



Would carvacrol be a supporting treatment option effective in minimizing the deleterious effects of COVID-19?

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Abstract

The pathophysiological process of the disease, Covid-19, is mediated by innate immunity, with the presence of macrophages responsible for secreting type 1 and 6 interleukins (IL), tumor necrosis factor (TNF) leading to dilation of endothelial cells with a consequent increase in capillary permeability. The treatment of this disease has been much discussed, but the variability in the clinical picture, the difficulties for diagnosis and treatment, especially of those patients who have the most severe clinical condition of the disease. Immunization is an effective tool for controlling the spread and overload of health services, but its effectiveness involves high investments in the acquisition of inputs, development of vaccines, and logistics of storage and distribution. These factors can be obstacles for countries with lower economic, technological, and infrastructure indexes. Reflecting on these difficulties, we raised the possibility of adjuvant therapies with imminent research feasibility, as is the case with the use of carvacrol, a monoterpenic phenol whose has biological properties that serve as a barrier to processes mediated by free radicals, such as irritation and inflammation, due to its antioxidant action. Many authors highlighted the activity of carvacrol as a potent suppressor of COX-2 expression minimizing the acute inflammatory process, decreasing the release of some pro-inflammatory mediators such as IL-1 β , TNF- α , PGE2. Anyway, the benefits of carvacrol are numerous and the therapeutic possibilities too. With this description, the question arises: would carvacrol be a supporting treatment option, effective in minimizing the deleterious effects of Covid-19? There is still a lot to discover and research.

Keywords SARS-Cov-2 · Covid-19 · Carvacrol · Monoterpene

SARS-CoV-2 has great potential for transmission and rapid replication. Its worldwide spread has caused high mortality and morbidity, and negative impacts on the economy of some countries (Asselah et al. 2021).

The pathophysiological process of the disease COVID-19 is mediated by innate immunity. When cell changes of

pathological origin are recognized, type I and III interferons associated with other inflammatory cytokines enter the transcription process (Khalaf et al. 2020). After viral infection reaches type II pneumocytes, the viral spike protein binds to SARS-CoV-2 receptor ACE-2. Soon after, the virus enters the nucleus of the ribosome, leading to the translation of

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its genome + ssRNA into different protein molecules (Letko et al. 2020).

In response, type II pneumocytes initiate the process of releasing inflammatory mediators, promoting macrophages to secrete type 1 and 6 interleukins (IL) and tumor necrosis factor (TNF) leading to dilation of endothelial cells with a consequent increase in capillary permeability. With the accumulation of fluids inside the alveoli, it is possible to observe edema with increased surface tension, leading the individual to present a decline in gas exchange, with a worrying prognosis when related to the respiratory function; the most commonly described is acute respiratory distress syndrome (ARDS) (Zhao et al. 2020).

The treatment of this disease has been much discussed, but the variability in the clinical picture and the difficulties for diagnosis and treatment, especially of those patients who have the most severe clinical condition of the disease, raise discussions about auxiliary methods, which holds the progression of the pathophysiology or that optimizes the effectiveness of the treatment. Immunization is an effective tool for controlling the spread and overload of health services, but its effectiveness involves high investments in the acquisition of inputs, development of vaccines, and logistics of storage and distribution. These factors can be obstacles for countries with lower economic, technological, and infrastructure indexes. Reflecting on these difficulties, we raised the possibility of adjuvant therapies with imminent research feasibility, as is the case with the use of carvacrol, a monoterpenic phenol whose therapeutic potentials are recognized by alternative or complementary medicine from several countries in the Asian continent (such as China), in the Mediterranean (for example, Lebanon), or in South America (Lima et al. 2013; Khoury et al. 2016; Silva et al. 2018).

This volatile compound, with a distinctive odor, is found in aromatic plants and essential oils, even being the main component of the fractions of *Origanum vulgare* (oregano) and *Thymus vulgaris* (thyme) (Ipek et al. 2005; Liolios et al. 2009). Carvacrol is recognized as safe and its use in food has been approved by the European Food Safety Authority and the Food and Drugs Administration (FDA) (). It is a safe additive that increases the shelf-life of food as a flavoring agent and that acts against microorganisms (Ultee and Smid 2001). Furthermore, in 2018, Ghorani et al. (2018) published a phase I clinical study, which was designed to evaluate the safety and tolerance of carvacrol at high doses (1 and 2 mg/kg/day) for 1 month in healthy subjects. The effects of carvacrol in healthy subjects showed clinical safety and tolerability for this agent.

