

## ORIGANUM VULGARE ESSENTIAL OIL AND CARVACROL: NATURAL ALTERNATIVES AGAINST RESISTANT BACTERIA

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**ABSTRACT:** Bacteria that are resistant to several antibiotics are a serious One Health problem, as new alternatives for treatment do not appear at the same speed. Thus, the aim of this work was to carry out a survey of studies involving the activity of the essential oil of *O. vulgare* and its isolated compound carvacrol on antibiotic-resistant bacteria. To this end, a qualitative review of the literature was carried out in the PubMed database from 2015 to 2020. Both for the essential oil and for the isolated compound, the inhibitory action extends to strains often associated with difficult-to-treat infections such as oxacillin and vancomycin-resistant *Staphylococcus aureus*,  $\beta$ -lactamase-producing strains, carbapenemases, among others. The point that distinguishes the studies is the type of methodology used in the tests, with studies with carvacrol more directed towards mechanisms of molecular action and application in cells and animals, while those with oils are more preliminary. Although these substances have potential to control resistant bacteria, more research is needed to enable their use.

**KEYWORDS:** Isolated compound; Oregano; Medicinal plant; Multiresistance.

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## ÓLEO ESSENCIAL DE *ORIGANUM VULGARE* E CARVACROL: ALTERNATIVAS NATURAIS CONTRA BACTÉRIAS RESISTENTES

**RESUMO:** Bactérias resistentes a vários antibióticos são um grave problema para a Saúde Única, pois novas alternativas de tratamento não aparecem na mesma velocidade. Assim, o objetivo deste trabalho foi realizar um levantamento de estudos envolvendo a atividade do óleo essencial de *O. vulgare* e seu composto isolado, carvacrol, sobre bactérias resistentes a antibióticos. Para tanto, foi realizada uma revisão qualitativa da literatura na base de dados PubMed no período de 2015 a 2020. Tanto para o óleo essencial quanto para o composto isolado, a ação inibitória se estende a cepas frequentemente associadas a infecções de difícil tratamento como *Staphylococcus aureus* resistente à oxacilina e vancomicina, cepas produtoras de  $\beta$ -lactamase, carbapenemases, entre outras. O ponto que diferencia os estudos é o tipo de metodologia utilizada nos testes, sendo os estudos com carvacrol mais direcionados para mecanismos de ação molecular e aplicação em células e animais, enquanto os com óleos são mais preliminares. Embora essas substâncias tenham potencial para controlar bactérias resistentes, mais pesquisas são necessárias para viabilizar seu uso.

**PALAVRAS-CHAVE:** Composto isolado; Orégano; Multirresistência; Planta medicinal.

## EL ACEITE ESENCIAL DE *ORIGANUM VULGARE* Y EL CARVACROL: ALTERNATIVOS NATURALES CONTRA LAS BACTERIAS RESISTENTES

**RESUMEN:** Las bacterias resistentes a diversos antibióticos son un grave problema para la Sanidad Única, ya que las nuevas alternativas de tratamiento no aparecen a la misma velocidad. Así pues, el objetivo de este trabajo fue realizar una encuesta sobre los estudios relativos a la actividad del aceite esencial de *O. vulgare* y su compuesto aislado, el carvacrol, sobre las bacterias resistentes a los antibióticos. Para ello, se realizó una revisión bibliográfica cualitativa en la base de datos PubMed en el periodo comprendido entre 2015 y 2020. Tanto para el aceite esencial como para el compuesto aislado, la acción inhibitoria se extiende a cepas frecuentemente asociadas a infecciones de difícil tratamiento como el *Staphylococcus aureus* resistente a la oxacilina y a la vancomicina, cepas productoras de  $\beta$ -lactamasas, carbapenemasas, entre otras. El punto que diferencia los estudios es el tipo de metodología utilizada en las pruebas, siendo los estudios con carvacrol más dirigidos a mecanismos de acción molecular y aplicación en células y animales, mientras que los de aceites son más preliminares. Aunque estas sustancias tienen potencial para controlar las bacterias resistentes, es necesario seguir investigando para que su uso sea viable.

