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Carvacrol: An Update of Biological Activities and Mechanism of Action

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ABSTRACT

Bioactive substances from the plants are defined as secondary metabolites, which have the ability to cause pharmacological or toxicological effects in humans and/or animals, served as an important source of drugs, that can be offer therapeutic benefit in treating diseases. These natural products are the active components not only of most traditional medicines but also many modern medicines. The main chemical structure of bioactive compounds in plants are ranged in phenolic, terpenoids and alkaloids groups. Monoterpenoïds are one of the groups of bioactive compounds found in a several essential oils from aromatic plants and they are responsible for the many biological activities such as antiviral, antibacterial, antifungal, insecticidal, antitumor, anti-inflammatory and neuroprotective activities. Among the active ingredients contained in essential oils, carvacrol. Carvacrol or cymophenol is a phenolic monoterpenoid present in many plant essential oils such as Satureja, Lippia, Oreganum and Thymus, widely used as a food additive. The therapeutic potential use of carvacrol to prevent and treat a wide range of diseases will be discussed and confirmed by several in vitro and in vivo scientific works, but all mechanisms of action are not elucidated. This paper present an update for scientific data and explains the possible mechanism of action of carvacrol for each biological activity verified experimentally.

Keywords: *Medicinal plant, Essential oils, Monoterpenoïds, Carvacrol, Bioactivity*

INTRODUCTION

Carvacrol is a monoterpene phenol, with the chemical name of 5-isopropyl-2-methylphenol (Table 1). This organic compound, isomeric with thymol, is produced by an abundant number of aromatic plants; including *Thymus*, *Oreganum*, *Coridothymus*, *Thymbra*, *Satureja* and *Lippia*. Carvacrol is used for preserving food and as condiments for culinary and industrial preparations. Considerable and significant research has been establish the biological and pharmacological properties of carvacrol for its potential use in clinical applications [1]. Diverse and various activities of carvacrol have been shown (Figure 1); such as antioxidant, antimicrobial, antitumor, anti mutagenic, anti genotoxic, analgesic, antispasmodic, anti-inflammatory, an giogenic, anti parasitic, anti platelet, AChE inhibitory, anti elastase, insecticidal, anti hepatotoxic or hepatoprotective [2]. The focus of this review paper highlights some activities of carvacrol and give details in the purpose to clarify the possible mechanism of action of this bioactive compound.

Table1. *Physico-chemical properties of Carvacrol.*

Chemical formula	$C_{10}H_{14}O$
Linear formula	$(CH_3)_2CHC_6H_3(CH_3)OH$
Molecular Weight	150.217 $g.mol^{-1}$
Density	0.976 at 20°C
Melting Point	1°C
Boiling Point	237-238°C
Index of refraction	1.5230
Odor	Thymol odor
Solubility in water	Insoluble or slightly soluble
Solubility in organic solvents	Soluble in ethanol, diethyl ether, alkalis and very soluble in acetone

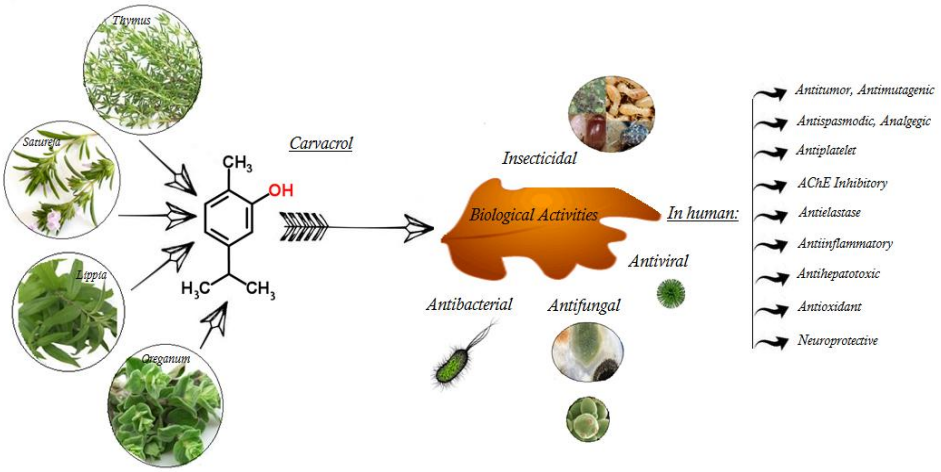

Figure1. *Structure and biological activities of Carvacrol*

CARVACROL: SYNTHESIS AND NATURAL SOURCES

Carvacrol is present in the essential oil of some aromatic plants such as *Origanum*, *Thymus* and *Satureja* species (Table 2). Carvacrol can be synthetically produce by: (1) hot treatment of carvol with phosphoric acid, (2) heating one part of iodine with five parts of camphor, (3) dehydrating carvone with a Pd/C catalyst, (4) fusing caustic potash with cymol sulfonic acid and (5) by reaction of methyl amino propylbenzene with nitrous acid (HNO_2).

