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Review

Pharmacological potential of *Maytenus* species and isolated constituents, especially tingenone, for treatment of painful inflammatory diseases

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ABSTRACT

Uses of medicinal plants by people around the world significantly contribute and guide biologically active compounds research that can be useful in the combat against various diseases. Due to a great chemical and structural variety found in their vegetal structures it consolidates ethnopharmacology as an important science for the pharmaceutical section. Inserted in the diversity of medicinal plants, is the *Maytenus* genus, whose research has already revealed lots of isolated substances which are responsible for a great variety of biological activities, among which we cite analgesic and anti-inflammatory, for the treatment of inflammatory diseases such as rheumatoid arthritis, gastritis, ulcers and gastrointestinal disorders. The aim of this review article is to make a compendium of the *Maytenus* genus and its isolated chemical compounds, among them tingenone. The elucidation of its mechanism of action reveals promising sources for the development of new drugs specially targeted for the treatment of painful inflammatory diseases.

Medicinal plants: source for discovery of new drugs

Research for the treatment of the main diseases that affect the humankind is a constant concern of the population, whose information is proven by the numerous records found in the first civilizations that lived on Earth (Calixto and Siqueira, 2008). Ancient civilization such as Chinese, Indian and North African have provided written evidence from the origin of man using plants for the treatment of a great variety of diseases. In Old Greece, for example, scholars classified plants and gave descriptions that helped in the identification process (Phillipson, 2001).

Nowadays, treatment through medicinal plants plays a fundamental role in the health systems of many countries (Bhatia et al., 2014). Researches of medicinal plants are becoming more important in the development of health care and maintenance programs in different parts of the world (Shil et al., 2014).

Brazilian biodiversity comprises more than 50,000 species of vascular plants (20–22% of the existent total in the planet) and, due to this, the interest in studies of medicinal properties of plants are explored by Brazilian researchers and the pharmaceutical industry (Calixto and Siqueira, 2008). Plant-derived medicines form a significant segment related to pharmaceutical products, since, 25% of prescribed drugs are originating from plants (Schmidt et al., 2007). Therefore, natural products are still representing a valuable source of inspiration for chemicals, working with synthesis of biological active compounds, developing new drugs (Ji et al., 2009).

Materials and methods

This review was prepared by databases Pubmed, Google Scholar, ScienceDirect and SciFinder on period September 2014 to January 2017. The keywords utilized were *Maytenus*, chemical compounds, tingenone and pharmacological activities.

The Celastraceae family

The Celastraceae family is formed by 106 genera and 1300 species, that are widely distributed in tropical and subtropical regions of the world, including North Africa, South America and east Asia, mainly China (Spivey et al., 2002; Simmons et al., 2008; Núñez et al., 2016). It is also commonly known, as a bittersweet family, due to its fruits' flavor (Gonzalez et al., 2000). The plants of this family are in general, characterized by small trees, bushes or lianas (Spivey et al., 2002). Representative genus of this

