

Pharmacological importance of *Haplophyllum* species grown in Iraq- A review

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Abstract: *Haplophyllum* species contained alkaloids, lignans, coumarins, flavanoids, essential oil and volatile oil. *Haplophyllum* species possessed many pharmacological activities included antioxidant, antimicrobial, insecticidal, antiprotozoal, molluscicidal, cytotoxic, cardiovascular, antiinflammatory and acetylcholinesterase inhibitory effects. The current review discussed the chemical constituents and pharmacological effects of grown in Iraq.

Keywords: chemical constituents, pharmacology, *Haplophyllum blanchei*, *Haplophyllum filifolium*, *Haplophyllum buxbaumii* (*Haplophyllum buxbaumii* sub *mesopotamicum*), *Haplophyllum propinquum*, *Haplophyllum tuberculatum*

Date of Submission: 28-05-2018

Date of acceptance: 11-06-2018

I. Introduction:

Herbal medicine is the oldest form of medicine known to mankind. It was the mainstay of many early civilizations and still the most widely practiced form of medicine in the world today. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives⁽¹⁻³⁰⁾. Five *Haplophyllum* species were recorded in Iraq included *Haplophyllum blanchei*, *Haplophyllum filifolium*, *Haplophyllum buxbaumii* (*Haplophyllum buxbaumii* sub *mesopotamicum*), *Haplophyllum propinquum* and *Haplophyllum tuberculatum*. *Haplophyllum* species contained alkaloids, lignans, coumarins, flavanoids, essential oil and volatile oil. *Haplophyllum* species possessed many pharmacological activities included antioxidant, antimicrobial, insecticidal, antiprotozoal, molluscicidal, cytotoxic, cardiovascular, antiinflammatory and acetylcholinesterase inhibitory effects. The current review was designed to highlight the chemical constituents and pharmacological effects of grown in Iraq.

Plant profile:

Synonyms:

Five *Haplophyllum* species were recorded in Iraq included *Haplophyllum blanchei*, *Haplophyllum filifolium*, *Haplophyllum buxbaumii* (*Haplophyllum buxbaumii* sub *mesopotamicum*), *Haplophyllum propinquum* and *Haplophyllum tuberculatum*⁽³¹⁻³⁷⁾.

Haplophyllum blanchei (no synonyms)⁽³⁸⁾

Haplophyllum filifolium: *Haplophyllum hispanicum* Spach, *Haplophyllum pubescens*, *Ruta linifolia*⁽³⁹⁾.

Haplophyllum buxbaumii: *Haplophyllum buxbaumii* sub *mesopotamicum*⁽⁴⁰⁾.

Haplophyllum propinquum: *Ruta propinqua*⁽⁴¹⁾.

Haplophyllum tuberculatum: *Haplophyllum arabicum* Boiss., *Haplophyllum candolleianum* Spach ex Jaub. & Spach, *Haplophyllum chesneyanum* Boiss., *Haplophyllum eremophilum* Boiss. & Hausskn., *Haplophyllum filifolium* Sp., *Haplophyllum glabrum* (DC.) G. Don, *Haplophyllum haussknechtii* Boiss., *Haplophyllum kotschyi* Spach, *Haplophyllum longifolium* Boiss., *Haplophyllum obovatum* Hand. Mazz., *Haplophyllum propinquum* Spach, *Haplophyllum stocksianum* Boiss., *Haplophyllum trichostylum* Bunge, *Haplophyllum tuberculatum* var. *leiocalycinum* Hand.-Mazz., *Haplophyllum tuberculatum* var. *linearifolium* Stapf ex Parsa, *Haplophyllum tuberculatum* subsp. *vermiculare*, *Haplophyllum vermiculare* Hand.-Mazz., *Haplophyllum vermiculare* var. *cyrenaicum* Pamp., *Haplophyllum villosulum* Boiss. & Hausskn., *Ruta ciliata* Savi ex Steud., *Ruta dichotoma* DC., *Ruta glabra* DC., *Ruta kotschyi* (Spach) Pau, *Ruta montbretii* Viv., *Ruta obovata* (Hochst. ex Boiss.) , *Ruta propinqua* (Spach), *Ruta telephifolia* Pau, *Ruta tuberculata* Forsk. and *Ruta tuberculata* var. *obovata* Steud⁽⁴²⁾.

