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*Review Article*

# *Bauhinia ungulata* L.: Medicinal Utilization, Botanical Aspects, Biological Properties and Chemical Constitution Reported in the Literature

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**ABSTRACT**

*Bauhinia ungulata* L. (Leguminosae) is a plant species popularly known as "mororó" or "pata-de-vaca", whose leaves are used in Brazil as infusion, mainly to treat diabetes. Due to its wide utilization and its therapeutic potential, this species has been investigated, producing data that were organized and arranged in this review, in order to provide an overview of different aspects of the species. A search for articles published until December 2021 on medicinal utilization, botanical characterization, bioactivities, and chemical constitution of the species was carried out, consulting the databases PubMed, Scopus, Lilacs, SciELO, Google Scholar, and Capes Journal Portal. The selected articles describe 31 different terpenes, characterized in essential oils from *B. ungulata* leaves; in addition, other 20 substances, including flavonoids, alkaloids, steroids, and triterpenoids, in other derivatives obtained from leaves, roots, or stems of the species were described. In these articles, different activities were reported, such as antioxidant, anti-inflammatory, antidepressant/anxiolytic, antimicrobial, antiproliferative, larvicidal, cytotoxic and wound healing. The published data on the species allow to infer a potential of use as a therapeutic ingredient with antioxidant activity, which is the most investigated activity and has been related to phenolic compounds, especially flavonoids. Despite the popular use of leaves of the species, as an infusion to treat diabetes, to be well described in the literature, no records were found on the evaluation of their antidiabetic potential or about the characterization of substances present in aqueous extracts from *B. ungulata*.

**Keywords:** Bioactivities, Flavonoids, Medicinal Uses, "pata-de-vaca", Phytochemical Constituents, Terpenes.

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## INTRODUCTION

Genus *Bauhinia* (Leguminosae) comprises 300 to 350 plant species that, due to the shape of their leaves, are popularly known in Brazil as "pata-de-vaca", "casco de vaca", "unha de boi", "pata de boi", or also "mororó", "miroró da caatinga", among others.[1-3] Many of these plants are used as remedies in folk medicine in various regions of the world, including Africa, Asia and Central and South America.[4,5] The hypoglycemic activity attributed to *Bauhinia* species is the most reported in the literature, which also describes activities such as antimicrobial, anti-inflammatory, analgesic, antidiuretic, anticoagulant, antifibrinogenic and antioxidant to species of the genus.[6,7]

Among the *Bauhinia* species popularly used to treat health problems, there is *Bauhinia ungulata* L., a plant species whose leaves, like by other species of the genus, are used in Brazil, as infusion, mainly to treat diabetes.[8,9] The species occurs in the neotropical zone, from Mexico to southeastern Brazil close to São Paulo, being also found in the Amazon rainforest.[10] In Mexico, it is distributed on the Gulf slope, widely on the Pacific slope and the Yucatan peninsula, in addition to Belize, Guatemala, El Salvador, Nicaragua, Costa Rica, Panama, Colombia, Venezuela, Peru, Brazil, Bolivia and Paraguay.[11]

*B. ungulata* species has as synonimia *B. benthamiana* Taub., *B. cavanillesii* Mill sp., *B. galpinii* var. *ungulata* L., *B. inermis* (Cav.) Pers., *B. inermis* Forssk., *B. macrostachya* Benth., *B. unguiculata* Sesse and Moc., *Cansenia ungulata* (L.) Raf., *Pauletia inermis* Cav. and *P. ungulata* (L.) A. Schmitz.[12] In addition, Tropicos (2022)[13] refers to the following varieties *B. ungulata* var. *ungulata*, *B. ungulata* var. *cuyabensis* Vaz, which occurs in a dry corridor from Midwest to Southeast Brazil;[10] *B. ungulata* var. *parvifolia* (Ducke) Vaz and *B. ungulata* var. *obtusifolia* (Ducke) Vaz that occur in the states Maranhão, Pará, Rondônia, Goiás, Piauí and Tocantins.[10]

The species *B. ungulata* L. has been investigated, due to its popular medicinal use and its therapeutic potential, to characterize its biological properties and chemical constitution. The bibliographic search carried out for this work shows that 31 terpenes were detected in essential oils obtained from leaves of *B. ungulata*. In addition, another 20 substances, including flavonoids, alkaloids, steroids and triterpenoids, have been described in derivatives obtained from leaves, roots or stems of this *Bauhinia* species. Activities such as antimicrobial, antioxidant, anti-inflammatory and cytotoxic were confirmed, some of which attributed to the substances characterized in the tested samples. This work presents a review of articles published until December 2021 about the species, until this time it was not possible to find, in the literature, publications reviewing the available information about *B. ungulata*.

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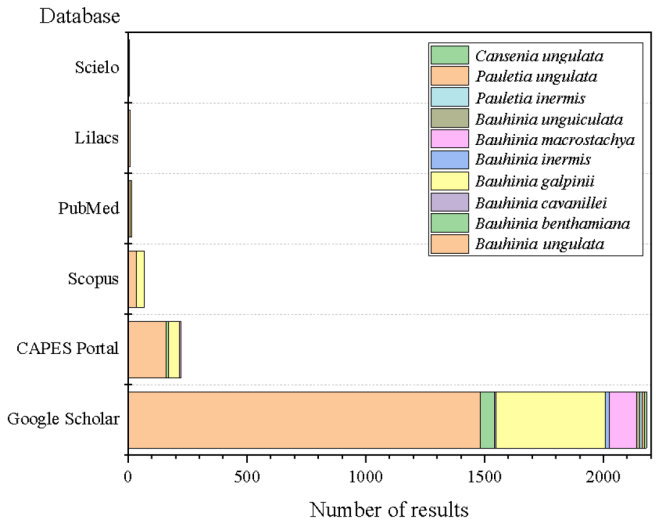
## MATERIALS AND METHODS

The literature search was carried out accessing databases including PubMed, Scopus, Lilacs, SciELO, Google Scholar and Capes Journal Portal to fetch articles published and available until December 2021. The binomial of the species, its synonyms and the combination of them with the terms, "chemical", "compounds", "toxicological" and "pharmacological" were used as keywords. The inclusion criteria used in the file selection were scientific articles about *B. ungulata* focusing on botanical description, medicinal uses, chemical constitution, toxicological evaluation and bioactivities *in vivo* or *in vitro* from extracts, fractions or isolated substances from the species. Only scientific articles published in journals were selected. Theses, dissertations, monographs and conference abstracts were not considered.