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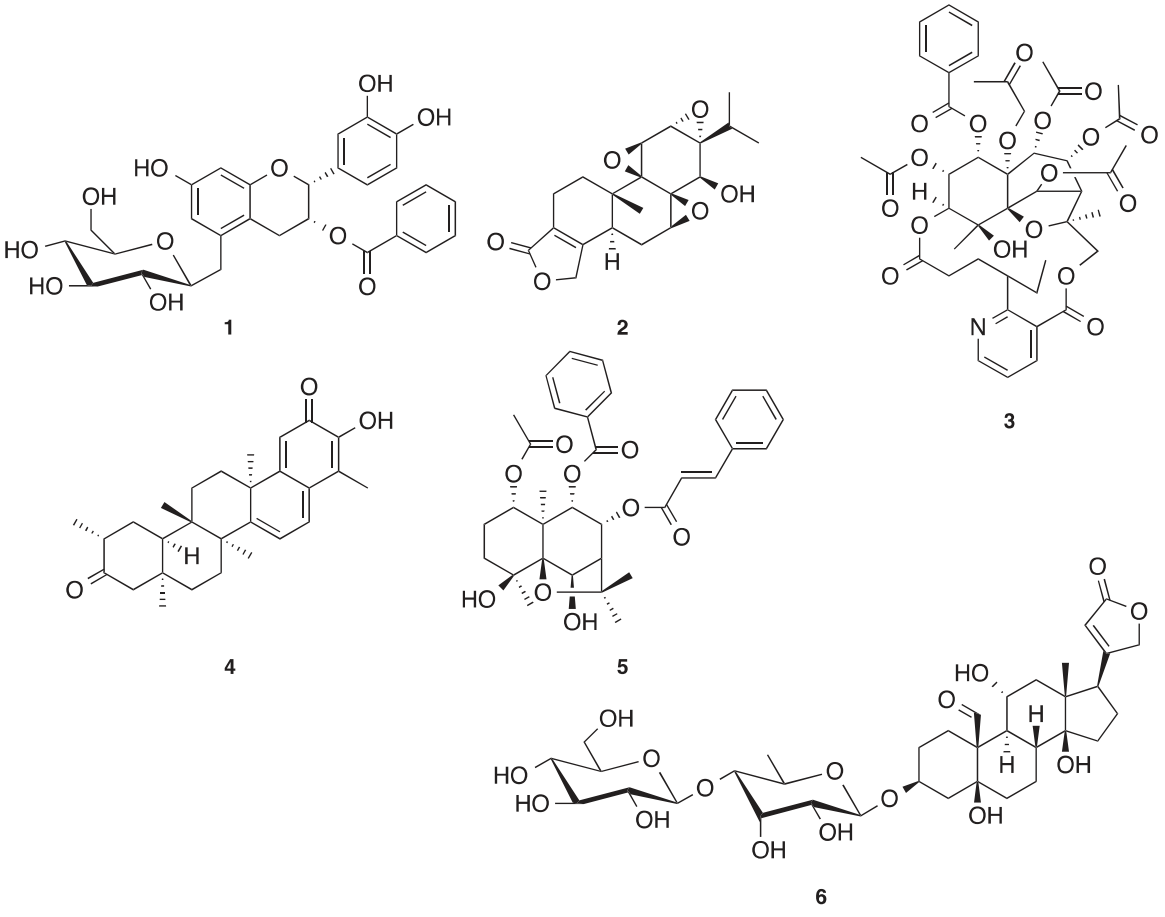
family are *Maytenus*, *Euonymus*, *Cassine* and *Celastrus* (Perestelo, 2009), that are studied not only because of their use in popular medicine, but also, because of the large geographical distribution, diversity and structural complexity of the isolated secondary metabolites (Coppede et al., 2014). Many species from the Celastraceae family are widely studied, except for *Zinowiewia* genus whose studies are very out dated probably due to its poor phytochemical and ethnopharmacological characterization (Núñez et al., 2016).

The Celastraceae family includes various plants species, and its extracts have been used for the treatment of stomach complications, fever, appetite suppressants, rheumatoid arthritis and cancer (Spivey et al., 2002). The *Tripterygium wilfordii* specie, largely used in China due to its insecticidal properties, is one of the most studied from this family and has several isolated bioactive substances (Brinker et al., 2007). Extracts of this species are used for the rheumatoid arthritis, autoimmune sicknesses and skin infections (Wang and Xie, 1999).

Examples of isolated compounds from the Celastraceae family and their respective biological activity, are: (−)-epicatequin-5-*O*-β-d-glucosyl 3-benzoate (**1**) (antioxidant activity) (Hwang et al., 2001), triptolide (**2**) (insecticidal activity) (Luo et al., 2004), oppositine A (**3**) (cytotoxic activity against tumor cells in human colon) (Whitson et al., 2006), tingenone (**4**) (antimicrobial and antinociceptive activities) (Mena-Rejón et al., 2007; Veloso et al., 2014a, 2014b, 2015), 1-acetyloxy-9-benzoyloxy-8-cinamoyloxy-4,6-dihydro-β-agarofuran (**5**) (inhibition of photosynthesis) (Torres-Romero et al., 2008) and elaeodendroside W (**6**) (antiproliferative activity against human ovarian cancer) (Hou et al., 2009).



