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(REVIEW ARTICLE)

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Traditional uses, bioactive constituents and pharmacological importance of *Origanum vulgare*- A review

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Abstract

Origanum vulgare (Family: Lamiaceae), is widely distributed in Africa, Asia and Europe. It is an important flavouring herb in Mediterranean cookery. Flowering branches were used as energy producer, as stomach booster, nervous calming, laxative, diarrhea, general weakness of the body, anticancer, migraine, for external use by rubbing in place of numbness and in toothache. Aerial parts were used as disinfection, pain reliever, relaxing, cardiorespiratory booster, antidiarrhoeal, stomach booster, cough suppressant, sexual dysfunction, sinusitis. Seed were bused as anticonvulsant, expectorant, pain reliever, cough suppressant, antidiarrheal, anti-inflammatory, menstrual regulator, diuretic and for the treatment of urinary tract infection. The phytochemical screening of the leaves extracts showed that Oreganum vulgare contained oils, carbohydrates, anthraquinones, coumarins, phenolic compounds, tannins, flavonoids, flavanonols, anthocyanins and many other bioactive compounds. The previous pharmacological studies revealed that Oreganum vulgare possessed antimicrobial, anti-inflammatory, analgesic, antioxidant, anticancer, protective antidiabetic, antiparasitic, reproductive, dermatological, gtastrointestinal antiurolithic, immunomodulatory and metal chelating activity. In the current review, Web Science, PubMed, Scopus and Science Direct, were searched to highlight the chemical constituents and pharmacological effects of Oreganum vulgare.

Keywords: Constituents; Pharmacology; Therapeutic; Safety; *Oreganum vulgare*

1. Introduction

In recent years, ethno medicinal studies has received much attention as this brings to light the numerous little known and unknown medicinal virtues especially of plant origin which needs evaluation on modern scientific lines such as phytochemical analysis, pharmacological screening and clinical trials (1-9). *Origanum vulgare* (Family: Lamiaceae), is widely distributed in Africa, Asia and Europe. It is widely used traditionally all over the world. The phytochemical screening of the leaves extracts showed that *Oreganum vulgare* contained oils, carbohydrates, anthraquinones, coumarins, phenolic compounds, tannins, flavonoids, flavanonols, anthocyanins and many other bioactive compounds. The previous pharmacological studies revealed that *Oreganum vulgare* possessed antimicrobial, anti-inflammatory, analgesic, antioxidant, anticancer, protective antidiabetic, antiparasitic, reproductive, dermatological, gtastrointestinal antiurolithic, immunomodulatory and metal chelating activity. The current review focused on the chemical constituents and pharmacological effects of *Oreganum vulgare*.

1.1. Synonyms

Origanum creticum, Origanum floridum, Origanum vulgare var. formosanum, Origanum vulgare var. glaucum, Origanum vulgare subsp. *glandulosum*,*Origanum vulgare* subsp. *gracile*,*Origanum vulgare* subsp. *hirtum*,*Origanum vulgare* subsp. *virens*, *Origanum vulgare subsp. viride*, *Origanum vulgare* subsp. *viridulum*, *Origanum vulgare* subsp. *vulgare*, and *Thymus origanum* (10).

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- **Kingdom**: Plantae,
- **Subkingdom**: Viridiplantae,
- **Infrakingdom**: Streptophyta,
- **Superdivision**: Embryophyta,
- **Division**: Tracheophyta,
- **Class**: Magnoliopsida,
- **Superorder**: Asteranae,
- **Order**: Lamiales,
- **Family**: Lamiaceae,
- **Genus**: *Origanum*,
- **Species:** *Origanum vulgare* (11).

1.2. Common names

- **Arabic**: Mardagosh, Raihan Jabali;
- **Chinese**: niu zhi;
- **English**: wild marjoram;
- **French**: origan vulgaire;
- **German**: gewöhnlicher Dost;
- **Swedish**: kungsmynta (12).

1.3. Distribution

It is distributed in **Africa** (Algeria, Morocco, Tunisia), **Asia** (Afghanistan, Iran, Iraq, Turkey, Armenia, Azerbaijan, Georgia, Russia, Kazakhstan, Kyrgyzstan, China, Taiwan, Bhutan, India, Nepal, Pakistan) and **Europe** (Denmark, Finland, Ireland, Norway, Sweden, United Kingdom, Austria, Belgium, Czechoslovakia, Germany, Netherlands, Poland, Switzerland, Estonia, Russian Federation- European part, Ukraine, Albania, Bulgaria, Former Yugoslavia, Greece, Italy, Romania, France, Portugal, Spain) (12).

1.4. Description

Rhizomatous aromatic perennial; roots are fibrous. Stems several, often branched from base, c. 40 (-100) cm, thinly to densely pilose with adpressed or spreading hairs, or glabrous, leafy, purplish or green. Leaves are simple and entire, ovate to narrow elliptic, 5-40 x 3-30 mm, gland-dotted, apex acute or obtuse, with scattered hairs or glabrous, leaf buds or young leaves usually in leaf axils; petiole to 20 mm. Inflorescence often much and regularly branched; branches rather slender. Verticillasters 2-flowered; spicules erect, 5-20 x c. 5 mm. Bracts 3-10 x 2-7 mm, pale green to purplish, imbricate, oblong-obovate to narrow oblong, glabrous and glaucous to pubescent. Calyx 2-4 mm long, tubular, glabrous or with few or many spreading hairs, teeth up to 1/2 length of tube. Corolla 5-10 mm, rose, purple or white. Anterior pair of stamens subexserted (in hermaphrodite flowers). Nutlets oblong, terete, c. 0.8-1 x 0.5 mm, dark or pale brown, minutely granulate (13-14).

1.5. Traditional uses

Oregano was an important flavouring herb in Mediterranean cookery, and was often used dried rather than fresh. The leaves were used as a flavouring for salad dressings, vegetables and legumes, and were frequently included in strongly flavoured dishes with chillies, garlic, onions, etc (15). Flowering branches were used as energy producer, as stomach booster, nervous calming, laxative, diarrhea, general weakness of the body, anticancer, migraine, for external use by rubbing in place of numbness and in toothache (16). Aerial parts were used as disinfection, pain reliever, relaxing, cardiorespiratory booster, antidiarrhoeal, stomach booster, cough suppressant, sexual dysfunction, sinusitis (17-19). Seed were bused as anticonvulsant, expectorant, pain reliever, cough suppressant, antidiarrheal, anti-inflammatory, menstrual regulator, diuretic and for the treatment of urinary tract infection (20).

Origanum vulgare was used In India, to treat food poisoning, indigestion, bloating, cough, urinary problem, bronchial problems, and headache (21).

1.6. Parts used

Aerial parts and essential oils were used medicinally (17-19).

1.7. Physicochemical characteristics

The physicochemical study showed that the leaves of *Oreganum vulgare* contained total ash 11.5%, acid insoluble ash 11%, water soluble ash 5% and sulphated ash 10.5%. Swelling index was zero, and the foaming index was 75% w/w (22).

1.8. Chemical constituents

The preliminary phytochemical screening of ethanol and aqueous leaves extracts showed that *Oreganum vulgare* contained carbohydrates, anthraquinones, coumarins, phenolic compounds, tannins, flavonoids, flavanonols and anthocyanins (22).