## RESULTS

The bibliographic search carried out using the botanical name of the species provided a higher number of references from the Google Scholar and Capes Journal Portal databases, where approximately 2,200 and 220 titles were found, respectively, excluding citations (Graph 1), while the lowest number of references was obtained from the SciELO platform. In all databases consulted, most articles corresponded to *B. ungulata*, followed by the synonyms *B. galpinii* and *B. macrostachya*.

All articles found were analyzed and from them 34 were selected to compose this review, according to the previously defined inclusion criteria. Additionally, ten important references to the topic were added that are not included in the searched data bases, then the review includes 44 references. Based on the information covered in the selected works, they were distributed in the sections "Botanical aspects", "Medicinal utilization", "Phytochemistry" and "Bioactivities". Although a considerable number of references about *B. galpinii* have been found, these articles were not considered, since they are about *B. galpinii* N. E. Br and not about its variety *B. galpinii* var. *ungulata* L., considered synonymous to *B. ungulata* L., according to the consulted botanical database.[12]




**Graph 1:** Number of results found using the botanical name and its synonyms, according to the databases consulted.

## Botanical Aspects

### *Taxonomy*

The main taxonomic data on *B. ungulata* were reported by Vaz and Tozzi,[10] who, based on the description made by Wunderlin *et al.*[14] affirm that the species, in Brazil, is representative of the *Cansenia* series, section *Pauletia*, subgenus *Bauhinia* and genus *Bauhinia*. The Wunderlin classification, which proposed a reorganization of the *Cercideae* tribe based on morphological aspects of the species, considered *Bauhinia* as a large genus in which the subgenera *Bauhinia, Piliostigma, Barklya* and *Phanera* were included.

The taxonomy of the genus *Bauhinia*, however, is quite complex and, based on later findings on species of the Cercideae tribe, other taxonomic descriptions have been proposed, also resulting in changes in the classification of the genus *Bauhinia*. Considering aspects of the chemical constitution of the Cercideae tribe species and data from previous classifications, Lewis and Forest,[15] for example, presented as discrete genera those that Wunderlin *et al.*[14] considered subgenera of a broad genus *Bauhinia*. They propose an amount of 12 genera in Cercideae (*Bauhinia, Piliostigma, Barklya, Phanera, Breniera, Lysiphyllum, Lasiobema, Tylosema, Gygasiphon, Cercis, Adenolobus* and *Griffonia*).

In 2010, Wunderlin[16] proposed a new reorganization of Cercideae tribe, based on the works of Lewis and Forest[15] and Sinou *et al.*[17] and on his more than thirty years own experience investigating Cercideae, and distributed the tribe's genera in two sub-tribes and *Bauhinia*, besides eight other genera, was classified in the sub-tribe Bauhiniinae. As from Vaz and Tozzi[10] and considering more recent works found in this research, a flowchart about the taxonomy of the species is proposed in Figure 1, where *Cansenia* is shown as a serie of *Pauletia* section.

## Morphoanatomical data

Vaz and Tozzi[10] provide key information on identification, synonymy, description, geographic distribution and habitat, as well as comments on taxonomy referring to 35 species and 4 varieties of *Bauhinia*, section *Pauletia*, *Cansenia* series, and report the form of shrubs, sub-shrubs or small trees for *B. ungulata*. Its leaves are bilobed, with ovate-oblong to oblong-triangular lobes, straight and apex parallel, slightly converging or even slightly divergent, even elliptical or suborbiculate, apex long accentuated or acute to obtuse or rounded. The upper face is glabrous, and the lower one is pubescent, with hair on the entire surface. Glandular trichomes and somewhat prominent primary veins are observed, the secondary are less prominent to immersed and the tertiary fully immersed.

In later research, which aimed to describe the genus *Bauhinia* in the biotic province of the Yucatan peninsula, *B. ungulata* was recognized as a native species of the region, and key information for its identification, morphological descriptions, distribution maps, species photographs, information on common names and uses in the region were presented.

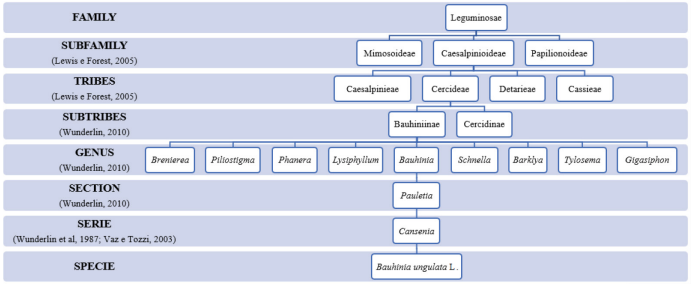



**Figure 1:** Flowchart of the taxonomy of the species *Bauhinia ungulata* L.

The species was described as shrubs, rarely trees, from 2 to 7 m in height, andromonoic, with leaves containing 7 to 9 ribs, bilobed, oval-lanceolate, cartaceous to subcoriaceous. The lobes of the leaves have an acute apex and a subchord to rounded base, with lanceolate stipules. Its inflorescences are presented in short racemes, with 10 to 30 flowers. It blooms bisexual and has tubular, ferruginous hypanthium. The calyx is spathaceous, 2-4-split, presenting spiraled, strigulous, ferruginous and reflexed lobes in anthesis. The petals are sessile, linear, patent, white, with 10 fertile stamens, didynamous, without staminodes, connates at the base, and the ovary is tomentous and ferruginous. The male flowers are similar, and the legume of the species is elastically dehiscent, linear and strigulous, with oblong-elliptical seeds.[11]