**PALABRAS CLAVE:** Compuesto aislado; Orégano; Multirresistencia; Planta medicinal.

### 1. INTRODUCTION

There were many benefits of using antimicrobials, especially in the 20th century. However, in a short period of time, antibiotic-resistant bacteria emerged causing great concern with regard to human and animal welfare (FALEIRO; MIGUEL, 2013).

Over time, the excessive and indiscriminate use of these drugs resulted in the spread of these resistant bacteria and became a public health problem worldwide. In addition, antimicrobial resistance associated with the use of these antibiotics culminates in reduced effectiveness and likelihood of cure during the treatment of common bacterial diseases (CHENG *et al.*, 2016).

Between 2012-2015, the microorganisms considered the main cause of infections in Brazilian hospitals were *Klebsiella pneumoniae*, coagulase-negative *Staphylococcus* (ECN), *Staphylococcus aureus*, *Acinetobacter* spp. and *Pseudomonas aeruginosa*. In addition, the rate of antibiotic resistance

is high, and in the case of *S. aureus*, about 60% of the isolates were resistant to oxacillin (BRAZIL, 2016).

The biggest problem related to their presence is that the growing number of resistant strains is not accompanied by the research and development of new antimicrobials. In 2004, only 1.6% of the drugs under development by the world's largest pharmaceutical companies were antibiotics. This reduced production has several causes, including the typically very limited duration of treatments, which makes them less profitable than drugs for use in chronic diseases. Another reason is prescription, newly approved drugs for most other diseases are immediately prescribed, while new antimicrobials are often kept in reserve and used to treat infectious diseases that more established antibiotics cannot treat, thus generating a delay in relation to the financial return for companies and their investors (ZIEMSKA; RAJNISZ; SOLECKA, 2013; FAIR; TOR, 2014).

Approaches to combat bacterial resistance range from education and better prescription control to the development of antibacterial vaccines, and the use of bacteriophages, probiotics and plant-derived substances such as essential oils (CARLET *et al.*, 2012). Plants contain numerous constituents and are valuable sources of new biologically active molecules that have antimicrobial properties. Although synthetic antimicrobials are approved in many countries, the therapeutic value of natural products has aroused interest and required the exploration of safe, effective and acceptable alternative sources (BAJPAI; BAEK; KANG, 2012; NEGI, 2012).

Characterized by a prominent odor, formed by the secondary metabolism of plants, essential oils are complex and volatile natural compounds extracted from various aromatic plants (BAKKALI *et al.*, 2008). They are liquid, volatile, limpid and rarely colored products, liposoluble and soluble in organic solvents, with a density generally lower than that of water. They can be synthesized in various plant organs such as buds, flowers, leaves, stems, twigs, seeds, fruits, roots, wood or bark and are stored in secretory cells, cavities, channels, epidermal cells or glandular trichomes (BURT; REINDERS, 2003; BAKKALI *et al.*, 2008). They can contain from twenty to sixty components in different concentrations and have mainly terpenes, terpenoids and other aromatic and aliphatic constituents characterized by low molecular weight. In nature, they play an important role in plant protection as antibacterial, antiviral, antifungal, insecticide and also against herbivores (BAKKALI *et al.*, 2008).

Because of these activities present in essential oils and their compounds, these can be effective against multiresistant bacteria, but efforts should be made to improve the use of these promising substances for the treatment of infections (FALEIRO; MIGUEL, 2013).

An example of an essential oil known for its antimicrobial potential is the essential oil of *Origanum vulgare*, popularly known as oregano, which has several biological properties in addition to antimicrobial as an antioxidant, and antimutagenic, being mainly composed of phenolic

components such as thymol and carvacrol has been widely studied against multiresistant microorganisms (GULLUCE *et al.*, 2012; BEDOYA-SERNA *et al.*, 2018).

Therefore, this review aims at the collection of scientific articles that relate the essential oil of *Origanum vulgare* and carvacrol as natural alternatives against resistant bacteria.