Table2. *Aromatic plants essential oils containing Carvacrol, analysed by GC–MS.*

Plant Name	Collection Area/country	part of plant	Extraction method	Yield (%)	Year of collecte	Ref.
Satureja montana L.	Mt. Kozjak/Croatia	flowering aerial parts	Hy-dist.	13.7%	2007	[3]
S. montana L.	Mt. Biokovo/Croatia	aerial parts	Hy-dist.	63.4%	2007	[4]
S. montana L.	Mt. Olympos/Greece	flowering aerial parts	Hy-dist.	33.4%	2005 and 2006	[5]
S. montana L.	Kakariq, Lezhë; Zogaj, Shkodër ; Dajt, Tiranë; Qafë Mali, Puk; Qafë Kerrabë, Elbasan; Xibrakë, Librazhd /Albania	flowering aerial parts	Hy-dist.	2.21% - 55.95%	–	[6]
Satureja cuneifolia Ten.	Mt. Biokovo/Croatia	aerial parts	Hy-dist.	17.7%	2007	[4]
S.cuneifolia Ten.	Mt. Kozjak/Croatia	flowering aerial parts	Hy-dist.	17.7%	2007	[3]
S.cuneifolia Ten.	Mt. Sogut, Sutculer-Isparta/Turkey	flowering aerial parts)	St-dist.	44.99%	2004	[7]
S.cuneifolia Ten.	Konya/Turkey	flowering aerial parts	Hy-dist.	59.28%	–	[8]
Satureja subspicata Vis.	Mt. Kozjak/Croatia	flowering aerial parts	Hy-dist.	2.7%	2007	[3]
Satureja visianii Šilic.	Pelješac Peninsula/Croatia	flowering aerial parts	Hy-dist.	0.6%	2007	[3]
Satureja bachtiarica Bunge.	Yazd/Iran	–	Hy-dist.	57.38%-71.43%	–	[9]
S.bachtiarica Bunge.	Boldaji, Chaharmahal va Bakhtiari province/Iran	aerial parts	Hy-dist.	44.87%	2011	[10]
S.bachtiarica Bunge.	Chaharmahal va Bakhtiari province/Iran	aerial parts	Hy-dist.	7.75%	2011	[11]
S.bachtiarica Bunge.	Ardabile	aerial parts	Hy-dist.	26.4%	–	[12]

	Province/Iran					
Satureja thymbra L.	Mt. Green/Libya	flowering aerial parts	Hy-dist.	4.18%	2010	[13]
S. thymbra L.	Mt. Athos, Chalkidiki/Greece	flowering aerial parts	Hy-dist.	50.4%	2005 and 2006	[5]
Satureja hortensis L.	Yusufeli, Artvin/Turkey	flowering aerial parts	W-dist.	13.98%	2004	[14]
S. hortensis L.	Tehran/Iran	flowering aerial parts	Hy-dist.	35.82%	2005	[15]
Satureja parnassica Helder. & Sart. ex Boiss**.** *subsp. hellenica* Halácsy.	Island of Samothrace/Greece	flowering aerial parts	Hy-dist.	74.2%	2005 and 2006	[5]
Satureja spicigera (K.Koch) Boiss.	Gazvin/Iran	flowering aerial parts	Hy-dist.	53.74%	2006	[16]
Satureja khuzistanica Jamzad.	Mazhin, Lorestan/Iran	flowering aerial parts	Hy-dist.	94.97	2009	[17]
S. khuzestanica Jamzad.	Poldokhtar, Lorestan/Iran	flowering aerial parts	Hy-dist.	94.1%	2014	[18]
S. khuzestanica Jamzad.	Mangreh, Khuzestan/Iran	flowering aerial parts	Hy-dist.	90.88%	2011	[19]
Satureja icarica P. H. Davis	Danakkale,Gökçeada/Turkey	aerial parts	Hy-dist.	59.2%	2001	[20]
Satureja pilosa Velen.	Balıkesir, Edremit/Turkey	aerial parts	Hy-dist.	42.1%	2001	[20]
Saturejaboissieri Hausskn. ex Boiss	Adıyaman/Turkey	aerial parts	Hy-dist.	44.8%	2001	[20]
Satureja intermedia C.A.Mey.	Talesh/Iran	flowering aerial parts	Hydro-dist.	6.9%	2009	[21]
Satureja sahendica Bornm.	Mt. Kordestan/Iran	pre-,full- and post flowering aerial parts	Hy-dist.	0.83%-1.75%	2010	[22]
Satureja darwinii (Benth.) Briq.	Pali Aike National Park, Punta Arenas/Chile	flowering aerial parts	Hy-dist.	4.8%	–	[23]
Origanum vulgare L.	Paraćin/Serbia	aerial parts	W-dist.	64.5%	2001	[24]
O. vulgare L.	Kashmir Himalaya (viz. Srinagar, Pulwama and Yaarikhah)/India	aerial parts (stem, branches and leaves)	Hy-dist.	0.897%-7.198%		[25]
O. vulgare L.	Field; Gerdrahmat valley; Khezr Abad forest; Mt. Perdanan; Gaderan highlands, Piranshahr district, Azarbaijan/Iran	pre-flowering aerial parts	Hydro-dist.	23.54%-67.09%	2010	[26]
O. vulgare L.	Tazouta, Sefrou/Morocco	leaves	Hy-dist.	18.06%	2009	[27]
O. vulgare L. *ssp. hirtum* (Link) Ietswaart.	Furore; Sanza and San Giovanni a Piro, Salerno province, Campania/Italy	inflorescences	Hy-dist.	0.46%-21.89%	2008	[28]
Origanum scabrum Boiss. & Heldr.	Mt. Taygetos, Peloponissos/Greece	flowering aerial parts	St-dist.	74.86%	1999	[29]
Origanum minutiflorum (O. Schwarz and P.H. Davis)	Mt. Sögüt, Sütçüler-Isparta/Turkey	flowering aerial parts	W-dist.	73.9%	2004	[30]
Origanum acutidens (Hand.-Mazz.) Ietswaart.	İspir, Erzurum/Turkey	flowering aerial parts	Hy-dist.	47.46%	2006	[31]