Taxonomic classification:

Kingdom: Plantae, **Phylum:** Tracheophyta, **Class:** Magnoliopsida, **Order:** Sapindales, **Family:** Rutaceae, **Genus:** *Haplophyllum*, **Species:** *Haplophyllum blanchei*, *Haplophyllum filifolium*, *Haplophyllum buxbaumii*, *Haplophyllum propinquum* and *Haplophyllum tuberculatum*⁽⁴³⁾.

Common names:

Arabic: Afna, Zifra, Kheisa, Juwaifah, Mesaka, Gergig, Shajarat El Reeh, Shajarat El Kalb, Shajarat El Ghazal, Krin El Ghazal, Mujanina; **English:** Plant of the mosquito^(31,43).

Distribution:

Haplophyllum blanchei: (Saudi Arabia, Iraq, Jordania and Syria). *Haplophyllum buxbaumii* (*Haplophyllum buxbaumii* sub *mesopotamicum*): (Iran, Iraq and Turkey). *Haplophyllum propinquum*, *Haplophyllum filifolium* and *Haplophyllum tuberculatum*: (Yemen, Turkey, Bahrain, Egypt, Iran, Iraq, Palestine, Jordan, Kuwait, Oman, Saudi Arabia, Syria, United Arab Emirates, Afghanistan, Pakistan, Algeria, Morocco, Tunisia, Libya, Sudan, Somalia and Chad)^(42,44-46)

Description:

A large genus comprising 70 species distributed from the Mediterranean region to Siberia. Perennial herbs and semishrubs, branching profusely and often woody below, glandular punctate and strongly aromatic. Leaves simple, alternate, mostly lanceolate to elliptic or linear or 3(-5)-sect. Inflorescence in corymbose cymes, bracteate. Sepals 5. Petals 5, concave. Stamens 10, filaments free, subulate and pubescent/barbate on the inner side. Ovary 3-5-locular; locules 1-6 (-10)-ovulate; styles fused; stigma capitate. Capsule 3-5-lobed, usually dehiscent. Seeds reniform, rugose⁽⁴⁷⁾.

Traditional uses:

Haplophyllum species: were used in Iraq, as a salve for wounds. The decoction was used as a cure in stomach-ache for children⁽³¹⁾. *Haplophyllum* species were suggested to have activity on central nervous system. For instance, the leaves of these plants were given to children as an infusion with vinegar for the treatment of convulsion and other nervous disorders⁽⁴⁸⁾.

However, *Haplophyllum tuberculatum* was used traditionally in Algeria for many complains as antiseptic, for injuries and ulcers, as calming, hypnotic neurological, for infertility, diabetes, bloating, fever, liver disease, otitis, rheumatism, as vermifuge, for obesity, constipation, colon, diarrhea, gases, hypertension, menstrual pain, cardiac disease, scorpion stings, flu, vomiting, throat inflammation, tonsillitis, cough and loss of appetite⁽⁴⁹⁾.

In the north of Oman, the juice expressed from the leaves was used as a remedy for headaches and arthritis. In Saudi Arabia, *Haplophyllum tuberculatum* was used traditionally for headaches and arthritis, to remove warts and freckles from the skin and to treat skin discoloration, infections and parasitic diseases. In Sudan the herb was used as an antispasmodic, to treat allergic rhinitis, gynecological disorders, asthma and breathing difficulties⁽⁵⁰⁻⁵³⁾.

Parts used medicinally:

The whole plant especially leaves^(31, 49-53).

Chemical constituents:

Haplophyllum species contained alkaloids, lignans, coumarins, flavanoids, essential oil and volatile oil^(32, 54).

Haplophyllum buxbaumii (Syn: *Haplophyllum buxbaumii* sub *mesopotamicum*) yielded furoquinoline compounds, γ -fagarine, kokusaginine, skimmianine; 4,5,6-trimethoxy furoquinoline; 4,5,7-trimethoxyfuroquinoline and an angular pyranoquinoline type alkaloid, N-hydroxymethylflindersine. Only one lignan, justicidin B was isolated from the plant⁽⁵⁵⁾.

