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Carvacrol: a potent anti-Candida bioactive molecule

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ABSTRACT

Carvacrol (Origanum vulgare), a phenolic monoterpenoid, has been examined for its antifungal activity. Origanum vulgare has a natural source of carvacrol, and its essential oils contain 80 percent of carvacrol. It has shown a wide range of antifungal activity in terms of growth inhibition, biofilm formation, and anti-virulence activity. The primary mode of action is endoplasmic reticulum disruption, which ultimately results in the disruption of components of cells membrane constituent, with cell membrane permeability, membrane lipids like ergosterol, Ca2+ efflux, and ROS production. This review is comprised of various studies on Carvacrol against fungal (Candida spp.) infections.

Keywords: Carvacrol, Candida albicans, non-albicans Candida, anti-virulence, antioxidant

INTRODUCTION

In the past few decades, the development of new antimicrobial agents for clinical application has declined (Sharifi-Rad et al. 2018). Since the late 20th century, a gradual increase in the prevalence of invasive fungal infections (IFIs) has been detected, with those caused by species of the genus *Candida* being more frequent (43–75%) worldwide (Bongomin et al. 2017; Frías-De-león et al. 2021). Approximately 90-95% of candidosis occurring by *Candida albicans* along with non-*albicans Candida* (*C.glabrata*, *C. tropicalis*, and *C. parapsilosis*) are the main causatives of superficial infection to nosocomial (Bohner, Gacser, and Toth 2021; Bongomin et al. 2017). Candidemia is the most frequent form of invasive candidiasis and is currently ranked fourth to seventh in terms of bloodstream infection prevalence(Kotey et al. 2021). This opportunistic fungus can live as a saprophyte or commensal in nature and is extremely common. Several host factors and pathogenicity are involved in the transition of Candida from a commensal to potent pathogen. Since candidiasis frequently affects immunocompetent and critically ill patients (Frías-De-león et al. 2021; Hassan, Chew, and Than 2021). Several virulence features, including adherence to host tissues, hydrophobicity, biofilm development, and extracellular enzyme release, are responsible for the pathogenicity of *Candida* spp. (Deorukhkar 2017).

Azole drugs, a potent class of antifungals drug, inhibit the ergosterol biosynthesis in the fungal plasma membrane by disrupting the lanosterol 14-demethylase. These drugs have fungistatic potential, and some of them, particularly fluconazole, be able to make adverse effects in patients who have been taking azoles for a long period. In this context, *Candida albicans* and non-*albicans*

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Candida rapidly develop resistance to fluconazole and the ability to resist currently available drugs(Kotey et al. 2021).

For this reason, studying novel and naturally occurring antifungal ingredients for clinical applications is necessary. According to recent reports from numerous studies and reviews, natural molecules derived from plants could be fascinating alternatives to synthetic drugs. (Sharifi-Rad et al. 2018). Due to their high antimicrobial and antioxidant activity, essential oils (EO) offer a significant deal of able to the treatment of infections. Essential oils are liquid, volatile, transparent, and infrequently colored; they can be soluble in lipid and an organic solvent; and generally, have densities lesser than that of water (Sharifi-Rad et al. 2018).

Carvacrol is a monoterpene that is present in several essential oils of the *Lamiaceae* family, including those belongs to Origanum, Coridothymus, and Satureia. The highest concentration (80%) of carvacrol is found in the essential oils of *Origanum vulgare*. A species of flowering plant known as *Origanum vulgare* belongs to the Lamiaceae family of mints. It was native to the Mediterranean region, but widely naturalized elsewhere in the temperate Northern Hemisphere (Sharifi-Rad et al. 2018). Carvacrol has been shown to have a wide range of clinical applications, such as antibacterial, antifungal, antivirals, antioxidant, and anticancer. This review aimed to provide significant evidence of carvacrol as anti-Candida activity including antioxidant, anti-virulence, and their mode of action.

Based on the literature search, conducted in September 2022 in different databases: Scopus, Google Scholar, and PubMed, the available research papers have covered the wide range of pharmacological potential of carvacrol or its sources. Several combinations of keywords used to search literature were "Carvacrol," "*antioxidant*," "anti-virulence," antifungal," and so forth.

Antifungal activity of Carvacrol

Antimicrobial activity can be defined as a collective term for all active principles (agents) that inhibit the growth of microbes. table 1. Showing minimum inhibitory concentration (MICs) of carvacrol on *Candida albicans* and non-*albicans Candida.*

Table 1. listed Candida spp. and their MICs.

