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RESEARCH ARTICLE

THE ESSENTIAL OILS IN THE QUORUM-SENSING

Flores-Encarnación, M.[1*], Valentín-Aguilar I.[1], Aguilar-Gutiérrez G.R.[2], Martínez-Alvarado, K.[1] and Cabrera-Maldonado, C.[3]

[1]Laboratorio de Microbiología Molecular y Celular. Biomedicina, Facultad de Medicina, Benemérita Universidad Autónoma de Puebla. Puebla. Puebla, México

[2]Centro de Investigación sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México

[3]Depto. de Microbiología, Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Puebla, Puebla, México

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ABSTRACT

In the bacterial communication intervene different signaling molecules, which control different bacterial processes such as the synthesis of antibiotics, bioluminescence, biofilm development, sporulation, virulence. Most of these processes are decisive in bacterial pathogenesis. Inhibition of bacterial quorum sensing offer an alternative to control infections. These allow the bacterial strains that cause infections to become more susceptible to antimicrobial agents.

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INTRODUCTION

The quorum sensing is a communication phenomenon in bacteria dependent by cell population density (Mangwani *et al.*, 2012; Waters and Bassler, 2006). This bacteria phenomenon was originally discovered in *Vibrio fischeri* and *V. harveyi*. In the bacterial communication intervene different signaling molecules that have called autoinducers, which have low molecular weight and are excreted and accumulate in the extracellular environment, controlling different bacterial processes, for example the synthesis of antibiotics and bioluminescence production (Dunlap, 1999; Flores-Encarnación *et al*., 2011; Voloshin and Kaprelyants, 2004; Winzer and Williams, 2001). Autoinducers have been reported in both Gram-positive and Gram-negative bacteria. In Gram-positive bacteria, autoinducers are constituted by amino acids, fatty acids and peptides (Lyon and Novick, 2004; Miller and Bassler, 2001; Voloshin and Kaprelyants, 2004). In Gram-negative bacteria, autoinducers are constituted by acyl-homoserine-lactones (Flores-Encarnación *et al*., 2011). In bacterial quorum sensing, autoinducers regulate important events such as biofilm development, stress responses, sporulation, competence, virulence, bioluminescence, exopolysaccharide secretion (Mangwani *et al*., 2012; Weber *et al*., 2009). Most of these processes are decisive in bacterial pathogenesis. On the other hand, it has been reported that several essetial oils have demonstrated antimicrobial effects against pathogenic bacteria, including bacteria forming biofilm (Jamal et al., 2018). In this context, many essential oils have showed also some bacterial anti-quorum sensing properties (Camele*et al*., 2019; Poli *et al*., 2018). Therefore, this work shows the most relevant aspects of some essential oils and the effect on bacterial quorum sensing.

***Corresponding author: Flores-Encarnación, M.,**
Laboratorio de Microbiología Molecular y Celular. Biomedicina, Facultad de Medicina, Benemérita Universidad Autónoma de Puebla. Puebla. Puebla, México.

ESSENTIAL OILS AND ANTIBACTERIAL PROPERTIES: The infectious diseases caused by bacteria, fungi, viruses or parasites represent of the causes of morbidity and mortality in the world; they are included in the list of the ten leading causes of death worldwide (Saranraj and Devi, 2017). The emergence of bacterial infections, as well as resistance to antibiotics, have been two important factors that have contributed significantly in the search for new substances with antimicrobial properties. The origin of emerging infectious diseases is associated to social and economic conditions as well as environmental and ecologic factors. A substantial risk of wildlife zoonotic and vector-borne emerging infectious diseases exists at developing countries (Fenollar and Mediannikov, 2018; Jones *et al*., 2008). Today, the USA has recorded the highest number of COVID-19 cases and deaths, further the rise in multidrug-resistant bacterial infections that are undetected, undiagnosed, and increasingly untreatable threatens the health of people in the USA and globally. Thus, in the midst of the COVID-19 pandemic it is not possible to ignore the antimicrobial resistance (Strathdee *et al*., 2020).

