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Haplophyllum tuberculatum: An overview

Abdolshakoor Raissi[1*], Mina Arbabi[2], Javad Roustakhiz[3], Masih Hosseini[4]

[1]Faculty of agriculture, Department of Horticulture, Velayat University, Iranshahr, Iran
[2]PhD Student of Medicinal Plant, Islamic Azad University, Science and Research Branch, Tehran, Iran
[3]Higher Educational Complex of Saravan, Saravan University, Saravan, Iran
[4]Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

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ABSTRACT

Introduction: *Haplophyllum tuberculatum*, belonging to the Rutaceae family, is distributed in south-eastern regions of Iran, particularly in Baloochestan. This study was aimed to investigate and collect scientific reports such as morphological characteristics, phytochemical compounds, ecology, biotechnology and evaluation of the therapeutic properties of this valuable medicinal plant.
Methods: In order to gather the information the keywords *Haplophyllum tuberculatum*, botany, genetic, biotechnology, therapeutic, and pharmacology were searched until 2016 from journals accessible in databases such as Scopus, EBSCO, Science Direct, Medline, PubMed, Embase, SID and Iran Medex.
Results: The results in this study revealed various pharmacological properties including anti-cancer, antioxidantant, uterus-relaxing, anti-bacterial and anti-HIV activities for this plant which are probably due to the presence of aromatic compounds such as two alkaloids named haplophytin-a and B, and essential oils.
Conclusion: *Haplophyllum tuberculatum* possesses various pharmacological properties and the bioactive molecules of this plant play an important role in human health, hence, it might be used for different drug productions.

Implication for health policy/practice/research/medical education:
The plant Haplophyllum tuberculatum in Sistan and Baluchistan province is an important medicinal plant that has many medicinal properties. The bioactive molecules of this plant play an important role in human health. Hence, it might be used for new drug preparation.
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Introduction

Sistan and Baloochestan is extended in 187502 square kilometer and has dedicated equally 11.5% of the country's area to itself. This province is located between 25 degree and 3 minutes to 31 degree and 29 minutes of northern width and 58 degree and 20 minutes of eastern length, and 49 minutes to 36 degree. It is limited to Sothern Khorasan from the north, to Afghanistan and Pakistan from the east, to Oman sea from the south and to Kerman and Hormozgan provinces from the west (1).
The genus *Haplophyllum,* belonging to the Rutaceae family, comprises about 70 species distributed from the Mediterranean area to eastern Siberia (2). Haplophyllum is distributed from Morocco and Spain in the west to China in the east. It extends north to Romania and south to Somalia and in the east it extends north to the Lake Baikal region (3). Its range spans five different floristic regions: Mediterranean, Saharo-Arabian, Irano-Turanian, and Sudano-Zambezian regions (4). The main center of diversity is the Irano-Turanian region, Iran, Turkey, and Central Asia which harbours 60% of the species diversity. *Haplophyllum tuberculatum* is found in central and eastern areas of Asia.
This genus consists of 22 species in the Asia to N. Africa. Among the 18 species present in Iran, 9 species is endemic (5). The *Haplophyllum robustum* is distributed in central to south-eastern of Iran. The Persian name of this plant is "Sodaby" and its Baluchi name is "Sadaap". In Oman trivially refer to the plant as "shagarat al baootha", which means "plant of the mosquito" (6). In Sudan it is called "a plant of all disease". It is used in most of Sudanese homes as emergency medication and is mostly used by old Sudanese in the rural areas. The purpose of this study was to investigate and collect scientific reports such as mor-

***Corresponding author:** Abdolshakoor Raissi,
Email: Shakoorraissi@gmail.com

phological characteristics, phytochemical compounds, ecology, biotechnology and evaluation of the therapeutic properties of this valuable medicinal plant.

Methods

In order to gather the information the keywords *Haplophyllum tuberculatum*, botany, genetic, biotechnology, therapeutic, and pharmacology have been searched until 2016 from journals accessible in databases such as Scopus, EBSCO, Science Direct, Medline, PubMed, Embase, SID and Iran Medex.