Origanum rotundifolium Boiss.	İspir/ Turkey	flowering aerial parts	Hy-dist.	54.56%	2006	[31]
Origanum glandulosum (Desf.)	Sétif/Algeria	–	St- dist.	32.9%	2004	[32]
Origanum majorana L.	Halkis/Greece	flowering aerial parts	St-dist.	3.60%	1989	[33]
O. majorana L.	Içel and Antalya/Turkey	aerial parts	Hy-dist.	78.27%-79.46%	1991	[34]
Thymus vulgaris L.	Pančevo/Serbia	aerial parts	W-dist.	3.5%	2001	[24]
T. vulgaris L.	Kerman/Iran	flowering aerial parts	Hy-dist.	8.32%	2012	[35]
T. vulgaris L.	Tehran/Iran	flowering aerial parts	Hy-dist.	7.68%	2005	[15]
T. vulgaris L.	Târgu Mureş/Romania	aerial parts (before the flowering period)	Hy-dist.	5.1%	2009	[36]
T. vulgaris L.	Maringá, Paraná/Brazil	leaves	St-dist.	45.5%	–	[37]
T. vulgaris L.	Mutah/Jordan	aerial parts	Hy-dist.	8.45%	–	[38]
Thymus kotschyanus Boiss. & Hohen.	Estahban Branch/Iran	aerial parts	Hy-dist.	50.40%	–	[49]
T. kotschyanus Boiss. & Hohen.	Lorestan/Iran	flowering aerial parts	Hy-dist.	7.6%	2009	[40]
T. kotschyanus Boiss. & Hohen.	Yazd/Iran	aerial parts	Hy-dist. Mw-dist.	64.6% 44.7%	2010	[41]
T. kotschyanus Boiss. & Hohen.	Dizin, Tehran/Iran	leaves and flowers	Hy-dist.	14.2%	1997	[42]
Thymus ciliatus (Desf.) Benth.	Imama; Ain el Hadjar; Koudia; Mansoura; Hamam Schiguer; Sebâa Chioukh; Sebdou and Remchi, Tlemcen province/Algeria	full-flowering aerial parts	Hy-dist.	72.4%-80.3%	2003 and 2005	[43]
Thymus munbyanus subsp. ciliatus (Desf.) Greuter & Burdet.	Bouhanak, Tlemcen/Algeria	aerial parts (full inflorescence)	Hy-dist.	80.1%	2011	[44]
Thymus daenensis Celak.	Sarvestan, Fars province/Iran	aerial parts	Hy-dist.	28.8%	–	[45]
Thymus serpyllum L.	Târgu Mureş/Romania	aerial parts (before the flowering period.)	Hy-dist.	25.8%	2009	[36]
Thymus pulegioides L.	Târgu Mureş/Romania	aerial parts (before the flowering period)	Hy-dist.	26.7%	2009	[36]
T. pulegioides L.	Moimenta, Trás-os-Montes/Portugal	flowering aerial parts	Hydro-dist.	21%	–	[46]
Thymus glabrescens Willd.	Târgu Mureş/Romania	aerial parts (before the flowering period)	Hy-dist.	7.3%	2009	[36]
Thymus bleicherianus Pomel.	Méknès/Maroc	aerial parts (leaves, flowers and steams)	Hy-dist.	2,93 %	2006	[47]
Thymus capitatus (L.) Hoffm. & Link	Tétouan/Maroc	aerial parts (leaves, flowers and steams)	Hy-dist.	70,92 %	2006	[47]
T. capitatus (L.) Hoffm. & Link	Sardinia/Italy	flowering aerial parts	SI dist. app.	10.8%	–	[48]
Thymus herba-barona L.	Limbara and Gennargentu,	flowering aerial parts	SI dist. app.	2.9%-20.6%	–	[48]