Daurinol derivatives, daurinol glucoside and mono-O-acetyldaurinol glucoside were isolated from *H. buxbaumii*⁽⁵⁶⁾

In Jordan, a lignan glycoside, monoacetyldiphyllin apioside, dictamnine, γ -fagarine, justicidin B, diphyllin, and (-)-tuberculatin were isolated from *Haplophyllum buxbaumii*⁽⁵⁷⁾.

Three type A lignin glycosides, majidine, qudsine, arabelline as well as cleistanthin B, diphyllin glycoside 4-O-[bis-a-L-xylopyranosyl (1→2, 1→5) b-D-apiofuranosyloxy] - 6,7-dimethoxy 1-(3,4-methylene dioxyphenyl)-3-hydroxy methyl naphthalene-2-carboxylic acid lactone (azidin) were isolated from *Haplophyllum buxbaumii*⁽⁵⁸⁻⁵⁹⁾.

Lignans as well as diphyllin diphyllin derivatives such as diphyllinine, diphyllidine monoacetate, diphyllidin crotonate and diphyllin methoxy derivative (justicidin A) were obtained from *H. hispanicum*⁽⁶⁰⁾.

Diphyllin acetyl apioside and tuberculation were isolated from the methanol extract of *Haplophyllum hispanicum*⁽⁶¹⁾

Two aryl-naphthalene lignans, diphyllin apioside and diphyllin acetylapioside were isolated from *Haplophyllum linifolium* (*Haplophyllum hispanicum*)⁽⁶²⁾.

The preliminary phytochemical analysis showed that *Haplophyllum tuberculatum* contained tannins, steroids, flavonoids, essential and volatile oils and carbohydrates⁽⁶⁵⁾.

Flindersine, γ -fagarine, skimmianine, evoxine and 3-(3,3-dimethylallyl)-4-(3,3-dimethylalloxy)-2-quinolone were obtained from *Haplophyllum tuberculatum* collected from Iraq. Alkaloid (+)-tuberine, haplotubinone and haplotubine were also isolated from *Haplophyllum tuberculatum*^(33,64-66)

Quinoline alkaloids and lignan lactones, included: quinoldione, 3-(1',1'-dimethylallyl)-3-(3'',3''-dimethylallyl)-1,2,3,4-tetrahydro-2,4-quinoldione, 4-(3',3'-dimethylallyloxy)-3-(3'',3''-dimethylallyl)-2(1H)-quinolone, Polygamain, kusunokinin and 1-methyl-2-n-nonyl-4(1H)-quinolone were isolated from *Haplophyllum tuberculatum*. Haplotubinone and haplotubine alkaloids, were also isolated from the aerial parts of *Haplophyllum tuberculatum*. Four lignans, diphyllin, justicidin A, justicidin B, and tuberculatin were isolated from *Haplophyllum tuberculatum*⁽⁶⁶⁻⁶⁹⁾.

Furocoumarin (psoralen) derivatives, ammoidin was isolated from *Haplophyllum tuberculatum* from Iraq⁽⁷⁰⁾.

The aerial parts of *Haplophyllum tuberculatum* collected in Sudan yielded the furoquinoline alkaloid skimmianine, the lignan justicidin-A, and 5,7,4'-trihydroxy-6-methoxy-3-O-glucosyl flavone⁽⁷¹⁾.

Total phenol content was 46.2 mg gallic acid/g in the ethanolic extract of *Haplophyllum tuberculatum* aerial parts⁽⁷²⁾.

However, Al-Brashdi *et al.*, found that the total phenolic content of *Haplophyllum tuberculatum* was 561.22 mg/g of gallic acid equivalent, and flavonoids were 165.54 mg/g of quercetin equivalent⁽⁶³⁾.

Chemical analysis of *Haplophyllum tuberculatum* naturally growing in Saudi Arabia revealed the presence of amide alkaloids, tuberine, tubacetine, tubasenicine and 7-Hydroxy-4-Methoxy-8-prenylfuro[2,3-b]quinolone⁽⁵¹⁾.

