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CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EFFECT OF *INULA GRAVEOLENS* (SYN: *DITTRICHIA GRAVEOLENS*)- A REVIEW

Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, University of Thi qar, Iraq.
Cell: +9647801397994. E mail: aboahmad61@yahoo.com

Abstract:
The phytochemical study showed that Inula graveolens contained polyphenols, tannins, flavonoids, oil, steroidal triterpenoides, sesquiterpene and anthraquinones. The pharmacological researches revealed that Inula graveolens exerted antimicrobial, insecticidal, anti- platelet aggregation, antiproliferative, anti-diarrheal, antipyretic, analgesic, antiinflammatory and anticholenergic effects. The current review discussed the chemical constituents and pharmacological effects of Inula graveolens.

Keywords: *chemical constituents, pharmacology, Inula graveolens*

Corresponding author:
Ali Esmail Al-Snafi
Department of Pharmacology,
College of Medicine,
University of Thi qar, Iraq
Cell: +9647801397994.
E mail: aboahmad61@yahoo.com

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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[1-14]. The phytochemical study showed that *Inula* graveolens contained polyphenols, tannins, flavonoids, oil, steroidal triterpenoides, sesquiterpene and anthraquinones**.** The pharmacological researches revealed that *Inula graveolens* exerted antimicrobial, insecticidal, anti- platelet aggregation, antiproliferative, anti-diarrheal, antipyretic, analgesic, antiinflammatory and anticholenergic effects. This review will discuss the chemical constituents and pharmacological effects of *Inula graveolens.*

Plant profile:

Synonyms:

Conyza minor Bubani, *Cupularia graveolens* [L.] Godr. & Gren., *Dittrichia graveolens* [L.] Greuter, *Erigeron graveolens* L., *Inula brahuica* Boiss., *Inula quadridentata* Lag and *Jacobaea graveolens*[L.] Merino[15].

Taxonomic classification:

Kingdom: Plantae; **Subkingdom**: Tracheobionta; **Superdivision**: Spermatophyta; **Division**: Magnoliophyta; **Class**: Magnoliopsida; **Subclass**: Asteridae; **Order**: Asterales; **Family**: Asteraceae ⁄ Compositae; **Genus**: Dittrichia/ Inula; **Species**: *Inula graveolens* and *Dittrichia graveolens*[16].

Common names:

Arabic: Inula, Shuwaser, Suawaid, Rasan, Teion; **English:** Camphor inula, Cape khakiweed, Stinking-fleabane, Stinkweed, Stinkwort; **German**: Drüsiger Alant, Klebriger Alant; **Iran**: Atre paizii **Swedish**: Kamferinula[17-20].

Distribution:

It was distributed in Africa [Egypt, Algeria, Libya, Morocco, Tunisia]; Asia [Iraq, Iran, Palestine, Jordan, Lebanon, Syria, Turkey, Pakistan]; Europe [Albania, Bosnia, Bulgaria, Croatia, Greece, Italy, Macedonia, Montene gro, Serbia, France, Portugal, Spain, Austria, Belgium, Czech Republic, Germany, Netherlands, Switzerland, United Kingdom, Slovenia]; Australasia [Australia, New Zealand] and Northern America [USA][17-19].

Description:

Plant viscid, rank smelling, 20–130 cm; stems ± pilose and stipitate-glandular. Leaf blades linear to lance-linear, 1–3[–7] cm × 1–3[–10] mm, margins entire or denticulate, apices acute, faces pilosulous to hirtellous and minutely stipitate-glandular. Phyllaries 1–8 mm. Ray florets [6–]10–12[–16]; corolla laminae 2–5[–7] mm. Disc florets 9–14+; corollas 3–4 mm. Cypselae 1.5–2 mm[21-22].

Traditional uses:

Inula graveolens was widely used in aromatherapy for the treatment of asthma. It was used as bronchospasmolytic and mucolytic[23]. *Inula graveolens* was widely used in Iraq for the treatment of rheumatic fever, infant convulsions, toothache, to reduce blood sugar, to dissolve internal blood clots, and to aid digestion[18]. In Iranian traditional medicine it was used as a anti-inflammation, antirheumatism, antitumor, antipathogene and antiinfection specially in the treatment of leishmaniosis[20]. It was also used for treatment of urinary tract infections, hemorrhoids, cold and wound infections[24].

