v. 4, n. 67, 2024

International Journal of Health Science

METHYL CHAVICOL: CHEMICAL ASPECTS AND THERAPEUTIC POTENTIAL

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Abstract: Methyl chavicol (MC), also known as estragole and *p*-allylanisole, is a phenylpropanoid found in essential oils and possesses various biological properties. This study was based on a literature review of scientific articles and other publications on the topic. Sources were accessed from recognized databases such as Google Scholar, Scielo, and PubMed, among others. The biosynthesis of MC occurs through the shikimic acid metabolic pathway, involving a series of reactions (decarboxylation, aromatization, and amination) that lead to phenylalanine, cinnamic acid, and the isomers atenol and MC. The synthesis of MC involves the formation of the aryl-allyl C-C bond from phenol, using aryl halides via Stille reaction, aryl Grignard and aryl zinc derivatives, and arylboronic substances. Structural modifications can be performed using the concepts of bioisosterism and classical isosterism. For example, treatment with meta-chloroperbenzoic acid leads to the synthesis of 2-[(4-methoxyphenyl)methyl]oxirane (**2**), which, after reacting with acetic anhydride, yields the derivative 3-(4-methoxyphenyl) propane-1,2-diol (**8**). The therapeutic potential of MC is related to its insecticidal, local anesthetic, anti-inflammatory, antimicrobial, antioxidant, pancreatic lipase inhibitory, and antiproliferative properties. However, its hepatocarcinogenic potential and the carcinogenicity linked to genotoxic metabolites are also highlighted. Based on these findings, MC and its derivatives may represent a therapeutic potential for treating conditions related to inflammatory, oxidative, metabolic, and infectious processes.
Keywords: Methyl chavicol. Chemical aspects. Therapeutic potential.

INTRODUCTION

Natural active substances are compounds extracted from biological sources such as plants, animals, and microorganisms, serving as the basis for many drugs used today (CHAACHOUAY; ZIDANE, 2024; CALIXTO, 2019). These substances can have various therapeutic properties, including anti-inflammatory, antioxidant, antibacterial, antifungal actions, among others, and can belong to different classes of secondary metabolism (NASIM et al., 2022). For example, alkaloids like morphine, extracted from *Papaver somniferum* (poppy), are potent analgesics for the treatment of severe pain and are widely used as medication. Quercetin, a flavonoid found in various plant species, has antioxidant, anti-inflammatory properties and possesses anticancer effects, while the terpenoid ursolic acid, well known in plants like apple and lavender, has anti-inflammatory, antitumor, and antimicrobial activities (CHAACHOUAY; ZIDANE, 2024; CALIXTO, 2019).

Regarding essential oils, these are aromatic compounds extracted from plants that have been used for medicinal and cosmetic purposes, offering a wide range of health benefits. They are complex mixtures of volatile compounds, usually lipophilic, extracted from various parts of plants, including flowers, leaves, bark, stems, roots, and seeds (PEZANTES-ORELLANA et al., 2024). Chemically, essential oils can be monoterpenes, composed of ten carbon atoms, such as limonene and pinene; sesquiterpenes, with fifteen carbon atoms, such as bisabolol and caryophyllene; diterpenes, with twenty carbon atoms, which are less volatile and include cafestol; and phenylpropanoids, such as eugenol and anethole (SOUSA et al., 2023). These compounds have different biological properties, such as anti-inflammatory, antibacterial, and antioxidant, among others (PEZANTES-ORELLANA et al., 2024; SOUSA et al., 2023).

Methyl chavicol (MC), belonging to the class of phenylpropanoids, is a major constituent of essential oils from plants in the families Apiaceae (*Pimpinella anisum* L., "anis"; *Foeniculum vulgare* Mill., "funcho"), Magnoliaceae (*Illicium verum* Hook f., "anis estrelado") and Asteraceae (*Artemisia dracunculus* L., "estragão") (PAULA et al., 2007). Biological activities such as antimicrobial, anti-inflammatory, antilipase, antioxidant, local anesthetic, and insecticidal are attributed to this substance (PAULA et al., 2003; SILVA-ALVES et al., 2013; SILVA-COMAR et al., 2014; SANTOS, 2017). This compound presents significant potential for the synthesis of new derivatives with therapeutic potential (SANTOS, 2017).

Assuming that natural substances are essential for the discovery of new medicines and the development of more effective and safe therapies with lower toxicity and greater compatibility, the present work carried out a review of the literature on the chemical aspects and therapeutic potential of MC.

