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Review Article

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Pharmacology and Toxicology of *Conium Maculatum*- A Review

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Abstract The chemical analysis of *Conium maculatum* revealed that the plant contained alkaloids, flavonoids, coumarins, polyacetylenes, vitamins, oils and many other active metabolites. The alkaloidal fraction of Conium maculatum aerial parts exhibited significant anti-inflammatory activity in rats and strong peripheral and central antinociceptive effects in mice with a narrow dose range (10–20 mg/kg). It was found to be lethal in doses higher than 20 mg/kg. However, hemlock (*Conium maculatum*) was one of the most poisonous plants for laboratory animals, farm animal and human being, due to the presence of piperidine alkaloids in all parts of the plant, including the leaves, flowers, fruits, seeds, and roots. In the current work, the chemical constituents, pharmacological and toxicological effects of *Conium maculatum* were reviewed.

Keywords Chemical Constituents, Pharmacology, Toxicology, *Conium Maculatum*

Introduction

Plants contained biologically active chemicals, some of these were extremely useful for the treatment of human diseases, but many plant constituents produced side effects and may life-threatening illnesses [1-30]. The chemical analysis of *Conium maculatum* revealed that the plant contained alkaloids, flavonoids, coumarins, polyacetylenes, vitamins, oils and many other active metabolites. The alkaloidal fraction of *Conium maculatum* aerial parts exhibited significant anti-inflammatory activity in rats and strong peripheral and central antinociceptive effects in mice with a narrow dose range (10–20 mg/kg). It was found to be lethal in doses higher than 20 mg/kg. However, hemlock (*Conium maculatum*) was one of the most poisonous plants for laboratory animals, farm animal and human being, due to the presence of piperidine alkaloids in all parts of the plant, including the leaves, flowers, fruits, seeds, and roots. In the current work, the chemical constituents, pharmacological and toxicological effects were reviewed.

Plant Profile

Synonyms: *Coriandrum maculatum* Roth, *Sium conium* Vest [31-32].

Taxonomic classification:

Kingdom: Plantae; **Subkingdom**: Viridiplantae; **Infrakingdom**: Streptophyta; **Superdivision**: Embryophyta; **Division**: Tracheophyta; **Subdivision**: Spermatophytina; **Class:** Magnoliopsida; **Order**: Apiales; **Family**: Apiaceae; **Genus**: Conium; **Species**: *Conium maculatum* [33].

Common names:

Arabic: shawkaran**,** bisbis bari; **Brazil:** cicuta, funcho-selvagem; **Chinese**: du shen; **English**: carrot-fern, fool's-parsley, hemlock, poison-hemlock, spotted-hemlock, spotted-parsley; **French**: grande ciguë, cigüe maculae**;** **Spanish**: sencaje cimarrón, panalillo, zanahoria silvestre, perejil de chucho, perejil de monte; **Swedish**: odört [34].

Distribution

It was native in **Africa**: Algeria, Morocco, Tunisia and Ethiopia; **Asia**: Afghanistan, Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, Armenia, Azerbaijan, Georgia, Russian Federation, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, India and Pakistan; **Europe**: Denmark, Finland, Ireland, Norway, Sweden, United Kingdom, Austria, Belgium, Czech Republic, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Belarus, Estonia, Latvia, Lithuania, Moldova, Ukraine, Albania, Bosnia and Herzegovina, Bulgaria, Greece, Italy, Macedonia, Montenegro, Romania, Serbia, Slovenia, France, Portugal and Spain. It was naturalized in **Africa**:

Mozambique, Zimbabwe, South Africa; **Asia**: China; **Australasia**; Australia, New Zealand; **Northern America**: Canada, USA, Mexico; **Southern America**: Costa Rica, Brazil, Bolivia, Ecuador, Peru, Argentina, Chile and Uruguay [34].