The morphology of leaves, inflorescence, flowers and fruits may vary among individuals of this species, however, the type of rudimentary stem column, with a bearded internal appendage, and the upper petal, measuring about 2 mm in width, are common characters to all individuals. Despite some morphological variability, *B. ungulata* presents local patterns, artificially recognized in the form of the species' varieties, which can be found by observing the morphology and size of some structures present in leaves and inflorescences, for example. Based on these standards, the *B. ungulata* var. *ungulata*, *B. ungulata* var. *cuyabensis* Vaz, *B. ungulata* var. *parvifolia* (Ducke) Vaz and *B. ungulata* var. *obtusifolia* (Ducke) Vaz, could be described.[10,13]

More recently, a study, aiming to produce data for the quality control of *B. ungulata* L. derivatives and provide information for its taxonomy description, reports morphoanatomical analyses of leaves collected in the state of Ceará (Brazil).[18] The authors observed that the consistency of the leaves is chartaceous, presenting an oval-oblong shape, the blade base is truncated, and the apex is acute. The abaxial face is sericeous-pubescent, with glands and a palminervous type venation. The petiole and pulvines are canalicular, with insertion of the proximal pulvine between the extrafloral nectaries, and their mobile region is glabrous. Among the anatomical characters, the authors describe the presence of anomocytic, anisocytic and paracytic stomata distributed on both the abaxial and adaxial surfaces of the leaves, which are therefore considered amphistomatic.

## Traditional/folk medicine uses in Central and South America

The main medicinal use of the species is to treat diabetes. Silva *et al.*[19] report that in rural communities of Piauí, a state in northeastern Brazil, barks of the species are used as an anti-diabetic under the synonymy *B. unguiculata*. The species is also used by urban communities in the state for the same therapeutic purpose,[20] however, leaves are more commonly used and the use of them, as an infusion for the treatment of diabetes, was observed in a city in Pará, a state in the Brazilian Amazon, under the synonym *B. benthamiana* Taub.[9] Brazilian indigenous people from the Northeast[21] also use the species to treat diabetes, however, the first reference found on its use reports the preparation of a tea with leaves of the species, which is used as an antidiabetic and for kidney problems in the Amazonian state of Roraima, the authors used the synonym *B. macrostachya* Benth.[8] This last article cited is a record of the use of this species for more than 30 years by the population, in a safe and effective way and this is important, since it justifies its use as traditional in Brazil, according to the current regulation.[22]

Despite its wide use mainly as an anti-diabetic, other properties are attributed to *B. ungulata* in Brazil. In the northeast, for example, barks are used to treat diarrhea,[23] and in the Midwest, leaves and flowers they are used by riverine people as an infusion, decoction or maceration for the treatment of intestinal constipation, cancer, obesity, hypercholesterolemia and diarrhea.[24] In Central America, under the synonymy of *B. inermis*, leaves of the species are also used as sudorifics.[25] Besides to the medicinal uses described so far, in Northeastern Brazil, barks of the species are used as insecticides and domestic repellents against mosquitoes and *Aedes aegypti* L., and in plantations, to combat ants and worms.[26]

## Phytochemistry

### *Essential oils*

The bibliographic survey performed for this review shows the characterization of several terpenes has been reported in essential oils obtained from leaves of the species, including monoterpenes α and β-pinene and cyclic and acyclic sesquiterpenes (Table 1), substances whose skeletons are shown in Figure 2. In qualitative terms, these sesquiterpenes are predominantly bicyclic, denoting those with cadalane skeleton with 7 substances characterized in *B. ungulata*: α and γ-muurulene, γ and δ-cadinene, α-cadinol, α-calacorene and cubenol. Furthermore, a tricyclic sesquiterpene, α-copaene, three bicyclic, spathulenol, β-caryophyllene and caryophyllene oxide, and a monocyclic, α-humulene (Figure 3) were found in this species in higher amount than the previously cited, in the investigated essential oils, which varies according to the sample considered.[27-29]

**Table 1: Sesquiterpenes detected and characterized in essential oils obtained from *B. ungulata* L. leaves.**

| Classification | Skeleton | Substance | Reference |
|---|---|---|---|
| Acyclic | Farnesane (1) | Farnesol | [28] |
| | | Nerolidol | |
| Monocyclic | Bisabolane (2) | α-bisabolol | [28] |
| | | α-bisabolol oxide B | |
| | Elemane (3) | β-elemene | [27–29] |
| | | 8-α-11-elemendiol | [27] |
| | Germacrane (4) | Germacrene D | [27] |
| | Humulene (5) | α-humulene | [27,29] |
| | | Humulene epoxide II | |
| Bicyclic | Cadalane (6) | α-muurolene | [29] |
| | | γ-muurolene | [27,28] |
| | | γ-cadinene | [27–29] |
| | | δ-cadinene | [28] |
| | | α-cadinol | [27,29] |
| | | α-calacorene | [29] |
| | | Cubenol | [29] |
| | Caryophyllene (7) | β-caryophyllene | [27–29] |
| | | Caryophyllene oxide | |
| | Eudesmane (8) | Epi-γ-eudesmol | [28] |
| | | β-selinene | [29] |
| | | Junenol | [29] |
| | Guaiane (9) | α-guaiene | [29] |
| | | 6,9-guaiadiene | |
| Tricyclic | Aromadendrane (10) | Aromadendrene | [28] |
| | | Allo-aromadendrene | [27,29] |
| | | Spathulenol | [27–29] |
| | Bourbonene (11) | β-bourbonene | [29] |
| | Copaene (12) | α-copaene | [27,29] |
| | | β-copaene | [29] |
| | | Copaene | [28] |
| | Cubebane (13) | α-cubebene | [29] |
| Tetracyclic | Cyclosativane (14) | Cyclosativene | [29] |

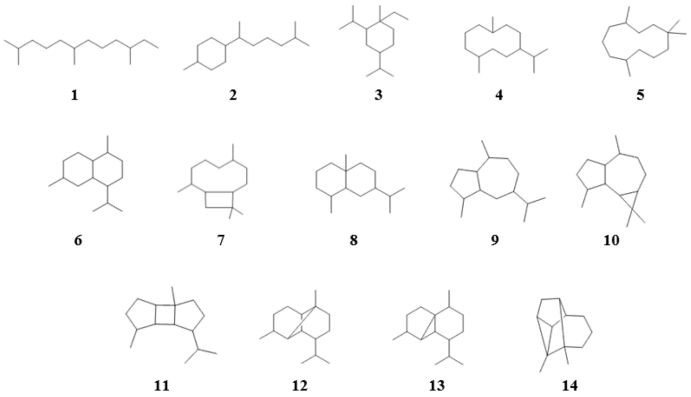



**Figure 2:** Skeletons of sesquiterpenes detected and characterized in essential oils obtained from *B. ungulata* L. leaves.