METHODOLOGY

This work consists of a literature review on the chemical aspects and therapeutic potential of methyl chavicol, a phenylpropanoid found in essential oils of medicinal plants. Keywords such as methyl chavicol, phenylpropanoids, essential oils, synthesis, biological activities, and therapeutic potential were searched in the Health Sciences Descriptors (DeCS). The searches were conducted in the databases of Google Scholar, Scielo, the Latin American and Caribbean Health Sciences Literature (LILACS) through the Virtual Health Library, the PubMed portal managed by the US National Library of Medicine/ National Institutes of Health, and the CAPES Periodicals Portal.

The inclusion criteria adopted for this research were as follows: scientific documents with complete identification, written in Portuguese, English, or Spanish, including study descriptions (full articles, short communications, reviews, case reports, scientific notes, etc.), published in indexed journals and available on scientific platforms, theses, dissertations, and books. Additionally, the reliability and fidelity of the sources, as well as the documentary veracity, were analyzed. Non-indexed documents and references with dubious identification were excluded from this research. Each reference was evaluated based on the title of the work, authors, foundations, objectives, methodologies, results, and conclusions. Concepts were defined based on the consensus of one or more documents (Soares et al., 2018).

RESULTS AND DISCUSSION

BIOSYNTHESIS AND SYNTHESIS OF METHYL CHAVICOL

1-Methoxy-4-prop-2-enylbenzene (Figure 1), also known as methyl chavicol, estragole, and *p*-allylanisole, is a secondary metabolite belonging to the phenylpropanoid class. Its chemical structure, with a molecular mass of 148.2 g/mol, consists of a benzene ring with a methoxy group (-OCH_3) and a propenyl group (-CH_3CHCH_2) at positions 1 and 4, respectively. It is a colorless liquid with an anise-like odor, insoluble in water but soluble in ethanol and chloroform. It is a major constituent of various essential oils from plants in the families Apiaceae (*Pimpinella anisum* L., "anis"; *Foeniculum vulgare* Mill., "funcho"), Magnoliaceae (*Illicium verum* Hook f., "anis estrelado"), and Asteraceae (*Artemisia dracunculus* L., "estragão") (PAULA et al., 2007).

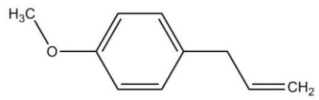

Figure 1. Structural formula of methyl chavicol.

The biosynthesis of MC occurs via the shikimic acid pathway, which is formed by the aldol condensation between phosphoenolpyruvate and erythrose-4-phosphate, two glucose metabolites. From chorismic acid, resulting from the transformation of 5-enolpyruvyl-shikimate 3-phosphate by a 1,4-elimination, aromatic amino acids are formed through intramolecular rearrangement (Claisen rearrangement) to produce prephenic acid (SOUSA et al., 2023). This acid undergoes a series of decarboxylation and aromatization reactions to form phenylpyruvic acid, which produces phenylalanine through a reductive amination. Through the action of phenylalanine ammonia-lyase (PAL), phenylalanine loses its ammonia group, resulting in cinnamic acid. This acid undergoes cytochrome P450-dependent action, receives a hydroxyl group, and generates *p*-coumaric acid. The introduced hydroxyl group undergoes methylation catalyzed by broad-specificity methyltransferase (SAM – specificity methyltransferase), while the reduction process produces the isomers: atenol and methyl chavicol (DEWICK, 2009) (Figure 2).

The typical approach for synthesizing allylphenolic constituents involves forming the aryl-allyl C-C bond. Thus, MC can be obtained through a convergent synthesis in three steps starting from phenol. The first step involves the preparation of the aryl ether through the Williamson reaction. The alkylation of the oxygen in the phenolic hydroxyl readily occurs when the phenoxide ion reacts with methyl chloride. This ion is formed by the deprotonation of the phenolic hydroxyl in the presence of sodium hydroxide (Figure 3A). The next step is a tosylation reaction of the alcohol, where prop-2-en-1-ol has its hydroxyl converted into a tosylate group by reacting with tosyl chloride and excess pyridine (Figure 3B). The formed product, in the presence of sulfuric acid, is protonated, resulting in the subsequent formation of the prop-2-en-1-yl carbocation. This electrophilic species attacks the aromatic ring, replacing one of the hydrogen atoms in a reaction called electrophilic aromatic substitution (Figure 3C) (SANTOS, 2017). However, allylation reactions are generally inefficient or non-selective (SHIMIZU, 1997).