The *Maytenus* genus

In Brazil, 76 species were found in different habitats, like the Atlantic forest (*M. distichophylla*, *M. macrophylla*), altitude forest (*M. erythroxylon*), rock fields (*M. opaca*) and in regions with caatinga vegetation (*M. truncata*, *M. imbricata*, *M. ilicifolia*, *M. catingarum*, *M. impressa*, *M. obtusifolia*), predominantly distributed between Bahia and Ceará state (Rocha et al., 2004; Niero et al., 2011).

The name *Maytenus* is derived from the word "Maytén", used by the "Mapuche" population from Chile, which means "man of the land" (Niero et al., 2011). Numerous medicinal uses are associated to the *Maytenus* genus species, with the use of roots, barks and leaves for the treatment of gastric ulcers, anti-inflammatory, analgesic, anti-allergy, antitumor, among others in South America (Sosa et al., 2007; Baggio et al., 2009; Niero et al., 2011; Martins et al., 2012). The leaves of the several existent species of *Maytenus* in Brazil, are traditionally used by Indians as infusion against gastric affections (hyperacidity, gastric ulcers, duodenal and chronic gastritis) (Rocha et al., 2004). As shown in Box 1, *Maytenus* genus is widely used in folk medicine for the treatment of various diseases.

Extracts and isolated substances of the *Maytenus* genus species present a range of biological activities. Among the 76 known species of the *Maytenus* found in Brazil, only 15% had their pharmacological effects studied (Niero et al., 2011), and most of these were performed in animal models of pain and inflammation. According to the literature, the ethanolic extract of the *M. putterlickoides* roots presents antileukemic activity (Schneberg et al., 2001), the methanol extract of *M. senegalensis* roots' barks shows antibacterial activity (Lindsey et al., 2006) and the chloroform, hexane and methanolic extracts of the roots present anti-inflammatory activity, decreasing ear edema induced by croton oil in mice (Sosa et al., 2007). Another study showed that the hydroalcoholic extract of *M. robusta* leaves presents gastroprotective property (De Andrade et al., 2007). The ethyl-acetate and methanolic extracts of the leaves of *M. truncata* show analgesic and antiulcer activities (Fonseca et al., 2007), the ethanolic extract of the *M. rigida* leaves presents anti-inflammatory, antiulcer and antidiarrheal activities (Santos et al., 2007). In addition to these effects, *M. rigida* also presented antinociceptive effect (Martins et al., 2012) and *M. heterophylla* specie showed anti-inflammatory effect (Da Silva et al., 2011).

Biological activities of various species of *Maytenus* genus plants are being studied. A large number of studies on *M. ilicifolia* are found in literature, one of the most commonly used, and herbal medicine prepared from this specie is already commercially available for the treatment of gastric ulcers. This specie is native to the Southern part of Brazil, Paraguay, Uruguay and northern Argentina and has biological activities besides its ornamental use. Preliminary studies of the hexane and ethyl acetate extracts of *M. ilicifolia* leaves inhibited the second phase of the formalin test in mice and paw edema induced by carrageenan in rats. Beside these effects, protection against gastric lesions was also observed (Jorge et al., 2004; Leme et al., 2013). This plant is popularly known as

Box 1: The *Maytenus* genus and its uses in folk medicine.