GS-MS analysis of the essential oil of the fresh twigs and flowers of *Haplophyllum tuberculatum* from Oman showed that β -phellandrene (23.3 %) was the main part of the oil, however it contained myrcene (11.3 %), β -phellandrene (10.9%), (*Z*)- β -ocimene (12.3 %), limonene (12.6 %), and β -caryophellene (11.6 %). Most of the 7remaining 23 compounds were less than 1 %⁽⁷³⁾.

The essential oil of *Haplophyllum tuberculatum* from Algeria was analysed by GC and GC-MS, the main constituents were alpha -phellandrene (2.1%), beta-phellandrene (3.0%), terpinene-4-ol (3.2%), p-cymene-8-ol (2.9%), piperitone (17.8), 2,4-bis(1,1-dimethylethyl)-phenol (28.3%), (1E,4E)-germacrene B (2.1%), hexadec-1-ene (3.2%) and octadec-1-ene (2.1%)⁽⁷⁴⁾.

Essential oils of *Haplophyllum tuberculatum* (Forssk.) A. Juss from the United Arab Emirates, were analyzed by GC and GC/MS. The composition of the oils varied considerably with the time of collection. Those obtained from plants collected in May (1997 and 2001) were similar, with α -phellandrene (10.7-32.9%) being the major component and with significant amounts of β -caryophyllene (6.3-12.8%), β -pinene (7.6-8.0%), limonene (4.0-9.6%) and δ -3-carene (5.5-6.0%). However, the oil distilled from plants collected in April (1998) had major components of linalool (15.0%), linalyl acetate (10.6%), β -caryophyllene (9.7%) and alpha-terpineol (6.7%)⁽⁷⁵⁾.

The essential oils of the aerial parts and flowers of *Haplophyllum tuberculatum* growing in Libya were identified by GC/MS analysis. Oil yield was found 0.4 and 1.5 (v/w %) on dry weight basis respectively. GC/MS analysis resulted in identification of total 35 compounds (1-butanol-3-methylacetate, α -thujene, α -pinene, pentanol, cyclohexen,1-methy-4-(1- ethylethyldiene, β -myrcene, pentane-2,2-dimethyl, octanal, isovaleric acid isobutyl ester, α -phellandrene, 3-carene, cineol, iso-terpinolene, 2-pentanone ethylacetone, acetophenone-4'-methyl, cyclooctadiene-3,7-dimethyl, β -phellandrene, eucalyptol, cis B-ocimene, 1-cyclo propyl pentane, non-2-en-1-ol, n-amyl iso valerate, linalool, butyric acid-2-methyl, isovaleric acid iso pentyl ester, n-amyl isovalerate, octanol (n-octan-1-ol), α -terpinen, β -terpinen, ocimenol, trans piperitol, γ -terpinen, piperitone, (-)-zingiberene, β -sesquiphellandrene)⁽⁷⁶⁾.

The aerial parts of *Haplophyllum tuberculatum* (Forssk.) A. Juss. From Iran yield 0.02% oil. The main components of the oil were linalool (15.5%), α -pinene (7.9%) and limonene (5.3%)⁽⁷⁷⁾.

Pharmacological effects:

Antioxidant effect:

The antioxidant and cytoprotective potential of ethanol extract of *Haplophyllum tuberculatum* aerial parts was investigated *in vitro*. Human astrocytoma U373-MG cell line was pretreated with ethanol extract (from 0.025 to 250 μ g/ml) for 24 h, prior to 1 mM H₂O₂ exposure (30 min). The antiradical activity (ORAC assay) was 1.283 μ mol TE/mg sample. Pretreatments with ethanol extract at the concentrations of 2.5, 0.25 and 0.025 μ g/ml significantly attenuated H₂O₂-induced loss in viability by 13.5, 17 and 20.5%, respectively. Furthermore, these ethanol extract concentrations markedly inhibited intracellular ROS production with IC₅₀ 0.026 μ g/ml⁽⁷²⁾.