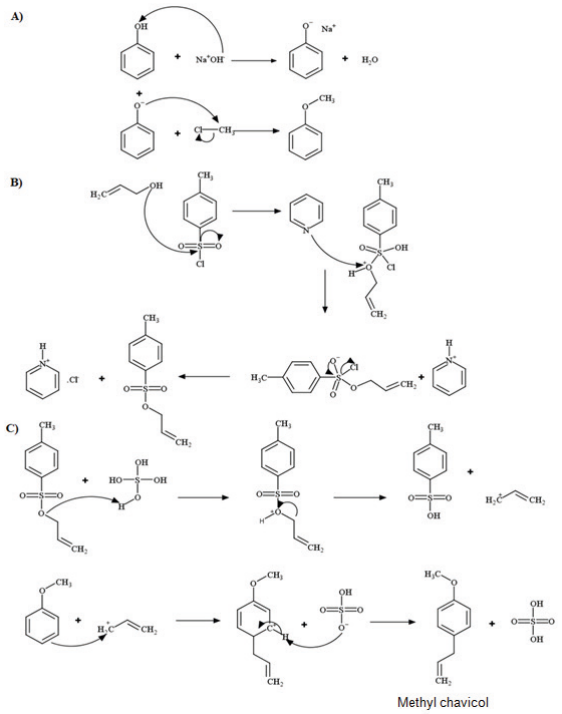

Figure 3. Mechanism of methyl chavicol synthesis.

Other approaches, such as cross-coupling, are preferably used. Efficient procedures involve aryl halides, mainly iodides or bromides, through the Stille reaction. This method consists of the reaction between organostannanes and organic halides catalyzed by palladium, but the use of aryl

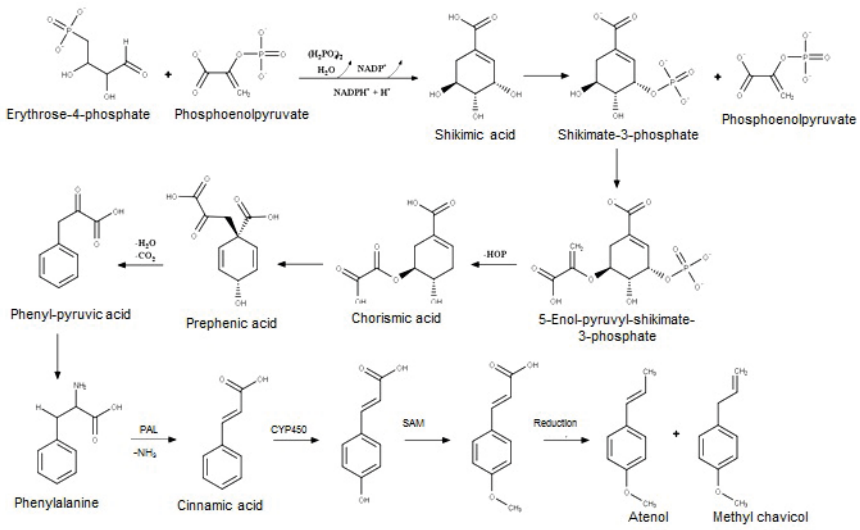

Figure 2. Biosynthesis of methyl chavicol.

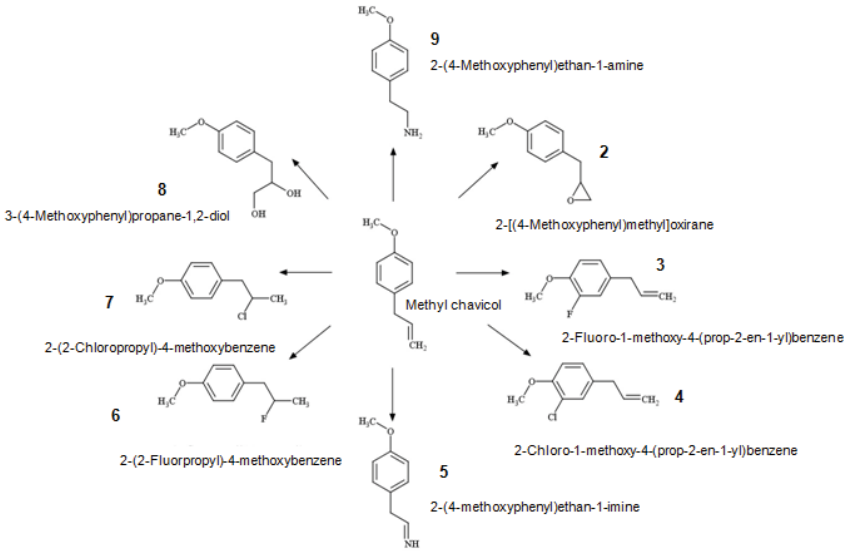

Figure 4. Possible synthesis of methyl chavicol derivatives through the concept of classical isosterism.

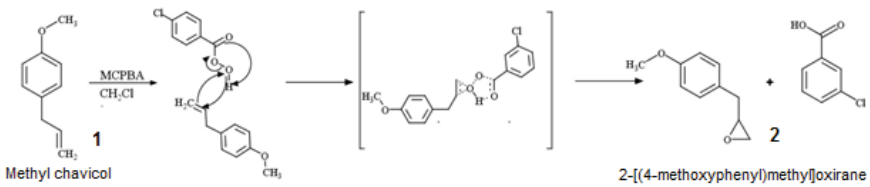

Figure 6. Epoxidation reaction of methyl chavicol using meta-chloroperoxybenzoic acid.