Oil was inhaled in low concentrations for desired mucolytic effect, as decongestant in sinusitis and respiratory inflammations, and for loosening mucus in unproductive coughs and asthmatic conditions. Topically, it was used as counteracts and was blended with Eucalyptus Dives, Spike Lavender, and Rosemary Verbenone, to releive acne caused by ovreactive sebaceous glands. Inula dissolved hardened sebum from clogged glands[25]. Essential oil was also used to support lymphatic circulation and the immune system, and to reduce acneic skin inflammation[26].

Part used medicinally:

The whole plant and its oil [18, 23-26].

Chemical constituents:

The preliminary phytochemical study showed that *Inula graveolens* contained polyphenols, tannins, flavonoids, oil, steroidal triterpenoides, sesquiterpene and anthraquinones[27-31].

The chemical composition of the essential oils of *Inula graveolens* varies depending on the plant origin. The main component found in the essential oils of *Inula graveolens* from Corsica was borneol [7.6%]. However, essential oil of *Inula graveolens* from Corsica contained santolinatriene 0.5, α-pinene 0.3, camphene 6.1, β-pinene 0.8, dehydrocineole 1.7, *p*-cymene 0.1, limonene 0.7, *p*-cymenene 0.1, camphor 0.1, *trans*-chrysenthemyl alcohol 0.1, *p*-mentha-1,5-dien-8-ol [α-phellandren-8-ol] 0.2, Borneol 7.6, and trace amounts of α-terpinene, camphene hydrate, yomogi alcohol, myrcene, α-phellandrene, santolina alcohol, β-phellandrene, [*E*]-

β -ocimene, γ -terpinene, artemisia alcohol, terpinolene, linalool, fenchol and lavandulol[29].

Analysis of oil of the aerial parts of *Inula graveolens* from Algerian origin, showed that the main constituents were: bornyl acetate [69.78%], borneol [4.25%], caryphyllene oxide [5.7 %], 1[7]5 -menthadien-8-ol [2.10 %], chamigrene [2.9 %] and the b selinene 0. 95%. However thirty compounds were isolated included [%]: camphre: 0.25, 1[7]5 -mentha –diene-2-ol: 0.09, bornyle acetate: 69.78, P-cymene -8- ol: 0.98, 1[7]2 mentha diene 8 ol: 2.10, isoborneol: 0.10 borneol: 4.25, menth-1-ene-9-ol acetate: 0.28, 4 -terpineol: 0.30, b-caryophyllene: 0.50, benzoate de geranyle: 0.18, allo-4-aromadendrene: 0.20, isogermacrène D: 0.15, isobornyl-2-methylbutyrate: 0.15, neryl acetate: 0.34, ocimenone: 1.00, caryphyllene oxide: 5.7, occidentallo acetate: 0.78, nerolidol acetate: 0.38, a-chamigrene: 2.90, epicadinol: 1.68, a -eudesmol: 1.17, 4-methyl valerate de neryl: 0.39, nerolidol: 0.63, *trans* verbenol: 0.18, *cis* eudesm-6-ene- 12 al: 0.10, farnesyl acetate: 0.24, isobornyl isobutyrate: 0.33, b -selinene: 0.95, and germacrene B: 0.67[32].