Scientific name	Popular name	Therapeutical indications	Authors
M. accuminata	–	Digestive system inflammation and pain, chest pain	Ahmed et al., 2013
M. acuminate	–	Sore throat, stomach diseases	Chukwujekwu and Van Staden, 2016
M. aquifolium	"Espinheira-santa", "cancerosa"	Gastric problems	Calou et al., 2014
M. cassineformis	"Coração-de-bugre"	Fever	Schwanz, 2012
M. dasyclada	"Coração-de-negra"	Fever	Schwanz, 2012
M. distichophylla	"Casca-amarela", "pau-colher"	Treatment of stomach ulcers	Duarte, 2013
M. erythroxylon	"casca-grossa", "bom-nome"	Antidiarrheal	Formiga, 2016
M. emarginata	"Kankero", "thorny staff tree"	Toothache, sores, jaundice	Sagwan et al., 2011
M. guyanensis	"Chichuá"	Rheumatism, arthritis, hemorrhoids, skin rashes	Conceição, 2010; Vargas et al., 2016
M. heterophylla	–	Digestive system inflammation and pain, chest pain	Ahmed et al., 2013
M. hookeri	–	Inflammations	Su et al., 2013
M. ilicifolia	"Espinheira-santa", "cancerosa", "cancerosa-de-sete-espinhos", "maiteno"	Gastritis, ulcers, dyspepsia, pain, wounds	Leme et al., 2013; Calou et al., 2014
M. macroparca (*M. krukovii*)	"Chuchuhuasi", "chuchuguaso"	Back pain, stomach pain, sore throat, rheumatism, gastrointestinal diseases	Torpocco et al., 2007; Salazar et al., 2008; Llumiluiza, 2013; Robles et al., 2014
M. obtusifolia	"carne-de-anta", "carrancudo", "bom-nome"	Treatment of ulcer, general inflammations and cancer	Sousa and Almeida, 2005; Mota et al., 2008
M. peduncularis	–	Digestive system inflammation and pain, chest pain	Ahmed et al., 2013
M. procumbens	–	Digestive system inflammation and pain, chest pain	Ahmed et al., 2013
M. rigida	"Bom-nome", "bom-homem", "cabelo-de-negro", "casca-grossa", "pau-de-colher", "chapéu-de-couro"	Inflammation, pain, rheumatism, infections, healing process	Lima et al., 2010; Vieira, 2013
M. robusta	–	Gastric ulcer	Silva et al., 2015
M. royleanus	–	Toothache, arthritis, gastrointestinal diseases	Shabbir et al., 2013; Shabbir et al., 2015
M. salicifolia	"Cafezinho"	Gastric ulcers	Magalhães et al., 2011
M. senegalensis	–	Malaria, fever, chest pain, rheumatism, wounds, snake bites, sore throat, stomach diseases	Conceição, 2010; Ahmed et al., 2013; Malebo et al., 2015; Chukwujekwu and Van Staden, 2016
M. spinosa	"Abriboca"	Stomach diseases	Gutiérrez-Nicolás et al., 2014
M. truncata	"Todo-lado", "todo-jeito", "árvore-de-natal"	Gastric ulcers	Fonseca et al., 2007
M. undata	"Blakelock", "kokoboom", "koko-tree", "idohame", "egqwabali", "ikhukhuze", "indabulovalo", "inqayi-elibomvu"	Digestive system inflammation and pain, chest pain	Ahmed et al., 2013; Mokoka et al., 2013

"erva-cancerosa", "espinho-de-deus", "salva-vidas", "espinheira-santa", among other names (Niero et al., 2011). Espinheira-santa is also a popular name for other species, such as: *M. aquifolium*, *M. robusta* and *M. truncada*, because of their marked morphological similarity. These plants have the traditional use for the treatment of diabetes, kidney problems, treatment of gastric ulcers, as anti-inflammatory and analgesic (Rocha et al., 2004; Niero et al., 2011; Leme et al., 2013). *M. obtusifolia*, *M. heterophylla*, *M. undata* and *M. putterlickioides* species present antiplasmodial activity. *M. heterophylla* is used in Africa by healers for the treatment of hernia and syphilis and anthelmintic (Muthaura et al., 2015). *Maytenus gonoclada*, known as "tiuzinho", is a Brazilian plant found in cerrado and rupestrian fields. Some triterpenes of this specie were isolated and evaluated, proving a giardicidal activity (Silva et al., 2012).

Thinking about possible new and future treatments for the Alzheimer's disease, Rodrigues et al. (2014) analyzed some triterpenes isolated from *M. imbricata* and *M. gonoclada*. Some of these compounds exhibited acetylcholinesterase inhibition properties.