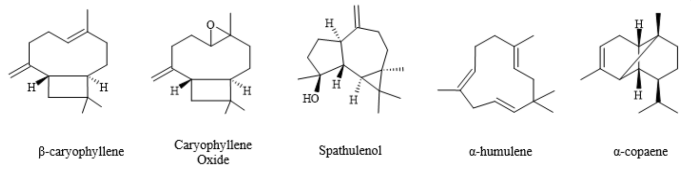



**Figure 3:** Main sesquiterpenes characterized in essential oils obtained from *B. ungulata* L. leaves.

The first characterization of volatile constituents of *B. ungulata* was carried out by Gramosa *et al.*[27] who analyzed an essential oil obtained from leaves of the species, by GC/MS and GC/FID, detecting thirteen sesquiterpenes, among which it was quantified, mostly spathulenol (47.7%) and caryophyllene oxide (18.3%). Using the same techniques, Medeiros *et al.*[28] also detected in a leaf essential oil eighteen terpenes, among them the following major substances: β-caryophyllene (15.9%), caryophyllene oxide (9.2%), α-humulene (8.1%), and a lower spathulenol content (only 2.1%), in comparison to that observed by Gramosa *et al.*[27]

More recently, the work developed by Sousa *et al.*[29] reports the characterization and the content of 22 substances present in the essential oil of the species, among them: caryophyllene oxide, sesquiterpene in higher content (23%); followed by (E)-caryophyllene (or β-caryophyllene) (14.5%), and α-copaene (7.2%). The authors infer that the variation in the content of the substances, in comparison to previous works, is related to geographic differences between the sites where the leaves used to obtain the oils were collected, among other factors.

### *Other Substances found in B. ungulata*

Analysis of samples obtained by different techniques, from roots, stems and leaves of *B. ungulata*, provided twenty substances, among which flavonoids, alkaloids, steroids and triterpenoids (Table 2), whose structures are shown in Figure 4. The substances first characterized in this species were detected in fractions obtained from an ethanol extract from leaves. The ethyl acetate fraction provided the flavonol quercetin, quercetin arabinofuranoside and quercitrin, in addition, 3-O-methyl-D-pinitol; and from the alkaloid fraction were isolated the β-carbonyl alkaloids harmana and eleaginine.[30]

Sousa *et al.*[31] isolated the flavanon liquiritigenin and the flavanols guibourtinidol and fisetinidol from ethyl acetate fractions obtained from ethanol extracts of roots and stem wood of the species, also

**Table 2: Substances characterized in derivatives of *B. ungulate* L.**

| Classification | Substance | Plant section | Sample | Reference |
|---|---|---|---|---|
| | Eriodictyol (1) | Stem bark | Ethanolic extract | [31] |
| | Fisetinidol (2) | Roots<br>Stem wood<br>Stem wood | Ethyl acetate fraction<br>Ethyl acetate fraction<br>Ethyl acetate fraction | [31]<br>[31]<br>[32] |
| Flavonoids | Guibourtinidol (3) | Roots<br>Stem wood<br>Stem wood | Ethyl acetate fraction<br>Ethyl acetate fraction<br>Ethyl acetate fraction | [31]<br>[31]<br>[32] |
| | Liquiritegin (4) | Roots<br>Stem wood<br>Stem wood | Ethyl acetate fraction<br>Ethyl acetate fraction<br>Ethyl acetate fraction | [31]<br>[31]<br>[32] |
| | Naringenin (5) | Stem bark | Ethanolic extract | [31] |
| | Quercetin (6) | Leaves | Ethyl acetate fraction | [30] |
| | Quercetin arabinofuranoside (7) | Leaves | Ethyl acetate fraction | [30] |
| | Quercitrin (8) | Leaves | Ethyl acetate fraction | [30] |
| Alkaloids | Harmane (9) | Leaves | Alkaloid fraction | [30] |
| | Eleagnine (10) | Leaves | Alkaloid fraction | [30] |
| | Betulinic acid (11) | Stem bark | Hexane extract | [31] |
| Triterpenoids | Glutinol (12) | Stem bark | Hexane extract | [31] |
| | Taraxerol (13) | Stem bark | Hexane extract | [31] |
| | Taraxerone (14) | Stem bark | Hexane extract | [31] |
| Steroids | Sitosterol (15) | Stem bark | Hexane extract | [31] |
| | Stigmasterol (16) | Stem bark | Hexane extract | [31] |
| | 3-*O*-methyl-D-pinitol (17) | Leaves | Ethyl acetate fraction | [30] |
| Other substances | Pacharin (18) | Stem bark | Ethanolic extract | [31] |
| | 2'-hydroxy-3,5-dimethoxy-4-methylbisbenzyl (19) | Roots | Ethyl acetate fraction | [31] |
| | 2'-hydroxy-3,5-dimethoxybisbenzyl (20) | Roots | Ethyl acetate fraction | [31] |