The main constituent of the oil of *Inula graveolens* from Iran were 1,8 cineole [54.89%], p-cymene [16.2%], β- pinene [6.94%] and borneol [5.44%]. However twenty compounds were isolated included [%]: α-pinene 3.21, β-pinene 6.94, myrcene 0.2, α-phellandrene 0.89, p-cymene 16.2, 1,8-cineol 54.89, γ-terpinene 0.56, linalool 0.51, undecane 0.28, fenchol 0.37, *trans*-pinocarveol 1.69, pinocarvone 0.53, borneol 5.44, terpin-4-ol 1.37, α-terpineol 1.31, myrtenol 0.35, dodecane 0.25, bornyl acetate 0.24, tridecane 0.19, β-caryophyllene 1.58, α-humulene 1.99 and α-muurolene 0.42[33]. On the other hand, the chemical analysis of the essential oil of the flowering aerial parts of *Dittrichia graveolens* [whole aerial part at flowering stage] from Shoshtar suburb [Khozestan Province, Iran] revealed the presence of sixty compounds . The major components were borneol [38.2%], bornyl acetate [14.86%] followed by 3,4-diethyl phenol [7.5%], β-cubebene [7.1%] and caryophyllene oxide [4.0%]. However, the compounds isolated from the sample were included [%]: α-pinene 0.09, camphene 0.12, 2-heptenal 0.02, benzaldehyde 0.04, 2β-pinene 0.05, 6-methyl-5-hepten-2-one 0.03, 2,4-heptadienal [cis,cis] 0.06, 4-ethyl-1,2-dimethylbenzene 0.04, limonene 0.09, 1,8-cineole 0.16, 2-methylene cyclopentanol 0.02, o-tolualdehyde 0.03, β,β-dimethylstyrene 0.08, α-terpinolene 0.26, nonanal 0.14, 6-methyl-3,5-heptadiene-2-one 0.04, β-thujone 0.03, trans-ρ-mentha-2,8-dienol 0.09, 2-ethyl hexanoic acid 0.04, trans-ρ-menthadien-1-ol 0.07, alcanfor 0.61, neroloxide 0.44, borneol 38.2, ρ-cymen-8-ol 0.53, trans-ρ-menth-2-en-1,8-diol 2.19, decanal 0.18, β-methyl-benzenepropanal 0.5, trans-carveol 0.1, nerol 0.4, carvol 0.09, vetiverol 0.08, piperitone 0.25, nonanoic acid 0.14, 4-hydroxy-3-methyl acetophenone 0.11, carvacrol 0.06, bornyl acetate 14.86, 1-5 [methyl-2-furanyl]-1-buten-3-one 0.13, ρ-mentha-1[7],2-dien-8-ol 0.39, 2,4-decadienal 0.32, 1-methylnaphtalene 0.04, hydragine 0.2, β-damascenone 0.4, caryophyllene 1.98, 6,10-dimethyl-5,9-undecadien-2-one 0.34, 3,4-diethylphenol 7.5, β-lonone 0.28, β-selinene 0.26, α-selinene 0.16, α-amorphene 0.4, 6,6-dimethyl-2-[2-[trimethylsilyl] ethyl cyclohex-2-enone 1.7, geranyl propionate 1.8, geranyl butyrate 2.0, caryophyllene oxide 4.0, cyercene 1.1, β-cubebene 7.1, α-cadinol 0.38, 5-epi-paradisiol 0.89, geranyl hexanoate 0.85, hexafarnesyl acetone 2.5 and isovaleric acid 3-phenylpropyl ester 2.1[24].

1,8-cineole [22.4%], borneol [20.4%] and a-cadinol [11.8%] were determined as the main compounds of *Inula graveolens* from Turkey. However, thirty six compounds were identified included [%]: 2-hexenal 0.4,a-pinene 2.3, benzaldehyde -, sabinene 1.2, b-pinene 3.6, myrcene -, santolinatriene 0.2, a-phellandrene 0.4, a-thujene 0.3, *p*-cymene 3.5, limonene 0.5, camphene 4.6, 1,8-cineole 22.4, g-terpinene 0.6, benzene, 1- methyl - 2 0.2, terpinolene -, linalool 0.3, *trans*-pinocarveole -, *α*-terpineol 1.5, camphor 0.4, 2-cyclohexan-1-ol -, thymol methyl oxide 0.4, thymol 1.8, a-cubebene -, b-elemene 0.6, a-copaene 0.4, b-bourbonene -, b-cubebene 0.1, b-caryophyllene 1.9, a-humulene -, d-cadinene 0.6, g-muurolene 1.3, bornylacetate 5.3, germacrene D -, b-selinene 0.9, bicyclogermacrene -, b-caryophyllene 4.8, a-muurolene 0.4, spathulenol 1.6, Borneol 20.4, caryophyllene oxide -, ledol 1.3, a-cadinol 11.8, b-eudesmol 0.1, hexadecanoic acid -, pentadecanal 0.2, nonadecane -, tricosane -, pentacosane 0.2 and hexacosane 0.4[34].