Some studies have reported biological activities related to *Maytenus* triterpenic compounds in the central nervous system. A study performed using the roots of *M. obtusifolia* revealed antipsychotic effect in the model of catalepsy (De Sousa and De Almeida, 2005). Santoyo et al. (2015) demonstrated antipsychotic effect and behavior modifying effect in a study using the *Maytenus macrocarpa* ethanolic extract.

Chemical compounds

Isolated constituents from species of *Maytenus* genus (Box 2) subjected to laboratorial tests also showed biological effects. Through phythochemical studies of plants of the *Maytenus* genus, many compounds classes were isolated, including flavonoids, pentacyclic triterpenes, alkaloids and condensed tannins (Niero et al., 2011).

Among the isolated secondary metabolites of these species, the fridelane pentacyclic triterpenes, quinonamethides and lupanes have been isolated. Lupanes and quinonamethides deserve special mention for presenting important biological activities (Vellosa et al., 2009; Martucciello et al., 2010).

Phytochemical studies performed from leaves, branches, stems and roots of *M. imbricata* showed six pentacyclic triterpenes isolated from the roots: 11α-hydroxylup-20(29)-en-3-one; 6-oxotingenol; 3,7-dioxofriedelane; 3-oxo-29-hydroxyfriedelane; 3β,11α-di-hydroxylup-20(29)-en and tingenone (Silva, 2007; Rodrigues et al., 2012).

Triterpenes are targeted because they present broad spectrum of activities, such as: analgesic, anticancer, anti-allergy, antiviral, among others (Patočka, 2003). Tingenone expressed insecticidal activity in *in vivo* essays (Avilla et al., 2000), potent activity against *T. cruzi* (Duarte et al., 2002), antitumor activity (Gomes et al., 2011) and antibacterial and antifungal properties (Rodrigues et al., 2012).

Sesquiterpenes with basic skeleton dihydro-β-agarofuran, presented inhibitory activity for *Leishmania* parasite resistant to other drugs (Delgado-Méndez et al., 2008) and fridelane triterpenes revealed antiulcer activity (Andrade et al., 2008).

A research by Andrade et al. (2008) verified the antiulcerogenic activity of 3,15-dioxo-21α-hydroxy friedelane (**7**), a triterpene isolated from *M. robusta*. This compound significantly reduced lesion area induced by HCl/ethanol. The effect of 3,15-dioxo-21α-hydroxy friedelane (**7**) as an antiulcer drug is due to triterpenes' ability to strengthen the defenses of the gastrointestinal tract by raising prostaglandin production, which is important for gastric mucosa protection.

Type II arabinogalactan is a polysaccharide found in plants cell walls. Baggio et al. (2012) evaluated the protective effect of this compound isolated from *M. ilicifolia* in models of gastric hypersecretion and ulcer. The results showed that type II arabinogalactan protected the mucosa against gastric ulcers in oral and intraperitoneal routes.

A friedelane derived, 3-oxofriedelane (friedelin), presents potent antiproliferative activity (Roberts, 2007) and a large spectrum of antimicrobial activity (against six gram positive bacteria,

Box 2: Isolated compounds from *Maytenus* genus.