Phenolic compounds (protocatechinic acid, its phenyl glucoside, caffeic acid, p-coumaric acid, chicoric acid, gallic acid, ferulic acid, neochlorogenic acid, salvianolic acid A, salvianolicacid C, rosmarinic acid and its phenolic derivative, origanol A, origanol B, 4'-O-beta-D-glucopyranosyl-3',4'-dihydroxybenzyl protocatechuate and 4'-O-beta-D-glucopyranosyl-3',4'-dihydroxybenzyl 4-O-methylprotocatechuate) were isolated from *Origanum vulgare* (23-26).

The phenolic compounds identified in the hydroalcoholic extract, infusion and decoction of *Origanum vulgare* from Garray – Soria, Spain, were: 3-O-caffeolyquinic acid, protocatechuic acid, 5-O-caffeolyquinic acid, apigenin 6,8-di-C-glucoside, kaempferol O-hexosyl-O-hexoside, myricetin 3-O-glucoside, quercetin O-hexoside, dihydroxybenzoyl)oxy]methyl]phenyl, O-b-D-glucopyranoside, taxifolin, quercetin 3-O-rutinoside, quercetin 7-O-hexoside, luteolin O-glucuronide, luteolin 7-O-glucoside, apigenin 7-O-rutinoside, rosmarinic acid, apigenin 7-O-glucuronide, kaempferol O-hexoside, kaempferide O-glucuronide, lithospermic acid A, eridictyol, methylapigenin O-glucuronide and naringenin. Luteolin 7-*O*-glucoside 20.88±0.00- 25.26 ±0.44mg/g, luteolin *O*-glucuronide 12.48±0.09- 28.27±0.24mg/g, rosmarinic acid 14.62±0.03- 15.91±0.34mg/g, and apigenin 7-O-glucuronide 5.78±0.03- 8.63 ±0.02mg/g, represented the major polyphenolic compounds in the hydroalcoholic extract, infusion and decoction of *Origanum vulgare* (27).

Flavonoids: apigenin, luteolin, naringenin, quercetin, kaempferol, dihydrokaempferol, isorhamnetin, salvagenin, cirsimartin, diosmetin, eriodictyol, taxifolin, desmethoxycentauridin, 5-hydroxy-6,7,3',4'-tetramethoxy-abigenin, apigenin 7-O-glucoside, apigenin 7-*O*-*β*-*D*-glucuronide, apigenin 7-*O*-*β*-*D*-(6 *β*-methyl) glucuronide, apigeninacetyl-diglycoside, luteolin 7- *O*-*β*-*D*-glucopyranoside, luteolin 7-*O*-*β*-*D*-glucuronide, luteolin 7-*O*-*β*-*D*-xylopyranoside, luteolin 7-O-glucoside, luteolin 7-O-glucoside-6''-methylester, luteolin 7-O-alpha-L-rhamnoside-4'-O-beta-D-glucoside and quercetin 3-O-beta-D-glucoside-4'-O-alpha-L-rhamnoside were isolated from *Origanum vulgare* (21, 25-31).

The quantity of the phenolic compounds identified in the aqueous and methanolic extract of *Origanum vulgare* ssp *hirtum*, were: salvianolic acid 0 and 5.9, rosmarinic acid 53.7 and 98.6, salvianolic acid B (lithospermic acid B) 22.5 and 19.4, salvianolic acid C 0 and 5.2, methyl salvianolate 0 and 5.3, eriodictyol 2.6 and 3.4 and naringenin 0.8 and 1.5 mg/g dry extract (32).

The total flavonoid content of ethanol extract of the aerial parts of *Origanum vulgare* from Armenian flora, was 3.9±0.7 mg/g catechin equivalents (33).

The leaves extracts of *Origanum vulgare* from Algeria contained high polyphenols and flavonoids contents (194.78 mg GAE / g and 36.63 ± 0.18 mg RE/g, espectively) (34).

The total phenolics of the dried aerial parts extracts of *Origanum vulgare* ssp *viride* from Giresun, a city in the Black Sea region of Turkey, was 9.73±0.07- 56.83±1.65 g gallic acid equivalent /kg, included: gallic acid: 0.012±0.001-0.027±0.001, caffeic acid: 0.172±0.010-0.367±0.008, hydroxybenzaldehyde: undetected- 0.009±0.00, p-coumaric acid: 0.065±0.003-0.365±1.050, rosmarinic acid: 4.303±0.113-19.269±1.03, chicoric acid: 0.160±0.004-0.910±0.040 g gallic acid equivalent /km. while, the total flavonoids was: 7.62±1.18- 35.25±0.56 g quercetin equivalent/ kg, included: apigenin-7-glucoside: 0.012±0.001-0.077±0.005, quercetin: 0.020±0.001-0.039± 0.002, naringenin: undetected-0.060±0.003, kaempferol: 0.011±0.003- 0.069±0.003 g quercetin equivalent/ kg (21).

Protocatechuic acid ester derivatives (origanol A, origanol B), ursolic acid, oleanolic acid, β-sitosterol, and triacontanol were isolated from the methanolic extract of the leaves of *Origanum vulgare* (23).

The percentage of the compounds identified in the *Origanum vulgare* essential oil from Santarem, Ribatejo- Portugal, were: monoterpene hydrocarbons: 26.4% (α-thujene: 2.2, α-pinene: 0.7, camphene: 0.1, sabinene: 1.0, β-pinene: 0.4, β-myrcene: 1.3, α phellandrene: 0.4, Δ^3 carene: 0.1, α-terpinene: 3.7, β-phellandrene: 0.9, cis-β-ocimene: 1.6, trans-β-

ocimene: 1.5, γ –terpinene: 11.6, α-terpinolene: 0.9, neo-allo-ocimene: trace); Sesquiterpene hydrocarbons: 3.6% (α-cubebene: trace, trans-caryophyllene: trace, α-bergamotene: 0.1, allo-aromadendrene: 0.1, germacrene D: 0.3, β-selinene: trace, ledene: trace, bicyclogermacrene: 0.3, α-muurolene: trace, β-bisabolene: 2.1, selina-3,7(11)-diene: 0.2, β-cadinene: 0.2, cis-α-bisabolene: 0.1, γ –cadinene: 0.1, copaene: trace); Oxygenated monoterpenes: 53.8% (eucalyptol: 0.3, linalool: 2.6, trans-1-Methyl-4-(1-methylethyl)-2-cyclohexen-1-ol: 0.3, α-terpineol: 0.2, menthone: 0.7, borneol: 0.4, δ-terpineol: 7.5, trans-piperitol: 0.1, β-fenchyl alcohol: 12.8, cis-p-menth-1-en-3-ol: 0.1, cis-piperitol: 0.1, pulegone: 1.0, piperitone: trace, carvacrol: 14.5); Oxygenated sesquiterpenes: 1.4% (spathulenol: 0.5, caryophyllene oxide: 0.6, veridiflorol: trace, isospathulenol: 0.1, cadinol: 0.1, α-cadinol: 0.1, oxygenated diterpenes: trace, epimanoyl oxide: trace); and others: 7.11% (1-octen-3-ol: 0.2 1, methyl-3-(1-methylethyl)-benzene: 6.8, p-cymen-7-ol: 0.1, thymyl methyl ether: 0.1, carvacryl methyl ether: 0.4, thymol: 12.6, methyleugenol: trace, hexadecanoic acid: trace, 2,3,5,6-tetramethylphenol: 0.1) (35).

The analysis of the essential oils of the dried aerial parts of *Origanum vulgare* ssp *viride* from Giresun- Black Sea region, Turkey, showed that the major constituents were caryophyllene oxide (25.01%), followed by linalool (8.32%), 1,8-cineol (7.98%), caryophyllene (6.40%), spathulenol (6.31%), p-cymene (4.11%) and caryophyllenol II (4.03%) (21).

