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Carvacrol: A Prospective Gold Mine of New Drug Discovery and Development

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Abstract

Carvacrol, a widely extracted monoterpenoid phenol from an abundant number of aromatic plant species including thyme and oregano. At present, carvacrol is being utilized in low concentrations as a preservative and food flavoring agent, in addition to serving as a fragrance element in cosmetic formulations. A great deal of study has been done in recent years as an effort to determine the biological effects of carvacrol for possible therapeutic application. Carvacrol has been identified to have a vast range of biological and pharmacological characteristics which include antidiabetic, antimicrobial, anti-inflammatory, anti-obesity, antitumor, hepatoprotective, gastroprotective, and neuroprotective effects based on both *in vitro* and *in vivo* experiments. The main objective of this review is to assess current understanding of carvacrol's pharmacological impacts as well as its biosynthesis and plant sources in order to potentially inform the future researchers. It can be postulated that upon extensive research, this noteworthy bioactive phytochemical can be a very promising source of next generation drug development.

Key words: Carvacrol, biosynthesis, antidiabetic, antimicrobial, anti-inflammatory, anti-obesity, anticancer, hepatoprotective, gastroprotective, neuroprotective

Introduction

Since the beginning of time, humanity has been inspired by nature, and all people, regardless of nationality or religion, hold nature in high regard. The history of medicine and the medical professions are as ancient as humanity itself. Today's modern period has seen advances in medical science along with a rise in illness severity (Asad *et al*., 2022; Nisar *et al.*, 2018). As new medications are created to treat complex illnesses, a variety of side effects ranging from mild to severe are also linked to these medications (Ashrafi *et al.*, 2023; Emon *et al*., 2021a). Throughout the history herbal remedies have long been used to treat a variety of conditions, including heart disease, infectious diseases, diabetes, oxidative stress, cancer, depression, and many more (Taher *et al*., 2023; Emon *et al.*, 2021b). Plant-derived medications and alternative therapies are becoming more and more popular despite the market's plethora of synthetic medications because of their pronounced therapeutic benefits and notably lesser side effects (Chowdhury *et al*., 2022; Zaman *et al.*, 2023). The World Health Organization stated that medicinal products based on plants are used by 80% of people worldwide as their main form of healthcare as plants have always proved to be an enduring and significant source of medications due to their significance in history, economy, and medicine (Alam *et al.*, 2021; Islam

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et al., 2022). Based on conservative estimations approximately 10,000 out of the 400,000 secondary plant metabolites on the earth have been successfully chemically isolated (Hasnat *et al.*, 2023, Alam *et al.*, 2022). Phytochemicals, the main pharmacological substances found in plants and their pharmacological activity and corresponding mechanisms of action are evaluated by numerous experimental methods which includes *in vivo*, *in vitro*, and *in silico* studies etc. (Alam *et al.*, 2020; Chakrabarti *et al.*, 2022; Ashrafi *et al.*, 2022a).

Carvacrol, chemically known as 2-methyl-5-(1-methylethyl)-phenol, represents a liquid monoterpenoid phenol that shares an isomeric relationship with thymol (Sharifi-Rad *et al.*, 2018; Suntres *et al.*, 2015). According to the International Union of Pure and Applied Chemistry, it is also known as 5-isopropyl-2-methylphenol (National Center for Biotechnology Information, 2023). It exhibits lipophilic properties with a density of 0.976 g/ml at room temperature. Carvacrol is highly soluble in ethanol, acetone, and diethyl ether but insoluble in water (Yadav and Kamble, 2009). This molecule demonstrates a wide range of biological effects, including strong antimicrobial, antioxidant, analgesic qualities and many more. Because of its adaptability to a wide range of health-related functions, it is a chemical that is of great interest for therapeutic applications (Can Baser, 2008).