	Minimum inhibitory concentration(µg/ml) on planktonic cells.	Name of species	References
Carvacrol	128	*C.tropicalis LM -10*	(Nóbrega et al. 2019)
	512	*C. krusei LM-120*	
	512	*C. guilliermondii LM-103*	
	128	*C. parapsilosis* ATCC 20019	
	128	*C.albicans*	(Miranda-Cadena et al. 2021)
	16-512	*C. glabrata*	
	32-128	*C. krusei*	
	64	*C. parapsilosis*	
	63-250	*C.auris*	(Shaban, Patel, and

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	250	*C.albicans*	Ahmad 2020)
	87.50-125	*C. krusei*	(Sharifzadeh, Shokri, and Abbaszadeh 2019)
	43.75-87.50	*C.albicans*	
Origanum vulgare L. essential oil (O-EO) .	0.01	*C. albicans* ATCC-90029	(Cid-Chevecich et al. 2022)
	5.3	*C. krusei* ATCC-6258	
	2.6	*C. dubliniensis* ATCC-CD36	

The minimum inhibitory concentration (MICs) of carvacrol compounds against tested *Candida* strains are shown in Table 1. MIC results depict that *C. albicans*, *C. glabrata,* and *C. auris* are less susceptible in comparison to other non-*albicans candida*.

The anti-virulent activity of Carvacrol

Candidiasis is a more frequent fungal infection of the skin, oral cavity, esophagus, gastrointestinal tract, the vulvovaginal and vascular system of humans. *Candida albicans* and followed by non-albicans candida is the most frequently responsible for the disease, produces multiple virulence factors that contribute to pathogenesis, contempt the fact that most infections occur in individuals who are immunocompromised or serious illnesses. These factors consist of host recognition biomolecules (adhesins), morphogenesis (the reversible change from yeast cells to hyphal cells, growing forms), secreted enzyme such as proteases, and phospholipases, which is responsible for tissue damage and cellular dysfunction (Deorukhkar 2017; Mayer, Wilson, and Hube 2013; Pappas et al. 2018; Staniszewska et al. 2012)**.** Actively turning on antigen expression, cellular morphology, and tissue affinities are also linked with "phenotypic transition" in *C. albicans* and several *Candida* species. Switching could give cells the plasticity required to assist cells to adapt to the antagonistic conditions executed by the host tissues(Antony et al. 2009). However, carvacrol has the potential to inhibit morphology by switching to enzyme activity. According to Shaban, P et al 2020, carvacrol significantly reduced the proteinase production in *C. albicans* and *C.auris* at the concentration of 250 and 125 μg/ml.

Antioxidant activity of Carvacrol

Antioxidants are a chemical composition that tends to inhibit oxidation, in living cells, millions of chemical reactions go on some time to produce free radicals (highly chemically reactive) that may damage the cells of an organism. Carvacrol was found to be the dominant component of investigated essential oils (Gavaric et al. 2015; Yildiz et al. 2021).

Mode of action of Carvacrol on *Candida* species

Carvacrol has shown potential to control the planktonic to sessile cell growth of many fungi containing *C. albicans* and non-*albicans Candida*. The primary mode of action is endoplasmic reticulum disruption, which finally results in the disruption of several components of membrane biology, including membrane permeability and membrane lipids like ergosterol. Although the mechanism of its action has been substantially outlined, other details, such as the precise nature of the cell death caused by carvacrol in *C. albicans*, remain unknown. Carvacrol could activate *C. albicans* apoptosis as well as cause cell membrane disruption. N-acetylcysteine (NAC) and mitoTEMPO, which are both ROS scavengers, were unable to reverse the growth inhibition of

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Candida albicans caused by carvacrol, indicating that apoptosis was the result of carvacrol therapy rather than ROS formation (Lima et al. 2013; Niu et al. 2020). Internal stresses can activate the Ca^{2+} influx system of the plasma membrane, resulting in a rapid influx of Ca^{2+}, which then binds to calmodulin and calcineurin, leading to cellular homeostasis, and drug tolerance. Calcium is also known to participate in the apoptotic process and was accumulated in the cytosol and mitochondria after treatment with carvacrol-induced *C. albicans* apoptosis (Rao et al. 2010).

Conclusion

Carvacrol may have positive effects on the treatment of integral risk of *Candida* infections, according to several research studies. The development of new pharmacological active ingredients for use in pharmaceuticals may be based on some of these bioactivities of carvacrol. Carvacrol has therapeutic potential to inhibit the growth of *Candida* spp. along with altering the cellular function of *Candida albicans*.

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