The essential oil components (%) identified in *Origanum vulgare* ssp *viride* from Mashhad Yazd –Iran, were: 2-hexenal: - and 0.08, α-thujene: 1.23 and 1.18, α-pinene: 0.7 and 0.77, camphene: 0.2 and 0.51, sabinene: 4.49 and 3.81, β-pinene: 0.55 and 0.41, octanone: 0.74 and 0.63, myrcene: 1.82 and 1.35, 3-octanol: 0.17 and 0.16, α-phellandrene: 0.67 and 0.37, δ-3-carene: 0.08 and 0.05, α-terpinene: 4.41 and 3.52, 13 p-cymene: 4.27 and 5.69, and limonene: 2.9 and 2.19% respectively (36).

Essential oil components of leaf and flower of *Origanum vulgare* ssp. *gracile* growing wild in Kurdistan province of Iran (%, respectively) were: α-thujene: 0.72 and 1.45, α-pinene: 0.47 and 0.85, octen-3-ol: 0.5 and 0.26, 3-octanone: 3.5 and 2.89, α-phellanderene: 0.24 and 0.46, α-terpinene: 1.23 and 2.39, ρ-cymene: 13.54 and 7.21, 1,8-cineol: 2.76 and undetected, (Z)-β-ocimene: 0.56 and 0.28, γ-terpinene: 13.91 and 16.64, terpinolene: 0.14 and 0.12, cis- ρ -menth-2-en-1-ol: 0.47 and undetected, terpinene-4-ol: 0.94 and 0.63, α-terpineol: 1.07 and 0.29, thymol methyl ether: 0.15 and undetected, carvacrol methyl ether: 7.19 and 2.04, thymol: 2.24 and 1.82, carvacrol: 46.5 and 60.6, E-caryophyllene: 0.85 and 0.35, germacrene D: 0.24 and 0.1, germacrene A: 0.19 and undetected, γ-elemen: 2.35 and 1.21 and spathulenol: 0.22 and undetected (37).

Essential oils of *Origanum vulgare* growing wild in Ardabil Province, Northwest Iran, contained *β*-caryophyllene as the major constituent (48.1%, 50.1% and 60.2%, in the flowers, leaves and stems respectively), followed by 1,8-cineole (11.6%), *α*- pinene (6.9%), and *γ*-cadinene (4.8%). While, the essential oil of *Origanum vulgare* growing wild in Kodjour, North Iran, contained linalyl acetate, sabinene, *γ*-terpinene, *trans*-ocimene, and *cis*-ocimene and low percentages of the phenolic monoterpenoids (thymol and carvacrol) together with sesquiterpenoid (44 %) fraction, *β*-caryophyllene, caryophyllene oxide, germacrene D, and *γ*-elemene (38-39).

Essential oils obtained from six different phenophases of *Origanum vulgare* grown in Kumaon region of Uttarakhand, India showed that the major constituents were thymol (40.9-63.4%), *p*-cymene, (5.1-25.9%), *γ*-terpinene (1.4-20.1%), bicyclogermacrene (0.2-6.1%), terpinen-4-ol (3.5-5.9%), *α*-pinene (1.6-3.1%), 1-octen-3-ol (1.4-2.7%), *α*-terpinene (1.0-2.2%) and carvacrol (<0.1-2.1%). Thymol, terpinen-4-ol, 3- octanol, *α*-pinene, *β*-pinene, 1,8-cineole, *α*-cubebene and (*E*)-*β*- ocimene were higher during full flowering season (40).

Essential oil of 4 new oregano clones from Greece, composed of : α-thujene: 0.07- 0.81, α-pinene: 0.07- 0.6, camphene: 0.06- 0.15, sabinene: 0.50- 1.12, mycrene: 0.13- 1.70, α-phellandrene: undetected- 0.17, α-terpinene: undetected- 0.73, p-cymene: 0.74-8.10, terpinolene: 0.08- 0.21, limonene: undetected- 0.17, 2-terpinene: 0.32- 2.43, trans-sabinen-hydrate: 0.02- 0.51, terpinen-4-ol: 0.42- 0.49, α-terpineol: 0.12 -0.31, thymol: 0.04 -0.32, carvacrol: 79.45-92.90, α-cubenene: 0.06- 0.09, β-caryophyllene: 0.30- 1.58, trans b-farnesene: 0.09- 0.14, ϒ-humulene: 0.06 - 0.19, muurolene: 0.04 -0.17 and 6-cadinene: 0.08- 0.70% (41).

The main components of *Origanum vulgare* essential oil from Özşen Lokman Hekim Company located in Gimat-Ankara-Turkey, was carvacrol (63.97%), p-cymene (12.63%) and linalool (3.67%), α-terpineol (2.54%) and (-)-terpinen- 4-ol (2.24%) (42).

The main chemical compounds in leaf essential oil of *Origanum vulgare* provided by the National German Genebank (IPK Gatersleben), (*Origanum vulgare* ssp *vulgare*, *Origanum vulgare* ssp *hirtum*, *Origanum vulgare* ssp *viride*, *Origanum vulgare* ssp *viride majorana*) were: sabinene: 0.007±0.023 -0.181±0.023, 1-octen-3-ol: 0.002±0.017 -0.116±0.017, myrcene: 0.003±0.008- 0.047±0.008, *ρ*-cymene: 0.006±0.02- 0.181±0.02, *cis*-*β*-ocimene: 0±0.035-0.143±0.032, *trans*-*β*-

ocimen: 0±0.015-0.088±0.014, *trans*-sabinene hydrate: 0±0.039- 0.151±0.036, thymol methyl ether: 0±0.013-0.067±0.012, thymol: 0±0.062- 0.401±0.062, *β*-Bourbonene: 0±0.01-0.092±0.009, germacrene D: 0±0.036-0.268±0.033, *β*-bisabolene: 0±0.004-0.017±0.004, and germacrene D -4-ol: 0±0.016-0.128±0.015% (43).

The major compounds identified in the essential oil of *Origanum vulgare* from Arab company for pharmaceuticals and medicinal plants- Egypt were terpinen-4-ol (38.35%) and *trans*-sabinene hydrate (10.06%) (44).

The major constituents of the oil extracted from *Origanum vulgare* subsp *glandulosum* from North East of Tunisia, were carvacrol (61.08%), p-cymene (9.87%), c-terpinen (6.34%), and borneol (2.38%) (45).

Chemical composition of the essential oil of *Origanum vulgare* from Algeria, were:

α-pinene: 0.2, camphene: 0.5, β-pinene: 1.11, myrcene: 0.09, β –phellandrene: 0.07, *p*-cymene: 24.01, 1,8-cineol: 0.4, γ –terpinene: 9.5, sabinene hydrate: 1.45, terpinolene: 0.2, linalool: 0.5, camphor: 0.2, borneol: 0.5, terpinene-4-: 1.3, α-terpineol: 3.4, bornyl acetate: 0.2, thymol: 23.49, carvacrol: 21.31, eugenol: 0.1, α-copaene: 0.3, β –caryophyllene: 0.4, α-humulene: 0.2, germacrene D: 0.06, α-muurolene: 0.3 and α-farnesene: 0.4% (46).

The yield of essential oil of *Origanum vulgare* from Leskovac, Serbia, was 4.1 ml/100 g. Seven components were identified: α-thujene, myrcene, α-terpinene, o-cymene, γ-terpinene, thymol and carvacrol. The major components were thymol (45%) and carvacrol (37.4%) (47).

The terpenes represented the greatest part of *Origanum vulgare* essential oil from Armenian flora (β-caryophyllene epoxide 13.3 %; β- caryophyllene 8.2 % and o-cymene 5.2 %) (33).