Thirty compounds were characterized in the essential oil of the fresh aerial parts of *Inula graveolens* from Algeria. The main compounds were isobornylacetate [50.8 %], borneol [18.3 %] and τ- cadinol [6.2.%][35].

The analysis of essential oil constituents of the aerial part without flowers [stems and leaves], flowers and roots of *Inula graveolens* from Monastir [Tunisia] revealed that the main compounds in the aerial part without flowers were α-cadmol [9. 2%], borneol [21 .4%], bornyl acetate [33. 4%]. While, the main components found in the flowers oil, were Camphene [5.5%], α-cadinol [11. 3%], borneol [19.3%] and bornyl acetate [39. 6%]. The major constituents in the oil roots were found to be carvone [5.0%], bornyl acetate [5.3%], p-mentha-I, 2-dien-8-ol [5.3%] and β-selinene [11.5%][36].

The oil of *Inula graveolens* from Jordan, *was* characterized by high percentages of oxygenated monoterpenes, they were the predominant fraction. Their percentage was found to increase with time, during the collection period [from 86.5% in August to 93.7% in January]. Simultaneously, the percentage of sesquiterpene hydrocarbons and monoterpene hydrocarbons decreased from 2.9% to about zero and from 4.4% to 1.6% respectively. Bornyl acetate [percent content ranged from 68.7% in August to 82.6% in January] was the principal component in all months of collection throughout the vegetative cycle[37].
More than 50 compounds were identified from the essential oil obtained from the aerial parts of Greek *Dittrichia graveolens*. The major constituents of the oil were found to be epi-α-cadinol [30.2%] and bornyl acetate [25.4%][38]. The total phenolic content of the methanolic extract of *Inula graveolens* from Iraq was 1.63% gallic acid equivalent, while the total flavonoid content was 0.52% quercetin equivalent of dry mass of plant extract[39].The total phenolic content of the *Inula graveolens* methanolic leaves extracts from Morocco was 86.19±3.04mg GAE/g extract, and the total flavonoids content was 9.72±0.94 mg QE/g extract[27]. Many sesquiterpene lactones, eudesmanolide, 11,13-dihydroivalin, ivalin, inuviscolide, 8-*epi*-inuviscolide, 8-*epi*-xanthatin-1β,5β-epoxide were isolated from the aerial parts of *Inula graveolens* [16]. Sesquiterpene derivatives, 3alpha-hydroxyilicic acid methyl ester, 2alpha-hydroxy-4-epi-ilicic acid, 2alpha-hydroxy-2R-xanthalongin, 4-epi-isoinuviscolide, 8-epi-helenalin, and bigelovin were isolated from the active epigeal parts extracts of *Dittrichia graveolens*[31].

Pharmacological effects:

Antimicrobial effects:
The antibacterial activity of *Inula graveolens* essential oils was evaluated against *Staphylococcus aureus* with studying the effect at the cellular level. A bactericidal mode of inhibition was established for the essential oils, it rapidly reduced the cell viability of S. aureus MIC [5 mg/ml]. No lysis occurred after treatments with the MIC and eight times the MIC of the essential oil. Thickenings of the cell wall as well as an aggregation of the cytoplasmic contents were observed in *S. aureus* cells treated with the MIC of the essential oils. The results suggest that the cytoplasmic membrane and the cell wall were involved in the toxic action of *Inula graveolens* essential oils[40].

The antimicrobial activity of the essential oil was studied against five bacterial and one fungal strain using a disk-diffusion assay. The essential oil was active only against Gram-positive bacteria[41].