Description

Erect annual or biennial, with foetid odour when crushed. Root is long, forked and pale yellow. Stems hollow, striate, up to 2-(3) m high, usually light green and purple spotted or blotched, sometimes tinged purplish or pink, particularly toward base. Leaves 2-4-pinnate; ultimate segments narrowly or broadly ovate to deltoid, pinnatisect or serrate, 5-40 mm long; petioles light green and purple blotched when mature; stem leaves similar to basal, but shortly petiolate and 1-3-pinnate. Umbels 1-8 cm in diameter; rays 4-16; bracts > 4-8, narrow-triangular, acuminate, reflexed; bracteoles 3-6, triangular, confined to outer side of umbellets. Flowers numerous, white, 2 mm in diameter. Fruit dark brown, 2.5-3 mm long; ribs slender, light brown, often crenulate [35].

History and Traditional Uses

The Ancients were familiar with the plant, which was mentioned in early Greek literature, and fully recognized its poisonous nature. The juice of hemlock was frequently administered to criminals. The generic name being derived from the Greek word Konas, meaning to whirl about, because the plant, when eaten, causes vertigo and death. The specific name is the Latin word, meaning (spotted), and refered to the stem-markings. The name Hemlock is derived from the Anglo-Saxon words hem (border, shore) and leác (leek or plant). Other authors mentioned that the name (hemlock) was derived from the Anglo-Saxon word healm (straw). , from which the word (haulm) was derived [36].

The ancients employed several methods to relieve surgical pain. The less violent form of sedation, was the use of ancient narcotics. Four plants were used for analgesic and anesthetic effects: opium poppy (*Papaver somniferum*), datura *(Datura stramonium),* hemlock *(Conium maculatum),* and withania *(Withania somniferum).* These plants were employed not only as narcotics but also as anodynes, administered in decoctions, poultices, suppostories, lozenges, pills and topical applications. The extracts from the poppy, as well as decoctions from datura, henbane, hemlock and mandrake were used (either alone or in combinations) to dull the pain of surgery in ancient times [37].

Greek and Arabian phsicians were use it to cure indolent tumors, to relieve swellings and pains of the joints as well as for affection of the skin [38].

Conium maculatum Linn. (Umbelliferae) has been traditionally used in the treatment of spasmodic disorders, and to relieve nervous excitation, rheumatic pains, pain in stomach, pain of gastric ulcer, nervousness and restlessness [39].

Poisonous Parts of the Plant

The whole plant is toxic, toxic parts included flowers, leaves, mature fruit, roots, seeds, stems and young shoots, but especially the root and seeds [40].

Chemical constituents

It contained piperidine alkaloids (coniine, N-methyl-coniine, conhydrine, pseudoconhydrine, gamma-coniceine), which were formed by the cyclisation of an eight-carbon chain derived from four acetate units. Gamma-coniceine was the precursor of the other hemlock alkaloids. All vegetative organs, flowers and fruits contained alkaloids. The concentrations (both absolute and relative) of the different alkaloids depend on plant varieties, on ecological conditions and on the age of the plant. Conmaculatin (2-Pentylpiperidine), a novel volatile alkaloid related to coniine was identified from the *Conium maculatum* L [40-41].

Chemical analysis showed that all tissues of *Conium maculatum* were very rich in alkaloids, fruits being the richest with up to 1% (w/w) alkaloid, but the amount and mutual ratio of the several different alkaloids depends on plant variety, ecological conditions and the stage of phenological development [40-42-43].

Conium maculatum also contained flavonoids, coumarins, polyacetylenes, vitamins, essential oils and non-volatile oils [44-47].

The oil of *Conium maculatum* grown in Iran, was characterized by higher amount of germacrene-D (46.1%), β-caryophyllene (15.3%) and cis-α-Farnesene (10.1%) [45].

The constituents of the essential oils of *Conium maculatum* was determined by hydro distillation (HD), microware assisted hydro distilation (MAHD) and solid phase micro extraction (SPME). 22 compounds were identified by HD in the essential oil, representing 73.8% of total oil obtained. The main constituents were α-pinene (16.2%), camphene (9.9%), limonene (8.6%) and linalool (5.3%). However, by MAHD method, 16 compounds were identified in essential oil, representing 74.6% of total oil. The major compounds were camphene(13.0%), limonene(8.7%), linalool (8.4%) and fenchyl acetate (7.6%). 9 compounds were identified in essential oil by SPME, representing 99.8% of total oil obtained by SPME. The main constituents were α-pinene (46.1%), sabinene (16.2%), limonene (11.3%), camphene (9.5%) and myrcene (7.9%). The results also showed that the essential oil extracted with HD method included monoterpenes (52.8%), sesquiterpenes (10%) and oxygenated compounds (27.4%), whereas the essential oil extracted with MAHD method contained sesquiterpenes (9.9%), monoterpenes (47.7%) and

oxygenated compounds (32.2%). Furthermore, the essential oil obtained by SPME, included monoterpenes (98.7%) and oxygenated compounds (4.3%) [46].