1-Methyl-4-(1-methylethyl) benzene- (p-cumene), 1-Methyl-4-(1-methylethyl)-1,4-cyclohexadiene (*γ*-terpinene), 1-Methoxy-4-methyl-2-(1-methylethyl) benzene (creosol), 2-(1-Methylethyl)-5-methylphenol (thymol), 2-Methyl-5-(1-methylethyl)-phenol (carvacrol), 3,7,11,15-Tetramethyl-2-hexadecen-1-ol (phytol) and 1-octacosanol were isolated from the ethanolic extract of the leaves of *Origanum vulgare* from Kynouria Peloponnese- Canada (48).

GC-MS analysis of the methanolic seed extract showed that the seeds contained 1,7-dioxaspiro [5,5]undec-2-ene, 2,4-dihydroxy-2,5-dimethyl-39(2H)-furan- 3-one, 2,4- difurobenzene, 1-benzyloxy, α-D- glucopyranoside, O-α-glucopyranosyl, 4-hexenal, 6-hydroxy-4-methyl,dimethyl acetal, acetate, 4H-pyran-4-one,2,3,-dihydro-3,5-dihydroxy-6-methyl, benzofuran, 4-amino-1,5-pentandioic acid, 2-methoxy-4-vinylphenol, d-Mannose, 7-Isopropyl-10-methyl- 1-oxo-1,5-dithia-spiro[5,5] undecane -2-carboxy, phytol, cis-vaccenic acid, N-Methyl-N benzyl tetradecanamine, 3,8,8-Trimethoxy-3-piperidyl-2,2-binaphthalene-1,1,4,4-tetrone, and 17-(1,5-Dimethylhexyl) 10,13-dimethyl (49).

Fatty acid contents of the seeds of *Origanum vulgare* ssp *gracile* were: palmitic acid: 4.4±0.1, stearic acid: 0 1.5±0.1 (the total saturated fatty acids: 5.9±0.1); palmitoleic acid: 0.4±0.1, oleic acid: 5.7±0.3 (the total monounsaturated fatty acids: 6.1±0.2); linoleic acid: 15.4±0.4, linolenic acid: 67.8±0.6, ϒ- linolenic acid: 1.2±0.1, stearidonic acid: 4.2±0.3 4.7, (the total polyunsaturated fatty acids: 88.6±0.4). Steroids contents of the seeds of *Origanum vulgare* ssp *gracile* were ergosterol: 56.3±2, stigmasterol: 2262.2±3.3 and β-sitosterol: 152.8±2.6 µg/g. Lipide-soluble vitamin and sterol contents in the seeds of *Origanum vulgare* ssp *gracile* were K1: 29.4±0.8, K2: 26.0±0.8, D2: 1.8±0.1, D3: 33.1±0.8, α-tocopherol: 7.8±0.2, and retinol acetate: 0.3±0.1 µg/g (50).

2. Pharmacological effects

2.1. Antimicrobial effects

The essential oils of *Origanum vulgare* ssp *gracile* were studied for antimicrobial effects on Gram-negative (*Salmonella thyphimurium* ATCC 13311 and *Escherichia coli* ATCC 43894) and Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538 and *Listeria monocytogenes* ATCC 19118). Flower essential oil showed more antibacterial activity (MIC: 125, 250, 250 and 250ppm, respectively) compared with leaves essential oil (MIC:500, 500, 1000, 500 pmm, respectively) against the tested microorganisms (37).

The aerial parts methanol, dichlormethane and cyclohexane extracts of *Origanum vulgare* were tested for antimicrobial activity against Gram positive: *Staphylococcus aureus* (ATCC 25923), *S. epidermidis* (ATCC 12228), M*icrococcus luteus* (ATCC 9341), *Bacillus subtilis* (ATCC 6633), *Enterococcus feacalis* (ATCC 29212) and Gram negative: *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (NCIMB 9111), *Salmonella abony* (ATCC 13076), *Pseudomonas aeruginosa* (ATCC

27853), and one strain of the yeast *Candida albicans* (ATCC 10231). The extracts of *Origanum vulgare* possessed antibacterial effects, especially against Gram positive bacteria with MIC between 62.5 and 125 µg/ml. All extracts showed no antifungal activity against *Candida albicans.* Only cyclohexane extract of *Origanum vulgare* did not show any activity against tested *H. pylori*, while all other tested extracts were active with MICs of 250-500 µg/ml(51).

The susceptibility of *Staphylococcus aureus* strains of swine origin to *Origanum vulgare* essential oil was examined *in vitro*. Oregano possessed an inhibitory activity against *S. aureus* strains. The MICs of of oregano essential oil, thymol and carvacrol were 0·01-0·04% (52).

The antibacterial effects of extracts and essential oils *Origanum vulgare* were investigated against *Brochothrix thermosphacta, Escherichia coli, Listeria innocua, Listeria monocytogenes, Pseudomonas putida, Salmonella typhimurium* and *Shewanella putrefaciens.* The ethanolic extract and essential oil revealed antibacterial properties. The essential oil of *Origanum vulgare* inhibited the growth of all bacteria with a greater activity against *Listeria monocytogenes* and *Listeria innocua* (35).

The antimicrobial activity of *Origanum vulgare* ssp *glandulosum* oils was investigated against Gram-positive bacteria: *Staphylococus aureus* and *Bacillus subtilis* and the Gram-negative bacteria: *Escherichia coli, Salmonella typhimurium*, and *Pseudomonas aeruginosa*. Oils possessed antibacterial activity against all the tested bacteria. The highest activity was observed against *E. coli* with the strongest inhibition zones (18-23 mm) and *S. typhimurium* (15-22.5 mm). Oils showed MIC = 250 µg/ml, against *E. coli* and *S.typhimurium* and MIC = 125 µg/ml, against *P. aeruginosa* and *B. subtilis* (45).

The antimicrobial activity of fatty acids, vitamins and flavonoids of O*riganum vulgare* ssp *gracile* was studied against *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Bacillus megaterium*, *Epidermophyton* sp, *Trichophyton* sp., *Candida albicans* and *Candida glabrata*. Vitamin constituents of *Origanum vulgare* ssp *gracile* showed inhibition zone of 8.3±0.2- 23.6±0.3mm against all the tested microorganisms except *C. glabrata,* flavonoids possessed antimicrobial activity (8.2±0.3- 15.4±0.2mm) against all the tested microorganisms except *Escherichia coli* and *Klebsiella pneumonia*, while fatty acids showed zone of inhibition of 8.2±0.3- 8.7±0.2mm against *Escherichia coli*, *Klebsiella pneumonia*, *S. aureus* and *Epidermophyton sp* (50).

The antibacterial effect of the essential oil of *Origanum vulgare* was evaluated against five strains of *Bacillus*: (*B. amyloliquefaciens* FZB42, *B. amyloliquefaciens* S499, *B. subtilis* ATCC 21332, *B. licheniformis* ATCC 14580, *B. pumilus*). The strains of *Bacillus* showed sensitivity toward the essential oil of *Origanum vulgare*, with inhibition zones ranging from 21.5 mm against strain *B. amyloliquefaciens* S499, to 41 mm against *B. pumilus*. MIC for all strains was 0.4 mg/ml (46).

The antibacterial activity of *Origanum vulgare* essential oils was investigated against *Staphylococcus aureus, S. coagulase negative, Enterobacter spp., Proteus spp., Acinetobacter spp* and *Klebsiella spp* isolated from the patients with conjunctivitis. The oil caused a prominent growth inhibitory effect against all the bacterial strains (27-32mm). MIC values were between 5-20µl/ml (53).