Maytenus genus	Isolated compounds	Literature
M. ilicifolia	Quercetrin, kaempferol, catechins, epigalocatequin-3-gallate, epigalocatequin, fridenelol, friedelan-3-ol, friedelan-3-on, friedelin, 4-o-metilepigalocatequina, type II arabinogalactan	Alberton, 2001; Pazzini, 2007; Santos-Oliveira et al., 2009; Leme et al., 2013; Calou et al., 2014; Dutra et al., 2016
M. robusta	Friedelin, β-friedelinol, 3-oxo-21β-H-hop-22(29)-ene, 3,4-seco-friedelan-3,11β-olide, 3β-hydroxy-21β-H-hop-22(29)-ene, 3,4-seco-21β-H-hop-22(29)-en-3-oic acid, 3,4-seco-friedelan-3-oic acid, 3,15-dioxo-21alpha-hydroxy friedelane, 3,12-dioxofriedelane, 11-hydroxylup-20 (29)-en-3-one, mayteine, 3,7-dioxofriedelane	Silva et al., 2015; Benvenutti et al., 2016
M. aquifolium	Quercetin 3-*O*-α-l-rhamnopyranosyl(1→6)-*O*-[β-d-glucopyranosyl(1→3)-*O*-α-l-rhamnopyranosyl(1→2)-*O*-β-d-galactopyranoside, kaempferol 3-*O*-α-l-rhamnopyranosyl(1→6)-*O*-[β-d-glucopyranosyl(1→3)-*O*-α-l-rhamnopyranosyl(1→2)-*O*-β-d-galactopyranoside, friedelin, friedelan-3-ol	Alberton, 2001; Dutra et al., 2016
M. truncata	Proanthocyanidin	Subarnas and Wagner, 2000; Fonseca et al., 2007
M. undata	3-Oxo-11α-methoxyolean-12-ene-30-oic acid, 3-oxo-11α-hydroxyolean-12-ene-30-oic acid, 3-oxo-olean-9(11),12-diene-30-oic acid, 3,4-seco-olean-4(23),12-diene-3,29-dioic acid (20-*epi*-koetjapic acid), 3,11-dioxoolean-12-ene-30-oic acid (3-oxo-18β-glycyrrhetinic acid), koetjapic acid, 12-oleanene artifact 3-oxo-11α-ethoxyolean-12-ene-30-oic acid	Muhammad et al., 2000
Maytenus buchananii	Polpunonic acid, sitosterol, tingenone, 22*β*-hydroxytingenone	Kutney et al., 1981
Maytenus heterophylla	1β-Acetoxy-9α-benzoyloxy-2β,6α-dinicotinoyloxy-β-dihydroagarofuran, β-amyrin, maytenfolic acid, 3α-hydroxy-2-oxofriedelane-20α-carboxylic acid, lup-20(29)-ene-1β,3β-diol, (−)-4′-methyl*epi*gallocatechin, and (−)-*epi*catechin	
Maytenus arbutifolia	β-Amyrin, (−)-*epi*catechin and (−)-4′-methyl*epi*gallocatechin	Orabia et al., 2001

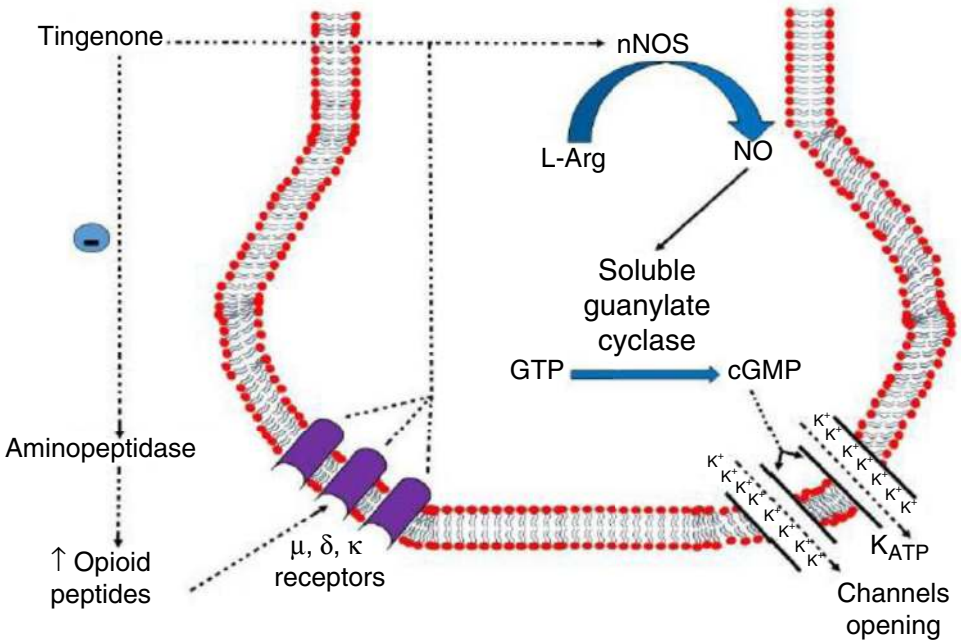


Fig. 1. Mechanism of action proposed for tingenone. nNOS, neuronal nitric oxide sintase; l-Arg, l-arginine; NO, nitric oxide; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; K_{ATP}, channels for sensitive potassium ATP.