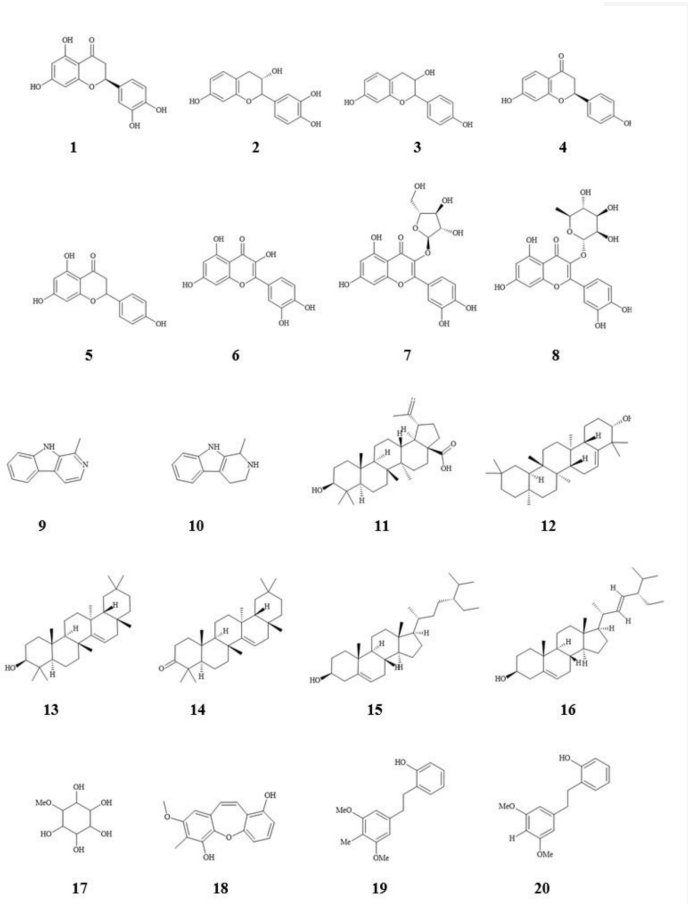



**Figure 4:** Structures of substances characterized in derivatives of *B. ungulata* L.

identifying two bisbenzyl substances (2'-hydroxy-3,5-dimethoxybisbenzyl and 2'-hydroxy- 3,5-dimethoxy-4- methylbisbenzyl) found in the roots, the last one not yet described at the time. In the stem bark, the authors identified the triterpenoids betulinic acid, taraxerol, taraxerone and glutinol, the flavanones naringenin and eriodictyol, pacharin and a mixture of the steroids sitosterol and stigmasterol. More recently, the flavonoids liquiritigenin, guibourtinidol and fisetinidol were again characterized in a fraction of ethyl acetate obtained from stem wood of the species, reinforcing the marked presence of these substances in different parts of *B. ungulata*.[32]

From seeds of the species, a lectin of specific binding to the galactose called BUL was isolated, with molecular mass of circa 30 kDa and 4.6% of carbohydrates in its composition. This glycoprotein was able to inhibit the growth of phytopathogenic fungi and showed *in vitro* antiproliferative activity against human colon adenocarcinoma cell lines.[33]

## Bioactivities

The surveyed literature describes some bioactivities investigated in *B. ungulata* derivatives, which are summarized in this topic. Until the elaboration of this review, the anti-inflammatory, antioxidant, antimicrobial, antiproliferative, healing, larvicidal, cytotoxic, antidepressant, anxiolytic and wound healing properties were demonstrated, in addition to the gelatinolytic activity of MMP-2 and MMP-9 and the inhibitory effects of acetylcholinesterase and of factors Xa, XII and Plasma Kallikrein (Table 3). Despite the widespread use of the species to treat diabetes, no papers describing the assessment of its anti-diabetic potential were found in the research.

### *Antioxidant Activity*

Port's *et al*.[34] determined the total phenolic and flavonoids in infusions obtained from *B. ungulata* var. *obtusifolia* and eight other plant species, popularly used in the Amazon region, and evaluated their antioxidant capacity using the DPPH free radical method and the β-carotene/linoleic acid system assay. The infusion prepared with leaves of *B. ungulata* was able to capture DPPH radicals, with $IC_{50}$ 210.66 μg/mL, an intermediate value compared to the other tested infusions, whose values ranged between 46.7 and 502.53 μg/mL. Concerning the analysis performed on the β-carotene/linoleic acid system, it was observed that the infusion inhibited the production of free radicals by the peroxidation of linoleic acid, presenting, however, an antioxidant capacity of 20.12 μg BHT/mL, a lower value when compared to the most active infusion, 93.29 μg BHT/mL. The antioxidant activity was positively correlated with the total phenolic content and suggests that this property is related to the phenolic compounds in the sample, quantified at 23.67 mg GAE/g.

The evaluation of the antioxidant potential of a crude ethanol extract obtained from *B. ungulata* leaves, and its fractions, revealed that all samples, especially the Ethyl Acetate fraction (FAE), were active. Concerning the total antioxidant capacity, evaluated by phosphomolybdenium complex reduction, the samples were active at 200 μg/mL, a FAE concentration that reduced 100% molybdenum VI to molybdenum V conversion, similarly to Rutin standard. In evaluating the samples for DPPH radical capture, $IC_{50}$ values between 7.68 and 124.74 μg/mL were found, the lowest of them recorded for FAE, which was similar to that observed for Rutin, 6.35 μg/mL. By the TBARS test (thiobarbituric acid reactive substances), which evaluates the reduction of the lipid peroxidation, FAE recorded up to 42.18% activity, a value with no statistically significant difference to the test using BHT standard (butyl-hydroxy-toluene).[35] The authors suggested that the antioxidant activity observed was related to the flavonoid quercetin, quercetin arabinofuranoside and quercitrin, previously characterized in leaves of the species by Maia Neto *et al*.[30]

The phosphomolybdenum complex reduction method was also used to determine the antioxidant activity of a flavonoid-rich ethyl acetate fraction (FABU) obtained from stem wood of *B. ungulata*. The sample showed greater activity than BHT, used as a control, and the antioxidant effect promoted by 1 mg of the fraction corresponded to that presented by 1.70 mg of BHT. The antioxidant potential of the sample was also evaluated by treating RAW 264.7 macrophages stimulated by lipopolysaccharide (LPS) with different concentrations of the fraction (15.63 - 62.5 μg/mL) and then measuring the production of reactive oxygen species (ROS), nitric oxide (NO), hydrogen peroxide ($H_2O_2$) and TBARS. A decrease in ROS, NO and $H_2O_2$ was observed in cells stimulated with LPS in the presence of the fraction, indicating its capacity to interfere in the cascade of ROS and RNS production. The FABU also reduced the TBARS production and inhibited lipid peroxidation, proving to be a promising natural antioxidant complex. The authors related the flavonoids liquiritigenin, guibourtinidol and fisetinidol isolated from the fraction to the observed activities.[32]