## 2. METHODOLOGY

A qualitative literature review was carried out (PEREIRA *et al.*, 2018), where the research was based on articles available in the PubMed databases, from 2015 to 2020.

For this proposal, the following keywords were used: “*Origanum vulgare*”, “bacteria”, “resistant” and “carvacrol”.

As inclusion criteria, articles related to essential oil and isolated compound used to combat bacteria were selected, including studies carried out *in vitro*, *in vivo* and *ex vivo*. Articles that were not available in full and review studies were excluded.

## 3. ANTIBACTERIAL ACTION OF *ORIGANUM VULGARE*

The literature has reported the inhibitory activity of the essential oil of *Origanum vulgare* (EOOV) and its compounds on several microorganisms of clinical interest in human and animal health, foodborne pathogens and bacterial toxins (HOLLEY; PATEL, 2005; SOUZA *et al.*, 2010; BARBOSA *et al.*, 2020). This information serves as a subsidy for studies with bacteria resistant to conventional antibiotics as they indicate the potential application of these substances.

Urinary tract infections are often associated with antibiotic-resistant microorganisms that are difficult to treat. Ebani *et al.* (2018) evaluated the antimicrobial activity of five essential oils obtained from seasoning plants against multiresistant strains of *Escherichia coli*, *Enterococcus* spp., *Candida albicans* and *Candida famata* previously isolated from dogs and cats with urinary tract infections. Oils of *O. vulgare* and *Thymus vulgaris* showed the best results against all tested isolates showing MIC values ranging from 0.293 mg/ml to 1.183 mg/ml for *O. vulgare*, and from 0.146 mg/ml to 2.342 mg/ml for *T. vulgaris*.

Acne-associated bacteria such as *Propionibacterium acnes* and *Staphylococcus epidermidis* often develop resistance to antibiotics due to the selective pressure they are exposed to in treating this condition. Taleb *et al.* (2018) using the disk diffusion test observed the susceptibility of these bacteria to seven essential oils. OEOV showed greater halos of inhibition than the antibiotics erythromycin and clindamycin and OEOV also exhibited the best antimicrobial activity with a MIC of 0.34 mg/mL and a minimal bactericidal concentration (MBC) of 0.67 mg/mL against *P. acnes*; and MIC of 0.67 mg/ml and MBC of 1.34 mg/ml against *S. epidermidis*. The authors also observed an antibiofilm

action, and the nanoemulsion formulated with the essential oil and applied to mice with acne, showed a superior curative effect compared to the reference antibiotic.

Clinical isolates that produce carbapenemases, enzymes responsible for resistance to carbapenems, have spread throughout the world and are associated with higher rates of morbidity and mortality. *Klebsiella pneumoniae*, *Serratia marcescens*, and *Acinetobacter baumannii* isolated from hospitalized patients and confirmed for the presence of carbapenemases by searching for *bla* genes were challenged against EOOV. In this research, Vasconcelos *et al.* (2019) observed that EOOV exhibited significant inhibitory effects against the bacterial strains tested, with a MIC of 0.059% v/v for *K. pneumoniae* and *S. marcescens* and 0.015% v/v for *A. baumannii*. Bacterial survival curves showed a linear decrease in viable cell counts of approximately  $5 \log_{10}$  CFU/mL, achieving complete inhibition after a period of 4 hours.

Hospital clinical isolates of drug-resistant *Staphylococcus aureus*, *Streptococcus pyogenes*, *E. coli* and *Streptococcus typhimurium* were tested against essential oils from various aromatic plants. The oils of *Mentha cervina*, *Ocimum basilicum* and *O. vulgare* were the most effective by the disk diffusion technique and the EOOV showed the lowest MIC values (0.025 mg/mL) for *S. aureus* and *S. pyogenes* (HELAL *et al.*, 2019).