Grignard and aryl zinc derivatives, catalyzed by nickel and/or cobalt, has been reported. Arylboronic substances have also been widely used in palladium-mediated reactions with allyl acetate (BOUYSSI et al., 2002; GOMES et al., 2003; INOUE et al., 2001; KONDO et al., 1994; LITTKE; FU, 1999; WENKERT et al., 1984). Despite the high yields obtained, these metal-mediated reactions have disadvantages since they require strictly anhydrous conditions and/or high temperatures, as well as involving expensive and sensitive reagents, additional additives, or a large amount of catalyst. Moreover, if the target molecule has free hydroxyl groups, a sequence of protection and deprotection must be carefully planned. In any case, when intended for pharmaceutical use, organometallic substances are toxic and must be completely removed (PROTTI et al., 2005).

Alternatively, the generation of the 4-methoxyphenyl cation by photolysis can be readily added to olefins. The reaction of this cation with allyltrimethylsilane would lead to the formation of the corresponding allylated aromatic compound, after the elimination of the trimethylsilyl cation (a good leaving group) (PROTTI et al., 2004; PROTTI et al., 2005).

SYNTHESIS OF METHYL CHAVICOL DERIVATIVES

From MC, it is possible to perform structural modifications on reactive groups to improve biological properties. As shown in Figure 4, the synthesis of derivatives can be based on the concept of classical isosterism, where the groups have the same electronic configuration and similar chemical properties.

MC derivatives can also be synthesized to obtain substances with lower hydrophobicity while maintaining the pharmacophore, using the concept of bioisosterism (Figure 5).

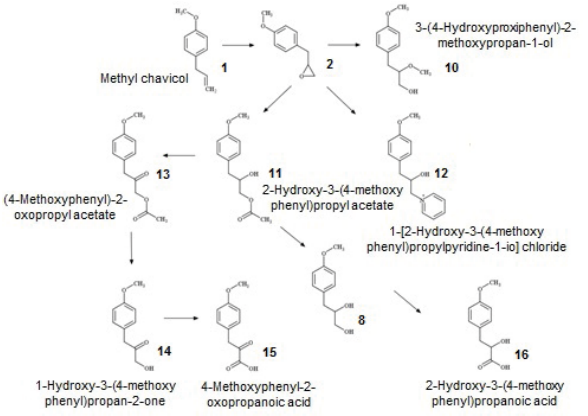

Figure 5. Possible synthesis of methyl chavicol derivatives through the concept of bioisosterism.

Based on the concept of bioisosterism, MC, in the presence of hydrogen peroxide in 4M NaOH (HENBEST; JACKSON, 1967), produced the epoxide compound 2-[(4-methoxyphenyl)methyl]oxirane (**2**) with a low yield (4.4%). However, treatment with meta-chloroperoxybenzoic acid (MCPBA) significantly increased the synthesis of this compound (2) to a yield of 75% (Figure 6) (SANTOS, 2017).

An esterification reaction can lead to the opening of oxirane (**2**) to synthesize derivative (**11**). For this purpose, the epoxide (**2**) is treated with 0.1% (v/v) acetic anhydride at 140°C under vacuum for 2.5 hours, resulting in the formation of diol (**8**) (COLCLOUGH et al., 1961) likely through the hydrolysis of ester (**11**). In this process, the derivative 3-(4-methoxyphenyl)propane-1,2-diol (**8**) is obtained with a yield of 68% (Figure 7) (SANTOS, 2017).

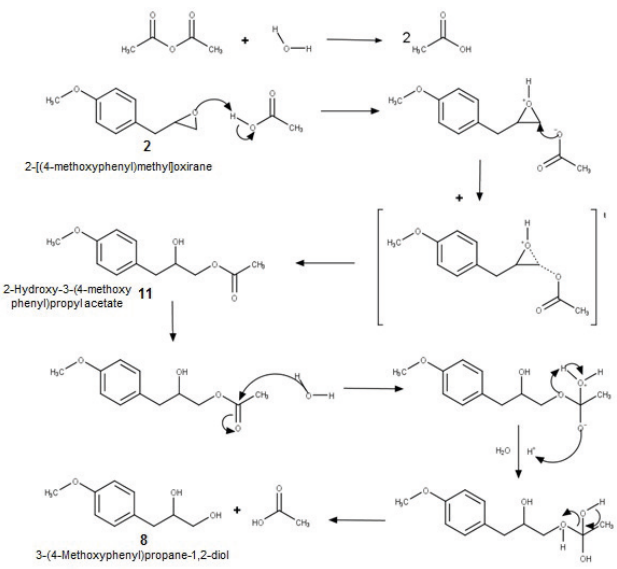

Figura 7. Formação de diol (**8**) via esterificação do epóxido (**2**).