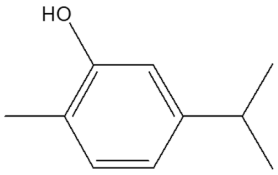

Figure 1: Structure of Carvacrol

The main objective of this review is to interpret and combine the broadly scattered information on the beneficial properties of carvacrol in cells, animals, and humans. The possible benefits of carvacrol for treating and preventing serious illnesses are discussed here. The aim of the work is to support progress in both basic and applied research by merging the perspective and expertise from multiple research areas.

Material and Methods

Article Search Strategy: To compile the data on carvacrol a literature search was carried out across the databases of ScienceDirect, PubMed, Google Scholar, Wiley Online Library, MDPI, Elsevier, and Scopus. The search strategy involved the use of specific terms such as 'carvacrol,' 'source,' 'plant-part,' 'biosynthesis,' 'antidiabetic,' 'anti-inflammatory,' 'antimicrobial,' 'anti-obesity,' 'anti-tumor,' 'hepatoprotective,' 'gastroprotective,' 'neuroprotective,' 'analgesic,' and others. We have tried to find and compile notable pharmacological attributes of carvacrol, a bioactive monoterpenoid. The focus was on choosing data solely from peer-reviewed scientific journals, and a rigorous inclusion criterion was implemented to narrow down the selection to a limited number of papers that strictly met the predefined criteria .

Biosynthesis

Carvacrol biosynthesis is proceed by the cyclization of geranyl diphosphate to γ-terpinene, subsequently followed by a sequence of oxidations via p-cymene. γ-terpinene is oxidized by P450s (cytochrome P450 monooxygenases) of the subfamily named CYP71D to form cyclohexa-dienol unstable intermediates, that are later dehydrogenated by a SDR (short-chain dehydrogenase/reductase) to the respective ketones. Following this, keto-enol tautomerisms lead to the synthesis of aromatic molecules. These enzymes produced carvacrol and thymol when combined with γ-terpinene in *in vitro* experiments *or in vivo* in *Nicotiana benthamiana* (Krause *et al.*, 2021)

In several plants, the mevalonate pathway was used to biosynthesize carvacrol. Glucose is initially broken down into phosphoenolpyruvate, which is further converted to mevalonic acid via decarboxylation and acetylation to acetyl CoA (acetyl

coenzyme A). Following this conversion, mevalonic acid is converted to gamma-terpinene which then produces p-cymene after aromatization. Finally, the hydroxylation of p-cymene yielded carvacrol (Friedman, 2014).

Plant Source

Carvacrol is a very common bioactive secondary metabolite abundantly found in nature but mostly in the plants of Lamiaceae family. Here is a list of some plants and plant-parts, along with their family names, which contain Carvacrol (Table 1).

Table 1. List of some plants and plant-parts along with their family name which contain carvacrol.