	Sardinia/Italy					
Thymus sipyleus subsp. sipyleus var. rosulans	İspir/Turkey	flowering aerial parts	Hy-dist.	29.99%	2006	[31]
Thymus eriocalyx (Ronniger) Jalas.	Lorestan/Iran	flowering aerial parts	Hy-dist.	32.3%	2009	[40]
Thymus daenensis subsp lancifolius (Celak) Jalas.	Lorestan/Iran	flowering aerial parts	Hy-dist.	52.3%	2009	[41]
Thymus longicaulis Presl.	Mt.Sharr and Rugovë/Kosovo	Full flowering aerial parts	Hy-dist.	0.17%-12.65%	2012	[49]
Thymus comosus Heuff. ex Griseb. et Schenk	Braşov; Păltiniş and Păltiniş/Romania	aerial parts	Hy-dist.	0.19%-1.67%	–	[50]
Thymus nummularis M. Bieb.	Mt.Soğanli, Bayburt/Turkey	lowering aerial parts	W-dist.	2.7%	2009	[51]
Thymus numidicus Poir.	Constantine/Algeria	aerial parts	St- dist.	3.8%	2012	[52]
Thymus broussonetii Boiss.	Al Hoceima/Morocco	leaves, flowers	Hy-dist.	15.7%	2012	[53]
Thymus algeriensis Boiss.	Oujda/Morocco	leaves, flowers	Hy-dist.	1.3%	2012	[53]
Thymus praecox ssp. scorpilii var. laniger	Turkey	flowering aerial parts	Hy-dist.	3.08%-46.02%	2008 and 2009	[54]
Thymus zygis subsp. gracilis (Boiss.) R. Morales	El Hajeb and Timahdite/Morocco	aerial parts (stems, leaves and flowers)	St- dist.	16.07%-74.33%	2008	[55]
Thymus syriacus Boiss.	Mishtaia; Mkalis and Mt. Faleh/Syria	leaves, flowers	St- dist.	33.4%-39.5%	–	[56]
Thymus longicaulis C. Presl.	Jasenice, Dalmatia/Croatia	flowering aerial parts	Hy-dist.	1.4%	2010	[57]
Coridothymus capitatus (L.) Reichb. fil.	Çeşme, Izmir/Turkey	leaves	Hy-dist. Th-desb.	35.6% 51.6%	2002	[58]
Lippia palmeri S. Wats.	Álamos and Puerto del Orégano, Sonora/México	leaves (right before flowering)	St- dist	8.76%-24.57%	2008	[59]
Lippia gracilis Schauer.	São Félix de Balsas, Maranhão/Brazil	thin stems	Hy-dist.	1.5%	2011	[60]
L.gracilis Schauer.	Pernambuco/Brazil	leaves	St-dist.	41.77%	–	[61]
Lippia origanoides Kunth.	Santarém, Pará State, Middle Amazon River/Brazil	leaves and thin stems	Hy-dist.	35.9%-47.2%	2012	[62]
Lippia multiflora Moldenke.	Brazzaville/Congo	leaves, flower tips, stems and roots	St- dist.	2.5% - 5.0%	2009	[63]
Hyptis leucocephala Mart ex Benth.	Casa Nova/Brazil	leaves	Hy-dist.	52.82%	–	[64]
Melissa officinalis L.	Tonekabon/Iran	aerial parts (before, after and flowering stage)	Hy-dist.	2.04%-37.62%	2011	[65]

Hy-dist.: *Hydrodistillation;* ***St-dist.:*** *Steam-distillation;* ***W-dist.:*** *Water-distillation;* ***Mw-dist.:*** *Microwave oven distillation;* ***SI dist. app.:*** *Semi-Industrial stainless steel distilling apparatus;* ***Th-desb.:*** *Thermal desorber*

Biological Activities and Mechanisms

Antiviral Activity

The carvacrol has shown antiviral action on DNA and RNA viruses. Pilau et al. [66] have observed that carvacrol was effective on rotavirus only when added after virus inoculation, they suggest that the mechanism of action for carvacrol is not on genome replication, but on another step, in relation to viral replication. Gilling et al. [67] have shown that carvacrol is very effective on human non enveloped murine nor virus (MNV) and this substance acting directly on the viral capsid and subsequently the RNA. Authors have observed under TEM (transmission electron microscopy) that the capsids enlarged from ≤ 35nm in diameter to up to 800nm with carvacrol, with

greater expansion, capsid disintegration could be observed. Virus adsorption to host cells did not appear to be affected.

Antibacterial Activity

Carvacro inhibit growth of several pathogens. It had demonstrated the most potent bactericidal activity against *Salmonella typhimurium* [68]. Measurement of the antimicrobial activities of carvacrol and compounds similar to carvacrol showed that the hydroxyl group of this compound and the presence of a system of delocalized electrons are important for the antimicrobial activity. Carvacrol disrupts and disorganizes the molecular architecture of plasma membrane and induces proton exchange, reduces the pH gradient across the cytoplasmic membrane. The resulting collapse of the proton motive force and depletion of ATP pool eventually lead to cell death [69]. these authors shows that carvacrol accumulates in hydrophobic phases and this accumulated antimicrobial compound occupies more space than the normal amount of space between fatty acid chains, resulting in conformational changes of the phospholipid bilayer. The presence of the hydroxyl group must be involved because carvacrol acts as a transmembrane carrier of monovalent cations by exchanging its hydroxyl proton for another ion such as a potassium ion. The carvacrol-ion complex crosses the cell membrane to the cytoplasm and releases its proton into the intra-cell medium. It is able to return to the external medium, associating with potassium or other ion of the cytoplasm. These observations are not only shown on *Bacillus cereus* but also shown on *E. coli* [70]. The last authors attribute the antimicrobial effect to the ability of carvacrol to permeabilize and depolarize the cytoplasmic membrane.

Antifungal Activity

Carvacrol exhibited better antifungal activity against the natural yeast flora and spoilage yeasts through membrane damage, leakage of cytoplasmic content and ergosterol depletion [71]. Carvacrol inhibit ergosterol biosynthesis and disruption of membrane integrity [72]. the investigation of the mode of action of carvacrol on *Debaryomyces hansenii* confirmed damage of the cell membrane and the increase in the permeability of the membrane leads to leakage of potassium ions and other cytoplasmic contents [71].

