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THERAPEUTIC APPLICATIONS AND PHARMACOLOGICAL EFFECTS OF *ORIGANUM VULGARE*, AND ITS IMPORTANT ACTIVE INGREDIENTS

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ABSTRACT

(*Origanum vulgare* L.,Wild marjoram, Labiatae) is known in Iran. Flowers and leaves have medicinal effects. Many subspecies and strains of *oregano* have been developed by humans over centuries for their unique characteristics. "Hippocarates" used *oregano* as a cure for stomach and respiratory ailments. The most active ingredient in wild *oregano* is carvacrol, a potent, naturally occurring compound which has remarkable effects against all types of microbes such as bacteria, virus (including most types of FLU), fungus and parasites. Oil of *oregano* contains over 5 compounds which possess immune promoting actions, although carvacrol is the main one. In addition, Oil of *oregano* has excellent antioxidant properties, notably labiatic and p-hydroxy-hydrocaffeic acid. The main chemical constituents include caravacrol, thymol, limonine, pinene, ocimene and caryophyllen. The leaves and flowering stems are strongly anticeptic, antispasmodic, carmonative, cholagogue, diaphoretic, emenagogue, expectorant, stimulant, antibacterial, immunostimulatory, treatment of cancer, antioxidant, anti-inflammatory, stomachic and mildly tonic. The plant contains tannins,

resins, sterols and flavonoids are compounds and essential oils contain thymol, carvacrol and beta - is borneol. This article is an overview on the traditional uses and pharmacological effects of total hole and the most active ingredient.

Keywords: Wild marjoram, *Origanum vulgare* L., Carvacrol

INTRODUCTION

(*Origanum vulgare* L.,Wild marjoram, Labiatae) growing in Asia, is known in Iran, and is widely used in traditional medicine. *O. vulgare* is also an important culinary herb, used for the flavor of its leaves, especially when dried than fresh is collected from natural sites and used as a raw material in the pharmaceutical, cosmetic and food industry (Melchior and Kastner, 1974; Tucker & Maciarello, 1994). The herb of this plant is perennial, growing to 20 inches, with pink spade-shaped flowers 3–4 mm long, olive-green leaves 1–4 cm long, preferring the PH range between 6.0 and 8.0, on dry sunny slopes and forest margins in rather smallclusters (Peter, K. V., 2004).

O. vulgare has been traditionally used in the treatment of urolithiasis. Therefore, we showed the crude draw out of *O. vulgare* for possible antiurolithic. In traditional medicine it is used for the treatment of common illnesses and has potential for positive modulation of oxidation-linked diseases such as diabetes. Here we showed the effect of aqueous extract of *Origanum* (leaves, stems and flowers) on spatial learning. *O. vulgare* has been used as a medicinal herb in treatment of various conditions: fevers, diarrhea, indigestion, jaundice and vomiting. Recent studies have shown that *oregano* displays anti-oxidant, anti-fungal and antibiotic properties. Because of its anti-oxidant functions, *oregano* could become useful agent in treatment of cancer, heart disease and high blood pressure. It is also useful as a digestive aid, since it increases salivation. Used externally, *oregano* is successful in treatments of rheumatism, muscle and joint pain, sores and swellings. *Oregano* oil can help skirmish toothache. In some cases, *oregano* could cause skin

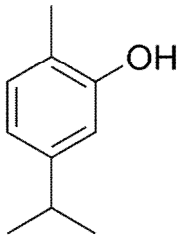
irritations. Use of a herbal infusion of *origanum* in hemophilia patients during tooth extraction is its clinical trial (Russian, no abstract) Klement 1978 Ethnobotanical survey of 130 informants revealed 16 species used for hypoglycaemia: Achillea, Ammi, Atriplex, Capparis, Ceratonia, Cleome, Eryngium, Inula, Matricaria, Origanum, Paronychia, Prosopis, Salvia.,Sarcopoterium, &TeucriumYaniv (1987)

" *Origanum dictamus* L., A Greek native plant " (no abstract) Skrubis (1979) Pregnancy associated aversions were meats, poultry, and sauces flavored with oregano and cravings were ice cream, sweets, candy (esp. chocolate), fruits, and fish - in a survey of 250 women (Hook, 1978)

