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Anticancer, antineurodegenerative, antimicrobial, and antidiabetic activities of carvacrol: recent advances and limitations for effective formulations

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ABSTRACT

Bioactive compounds isolated from medicinal plant species can synergize therapeutic properties of conventional drugs. At this regard, improved biocompatibility and bioavailability have been obtained. Carvacrol as a monoterpenic phenol has pharmacologic features including antimicrobial, anticancer, antineurodegenerative activities and antioxidant properties toward periodontal disease and diabetes mellitus. This metabolite can be applied to reducing inflammation and oxidative stress caused by reactive oxygen species (ROS) generation in neurodegenerative diseases. Carvacrol has anticancer activity by induction of apoptosis in tumor cells. Growth inhibition of bacteria, fungi, and viruses can be possible by this metabolite in a dose-dependent way. In the case of diabetes, α-amylase and α-glucosidase enzymes were inhibited by carvacrol. In this review, we have provided recent advances and challenges for formulations of this bioactive compound in both nano and micro scales. In this way, loading carvacrol by lipid and polymeric nanocarriers exhibited effective therapeutic activity in vivo and in vitro.

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1. Introduction

Various herbal secondary metabolites belong to polyphenols, alkaloids, and terpenoids have been found to have a wide range of therapeutic activities including anticancer, antimicrobial, antineurodegenerative, and antidiabetic activities. Micro and nanoformulations of these bioactive compounds can be applied to synergize therapeutic effects of conventional drugs [1-3]. Carvacrol ($C_{10}H_{14}O$) is a plant metabolite, a monoterpenoid phenol that has been shown to be an effective antimicrobial, anticancer, and neuroprotective agent with a capacity for decreasing inflammation (Figure 1) [4]. There are several main herbal sources including *Monarda didyma* [5], *Nigella sativa* [6], *Origanum dictamnus* [7], *Origanum onites* [8], *Origanum syriacum* [9], *Origanum vulgare* [10], *Plectranthus amboinicus* [11], *Lavandula multifida* [12], and *Satureja thymbra* [13] for this metabolite. In addition to these natural sources, synthetic carvacrol can be prepared via several chemical reactions such as alkylation of o-cresol with isopropyl alcohol or propylene over solid acid catalysts [14]. This metabolite shows solubility in diethyl ether, ethanol, acetone, and carbon tetrachloride. In the case of therapeutic applications, considering anticancer, antidiabetic antineurodegenerative, and antimicrobial activities of carvacrol is critical issue. Therefore, recent advances

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and limitations for micro ore nano formulations of this bioactive compound have been discussed in this review.

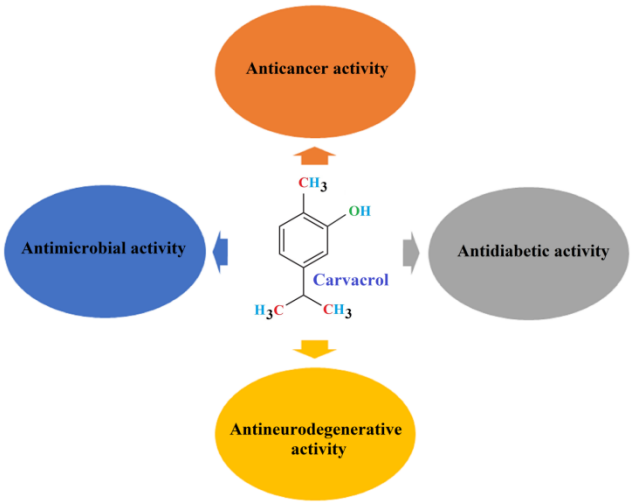

Fig. 1. Chemical structure of carvacrol with related therapeutic activities [15].

2. Anticancer

Severe side effects and the systemic toxicity of many conventional drugs can worsen the quality of life of patients with cancer disease [16]. The growth of A375 cells (cell line of malignant melanoma) was blocked under treatment of carvacrol by inducing apoptosis after 24 h incubation. Induction of apoptosis was resulted from the cleavage of PARP (poly(ADP-ribose) polymerase), reduced Bcl-2 (B-cell lymphoma 2) gene expression, and direct activation of the mitochondrial pathway [17].