The potential protective activity of *Haplophyllum tuberculatum* essential oils against oxidative stress was alsoevaluated, employing H₂O₂ as oxidant inductor and astrocytes as the cell model. *Haplophyllum*

tuberculatum essential oils showed high scavenging activity and protected human astrocytoma U373-MG cells against H₂O₂ damage. The essential oils prevented cell death and inhibited ROS production caused by H₂O₂⁽⁷⁸⁾.

The antioxidant activity of polyphenols and alkaloids of *Haplophyllum tuberculatum* was evaluated with the β-carotene bleaching test and the reducing power test, the two substances showed good antioxidant activity with a better activity of the polyphenols compared to the alkaloids⁽⁷⁹⁾.

The ethanolic extract was evaluated for antioxidant effect by determination of glutathione in blood of alloxan-induced diabetic rats. The ethanolic extract of the aerial parts of *Haplophyllum tuberculatum* exhibited significance anti-oxidant activity (98%) as compared to vitamin E. The reduced level of glutathione in diabetic rats was also greatly restored by the essential oils of the aerial parts and flowers relative to vitamin E⁽⁸⁰⁾.

The *in vitro* antioxidant power of *Haplophyllum tuberculatum* leaves extracts of varying polarities was investigated by using 1,1 diphenyl-2-picrylhydrazyl radical and phosphomolybdenum reagent with the using of ascorbic acid as a reference antioxidant. The free radical scavenging activity of leaves fractions was slightly lower than the reference compound. However, leaves fractions exhibited significant total antioxidant capacity equivalent to ascorbic acid. A direct relationship was observed between phenolic content and *in vitro* antioxidant activity⁽⁶³⁾.

Antimicrobial effect:

Ethanolic extract of the aerial parts of *Haplophyllum tuberculatum* demonstrated an efficient anti-fungal activity against *Aspergillus fumigates*, *Geotricum candidum* and *Syncephalastrum racemosum* with (MIC 0.49, 0.12 and 1.95 µg/ml). *Haplophyllum tuberculatum* also exhibited a significant effect (at concentration of 1 mg/ml) against Gram -ve and Gram +ve microorganisms [*Staphylococcus aureus* (RCMB 010028), *Enterococcus faecalis* (RCMB 010084), *Streptococcus mitis* (RCMB 010039), *Lactobacillus acidophilus* (RCMB 010094), methicillin-resistant *Staphylococcus aureus* [MRSA] (RCMB 010028) and *Escherichia coli* (RCMB010052)], but inactive against *Pseudomonas aeruginosa*. Ethanolic extract showed remarkable antibacterial potency against *Staphylococcus aureus* and *Escherichia coli* (MIC 1.95 and 15.63 µg/ml). Volatile oil of the aerial parts of *Haplophyllum tuberculatum* possessed significant antibacterial effect against *Enterococcus faecalis* and *Lactobacillus acidophilus* (MIC 1.95 and 0.98 µg/ml)⁽⁸⁰⁾.

The antimicrobial activity of the essential oil of *Haplophyllum tuberculatum* was determined using the broth microdilution method against various human pathogens. Furthermore, the oil was evaluated for its antifungal activity against the strawberry anthracnose-causing fungal plant pathogens *Colletotrichum acutatum*, *C. fragariae* and *C. gloeosporioides* using the direct overlay bioautography assay. The essential oil showed no antifungal activity at 80 and 160 µg/spot concentrations compared to commercial antifungal standards⁽⁸¹⁾.

The alkaloid, (+)-tuberine isolated from *Haplophyllum tuberculatum*, showed high antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Saccharomyces cerevisiae* at 1µg/ml. It was slightly inhibitory to *Escherichia coli*⁽⁶⁸⁾.

25 mg of pure essential oil of *Haplophyllum tuberculatum* partially inhibited the growth of *Escherichia coli*, *Salmonella choleraesuis* and *Bacillus subtilis* to the same extent as 0.10 microg of gentamycin sulfate. The oil also affected the mycelial growth of *Curvularia lunata* and *Fusarium oxysporium* in a dose-dependent manner but had no effect on the germination of their spores⁽⁷³⁾.