Insecticidal Activity

Carvacrol had broad insecticidal and acaricidal activity against agricultural, stored-product, and medical arthropod pests [73]. It is more active against larvae, at 1%, carvacrol caused mortality of 85% of young larvae from *Alphitobius diaperinus* and application of 2%, carvacrol killed 97% of young larvae [74]. Insecticidal activity of carvacrol was due to fumigant action [73]. Szczepanik et al. [74] linked mortality of larvae to different reasons and supposed that carvacrol act in many ways on various insect; as neurotoxins, growth regulators, anti feedants and repellents.

Tong [75] has investigated the possible mechanisms of action of monoterpenoid insecticides such as carvacrol in the insect nervous system from the American cockroach (*Periplaneta Americana*), including an inhibitory neurotransmitter receptor, the GABA receptor, and an excitatory neurotransmitter, the nicotinic acetylcholine receptor (nAChR). Results have showed that carvacrol and two other monoterpenoids (pulegone and thymol) are positive modulators of the insect GABA receptor and they could cause inhibitory effects on the insect nervous system and the carvacrol was the potent monoterpenoid insecticide. Also, authors have tested modulating effects of only the potent monoterpenoid insecticide (carvacrol) on another neurotransmitter, nAChR. Carvacrol binding to an allosteric binding site other than the nicotine binding site and cause an inhibitory effect on the insect nervous system.

Anti-Inflammatory Activity

Carvacrol showed an important anti-inflammatory activity [76]. This monoterpenoid acts on different pharmacological targets, probably interfering in release and/or synthesis of inflammatory mediators, such as the prostanoids [77]. Carvacrol inhibited production of prostaglandin E2catalysed by COX-2 (cyclooxygenase) and also inhibited COX-1 [78]. These authors suggest non selective inhibition of both enzyme isoforms. Lima et al. [79] have studies the contribution of cytokine modulation to the anti-inflammatory effects of carvacrol in a classical inflammation model: the complete Freud's adjuvant (CFA)-induced PAW inflammation in mice. Anti-inflammatory activity was registered in carvacrol-treated mice. Carvacrol attenuates the PAW edema, reduces the IL-1β (interleukin 1 beta), PGE2 (prostaglandin E2), but not TNF-α (tumor necrosis factor) local levels, decreases the COX-2 and IL-1β mRNA expression and enhances IL-10 levels and IL-10 mRNA expression in inflamed PAW. According to these authors, the

anti-inflammatory action of carvacrol would be related to the decrease in the production of prostanoïds and IL-10, through the induction of the anti-inflammatory cytokine IL-10 [79].

Anti-Tumor Activity

Anti-tumor effects of carvacrol have been demonstrated against breast cancer cells. The antiproliferative effects of Carvacrol in metastatic breast cancer, MDA-MB231, cells was observed at IC50 value of 100µM, with cytological changes, like cell shrinkage, rounding form and membrane budding, indicating cells death by apoptosis. This induction of apoptosis appears to be mediated by cell cycle arrest at S phase, increase in Annexin V positive cells, and decrease in mitochondrial membrane potential and increase in cytochrome C release from mitochondria in caspase activity and cleavage of PARP and fragmentation of DNA [80]. antiproliferative effect was also observed in human hepatoma HepG2 cells. Incubation of HepG2 cells with carvacrol for 24h induced apoptosis by the activation of caspace-3, cleavage of PARP and decreased Bcl-2 gene expression. The carvacrol acts on the superfamily of the MAPK, reduces phosphorylation of ERK1/2 and activates phosphorylation of p38. Carvacrol induce apoptosis by direct activation of the mitochondrial pathway and the mitogen-activated protein kinase pathway may play an important role in the anti-tumor effect [81].

NEURO PROTECTIVE EFFECTS

Carvacrol preventes the memory deficit induced by scopolamine or amyloid β, via decreasing in time spent in target quadrant and increasing in escape latency in treated rats. Anticholinesterase, antioxidant and anti-inflammatory activities may be the mechanisms contributing toward the beneficial effects of carvacrol in rat models of dementia [82, 83]. Acetyl cholinesterase (AChE) is the principal enzyme involved in the hydrolysis of acetylcholine (ACh). The great reduction of this neurotransmitter in the cerebral cortex is a significant factor in Alzheimer's disease [84]. Several studies have registered a notable inhibitory activity against AChE. The position of hydroxyl group in the molecular structure of carvacrol play an important role in the puissant power on AChE inhibitory activity, confirmed by the comparative studies between carvacrol and thymol, where the carvacrol showed stronger inhibitory effect than that exerted by its isomer thymol [85, 86].

Carvacrol has been shown to have protective effects on cerebral ischemia/reperfusion injury by reducing infarct volume and decreasing the expression of cleaved caspase-3 [87, 88]. experiment on mouse model demonstrate that treatment with carvacrol increase the level of phosphorylated Akt and the neuroprotection of carvacrol was reversed by a PI3K inhibitor LY-294002, show the involved of the PI3K/Akt pathway in the anti-apoptotic mechanisms of carvacrol [87]. Also in a rat model, carvacrol inhibits the inflammatory response via inhibition of the NF-kB signaling pathway of focal cerebral ischemia, decreases the rate of MDA, and inhibits inflammatory cytokines, expression of iNOS and COX-2 and myeloperoxidase activity. In addition, carvacrol treatment suppressed the ischemia/reperfusion-induced increase in the protein expression of nuclear NF-kB p65 [88].

