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Ethnopharmacology, Pharmacological activities and Toxicology profile of Origanum majorana

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ABST RACT
Origanum Majorana leaves isa cold-sensitive perennial herb or undershrub with sweet pine and citrus flavors. In Middle east and Africa, the plant has various traditional uses such as to relief many types of pain,cough and cold and menstrual regulation.
Experimental studies proved many pharmacological activities for the plant extract and its oil that explained its use in the popular remedies.
In some experimental and clinical trials, the leaves and the oil of the plant proved toxic effects at the acute and the chronic levels of toxicity such as bleeding, affecting total serum proteins and serum transaminase concentrations, teratogenic and toxic effects on embryo as well as some toxic effects on reproductive system physiological functions.
This article reviews the reported the pharmacological properties, toxiceffects and the safety ofOriganum Majorana in animals and human.
Key words:*Origanum Majorana ,Bardagosh, animal toxicity, human toxicity, LD50*

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I. Introduction:

Origanum Majorana*(*Lamiaceae), is a bushy half-hardy perennial sub-shrub, growing to a height of 1 to 2 feet, with descending, multibranched stems, the stems taking root as they touch the ground. [1].

Leaves are simple, opposite and stalked, elliptic, 10 to 13 millimeters long, exuding a fragrance when bruised. The well dried leaves of the herb used in medicinal products. It has fragrant, sharp, bitter, camphor like and spicy flavored herb. Flowers are small, purple or white, few too many, arranged in spikelets. Inflorescences with enlarged overlapping bracts.[2]

Vernacular names:Doash, Bardagosh, Portuguese,Marwa,Manjerona.

Geographic distribution: North Africa, the Mediterranean, Turkey, Cyprus, Western Asia, India and the Peninsula Marjoram is indigenous to , Turkey, Asia, , and the Levant [3,4]

Phytochemistry: monoterpene hydrocarbons, oxygenated monoterpenes, phenolic compounds, flavonoids, tannins, sterols, Alkaloids, glycosides, cardiac glycosidessaponin, carbohyderate, and vitamin A&C [5,6]

1. Ethnopharmacological uses

Ethnopharmacology is the scientific exploration of biologically active agents traditionally employed or observed by man.Origanum Majoranaleavesand oil has various Ethnopharmacological uses through the popular medicine in the Middle east, Mediterranean countries and Africa [7,8,9,10,11] to treat:

- Toothache, headaches, muscle aches, Insomnia, Arthritis, paralysis
- Convulsions and anxiety
- Gastrointestinal problems
- Respiratory tract disorders and congestion
- Skin, ear, ocular infections
- Sore throat, cough
- Scorpion bite
- Stimulates menstrual flow, aphrodisiac
- Cystic ovaries

2. Pharmacological activities

i. Anticonvulsant activity:

An anticonvulsant effect of O. majorana was investigated using the Pentylenetetrazole (PTZ) and maximal electroshock (MES) test. The pet ether, chloroform, acetone, methanol and aqueous extracts of O. majorana exhibited anticonvulsant effect in both the PTZ and MES induced seizure models at the doses of 250 and 500 mg/kg, i.p. The extracts of O. majorana delayed the onset of seizures and reduced the duration of seizures in PTZ test and decreased the duration of seizures in MES test compared to the control group. [12]

Anti-anxiety:

Leaves extract of O. majorana showed anti-anxiety effects on rats in open maze model at dose of 200 mg/kg. i.pThe effects was dose dependent compared to diazepam. [13]

ii. Antimicrobial, Antibacterial, Antifungal and Antiprotozoal activities:

The essential oils of O. majorana:

The essential oils of O. Majorana leaves showed antibacterial effect on various bacteria (Bacillus cereus, Escherichia coli, Staphylococcus coagulase, Enterobacter spp., Proteus spp., Acinetobacter spp., S. aureus, e.coli, K.pneumoniae and pseudomonas spp.) [14].

