs (23 to 32% increase) was seen in 90-120 min and the effect of extract decline after 150 min following administration similar to the effect of theophylline. In addition the placebo did not cause any significant increase in PFT values. In conclusion, the results of the present study showed that *Carum copticum* has a relatively bronchodilatory effect on asthmatic airways which was comparable with the effect of theophylline at concentrations used[16].

Cholinomimetic effects

Cholinomimetic effects of aqueous extracts from *Carum copticum* seeds have been confirmed[17].

Digestive stimulant activity

In vitro influence of 14 individual spices (curcumin, capsaicin, piperine, garlic, onion, ginger, mint, coriander, cumin, ajowan, fennel, fenugreek, mustard, and asafoetida) on the activities of digestive enzymes of rat pancreas and small intestine was examined by including them in the reaction mixture at two different concentrations. A majority of spices enhanced the activity of pancreatic lipase and amylase when they are directly in contact with the enzyme. It is inferred that this positive influence on the activity of enzymes may have a supplementary role in the overall digestive stimulant action of spices, besides causing an enhancement of the litres of digestive enzymes in pancreatic tissue[18].

Ejaculation activity

The effect of 7 volatile oils - oils of clove, peppermint, ajowan, dill, basil, cinnamon, and eugenol and 4 fixed oils - groundnut, coconut, vegetable, and pure clarified butter - on human spermatozoa in vitro were studied. Fresh ejaculates were obtained from male partners of infertile couples. Semen samples from 6 different donors were used for each dilution. Percent change in motility over control was calculated. All the volatile oils studied revealed a potent spermicidal action. This was confirmed by a supra-vital staining. The oils differed in the potency of their action. In decreasing order of immediate spermicidal activity, the oils could be graded as fo!lows:oil of cinnamon, eugenol, clove oil, oil of basil, oil of ajowan, oil of peppermint, and dill. Higher dilutions of volatile oils also were spermicidal when they were incubated with semen samples for a longer period. The fixed oils were devoid of action on spermatozoa[19].

Hepatoprotective activities

This study describes the antihypertensive, antispasmodic, bronchodilator and hepatoprotective activities of the aqueous-methanolic extract of *Carum copticum* Benth. seeds (CSE) to rationalize some of its traditional uses. CSE (3-100 mg/kg) caused a dose-dependent fall in arterial blood pressure in anaesthetized rats. In isolated rabbit aorta and jejunum preparations, CSE (0.1-3.0 mg/ml) caused an inhibitory effect on the K^+-induced contractions. The calcium channel blocking (CCB) effect was confirmed when CSE shifted the Ca^{2+} dose-response curves (DRCs) to right similar to verapamil. In isolated guinea-pig tracheal preparations, it caused inhibition of carbachol and K^+-induced bronchoconstriction at 0.1-1.0 mg/ml as well as shifted the dose-response curves (DRCs) of carbachol and histamine to the right with suppression of maximum response suggestive of non-specific bronchodilator effect mediated possibly through CCB. Pretreatment of rats with CSE (500 mg/kg orally for 2 days at 12 h intervals) prevented paracetamol (640 mg/kg) and CCl_4 (150 ml/kg)-induced rise in serum alkaline phosphatase (ALP) and aminotransferases (AST and ALT). The same dose of CSE was able to prevent the CCl_4-induced prolongation in pentobarbital-induced sleeping time in mice confirming its hepatoprotectivity. These results indicate the presence of calcium antagonist(s) in *Carum copticum* seeds and thus provide sound mechanistic basis for some of their folkloric uses[20].

Inhibitory effect

To elucidate the other mechanisms responsible for this relaxant effect, the inhibitory effect of this plant on histamine H1 receptors was examined in this study. The anti-histaminic effects of extracts, essential oil, 5 nM chlorpheniramine, and saline were tested by performing the cumulative log concentration-response curves of histamine induced contraction of isolated guinea-pig tracheal chains incubated with three different conditions: 1.4 μM indomethacin (group 1, n = 9); indomethacin, 1 μM propranolol, and 10 nM atropine (group 2, n = 8); and indomethacin and propranolol (group 3, n = 7). The results showed clear rightward shifts in histamine response curves obtained in the presence of extracts, essential oil, and chlorpheniramine in all three sets of experiments compared with the curves obtained in the presence of saline. The effective concentrations of histamine causing 50% of maximum response (EC_{50}) obtained in the presence of extracts, essential oil, and chlorpheniramine in all three sets of experiments were significantly higher than those of saline ($P < 0.05 < 0.001$) except EC_{50} of macerated

extract in group 1. However, maximum response to histamine obtained in the presence of extracts and essential oil were lower ($P = 0.005 < 0.001$) except maximum response of essential oil in group 2. In addition, the maximum responses obtained in the presence of extracts in group 2 experiments compared to the other two sets of experiments were improved. Comparison of the slope of histamine-response curves showed parallel shifts of the curves obtained in the presence of all extracts and essential oil in group 2 experiments. The results of this study indicated a competitive antagonism effect of *C. copticum* at histamine H1 receptors. A beta-adrenergic stimulatory effect of essential oil and an anti-cholinergic property of the plant were also suggested[21].