O. vulgare analyzed by gas chromatography−mass spectrometry (GC−MS) contained 64 components with the predominance of carvacrol, thymol, γ-terpinene, sabinene, linalyl acetate, germacrene D, E-caryophyllene, *p*-cymene (Table 1); which two phenol Compounds: thymol and carvacrol exhibited the highest bactericidal and fungicidal substances (Melegari et al., 1995; Leto et al., 1996; Kokkini, 1997; Pasquier, 1997; Russo et al., 1998). the major constituent Carvacrol, or cymophenol, $C_6H_3CH_3(OH)(C_3H_7)$, is a monoterpenoid phenol, made up of attaching cymol sulfonic acid to caustic potash (shape 1) (Smid EJ, 2000). In the extract of dried leaves of *O. vulgare*, 1, 1-Dipehnyl-2-picrylhydrazyl (DPPH) radical scavenging effects were found. Also by ^{1}H-, ^{13}C-NMR, DEPT, HMQC, and HMBC spectral analyses, and by NOE experiments, structures of the isolated water-soluble active ingredients were 4′-*O*-β-D-glucopyranosyl-3′, 4′-dihydroxybenzyl protocatechuate and 4′-*O*-β-D-glucopyranosyl-3′, 4′-dihydroxybenzyl 4-*O*-methylprotocatechuate. The glycosidically bound volatiles in dried leaves and flowers of *O. vulgare* amounted to 20 mg kg^{-1}, which fourteen of them were identified with thymoquinone as the major component. Other important aglycones

were determined to be benzyl alcohol, eugenol, 2-phenyl-ethanol, thymol, 3-hexen-1-ol and carvacrol (table1) (Adams, 1995).

Carvacrol may be synthetically prepared by heating carvol with glacial phosphoric acid or by performing a dehydrogenation of carvone with a Pd/C catalyst; by heating one part of iodine with five parts of camphor; or by the interaction between nitrous acid and 1-methyl-2-amino-4-propyl benzene. Carvacrol also exists in *Origanum compactum* (Bouchra, chebli et al.,Achouri, Mohamad; Idrissi Hassani, L.M;2003), *Origanum dictamnus* (Liolios, C.C. et al.; Gortzi, O; Lalas, S; Tsaknis, J; Chinou, 2009), *Origaum microphyllum* (Aligiannis, et al.; Kalpoutzakis, 2001) *Origanum onites* (Coskun, Sevki et al.; Girisgin, 2008; Ruberto, Giuseppe et al.; Biondi, Daniela; Piattelli, Mario,2006), *Origanum scabrum* (Aligiannis, et al.; Kalpoutzakis; Mitaku, Sofia; Chinou, Ioanna, 2001), *O. vulgare* (Kanias, et al., 1998; Figiel, Adam et al.; Szumny, Antoni, 2010). This article reviews the traditional uses and pharmacological effects of total extract and the most active ingredient of *O. vulgare.*



Shape 1

Table1: The chemical composition of essential oils of leaves of *O. vulgare*

Compound		PC	abundance (% chromatogram area) in sample group
1	2-hexenal	0.95	0.07+ 0.04 (0.03±0.09)
2	3-hexenol	0.35	0.01+ 0.01 (0.00±0.02)
3	a-thujene	0.38	0.39+ 0.16 (0.26±0.56)
4	a-pinene	0.19	0.15+ 0.02 (0.13±0.18)
5	Camphene	-0.37	0.02+ 0.01 (0.02±0.03)
6	Sabinene	-0.52	0.72+ 0.31 (0.47±1.06)
7	1-octen-3-ol	0.28	0.80+ 0.16 (0.63±0.94)

