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The Essential Oils and the Effect on Infection-Causing Pathogenic Viruses

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Abstract: *It has been necessary to search for new substances to combat infectious diseases caused by bacteria, especially bacteria that are multi-resistant to antibiotics. The same happens to be able to fight some viral diseases, especially emerging infections. As result of the above, the use of various substances of plant origin have been proposed. In this context, essential oils of plants, composed of aldehydes, alcohols, terpenoids and other compounds, have found wide application as alternatives to conventional therapy and food preservation, as also the treatment of various viral diseases.*

Keywords: *Essential oil, pathogen, virus, antiviral, antibacterial.*

1. INTRODUCTION

The antibiotic resistance that bacteria have shown has been one of the great public health problems that have been registered in the world. Microorganisms seem to adapt quickly to their environment, especially to stressful environmental conditions and the presence of antibiotics or disinfectants used by man (Marton *et al*., 2016). For this reason, it has been necessary to search for new substances to combat infectious diseases caused by bacteria, especially bacteria that are multi-resistant to antibiotics. As result of the above, the use of various substances of plant origin have been proposed (Flores-Encarnación *et al*., 2016). Different research groups in the world have reported the use of plant extracts or their derivatives, which have antibacterial properties. As antibacterial agents, the essential oils act against a wide range of pathogenic bacteria including *Bacillus cereus, Listeria monocytogenes, Staphylococcus aureus, Salmonella typhimurium, Shigella dysenteriae, E. coli* O157:H7, uropathogenic *E.coli* (Al-Shuneigat *et al.*, 2014; Flores-Encarnación *et al*., 2018; Hussein *et al.*, 2014; Sambyal *et al*., 2017; Shuaib *et al*., 2016; Upadhyay *et al*., 2013). In the last decades, numerous infectious diseases have emerged and re-emerged affecting to humanity. As microbial causative agents have been the so-called 'exotic agents', which have been impacted to public health systems due to limited experience in case management and lack of appropriate resources (Ahmed *et al*., 2017). In most cases, these 'exotic agents' are zoonotic agents transmitted directly from animals to man or via vectors (Feldmann *et al*., 2002). As they are new infectious diseases for humans, they often lack the necessary experience to combat these infections, both in the use of antimicrobials (for example, antivirals) and in the existence of vaccines (Ahmed *et al*., 2017). Therefore, this work shows the most relevant aspects ofsome essential oils and the effect of them on infection-causing viruses of medical importance.

2. The Essential Oils

Plants can produce different types of metabolites which have been exploited by humans with beneficial roles. So, many of the secondary metabolites that are produced in plants have been used as pesticides over time (Adeyemi, 2010). As is known, primary metabolites include amino acids, simple sugars, nucleic acids and lipids are compounds necessary for cellular processes, while secondary metabolites include compounds produced in response to stress, such as the case when acting as a repellent to herbivorous organisms or in response to external stimuli such as nutritional changes (Adeyemi, 2010; Hamid *et al.*, 2011). In addition to use as a pesticide, plant extracts or their metabolites have been used for centuries to treat infectious diseases and they are considered as an important source of new antimicrobial agents (Bereksi *et al*., 2018; Cowan, 1999). Several works have been done to examine the antimicrobial effects of herbal plants extracts, including roots, stem, leaves or flowers (Abbassi and Hani, 2012; Abu-Shanab *et al.*, 2005; Cowan, 1999). Currently, the antimicrobial properties of plant extracts and essential oils and the research of alternatives for treatment of infectious diseases are being studied.