As well asthe essential oils obtained the leaves showed antifungal activity against Aspergillus flavus and A. parasiticus, against six Candida spp and many Yeast strains.[15]

The ethanolic, methanolic and water extract:

The methanol extract showed activity against Aspergillusniger, Fusariumsolani and Bacillus subtilis more than nystatin [16]. Also, methanolic extract have strong activity against Proteus vulgaris, Salmonella stanley, Bacillus anthracis, S. newport, Streptococcus, agalactiae, S. guneuswhile The ethanol and water extracts of O. majorana L. showed antimicrobial activity against Gram positive and Gram negative [17]

iii. Antidiabetic activity:

O. majorana leaves methanolic extract showed antidiabetic activity in streptozotocin induced mice through various in vitro and in vivo assay. has shown significant effects on in-vitro inhibition of advanced Glycation End product formation. The effect was more than the standard antiglycation agent, aminoguanidine.[18]

iv. Antimutagenic anti-cancer activities:

125 mg/kg of marjoram extract protected mice against cyclophosphamide induced mutation as no changes in RNA, DNA and protein contents in liver and testes of mice as compared with control [19].

O. majorana promotes inhibition of tumor growth and metastasis in vivo as the non-cytotoxic concentrations of O. majorana significantly inhibited the migration and invasion of the MDA-MB-231 cells by wound-healing and matrigel invasion assays and decreases the adhesion of MDA-MB-231 to HUVECs and inhibits trans endothelial migration of MDA-MB-231 through TNF-α- activated HUVECs. Also, It suppresses the activities of matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9) and phosphorylation of IκB, downregulates the nuclear level of NFκB. It reduces Nitric Oxide (NO) production in MDA- MB-231 cells [20&28]

v. Anti-ulcerogenic activities:

The methanol extract and the volatile oil of O. majorana leaves showed ulcer healing properties in diabetic rats at three different doses (100, 200 and 400 mg/kg, p.o.), the effect was dose dependent and more effective than glibenclamide and comparable to ranitidine. [21]

*Organum spp.*were tested using prophylactic and curative models of absolute ethanol-induced ulcer, at three doses (125, 250 & 500 mg/kg). the extract possessed dose dependent anti-ulcerogenic activities in both models. The antisecretory activity appears to be mainly related to the suppression of gastrin release. The *in vitro* potential radical (DPPH) scavenging activity of the investigated extract was well supported with the reduction in gastric MDA and enhancing the level of reduced GSH. In addition, suppression of the inflammatory mediator TNF-α may be one of the possible mechanisms of action. The presence of flavonoids, tannins and sterols could be related to these activities [27].

vi. Anti-platelet Analgesic, Anti-inflammatory, and Antispasmodic Activities:

An active compound, arbutin, was isolated from sweet marjoram proved as inhibitor of platelet aggregation induced by collagen; ADP, arachidonic acid (AA) and thrombin as well as inhibition of prostaglandin [22].

Origanum extract studied for antispasmodic activity using different smooth muscle preparations of rat and guineapigin vitro. Aqueous extract of Origanum powder inhibits responses to acetylcholine, histamine, Serotonin, BaCl 2, 1, 1-dimethyl-4-phenylpiperazinium iodide and nicotine in the guinea-pig ileum. The extract also blocked the contractions elicited by electrical coaxial stimulation and the responses to cumulative Ca 2+ concentrations increased [23]

vii. Antiparasitic and Insecticidal activities:

Essential oil of O. majorana with terpinen affected the soil stages of Phyto nematodes (Rotylenchulusreniformis, Criconemella spp., Hoplolaimus spp.) [24]

viii. Cardioprotective activity:

50 and 100 mg/kg p.o for 30 consecutive days of sweet marjoram leaf powder (MLP) and marjoram leaf aqueous extract (MLE) against isoproterenol (ISO)-induced myocardial infarcted rats showed that both MLP and MLE (especially the high dose) significantly alleviated ($P < 0.05$-0.001) erythrocytosis, granulocytosis, thrombocytosis, shortened clotting time, the increase in relative heart weight, myocardial oxidative stress and the leakage of heart enzymes (creatine phosphokinase (CPK), CPK-MB isoenzyme, lactate dehydrogenase and aminotransferase) in ISO-treated rats through reactivating non-enzymic (reduced glutathione) and enzymic (catalase, glutathione peroxidase, glutathione S-transferase, superoxide dismutase) antioxidant defense system and inhibiting the production of nitric oxide and lipid peroxidation in heart tissues [25].