8	3-octanone	0.43	0.17+ 0.02 (0.16±0.19)
9	Myrcene	0.19	0.55+ 0.10 (0.43±0.62)
10	3-octanol	0.28	0.29+ 0.04 (0.25±0.33)
11	a-phellandrene	0.38	0.06+ 0.01 (0.05±0.07)
12	d3-carene	0.25	0.03+ 0.00 (0.03±0.03)
13	a-terpinene	0.20	1.08+ 0.52 (0.66±1.66)
14	p-cymene	0.40	2.18+ 0.79 (1.43±3.01)
15	Limonene	-0.05	0.26+ 0.22 (0.11±0.51)
16	z-b-ocimene	-0.68	1.74+ 1.71 (0.69±3.71)
17	e-b-ocimene	-0.56	0.57+ 0.36 (0.16±0.80)
18	g-terpinene	0.20	4.85+ 2.54 (2.17±7.22)
19	cis-sabinene hydrate	-0.42	0.47+ 0.35 (0.17±0.85)
20	cis-linalool oxide	-0.03	0.22+ 0.20 (0.05±0.44)
21	Terpinolene. Trans-linalool oxide	-0.27	0.44+ 0.49 (0.07±1.01)
22	trans-sabinene hydrate	-0.18	0.59+ 0.92 (0.04±1.66)
23	Linalool	-0.50	28.18 +13.10 (18.39±43.06)
24	trans-pinene hydrate	-0.10	0.14+ 0.20 (0.01±0.37)
25	1-3-8-p-menthatriene	-0.31	0.02+ 0.02 (0.00±0.04)
26	Borneol	-0.10	0.05+ 0.04 (0.02±0.09)
27	Terpin-4-ol	-0.14	2.00+ 2.87 (0.28±5.31)
28	P-cymen-8-ol	0.50	0.04+ 0.04 (0.00±0.08)
29	a-terpineol	-0.34	0.88+ 0.93 (0.11±1.92)
30	cis-dihydro carvone	-0.47	0.01+ 0.01 (0.00±0.02)
31	Myrtenyl acetate	0.28	0.02+ 0.02 (0.00±0.05)
32	Thymol methyl ether	0.15	0.29+ 0.30 (0.10±0.64)
33	Carvone	0.50	0.01+0.00 (0.00±0.01)
34	Carvacrol methyl ether	0.34	1.29+0.22 (1.07±1.51)
35	Bornyl acetate	-0.42	0.01+0.01 (0.00±0.02)
36	Indole	0.20	0.01+0.00 (0.01±0.02))
37	Thymol	0.20	10.88+8.50 (3.96±20.37
38	Carvacrol	0.28	1.23+1.08 (0.30±2.41
39	Eugenol. Thymol acetate	0.48	0.02+0.00 (0.02±0.02)
40	a-cubebene	-0.42	0.10+0.07 (0.02±0.14)
41	a-copaene	0.36	0.12+0.06 (0.05±0.16
42	b-bourbonene	0.41	0.46+0.19 (0.26±0.65)
43	b-cubebene	0.46	0.10+0.06 (0.05±0.16)
44	b-elemene	0.25	0.13+0.05 (0.08±0.17)
45	Jasmone	-0.91	0.02+0.00 (0.01±0.02

46	(E)-caryophyllene	-0.67	13.24+5.98 (6.63±18.28)
47	b-gurjunene	0.43	0.10+0.02 (0.08±0.12)
48	Aromadendrene	0.15	0.09+0.09 (0.04±0.19
49	a-cadinene	0.41	0.03+0.01 (0.02±0.04)
50	a-humulene	-0.64	1.35+0.50 (0.81±1.78)
51	allo-aromadendrene	0.11	0.18+0.06 (0.12±0.24)
52	cis-b-farnesene	-0.30	0.05+0.02 (0.03±0.07)
53	g-muurolene	-0.76	10.48+4.74 (7.39±15.94
54	Germacrene-D	-0.51	2.48+1.46 (1.10±4.02)
55	a-muurolene	-0.30	0.07+0.03 (0.03±0.09)
56	b-bisabolene	-0.67	3.29+0.85 (2.65±4.25)
57	d-cadinene	-0.23	0.78+0.17 (0.60±0.93)
58	trans-g-bisabolene	0.18	0.14+0.15 (0.03±0.32)
59	Germacrene-d-4-ol	0.36	1.49+1.16 (0.73±2.83)
60	Caryophyllene oxide	0.21	3.56+2.88 (0.80±6.55)
61	Globulol	0.27	0.17+0.11 (0.09±0.29)
62	t-cadinol	-0.90	0.23+0.11 (0.11±0.33)
63	Torreyol	-0.08	0.05+0.04 (0.01±0.10)
64	a-cadinol	-0.47	0.58+0.31 (0.22±0.76

The first column represents the relative amount of the first principal components, PC. The last column indicates the average relative amount (% chromatogram area) (Adams, 1995).