The antibacterial potential of infusion, decoction and essential oil of *Origanum vulgare* was studied against 111 Gram-positive bacteria, belong to 23 different species of 3 genera. Infusion and essential oil exhibited antibacterial activity against *Staphylococcus saprophyticus, S. aureus, Micrococcus roseus, M. kristinae, M. nishinomiyaensis, M. lylae, M. luteus, M. sedentarius, M. varians, Bacillus megaterium, B. thuringiensis, B. alvei, B. circulans, B. brevis, B. coagulans, B. pumilus, B. laterosporus, B. polymyxa, B. macerans, B. subtilis, B. firmus, B. cereus* and *B. lichiniformis*. The oil possessed maximum activity against *S. saprophyticus* (16.8±1.8 mm) followed by *B. circulans* (14.5±0.5mm). The infusion exhibited maximum activity against *B. laterosporus* (zone of inhibition :17.5±1.5 mm) followed by *B. polymyxa* (17.0 ±2.0 mm). All the tested isolates resisted the decoction of oregano (54).

The essential oil of oregano showed very strong antimicrobial activity against *B. subtilis*, *C. albicans*, *E. faecalis*, *E. aerogenes*, *E. durans*, *E. faecium*, *E. coli*, *K. pneumoniae*, *L. monocytogenes, L. innocua, P. aeruginosa*, *P. fluorescence*, *S. infantis, S. kentucky*, *S. typhimurium, S. aureus* and *S. epidermidis* with a MIC value of <0.195 µg/ml for all microorganisms (42).

Origanum vulgare essential oil possessed high activity against *Bordetella bronchiseptica*, *Saccharomyces cerevisiae*, *Bacillus subtilis* and *Staphylococcus epidermidis* with inhibition zones of 38 ± 1.5, 29.5 ± 0.8, 26.9 ± 0.9 and 26.9 ± 1.1 mm, respectively (44).

The antibacterial activity of the essential oil of *Origanum vulgare* was evaluated against Gram negative (*Escherichia coli* ATCC25921, *Klebsiella pneumoniae, Enterobacter cloacae* and *Pseudomonas aeroginosae* ATCC27853) and Gram positive (*Acinetobacter sp* and *Staphylococcus aureus* ATCC25923). The essential oil possessed wide range of antimicrobial effects. The maximum growth inhibitory activity of essential oil was recorded against *Staphylococcus aureus* and *Acinetobacter* sp (23 mm), followed by *Escherichia coli* ATCC25921 (22mm), *Enterobacter cloacae* (17mm), and *Klebsiella pneumonia* (14mm) (55).

The antimicrobial activity of the essential oil from *Origanum vulgare* was studied against the main bacteria responsible for bad perspiration odor (*Corynebacterium xerosis* IAL 105, *Micrococcus luteus* ATCC 7468, *Proteus vulgaris* ATCC 13315 and *Staphylococcus epidermidis* ATCC 12228). Seventeen constituents were identified, γ-terpinene and carvacrol (30.5 and 15.7%, respectively) were the major components. The essential oil exhibited antimicrobial activity against all the tested microorganisms and the MIC values ranged from 0.7 to 2.8 mg/ml. The formulated deodorant from the oils demonstrated bactericidal activity and it was able to cause damage in the morphological structure of the treated bacteria (56).

The antibacterial effect of the ethanolic *Origanum vulgare* extract was studied against *P. aeruginosa*, *Bordetella bronchiseptica*, *Escherichia coli*, *Burkholderia cenocepacia*, *Acinetobacter lwoffii*, *Acinetobacter baumannii*, *Moraxella catarrhalis*, *Bacillus subtilis*, and *S. aureus*. The oregano extract showed wide range of antibacterial activity against Gram-negative and Gram-positive bacterial strains (48).

Non-phenolic fraction of of *Origanum vulgare* was found to act antagonistically along with ciprofloxacin against *B. cereus* and *B. subtilis*, while the phenolic fraction exhibited indifferent activity along with ciprofloxacin against *Bacillus species* (57).

A bactericidal activity was possessed by high concentration of aqueous extract and moderate to high concentrations of ethanolic extract, against *Vibrio harveyi, V. anguillarum* and *Photobacterium damselae* (58).

The antibacterial activities, of the infusion, decoction and hydroalcoholic extract of oregano were evaluated against Gram positive species: *Staphylococcus aureus* (ATCC 25923) and *Staphylococcus epidermidis* (ATCC 35983), and Gram negative species: *Escherichia coli* (ATCC 25922), *Klebsiella spp*., *Pseudomonas aeruginosa* (ATCC 10145), *Enterococcus aerogenes* (ATCC 2048), *Proteus vulgaris* (ATCC 6380) and *Enterobacter sakazakii* (ATCC 29544). *Origanum vulgare* extracts possessed antimicrobial activity against Gram-negative and Gram-positive bacteria. The hydroalcoholic extract showed the highest activity against *Escherichia coli, Proteus vulgaris* and *Pseudomonas aeruginosa* (27).

The antifungal effects of essential oil of the flowers and leaves of *Origanum vulgare* ssp. *gracile* were assessed against *Aspergillus flavus* and *A. niger* by agar disk diffusion and micro well dilution methods. Minimum fungicidal concentration (MFC) values for *A. niger* and *A. flavus* were 200 and 100 µg/ml, respectively. The flower essential oil possessed significantly ($P<0.05$) higher growth inhibitory activities against both fungal species compare with leave essential oil (59).

The antifungal activity of *Origanum vulgare* essential oil was investigated against *Cryptococcus neoformans* FGF-5, *Aspergillus flavus* LM-02, *A. fumigatus* IPP-21, *T. rubrum* ATCC 28184, *T. mentagrophytes* LM-64, *Microsporum gypseum* ATCC 184, *M. canis* LM-36, *Cladosporium herbarium* ATCC 26362, *Candida albicans* ATCC 7645, *C. tropicalis* LM-14 and *C. krusei* LM-09*. Origanum vulgare* essential oil showed MIC value of 80 µl/ml. *C. krusei* LM-09 was the only strain resistant to all assayed concentrations of the essential oils. *Origanum vulgare* essential oil at their MIC values provided a cidal effect against *C. albicans* ATCC 7645 after 4 h of exposure. At 80 µl/ml, it exhibited 100 % inhibition of the radial mycelia growth of *T. rubrum* ATCC 28184 and *M. canis* LM-36 for 14 days. The main morphological changes observed in *A. flavus* LM-02 were decreased conidiation, leakage of cytoplasm, loss of pigmentation and disrupted cell structure indicating fungal wall degeneration (60).

The antifungal properties of essential oils extracted from flowers and leaves of *Origanum vulgare* ssp *gracile* was studied against *Aspergillus flavus* and *A. niger.* The minimum fungicidal concentration (MFC) values for *A. niger* and *A. flavus* were 200 and 100 µg/ml, respectively. The flower essential oils had significantly ($P<0.05$) higher inhibitory activities against both fungal species comparing to leave essential oils. *A. flavus* was significantly ($P<0.05$) more susceptible to the essential oils than than *A. niger* (59).

Oregano powder added to culture broths of *Aspergillus parasiticus* and *Aspergillus flavus* with a final concentrations of 0, 0.25, 0.5, 1, 2, and 4% stimulated the growth of both strains of molds, but it possessed antiaflatoxigenic activity (61).