3. Antidiabetic

In a comparative study, leaf essential oil of *Coleus aromaticus* and its purified secondary metabolite, carvacrol was tested against α-amylase (this enzyme hydrolyze 1, 4-glycosidic linkages of polysaccharides to disaccharides) and α-glucosidase (this enzyme catalyzes the disaccharides to monosaccharides). Inhibition of these enzymes can reduce hyperglycemia in diabetic patients. The IC_{50} values for α-glucosidase (94.02 and 29.29 µg/mL) and α-amylase (152.3 and 34.64 µg/mL) were obtained for the carvacrol and essential oil respectively [17]. The anti-inflammatory functions of carvacrol in diabetes have been presented in figure 2a [18].

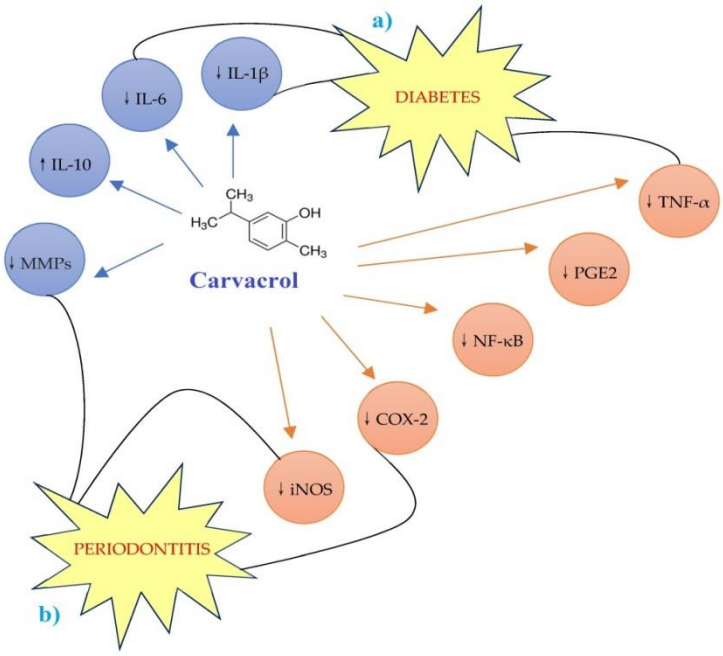

Fig. 2. Schematic image showing the anti-inflammatory of carvacrol in diabetes (a) and periodontitis (b). Matrix metalloproteinases (MMPs); tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) (adopted and modified from [18].

4. Antineurodegenerative

The progressive inefficiency or impairment of neuron function is the main reason for neurodegenerative diseases including Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), prion, and multiple system atrophy [19]. Inflammation and oxidative stress resulted from reactive oxygen species (ROS) production are the two main contributing factors to these diseases [20]. Therefore, finding a chelating agent as the effective antioxidant is critical for reducing of manifestations of these diseases.

4.1. Alzheimer's disease (AD)

AD is the most common cognitive impairment in elderly persons. Aggregation of amyloid-β (Aβ) (4 kDa peptide of the amyloid precursor protein) and tau neurofibrillary tangles were described as the main pathological hallmark of AD [21]. Carvacrol treatment is indicated to reducetoxicity induced by Aβ in rat model of AD via stimulating hippocampal protein kinase C alpha (PKCα) signaling [22]. Sulfonamides derived from carvacrol were used as antioxidant and anxiolytic agents to attenuate the symptoms of AD by the inhibition of

acetylcholinesterase (AChE), an enzyme responsible for the degradation of acetylcholine and termination of neurotransmission. According to molecular docking results, carvacrol forms a π–π interaction and a hydrogen bond with the amino acids side chain of Tyr341and Asp74 in the enzymatic cavity of the AChE enzyme, respectively [23]. Cell viability and a low level of oxidative stress were observed by pretreatment of cell with carvacrol. This metabolite showed improved memory impairment and inhibited lactate dehydrogenase (LDH) release, Aβ1–42-induced cytotoxicity, malondialdehyde (MDA), and H_2O_2 production. However, carvacrol did not affect Tau-peptide levels and SOD [24].