ANTIMICROBIAL ACTIVITY

O. vulgare L., usually known as *oregano* or wild marjoram, is a famous flavouring for many international dishes and has antioxidant practical uses in human health (Dorofeev *et al*., 1989; Deighton *et al*., 1993). Antimicrobial action is reported for *O. vulgare* extracts, which had phenolcarboxylic acids (cinamic, caffeic, *p*-hydroxybenzoic, syringic, protocatechuic, vanillic acid) as likely active substances (Mirovich *et al*., 1989). Traditionally, *Origani vulgaris herba* was used in respiratory tract disorders such as cough or bronchial catarrh (as expectorant and spasmolitic agents), in gastrointestinal disorders (as choleretic, digestive, eupeptic and spasmolitic agents) as mouth antiseptic, in urinary tract disorders (as diuretic and antiseptic) and in dermatological affections (alleviation of itching, healing crusts, insect stings) (Blumenthal, 1998; Bruneton, 1999).

ANTIFUNGAL ACTIVITY

Authors usually agree that there is a relationship between the chemical building of the most plentiful essential oil components and their antifungal and anti-aflatoxigenic potency. Phenols are accepted to be the most powerful antimicrobials followed by alcohols, ketones, ethers and hydrocarbons (Bullerman, 1977; Hitokoto *et al*., 1980; Hussein, 1990; Daw *et al*., 1994; Charai *et al*., 1996).

An effective antifungal effect of *O. vulgare* essential oil (rich in carvacrol and thymol) at concentration of 1 µl/ml against the common spoilage fungus *A. niger* was observed also by Baratta *et al.* (1998a).

There are many differences among genera of fungi with regard to sensitivity to the antifungal effects of *oregano* as the concentration of necessary oil and its origin may significantly effects their antifungal activity (Baricevic and Bartol, 2002). The ground *O. vulgare* was found to have a strong antifungal potential against several food-contaminating moulds like Trichoderma harzianum Rifai, Alternaria alternata Keissler, Fusarium oxysporum Schlecht, Mucor circinelloides f. griseo-cyanus Schipper, Cladosporium cladosporioides de Vries, Fusarium culmorum Saac., Aspergillus versicolor Tiraboschi, but allowed selective increasing of Rhizopus stolonifer Lind and Penicillium Citrinum Thom in potato dextrose agar (Schmitz *et al*.., 1993). The antifungal effect was due to the being of phenolic components in the essential oil, like carvacrol and/or thymol, which are famous for their antifungal potency (Kurita *et al*., 1981; Farag *et al*., 1989; Curtis *et al*., 1996). Phenolic compounds removed from *O. vulgare* L. are likely responsible for the high inhibitory activity of carvacrol/thymol chemotypes of oregano against fungal growth, conidial germination and production of *Penicillium digitatum* (at essential oil concentration of 250–400 ppm) (Daferera *et al*., 2000).

ANTIBACTERIAL ACTIVITY

Based on a broad opinion of antibacterial activity, *oregano* appears to be one of the inhibitoriest spices tested. 52 essential oils (including *O. vulgare* and *O. majorana*

essential oils) and extracts of different plant genera have been found out (Hammer *et al*., 1999) for their activity against *Acinetobacter baumanii, Aeromonas veronii* biogroup *sobria, C. albicans, Streptococcus faecalis, E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella enteric* subsp. *enterica* serotype *typhimurium, Serratia marcescens* and *S. aureus.*