The essential oil of *Origanum* ssp *hirtum,* exhibited antifungal effect against *Malassezia furfur, Trichophyton rubrum*, and *Trichosporon beigelii*. It showed high fungicidal activity at a dilution of 1/50000 (95% reduction in the number of metabolically active cells within 6 h of exposure). The main components of the oil, (carvacrol and thymol) exhibited the highest levels of antifungal activity (62).

Origanum vulgare showed antifungal activity against *Sporothrix brasiliensis*, including strains resisted the antifungal drugs (63).

Twenty-one phenolic compounds isolated from *Origanum vulgare* were subjected to *in vitro* antiviral evaluation against RSV, CVB3 and HSV-1. Only apigenin showed moderate to weak inhibitory activity against RSV with IC_{50} value of 23.1 μM, and compound (acacetin 7-O-[4000-O-acetyl-b-D-apiofuransyl-(1 → 3)]- b-D-xylopyranoside) exhibited weak activity against RSV with IC_{50} value of 81.7 μM. Compounds (acacetin-7-O- [6‴-O-acetyl-b-D-galactopyranosyl-(1→2)]-b-D-glucopyranoside and 2,5-dihydroxybenzoic acid) also exhibited weak effects against HSV-1 with IC_{50} values of 38.5 and 32.7 μM, respectively (64).

2.2. Antiinflammatory and analgesic effects

A decrease in pro-inflammatory TNF-α, IL-1β and IL-6 cytokines synthesis, as well as an increase in the production of anti-inflammatory cytokine IL-10 were caused by two fractions (S1 and S2) of *Origanum vulgare* extract, in THP-1 macrophages (65).

The analgesic effect of aqueous leaf extract of *Origanum vulgare* (84 mg/kg, po) was studied using tail flick method in mice. *Origanum vulgare* showed significant increase in the reaction time after 30 min of administration as compared to control group (66).

The possible involvement of GABA- ergic mechanism in analgesic effect of aqueous extract of *Origanum vulgare* (ORG) was studied in a rat model of acute pain test. Rats were cannulated into the left ventricle, 5-7days after the recovery from surgery, the extract was intraventricularly injected at dose of 3 μg/rat icv, baclofen (10 mg/kg, ip), CGP35348 (100 nmol/kg, icv), muscimol (1 mg/kg, ip) and bicuculline (5 mg/kg, ip) were separately injected 20 min before the injection of the extract. The response latency of rats to thermal stimulation was recorded using tail-flick test. Injection of the extract resulted in a significant and dose-dependent increase in the response latency, there was also a significant increase in the response latency after co-administration of the extract with baclofen compared with control group, while, co-administration of the extract/bicuculline, caused significant decrease in the response latency which indicated that the antinociception of the extract might be mediated, at least in part, by GABA receptors (67).

The antinociceptive effect of intracerebroventricular microinjection of *Origanum vulgare* extract was investigated in rats, with the studying of possible involvement of opioid receptors. The co- administration of the extract with morphine showed a significant increase in tail flick latency, while, naloxone, pretreatment significantly inhibited the antinociceptive activity of the extract and morphine (68).

The antinociceptive effect of combined *Achillea millefolium* (31.6, 100, 178, and 316 mg/kg) and *Origanum vulgare* extract (5.6, 10, 17.8, and 31.6 mg/kg), encapsulated in liposome, and administered ip, was assessed using 3% formalin test in rat. The results revealed a synergistic effect between the extracts. Naloxone also reduced the antinociceptive effect of the liposome encapsulated co-administered extract (69).

2.3. Antioxidant effect

The methanol extract was recorded to be the most effective against the DPPH radical. The radical scavenging activity of the methanol extracts of the seeds of *Origanum vulgare* was 87.4±1.2% (for 25 μl) and 89.3±0.4% (for 50 μl) (50).

The antioxidant properties of both aqueous and methanolic extracts of *Origanum vulgare* were studied *in vitro*. They were inhibited all phases of the peroxidative process: through neutralizing free radicals (superoxide anion, hydroxyl radical and 1,1-diphenyl-2-picrylhydrazyl radical), blocking peroxidation catalysis by iron (through iron-chelating and iron-oxidizing properties), and interruption with lipid-radical chain reactions (chain-breaking activity) (70).

The antioxidant effects of essential oil of the flowers and leaves of *Origanum vulgare* ssp. *gracile* were investigated by DPPH and ABTS assays. Remarkable antioxidant capacity was observed in both essential oils, but it was significantly ($P<0.05$) lower than butylated hydroxy toluene (59).

The antioxidant effects of ethanolic extract and oils of *Origanum vulgare* were investigated using DPPH method. The leaves extracts and essential oils showed high antioxidant activity (IC_{50} = 1.37 g/l, and 15.360 mg/l, respectively) (34).

Antiradical activities of essential oil and ethanol extract of *Origanum vulgare* (IC_{50}) were 1057 µg/ml and 19.97 µg/ml. The antioxidant index for 1000 µg/ml was 77.3±1.5% (33).

The antioxidant activity of the *Origanum vulgare* oil was examined by DPPH test. The oil showed the best antioxidant activity, the concentrations of essential oil, required for neutralization of 50% of initial DPPH radical concentration (EC_{50}), were 0.761, 0.590, 0.360 and 0.326 mg/ml, after 20, 30, 45 and 60 minutes of incubation, respectively. 92.3% lipid peroxidation inhibition was achieved by 1.35 mg/ml essential oil concentration (47).

The antioxidant activities, and phenolic compounds of the infusion, decoction and hydroalcoholic extract of oregano were evaluated using scavenging effects on DPPH; reducing power assay; inhibition of b-carotene bleaching; and inhibition of lipid peroxidation in brain cell homogenates. The antioxidant activity was correlated with phenolic compounds, mostly flavonoids, since decoction presented the highest concentration of flavonoids, phenolic contents and antioxidant effects, followed by infusion and hydroalcoholic extract (27).

The antioxidant properties of essential oils extracted from flowers and leaves of *Origanum vulgare* ssp *gracile* was studied using DPPH and ABTS models. Remarkable antioxidant capacity was exhibited by both flowers and leaves essential oils, but it was significantly ($P<0.05$) lower than Butylated Hydroxy Toluene (BHT) (59).

The antioxidant activity of the extract of dried leaves of *Origanum vulgare* and two water soluble compounds isolated from the leaves extract (4'-O-beta-D-glucopyranosyl-3',4'-dihydroxybenzyl protocatechuate and 4'-O-beta-D-glucopyranosyl-3',4'-dihydroxybenzyl 4-O-methylprotocatechuate) was determined by DPPH radical scavenging model compared with quercetin and rosmarinic acid. The antioxidant effect of 4'-O-beta-D-glucopyranosyl-3',4'-dihydroxybenzyl protocatechuate was almost the same as that of quercetin and rosmarinic acid, but that of 4'-O-beta-D-glucopyranosyl-3',4'-dihydroxybennzyl 4-O-methylprotocatechuate was less than that of quercetin, rosmarinic acid and 4'-O-beta-D-glucopyranosyl-3',4'-dihydroxybenzyl protocatechuate (24).

The antioxidant properties of phenolic, non-phenolic fractions of chloroform extract and volatile oil of *Origanum vulgare* were evaluated by free radical-scavenging, hydrogen peroxide radical-scavenging assay, reducing power, and metal chelating assays. The IC_{50} values of volatile oil were 15, 30, and 30 µg/ml and that of phenolic fraction were 60, 120, and 120 µg/ml for free radical-scavenging, hydrogen peroxide-scavenging, and metal chelating assays respectively (57).