The persistence of antibiotic resistance urges the need of finding new therapies against the multi-drug resistant bacteria. So, extracts from different parts of plants have been widely explored for their capability in modulating bacterial drug resistance (Yap *et al*., 2014). In this sense, the essential oils have demonstrated antibacterial, antifungal, antiviral and insecticidal properties (Gracia-Valenzuela *et al*., 2012; Kim and Park, 2013; Wojnicz *et al*., 2012). Por example, the *Lippia berlandieri* (oregano), *Thymus vulgaris* (thyme) and *Cinnamomum verum* (cinnamon) essential oils have shown antibacterial activity, which is attributed to phenolic compounds it contains, such as carvacrol and thymol. Usually, terpenes are considered to be major essential oils compounds (Amiri *et al.*, 2020; Flores-Encarnación *et al*., 2016). The aromatic essential oils are secondary metabolites produced by plants in order to provide a defense function or attraction. The substances are obtained from plant materials as flowers, leaves, fruits, branches, seeds, bark by different methods (Butkiené *et al*., 2015). In other plant products such as *Syzygium aromaticum* (clove), the main component of essential oil is eugenol (68.52%); caryophyllene is present in trace amounts (Fu *et al*., 2007).

The T. vulgaris essential oil contains thymol (57.7%), Origanum majorana L. essential oil (marjoram) contains terpinen-4-ol (30.41%), Lantana camara L. essential oil (lantana) contains bicyclogermacrene (26.1%) and β-caryophyllene (24.4%), Salvia officinalis L. essential oil (salvia) contains α-thujone (41.48%) (Sousa *et al*., 2010; Yap *et al*., 2014). Some studies reported that essential oils have antibacterial activity on both Gram-positive and Gram bacteria. It has been reported that Gram-positive bacteria are more sensitive to essential oils that Gram-negative bacteria (Amiri *et al*., 2020; Flores-Encarnación *et al*., 2016). The *Staphylococcus aureus* strains have been more susceptible to a high number of essential oils: eucalyptus, lemongrass, patchouli, black pepper, clary sage, tea tree, vetiver. The antibacterial activity has been recorded at values below 0.30 $mgmL^{-1}$ (Flores-Encarnación *et al*., 2020; Silva and Fernandes-Junior, 2010; Teles-Andrade *et al.*, 2014). It has been reported that the Gram-negative bacteria are more resistant to the action of essential oils because they have an envelope consisting of lipopolysaccharides linked to outer membrane, which restrict diffusion of hydrophobic molecules (Nazzaro *et al*., 2013). So far, some studies have been reported regarding the antibacterial action mechanism of essential oils. The one that has been studied the most is the destabilization of bacterial membranes because essential oils are hydrophobic subtances that penetrate the bacterial membranes, leading to disruption of cell membrane integrity (O'Bryan *et al.*, 2015). It results in changes in bacterial membrane structure, alteration of the cell permeability, potassium leakage from cells, changes in pH gradient and ATP production, modification of bacterial quorum sensing (Flores-Encarnación *et al*., 2020; O'Bryan *et al*., 2015).

BACTERIAL QUORUM SENSING

As mentioned earlier, quorum sensing is a communication phenomenon in bacteria dependent by cell population density (Mangwani *et al.*, 2012; Waters and Bassler, 2006). Bacteria continually generate autoinducers, as signaling molecules, which accumulate in the local environment as the population density increases. Once a threshold concentration is reached, the autoinducers interact with a receptor protein, causing a coordinated change in gene expression in the population (Abisado *et al*., 2018). Gram-negative bacteria communicate using small molecules as autoinducers, are constituted by acyl-homoserine-lactones, while Gram-positive bacteria autoinducers mainly are constituted by short oligopeptide, regulating cell events such as production of secreted toxins, virulence factors, biofilm matrix components, DNA conjugation, stress responses, sporulation, competence, bioluminescence, exopolysaccharide secretion (Abisado *et al*., 2018; Flores-Encarnación *et al*., 2011; Lyon and Novick, 2004; Mangwani *et al*., 2012; Miller and Bassler, 2001; Voloshin and Kaprelyants, 2004; Weber *et al.*, 2009). It has been reported that final result of the action of autoinducers isto modulate the transcription factor's activity effecting gene expression.