ix. Antioxidant, Anti-inflammatory and antinociceptive activities:

marjoram was investigated for its antioxidant, anti-inflammatory and antinociceptive activities at doses of 250, 500 and 1000 mg/kg in rats. The antioxidant activity was estimated using DPPH free radical scavenging activity method for the alcoholic extracts of the investigated plants at different concentrations (2, 4, 6, 8 and 10 mg/ml). The anti-inflammatory activity was estimated using carrageenan-induced rat paw edema method and the activities were compared to that of diclofenac sodium (30 mg/kg). The antinociceptive activity was estimated peripherally and centrally using the writhing and the hot plate tests, respectively.

The plant proved antioxidant, anti-inflammatory and antinociceptive activities in a dose dependent manner. These activities could be explained by its antioxidant properties due to the high flavonoid contents [26].

3. Toxicology Profile

i. Acute Toxicity studies on*Origanum Majorana*

Doses of 1250, 2500, and 5000 mg/kg of *Majorana* extract were administered to mice orally and were kept to observe the signs of toxicity, number of deaths per dose within 24 h and then LD50 was calculated.

All the doses did not produce any behavioral changes and mortality in mice up to 5000 mg/kg. Accordingly, it suggested that oral LD50 of the tested extract was higher than 5g/kg. Therefore, the tested plant can be categorized as highly safe since substances possessing LD50 higher than 5g/kg are non-toxic [27].

ii. Subacute Toxicity studies on*Origanum Majorana*

The toxicity of the aqueous extract of *Origanum Majorana* was tested (5 and 10 g/kg) in albino mice. No symptoms of toxicity or mortality were observed. The mice survived being active and healthy during all 14 days of observation. The weight measurement of the left and right kidneys, heart, and liver shows no significant difference between the control and the tested doses [28].

In an invitro study, the methanol extract of Origanum Majorana (marjoram) was used as blood anti-coagulator in human platelets that prepared and incubated with different concentrations of the test samples (equivalent to 50-200 microg of the plant leaves powder/mL) for 60 min. The treated and untreated platelets were then activated with thrombin (0.25 U/mL) and their adhesion to laminin-coated plates was investigated. The methanol extract of O. majorana, at a concentration of 200 microg/mL, inhibited platelet adhesion to laminin-coated wells by 40%. In addition to alternation of cell adhesive properties, self-aggregation and protein secretion of the treated platelets were also affected upon treatment with the crude methanol extract [29]. These evidences must provide a hazard of the continuous use of the plant specially for those with bleeding problem.

iii. Sub-chronic toxicity studies of *Origanum Majorana*

Orally administered *Organum spp.*extract to rats in a dose of 500 mg/kg for 35 days did not show any significant effect on the levels of ALT, AST, urea and creatinine in their sera as compared to control [27].

iv. Chronic Toxicity studies of*Origanum Majorana L*

*Origanum Majorana*L powder increases concentrations of total serum protein, serum glutamic oxalo-acetic transaminase (SGOT) and testosterone when feed to lambs at 4% in diet for 3 months [30]. While, 100 mg/kg, orally for 30 days in rats significantly alleviated erythrocytosis, granulocytosis, thrombocytosis, shortened clotting time, leakage of heart enzymes (creatine phosphokinase (CPK), CPK-MB isoenzyme, lactate dehydrogenase and aminotransferase) [25].

This evidence must raise a hazard of the continuous/ traditional daily use of the plant specially for those with Arrhythmia.

v. Human Toxicity of O. *majorana L*

From scientific databases of clinical studies on pregnant women, O. *majorana L* reported to have teratogenic and toxic effects on embryo beside induction of menstruation by affecting menstruation hormones [31].

vi. From the previous data, these Precautions & Warnings according to *Origanum Majorana L* Toxicity should be considered during the using of the plant in the traditional medicine:

- All bleeding types
- Arrhythmia & Bradycardia
- GIT&Urinary obstruction
- Gastric ulcers
- Surgery
- Diabetes

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