Twenty-one phenolic compounds isolated from *Origanum vulgare* were evaluated for their *in vitro* antioxidant activity using DPPH radical-scavenging and ferric-reducing antioxidant power assays; twelve of them exhibited significant antioxidant activity comparable to that of ascorbic acid (64).

Hot water extract, cold water extract, ethanolic extract and essential oils of *Origanum vulgare* possessed strong antioxidant properties with the using of FRAP, reducing power and DPPH tests, and also showed high phenolic content. Total phenolic content revealed statistically higher values in hot water extract, followed by essential oil, ethanolic extract, and cold water extract (35).

2.4. Anticancer effects

The hydroalcoholic extract of *Origanum vulgare* ssp *viridulum* was evaluated for their antiproliferative activity against three human cancer cell lines (breast cancer MCF-7, hepatic cancer HepG2 and colorectal cancer LoVo). *Origanum vulgare* ssp *viridulum* showed a selective antiproliferative activity on hepatic cancer with IC_{50} of 32.59 µg/ml (71).

Treatment of A549 human lung adenocarcinoma epithelial cells with oregano extract (0-250 μg/ml final concentration) resulted in a concentration-dependent decrease in cell viability with a calculated LC_{50}= 14μg/ml. Incubation of A549 cells with increasing concentrations of thymol, carvacrol, p-cymene, or 1-octacosanol alone resulted in a concentration-dependent decrease in cell viability, with thymol being the most cytotoxic (48).

The effect of *Origanum vulgare* ethanolic extracts on redox balance, cell proliferation, and cell death was investigated in colon adenocarcinoma Caco2 cells. Oregano extract caused growth arrest and cell death in a dose- and time-dependent manner. Both extrinsic and intrinsic apoptotic pathways were activated by the extract (72).

The cytotoxic effect of methanolic extract of *Origanum vulgare* was studied against HCT-116 and MDA-MB-231 cell line *in vitro*. The results showed that cell growth was significantly lower in extract treated cells compared to untreated control. It possessed more cytotoxic effect against HCT-116 cell line than in MDA-MB-231(73).

The anticancer effect of a crude extract of *Origanum vulgare* was studied against SW13 and H295R cell lines. The crude extract decreased cell viability, survival, modified cell cycle and induced cell death (through necrotic process), the effect which attributed to a blockade of MAPK and PI3 K/Akt pathways (74).

Only the highest concentration of the aqueous extract and medium to high concentrations of the ethanolic extracts showed cytotoxic activity against the tumor PLHC-1 cell line (58).

The effect of an aqueous extract of *Origanum vulgare* (20, 40 or 60 mg/kg, po, for 15 weeks) on lipid peroxidation and anti-oxidant status was evaluated in 1,2-dimethylhydrazine (DMH)-induced rat colon carcinogenesis. The levels of lipid peroxidation products, such as thiobarbituric acid reactive substances and conjugated dienes were significantly higher in the liver whereas in caecum and colon the levels were lower in DMH-treated animals as compared with control rats. The levels of the superoxide dismutase, catalase, reduced glutathione, glutathione reductase, glutathione peroxidase and glutathione-S-transferase were decreased in DMH-treated rats, but were significantly reversed on oregano supplementation (75).

2.5. Protective effects

The protective effect of the aqueous leaves extract of *Origanum vulgare* (50, 100, 150 mg/kg bw, po, for 15 days) on CCl_4-induced hepatotoxicity was investigated in rats. The extract administration possessed significant protection against CCl_4-induced hepatotoxicity in dose-dependent manner, maximum activity was recorded at150 mg/kg bw, it significantly decreased serum ALT, ALP, and AST levels, significantly enhanced antioxidant status, and ameliorated the histological alterations (76-77).

The hepatoprotective effect of the ethanolic extract of aerial parts of *Origanum vulgare* (50, 100, 200, and 400 mg/kg, ip, for 7 consecutive days) was studied against cyclophosphamide- induced liver toxicity in mice. Serum levels of hepatic markers were increased after cyclophosphamide treatment but restored in the *Origanum vulgare* - pretreated groups, pretreatment with 400 mg/kg *Origanum vulgare* significantly decreased the serum ALT, AST, and ALP ($P< 0.001$). Histological examinations also confirmed the protective effects of *Origanum vulgare* against cyclophosphamide - induced liver toxicity (78).

The protective effects of *Origanum vulgare* leaf extract against paraquat liver damage was investigated in rats. Paraquat induced remarkable increase in the lipid profiles and serum ALT, AST, ALP, and liver TNF-α gene expression. The groups which received *Origanum vulgare* leaf extract exhibited significant ameliorations of the abnormalities of paraquat-induced liver damage and serum biochemical parameters (79).

The protective effects of *Origanum vulgare* hydroethanolic leaf extract (200, 400, 800 mg/kg bw/day, po) was evaluated against the acute nephrotoxicity and renal oxidative stress induced by paraquat in rats. Oral administration of paraquat significantly increased ($P<0.05$) serum urea, creatinine, protein carbonyl, and renal TNF-α gene expression relative to control group. Renal catalase, SOD, and vitamin C levels were declined significantly ($P<0.05$). Administration of *Origanum vulgare* leaf extract increased the renal vitamin C, catalase, superoxide dismutase, and decreased the renal TNF-α gene expression, malondialdehyde, serum urea and creatinine in paraquat-induced nephrotoxicity in rats (80).

The protective effect of the extract of *Origanum vulgare* (50, 100, 200, and 400 mg/kg for 7 consecutive days) was studied against cyclophosphamide -induced oxidative lung damage in mice. A single dose of cyclophosphamide markedly altered the levels of several biomarkers associated with oxidative stress in lung homogenates. Pretreatment with *Origanum vulgare* significantly reduced the levels of lipid peroxidation and attenuated the alterations in glutathione content and superoxide dismutase activity induced by cyclophosphamide in lung tissue. In addition, *Origanum vulgare* effectively alleviated cyclophosphamide -induced histopathological changes in lung tissue (81).

Origanum vulgare extract possessed significant protective effect against selenite induced cataract when injected 1 and 2 day (2 g/kg, ip 2 times) before selenite injection in rats. The anticataract effect of *Origanum vulgare* extract could be attributed to direct or indirect antioxidant mechanisms (82).

The protective effect of *Origanum vulgare* extract on the toxic effects of organophosphate pesticide (diazinon), on growth and some metabolism associated components, was studied in rainbow trout, *Oncorhynchus mykiss*. During exposure period, diazinon induced ranges of histological lesions in liver, but, the severity of theses lesions was lower in origanum extract -supplemented fish ($P<0.05$) (83).

The radioprotective effects of *Origanum vulgare* extract (12.5, 25, 50 and 100 µg/ml) was studied against genotoxicity induced by $^{(131)}I$ in human blood lymphocyte. Origanum at 25, 50 and 100 µg/ml significantly reduced the micronuclei frequency in cultured lymphocytes. The maximum protective effect and the maximum decrease in the frequency of micronuclei were observed at 100 µg/ml, which caused 70% reduction ($P<0.0001$). Origanum extract also exhibited an excellent and dose-dependent radical-scavenging activity against 1,1-diphenyl-2-picrylhydrazyl-free radicals (84).

The genoprotective effect of the aerial parts of *Origanum vulgare* ethanolic extract (50, 100, 200, or 400 mg/kg, for 7 days) was studied against cyclophosphamide -induced genotoxicity in mouse bone marrow cells. At 400 mg/kg, *Origanum vulgare* displayed its maximum protective effect, reduced the number of micro nucleus from 10.52 ± 1.07 for cyclophosphamide group to 2.17 ± 0.26 and completely normalized the mitotic activity ($P< 0.001$). *Origanum vulgare* also led to significant proliferation and hypercellularity of immature myeloid elements after treatment with cyclophosphamide, mitigating the bone marrow suppression (85).