O. vulgare essential oil, characterised by high thymol (32.4 per cent) and carvacrol (16.7 per cent) content, showed a strong inhibitory effect against a broad spectrum of tested bacteria, that were both gram negative or gram possitive (Alcaligenes faecalis, Bacillus subtilis, Beneckea natriegens, Brevibacterium linens, Brocothrix thermosphacta, Citrobacter freundii, Clostridium perfringens, Enterobacter aerogenes, Erwinia carotovora, Klebsiella pneumoniae, L. plantarum, Leuconostoc cremoris, Moraxella spp., Proteus vulgaris, Salmonella pullorum, Serratia marcescens, S. aureus, Streptococcus faecalis, Yersinia enterolitica) (Baratta *et al*., 1998a). Great inhibitory activity was observed also against *E. coli, Flavobacterium suaveolens, Micrococcus luteus, Pseudomonas aeruginosa,* whilst two bacteria (*Acinetobacter calcoaceticus, Aeromonas hydrophila*) were not easily influenced by *oregano* essential oil. *Oregano* essential oils have been believed as an alternate natural additive in gastronomy and in the food processing business. It was found that *O. vulgare* essential oil was effective in inactivation of *E. coli* in concentrations as low as 0.7 per cent, acting synergistically with the pH and storage temperatures, thus contributing to the intrinsic safety of salad that is made at home (Skandamis and Nychas, 2000)

ANTIOXIDANT ACTIVITY

A great number of reports on the antioxidant effects of *Origanum* species have been reported *O. vulgare* essential oil (Italian origin) showed protective antioxidant properties in an egg yolk assay. At high concentrations (1000 ppm and 750 ppm), the antioxidative potency of oregano

oil was higher than those of butylated hydroxytoluene (BHT) or of -tocopherol. However, in a rat liver assay the antioxidative effect of oregano essential oil was much lower, at 750 ppm showing the same limit of antioxidant activity as tocopherol at 250 ppm (Baratta *et al*., 1998a). Vekiari *et al*. (1993a) have studied the extracts of *O. vulgare* of different polarity, to discover the active compounds responsible for the antioxidative effect of oregano. The vital antioxidant factor of the non-polar hexane extract was isolated by repeated fractionations, and consisted mainly of terpene derivatives. Among polar combination that were extracted from *O. vulgare* leaves, the most effective in stabilising lard against oxidation, with same potency to BHT, were flavonoids (flavanone eriodictyol, the dihydroflavonols dihydrokaempferol and dihydroquercetin and flavone apigenine) (Vekiari *et al*., 1993b). The antioxidative effects of *O. vulgare* drug plant (*Origani herba*) have been studied in the brightness of both direct use as stabilisers of fat and, indirectly, as feed additives in order to improve the shelf-life of meat and fat-containing food (Vichi *et al*., 2001).

IMMUNOSTIMULANT ACTIVITY

Some studies have showed that *oregano* extracts or herbal combination with *Origanum* spp. possess *in vitro* antiviral activity or have immunostimulating effects both *in vitro* and *in vivo*. A mixture of herbal preparation having rosemary, sage, thyme and *oregano* (*O. vulgare*) showed radical scavenging activity and inhibition of the human immunodeficiency virus (HIV) infection at very low concentrations (Aruoma *et al*., 1996). It was indicated that the main active compounds of herbal preparations were carnosol, carnosic acid, carvacrol and thymol. Significant inhibitory effects of *O. vulgare* extracts against HIV-1 induced cytopathogenicity in MT-4 cells were also observed by Yamasaki *et al*. (1998).

CANCER TREATMENT

The anti-inflammatory and antimicrobial effects of O. *vulgare* are well known, only few data are available on its activity in cancer prevention.

O. vulgare markedly inhibites DMH induced colon carcinogenesis. The effect of *O. vulgare* on fecal bacteria enzyme activities in 1,2-dimethylhydrazine (DMH)-induced experimentalcolon carcinogenesis in rats, which were divided into 6 groups with or without supplemented DMH-traeted and with different adminstrated doses, was that the fecal bacteria enzyme activities are significantly higher in the group treated with DMH (Nalini et al., 2008). *Oregano* supplementation covered up the bacterial enzyme activities and modulated oxidative stress. And the optimal dose of 40 mg.kg (-1) b.w. was more effective than either the higher or lower dose (Srihari *et al*., 2008).

O. vulgare induces apoptosis in colon cacer coca2 cells, so can be curative for colon cancers. Ethanolic extract of *O. vulgare* has some effects on redox balance, cell proliferation, and cell death in colon adenocarcinoma Caco2 cells.It stops cell growth and leads to cell death in a dose- and time-dependent way (Avigliano et al., 2009). Changes in glutathione content, like the increase in its oxidized form, may cause *oregano*-triggered death. Spice extract activates extrinsic and intrinsic apoptotic pathways. Moreover, whole extract, instead of a specific component, can be selective for cytotoxic effects (Savini *et al*., 2009).