CONCLUSION

Carvacrol is responsible of multiple biological activities, some scientists have attempts to explain the possible in vivo mechanism, but information's of mechanism of action from carvacrol are limited. Carvacrol is active against a several pathogens bacteria; destabilizes the bacteria cytoplasmic membrane and provide depletion of ATP pool, effective on viruses; through disintegration of capsid and effects on DNA and RNA viruses, very effective on fungi; through Inhibition of ergosterol biosynthesis; leakage of cytoplasmic content and the disruption of membrane integrity, insecticidal and acaricidal properties, Antiplatelet and anti-inflammatory activity; inhibited production of prostaglandin, Anti carcinogenic, anti proliferative properties against cancer cell lines; induce apoptosis, inhibition of the NF-kB signaling pathway, efficacy against cognitive deficits induced by amyloid β, Anticholinesterase, antioxidant activity; increase SOD activity, decrease MDA level and Protects against DNA damage. In conclusion, diverse activities are promoted by this bioactive substance; there are a number of points to be clarified to understand the various pathways of this molecule and the molecular target of carvacrol for each pathway.

REFERENCES

[1] ZE Suntress; J Coccimiglio; M Alipour. *Crit Rev Food Sci Nutr*, 2015, 55(3), 304-318.

[2] KH Baser. *Curr Pharm Des*, 2008, 14(29), 3106-3119.

[3] N Bezić; I Šamanić; V Dunkić; V Besendorfer; J Puizina. *Molecules*, 2009, 14(3), 925-938.

[4] S Ćavar; ME Šolić; M Maksimović. *Botanica Serbica*, 2013, 37(2), 159-165.

[5] M Papadatou; C Argyropoulou; C Grigoriadou; E Maloupa; H Skaltsa. *Nat Volatiles & Essent Oils*, 2015, 2(1), 37-48.

[6] A Ibraliu; BS Dhillon; N Faslia; B Stich. *J Med Plants Res*, 2010, 4(14), 1359-1364.

[7] F Oke; B Aslim; S Ozturk; S Altundag. *Food Chemistry*, 2009, 112(4), 874-879.

[8] Y Kan; US Uçan; M Kartal; ML Altun; S Aslan; E Sayar; T Ceyhan. *Turk J Chem*, 2006, 30, 253-259.

[9] H Salehi-Arjmand; D Mazaheri; J Hadian; N Majnoon Hosseini; M Ghorbanpour. *Journal of Medicinal Plants*, 2014, 13(51), 1-9.

[10] E Solaymani Babadi; AG Pirbalouti; H Nourafcan; B Hamedi. *Electronic Journal of Biology*, 2012, 8(4), 73-78.

[11] AG Pirbalouti; S Dadfar. *Acta Poloniae Pharmaceutica-Drug Research*, 2013, 70(5), 933-938.

[12] M Teimori. *Journal on Plant Science Researches*, 2009, 14(2), 19-26.

[13] A Giweli; AM Džamić; M Soković; MS Ristić; PD Marin. *Molecules*, 2012, 17(5), 4836-4850.

[14] A Adiguzel; H Ozer; H Kilic; B Cetin. *Czech J. Food Sci*, 2007, 25(2), 81-89.

[15] R Karami-Osboo; M Khodaverdi; F Ali-Akbari. *J. Agr. Sci. Tech*, 2010, 12, 35-45.

[16] F Eftekhar; F Raei; M Yousefzadi; SN Ebrahimi; J Hadian. *Z. Naturforsch*, 2009, 64c(1-2), 20-24.

[17] M Moazeni; MJ Saharkhiz; AA Hoseini; AM Alavi. *Asian Pac J Trop Biomed*, 2012, 2(8), 616-620.

[18] M Mahboubi; N Kazempour. *Jundishapur J Nat Pharm Prod*, 2016, 11(2): e30034, 1-6.

[19] AG Pirbalouti; E Moalem. *Indian Journal of Traditional Knowledge*, 2013, 12(4), 623-629.

[20] D Azaz; F Demirci; F Satil; M Kürkçüoğlu; KH Başer. *Z. Naturforsch*, 2002, 57c(9-10), 817-821.

[21] I Sadeghi; M Yousefzadi; M Behmanesh; M Sharifi; A Moradi. *Iran Red Cres Med J*, 2013, 15(1), 70-74.

[22] FS Ghotbabadi; A Alizadeh; M Zadehbagheri; MM Kamelmanesh; M Shaabani. *J Med Plants Res*, 2012, 6(19), 3525-3534.

[23] HM Niemeyer. *Journal of Essential Oil Research*, 2010, 22(6), 477- 482.

[24] M Soković; J Glamočlija; PD Marin; D Brkić; LJ Van Griensven. *Molecules*, 2010, 15(11), 7532-7546.

[25] S Chishti; ZA Kaloo; P Sultan; H Tun-Nisa; N Tun-Nisa. *International Journal of Applied Research*, 2016, 2(2), 552-557.

[26] M Pirigharnaei; S Zare; R Heidary; J Khara; R EmamaliSabzi; F Kheiry. *Avicenna Journal of Phytomedicine*, 2011, 1(2), 106-114.

[27] E Derwich; Z Benziane; A Manar; A Boukir; R Taouil. *American-Eurasian Journal of Scientific Research*, 2010; 5(2), 120-129.