The antimicrobial of polyphenols and alkaloids of *Haplophyllum tuberculatum* was investigated. Antimicrobial tests based on polyphenolic and alkaloid extracts of the plant showed average activity on a few bacterial strains (*Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27953), with MICs varying from 0.625 mg/ml to 10 mg/ml for alkaloids and from 5 mg/ml to 20 mg/ml for polyphenols. However, the fungal strains tested *Aspergillus flavus* NRRL 3251T, *Aspirinillus parasiticus* CBS 100926T, *Aspirigillus fumigatus* and *Mucor sp* were all resistant^(79,82).

Insecticidal, antiprotozoal and molluscicidal effect:

The oil of *Haplophyllum tuberculatum* was investigated for its insecticidal and repellent activity against *Aedes aegypti*. The oil was repellent to the yellow fever mosquito *Ae. aegypti* using the cloth patch assay, down to a concentration of 0.074 mg/cm²; however, the oil had low toxicity against first instar larvae and adults of *Ae. aegypti* in a high throughput larval bioassay and adult topical assay⁽⁸¹⁾.

The methanol extract of flowering aerial parts of *Haplophyllum linifolium* (*Haplophyllum hispanicum*) was very active against epimastigotes of *T. cruzi*, with a 65% of growth inhibition at 250 µg/ml. The obtained results indicated that the aryl-naphthalene lignans contribute to the anti-protozoal activity of the plant⁽⁸³⁾.

The effect of two aryl-naphthalene lignans, diphyllin apioside and diphyllin acetylapioside isolated from *Haplophyllum linifolium* (*Haplophyllum hispanicum*) was evaluated against epimastigotes of *T. cruzi* in axenic cultures. The results showed that the diphyllin derivatives aryl-naphthalene lignans, diphyllin apioside and diphyllin acetylapioside were only endowed with a mild *in vitro* antitrypanosome activity, with IC₅₀ values of 62.9 and 60.1 µM respectively, but they appeared toxic to normal mammal cells at the same concentration.

Furthermore, the plant methanolic extract exhibited a potent topical toxicity, causing necrosis of the skin, when applied chronically⁽⁶²⁾.

Haplophyllum tuberculatum was evaluated as a plant molluscicide. The mortality rate of *Biomphalaria alexandrina* snails were monitored after treatment with three extracts of the plant aerial parts (petroleum ether, chloroform and ethanol). Chloroform extract that recorded the most potent effect was further evaluated through measuring the toxicity pattern against *B. alexandrina* snails, egg laying capacity, cercarial shedding, phenol oxidase enzyme and the levels of steroid sex hormones. Histopathological examination of hepatopancreas and ovotestis of treated snails were also carried out for confirmation. Treatment of snails by chloroform extract showed reduction in egg laying capacity, decrease in cercarial shedding, diminution in phenol oxidase enzyme, disturbance in steroid sex hormones and sever alternation of the histopathological picture of snails tissue⁽⁸⁴⁾.

Cytotoxic effect:

A resazurin assay was used to assess the cytotoxicity of twenty six Saudi Arabian medicinal plants extracts on a panel of human cancer cell lines. The best activity on leukemia cell lines were recorded with *Haplophyllum tuberculatum* extract (IC₅₀ of 9.94 µg/ml). It induced cell cycle arrest in G0/G1 and S phases^(52,79).

Oil of *Haplophyllum tuberculatum* exhibited antitumor activities against liver carcinoma cell line (HEPG2) and lung carcinoma cell line (H1299). IC₅₀% was 4.7 µg/ml and 4.1 µg/ml respectively⁽⁷⁶⁾.

In studying the cytotoxicity of four lignans and two other closely-related compounds isolated from *Haplophyllum hispanicum*, it appeared that diphyllin, possessed greater specific cytostatic activity (at a concentration of 0.05 µg/ml) than 6-mercaptopurine⁽⁶⁰⁾.

The cytotoxicities of *Haplophyllum linifolium* (*Haplophyllum hispanicum*) extracts and compounds were assessed on elicited peritoneal leukocytes obtained from rats with viability greater than 95% as determined by the trypan blue exclusion test. The cell viability was assessed by the capacity of PMN mitochondrial dehydrogenase enzymes to convert the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) into a dark blue formazan. It appeared that aryl naphthalene lignans were cytotoxic just over 40 µM⁽⁶²⁾.