FABU was able to inhibit lipid peroxidation of cell membranes, when tested *in vivo*, due to the action of free radicals, in excised mice treated for five days with gels containing the fraction. Analysis of a tissue section removed from the wound after the treatment period revealed that gels containing 0.25% and 0.50% FABU produce an effective reduction in tissue malondialdehyde (MDA) levels, product of lipid peroxidation in animals, in comparison to non-treated group.[36]

**Table 3: Biological activities characterized in derivatives of *B. ungulata* L.**

| Activities | Tested samples (Plant section)* | Observed effects | Substances | Reference |
|---|---|---|---|---|
| Antioxidant | Infusion (L) | Intermediate capacity to capture DPPH radicals, compared to other infusions tested;<br>Inhibition of free radicals in the β-carotene/linoleic acid system. | Phenolic compounds | [34] |
| | Ethanolic extract and fractions (L) | Reduction of the phosphomolybdenum complex by all samples, highlighting the FAE, with 100% reduction, similar to rutin;<br>Capture of DPPH radicals by all samples and FAE was the most active;<br>Inhibition of lipid peroxidation by the samples, recording up to 42.18% reduction by FAE. | Quercetin**<br>Quercetin arabinofuranoside**<br>Quercitrin** | [35] |
| | Ethyl acetate fraction (Sw) | Reduction of the phosphomolybdenum complex greater than that presented by BHT (control). The antioxidant activity of 1 mg of fraction corresponded to that presented by 1.70 mg of BHT;<br>Reduction of ROS, NO and $H_2O_2$ levels in RAW 264.7 cells stimulated with LPS, reduction in TBARS production and inhibition of lipid peroxidation. | Liquiritigenin<br>Guibourtinidol<br>Fisetinidol | [32] |
| | Ethyl acetate fraction (Stw) | Inhibition of lipid peroxidation in excised mice, treated with gels containing the fraction. Analysis of a tissue section taken from the lesion site after the treatment showed that the use of gels with 0.25% and 0.50% FABU resulted in an effective reduction in tissue malondialdehyde (MDA) levels in the animals compared to the untreated group with fraction. | Liquiritigenin<br>Guibourtinidol<br>Fisetinidol | [36] |
| Antimicrobial | Essential oil (L) | Growth inhibitory activity of *Staphylococcus aureus, Salmonella typhimurium* and *Candida albicans* by oil, which ranged from 80-85% with the three largest concentrations tested (250, 125 and 62.5 μg / mL). | 18 terpenes<br>(β-caryophyllene, caryophyllene oxide and α-humulene were the majority) | [28] |
| | BUL lectin (S) | Growth reduction of *Fusarium lateritium, F. moniliforme, F. oxysporum fungi, F. solani, Aspergillus niger* and *Colletotrichum lindemuthianum*;<br>Greater activity against *F. solani* and *F. moniliforme* (40 and 30% inhibition, respectively). | N/A | [33] |
| Anti-inflammatory | Ethyl acetate fraction (Sw) | Reduction in the relative levels of genes expressing the pro-inflammatory mediators IL-1β and TNF-α in mice submitted to surgical excision and treated with gels containing the fraction. | Liquiritigenin<br>Guibourtinidol<br>Fisetinidol | [36] |
| Acetylcholinesterase inhibition | Hexane extracts (F, B, L) | Inhibition of the enzyme by the extracts. The sample prepared with flowers was the most potent. | N/D | [39] |
| | Essential oil (L) | Inhibition of more than 95% of the enzyme by the oil, which showed to be more active than the standards eserine and galantamine tested in the work. | 18 terpenes<br>(β-caryophyllene, α-bisabolol, α-pinene, β-pinene and caryophyllene oxide may be related to activity) | [28] |
| Cytotoxic | Essential oil (L) | High toxicity of the sample against *Artemia salina*, with $LC_{50}$ 144.75 μg/mL. | N/D | [28] |
| | 2'-hydroxy-3,5-dimethoxy-4-methylbibenzyl (R) | Cytotoxicity against HL-60, MCF-7, NCI-H292 and HEP-2 cell lines, being more active against HL-60 and HEP-2, with $IC_{50}$ 4.3 and 6.5 μg/mL, respectively. | N/A | [31] |
| Antiproliferative | BUL lectin (S) | Inhibition of HT-29 cell proliferation in a dose-dependent manner, starting at 60 μg/mL and reaching 80% inhibition with 160 μg/mL of the lectin. | N/A | [33] |
| Larvicidal | Essential oil (L) | Death of part of the instar III larvae of *Aedes aegypti* by the oil after 24 h, with a $LC_{50}$ value calculated at 75.1 ± 2.8 μg/mL. | 19 sesquiterpenes, among which caryophyllene oxide | [29] |

continued...

**Table 3: Cont'd**

| Activities | Tested samples (Plant section)* | Observed effects | Substances | Reference |
|---|---|---|---|---|
| Inhibition of the gelatinolytic activity of MMP-2 and MMP-9 | Hydroalcoholic, hexane, chloroform and ethyl acetate partitions (St) | Inhibitory activity of MMPs by the tested samples, highlighting the hydroalcoholic and ethyl acetate partitions, whose inhibition percentage was greater than 90%;<br>The ethyl acetate partition was considered the most potent among the tested samples. | Flavonoids and alkaloids | [40] |
| Healing | Ethyl acetate fraction (Sw) | Progressive reduction of an injured area by surgical excision, especially in mice treated with gel containing 0.5% FABU fraction, which showed the best healing effect compared to the others tested, including the standard. | Liquiritigenin<br>Guibourtinidol<br>Fisetinidol | [36] |
| Inhibition of fractions Xa and XII and plasma kallikrein | BuXI (S) | The BuXI protein inhibited factor XII and kallikrein, which showed, after incubation, Ki $8.0x10^{-8}$ and $0.7x10^{-8}$ M, respectively;<br>Factor Xa was strongly inhibited by BuXI, presenting a Ki of $1.4 \times 10^{-8}$ M at the end of the process. | N/A | [41] |
| Antidepressant and anxiolytic | Alkaloid extract (L) | Significant increase in the number of stalks in the last three days of treatment when compared to the negative control group (elevated plus maze test);<br>Increase in the time spent by the animals in the bright field when compared to the negative control (light/dark test);<br>No changes in water consumption, feed and excreta production during the 14 days after the administration of a single dose (2000 mg/kg) of the extract and occasional changes in the animals' breathing. The treatment with the alkaloid extract did not promote significant cellular changes in the liver of animals. | Alkaloids | [44] |

* B: branches, F: flowers, L: leaves, S: seeds, St: Stem, Sw: stem wood, R: roots.