[28] L De Martino; V De Feo; C Formisano; E Mignola; F Senatore. *Molecules*, 2009, 14(8), 2735-2746.

[29] N Aligiannis; E Kalpoutzakis; S Mitaku; IB Chinou. *J Agric Food Chem*, 2001, 49(9), 4168-4170.

[30] B Aslim; N Yucel. *Food Chemistry*, 2008, 107(2), 602-606.

[31] B Çetin; S Çakmakçi; R Çakmakçi. *Turk J Agric For*, 2011, 35, 145-154.

[32] N Sahraoui; F Bentahar; C Boutekedjiret. *Jeobp*, 2007, 10(2), 145-150.

[33] ME Komaitis; N Ifanti-Papatragianni; E Melissari-Panagiotou. *Food Chemistry*, 1992, 45(2), 117-118.

[34] KHC Baser; N Kirimer; G Tümen. *J. Essent. Oil Res*, 1993, 5(5), 577-579.

[35] M Moghtader. *J Yeast Fungal Res*, 2012, 3(6), 83-88.

[36] E Varga; A Bardocz; Á Belák; A Maráz; B Boros; A Felinger; A Böszörményi; G Horváth. *FARMACIA*, 2015, 63(3), 357-361.

[37] F Fachini-Queiroz; R Kummer; CF Estevão-Silva; MD De Barros Carvalho; JM Cunha; R Grespan; CA Bersani-Amado; Rk Nakamura Cuman. *Evid Based Complement Alternat Med*, 2012, ID 657026, 1-10.

[38] J Al-Shuneigat; S Al-Sarayreh; Y Al–Saraira; M Al-Qudah; I Al-Tarawneh; S Al-Dalaen. *IOSR Journal of Pharmacy and Biological Sciences*, 2014, 9(5), 78-82.

[39] R Ahmadi; A Alizadeh; S Ketabchi. *Int J Biosci*, 2015, 6(3), 239-248.

[40] H Amiri. *Evid Based Complement Alternat Med*, 2012, ID 728065, 1-8.

[41] M Khanavi; H Hajimehdipoor; F Emadi; NK Khandani. *TEOP*, 2013, 16(1), 117-122.

[42] A Rustaiyan; T Lajevardi; M Rabbani; M Yari; S Masoudi. *DARU Journal of Pharmaceutical Sciences*, 1999, 7(4), 27-28.

[43] L Bousmaha-Marroki; F Atik-Bekkara; F Tomi; J Casanova. *J. Essent. Oil Res*, 2007, 19(5), 490-493.

[44] A Khadir; M Bendahou; F Benbelaid; C Bellahcene; DE Abdelouahid; A Museili; J Paollini; J Desjober; J Costa. *J. App. Pharm. Sci*, 2013, 3(7), 18-24.

[45] V Rowshana; A Bahmanzadegana; MJ Saharkhiz. *Industrial Crops and Products*, 2013, 49, 97-101.

[46] E Pinto; C Pina-Vaz; L Salgueiro; MJ Gonçalves; S Costa-de-Oliveira; C Cavaleiro; A Palmeira; A

Rodrigues; J Martinez-de-Oliveira. *J Med Microbiol*, 2006, 55(pt 10), 1367-1373.

[47] M El Ajjouri; B Satrani; M Ghanmi; A Aafi; A Farah; M Rahouti; F Amarti; M Aberchane. *Biotechnol. Agron. Soc. Environ*, 2008, 12(4), 345-351.

[48] S Cosentino; CIG Tuberoso; B Pisano; M Satta; V Mascia; E Arzedi; F Palmas. *Lett Appl Microbiol*, 1999, 29(2), 130-135.

[49] M Hatipi Ibrahimi; V Papajani; S Ćavar; V Matevski. *Bulletin of the Chemists and Technologists of Bosnia and Herzegovina*, 2013, 41, 6-10.

[50] I Boz; I Burzo; MM Zamfirache; R Efrose. *Analele Stiint. Univ. Al. I. Cuza Iasi*, 2014, 60(1), 40-45.

[51] E Bektaş; D Daferera; M Sökmen; G Serdar; M Ertürk; MG Polissiou; A Sökmen. *Indian J Tradit Know*, 2016, 15(3), 403-410.

[52] F Benayache; P Chalard; G Figueredo; F Benayache; S Benayache. *Der Pharmacia Lettre*, 2014, 6(1), 182-185.

[53] E El Ouariachi; I Hamdani; A Bouyanzer; B Hammouti; L Majidi; J Costa; J Paolini; A Chetouani. *Asian Pac J Trop Dis*, 2014, 4(4), 281-286.

[54] AB Avci. *Int. J. Agric. Biol*, 2011, 13(4), 607-610.

[55] S Yakoubi; A Cherrat; M Diouri; F EL Hilali; T Zair. *Med J Chem*, 2014, 3(1), 746-758.

[56] A Al-Mariri; G Swied; A Oda; L Al Hallab. *Iran J Med Sci*, 2013, 38(2), 180-186.

[57] S Vladimir-Knežević; I Kosalec; M Babac; M Petrović; J Ralić; B Matica; B Blažeković. *Cent. Eur. J. Biol*, 2012, 7(6), 1109-1115.

[58] A Goren; G Bilsel; M Bilsel; H Demir; EE Kocabaş. *Z. Naturforsch*, 2003, 58c(9-10), 687-690.