4.2. Parkinson's disease (PD)

Parkinson's disease (PD) as the second most common type of neurodegenerative disease is characterized by impaired motor function [25]. Alpha synuclein aggregation is the main pathological hallmark of the disease leading to neural death in substance nigra [26]. PD is a multidimensional disease. Oxidative stress and neuroinflammation play important role in its progression [27, 28]. Accumulating studies have indicated the neuroprotective effect of Carvacrol against both inflammation [29, 30] and oxidative stress [31, 32]. COX-2 is an enzyme involved in neuroinflammation and PD[33]. Carvacrol exhibits a strong inhibitory activity against COX-2 activity and reduces its expression [30, 34]. Alpha synuclein activates microglia result in increase of pro inflammatory cytokines release [35]. Carvacrol prevents the release of inflammatory cytokines such as TNF-α and IL-1β [30]. Moreover, Carvacrol has shown a protective effect in a rat model of PD by preventing the catalepsy behavior and vacuous chewing movements induced by neurotoxins reserpine [36]. Administration of Carvacrol is also neuroprotective against toxicity induced by 6-hydroxydopamine (6-OHDA) in in vitro and in vivo models of PD by decreasing ROS levels [37]. Long-term treatment with carvacrol ameliorated motor and memory deficits as well in hemiparkinsonian rats [38]. Furthermore, Carvacrol promotes neuroprotection in the 6-OHDA model of Parkinson's disease through blocking TRPM7 channels [39].

4.3. Multiple sclerosis (MS)

The common non-traumatic neurodegenerative disease is MS, resulting in atrophy of the central nervous system (CNS) by axonal degeneration and loss of myelin [40]. Some natural compounds with antioxidant activities such as carvacrol have been considered to treat MS owing to the inadequate efficiency of conventional drugs. The entry of inflammatory cells into the CNS was reduced by carvacrol via stimulating myelination-related processes [41]. In addition, this compound ameliorated experimental autoimmune encephalomyelitis via modulating anti- and pro-inflammatory cytokines and decreasing the expression of inflammatory genes [42]. Treatment of EAE (experimental autoimmune encephalomyelitis) rats, an animal model of MS, by carvacrol increased interleukin-10 (IL-10) (an immunosuppressive and anti-inflammatory cytokine) gene expression and debris clearance, and decreased inflammation. Moreover, the remyelination process (generation of new myelin sheaths around CNS and axons) was triggered by this bioactive compound [43].

5. Antimicrobial

5.1. Antibacterial activity

Multidrug resistance properties in bacteria should be considered to obtain effective antibacterial formulations [44, 45]. Nanoformulations of bioactive compounds by various types of nanomaterials (NMs) including metal/metal oxide nanoparticles (NPs), quantum dots, liposomes, phytoliposomes, micelles, solid lipid NPs, and polymeric NPs can improve their therapeutic applications [46]. Increased therapeutic reactivity, biocompatibility, and biodegradability are the main benefits aspects of nanoformulations [47]. Changing the structural and functional features of cytoplasmatic membrane has been found as the main antibacterial mechanisms of carvacrol [48]. Another antibacterial mechanisms such as anti-desiccation resistance against *Salmonella* Tennessee at the minimum inhibitory concentrations (MICs) of 200 µg/mL has been also reported [49]. In the case of organic polymers, carvacrol was loaded on hydrophobic chitosan NPs (the covalent binding of octanoic acid with chitosan). Carvacrol-octanoic acid modified chitosan NPs in spherical shape exhibited Z potential of 10.4 mV and

a size of 200 nm with encapsulation efficiency of carvacrol by 56.28%. By this formulation, the entrapping of carvacrol and its release behavior in aqueous media were improved via hydrophobic properties octanoic acid. This nanoformulation inhibited the growth of *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive) bacteria, significantly [50]. Moreover, antioxidant property of carvacrol can impact on periodontitis disease, a severe gum infection (Figure 2b) [18].

5.2. Antifungal activity

Aspergillus flavus contaminant in oil and grain crops can produce aflatoxin B1 with carcinogenic effect [51]. The aflatoxin B1 production, germination of spores, and mycelia growth of *A. flavus* was inhibited at concentration of 200 µg/mL of carvacrol. Ergosterol is a main component of the fungal cell membrane was reduced at 50, 100, and 200 concentrations, dose-dependently. This study showed carvacrol can down regulate the glycerolipids (neutral lipid and diglyceride) and phospholipids (phosphatidylcholines, phosphatidylethanolamine, and phosphatidylserine) with upregulation of phosphatidylinositols and phosphatidylglycerols [52].