Essential oils of plants are composed of a mixture of aldehydes, alcohols, terpenoids and other compounds (Diao *et al*., 2013). Currently the plant products have found wide application as alternatives to conventional therapy and food preservation, as also the treatment of various diseases by theirs antioxidant and anti-inflammatory properties (Patra and Baek, 2016; Rincón-Mejía *et al.*, 2012; Sacchetti *et al*., 2005). Also they have been associated with modulation of various genetic pathways (Khoury *et al*., 2016). In recent years there has been increasing interest in the use of biologically active organic compounds that have the ability to eliminate pathogenic bacteria; this is mainly due to the resistance that bacteria have developed to antibiotics (Marston *et al.*, 2016). Examples of essential oils that have shown insecticidal, antioxidant, antibacterial, antifungal and antiviral properties are: *Lippia berlandieri* (oregano), *Thymus vulgaris* (thyme), *Cinnamomum verum* (cinnamon) and others. These essential oils contain phenolic compounds, such as carvacrol and thymol (monoterpenic substances), as main components of potent antimicrobial activity (Ali *et al*., 2015; Burt, 2004; Cowan, 1999; Flores-Encarnación *et al*., 2016). Studies reported by some authors have shown that the *S. 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 $mgmL^{-1}$ (Teles-Andrade *et al.*, 2014). In general, it has been reported that Gram-positive bacteria are more sensitive to natural products that Gram-negative bacteria (Flores-Encarnación *et al*., 2016; Silva and Fernandes-Junior, 2010; Trombetta *et al.*, 2005). As it is known Gram-negative bacteria have an envelope consisting of lipopolysaccharides linked to outer membrane, which restrict diffusion of hydrophobic molecules (Nazzaro *et al.*, 2013). Gram-negative bacteria require greater concentrations of essential oils to inhibit their growth (Trombetta *et al*., 2005). The mechanisms from antibacterial activity of essential oils have been determined. The essential oils are hydrophobic subtances that penetrate the bacterial membranes, leading to disruption of cell membrane integrity; it results in the destabilization of bacterial membranes, changes in bacterial membrane structure, alteration of the cell permeability, disturbance on respiration, modification of bacterial quorum sensing, potassium leakage from cells, effects on membrane potential (proton translocation), changes in pH gradient and ATP production of bacterial cell dissolution of the proton motive force and subsequent reduction in ATP synthesis (Flores-Encarnación *et al*., 2016; Flores-Encarnación *et al*., 2019; Nostro and Papalia, 2012; O'Bryan *et al.*, 2015; Rajendran *et al.*, 2014).

3. Emergence of Viral Infections

In recent years, outbreaks of different infectious diseases have been recorded worldwide (Ahmed *et al.*, 2017). Some urban practices, such as the change in land use, the uncontrolled growth of populations, frequent contact with domesticated and wild animals, the human invasion of natural areas, the deficiency in health services (among them, the no use of vaccines) and the climate change, have been factors that promoted the emergence and re-emergence of various infectious diseases, including those of viral origin. In this case, the passage of certain viruses present in wild and domestic animals to man has been observed, causing the emergence of new diseases (Ahmed *et al.*, 2017; Daszak *et al*., 2001; Ołpiński, 2012; Rahim and Uddin, 2017).Viral infections that are considered emerging today are not new. For example, the dengue fever emerged simultaneously in South-East Asia, Africa, and North America during the 18th century, whereas influenza (Spanish flu) emerged at the beginning of 20^{th} century, killing between 25 and 40 million people in five continents (Chastel,

2007; Taylor *et al.*, 2001). The severe acute respiratory syndrome virus (SARS), bird flu, swine flu, Ebola virus disease, Zika and Chikungunya fever have emerged in recent years (Ahmed *et al*., 2017). In all cases, the participation of animal reservoirs or vectors are considered for the transmission of the viral disease to human populations.