Sl.No.	Carvacrol containing plant	Family	Plant part	Reference
1	*Coleus aromaticus* Benth.	Lamiaceae	Flower and aerial part	Joshi *et al.*, 2011.
2	*Thymus caramanicus* Jalas	Lamiaceae	Aerial part	Safaei-Ghomi *et al*., 2009
3	*Mentha suaveolens* subsp. insularis	Lamiaceae	Aerial part	Zerkani *et al.*, 2021
4	*Origanum onites* L.	Lamiaceae	Leaves and Flowers	Spyridopoulou *et al.*, 2019
5	*Coridothymus capitatus* Rchb.f.	Lamiaceae	Leaves	Goren *et al.*, 2003
6	*Satureja thymbra* L.	Lamiaceae	Aerial part	Giweli *et al.*, 2012
7	*Origanum vulgare* L.	Lamiaceae	Whole Plant	Zinno *et al.*, 2023
8	*Rosmarinus officinalis* L.	Lamiaceae	Leaves and stems	Chraibi *et al.*, 2020
9	*Thymus maroccanus* Ball	Lamiaceae	Aerial part	Jamali *et al.*, 2013
10	*Thymus leptobotris* Murb.	Lamiaceae	Leaves and flowers	Jaafari *et al.*, 2007
11	*Thymus pallidus*Coss.	Lamiaceae	Aerial part	Ichrak *et al.*, 2011
12	*Thymus satureoides* Coss.	Lamiaceae	Aerial part	Ichrak *et al.*, 2011
13	*Thymus zygis* Sm.	Lamiaceae	Aerial part	Gonçalves *et al*., 2010
14	*Thymus broussonettii* Boiss.	Lamiaceae	Aerial part	Chebli *et al.*, 2019
15	*Thymus algeriensis* Boiss. & Reut.	Lamiaceae	Aerial part	Giweli *et al.*, 2013
16	*Plectranthus amboinicus* (Lour.) Spreng	Lamiaceae	Leaves	Hassani *et al.*, 2012
17	*Satureja khuzestanica* Jamzad	Lamiaceae	Whole Plant	Siavash Saei-Dehkordi *et al.*, 2012
18	*Oliveria decumbens* Vent.	Apiaceae	Whole Plant	Behbahani *et al*., 2018
19	*Thymus daenensis* Celak	Lamiaceae	Seeds	Pirbalouti *et al.*, 2013
20	*Zataria multiflora* Boiss.	Lamiaceae	Aerial part	Pourhosseini *et al.*, 2020
21	*Satureja bachtiarica* Bunge	Lamiaceae	Aerial part	Falsafi *et al.*, 2015
22	*Lippia origanoides* Kunth.	Verbenaceae	Aerial part	Oliveira *et al.*, 2007
23	*Nigella sativa* Linn.	Ranunculaceae	Seeds	Benkaci–Ali *et al.*, 2007
24	*Lavandula multifida* L.	Lamiaceae	Inflorescences and leaves	Saadi *et al*., 2016
25	*Lavandula coronopifolia* Poir.	Lamiaceae	Whole Plant	Ait Said *et al.*, 2015
26	*Ocimum sanctum* L.	Lamiaceae	Leaves	Kumar *et al.*, 2010
27	*Citrus aurantium* L.	Rutaceae	Leaves	Majnooni *et al.*, 2012
28	*Coriandrum sativum* L.	Apiaceae	Seeds	Lasram *et al.*, 2019

Pharmacological Potentials of Carvacrol

Antidiabetic effect : According to a report of Ezhumalai *et al.,* 2014, C57BL/6J mice were given carvacrol (20 mg/kg body weight) along with thiazolidinedione and rosiglitazone (4 mg/kg body weight) to find out the combined antihyperlipidemic and antidiabetic effects. A high-fat diet raised plasma glucose, enhanced insulin, lowered haemoglobin, enhanced levels of the metabolism-related enzymes fructose-1,6-bisphosphatase and glucose-6-phosphate, and lessened glucose-6-phosphate dehydrogenase. Alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and alanine aminotransferase concentrations were all lowered by carvacrol. Carvacrol improved insulin production, plasma glucose levels, and liver function when given combinedly with rosiglitazone or thiazolidinedione (Ezhumalai *et al.,* 2014).

In an earlier study, 32 adult male Wistar diabetic rats which were given streptozotocin at 50 mg/kg body weight, were used to examine the antidiabetic activity of carvacrol. The activities of superoxide dismutase and glutathione peroxidase enzymes were increased by carvacrol. It also lowered the rate of germ cells apoptosis, tissue malondialdehyde, and Bax expressions, as well as boosted Bcl-2 protein expression (Shoorei *et al.,* 2019)

Anti-inflammatory effect: A study concluded that caspase-independent and caspase-dependent apoptosis were significantly inhibited by carvacrol in PC12 cells when exposed to cadmium-induced oxidative stress. The contact with carvacrol raised the amount of glutathione in cells, enhanced the production of glutathione reductase, and improved the amount of DNA fragmentation brought on by cadmium. Carvacrol elevated the expression of nuclear strand called kappa-light-chain-enhancer of activated B cells (NFKB), and downregulated protein kinase B (Akt), mTOR (mammalian target of rapamycin) and ERK-1 (extracellular signal-regulated kinase-1). Moreover, carvacrol dropped the levels of cytosolic cytochrome c and AIF (apoptosis-inducing factor), inhibited the cleavage of caspase 3, and raised the amount of intracellular metallothionein (Banik *et al.,* 2019).