5.3. Antiviral activity

Secondary metabolites extracted from medicinal plant species have been applied for treatment of various viral infections [3]. Influenza virus A infection is one of the common viral disease infecting the lungs, nose, and throat [53]. Damage of lung tissue was attenuated by carvacrol concomitant with the inhibition of cytokines including IFN-γ, TNF-α, IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, and IL-12. Additionally, reduction in levels of Interferon regulatory factor (IRF), (Toll-like receptors-7) TLR7, IPS-I, MyD88, retinoic-acid-inducible gene I (RIG-I), TNF receptor-associated factor 6 (TRAK6), interleukin-1 receptor associated kinase-4 (IRAK4), and nuclear factor-κB (NF-κB) mRNA were found in carvacrol-treated mice [54]. Carvacrol can be applied to target viral protease (M^{pro}) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Angiotensin-converting enzyme 2 (ACE_2) in host cells (Figure 3) [55].

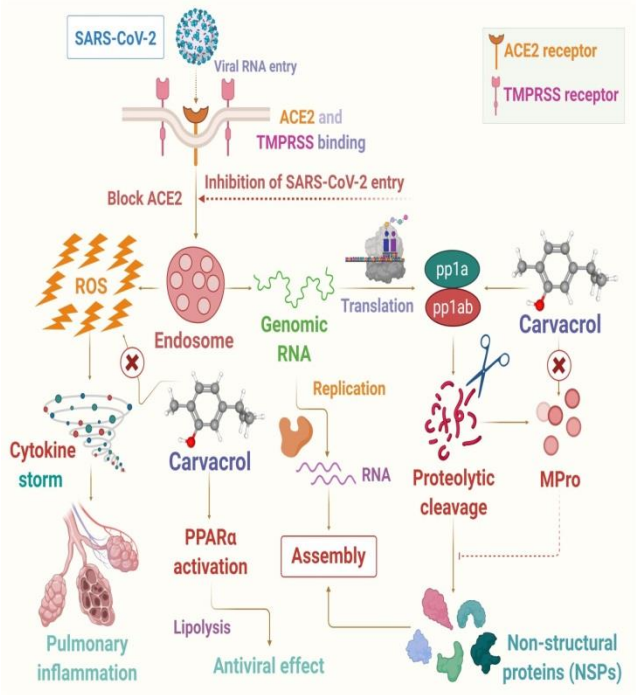

Fig. 3. The significant antiviral mechanisms of carvacrol against SARS-CoV-2 (adopted and modified from [55]).

The host's immune response has a great influence on the outcome of the disease, and also enhancing the host's immune response is important to face pathogens and toxins. Carvacrol (2-methyl-5-(1-methyl ethyl)-phenol) is a phenolic monoterpene found in essential oils extracted from thyme (*Thymus vulgaris*) and oregano (*Origanum vulgare*). The nutrient carvacrol has antiviral, antioxidant, and anti-inflammatory activities [56]. Recently, due to the antiviral activity that carvacrol has, there have been suggestions as alternative adjuvant therapy, to whether it can be an acceptable candidate for the development of anti-Covid-19 drugs or not, this debate has been taken into consideration again [57]. Carvacrol acts as an antiviral against influenza by reducing the proportion of T helper 17 cells (Th17) cells that are increased by influenza A virus infection, which can be a potential antiviral drug and its use. However it can be used to control inflammation caused by influenza A virus infection [58]. In another study, the mechanism of carvacrol and its antiviral activity against herpes simplex virus in vitro. The results exhibited that carvacrol solution and pure carvacrol (2%) can have antiviral effects for the treatment and direct inactivation of HSV-2 infection. However, carvacrol can show acceptable anti-HSV-2 activity in laboratory conditions [59]. As

the main antiviral mechanism, carvacrol can change the cholesterol content of the viral membrane and prevent HIV-1 from entering the target cell [60].