Results

Genetic evaluations

The phylogenies established from DNA sequences and morphological as well as cytogenetic analyses support the separation of *Haplophyllum* species. The change in the number of chromosomes might be the main mechanism of speciation of the genus *Haplophyllum* (7). Phylogenetic analysis of the internal transcribed sequences of the ribosomal DNA was performed using neighbour-joining (NJ) and maximum-parsimony methods. Results showed that the *Haplophyllum bastetanumis* a diploid species (2n = 18) distinguished primarily for its non-trifoliate glabrous leaves, dark-green petals with a dorsal band of hairs, and a highly hairy ovary with round-apex locules. Another two Iberian species (*H. linifolium* and *H. rosmarinifolium*) are tetraploid (2n = 36) and have yellow petals. The species diversity in Haplophyllum in a phylogenetic and biogeographic context was evaluated. It was generated gene trees from DNA sequences of four regions of the chloroplast genome for 118 accessions, representing 66% of the species diversity. Additionally, Haplophyllum was examined morphologically. The phylogenetic analyses revealed that a number of species do not form reciprocally monophyletic groups. Optimization of morphological characters on the chloroplast DNA revealed that most of the species, in particular those with a widespread geographic distribution, might only be diagnosed by homoplasious character states. Homoplasy notwithstanding, the predominant characters used to classify the genus are consistent with the molecular phylogeny of Haplophyllum. The Mediterranean representatives of Haplophyllum were found to be embedded within a clade that include primarily Irano-Turanian species, suggesting multiple invasions of the Mediterranean basin from the east (8).

Botany

Synonyms: *Haplophyllum villosulum*
The mode of propagation: by seed or root suckers.
Life form: Hemicryptophyte
Floristic categories (Chorotype): IR-TR + SA-SI
Habit: Shrub
Habitat: Sandy soils and resistant to Swamp and Saline Habitats
Chromosome number: 2n = 18
Haplophyllum (5-locular ovary and dehiscent fruit).
Perennial herb, up to 40 cm tall, glabrous to short-hairy; stem usually much branched from the base, yellowish green to almost white; glands numerous on all parts; and very variable. Leaves alternate, strong smelling, variable in shape, from narrowly linear to short in size. Flowers are yellow and variable in size. Petiole short below, absent above; blade very variable, shortly obovate, elliptical, lanceolate or linear, sometimes deeply cut into 3 lobes. Inflorescence a lax corymbose cyme, upper leaf axils, 2–10 (–15) cm in diameter, many-flowered, but flowers well-separated; bracts small, green. The flowers are in loose corymbose terminal panicles, with five free ovate sepals. The stamens 10 are filamentous and hairy. The petals are five and bright yellow in color (9). Flowers bisexual, 5-merous, regular; sepals deltoid-ovate to broadly lanceolate, c. 1 mm long, free; petals elliptical-oblong, 3–5.5 mm long, boat-shaped, narrowed into a claw, bright yellow, glabrous; anthers twice as many as the petals; ovary almost round, 5-lobed, style 1.5–2.5 mm long. Fruit a 3–5-lobed capsule, 2.5–4.5 mm × 1.5–2 mm, hairy, with a lot of inconspicuous to warty glands, segments apically opening, 5–10-seeded. Seeds are kidney-shaped, dark brown or brownish-black, densely ridged.

Ecology

This common perennial herb is found wild even growing as a common weed among summer crops. *Haplophyllum tuberculatum* occurs in sandy desert, on a variety of soils, often on silt deposits, and also in dried watercourses, cultivated and ruderal localities, from sea-level up to 1330 m altitude. The psammophytic community inhabits the sand dunes of *Haplophyllum tuberculatum* on the upper positive part of axis 1 are correlated with species concentration of dominance. These combinations are typical of grass communities inhabiting the wadi bed and sand dunes (10). This genus distributed throughout temperate and subtropical zones of Eurasia and the northern tropical zone of eastern Africa (Somalia). The plant's chemical composition has been shown to vary as a function of geographic location and time of collection. It includes alkaloids, lignans, flavonoids and essential oils (11-13).

Traditional use

It is used in traditional medicine as a remedy for headaches and arthritis, skin discoloration, the juice is applied as a wart removal, and against parasitic diseases and other infections (12). It is also used to treat nervous system, infertility and fever (14). Decoctions of the plant are recommended by herbalists for preparations used as carminatives for children. In the north of Oman, the juice expressed from the leaves is used as a remedy for headaches and arthritis (15). In Saudi Arabia, *Haplophyllum tuberculatum* is used to treat malaria, rheumatoid arthritis and gynecological disorders (16). While, in Sudan the herb is used as an antispasmodic, to treat allergic rhinitis and gynecological disorders, asthma and breathing difficulties (17) and so on, indicating a large degree of variability in its traditional uses as a function of geographic and ecological location.

Phytochemical studies

Many studies have evaluated the medicinal properties and phytochemistry of some of these species, analyzing their contents for alkaloids, lignanes, glycosides and flavonoids, etc. During the phytochemical investigation of *Haplophyllum acutifolium*, two alkaloids named haplophytin-A and B have been obtained. In addition, some known constituents: flindersine, kusunokinin, β-sitosterol, cholesterol, oleanolic acid, and hexadecanoic acid, have also been obtained. Two new alkaloids, haplotubinone and haplotubine, were isolated from the aerial parts of *Haplophyllum tuberculatum* together with the known Lignan Diphyllin (18).