The antimicrobial effects of *Inula graveolens* petroleum ether, chloroform and ethanol extracts were investigated [at concentration of 20, 40 and 80 µl of 5% concentration in dimethyl sulphoxide] against *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherishia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Candida albicans*. The extracts showed concentration dependent antimicrobial effects against *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureu*s and *Candida albicans*. The most potent effect was recorded for petroleum ether extract. However, all extract in the higher concentrations [40 µl of 5% concentration in dimethyl sulphoxide] also showed antimicrobial effects against *Escherishia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [28].

The antibacterial effects of *Dittrichia graveolens* essential oil were investigated against nine different ATCC type strains of microbial species, including Gram-positive bacteria [*S. aureus*, *E. faecalis*, *B. subtilis*], Gram-negative bacteria [*E. coli*, *P. aeruginosa*], yeast [*C. albicans*, *C. glabrata*] and fungi [*A. niger*, *A. parasiticus*] . The MICs and MLCs of oil against all tested microorganisms were in the range of 0.25–4 and 1–8 µl/ml, respectively. *E. faecalis* and *C. glabrata* were the most sensitive microorganisms with the lowest MIC and MLC values [0.5 and 1 µl/ml], whereas the least susceptible microorganisms were *S. aureus* and *E. coli* [4 and 8 µl/ml][24].

The antibacterial activity of methanolic and acetone extract of aerial parts of *Dittrichia graveolens* was tested against *Shigella dysenteriae* [PTCC1188], *Pseudomonas aeruginosa* [PTCC1430], *Escherichia coli* [PTCC1399], *Staphylococcus aureus* [PTCC1431], *Bacillus cereus* [PTCC1015] and *Salmonella typhimurium* [ATCC1596], Methanolic extract showed more potent antibacterial activity against *Staphylococcus epidermidis* [PTCC1114], *Enterococcus faecalis* [PTCC1393] and *Klebsiella pneumoniae* [PTCC1291]. *Staphylococcus aureus*, *Staphylococcus epidermis*, E. *faecalis* and *B. cereus* with inhibition zone 35, 30, 26, 21 mm were the most sensitive bacteria, with minimum inhibitory concentrations [MIC] ranging from 12.6 to 112 µg/ml, respectively. *E. coli* and *Salmonella typhimurium* showed moderate sensitivity and other bacteria were resistant to the plant extract[20].

The antibacterial activity of *Dittrichia graveolens* essential oil was investigated by the broth microdilution method against thirteen bacterial strains. The interactions of the essential oil and three standard antibiotics [chloramphenicol, tetracycline and streptomycin] toward five selected strains were evaluated using the microdilution checkerboard assay in combination with chemometric methods, principal components analysis and hierarchical cluster analysis. The essential oil exhibited slight antibacterial activity against the tested bacterial strains *in vitro*, but the combinations *Dittrichia graveolens* essential oil-chloramphenicol and *Dittrichia graveolens* -tetracycline exhibited synergistic or additive interactions. These combinations reduced the minimum effective dose of the antibiotics and, consequently, minimized their adverse side effects. In contrast, the using of *Dittrichia graveolens* essential oil and streptomycin was characterized by strong antagonistic interactions against *E. coli* ATCC 25922, *S. aureus* ATCC 29213 and *P. aeruginosa* ATCC 27853[42].

Anti-*Candida* activity of the volatile oil of the aerial parts of *D. gravolence* against different isolates of *Candida albicans* was studied *in vitro* using serial dilutions of volatile oil in Sabouraud's dextrose agar. MIC of the volatile oil for 10 *Candida albicans* isolates was 30.675 mg/ml[33].
However, it was reported that *Inula graveolens* extracts, obtained by extraction with hot and cold water and then lyophilization, were inactive against S. *aureus and S. faecium* cells [40, 43].

Insecticidal effect:
In studying of insecticidal activity of *Inula graveolens*, oil caused 0, 10, 16.66 and 33.33% mortality of adult *Mayetiola destructor* at concentration of 15, 30, 60 and 90 µg/l of air, respectively[44].