four gram negative and two fungi (Kuete et al., 2007). Another fridelane derived, 1,3-dioxofriedelane, has inhibitory activity against tumor cells (Bishayee et al., 2011).

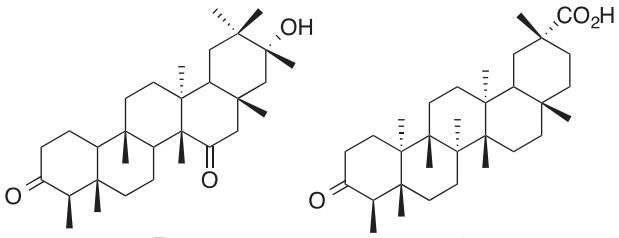
Lupane derivatives have many biological activities, such as, anti-HIV, anticancer and anti-inflammatory (Xiong et al., 2010). The betulinic acid, lupane derivative, has anti-HIV activity. Bevirimat, a synthetic derivative of betulinic acid, is in the phase II clinical assays. This derivative is the first of a new anti-HIV agent class, known as maturation inhibitors (Lee, 2010).

Lupane triterpenes showed potent anti-inflammatory activity (Reyes et al., 2006), while secotriterpene acid compound from *M. undata* presented some effect in thromboxane B_2 inhibition and in decreasing the superoxide anion formation (Muhammad et al., 2000).

Secondary metabolites, such as flavonoids, triterpenes, steroids, among others, are found in *Maytenus* genus species (Niero et al., 2011). Their anti-inflammatory mechanism of action is reported on literature. Among the effects, stand out: reduction of chemokines production and reduction of pro-inflammatory cytokines TNF-α, IL-6 and IL-1β, inhibitory activity against the nuclear factor κB (NF-κB), a factor that activates the transcription of cytokines (Matsusaka et al., 1993; Pinto et al., 2008; Dat et al., 2009; Valerio and Awad, 2011; Choi et al., 2012; Fan et al., 2012).

To some isolated triterpenoids from *Maytenus* species, was assigned inhibitory effects of E_2 prostaglandin (PGE_2) in macrophages stimulated with bacterial endotoxin (Reyes et al., 2006). Antinociceptive effect was demonstrated for the triterpenes in the formalin test (Lima et al., 2005; Gaertner et al., 1999). Longhi-Balbinot et al. (2011) showed the involvement of the opioid system in the mechanism of action of a triterpene in the formalin test, in which the antinociception was reverted by nonspecific and specific μ, δ and κ opioid receptors antagonism.

In a study of isolated compounds from *M. senegalensis*, Sosa et al. (2007) demonstrated anti-inflammatory activity for three triterpenes derivatives, which were the maytenoic acid (**8**), the lupenone and the β-amyrin. These substances significantly inhibited edema in a dose-dependent relationship. In this research, the maytenoic acid showed effectiveness, being twice as active as indomethacin and even though lupenone and β-amyrin had less effectiveness, they demonstrated a good biological activity.



Mattos et al. (2006) reported antiedematogenic effect from am steroid that was able to reduce the edematogenic response induced by carrageenan. Flavonoids exert important effect in many biologic systems, such as antitumor, anti-allergy, and anti-inflammatory, among others (Di Carlo et al., 1999). A previous study showed that a flavonoid compound presented inhibitory activity against the NF-κB, a protein that regulates the pro-inflammatory and inflammatory cytokines transcription (Schmidt et al., 2010). Landolfi et al. (1984) reported that some flavonoids block the lipoxygenase and cyclooxygenase (COX) pathways, inhibiting the inflammatory mediators such as leukotrienes and prostaglandins.