The chemical components of the *Haplophyllum tuberculatum* essential oil was analyzed by gas chromatography–mass spectral (GC–MS) as well as ^{13}C NMR spectroscopy. More than 30 compounds, constituting about 99.7% of the total oil, were identified. The most abundant oil components were β-phellandrene (23.3%), limonene (12.6%), (Z)-β-ocimene (12.3%), β-caryophyllene (11.6%), myrcene (11.3%), and α-phellandrene (10.9%) (9).

The GC-MS analyses on the essential oils from the aerial parts of *H. tuberculatum* led to the identification of 39 compounds, representing 91.3% of the whole oil. *H. tuberculatum* essentials oils were mainly composed by oxygenated monoterpenes (71.0 % of the whole oil). The major compounds of *H. tuberculatum* in essential oil of the plant were cis-*p*-menth-2-en-1-ol as well as *trans-p*-menth-2-en-1-ol (22.9 and 16.1 %, respectively) (19). In an investigation in Larestan, Iran, main components of *Haplophyllum tuberculatum* was borneol (25.73%). Other major compounds were α-Pinene (14%), Bornyl acetate (18.07%) and β-caryophyllene (7.43%) (20).

The main constituents were terpinene-4-ol (3.2.%) hexadec-1-ene (3.2%), -phellandrene (2.1%), -phellandrene (3.0%), p-cymene-8-ol (2.9%), piperitone (17.8), 2,4-bis(1,1-dimethylethyl)-phenol (28.3%), (1E,4E)-germacrene B (2.1%) and octadec-1-ene (2.1%), (63). The oil of this species from Oman revealed that the most abundant components were limonene (12.6%), α-phellandrene (23.3%), (Z)-β-ocimene (12.3%), β-caryophyllene (11.6%), myrcene (11.3%) and β-phellandrene (10.9%) (4). In other sample the major components were *cis-p*-menth-2-en-1-ol (13.2%), *trans-p*-menth-2-en-1-ol (19.2%), myrcene (10.1%), δ-3-carene (8.8%), β-phellandrene (6.9%), limonene (6.6%) and cis-piperitol (6.4%) (21).

Previous investigations on the essential oil of this species showed variable chemical compositions. Sample from Iran was found to contain limonene (27, 3%) and α-pinene (21, 9%) as major constituents (22). The air-dried aerial parts of *Haplophyllum robustum* growing in Iran and analyzed by gas chromatography (GC) and gas chromatography-mass spectrometry (GCMS) was poor in essential oil (yield = 0.5%). However, thirty constituents representing 99.23% of total essential oil were identified in it. The main constituents of the oil were found to be 1,8-cineole (38.1%), myrcene (10.69 %), α-pinene (8.46%), 4-terpineol (6.96%) and sabinene (6.15%). Other representative compounds were identified as methyl geranate (4.69%), γ-terpinen (4.3%) and α-terpinene (3.43%) (23). An earlier report shows the major components of *C. copticum* fruits essential oil as 1,8-cineole. But there is not any trace of sesquiterpenes in all samples of this work (24). These differences might have been derived both from harvest time and local, climatic and seasonal factors or we may hypothesize that this sample belongs to a different chemotype. However, further investigations are needed to elucidate this hypothesis.

Pharmacological aspects

Effect on skin diseases remedy

Natural products are considered as important source for new drug preparation. Many natural products, semi-synthetic or NP derived candidates are now in clinic or in clinical trials (25). This plant is a member of Rutaceae family, a family reported to be rich in furocoumarin (psoralen). These compounds are considered as one of the important class of natural compounds, widely used to treat dermatological conditions for different skin diseases. The available imported preparations of these compounds are very expensive. They have been prominent in the United States for phytochemotherapy of vitiligo, psoriasis, parapsoriasis, mycosis fungoides (26). Recently some other biological activities of Psoralens and related compounds have been reported, including anti-inflammatory, analgesic, antitumor, and calcium antagonist activities. Also these compounds show encouraging levels of phytochemicals against *Fusarium culmorum* and may have a potential use as phytoactive pesticides.

Anticancer effect

The extracts from *Haplophyllum tuberculatum* was toxic against the seven solid cancer cell lines studied with the highest IC_{50} values of 31.64 µg/mL (against Hep-G2 cells). *Haplophyllum tuberculatum* induced cell cycle arrest in G0/G1 and S phases. *Haplophyllum tuberculatum* extract caused apoptosis in CCRF-CEM cells by the alteration of the mitochondrial membrane potential (9).