Antioxidant effect:
The methanolic extract of *Inula graveolens* possessed strong antioxidant activity [64.28%], strong reducing power [increasing as the extract concentration increases] and ferrous ion chelating [96%] abilities. Moreover, the methanolic extract showed the highest free radical scavenging activities for superoxide anion and hydroxyl radical [93.43% and 91.38%, respectively] [45].
The antioxidant activity of methanol leaves extracts of *Inula graveolens* was evaluated using the DPPH method. The IC50 of the extracts was 86.67±1.59 mg/l[27].

The antioxidant activity of methanolic and acetone extract of aerial parts of *Dittrichia graveolens* was evaluated spectrophotometrically by DPPH, total antioxidant capacity and reducing power activity. The methanolic extract of plant showed strong antioxidant activity against free radical scavenging specially in DPPH methode than aceton extract with IC50 of 6.2 ± 0.13µg/ml[20].

The total phenolic, flavonoid and flavonol content, the antioxidant activities of *Dittrichia graveolens* were evaluated. The total amount of phenols and flavonoid in different plant organs of *Dittrichia graveolens* were different, the content of total phenols and flavonoid in the flowers and leaves were significantly more than the stems and roots. The content of flavonol in the flowers, leaves and stems were not significantly different, and the lowest content was observed in the roots. A linear and significant correlation coefficient was found between the antioxidant activity and the phenolic compounds in the extracts of different organs of the plant[45].
In studying of antioxidant activity of the oil of *Dittrichia graveolens*, 10 µl of essential oil reduced the concentration of DPPH free radical with an efficacy higher than that of 1mM Trolox [t=70 min]. *Dittrichia graveolens* oil reduced the DPPH to 32.3%[24].

Anti- platelet aggregation effect:
The methanolic extract of *Inula graveolens* showed potential platelet aggregation inhibitory activity in a dose-dependent manner. The maximum inhibition was observed at the dose of 400 µg/ml [P<0.01] compared to heparin [20 µg/ml][18].

Antiproliferative effect:
The extract showed strong antiproliferative [IC50 3.83 mg/ml] and cytotoxic activity [IC50 5.83 mg/ml] against MCF-7 cell line, while it showed no activity against A549 and HL60 cells at 50 mg/ml[46].

Anti-diarrheal effect:

The Anti-diarrheal effects of the methanolic extract of *Inula graveolense* were examined in rats. At the doses of 200 [P < 0.05] and 400 mg/kg body weight [P<0.01], the extract displayed remarkable antidiarrheal activity by reducing the rate of defecation and intestinal transit time of charcoal meal compared to normal saline control group, the effect was dose dependent and similar to loperamide [5 mg/kg][18].

Antipyretic, analgesic and antiinflammatory effects:

The antipyretic activities of the methanolic extract of *Inula graveolens* were examined in rats. The methanolic extract [400 mg/kg] showed a significant [P<0.01] dose dependent anti-pyretic effect in yeast induced elevation of body temperature in rats. Anti-inflammatory and antinociceptive effects of the methanolic extract of *Inula graveolens* were studied in mice. The methanolic extract showed significant antiinflammatory and antinociceptive activity at the dose of 400 mg/kg [P < 0.01] as compared to diclofenac sodium [50 mg/kg]. The extract inhibited paw and ear edema in a dose-related manner. A dose-dependent analgesic action was obtained against chemical [writhing test] and thermal [hot-plate test] stimuli. The effect of methanolic extract of *Inula graveolens* was evaluated against heat induced and anti-platelet aggregation of human blood activity. It was observed that the extract showed greater percentage of inhibition of BSA [P<0.01] at the highest concentration [400 µg/ml]. Denaturation of tissue proteins was one of the well documented causes of inflammatory and rheumatoid arthritis. This effect could be represented one of the mechanisms of antiinflammatory effects of the extract[18].

AChE inhibitory effect:

Inula graveolens essential oil also possessed AChE inhibitory activity[47].

CONCLUSION:

The current review discussed the chemical constituent, pharmacological and therapeutic effects of *Galium verum* as promising herbal drug because of its safety and effectiveness.

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