Some constituents of *O. vulgare* have antitrombin effect.Isolated Aristolochic acid I, aristolochic acid II, and D-(+)-raffinose from *O. vulgare*, indicated inhibitory effects against thrombin; So are confirmed as constituents against leukemia and cancer (Goun *et al*., 2002).

ANTIHYPERGLICEMIC ACTIVITY

Oregano is a rich source of natural phenolic antioxidants and has capability of being a source of nutritional ingredients for functional foods. Herbs such as *oregano* have long been used in food protection and in traditional medicine in the curing of common sicknesses and have capability for positive variation of oxidation-linked diseases such as diabetes. One of the potentially important constituent of anti-diabetic activity by *oregano* extract is mild amylase inhibition by phenolic antioxidants to help donate towards management of hyperglycemia. (McCue P *et al*., 2004).To this end, McCue P *et al*. processed extract total soluble phenolic components by the Folin-Ciocalteu reagent method, rosmarinic acid (RA), protochatechuic acid (PA), quercetin, and p-coumaric acid (pCA)

contents by HPLC, antioxidant activity as1, 1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging, and PPA-inhibitory activity by incubation of the enzyme with clonal oregano extracts and description of the activity of the phenolic-bound enzyme. Clonal *oregano* extracts inhibited the activity of PPA in vitro by 9-57%. Amylase inhibition by *oregano* extract was related to extract total phenolic component and RA, quercetin, PA, and pCA constituent, as well as extract antioxidant activity and protein content. McCue P *et al.* find that clonal *oregano* extracts can inhibit PPA support a potential new usefulness for *oregano* as an anti-hyperglycemic agent. This provides a chance for food-based plans for modulation of starch breakdown to glucose, which could contribute to the controlling of hyperglycemia and diabetes complications in the long term. (McCue P *et al*. 2004).The effect of an aqueous extract of *O. vulgare* (OV) leaves on blood glucose levels was studied by Lemhadri A *et al*. in normal and streptozotocin (STZ) diabetic rats. Lemhadri A *et al.* conclude that an aqueous extract of OV demonstrates an anti-hyperglycaemic activity in STZ rats without affecting basal plasma insulin concentrations. (Lemhadri A *et al*. 2004).Five polar components of *O. vulgare* L. ssp. hirtum were studied for their capability of inhibiting aldose reductase (ALR2), the first enzyme of the polyol pathway involved in the secondary complications of diabetes by Koukoulitsa C *et al*. The most active constituent was found to be lithospermic acid B. Caffeic acid was inactive as it exhibited no inhibitory activity against the enzyme. The order of the inhibitory activity of the remaining constituents was: rosmarinic acid >12-hydroxyjasmonic acid 12-O-beta-glucopyranoside > p-menth-3-ene-1, 2-diol 1-O-beta-glucopyranoside. Studies have been undertaken to gain insight into the binding mode of the studied substances at the active site of ALR2. The predicted hydrogen bonding and hydrophobic interactions may describe the experiential inhibitory activity. (Koukoulitsa C *et al*. 2006).The effect of methanol and aqueous