4. Essential Oils and Pathogenic Viruses

Over the years, different properties that essential oils possess have been observed. One of the most important properties for humans is that them have anti-inflammatory, antioxidant and antiviral activity. Inflammation is a physiological response to a variety of agents including infectious microorganisms, toxic chemical compounds and physical injury (Pérez *et al*., 2011).For example, the seed essential oil of *Afromomum melengueta* (widespread across tropical Africa as well as on some islands of the Indian Ocean) showed great potential antioxidant and anti-inflammatory properties (Jazet *et al*., 2008). It has been reported that essential oil of *A. melengueta* is rich in sesquiterpenes and monoterpenes like limonene, 1, 8-cineole, pinenes, linalool and (E)-b-ocimene, as the major components (Pérez *et al*., 2011). The essential oil of *Aucoumea klaineana*, *Canarium scheinfurthii*, *Calycorectes sellowianus* also have shown anti-inflammatory properties and it has been reported that they contain as components; alfa-pinene, alfa-phelandrene, para-cymene, 1, 8-cineole, limonene, alfa-terpineol, guaioland beta-caryophyllene (Apel *et al*., 2010; Jazet *et al*., 2008). The essential oil of *Cinnamomum insularimontanum* and its major constituents, such as trans-cinnamaldehyde, caryophyllene oxide, L-borneol, L-bornyl acetate, eugenol, beta-caryophyllene, E-nerolidol, and cinnamyl acetate have anti-inflammatory activity (Tung *et al.*, 2008). Essential oils contained in *Citrus sinensis* L. (*Rutaceae*) and *Citrus sunki* (Hayata) Tanaka (*Rutaceae*) showed anti-inflammatory activity. It has been reported that they contain as major components dl-limonene and beta-myrcene (Jazet *et al.*, 2008; Yang *et al*., 2010). It has been reported that in inflammation a variety of intracellular signaling pathways are activated, which comprise cell surface receptors, tyrosine kinases and transcription factors, leading to over expression of pro-inflammatory genes. Cellular components such as mast cells and leukocytes recruit to the site of damage causing a respiratory explosion. The respiratory explosion is accompanied by increased oxygen consumption: the releasing and accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) occurs at the site of damage (Grivennikov *et al*., 2010; Kodydkova *et al*., 2013; Martins de Lavor *et al.*, 2018; Vendramini-Costa *et al*., 2012). When ROS and RNS production is greater than cellular antioxidant capacity (by superoxide dismutase, glutathione peroxidase, catalase and others), oxidative stress can damage DNA, proteins, and lipids. In addition to the above, in the inflammatory process diverse protein kinases are activated altering cell proliferation. It has been observed that in the chronic inflammatory process, the excessive activation of signaling pathways causes also the activation of certain transcription factors (such as NF-κBand activator protein-1, AP-1). The cyclooxygenase (COX) and inducible nitric-oxide synthase (iNOS) enzymes, cytokines and chemokines have also been reported to play a role in oxidative stress-induced inflammation (Federico *et al*., 2007; Martins *et al*., 2018; Wu *et al*., 2014).

Another of the properties observed in essential oils is their antioxidant activity. Essential oils contain more than 200 diverse compounds mostly made of monoterpenes and sesquiterpenes and branched chemicals as aliphatic aldehydes, ketones, esters and alcohols. The presence of these substances in essential oils produces antioxidant and antimicrobial effects (Moattar *et al*., 2018; Pellegrini *et al.*, 2018). It's known that ROS (the superoxide anion and hydroxyl radical) are cytotoxic and promote tissue injury, while the antioxidant substances act as the major defense mechanism protecting to cells from the damages caused by free radicals (Moattar *et al*., 2018).Essential oil of *Calamintha officinalis* (commonly called melissa) has antioxidant activity. Different authors have reported the chemical composition of essential oil of *C. officinalis*,which contains:1,8-cineole, pulegone, limonene, carvone, pulegone, para-menthone, beta-bisabolene, germacrene, beta-bourbonene, piperitenone, trans-caryophyllene, neo-dihydrocarveol, dihydrocarveol, as the major components of their essential oil (Astani *et al*., 2011; Bouchra *et al*., 2003; Morteza-Semnani and Akbarzadeh, 2007; Nickavar and Mojab, 2005).Moattar *et al.*, (2018) observed that essential oil of *C. officinalis* had free radical scavenging activity and that catalase and superoxide dismutase activities significantly were increased. Catalase activity is a major antioxidant defense enzyme that produce the decomposition of H_2O_2 protecting to DNA, proteins, and lipids from oxidative stress.