However, *Conium maculatum* from Serbia produced yellowish, transparent essential oils of noxious odor. It was obtained from fresh leaf and inflorescence, represented 0.04 and 0.06% (v/w), respectively. The essential oils were analyzed by GC and GC-MS, twenty-three and fifty-seven constituents were identified in the leaf and flower oils of *Conium maculatum*, accounting for 96.2 and 97.5% of the total oils, respectively. The major constituent in both flower and leaf oils was germacrene D (27.2 and 41.0%, respectively). The two runnersup in the leaf oil were the acyclic monoterpenes (Z)-β-ocimene (7.1%) and (E)-β-ocimene (22.3%), while in the inflorescence oil the second and third most abundant components were (Z)-β-ocimene (14.3%) and β-myrcene (9.3%). The relative amounts of (E)-b-ocimene was (7.7%) and (E)-nerolidol was (7.1%) in the flower oil. The monoterpene and sesquiterpene fractions of the oils were comparable in their relative amounts (flower oil: 40.1% monoterpenes versus 46.3% sesquiterpenes, leaf oil: 33.6% monoterpenes versus 54.6% sesquiterpenes) and the number of identified monoterpenes and sesquiterpenes followed the same trend (13 and 19) [48].

The steroid content of *Conium maculatum* was studied by GC–MS in twenty two samples (dichloromethane extracts of different plant organs of *Conium maculatum* at three or four different stages of phenological development, collected from three locations). In total, twenty four different steroids were identified. Six steroids had an ergostane nucleus, while the other ones possessed a stigmastane carbon framework. Steroid compounds were noted to be the main chemical constituents of root extracts of this plant species in the last phase of development. The predominant ones were stigmasta-5,22-dien-3β-ol (stigmasterol) and stigmast-5-en-3β-ol (β-sitosterol). However, the steroids isolated from *Conium maculatum* were included: Ergosta-5,7,9(11),22-tetraen-3 β -ol , Ergosta-5,8,22-trien-3 β -ol , Ergosta-5,7,22-trien-3 β -ol , 5 α -Ergosta-7,22-dien-3 β -ol , Ergost-5-en-3 β –ol , Stigmasta-5,22-dien-3 β-ol, 5 α -Stigmast-22-en-3 β -ol , 5α-Stigmasta-7,22-dien-3 β -ol , Stigmast-5-en-3 β –ol, 5 α -Stigmastan-3 β –ol, Ergost-4-en-3-one, 5 α -Stigmastan-3-one, 5 α -Stigmast-7-en-3 β –ol, 5 α -Stigmasta-7,22-dien-3-one, Stigmasta-4,22-dien-3-one, 5 α -Stigmasta-7,16-dien-3 β –ol, 5 α-Stigmast-7-en-3-one, Stigmast-4-en-3-one, Stigmasta-4,6-dien-3-one, Stigmasta-4,22-diene-3,6-dione, Stigmast-4-ene-3,6-dione, 5α-Stigmasta-22-ene-3,6-dione, 5α-Stigmastane-3,6-dione, 3β-Hydroxystigmast-5-en-7-one, Stigmast-4-en-3-one, Stigmasta-4,6-dien-3-one, Stigmasta-4,22-diene-3,6-dione, Stigmast-4-ene-3,6-dione, 5α-Stigmasta-22-ene-3,6-dione, 5α-Stigmastane-3,6-dione and 3β-Hydroxystigmast-5-en-7-one [44].