Lactogenic effects

The diet of mothers during pregnancy and lactation has a direct influence on her infant's health status. A study was conducted in India's Udaipur region to learn more about the nutritional content of supplementary foods consumed by mothers during the 1st 3 months of lactation. A food consumption survey revealed that 6 different supplementary food items-ajwain ka laddu, gond ka laddu, battia ka laddu, haldi laddu, lidh ka laddu, and soth ka laddu-were widely consumed by lactating women in ball form. A nutritional analysis of these supplementary foods indicated that a 250-gram serving is sufficient for meeting a third of the protein and carbohydrate requirements of a lactating woman. All foods analyzed were rich sources of iron, calcium, phosphorus, and magnesium. Of all the forms of laddu, ajwain contained the maximum amount of protein, calcium, phosphorus, and moisture while battia provided the most iron. The fat content was generally high in all cases to enable the ingredients to be formed into balls. It appears that the diet of lactating women is given greater attention in the immediate postpartum period than in is in later stages of lactation[22].

Protease activity

The protease activity of medicinal seeds commonly used in Pakistan on empirical basis or in medicinal context for cure of gastrointestinal diseases was determined. Most of the samples analyzed, exhibited high protease activity and thus their use as cures of said diseases sounds rational. *Carum copticum* (Ajwain) potentially effective in gastrointestinal diseases was associated with the highest protease activity out of the samples analyzed. Next in this potential was *Punica granetum* (Anardana), *Carum copticum*, being with the highest potential and *Allium sepa* (Pias seeds) being a parallel subject of the study with *Carum copticum* in the pilot research program, were subjected to further investigation. Their characteristics such as effect of pH, temperature and prolonged heating on protease activity were determined. Former was found active both in acidic and alkaline medium (pH optimum 3 and 7), while latter was effective in the alkaline medium only (pH optimum 10). It was, thus, concluded that *Carum copticum* was effective in stomach and small intestine, while *Allium sepa* was effective only in small intestine as digestive aid to humans. The temperature optimum of both *Carum copticum* and *Allium sepa* protease was 70°C. It, being cell bound, seemed more thermo-stable than the protease already reported in literature[23].

Relaxant effects

To investigate the effective component(s) of this plant, responsible for the observed bronchodilatory effect, fractionation of the essential oil from *Carum copticum* was carried out and the relaxant effects of different fractions were examined in this study. The bronchodilatory effect of different fractions of essential oil from *Carum copticum* and theophyliine in comparison with ethanol was examined by their relaxant effects on precontracted trachea! chains of guinea pig by 60 mM KCI (group 1) and 10 μM methacholine in two different conditions including: non-incubated tissues (group 2) and incubated tissues with 1 μM propranolol and 1 μM chlorpheniramine (group 3). In addition the relaxant effect of carvacrol was also examined on pre-contracted tracheal chains of guinea pig by 10 μM methacholine (group 4), (for each group, n = 5). In group 1 experiments, only theophylline and fraction 2 showed significant relaxant effects compared to that of ethanol. Fraction 2 and 3 of essential oil from *Carum copticum* showed potent and volume (concentration) dependent relaxant effects comparable to that of theophylline in groups 2 and 3 experiments. The relaxant effects of different volumes of these two fractions were significantly higher than that of ethanol ($p < 0.05$ to $p < 0.002$). The volumes of fraction 1 showed relatively small relaxant effects in groups 2 and 3 experiments which were not significantly different from that of ethanol. However, the relaxant effect of different volumes of fractions 2 and 3 obtained in group 2 experiments were not significantly different from those of group 3 experiments. The volumes of fraction 4 did not show any relaxant effects. In addition volumes of carvacrol also showed comparable relaxant effect with those of fraction 2 and theophylline which was significantly greater than that of ethanol. These results indicate that the relaxant effect of essential oil from *Carum copticum* is mainly due to its fraction 2 which is presumably carvacrol and to lesser extent due to fraction 3, and their relaxant effects are not due to anticholinergic or beta-adrenegie stimulatory effects[24].

Toxicity

Plant secondary metabolites play an important role in plant-insect interactions and therefore such compounds may have insecticidal orantifeedant activity against insects. *Carum copticum* C. B. Clarke (Apiaceae) is one of these plants that have medicinal effects on humans. The chemical composition of the essential oil from dry seeds of *C. copticum* was studied by gas chromatography (GC) and gas chromatography mass spectrometry (GC-MS). Thymol (41.34%), γ-terpinolene (17.46%) and p-cymene (11.76%) were found to be the major constituents of the oil. In fumigant toxicity tests with the essential oil against adults of *Sitophilus oryzae* (L.) and *Tribolium castaneum* (Herbst) at 27 ± 1°C and 60% ± 5% RH, it was observed that S. *oryzae* (LC_{50} = 0.91 iL/L) were significantly susceptible than *T. castaneum* (LC_{50} = 33.14 iL/L). The mortalities of the insect species reached 100% at concentrations higher than 185.2 iL/L and 12-h exposure time. The findings indicate the strong insecticidal activity of *C. copticum* oil and its potential role as a fumigant for stored-product insects[25].

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