*Staphylococcus* spp. are bacteria normally associated with skin infections and with recurrent treatment failure due to antibiotic resistant strains. In research developed by Ebani *et al.* (2020) EOOV showed the best antibacterial activity, among nine plant oils, against all selected strains, with MIC ranging from 0.29 to 0.58 mg/mL, showing potential for the control of human and animal infections.

Although studies reveal the potent antimicrobial activity of EOOV, its strong odor and taste may limit its application. In this sense, the use of nanoparticles can be an option for the applicability of this oil. Silver nanoparticles and EOOV showed bactericidal effects against Gram-positive and Gram-negative. When combined, the products exhibited additive or synergistic antibacterial effects for strains such as methicillin-resistant *S. aureus* (MRSA), *E. coli* producing extended-spectrum  $\beta$ -lactamase (ESBL) and *E. coli* producing carbapenemase (SCANDORIEIRO *et al.*, 2016).

Biofilm-producing strains also cause difficult-to-treat infections. Thus, EOOV was evaluated on the biofilm of Gram-positive bacteria and in association with antibiotics such as norfloxacin, oxacillin and gentamicin. The interaction of essential oils and norfloxacin was effective in destroying the biofilm, suggesting that the combination of antimicrobials from different sources may be promising therapeutic strategies (ROSATO *et al.*, 2020).

In an attempt to discover new healing and treatment strategies, several researchers have been researching the different aspects of medicinal plants. Castronovo *et al.* (2020) analyzed a pool of plants belonging to the species *O. vulgare* through their microbiota and found a high diversity of

genera capable of inhibiting human pathogens, including strains resistant to several antibiotics. These data reveal that the association of medicinal plants and their microbiome are sources of antimicrobial bioactive compounds with therapeutic value, especially for multiresistant pathogens.

When evaluating the mechanisms of action against *Salmonella* Enteritidis, Barbosa *et al.* (2020) saw that sublethal concentrations of EOOV can lead to bacterial death acting at different levels: alteration of stress-related chaperones and proteins; alteration in cell communication and penetration into the bacterial cell acting on the synthesis of genetic material.

Another widely studied potential of EOOV is its role as a preservative in animal products, especially cheeses (KIM; MARSHALL; WEI, 1995; GULLUCE *et al.*, 2012; GURDIAN *et al.*, 2017; BEDOYA-SERNA *et al.*, 2018; KHORSHIDIAN *et al.*, 2018; SANTOS *et al.*, 2022). However, there are limitations in the use of this essential oil in the food industry because essential oils (EO) can change the organoleptic characteristics of the product and the constituents of the food can interact with the oil, thus causing an increase in the concentration needed to achieve the effect desired (TAJKARIMI; IBRAHIM; CLIVER, 2010; HYLDGAARD; MYGIND; MEYER, 2012).

Thus, studies on the use of EOOV in food preservation should be further developed, thus seeking alternatives for the use of this EO as a natural way of preserving food.

#### **4. ANTIBACTERIAL ACTION OF CARVACROL**

The antimicrobial activity is a result of the interaction of essential oil components, but, in some cases, compounds tested in isolation were also effective in controlling microorganisms. The activities of EOs of the genus *Thymus* and *Origanum*, for example, have been attributed to their phenolic components such as thymol and carvacrol (KIM; MARSHALL; WEI, 1995; BURT; REINDERS, 2003; BUSATTA *et al.*, 2007).

Thymol and carvacrol are structurally similar components of EOOV. Generally, the antimicrobial activities of EO are difficult to correlate with a specific compound due to its complexity and variability; however, some researchers have stated that there is an association between the chemical composition of the most predominant compounds in the essential oil and the antimicrobial activity (EL ABED *et al.*, 2014).

Carvacrol is responsible for increasing the permeability of the microbial cytoplasmic membrane, causing loss of cytoplasmic ATP. This action is due to its ability to interact with the cytoplasmic membrane, being able to dissolve in the lipid bilayer, aligning itself between the fatty acid chains (ARAUJO; LONGO, 2016). The presence of the hydroxyl group (OH) in the molecule of these phenolic compounds is an important agent against bacteria (ULTEE; BENNIK; MOEZELAAR, 2002).