It is important to emphasize that the epoxidation synthesis of derivative **2**, due to its chirality, results in a more versatile compound. Because of the three-membered ring strain and polarity, this derivative is susceptible to reactions with a wide variety of nucleophiles, electrophiles, acids, bases, reducing agents, and some oxidants (**1**). However, hydrogen peroxide, when used as an epoxidizing agent in a basic medium, exhibits low electrophilicity and requires activation to react with olefins either through the conjugation of the hydroperoxide group with multiple bonds or by the action of a metallic catalyst (VON HOLLEBEN; SCHUCH, 1996). Furthermore, this reaction system is more efficient as an epoxidizing reagent in olefins that possess a hydroxyl group (allylic alcohols, homoallylic alcohols, or bis-homoallylic alcohols) (HENBEST; JACKSON, 1967).

Derivative **2** is synthesized via the Prilezhaev reaction using meta-chloroperoxybenzoic acid as the epoxidizing agent. This reaction modifies the starting olefin **1** through a biomolecular electrophilic mechanism, forming a chelate with intramolecular hydrogen bonds in a cyclic structure. Electronic substituents on the peracid increase the electrophilicity of the O-O bond, while electron-donating groups enhance the nucleophilicity of the C-C bond, thereby accelerating the reaction. The reaction rate is influenced by the basicity of the solvent, which can disrupt intramolecular hydrogen bonds. Hence, epoxidation of olefins with peracids is most effective in low polarity, aprotic solvents like dichloromethane (VON HOLLEBEM, SCHUCH, 1996).

The process of opening the epoxide of derivative **2** to synthesize ester **11** results in the formation of diol **8** due to ester hydrolysis. Esterification in acidic medium can be reversed by hydrolysis, where the ester is converted into acid and alcohol in aqueous and acidified medium. Therefore, to obtain derivative **11**, milder conditions and the use of anhydrous solvent are required. The methodology of Wiberg and Saegebarth (1957) can be applied to obtain diol 8 from MC, using potassium permanganate as an oxidizing agent, which facilitates the subsequent oxidation of the glycol. Additionally, alkenes with monosubstituted carbon are susceptible to oxidative cleavage, as in the propionoid portion, forming para-methoxybenzaldehyde.

The ring opening occurs through a nucleophilic bimolecular substitution (SN_2) reaction of epoxide (2), treated with 5% (v/v) H_2SO_4 in methanol (Figure 8). Derivatives (**10**) and (**17**) are obtained in this reaction and purified by column chromatography eluted with hexane/ethyl acetate (1:1), with a yield of 77% (SANTOS, 2017).

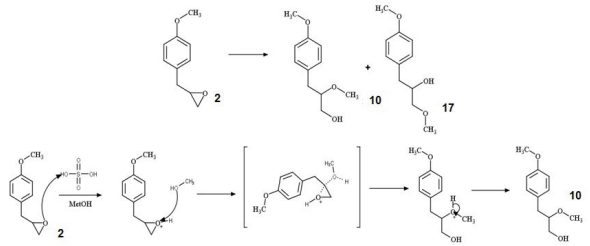

Figure 8. Reaction of epoxide 2-[(4-methoxyphenyl) methyl]oxirane (2) with methanol.

The opening of the epoxide group exhibits regioselectivity depending on the experimental conditions used. For example, derivative **2**, treated with methanol in acidic medium, undergoes a nucleophilic bimolecular substitution (SN_2), resulting in attack on the more substituted carbon and forming the thermodynamic product (derivative **10**). On the other hand, when the reaction is initiated at room temperature, it generally favors the formation of the kinetic product (derivative **17**) obtained by SN_2 in basic medium, with attack occurring on the less substituted carbon (KADESH, 1946).

Another alternative for the opening of epoxide (**2**) is aminolysis; however, treatment of oxirane (**2**) with pyridine catalyzed by phenol (under vacuum at 140°C for 5 hours) does not yield the desired salt (COLCLOUGH et al., 1961) (Figure 9).

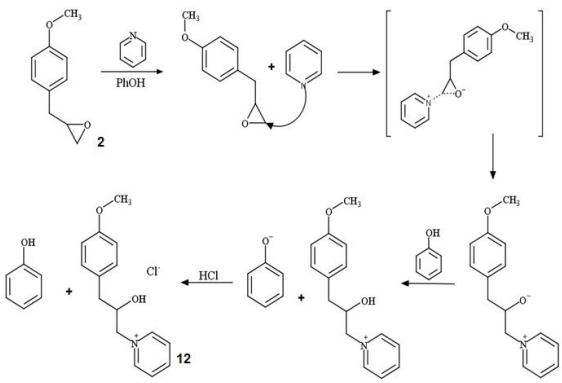

Figure 9. Formation of (**12**) via aminolysis of epoxide (**2**).