A research found that carvacrol suppressed the creation of inflammatory cytokines of rheumatoid arthritis-induced fibroblast-like synoviocytes, LPS-induced cell proliferation, and the synthesis of matrix metalloproteases such as MMP-1, MMP-3, and MMP-13. Furthermore, it blocked the pathways that activate TLR4/MyD88/NF-κB, p38, and ERK1/2, in that order (Li *et al.,* 2019).

Antimicrobial effect: Carvacrol exhibited antimicrobial activity against *Salmonella enterica* and *Staphylococcus aureus* when co-administered with thymol. The minimum inhibitory concentration of *S. enterica* and *S. aureus* by carvacrol and thymol were 0.331 mg/ml and 0.662 mg/ml, respectively. To prevent biofilm development at the early phase of microbial attachment, food products can be treated with carvacrol and thymol at different contact periods and antimicrobial concentrations (Engel *et al.,* 2017).

Combining essential oil containing carvacrol and thymol with soya sauce had a synergistic impact that demonstrated antibacterial activity against *E. coli*, *S. aureus* and *L. monocytogenes*. Bacterial cells were left inactive and unable to keep their osmotic balance when exposed to carvacrol, thymol and soya sauce which caused the membrane rupture (Moon *et al*., 2017). A mixture of carvacrol, hydroxypropyl methylcellulose, glycerol, tapioca starch, and potassium sorbate exhibited noteworthy antimicrobial activity against *Zygosaccharomyces bailii*, *Lactobacillus plantarum* and *Pseudomonas fluorescens* (Alzate *et al.,* 2017).

Anti-obesity ffect: Carvacrol was observed to decrease adipogenic differentiation in murine 3T3-L1 and Wharton' jelly-derived mesenchymal stem cells by around 40% and 30%, accordingly. There was a correlation found between the impact of carvacrol on adipogenic differentiation and the decrease in autophagy and ChREBP expression (Spalletta *et al.,* 2018).

Carvacrol can regulate obesity by blocking intracellular fat formation and adipocyte differentiation as revealed in high-fat diet induced

male C57BL/6N mice embryo 3T3-L1 cells as well as the method involved in the expression of genes in adipogenesis, thermogenesis and inflammation. Carvacrol seems to reduce visceral adipogenesis through suppressing of bone morphogenic protein-, galanin-mediated signaling, and fibroblast growth factor-1. Additionally, it diminishes the generation of pro-inflammatory cytokines through inhibition of toll like receptor 2 (TLR2) and TLR4 in visceral adipose tissues (Cho *et al.*, 2012).

Antitumor effect: Using a human non-small cell (lung cancer cell line A549), effect of carvacrol was investigated at doses of 100, 250, 500, and 1000 μM. Carvacrol reduced the total protein content and the number of cancer cells, and the deterioration of cell shape as a sign of its ability to prevent cancer (Koparal and Zeytinoglu, 2003).

Carvacrol significantly reduced the risk of cancer in rats given 3,4-benzopyrene. After incubating cells for 24 hours, carvacrol's antiproliferative activity (IC_{50}) was 90 μM, and after 48 hours, it was 67 μM. Additionally, carvacrol had a slight antiplatelet impact, causing less production of thromboxane A2 in platelets, which in turn restricted the expression of the GPIIb/IIIa platelet receptor (Karkabounas *et al.*, 2006).

Hepatoprotective and gastroprotective effects: Based on a study, it was indicated that carvacrol protected liver tissues over toxicity in rats which was originated by sodium fluoride. Each one of the antioxidant enzymes and hepatic indicators in rats exposed to sodium fluoride poisoning restored normalcy after carvacrol supplementation. Strong free-radical scavenging actions were demonstrated by hydrogen peroxide, diphenyl-1-picrylhydrazyl (DPPH), and hydroxyl radical activities concluding that carvacrol modified the anti-oxidant enzymes and hepatic stress markers in rats (Shanmugam *et al.*, 2019).