Uterus-relaxing activity

The pharmacological profile of 6-MKG (6-Methoxykaempferol-3-O-glucoside) isolated from *Haplophyllum tuberculatum* was determined basis on its uterus-relaxing property, employing β_2-adrenoceptors as main target. It was tested on isolated pregnant or none-pregnant rats uteri, whilst docking studies were carried out modeling of the binding of 6-MKG to the rat β_2-adrenoceptorin. Studies have shown that 6-MKG was able to relax both the late-pregnant and the none-pregnant uterine contractility equalto 50% of the E_{max} of terbutaline, whilst the EC_{50} for 6-MKG was at least half of terbutaline result. A β_2-adrenoceptor antagonist 3-(isopropylamino)-1-[(7-methyl-4-indanyl) oxy]butan-2-ol (ICI118,551) antagonized competitively the relaxing effect of 6-MKG. Radioligand binding and cAMP studies confirmed the β2-adrenoceptors agonistic activity of this compound. In a study, 6-MKG bound

to rat β_2-adrenoceptors with low ΔG_{bind} value interacted with four residues of the active site (Asp^{113}, Asn^{312}, Cys^{191} and Tyr^{316}). It is concluded that 6-MKG exerts weak β_2-adrenoceptor agonistic activity and might be considered as a natural compound with therapeutic effect in the field of premature pregnant uterine contractions and asthmatic problems (27). β_2-Adrenoceptor agonists have therapeutic potential due to their use for asthma (28) and to inhibit pre-term labour (19), which is still a medical challenge (29). A few β_2-adrenoceptor drugs are of a natural origin. The effects of a methanolic extract of *H. tuberculatum* and teflubenzuron on several reproductive variables and ecdysteroid titers were investigated. The test products were administered orally to newly emerged females at doses of 1500 and 10 µg/female of *Haplophyllum tuberculatum* and teflubenzuron, respectively. Both were able to delay the first oviposition and reduce fecundity and fertility. *Haplophyllum tuberculatum* and teflubenzuron also showed similar properties on ovarian growth, ecdysteroid titers and vitellogenesis. Both treatments induced a drop in hemolymph protein and reduced vitellogenin uptake by oocytes. This delay in oogenesis was accompanied by a resorption of terminal oocytes. However, whereas teflubenzuron completely blocked egg hatch, *Haplophyllum tuberculatum* had a modest preventive effect on this factor. Hemolymph and ovarian ecdysteroid titers, as measured by radioimmunoassay, were similarly low in control and treated females, except for a peak observed only in control females at the end of vitellogenesis. Assayed against various organisms, *H. tuberculatum* extracts have been observed to display insecticidal (5), nematicidal (30), antifungal and antibacterial (12,31) properties. The plant is used to cure scorpion stings. It is usually used to strengthen the children back muscles, chest pains, flatulence, stomach problems and has sedative effects (32).

Effect on nervous system

Four amides (veskamide, enferamide, becatamide, and oretamide) were investigated for their protective effects on H_2O_2-induced apoptosis in PC-12 cells. These compounds are Nphenylethylbenzoylamide-type phenolic amides, found in plants such as *Aniba riparia Begonia nantoensis*, *Haplophyllum tuberculatum*, and *Houttuynia cordata*. The decreasing order of the protective effects on H_2O_2-induced apoptosis was becatamide > enferamide ≥ oretamide > veskamide. Becatamide suppressed H_2O_2-induced mitochondrial membrane depolarization in a dose-dependent manner. At the concentration of 10 µM, becatamide maintained mitochondrial membrane depolarization at 16% compared to 51% in H_2O_2-treated PC-12 cells (33). Certain neurodegenerative diseases progressively deteriorate the structure and/or the function of neurons in the central nervous system, eventually leading to cell death (34,35). Neurodegenerative processes are very much responsible for several neuronal diseases such as Alzheimer's, Parkinson's, and Huntington's diseases (7,36). Although there are several mechanisms involved in neuronal cell death, a most common mechanism is through the well-known intrinsic mitochondrial apoptotic pathway (38). Depolarization of mitochondria membrane potential caused damage to outer membrane resulted in the loss of its dye from the mitochondria decreasing the intracellular fluorescence (39).