On the other hand, the structural characterization of the formed product indicates the synthesis of 3-(4-methoxyphenyl) propanal (**18**), possibly due to an epoxide rearrangement into carbonyl compounds. Oxiranes can undergo isomerization into carbonyl compounds in the presence of a Lewis acid (Figure 10) (MARUOKA et al., 1994). The rearrangement of epoxide (**2**) results in product (**18**), which is purified by column chromatography eluted with hexane/ethyl acetate (8:2) with a yield of 52.30%.

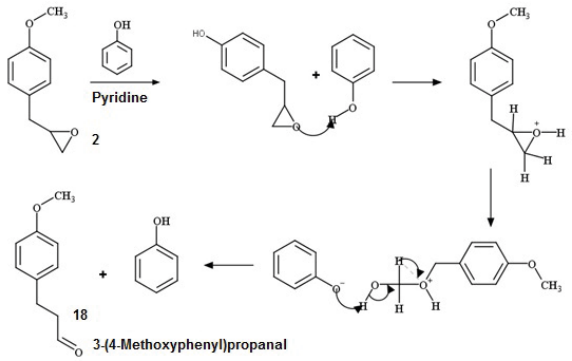

Figure 10. Formation of aldehyde (**18**) from the rearrangement of epoxide (**2**).

The reaction mechanism of derivative **12** involves the attack of the amine on the less substituted carbon atom of the epoxide. In a basic medium, phenol acts as a Lewis acid, protonating the oxygen of the epoxide, which becomes the oxygen of the new carbonyl group, forming aldehyde **18**, 3-(4-methoxyphenyl)propanal. Intermediate carbocations participate in the structure and stereochemistry of the product, resulting in efficient and high-yield reactions. Boron trifluoride and other reagents such as tin tetrachloride and antimony pentafluoride are often used for selective rearrangements into aldehydes (CAREY, 2007). It is relevant to note that vicinal diols can also undergo this type of rearrangement in acidic medium, as exemplified by pinacol, which, under heated sulfuric acid, forms pinacolone, a ketone (HILL; FLOSDORF, 1941).

THERAPEUTIC POTENTIAL

The insecticidal activity of MC is associated with the essential oils of *Ocimum* spp. (Lamiaceae), as it is a plant that has traditionally been used to kill or repel insects (Paula et al. 2003). Paula et al. (2003) revealed that the oil of *O. selloi* contains MC (55.3%), trans-anethole (34.2%), cis-anethole (3.9%), and caryophyllene (2.1%). Using a field test,

O. selloi oil showed a repellent effect on the mosquito (*Anopheles braziliensis*), as the average number of mosquito bites on the skin of volunteers was much lower than that observed after the application of the solvent alone. This data confirmed the repellent action of *O. selloi* oil against the *A. braziliensis* mosquito, considered a secondary or potential vector in malaria-endemic areas.

Joshi (2014) identified 25 constituents in the essential oil of *O. basilicum*, with the major components being methyl eugenol (39.3%) and MC (38.3%). The oil inhibited the growth of Gram-positive bacteria, Gram-negative bacteria, and fungi with minimum bactericidal concentration values in the range of 0.143 ± 0.031 to 0.572 ± 0.127 mg/mL, 0.781 ± 0.382 to 1.875 ± 0.684 mg/mL, and 0.312 ± 0.171 to 0.442 ± 0.207 mg/mL, respectively. In this context, as one of the most abundant components, MC may contribute to the antimicrobial properties of the essential oil of *O. basilicum*. Another study conducted by Everton et al. (2020) showed that the essential oil of *O. basilicum* (62.39% of MC) exhibited an inhibition zone of 18 mm for *E. coli* and 20 mm for *S. aureus*, with minimum inhibitory concentration and minimum bactericidal concentration values demonstrating more effective bactericidal action against S. aureus. Additionally, the oil of this species showed an LC_{50} between 582 mg/L and 282 mg/L against *Artemia salina* (EVERTON et al., 2020).

Experiments conducted on the sciatic nerves of Wistar rats measuring compound action potentials showed that MC induced a dose-dependent blockade of these potentials. In the presence of MC (2.0 and 6.0 mM), the peak-to-peak amplitude was significantly reduced at the end of 180 minutes of nerve exposure to the drug to 85.6 ± 3.96% and 13.04 ± 1.80% of the control, respectively. MC also altered the peak-to-peak amplitude, conduction velocity, chronaxie, and rheobase to 49.3 ± 6.21% and 77.7 ± 3.84%, 125.9 ± 10.43% and 116.7 ± 4.59% of the control, respectively. The data showed that MC dose-dependently blocks nerve excitability (LEAL-CARDOSO et al., 2004).