5. Effect of Essential Oils on Infection-Causing Pathogenic Viruses

In this section, some examples of essential oils and their antiviral activity against pathogenic viruses are are shown. Haddad *et al.*, (2019) report edon A549 human epithelial cells infected with Zika virus that the *Ayapana triplinervis* essential oil inhibited infection. The effect was observed using both essential oil as thymhydroquinone dimethyl ether (main component of this essential oil) at non-cytotoxic concentrations. They reported IC_{50} values of 38 µg mL^{-1} by *A. triplinervis* essential oil and 45 µg mL^{-1} by thymhydroquinone dimethyl ether. This authors proposed that thymhydroquinone dimethyl ether could block the early stages of virus infection (Haddad *et al*., 2019).It's known that Zika virus is an emerging mosquito-borne virus of medical importance. Zika infection has been associated with serious neurological disorders, such as neonatal microcephaly, Guillain-Barré syndrome and meningoencephalitis in infected adults and birth defects in affected infants. Sexual, vertical, and blood transmissions have also been reported (Cao-Lormeau *et al*., 2016; Noorbakhsh *et al*., 2019; Parra *et al*., 2016). Other emerging infections in the world is dengue transmitted by vectors. There is no antiviral drugs for treatment for any of the Flavivirus and an effective vaccine for human use is not yet available to prevent dengue (Ocazionez *et al.*, 2010).

Dengue fever is the most prevalent human arboviral disease in tropical and subtropical regions worldwide. Dengue virus is a global health threat that is primarily acquired through the bites of infected mosquitoes and responsible for over 100 million infections and 20,000 deaths annually (Douglas *et al*., 2020; Murray *et al*., 2013). It has been reported *in vitro* that the *Lippia alba* and *Lippia citriodora* essential oils inhibited the replication of dengue virus serotypes. The use of the *Lippia* sp. essential oils could be a potential resource for treatment of tropical disease like dengue, especially in developing countries (Ocazionez *et al.*, 2010). The *L. citriodora* infusions have been used for the treatment of colds, flu, bronchitis, coughs, asthma and others (Ocazionez *et al.*, 2010; Pascual *et al.*, 2001). It has been reported that *L. alba* essential oil contains as major components: carvone (40-51%), limonene (30-33%) and bicyclesesquiphellandrene (7-9%). The IC_{50} of *L. alba* essential oil for dengue virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) were also determinated. The values reported by authors were: 10.1, 0.4, 32.6 and 21.1 µg mL^{-1}, respectively (da Silva *et al*., 2020; Ocazionez *et al*., 2010). Viral inhibitory effect was not observed by addition of the essential oil after virus adsorption. It seems that inhibitory effect of *Lippia* sp. essential oil is attributed to direct inactivation of virus before adsorption on the host cell (da Silva *et al*., 2020).

Several authors have reported the effect of essential oils on the yellow fever virus. Yellow fever virus belongs to the family *Flaviviridae*. This virus has been responsible for devastating epidemics and for hepatic and hemorrhagic diseases (Gómez *et al.*, 2013).Yellow fever is a viral hemorrhagic fever endemic in South America and sub-Saharan Africa. It is transmitted to humans through the bite of the *Aedes* or *Haemagogus* mosquitoes (Meneses *et al*., 2009; Monath and Barrett, 2003).It has been reported *in vitro* that the *L. alba* and *L. citriodora* essential oils have showed antiviral activity; the major components of this essential oils were reported with: carvone (40-51%), limonene (30-33%) and bicyclosesquiphellandrene (7-9%) in *L. alba* and geranial (19%), neral (15.6%), limonene (11%) and 1,8-cineole (5%) on *L. citriodora* (da Silva *et al*., 2020; Ocazionez *et al*., 2010). To investigate the antiviral mode of action, essential oils were added before and after adsorption of virus to Vero and HeLa. In both cases it was observed the antiviral activity (Gómez *et al., 2013*).It is speculated that direct inactivation of virus by the essential oils can be due to disruption of lipid viral envelope because the major components in the essential oils are terpenes and terpenoids (Meneses *et al*., 2009). Other authors have reported that these compounds have showed anti-HIV activity inhibiting the virus adsorption to target cell and causing inactivation of virus reverse transcriptase (Meneses *et al*., 2009; Sun *et al*., 1996). In case of yellow fever virus, the antiviral effect of *L. alba* and *L. Citriodora* essential oils could be explained by the presence of lipid compounds as carvone, limonene, geranial, neral, and others. Another of the medically important viral infection-causing agents is the herpes simplex virus. Herpes simplex virus (HSV) belongs to the alpha subfamily of the human herpesvirus family and includes HSV1 and HSV2, which are responsible for pandemics of various herpes diseases (Lan and Luo, 2017; Xu *et al*., 2019). HSV1 is transmitted through contact with saliva and causes recurrent cold sores, while HSV2 is transmitted primarily through sexual contact and is associated with urogenital and neonatal infections (Schuhmacher *et al.*, 2003). In this context, essential oils are promising candidates for the topical treatment of recurrent herpes infections. It has been that, the essential oils of *Melaleuca alternifolia*, *Mentha piperita, Thymus vulgaris* and *T. capitatus* have