[59] MM Ortega-Nieblas; MR Robles-Burgueño; E Acedo-Félix; A González-León; A Morales-Trejo; L Vázquez-Moreno. *Fitotec. Mex*, 2011, 34(1), 11-7.

[60] CS Franco; AF Ribeiro; NCC Carvalho; OS Monteiro; JKR Silva; EHA Andrade; JGS Mala. *Afr. J. Biotechnol*, 2014, 13(30), 3107-3113.

[61] CC Albuquerque; TR Camara; AEG Santána; C Ulisses; L Willadino; C Marcelino Júnior. *Rev. Bras. Pl. Med*, 2012, 14(1), 26-33.

[62] SLF Sarrazin; L Andrade Da Silva; AP De Assunção; RB Oliveira; VYP Calao; R Da Silva; EE Stashenko;. JGS Maia; RHV Mourão. *Molecules*, 2015, 20(2), 1860-1871.

[63] T Gouollaly; C Nkounkou Loumpangou; M Yaya; JM Ouamba; A Abena Ange; JC Chalchat; G Figueredo. *Afr. J. Biotechnol*, 2010, 9(41), 7009-7013.

[64] SN Santos; RF Castanha; LJ Silva; MOM Marques; S Scramin; SI Melo. *Asa, São Paulo*, 2015, 2(3), 3-11.

[65] K Saeb; S Gholamrezaee. *Asian Pac J Trop*, 2012, 2(2), S547-S9.

[66] MR Pilau; SH Alves; R Weiblen; S Arenhart; AP Cueto; LT Lovato. *Braz J Microbiol*, 2011, 42(4), 1616-1624.

[67] DH Gilling; M Kitajima; JR Torrey; KR Bright. *J Appl Microbiol*, 2014, 116(5), 1149-1163.

[68] JM Kim; MR Marshall; JA Cornell; JF Preston; CI Wei. *Journal of Food Science*, 1995, 60(6), 1364-1368.

[69] A Ultee; MHJ Bennik; R Moezelaar. *Appl Environ Microbiol*, 2002, 68(4), 1561-1568.

[70] J Xu; F Zhou; BP Ji; RS Pei; N Xu. *Lett Appl Microbiol*, 2008, 47(3),174-179.

[71] PS Chavan; SG Tupe. *Food Control*, 2014, 46, 115-120.

[72] A Ahmad; A Khan; F Akhtar; S Yousuf; I Xess; LA Khan; N Manzoor. *Eur J Clin Microbiol Infect Dis*, 2011, 30(1), 41-50.

[73] YJ Ahn; SB Lee; HS Lee; GH Kim. *Journal of Chemical Ecology*, 1998, 24(1), 81-90.

[74] M Szczepanik; B Zawitowska; A Szumny. *Allelopathy Journal*, 2012, 30(1), 129-142.

[75] F Tong. Investigation of mechanisms of action of monoterpenoid insecticides on insect gamma-aminobutyric acid receptors and nicotinic acetylcholine receptors. PhD Thesis, Iowa State University, 2010, Paper 11665. http://lib.dr.iastate.edu/etd

[76] PG Salud; ZS Miguel; AG Lucina; RL Miguel. *Journal of Essential Oil Research*, 2011, 23(5), 38-44.

[77] FV Silva; AG Guimarães; ERS Silva; BP Sousa-Neto; FDF Machado; LJ Quintans-Júnior; DDR Arcanjo; FA Oliveira; RCM Oliveira. *Journal of Medicinal Food*, 2012, 15(11), 984-991.

[78] P Landa; L Kokoska; M Pribylova; T Vanek; P Marsik. *Arch Pharm Res*, 2009, 32(1), 75-78.

[79] MS Lima; LJ Quintans-Junior; W Alcântara de Santana; CM Kaneto; MBP Soares; Villarreal CF. *European Journal of Pharmacology*, 2013, 699(1-3), 112-117.

[80] KM Arunasree. *Phytomedecine*, 2010, 17(8-9), 581-588.

[81] Q Yin; F Yan; X Zu; Y Wu; X Wu; M Liao; S.W Deng; LL Yin; YZ Zhuang. *Cytotechnology*, 2012, 64(1), 43-51.

[82] Z Azizi; S Ebrahimi; E Saadatfar; M Kamalinejad; N Majlessi. *Behav Pharmacol*, 2012, 23(3), 241-249.

[83] F Celik; C Gocmez; M Bozkurt; I Kaplan; K Kamasak; E Akil; E Dogan; A Guzel; E Uzar. *Eur Rev Med Pharmacol Sci*, 2013, 17(22), 2988-2993.

[84] M Fujiwara; N Yagi; M Miyazawa. *J Agric Food Chem*, 2010, 58, 2824-2829.

[85] M Jukic; O Politeo; M Maksimovic; M Milos. *Phytother Res*, 2007, 21(3), 259-261.

[86] I Orhan; M Kartal; Y Kan; B Sener. *Z. Naturforsch*, 2008, 63c (7-8), 547-553.

[87] H Yu; ZL Zhang; J Chen; A Pei; F Hua; X Qian; J He; CF Liu; X Xu. *PloS ONE*, 2012, 7(3): e33584, 1-8.

[88] Z Li; C Hua; X Pan; X Fu; W Wu. *Inflammation*, 2016, 39(4), 1566-1572.