Anti-HIV effect

Anti-HIV agents from natural resources are belonged to various classes including terpenoids, coumarins, alkaloids, polyphenols, tannins and flavonoids (40). The buchapine, quinolone alkaloid, was isolated from methanolic extract of the epigeal part of *Haplophyllum bucharicum* (41), *Haplophyllum tuberculatum* (42). The natural products of this plant exhibit anti-HIV activity against HIV-1 in cultured human lymphoblastoid CEM-SS cells (EC_{50} 0.94 µM, IC_{50} 29.0 µM and EC_{50} 1.64 µM, IC_{50} 26.9 µM), respectively (43). Naturally occurring quinolone alkaloid buchapine was evaluated for anti-HIV activity on CEM-GFP (human CD4+ T cell line), infected with HIV-$1_{NL4.3}$ virus by p24 antigen capture ELISA assay. The compounds1and 2 revealed inhibitory activity with IC_{50} value of 2.99 and 3.80 µM, respectively (44). Further, 45 alkylated derivatives of a base compound, quinoline 2,4-diol were then synthesized and tested for anti-HIV potential in human CD_4^+ T cell line CEM-GFP. Among these, 13 derivatives have shown more than 60% inhibition. All active compounds showed higher CC_{50} values which indicate that they have better therapeutic indices. Bevirimat, a semi-synthetic derivative of betulinic acid, is in phase IIb trials in HIV-infected patients (25). Bevirimat blocks HIV maturation by inhibiting the final step of the HIV Gag protein processing. Batzelladines (45), harmine (46), michellamine B (47), calanolide A and B, calceolarioside B (48), mallotojaponin (49); and macrocarpals (50) are a few other examples of anti-HIV natural products.

Antimicrobial effect

Ten microlitres (25 mg) of pure oil of *Haplophyllum tuberculatum* partially inhibited the growth of *Escherichia coli*, *Salmonella choleraesuis*, and *Bacillus subtilis* to the same extent as 0.10 µg of gentamycin sulfate. The oil also affected the mycelial growth of *Curvularia lunata* and *Fusarium oxysporum* in a dose-dependent manner, however,it had not any effect on the germination of their spores (9). Antimicrobial testing of polyphenolic and alkaloid compounds, on solid medium, showed the presence of antibacterial properties of some tested strains including *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923 and *Pseudomonas aeruginosa* ATCC 27953. Their MICs ranged from 0.625 mg/mL to 10 mg/mL for alkaloids and 5 mg/mL to 20 mg/mL for polyphenols (51).

Insecticidal effect

Haplophyllum tuberculatum is used to protect livestock from biting insects and flies (6). The ethanol extract of the aerial parts of *Haplophyllum tuberculatum* possess good insecticidal activity against *Culex quinquefasciatus* (52). The nematicidal properties of *Haplophyllum tuberculatum*

against root-knot nematode were reported, which is due to the presence in the plant of three known alkaloids: fagarine, skimmianine and evoxine. The effects of *Plectranthus cylindraceus* and *Haplophyllum tuberculatum* oils to control *Meloidogyne javanica* were investigated. A mixture of plectranthus and haplophyllum oils (1:1) was highly toxic to *M. javanica* in vitro, as it killed all nematode juveniles and inhibited hatching of eggs at 12.5 mg/mL concentration after 24 hours exposure time. In the green-house, tomatoes grown in soil treated with a combination of the two essential oils caused fewer root galls than those grown in soil treated with higher doses of either oil. The oil mixture, at 2.5 and 5.0 mg/mL of soil, was not phytotoxic to tomato plant after 12 weeks exposure time, compared to treatment over the same period at lower effective doses (53). Nematicidal activities of the combined essential oils were suggested by the presence of C_{10} dienes, C_{10} trienes and C_{10} phenol (54). *Meloidogyne javanica* (Treub) Chitwood is one of the most common and widespread species of root-knot nematodes in world. This Meloidogyne species can cause severe yield losses on tomato, okra, eggplant, melon, onion, carrot, cabbage, pepper, sweet potato and lettuce in greenhouse (53). The major chemical components with nematicidal activities have been previously identified as thymol, carvacrol, pulegone, limonene, anethole, geranial and artemisia ketone (54).

Conclusion

Sistan and Baloochestan province is a rich center of medicinal plants. One of the important medicinal plants in this region, distributed in three locations of this province, is *Haplophyllum tuberculatum*. It is used in traditional medicine as a remedy for headaches and arthritis, the juice is applied as a wart removal, infections skin discoloration, and parasitic diseases. In Baloochestan, it is use by women for healing after childbirth ailments. It has many other medicinal properties and the bioactive molecules of this plant play an important role in human health, hence, it might be used for different drug productions. Because of importance of this plant, cultivation of it is very necessary.

Authors' contributions

All the authors wrote the manuscript equally.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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