Carvacrol also fights against stomach ulcer, a global health concern. In an experiment, carvacrol was discovered to have gastroprotective activities on rats that had stomach lesions caused by ischemia, reperfusion and NSAIDs. The endogenous prostaglandins, increased mucus production, KATP channel opening, NO synthase activation, and anti-oxidant qualities all contributed to a significant gastroprotective effect that carvacrol induced. Carvacrol presented a marked gastro protective effect mediating through endogenous prostaglandins, increasing mucus production, nitric oxide synthase activation, ATP sensitive potassium channels opening, and anti-oxidant properties (Oliveira *et al.*, 2012).

Neuroprotective effect: It was demonstrated that giving rats 12.5 mg/kg of carvacrol affected their prefrontal cortex and hippocampus's neurochemistry and behaviours, raising their serotonin and dopamine levels of tissue content. On the contrary, a notable reduction in dopamine was seen when exposed to 450 mg/kg of carvacrol. The findings indicated that it is a strong brain-activating chemical that alters neurotransmitter levels and neuronal activity. Consumed frequently in little doses, it may influence emotions of wellbeing and may even have beneficial reinforcer effects (Zotti *et al.*, 2013).

Carvacrol guards against 6-hydroxydopamine-induced neurotoxicity as determined by a Parkinson's disease investigation where neuroprotective effects of carvacrol were looked at the models of Parkinson's disease in both *in vivo* and *in vitro*. After receiving *in vitro* treatment adrenal pheochromocytoma PC12 cells of rat were found to be protected in a dose-dependent manner from the toxicity caused by 6-hydroxydopamine (6-OHDA) by reducing intracellular lipid peroxidation, annexin-positive cells, intracellular reactionary oxygen species and boosting cell viability. *In vivo* treatment with carvacrol was proved protective towards neurodegenerative phenotypes linked with systemic delivery of 6-OHDA at the dose of 15 and 20 mg/kg body weight. Results revealed that the locomotor activity, akinesia, catalepsy, motor coordination and bradykinesia were improved and the amount of apomorphine was reduced (Manouchehrabadi *et al.*, 2019)

Pain management: Carvacrol substantially reduced mechanical hyperalgesia, enhanced use of paw, and palpation-induced nociception, according to

a research that examined the relationship of carvacrol with IL-10 and GABAA by administering in mice at the dose of 12.5-50 mg/kg daily for 15 days. Carvacrol minimized the number of neurons in the lumbar spinal cord, locus coeruleus, and nucleus raphe Magnus, and enabled peri-aqueductal gray exhibiting its potential to cure pain (Guimarães *et al.*, 2014).

In a different investigation, the analgesic and anti-inflammatory effects of carvacrol was found in combination with eugenol. They functioned as an agonist of transient receptor potential cation channel, subfamily V, member 3 (TRPV3s), which is engaged in the heat and pain transduction (Klein *et al.*, 2013).

Discussion

Secondary metabolites are a large group of chemical components that are generated by plants though they play no direct role in plant development (Sultana *et al.*, 2022; Chakrabarty *et al.*, 2022). These compounds have showed pharmacological effects on the human body (Ashrafi *et al.*, 2022b). So, these secondary bioactive metabolites have presently drawn attention as a significant means of obtaining novel, potent and safe therapeutic possibility (Obonti *et al.*, 2021).

Carvacrol, the phenolic monoterpene, is an element of several aromatic plants (Can Baser, 2008). It has been recognized and approved as safe for consumption by the Food and Drug Administration (FDA). It is also included in the list of flavoring chemicals by the Council of Europe and can be incorporated to food stuffs like beverages, candies and meals at 2 ppm, 25 ppm, and 5 ppm, respectively (De Vincenzi *et al.*, 2004). The current review has covered a number of pharmacological properties shown by carvacrol (**Figure2**) Carvacrol's antibacterial effectiveness surpasses various volatile chemicals found in essential oils because of its hydrophobicity, phenol moiety, and free hydroxyl group (Sharifi-Rad *et al.*, 2018). Rather than using synthetic chemicals, it may be a natural remedy for many physiological conditions.