2.6. Antidiabetic effect

The methanolic extract of *Origanum vulgare* ssp *hirtum* reduced diabetes incidence and preserved normal insulin secretion in streptozotocin-induced type 1 diabetes in mice. The extract also scavenged reactive oxygen and nitrogen species and alleviated the need for the up-regulation of antioxidant enzymes. The methanolic oregano extract specifically attenuated the pro-inflammatory response mediated by T helper 17 cells and enhanced anti-inflammatory T helper 2 and T regulatory cells through the impact on specific signalling pathways and transcription factors. The extract preserved β-cells from *in vitro* apoptosis via blockade of caspase. Rosmarinic acid, a predominant compound in the extract, exhibited only partial protection from diabetes induction (32).

The antidiabetic activity of the aqueous extract of the leaves of *Origanum vulgare* was studied in normal and streptozotocin diabetic rats. In normal rats, the blood glucose levels were slightly decreased 6 h after a single oral administration ($P<0.05$) as well as 15 days after once daily repeated oral administration (20 mg/kg) of aqueous extract ($P<0.05$). A single dose (20 mg/kg) or 15 daily oral doses of the aqueous extract produced significant decrease of blood glucose levels in STZ diabetic rats ($P<0.001$). The blood glucose levels were normalized from the 4^{th} day after daily repeated oral administration of aqueous extract (20 mg/kg) in STZ diabetic rats ($P<0.001$) (86).

2.7. Antiparasitic effect

The antiprotozoal effect of *Origanum vulgare* hydroalcoholic extract was evaluated against *Giardia lamblia* cysts compared with metronidazole *in vitro*. 500µl of of 10, 100 and 200 mg/ml of hydroalcoholic extract and also 125 mg/kg of metronidazole were added to the purified cysts of giardia. The results revealed that the extract possessed anti-Giardia activity, the best response was achieved at higher concentrations, the effect of 200 mg/kg was comparable with metronidazole ($P>0.05$) (87).

The diet supplemented with oregano at 5.0 and 7.5 g/kg of feed was effective against the infection with in broiler chickens challenged with *Eimeria tenella* (88).

The antiparasitic effect of essential oils of *Origanum vulgare* was evaluated on the growth and ultrastructure of diverse evolutive forms of *Trypanosoma cruzi*. Culture epimastigotes and bloodstream trypomastigotes were incubated for 24 h with different concentrations of essential oils. Crude extract of *Origanum vulgare* essential oil inhibited epimastigote growth (IC_{50} /24 h = 175 microg/ml) and also induced trypomastigote lysis (IC_{50}/24 h = 115 microg/ml). The treated cells revealed few morphological changes in the plasma membrane. Observation by transmission electron microscopy revealed cytoplasmic swelling with occasional morphological alterations in plasma and flagellar membrane (89).

2.8. Reproductive effect

The effect of *Origanum vulgare* extract (0.18 g/kg bw for 3 weeks) on male fertility was studied in normal and alloxan diabetic mice, via estimation of testosterone, LH and FSH level, sperm viability, activity, motility and sperm abnormalities. Its effects on GOT, GPT, alkaline phosphatase and lipid profile status were also studied. Testosterone, LH, FSH levels and sperm motility were increased with a decreased in dead sperms, sperm abnormalities, GOT, GPT, alkaline phosphatase and lipid profile, in extract treated group in comparison with alloxan diabetic mice (90).

The effect of the aqueous extract of *Origanum vulgare* on the preimplantational embryo development was investigated in mice. The oregano aqueous extract was given to pregnant mice: 0, 9, 18 and 36 mg/ml respectively. It caused slight delay in the embryo development only at the highest dose, without embryo toxicity (91).

2.9. Dermatological effects

The ethanol oregano extracts significantly suppressed *Propionibacterium acnes* - induced skin inflammation, as measured by ear thickness (32%) and biopsy weight (37%). The extract also reduced the production of IL-8, IL-1β and TNF-α up to 40%, 37%, and 18%, respectively, as well as the expression of these three pro-inflammatory mediators at the transcriptional level, in co-culture of *P. acnes* and human THP-1 monocytes. The extract also inhibited the translocation of nuclear factor-kappa B (NF-κB), possibly by inactivating toll-like receptor-2 (TLR2) (92).

The titanium dioxide nanoparticles (TiO2·NPs) synthesized by utilizing *Origanum vulgare* under room temperature, was tested for wound healing activity in the excision wound model in rats by measuring wound closure, histopathology and protein profiling. The results revealed significant wound healing activity in Albino rats (93).

2.10. Gastrointestinal effects

The protective effects of *Origanum vulgare* leaves extract (200 and 400 ppm, po), for 1 week before inducing intestinal ischemia/ reperfusion (I/R) injury in rats. *Origanum vulgare* extract significantly decreased mucosal damages compared to I/R group (94).

2.11. Antiurolithic effect

The antiurolithic effect of the crude aqueous- methanolic extract of Origanum was studied using *in vitro* and *in vivo* methods. In the *in vitro* experiments, kidney epithelial cell lines and urinary bladder of rabbits were used, whereas, in the *in vivo* studies, rat model of urolithiasis was carried out to study the preventive and curative effect of the extract. In the *in vitro* experiments, the extract exhibited a concentration-dependent (0.25-4 mg/ml) inhibitory effect on the slope of nucleation and aggregation and also decreased the number of calcium oxalate monohydrate crystals produced in calcium oxalate metastable solutions. It also showed concentration-dependent antioxidant effect. The extract reduced the cell toxicity and LDH release in renal epithelial cells exposed to oxalate crystals. The extract also relaxed high K^+ induced contraction in rabbit urinary bladder strips. In male Wistar rats receiving lithogenic treatment, the extract treatment (10-30 mg/kg) prevented as well as reversed toxic changes including loss of body weight, polyurea, crystalluria, oxaluria, raised serum urea and creatinine levels and crystal deposition in kidneys compared to their respective controls (95).

2.12. Immunomodulatory effect

The immunomodulatory effects of the extract were tested on human monocyte derived dendritic cells (DC), type-1 (M1) and type-2 macrophages (M2) infected with *M. bovis* Bacille Calmette-Guérin (BCG), used as a model of persistent intracellular bacterium. DC, M1 and M2 treated with the extract significantly enhanced their mycobactericidal activity, which was associated with phagosomal acidification in M1 and M2 and increase of phagosomal, but not mitochondrial ROS production in M1, M2, and DC. Treatment of BCG-infected DC with the extract, significantly reduced TNF-α and IL-12 production and increased TGF-β synthesis (96).

2.13. Other effects

The metal chelating activity of ethanol extract of *Origanum vulgare* was 74.5±0.2 %. The tyrosinase inhibitory activities of essential oil, ethanol extract and arbutin were 26.5±0.3%, 6.5±0.2% and 50±0.1%, respectively (33).

2.14. Safety

The effect of oregano tea (30 days received an infusion of oregano as the only fluid intake) on biochemical profile and body weight was studied in rats. Rat received the infusion had a lower blood glucose (135.20±22.09 mg/dl) compared to the control group (152.00±16.51) ($P<0.05$). There were no significant changes in total cholesterol, triglyceride, HDL-cholesterol, weight gain and the rate of weight gain, aspartate aminotransferase, alanine aminotransferase, C reative protein and creatinine seum levels (97)

3. Conclusion

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

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