Veloso et al. (2014a) verified antinociceptive effect of the extracts and tingenone obtained from the *M. imbricata* roots. The antinociceptive peripheral mechanism of action of tingenone was also demonstrated. It involves opioidergic pathways activation and nitric oxide (NO)/cyclic guanosine monophosphate (GMPc)/channels for sensitive potassium ATP (K_{ATP}) (Veloso et al., 2014b, 2015) against mechanical hyperalgesia induced by E_2 prostraglandin (PGE_2). Cunha et al. (2010) demonstrated that activation of the nitric oxide pathway by morphine was dependent on an initial stimulation of PI3Kγ/AKT protein kinase B (AKT) that in turn might cause the stimulation of nNOS and an increase in NO production.

In a study performed by Veloso et al. (2014b), it was showed that tingenone, when administrated in the right hind paw, induced

local antinociceptive effect that was antagonized by naloxone, a nonspecific antagonist for the opioid receptors. Clocinnamox, naltrindole and nor-binaltorphimine, which are specific antagonists for the μ, δ and κ receptors, respectively, reverted the peripheral antinociception induced by tingenone. Bestatin, an aminopeptidase inhibitor, an enzyme that degrades opioid peptides, intensified the antinociceptive effect of tingenone. Thus, the results suggested the participation of the opioidergic system in the peripheral antinociception induced by tingenone.

Tingenone, when administrated in the right hind paw, also induced a local antinociceptive effect that was antagonized by l-NOArg, a nonspecific inhibitor of nitric oxide sintase (NOS), and by L-NPA, an specific inhibitor of neuronal NOS (Veloso et al., 2015). l-NIO, an specific inhibitor of the endothelial isoform, and the l-NIL, an specific inhibitor of the inducible form, did not change the peripheral antinociceptive effect of tingenone (**4**). ODQ, an specific inhibitor of soluble guanylate cyclase, prevented the peripheral antinociceptive effect of tingenone, and zaprinast, a phosphodiesterase inhibitor, enzyme that degrades GMPc, intensified the peripheral antinociceptive effect of the lowest dose of tingenone. Glibenclamide, a K_{ATP} channel blocker, but not tetraethylammonium chloride, a blocker of the voltage-dependent channels for potassium; dequalinium chloride, a blocker of the activated by small conductance calcium channels for potassium, and paxillin, a potent blocker of the channels for potassium activated by high conductance calcium, prevented the peripheral antinociceptive effect of tingenone (Fig. 1). The results showed that tingenone induced a peripheral antinociceptive effect by activation of the l-arginine/NO/GMPc/K_{ATP} pathway, revealing a potential to become a new analgesic drug.

Conclusion

Studies of natural products are multidisciplinary. The path involves preliminary experimental tests of a plant crude extract and several steps that cost a lot of time and investment, before the main objective, that is the development of a drug (herbal or traditional) that can reach a population in need. This is very important in poor or under developed countries such as Brazil that presents a big biodiversity and a poor population.

Due to the popular use of *Maytenus* species for the treatment of inflammatory diseases, studies of pharmacological properties and characterization of the chemical compounds in the extracts and infusions are necessary to define and elucidate a safe and non-toxic use. This is also the base for the development of new drugs from natural products, but always targeting to elucidate the mechanism of action and to disclose the biological activity and the chemical structure responsible.

Tingenone has a big potential to become an analgesic, as demonstrated by its biological activities evaluation. It was demonstrated the opioidergic pathway activation by tingenone, whose peripheral antinociceptive action occurs by activation of l-arginine/NO/cGMP/K_{ATP} pathway. This mechanism of action is associated with various opioid analgesics. However, more studies are required to further elucidate its mechanism of action and new therapeutic actions.

Authors' contributions

CCV, VGR and FCS contributed with data collection and writing of the manuscript. GLS contributed with writing and format of the manuscript. ACP participated in final editing of the manuscript. All the authors contributed to the critical reading of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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