Based on electrophysiological recordings, Silva-Alves et al. (2013) showed that MC blocked action potentials in ganglion neurons with or without inflections in their descending phase (repolarization) in a concentration-dependent manner. This compound also inhibited the total Na^+ current and the tetrodotoxin-resistant Na^+ current (IC_{50} of 3.2 and 3.6 mM, respectively). In the presence of 4 mM, kinetic analysis of the Na^+ current showed a reduction in the time constants of both fast and slow inactivation, indicating an acceleration of the inactivation process. These data demonstrated that MC blocks neuronal excitability by directly inhibiting the activation of Na^+ channel conductance in a manner similar to local anesthetics (SILVA-ALVES, 2013).

A comparative study of the antiedematogenic effects of anethole and estragole, conducted by Ponte et al. (2012), showed that, like anethole, MC reduced carrageenan-induced paw edema. Additionally, these compounds similarly inhibited edema caused by substance P, bradykinin, histamine, and TNF-α, but differed in the inhibition of edema caused by serotonin, although MC inhibited edema induced by sodium nitroprusside.

In an *in vivo* peritonitis model, MC (500 and 750 mg/kg) was able to reduce leukocyte infiltration in the peritoneal exudate, while the *in vitro* chemotaxis assay showed that MC (3, 10, 30, and 60 μg/mL) inhibited neutrophil migration. In the *in vivo* microcirculation test, MC (250, 500, and 750 mg/kg) significantly reduced the number of rolling and adherent leukocytes, and the doses of 250 and 500 mg/kg decreased the number of leukocytes migrating to the perivascular tissue. MC also

stimulated macrophage phagocytosis, and the data obtained suggested its potential anti-inflammatory effects (SILVA-COMAR et al., 2014).

The systemic anti-inflammatory activity of the essential oil of *O. basilicum* and its main component, MC, as well as their possible mechanisms of action, were investigated by Rodrigues et al. (2016). The results of *in vivo* tests showed that treatment with the essential oil (100 and 50 mg/kg) and MC (60 and 30 mg/kg) significantly reduced paw edema induced by carrageenan and dextran. The lower doses of the oil (50 mg/kg) and MC (30 mg/kg) were effective in reducing paw edema induced by histamine and arachidonic acid, inhibiting vascular permeability, and leukocyte migration in the peritoneal fluid. These doses were able to reduce the chronic inflammatory process. Thus, the essential oil and MC demonstrated effectiveness in anti-inflammatory activity, with the essential oil being more effective in acute and chronic anti-inflammatory action.

MC reduced the thickness and mass of ear edema induced by croton oil, phenol, and histamine,corroboratingitsanti-inflammatory effect (SANTOS, 2017). Additionally, there was a decrease in myeloperoxidase, N-acetyl-β-D-glucosaminidase, nitric oxide, tumor necrosis factor (TNF-α), and interleukin 6 (IL-6), although it did not show the ability to inhibit COX-1 and COX-2 in an *in vitro* assay (SANTOS, 2017).

MC and its derivative 2-[(4-methoxyphenyl) methyl]oxirane (MPMO) demonstrated antioxidant activity by inhibiting the DPPH free radical and lipid peroxidation in the β-carotene/linoleic acid co-oxidation and thiobarbituric acid assays (SANTOS et al., 2018). In *in vitro* tests, the inhibitory activity of MC and MPMO on pancreatic lipase was 58.12% and 26.93%, respectively. *In silico* assays showed that MC and MPMO have a free energy value of -6.1 kcal.mol^{-1}, lower than that of diundecylphosphatidylcholine (-5.6 kcal.mol^{-1}), indicating potential for inhibition of this enzyme related to conditions of obesity and dyslipidemia (SANTOS et al., 2018).

Analyses by GC/MS identified MC (74.9%) as the major constituent in the essential oil of *O. basilicum* (FITSIOU et al., 2016). In this study, the antiproliferative activity of this species was more cytotoxic against the in vitro model of human colon cancer (Caco2 cell line), followed by human hepatocellular carcinoma (HepG2 cell line) and human breast adenocarcinoma (MCF-7 cell line).