Pharmacology and Toxicology

Pharmacology

The alkaloidal fraction of *Conium maculatum* aerial parts was evaluated for analgesic and antiinflammatory activities. Test doses (100 or 200 mg/kg, po) of alkaloidal fraction were evaluated for analgesic activity using tail flick test and antiinflammatory activity using carrageenan-induced paw oedema test in rats. Morphine (5 mg/kg, po) and indomethacin (5 mg/kg, po) were used as standard analgesic and antiinflammatory drugs, respectively. Alkaloidal fraction of the plant exhibited significant analgesic activity at a dose of 200 mg/kg as it showed significant increase in tail flicking reaction time with respect to the control, during 2 h intervals of observation. It also exhibited significant antiinflammatory activity at a dose of 200 mg/kg as it inhibited paw oedema in rats to 71% and reduced the paw volume one-fourth to the control during 1st h of the study [39].

Conmaculatin (2-Pentylpiperidine), a novel volatile alkaloid related to coniine identified from *Conium maculatum* showed strong peripheral and central antinociceptive activity in mice, which observed in a narrow dose range (10–20 mg/kg). It was found to be lethal in doses higher than 20 mg/kg [41].

Variation in the amount and proportion of the antifungal furanocoumarins was observed following treatment with various biotic and abiotic elicitors. $CuCl_2$ produced the largest increase in the amounts of antifungal compounds. The simple coumarin, umbelliferone was the main induced compound in the $CuCl_2$ treated leaves, xanthotoxin in inoculated leaves and in $CuCl_2$ treated seedlings of *Conium maculatum*. Variation was also observed in the rate of accumulation of individual compounds using the unspecific elicitor $CuCl_2$ [47].

Toxicology

Hemlock (*Conium maculatum*) was one of the most poisonous plants, due to the presence of piperidine alkaloids in all parts of the plant, including the leaves, flowers, fruits, seeds, and roots. Hemlock was purportedly the poison used in ancient Greece to execute condemned prisoners. The actions of three hemlock alkaloids (coniine, *N*-methylconiine and α-coniceine) have been examined on isolated tissues, the most pronounced action of the alkaloids was the blocking of spinal reflexes by an action exerted in the spinal cord. Their peripheral actions on autonomically innervated structures were mainly a consequence of an initial stimulant and a secondary depressant action on autonomic ganglia. Large doses of the alkaloids stimulated skeletal muscle and subsequently caused neuromuscular block. This blocking action differed in many respects from that produced by decamethonium or tubocurarine [48].

Cattle, goats, horses, pigs, sheep, rabbits, poultry, deer and humans have been poisoned after ingesting poison, Hemlock. The information on the acute toxicity of hemlock to farm animals after ingestion (Toxic dose rate mg / kg body weight, and time to death) were: cows 3.3/ 2 hours, horses 15.5/ 30-40 minutes, sheep 44/ 1.5-2 hours respectively. The LD_{50} in mice mg/kg and the time of death for different alkaloids were: gamma-coniceine (iv:19 mg/kg / 30mins, sc:12.0 mg/kg/12 mins and op: 12.0 mg/kg/ 8mins), coniine (iv:2.6 mg/kg / 30mins, sc: 80 mg/kg/15 mins and op: 100 mg/kg/ 10mins), N-methylconiine (iv:27.5 mg/kg / 30mins, sc:150.5 mg/kg/16 mins and op: 204.5 mg/kg/ 12 mins) [49].

The general symptoms of poisoning for sheep were: ataxia, carpal joint flexure, death, defecation, frequent salivation, kinked tail, trembling, urination, frequent weakness and death [50]. The clinical signs of intoxication in swine included ataxia, tremors, severe lacrimation, mydriasis, tachycardia, polypnea and fever, recumbency and tonic/clonic movements in both rear legs, green faeces [51-52].

Conium maculatum is more poisonous to cows than to other animals. The symptoms of poisoning were included arthrogryposis, breathing, carpal joint, elbow joint, depression, diarrhoea, gait, incoordination, ataxia, bloating, increased salivation and lacrimation, depression, lateral rotation of limbs, muscle spasms, salivation, teeth grinding, torticollis, trembling, coffee-coloured urine, vomiting and respiratory distress and death. Clinical signs of toxicity were evident after 30–40 minutes of oral intake [53-56].