shown antiviral properties against enveloped viruses. The major components of this essential oils were reported with: terpinen-4-ol (30-48%), γ-terpinene (10-28%), α-terpinene (5-13%), 1,8-cineole (up to 15%), terpinolene (1.5-5%), p-cymene (0.5-12%), α-pinene (1-6%), α-terpineol (1.5-8%) on *M. alternifolia;* menthol (43.8%), menthone (19.7%), menthyl acetate (6.5%), 1,8-cineole (5.0%) on *M. piperita*; thymol (43.9%), carvacrol (14.4%), p-cymene (10.5%), β-caryophyllene (7.0%), γ-terpinene (5.1%); carvacrol (68.6%), p-cymene (4.8%), γ-terpinene (3.0%), and β-caryophyllene (2.9%) on *T. capitatus* (da Silva *et al*., 2020; El Moussaoui *et al*., 2013; Koch *et* al., 2008; Minami *et al*., 2003; Setzer, 2016).It has been reported that these compounds exhibit direct virucidal activity to inhibit intracellular replication, o well interacting with HSV particles, thus inhibiting cell binding and adsorption (Schnitzler, 2019). The mechanism of action of the compounds consists mainly in the direct inactivation of the extracellular HSV2 particles together with a lesser spread of the virus from cell to cell, limiting the production of viral progeny (Toujani *et al.* 2018).

Other essential oils reported with antiviral activity against HVS1 and HSV2 are: *Artemisia douglasiana*, *A. arborescens* and *Eugenia caryophyllus* essential oils (Schnitzler, 2019).The 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is rapidly spreading from its origin in Wuhan City of Hubei Province of China to the rest of the world. It is a positive single-stranded RNA virus from the enveloped coronavirus family. Symptoms of SARS-CoV-2 infection are cough, fever, digestive disturbances, respiratory problems, which cause more than 15% of mortality worldwide (Singhal *et al.*, 2020; Wang *et al.*, 2020). Angiotensin converting enzyme receptor 2 (ACE2), a host cell receptor, has been found to play a crucial role in viral cell entry; therefore, ACE2 blockers may be a potential target for antiviral intervention. It has been reported that geranium and lemon essential oils have powerful ACE2 inhibitory effects, so the components of them are valuable natural antiviral agents that could contribute to prevention of invasion by SARS-CoV-2 in the human epithelial cells (Kumar *et al*., 2020). Recent *in silico* studies reported that organosulfur compounds in garlic essential oil and other natural products, such as baicalin, scutellarin, hesperetin, nicotianamine, glycyrrhizin, (E,E)-α-farnesene, (E)-β-farnesene, and (E, E)−farnesol, have the potential to bind the human ACE2 receptor, thereby possibly blocking SARS-CoV-2 cell entry (da Silva *et al*., 2020; Kumar *et al*., 2020; Thuy *et al.*, 2020).At present, there is no definite treatment or vaccine developed for the coronavirus that causes SARS-CoV-2. More studies have to be done in this regard.

6. Conclusion

The essential oils have shown antioxidant, antibacterial, antifungal and antiviral properties. In the search for new drugs to combat antibiotic-resistant bacterial infections, some essential oils and their components seem to be a potential alternative. The same occurs in viral infections, especially in some emerging infections for which there is neither optimal treatment nor vaccines. At present, essential oils are very likely not going to solve the problem of emerging viral infections, however these substances or their components could be used as prophylactic measures. It is important that more studies are done on the benefits that essential oils can offer for human health.

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