The oil of *O. selloi*, with 55.3% of MC, administered to Swiss mice did not produce adverse effects at doses up to 1,250 mg/kg. However, deaths and symptoms (such as hypoactivity, ataxia, and lethargy) were observed at doses ≥ 1,500 mg/kg, with females apparently being more susceptible than males (PAULA et al., 2003). Additionally, the genotoxicity of this oil, evaluated in the *Salmonella typhimurium*/microsome assay (strains TA100, TA97a, TA98) up to the toxicity limit (500–700 μg/plate), was not mutagenic for the TA97a, TA98, and TA100 strains. In this study, Paula et al. (2003) also revealed that none of the 30 volunteers of both sexes exposed to oil showed a positive skin irritation reaction. Thus, *O. selloi* oil has low acute toxicity, does not present a mutagenic risk, and appears to be non-irritating to human skin.

On the other hand, high doses of MC have a hepatocarcinogenic potential in different rodents. The carcinogenicity of this substance is linked to its metabolic conversion into genotoxic products (DRINKWATER et al., 1976; MILLER et al., 1983; WISEMAN et al., 1985). The bioactivation of MC begins with a conversion catalyzed by cytochromes P450 1A2 and P450 2A6 into a carcinogenic metabolite: 1'-hydroxy-methyl chavicol

(Figure 11) (JEURISSEN et al., 2007). Phase I metabolism includes O-demethylation, epoxidation, and 3'-hydroxylation, forming 4-allylphenol, methyl chavicol-2',3'-oxide, and 3'-hydroxyanethole, respectively (ANTHONY et al., 1987; GUENTHNER; LUO, 2001; LUO et al., 1992; PHILLIPS et al., 1981; SANGSTER et al., 1987; SOLHEIM; SCHELINE, 1973). The sulfonation of 1'-hydroxy-methyl chavicol produces the carcinogenic metabolite that, due to its instability, degrades into a carbocation capable of binding to DNA (Figure 11) (PHILLIPS et al., 1981; PHILLIPS et al., 1984; RANDERATH et al., 1984; WISEMAN et al., 1985).

Due to its potential toxic properties, the use of MC is regulated in various countries. The European Union, for example, has established limits on the amount of MC permitted in food and cosmetics because this compound can be metabolized into products that bind to DNA, contributing to its carcinogenicity (EUROPEAN COMMISSION, 2001).

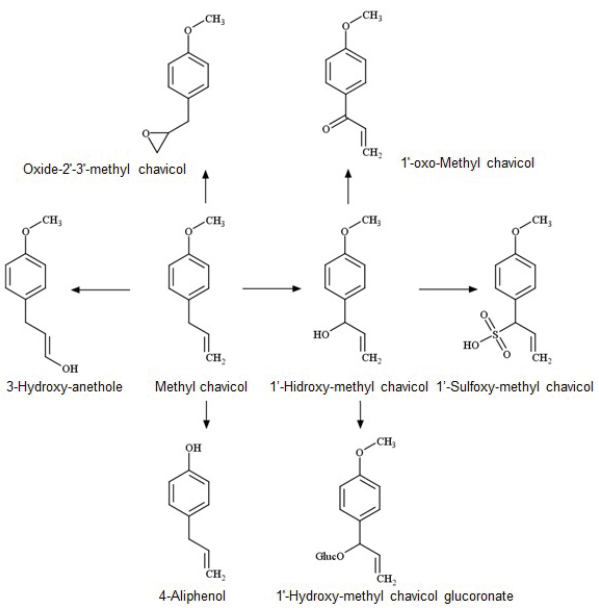

Figure 11. Metabolism of methyl chavicol.

Source: Adapted from PUNT et al., 2009.

FINAL CONSIDERATIONS

MC, or estragole, is a volatile phenylpropanoid belonging to the allylbenzenes group found in essential oils. Chemically, it is a phenolic ether with a molecular structure that includes a benzene ring attached to a methoxy group and a propenyl group. This compound can be obtained through convergent synthesis from phenol, cross-coupling, and photolysis generating the 4-methoxyphenyl cation.

MC can participate in oxidation reactions and be converted into various derivatives, including oxides and peroxides, as well as undergoing allylation and methoxylation reactions. It is noted that several derivatives can be obtained from MC, such as 2-[(4-methoxyphenyl)methyl]oxirane (2), 3-(4-methoxyphenyl)propan-1,2-diol (8), 2-methoxy-3-(4-methoxyphenyl)propan-1-ol (10), 1-methoxy-3-(4-methoxyphenyl) propan-2-ol (17), and 3-(4-methoxyphenyl) propanal (18), with promising therapeutic potentials.

Therefore, MC is a compound with a simple chemical structure that can be used as a prototype for obtaining a variety of derivatives, representing potential in the search for new drugs applicable in therapeutics. However, investigating its biological effects and developing methods to minimize the risks associated with its use are crucial to ensuring its safety.

ACKNOWLEDGMENTS

This study was supported by the Fundacão de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG - Grant **Nº: APQ-03302-18**) and the Pró-Reitorias de Pesquisa and Pós-Graduacão of the Universidade Federal de Juiz de Fora.

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