So, the Agr system regulate adhesion and production of virulence factors in *S. aureus*; the PlcR/PapR system controls the production of virulence factors in *Bacillus cereus*; the LuxI/LuxR system control the biofilm production and formation in *Pseudomonas aeruginosa* (Rutherford and Bassler, 2012). Below are some examples of autoinducers and the cellular processes they produce in some pathogenic bacteria. So, N- (3-oxo-octanoyl)- acyl-homoserine-lactone induces the synthesis of virulence enzymes and biofilm formation in *P. aeruginosa* and conjugation in *Agrobacterium tumefaciens*; N- (3-oxohexanoyl)-acyl-homoserine-lactone induces the bioluminescence production in *V. fischeri*, the motility in *Yersinia pseudotuberculosis*, the carbapene synthesis in *Erwinia carotovora* and the synthesis of exopolysaccharides in *Erwinia stewartii* (Flores-Encarnación *et al*., 2011; Hall-Stoodley *et al.*, 2008; Winzer and Williams, 2001). Other authors have reported effects associated to autoinducers such asthe synthesis of lectin, exotoxin A, pyocyanin and elastase in P. aeruginosa (during bacterial growth and infection), and synthesis and secretion of hemolysins, protein A, enterotoxins, lipases, and fibronectin protein in S. aureus. At least those virulence factors help bacteria evade the host immune and obtain nutrition from the hosts (Jiang *et al*., 2019).

THE ESSENTIAL OILS IN THE BACTERIAL QUORUM-SENSING: In hibition of bacterial quorum sensing offers an alternative to control infections. These allow the bacterial strains that cause infections to become more susceptible to antimicrobial agents (Martínez-Matamoros et al., 2016). In this context, some essential oils have been found to have the potential to impede bacteria-bacteria communication, acting as antimicrobial agents (Ahmad *et al.,* 2015). It has been reported that *Thymus daenensis* plant contains essential oils such as carvacrol, γ- and α-terpinene, which showed a strong antimicrobial activity. Carvacrol inhibited bacterial quorum sensing limiting significantly the biofilm formation of *S. aureus* (Kerekes *et al.*, 2013; Sharifi *et al.*, 2018). It has been reported also that essential oils containing phenolic compounds such as eugenol, thymol (in addition to carvacrol) have the strongest antimicrobial activity. Monoterpenes such as α-pinene and limonenehave inhibited biofilm formation in a higher degree than terpene alcohols such as terpinene-4-ol and linalool. The main target of these components is the cell wall and cytoplasmic membrane or proteins embedded in the membrane (Burt 2004; Dorman and Deans, 2000; Kerekes et al., 2013).

The α-pinene is also contained in rosemary essential oil; linalool and α-humulene are present in rose essential oil; limonene is present in lavender essential oil (Olivero *et al.*, 2011; Wom *et al*., 2009). Other mechanisms that have been suggested for anti-quorum sensing activity are the following: inhibition of signal molecule biosynthesis or acyl- homoserine-lactone signal reception; the enzymatic inactivation and biodegradation of quorum sensing molecules; a possible competitive inhibition with the acyl-homoserine-lactone receptor given the apolar nature and relative size of the components of these essential oils (Defoirdt *et al*., 2004; Hentzer and Givskov, 2003; Olivero *et al.*, 2011; Vattem *et al*., 2007). It has been reported that the essential oils from *Lippia origanoides* showed anti-quorum sensing activity at the concentrations of 2.5-25.0 $\mu g mL^{-1}$ and that thymol and carvacrol were responsible of this activity (Cáceres *et al*., 2020; Cervantes-Ceballos *et al.*, 2015). Finally, it is important that more studies are carried out on interruption of bacterial quorum sensing by essential oils as a possible alternative to control microbial pathogenesis, or to complement the treatment of bacterial infections by interrupting the intercellular communication.

Conclusion

Nowadays, the problem of antibiotic resistance has spread throughout the world. Bacteria have developed various resistance mechanisms to antibiotics. For this reason, the search for new substances with antibacterial activity has been important. Thus, essential oils represent a possible alternative by showing antimicrobial, anti-biofilm and anti-quorum sensing properties.

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