** Substances not detected in the sample, but their presence and relation to characterized activity were suggested by the authors, based on previously published results.

N/A: Not applicable.

N/D: Not determined by authors.

### *Antimicrobial Activity*

An essential oil, obtained from leaves of *B. ungulata,* was tested *in vitro* against strains of five pathogenic micro-organism and showed growth inhibitory activity on *Staphylococcus aureus*, *Salmonella typhimurium* and *Candida albicans*, which ranged from 80 to 85% with the three highest concentrations (250, 125 and 62.5 µg/ml) of the tested sample. The chromatographic analysis of the oil allowed the characterization of eighteen terpenic substances and revealed the majority presence of β-caryophyllene, caryophyllene oxide and α-humulene.[28]

The BUL lectin, a protein isolated from *B. ungulata* seeds, was evaluated *in vitro* for its ability to inhibit the growth of phytopathogenic fungi *Fusarium lateritium, Fusarium moniliforme, Fusarium oxysporum, Fusarium solani, Aspergillus niger* and *Colletotrichum lindemuthianum*, distributing 160 µg of the glycoprotein in plates containing the microorganisms. It was observed that BUL reduced the growth of all tested fungi, being more effective against *F. solani* and *F. moniliforme* (40 and 30% inhibition, respectively) and showing less inhibition against *F. lateritium* (about 5% growth reduction). This activity was considered fungistatic.[33]

The analysis of other derivatives of the species, regarding their antimicrobial potential, revealed different results from those observed for the essential oil or for the BUL lectin. The evaluation of a hydroalcoholic extract and fractions (hexane, chloroform, ethyl acetate and residual hydroalcoholic) obtained from leaves of the species, for example, showed a low inhibitory potential for the growth of *Staphylococcus aureus, Escherichia coli, Enterococcus faecalis* and *Pseudomonas aeruginosa* strains, and the samples were considered inactive.[37] Similarly, an ethyl acetate fraction obtained from stem wood of *B. ungulata* was tested against *Candida albicans*, methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains, and were presented MIC values greater than 500 µg/mL, not demonstrating significant antimicrobial activity.[32]

On the other hand, an aqueous extract obtained from leaves of *B. ungulata* and tested for the modulating activity of antibiotics (amikacin, gentamicin, ciprofloxacin and imipenem) against strains of *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* was showed relevant synergistic activity on the drugs used, especially imipenem and ciprofloxacin, for which synergism was observed with the three bacteria tested.[38]

### *Anti-inflammatory Activity*

A flavonoid-rich ethyl acetate fraction obtained from stem wood of *B. ungulata* (FABU) was tested at 15.63-62.5 µg/mL for its anti-inflammatory activity on RAW 264.7 macrophages stimulated by lipopolysaccharide (LPS) and did not change the levels of cytokines TNF-α, TGF-β and IL-10 produced, indicating its low immunomodulatory potential.[32] On the other hand, the treating mice submitted to surgical excision with gels containing FABU promoted a significant reduction in the relative levels of genes expressing the pro-inflammatory mediators IL-1β and TNF-α in injured region of these animals, compared to those that did not receive the treatment, suggesting that the fraction acts by regulating the inflammatory environment during the first stages of the healing process.[36]

### *Healing Activity*

The FABU was evaluated for its healing potential in a model that used mice in the experimentation. An injury made on the animals' back was

treated daily, for five days, with two different doses of the ethyl acetate fraction, incorporated in a 940 carbomer gel and then the lesion size was evaluated. The authors observed that during treatment, in addition to no bacterial growth, there was a progressive reduction in the injured area, especially in animals treated with the gel containing 0.5% FABU, which showed a better healing effect compared to the other samples tested, including the standard used in the test.[36]

### *Acetylcholinesterase Inhibition*

Hexane extracts, obtained from flowers, branches and leaves of *B. ungulata,* were investigated for their ability to inhibit acetylcholinesterase using a thin layer chromatography method. Of the samples tested, only the extract from the leaves did not show activity and the one obtained from the flowers was the most potent, suggesting that this is the plant organ with highest concentration of enzyme-inhibiting substances.[39] An essential oil from leaves of the species was analyzed *in vitro* and inhibited the acetylcholinesterase in a percentage higher than 95%, and being more active than the eserine and galantamine, standards also analyzed in the test. This activity was related by the authors to constituents detected in the sample, including β-caryophyllene, which was the major substance in the oil (15.9%) and α-bisabolol, which represented 4.7% of the constituents present. The authors also highlight the presence of α-pinene, β-pinene and caryophyllene oxide, which could have a synergistic action in the inhibitory effect of acetylcholinesterase by the essential oil.[28]

### *Cytotoxic Effect*

The cytotoxic effect of an essential oil obtained from leaves of *B. ungulata* was evaluated against *Artemia salina* and showed a high toxicity, with $LC_{50}$ 144.75 µg/mL, indicating its potential for biological activities.[28] On the other hand, a hydroalcoholic extract and fractions (hexane, chloroform, ethyl acetate and residual hydroalcoholic) of *B. ungulata* proved to be non-cytotoxic when analyzed by the same model.[37] The *in vitro* evaluation of 2'-hydroxy-3,5-dimethoxy-4-methylbisbenzyl isolated from *B. ungulata* roots against cell lines HL-60 (human promyelocytic leukemia), MCF-7 (human adenocarcinoma of the breast), NCI-H292 (human lung carcinoma) and HEP-2 (human cervical adenocarcinoma), revealed its cytotoxic potential, which was higher against HL-60 and HEP-2, with $IC_{50}$ 4.3 and 6.5 µg/mL, respectively.[31]