Human poisoning was recorded with the intake of the leaves, roots, or seeds of the plant. Human signs of *Conium maculatum* intoxication were included rapid loss of power of the lower extremities (muscular weakness), ataxia, staggering and trembling. As the effects ascended, there was loss of control of the upper extremities. Total paralysis of the legs and arms, loss of the power to chew and loss of sensation, the pupils became fixed, slow and weak pulse (becoming later rapid), rapid respiration, heavy salivation, frequent urination, nausea, convulsions, decrease of the body temperature. Finally, death was due to paralysis of respiration and asphyxia, the intellect was clear until death occurred. In comparison with animal intoxication, the acute renal failure seems to be a symptom only of the human poisoning [48, 57-59].

It was recommended: that there is no proven safe effective dose for therapeutic purposes for hemlock in adults and children. Do not ingest hemlock orally, do not inhale hemlock alkaloids, and do not use the hollow stems. It was a poison. Avoid in pregnant or breastfeeding mothers due to extreme toxicity [60].

Teratogenicity

Coniine, an alkaloid from *Conium maculatum*, was a known teratogen in many domestic species with maternal ingestion resulting in arthrogryposis (twisted limbs) of the offspring. Coniine-induced arthrogryposis was carried out using a laboratory animal to design and perform mechanistic studies to understand mechanisms of arthrogryposis. Coniine-induced teratogenicity was evaluated in Sprague-Dawley rats, New Zealand white rabbits, and New Hampshire X White leghorn chicks. Fetal weights were significantly lower in coniine-exposed rat and rabbit fetuses but the only statistically significant treatment-related visceral or skeletal malformation was a reduction of cranial ossification of rabbit fetuses. Coniine-exposed rabbit litters were affected by arthrogryposis more than controls (2/6 vs. 0/9) with the lesion characterized as hyperflexion of the antebrachial-carpal joint with supination. Chicks treated with coniine showed a dose-dependent teratogenic response of excessive flexion or extension of one or more toes. Coniine caused malformations in the chick similar to those caused by nicotine and there was a statistically significant ($P < 0.01$) decrease in movement in coniine and nicotine sulfate treated chicks as determined by ultrasound. Control chicks were in motion an average of 33.67% of the time while coniine (1.5%) treated chicks were only moving 8.95% of a 5 minute interval and no movement was observed for nicotine sulfate (5%) treated chicks. Neither the peripheral nicotinic receptor antagonist (d-tubocurarine chloride) nor the central nicotinic receptor antagonist (trimethaphan camsylate) blocked the teratogenesis of 1.5% coniine in chicks. Differences in the receptor affinity for coniine between susceptible and nonsusceptible species may explain, in part, cross-species variation in teratogenicity of coniine [61].

Fetal movements in pregnant ewes gavaged with hemlock twice daily for 30 days (5–10 g/kg bw) were reduced significantly, but temporarily. Fetal movement was observed by sonography on days 45, 54 and 60 of gestation, immediately before and 1 h following hemlock feeding. The fetal movement was significantly reduced after hemlock administration, but returned to normal level within 18 h after treatment. Seven of eleven lambs born to seven treated ewes had varying degrees of front limb abnormalities which resolved spontaneously by eight weeks after lambing. The maternal effects of hemlock treatment included trembling, muscular weakness in the neck initially then progressing to the limbs, ataxia, frequent urination, defecation and death [50].

Fetal movement was significantly reduced in pregnant goats gavaged with seeds and was temporarily reduced with fresh plant. Seed induced cleft palate, torticollis, scoliosis, lordosis, arthrogryposis, rib cage anomalies, over extension and flexure and rigidity of the joints in kids born to hemlock treated pregnant goats [40].

Teratogenic effects including skeletal malformations have been reported in calves from ingestion of hemlock. Skeletal malformations were induced in calves both with fresh plants and pure coniine [62-64].

Conclusion

In the current paper, the chemical constituents, pharmacological, toxicological and teratogenic effects of *Conium maculatum* were reviewed.

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