5.4. Anti-parasitic activity

In developing countries, Leishmaniasis is a parasitic disease with a wide incidence (in parts of the tropics and subtropics regions), which the conventional drugs for treatment of this disease have high toxicity to healthy cells [61, 62]. Therefore, finding effective biocompatible antileishmanial agents is the critical affair. The limonene–carvacrol combination in the ratio of 1:4 exhibited antileishmanial activity in vitro against *Leishmania major* promastigote and amastigote forms by inhibition of trypanothione reductase (TryR) enzyme and induction macrophages activation. Antileishmania property was found by average inhibitory concentration (IC_{50}) in range of 5.8-19.0 µg/mL [63]. It has been reported that essential oils of Mexican Oregano (*Poliomintha longiflora* Gray and *Lippia berlandieri* Schauer) containing carvacrol and thymol induces cell death in the *leishamani promastigotes* by apoptosis mechanism. For this study, carvacrol had leishmanial inhibitory activity as IC_{50} value of 61.52 µg/mL [64]. In similar study, carvacrol as main component (70.6%) of Turkish *Origanum onites* essential oil showed antiprotozoal activity against *Trypanosoma brucei rhodesiense*, *Leishmania donovani*, and multidrug-resistant *Plasmodium falciparum* [65]. Carvacrol has significant in vitro leishmanicidal activity against *Leishmania chagasi* promastigotes with lower IC_{50} (54.8 µg/mL) than thymol (74.1 µg/mL) [66]. Carvacrol nanostructured lipid carriers (NLCs) by the particle size of 98.42 nm exhibited leishmanicidal activity against *L. amazonensis* promastigotes and *L. amazonensis* amastigotes as IC_{50} values of 28.2 and 19.65 ppm, respectively [67]. In a comparative study, carvacrol showed antileishmanial activity against *Leishmania infantum* by IC_{50} of 9.8 µg/mL compared to thymol with 7.2 µg/mL [68]. Carvacrol-loaded nanoemulsion significantly improved antischistosomal activity towards *Schistosoma mansoni*, showing efficiency in reducing worm and egg burden by 85% up to 90% [69]. The second leading cause of persistent diarrhea among children is an important intestinal parasite of *Cryptosporidium parvum* [70]. Reduction of relative *C. parvum* infectivity in HCT-8 cell monolayers at a dose-dependent way was found as amount as 45.8 % 30 µg/mL of carvacrol [71].

6. Conclusions

Carvacrol metabolite may be considered as an effective antioxidant to reducing inflammation and oxidative stress caused by ROS production in neurodegenerative diseases. Carvacrol leads to neuroprotective effect on hippocampal neurons injury by increasing the expression of PKCα. In AD, sulfonamides derived from carvacrol can inhibit the acetylcholinesterase. Induction of apoptosis in tumor cells was found for this compound as the main anticancer mechanism. Growth of fungi can be blocked by the reduction of ergosterol synthesis in fungal cell membrane in a dose-dependent way. Changing the structural and functional properties of cytoplasmatic membrane and anti-desiccation resistance has been found as the main antibacterial mechanisms of carvacrol. As the main future prospect, nanoformulation of carvacrol can improve its release behavior in aqueous media. For example, loading carvacrol by nanoemulsion and NLC exhibited effective anti-parasitic activity in vivo and in vitro.

Study Highlights

- Carvacrol can be regarded as an effective antioxidant to reducing inflammation and oxidative stress caused by ROS production in neurodegenerative diseases.
- Carvacrol leads to neuroprotective effect on hippocampal neurons injury by increasing the expression of PKCα.
- Induction of apoptosis in tumor cells was found for this compound as the main anticancer mechanism.
- Growth of fungi can be blocked by the reduction of ergosterol synthesis in fungal cell membrane in a dose-dependent way.
- Changing the structural and functional properties of cytoplasmatic membrane and anti-desiccation resistance has been found as the major antibacterial mechanisms of carvacrol.
- Nanoformulation of carvacrol can improve its release behavior in aqueous media.

Abbreviations

AD: Alzheimer's disease
ALS: Amyotrophic lateral sclerosis
Aβ: Amyloid-β
CNS: Central nervous system
EAE: Experimental autoimmune encephalomyelitis
HD: Huntington's disease
IL-10: Interleukin-10
IL-1β: Interleukin-1β
IL-6: Interleukin-6
MMPs: Matrix metalloproteinases
MS: Multiple sclerosis
NLCs: Nanostructured lipid carriers
PD: Parkinson's disease
PKCα: Protein kinase C alpha
TNF-α: Tumor necrosis factor alpha
TryR: Trypanothione reductase
M^{pro}: Viral protease
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
ACE_2: Angiotensin-converting enzyme 2

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution

All authors: conceptualization, preparing the first draft, and revising the manuscript.

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