methanol extract of *O. vulgare* L. ssp.hirtum on aldose reductase and soybean lipoxygenase was examined. The results showed an encouraging ability of *oregano* for preventing diabetes additional problems in the long term and an anti-inflammatory effectiveness by inhibiting soybean lipoxygenase. (Koukoulitsa C *et al*. 2006).The investigation that was done by Mueller M *et al*. showed a dose-dependent protective effect of the tested essential oils and aqueous tea infusions on the copper-induced LDL oxidation. The protective effect of essential oils is appointed to the presence of phenolic monoterpenes, thymol and carvacrol, which are recognized as the dominant constituents in these essential oils. The intensive protective effect of aqueous tea infusions is suggested to be the outcome of large amounts of polyphenols, namely rosmarinic acid and flavonoids (quercetin, eriocitrin, luteolin-7-O-glucoside, apigenin-7-O-glucoside, luteolin, apigenin), with the most significant effect in the case of oregano. These findings may have implications for the effect of these constituents on LDL in vivo. (Kulisi T *et al*. 2007).Peroxisome proliferator-activated receptors (PPARs) are drug targets for several disorders of metabolic syndrome, defined as the coexistence of obesity, hyperglycemia, hypertension, and hyper/dyslipidemia. *Oregano* extracts bind but do not transactivate PPARgamma, and binding affinity is different among various oregano extracts. The extracts include PPARgamma antagonists (e.g., quercetin, luteolin, rosmarinic acid, and diosmetin), selective PPARgamma modulators (e.g., naringenin and apigenin), and PPARgamma agonists (e.g., biochanin A). *Oregano* extract and isolated constituents in the extract antagonize rosiglitazone-mediated DRIP205/TRAP220 recruitment to PPARgamma, indicating oregano extracts as generally accepted food supplements for weight reduction. Rosmarinic acid and biochanin A, PPARalpha agonists, may improve the lipid profile. By endothelial nitric oxide synthase activation, oregano

extract could prevent atherosclerosis. (Mueller M *et al*. 2008).

ANTIUROLITIC ACTIVITY

O. vulgare Linn has been used in the curing of urolithiasis by tradition. The crude aqueous-methanolic extract of *O. vulgare* (Ov.Cr) was investigated in vitro and in vivo methods by KhanA *et al*. In the in vitro experiments, Ov.Cr indicated a concentration-dependent (0.25-4 mg/ml) inhibitory effect on the slope of nucleation and compaction and also decreased the number of calcium oxalate monohydrate crystals (COM) formed in calcium oxalate metastable solutions. It also exhibited concentration-dependent antioxidant effect against DPPH free radical and lipid peroxidation induced in rat kidney tissue homogenate. Ov.Cr reduced the cell toxicity using MTT assay and LDH release in renal epithelial cells (MDCK) uncovered to oxalate (0.5 mM) and COM (66 ¼g/cm (2)) crystals. Ov.Cr relaxed high K (+) (80 mM) induced contraction in rabbit urinary bladder strips, and transferred the calcium concentration-response curves (CRCs) towards right with inhibition of the maximum response similar to that of verapamil, a standard calcium channel blocker. In male Wistar rats getting lithogenic therapy including of 0.75% ethylene glycol in drinking water given for 3 weeks along with ammonium chloride (NH (4) Cl) for the first 5 days, Ov.Cr treatment (10-30 mg/kg) prevented as well as reversed toxic changes containing loss of body weight, polyurea, crystalluria, oxaluria, raised serum urea and creatinine levels and crystal deposition in kidneys compared to their respective controls. These data demonstrating the antiurolithic activity in Ov.Cr, possibly mediated through inhibition of CaOx crystallization, antispasmodic activities, renal epithelial cell protective and antioxidant, explains its medicinal use in urolithiasis. (Khan A *et al*. 2011).

ANTIMELANOGENIC ACTIVITY

Utilization of natural substances are growingly increased as tyrosinase inhibitors of depigmentation and developed cosmetic industry. A research by Liang CH et al. has

indicated that a new compound isolated from *O. vulgare* has some antimelanogenic effects. This compound contains: Origanoside, Vanilin, Vanilic acid and Protocatechuic acid.

Origanoside is a new phenolic glucoside which according to the research has a skin-whitening capacity in skin fibroblast Hs68 and melanoma B16 cells. This substance has the ability to inhibit tyrosinase and DOPA oxidase in B16 cells. It also reduces expressions of microphtalmia-associated transcription factor (MITF) and tyrosinase-related proteins 2 (TRP-2).

Vanilin, Vanilic acid and Protocatechuic acid are antioxidants that may be used for antimelanogenesis. These compounds reduse cellular tyrosinase activity, DOPA oxidase and melanin contents and down-regulate expressions of melanocortin-1 receptor (MC1R), microphtalmia-associated transcription factor (MITF), tyrosinase, tyrosinase-related proteins 2 (TRP-2) and TRP1. Vanilic acid is a stronger antioxidant than Vanilin and has a higher antimelanogenesis performance. (Liang CH *et al*., 2010)

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