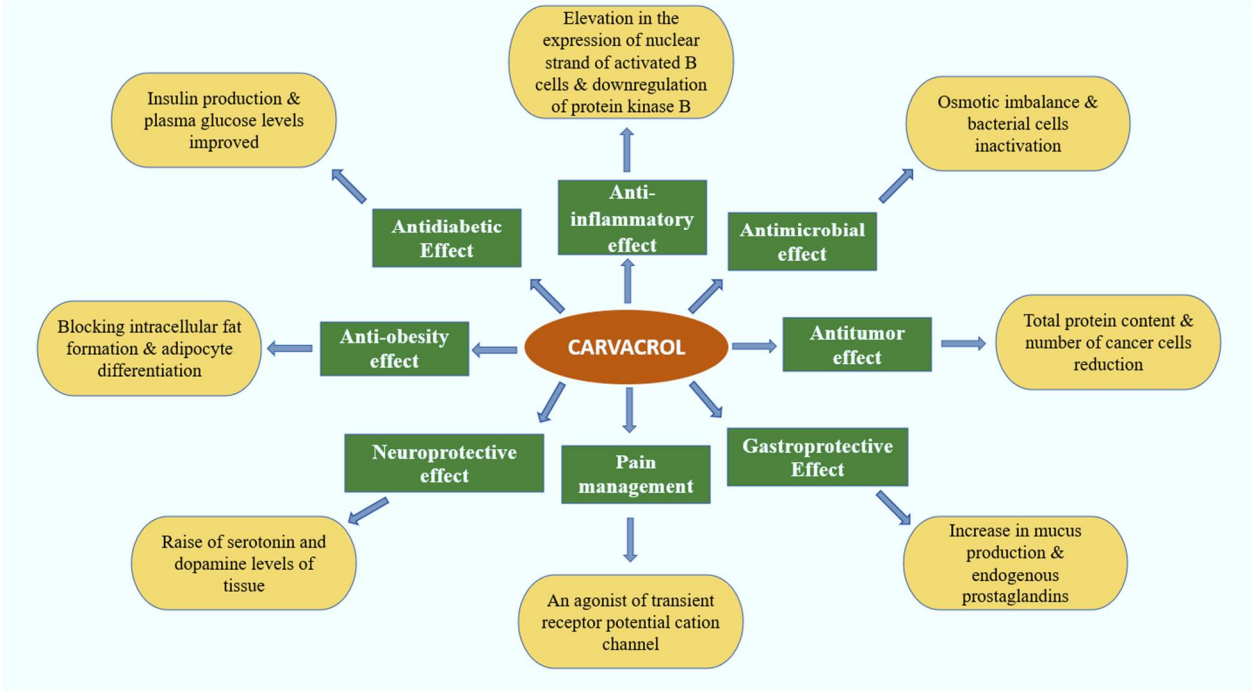

Figure 2: Pharmacological potentials of carvacrol.

Conclusion

Bioactive chemicals and essential oils have attracted attention of many researchers for having well-known rich therapeutic qualities. The intention of this review was to emphasize and explain the biosynthesis system of carvacrol as well as its noteworthy protective effects like anti-obesity, antidiabetic, antitumor, anti-inflammatory, antimicrobial, hepatoprotective, gastroprotective and neuroprotective effects. Researchers and scientists have looked into carvacrol's potential for pain management, cancer prevention, anti-inflammatory effect, and prevention of diabetes in different assays. There is a great deal of promise in carvacrol for the creation of novel medicinal approaches to treat human diseases. Nevertheless, a number of long-term human effectiveness trials, particularly with regard to carvacrol's toxicity and lethal dose, are still necessary to fully understand the possible therapeutic impact of the drug at the molecular level.

Declarations

All authors have read and approved the article for submission. The entire document has never been published, and it is not currently under consideration for publication in any journal in any portion. They have also declared no conflict of interest.

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