Carvacrol is one of the major compounds in OEOV and in the essential oil of several other plants, so it is often evaluated in isolation for its potential against several pathogens. In this sense, strains of *S. aureus* were isolated from pasteurized milk and shrimp where antibiotic resistance was detected in 80% of them and about 34% were resistant to oxacillin and vancomycin (OVRSA). Despite this, all were sensitive to carvacrol by the disk diffusion method and by the microdilution test, carvacrol had MIC values of 0.25 mg/mL and MBC of 0.5 mg/mL against OVRSA (VASCONCELOS *et al.*, 2017).

Extended spectrum  $\beta$ -lactamase-producing bacteria (ESBL) encode the  $\beta$ -lactamase enzyme that confers resistance to most  $\beta$ -lactam antibiotics, generating a great constant challenge to antibiotic therapy. *E. coli* ESBL was inhibited by carvacrol with MIC of 450  $\mu$ g/ml. This action was time-dependent with a reduction of 2 log CFU/mL after sixty minutes and complete inhibition after two hours. According to the authors, carvacrol has the ability to change the integrity of the membrane, resulting in the release of cellular content with potential application in bacteria causing urinary tract infection (KHAN *et al.*, 2017).

Due to its antimicrobial activity, carvacrol was used in association with cinnamaldehyde to inhibit *Acinetobacter baumannii*. The mixture increased the expression of heat shock proteins, such as groES, groEL, dnaK, clpB and the catalase katE, and it was observed that carvacrol exerts a potent bactericidal activity, leading the bacteria to synthesize reactive oxygen species in response to the stress caused by it (MONTAGU *et al.*, 2016).

In the current scenario, the interest in using natural antimicrobials in animal production has increased and compounds of essential oils have been evaluated to reduce colonization by pathogens. Thus, Szott *et al.* (2020) added carvacrol to the feed (120 mg/kg of feed) of birds before slaughter age and observed a significant reduction in colonization by *C. jejuni* in the initial period of growth, opening space for studies to confirm the efficacy and commercial suitability and economical of the compost. Giovagnoni *et al.* (2020) analyzed the integrity of the Caco-2 cell monolayer and the findings indicate that carvacrol and thymol are candidate compounds for the control of *Salmonella Typhimurium*.

To promote the best antibacterial action, carvacrol was incorporated into nanoparticles and these were incorporated into dissolution microneedles in order to promote direct action on infected wounds. Effectiveness in releasing carvacrol at the wound site and a two- to four-fold increase in antimicrobial activity were observed in an ex vivo model (MIR *et al.*, 2020). Otherwise, García-Salinas *et al.* (2018) evaluated the components of essential oils and observed action against *E. coli*, *S. aureus* and biofilm. An interesting fact of this research is that carvacrol, cinnamaldehyde and thymol presented lower cytotoxicity than chlorhexidine, usually used as a sanitizer.

## 5. CONCLUSIONS

The antibacterial activity of EOOV and carvacrol has been widely reported in the literature, mainly associated with the control of foodborne pathogens due to the plant's spice character. However, when research is restricted to antibiotic-resistant bacteria, the number of works significantly reduces. Publications involving the EOOV show the use of more preliminary methodologies such as disk-diffusion and determination of the minimum inhibitory and bactericidal concentration. There is still a paucity of data on the mechanisms of antibacterial action. As for carvacrol, which integrates the composition of several essential oils, techniques aimed at antibacterial action are observed, as well as the molecular mechanisms of this activity, as well as tests applied to more complex models. The potential of EOOV and carvacrol as alternatives for the control of antibiotic-resistant bacteria alone or in association with other antimicrobial substances is undeniable. There is an urgent need for therapeutic alternatives to control resistant microorganisms. Thus, substances extracted from spice plants, due to their low toxic potential, should be further studied, particularly on the molecular basis of their antibacterial mechanism of action. In this way, it will be possible to move towards its use in the promotion of single health.

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