The natural antimicrobial action (Mastelic et al. 2008; Beena and Rawat 2013) is based on disturbance of the cytoplasmic membrane, disruption of electron flow, interference with active transport, inhibition of coagulation of cytoplasmic content, and enzyme activity. Its inhibitory action on

the production of toxins has been proven in food (Ultee and Smid 2001), which demonstrates great potential for use in large populations.

Carvacrol has biological properties that serve as a barrier to processes mediated by free radicals, such as irritation and inflammation, due to its antioxidant action (Silva et al. 2018; Mastelic et al. 2008; Beena and Rawat 2013; Guimarães et al. 2010). Moreover, through experimental studies, it was observed that carvacrol is also responsible for hepatoprotective actions (increasing the rate of liver regeneration) (Uyanoglu et al. 2008), anti-bactericidal (Lambert et al. 2001; Mathela et al. 2010), antifungal (Pina-Vaz et al. 2004; Pete et al. 2012), antitumor (He et al. 1997), anti-elastase (Baser 2008), and antiapoptotic and antiplatelet (Son et al. 2005), which is important to highlight, given that SARS-CoV-2 causes a state of hypercoagulability, possibly due to, among other factors, the tissue damage that is generated, stimulating platelet activation and aggregation, leading to the microthrombus formation and greater platelet consumption. Carvacrol is also related to reparative and tissue protective action (Lima et al. 2013; Guimarães et al. 2010, 2012; Landa et al. 2009).

In the last fifteen years, experimental researches testing this product have proven beneficial effects in the combat of several diseases, among which it is worth mentioning: lung injuries (Şen et al. 2014) or chronic obstructive pulmonary disease (Boskabady and Gholami 2015); cardiovascular diseases (Wei et al. 2013); cerebral edema (Zhong et al. 2013).

Many authors, such as Wagner et al. (1986), Guimarães et al. (2010), Botelho et al. (2009), Hotta et al. (2010), Landa et al. (2009), Guimarães et al. (2012), and Lima et al. (2013), highlighted, in their preclinical studies with animals, the activity of carvacrol as a potent suppressor of COX-2 expression; and therefore, its anti-inflammatory effect is certainly associated with prostaglandin inhibition, minimizing the acute inflammatory process and decreasing the release of some pro-inflammatory mediators such as IL-1 β and TNF- α , as well as inhibiting NO release. In addition, a clinical trial published in 2019 showed that levels of IL-10, an anti-inflammatory cytokine, were enhanced (Lima et al. 2013; Hotta et al. 2010; Khazdair and Boskabady 2019a, b).

However, it is crucial to mention the study that was published by Reese et al. (Reese et al. 2021), which addresses the use of COX inhibitors associated with increased severity of COVID-19. In this paper, the authors performed a retrospective observational study, analyzing eight COX inhibitors and demonstrated a significant association of the use of five of eight different COX inhibitors with increased clinical severity and mortality. The other three inhibitors that did not obtain evidence of an association of increased severity of COVID-19 were those selective for COX-2, as carvacrol is, increasing the possibility of agent-specific risk profiles for individual COX inhibitors. Therefore, the authors

themselves state that it seems plausible that the adverse effect profile of COX inhibitors in COVID-19 subjects may differ from drug to drug.

It is important to highlight the preventive effect of carvacrol on the levels of total and differential leukocytes and serum levels of MDA and IL-8, in a COPD model in guinea pigs, comparable to the effect of dexamethasone, a product used in the treatment of patients with COPD. In this study, the researchers evaluated 3 different concentrations of carvacrol in addition to dexamethasone and obtained positive results in all three concentrations (Mahtaj et al. 2015).

According to the study by Ferrara and Vitiello (2021), epidemiological evidence showed the efficacy of dexamethasone in severe COVID-19 in reducing mortality. Can such a finding be extended to the effects of carvacrol, considering that there are already experimental studies with it that resulted in stabilization of the vascular endothelial barrier, as mentioned above? This question is important, since most of the studies cited here are experimental.

Just in 2019, the first clinical trial with 20 patients with non-infectious obstructive pulmonary disease secondary to prolonged exposure to sulfur mustard using carvacrol was published, yielding two publications. This study showed that there was a reduction in inflammatory cells and oxidative biomarkers, in addition to showing improvement in the results of pulmonary strength tests in patients treated with carvacrol (Khazdair and Boskabady 2019a, b).

Anyway, the benefits of carvacrol are numerous and the therapeutic possibilities too. With this description, the question arises: would carvacrol be a supporting treatment option, effective in minimizing the deleterious effects of COVID-19? Helping to control viral duplication, cytokine storm, and oxidative stress? COVID-19 has negatively impacted the lives of thousands of people, whether due to mortality or its economic, mental, and social impacts. There is still a lot to discover and research.

Declarations

Conflict of interest The authors declare no competing interests.

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