### *Antiproliferative Activity*

The *in vitro* antiproliferative potential of the BUL lectin isolated from *B. ungulata* seeds was evaluated against human colon adenocarcinoma (HT-29 cell line), using glycoprotein concentrations ranging from 20 to 160 µg/mL. The tested lectin inhibited cell proliferation in a dose-dependent manner, starting its activity at 60 µg/mL and reaching 80% inhibition with the highest concentration tested. The preliminary results observed by the authors suggest that BUL possesses the potential to be used as a tool in studies involving cancer cells.[33]

### *Larvicidal Activity*

Sousa *et al.*[29] evaluated the larvicidal activity of an essential oil obtained from leaves of *B. ungulata* against instar III larvae of *Aedes aegypti*. Briefly, the parasites were kept in contact with the sample at concentrations ranging from 50 to 500 µg/mL for 24 hr and the number of dead larvae was evaluated after this period. Based on these results it was possible to determine the $LC_{50}$ value of the oil, calculated at 75.1 ± 2.8 µg/mL. The authors related the larvicidal activity to sesquiterpenes detected in the sample, including caryophyllene oxide, characterized as the major substance in the oil.

### *Inhibition of Gelatinolytic Activity of MMP-2 and MMP-9*

The inhibition of the gelatinolytic activity of MMP-2 and MMP-9, proteases related to tumor invasion and metastasis in several types of cancer, represents an important property presented by *B. ungulata* L. In this investigation, the hydroalcoholic, hexane, chloroform and ethyl acetate partitions obtained from a crude extract of stems of the species were tested, and the inhibitory activity was observed for all samples tested, highlighting the hydroalcoholic and ethyl acetate partitions, with inhibition greater than 90%. The phytochemical investigation of the ethyl acetate partition revealed the presence of steroids, tannins, coumarins, alkaloids and flavonoids in the sample, however, the analysis of fractions obtained by chromatographic separation of this partition regarding the present metabolites and inhibitory potentials of MMPs, revealed that the activity of the sample is related to its flavonoids and/or alkaloids.[40]

### *Inhibition of Factors Xa and XII and Plasma Kallikrein*

From seeds of *B. ungulata* the protein BuXI was isolated and characterized as an inhibitor of serine proteases factor Xa, factor XII and plasma kallikrein, involved in the blood coagulation cascade. This determination was carried out by incubating the BuXI factor with the enzymes at different concentrations. At the end of the process, the residual activity of the enzyme was evaluated, based on its dissociation constant (Ki). As a result, it was observed that the protein inhibited factor XII and kallikrein, which presented, after incubation, a Ki of $8.0x10^{-8}$ and $0.7x10^{-8}$ M, respectively. In addition, factor Xa was strongly inhibited by BuXI, with a Ki $1.4 \times 10^{-8}$ M at the end of the process, and this result characterized the protein as a plant protease inhibitor with greater affinity for factor Xa described so far.[41] Further work was carried out to characterize the interactions between blood coagulation proteases and the BuXI inhibitor.[42,43] The inhibitory effect of the protein isolated from *B. ungulata* on coagulation factors is important, as it suggests its potential as an anticoagulant agent.

### *Antidepressant and Anxiolytic Activity*

An alkaloid extract obtained from leaves of *B. ungulata* was evaluated for its ability to reduce the depressive behavior of mice, and its acute toxicity was also evaluated.[44] Initially, depression was induced in the animals by forced swimming and after this step, the alkaloid extract was administered by gavage, for 12 days, 30 min before the behavioural tests (light/dark test and elevated plus maze test). As for the elevated plus maze test, it was observed that the animals treated with the extract showed a significant increase in the number of stalks in the last three days of treatment when compared to the negative control group, which indicates an improvement in the depressive state of the mice and suggests the activity anxiolytic of the extract. Similarly, in the light/dark test, an increase in the time spent by the animals in the bright field was observed compared to the negative control, which represents an indication of non-anxious and non-depressive behaviour in the mice. As for acute toxicity, it was noted that the administration of a single dose (2000 mg/kg) of the extract did not promote changes in water consumption, feed and excreta production during the 14 days after treatment. Only occasional changes in the animals' breathing were observed, which could be related to stress during the experiment. In addition, the histological analysis of the livers revealed that the treatment with the extract did not promote significant cellular changes, indicating a low level of toxicity of the extract.

## CONCLUSION

Despite the limited number of articles published about *Bauhinia ungulata*, the selected works deal with different bioactivities and provide information on many metabolites present in different derivatives investigated, indicating that the phytochemical and biological data

published on this species allow to infer a potential of use as a therapeutic ingredient with antioxidant activity, which is the most investigated activity and has been related to phenolic compounds, especially flavonoids, detected in the species. It is also observed and reported that *Bauhinia* spp. is popularly used as an infusion to control diabetes, however, the search has found no published data reporting the evaluation of the antidiabetic or hypoglycemic activity of *B. ungulata*. As for the phytochemical analysis of the leaves, the selected works focused on the investigation of its essential oils, with no data being found on the substances present in aqueous extracts, which represent the main popular form of use reported for *Bauhinia* leaves, according to the consulted references.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**BHT:** Butylated hydroxytoluene; **BUL:** Lectin from *Bauhinia ungulata*; **BuXI:** *Bauhinia ungulata* factor Xa inhibitor; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; **FABU:** Flavonoid-rich ethyl acetate fraction obtained from stem wood of *B. ungulata*; **FAE:** Ethyl acetate fraction; **GAE:** Gallic acid equivalents; **GC-FID:** Gas chromatography-flame-ionization detection; **GC-MS:** Gas chromatography-mass spectrometry; **$IC_{50}$:** Half maximal inhibitory concentration; **IL-10:** Interleukin 10; **$LC_{50}$:** Lethal concentration 50; **LPS:** Lipopolysaccharide; **MDA:** Malondialdehyde; **MIC:** Minimum inhibitory concentration; **MMP-2:** Matrix metalloproteinase 2; **MMP-9:** Matrix metalloproteinase 9; **RNS:** Reactive nitrogen species; **ROS:** Reactive oxygen species; **TBARS:** Thiobarbituric acid reactive substances; **TGF-β:** Transforming growth factor beta; **TNF-α:** Tumor necrosis factor alpha.

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