Acetylcholinesterase inhibitory effect:

The oil showed weak acetylcholinesterase (AChE) inhibitory activity, compared to standard substances, whereas no inhibition on butyrylcholinesterase (BuChE) activity was observed⁽⁸¹⁾.

Haplophyllum tuberculatum was studied for AchE inhibitory activity. The inhibitory activity of acetyl cholinestrace was mainly accumulated in the chloroform and ethyl acetate fractions of different parts extracts of *Haplophyllum tuberculatum*. The most active was the stem ethyl acetate fraction with an inhibitory effect of 79% and IC₅₀ of 0.45 µg/ml. Other fractions possessed an inhibitory effect at arrange between 70 – 77%⁽⁸⁵⁾.

Cardiovascular effect:

The aqueous extract of *Haplophyllum tuberculatum* significantly decreased the contractility and the heart rate but did not affect the flow rate of isolated perfused rabbit heart. The effect of the aqueous extract was not blocked by atropine. Aqueous extract caused fall in the blood pressure when administered to anaesthetized cats, muscarinic antagonist blocked the fall in blood pressure in cats. The extract also stimulated rabbit aortic strip, rat vas deferens, and rat anococcygeus muscles. These adrenergic effects were largely reduced by phentolamine⁽⁸⁶⁾.

Antiinflammatory effect:

The essential oils from aerial parts and flowers of *Haplophyllum tuberculatum* exhibited a remarkable acute anti-inflammatory activity against carrageenan induced oedema in rats comparable to the standard drug, indomethacin⁽⁸⁰⁾.

The methanolic extract of *Haplophyllum hispanicum* was tested against two experimental models of acute inflammation, TPA-induced ear and carrageenan-induced paw edemas in mice. It possessed a 50% reduction of the ear edema when it was administered topically compared with indomethacin (86%), when the extract was given orally it did not inhibit the paw edema to a significant degree in 5 h (inhibition = 37%). In a second stage, the extract was assayed against two other inflammatory conditions, oxazolone-induced delayed hypersensitivity and the multiple-dose TPA-induced response, which differ in their inflammation generating mechanism. The increase in ear thickness produced by oxazolone was magnified (+ 18%) by treatment with the plant extract, indicating that some constituents may cooperate with the sensitizing agent. Two topical anti-inflammatory aryl naphthalide lignans were isolated from the active fractions of the methanol extract. They were identified as diphyllin acetyl apioside and tuberculation. The former was the most active on acute TPA edema with ID₅₀ of 0.27 µmol/ear^(61,87).

It appeared that the topical anti-inflammatory activity of *Haplophyllum hispanicum* was attributed to the presence of aryl naphthalene-type lignans acting as 5-lipoxygenase (5-LOX) inhibitor⁽⁸⁸⁾.

The methanol extract of *H. linifolium* (*Haplophyllum hispanicum*) applied twice daily (15 µL, 1 mg/ml) during four days onto the left ears of Swiss mice in the morning immediately after TPA 2.5 µg/ear application and 6 h later, showed a potent topical anti-inflammatory activity with no apparent toxicity⁽⁶²⁾.

Toxicity and side effects:

The 24- hours LD₅₀ was approximately more than 0.05ml and 10 g/kg bw for the essential oils and the ethanolic extract of aerial parts of *Haplophyllum tuberculatum*.

These results showed that the essential oils and the ethanolic extract were safe and non-toxic⁽⁸⁰⁾.

Haplophyllum genus contained potent topical photodynamic compounds, skin contact with these plant, followed by exposure to the sunlight or UV radiation, induced burns and hyperpigmentation. This phenomena attributed to arylnaphthalene lignans⁽⁸⁹⁻⁹⁰⁾.

II. CONCLUSION:

The current review discuss the chemical constituent, pharmacological and therapeutic effects of *Haplophyllum* species grown in Iraq as promising herbal drugs.

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Prof Dr Ali Esmail Al-Snafi " Pharmacological importance of Haplophyllum species grown in Iraq- A review." IOSR Journal of Pharmacy (IOSRPHR), vol. 8, no. 05, 2018, pp. 54-62