Artículo original

Phytochemical constituents and antifungal and antibacterial activities of *Zanthoxylum riedelianum* Engl trunk bark extract

Constituyentes fitoquímicos y actividades antifúngicas y antibacterianas del extracto de corteza de tronco de *Zanthoxylum riedelianum* Engl

Antonio Carlos Pereira de Menezes Filho[1,2*] https://orcid.org/0000-0003-3443-4205
Matheus Vinicius Abadia Ventura[3] https://orcid.org/0000-0001-9114-121X
Cinthia Alves Porfiro[4] https://orcid.org/0000-0002-4398-0323
Carlos Frederico de Souza Castro[2] https://orcid.org/0000-0002-9273-7266
Marconi Batista Teixeira[1] https://orcid.org/0000-0002-0152-256X
Frederico Antônio Loureiro Soares[1] https://orcid.org/0000-0002-4152-5087

[1]Instituto Federal Goiano, Laboratório de Irrigación e Hidráulica, Rio Verde. Goiás State, Brazil.
[2]Instituto Federal Goiano, Laboratório de Química Tecnológica, Rio verde. Goiás State, Brazil.
[3]Instituto Federal Goiano, Laboratório de Microbiologia Agrícola, Rio Verde. Goiás State, Brazil.
[4]Faculdade UniBRAS, Laboratório de Fitoquímica Farmacêutica, Rio Verde. Goiás State, Brazil.

[*]Autor para la correspondencia: astronomoamadorgoias@gmail.com

RESUMEN

Introducción: *Zanthoxylum riedelianum* es una especie arbórea típica del dominio del Cerrado brasileño, perteneciente a la familia Rutaceae.

Objetivo: Evaluar la constitución fitoquímica cualitativa y las actividades antifúngica y antibacteriana del extracto etanólico de la corteza del tronco de *Z. riedelianum*.

Métodos: Las cortezas de los troncos se obtuvieron de árboles en Cerrado *sensu stricto*. Con la producción del extracto etanólico se realizaron los análisis fitoquímicos con diferentes reactivos colorimétricos y de precipitación. La actividad antifúngica se realizó

sobre el género *Candida* y la actividad antibacteriana sobre *Staphylococcus*, *Escherichia*, *Salmonella* sp. en diferentes concentraciones.

Resultados: La fitoquímica reveló la presencia de varios grupos del metabolismo especial de la corteza del tronco de *Z. riedelianum*. Potencial efecto antifúngico sobre *C. tropicalis, C. Guilliermondii y C. Krusei*. Además mostró buena actividad antibacteriana contra *E. coli y S. serovar Enteritidis*.

Conclusiones: El extracto etanólico de la corteza del tronco de *Z. riedelianum* exhibió potencial actividad antifúngica y antibacteriana frente a cepas de interés médico. Estas actividades contrastan con los numerosos grupos fitoquímicos presentes en el extracto. Se deben realizar nuevos estudios que evalúen cuantitativamente los grupos fitoquímicos y otras actividades biológicas sobre el extracto etanólico de la corteza del tronco de *Zanthoxylum riedelianum*.

Palabras clave: género *Zanthoxylum*, *Escherichia coli*, *Staphylococcus aureus*, Família Rutaceae, Extracto vegetal.

ABSTRACT

Introduction: *Zanthoxylum riedelianum* is a species of tree species typical of the Brazilian Cerrado domain, belonging to the family *Rutaceae*.

Objective: To evaluate the qualitative phytochemical constitution and the antifungal and antibacterial activities of the ethanolic extract of the bark of the trunk of *Z. riedelianum*.

Methods: Trunk bark was obtained from trees in Cerrado *sensu stricto*. The analysis of phytochemicals was performed on different colorimetric and precipitation reagents. Antifungal activity against Candida and antibacterial activity against *Staphylococcus, Escherichia and Salmonella sp*. were performed at different concentrations of extract.

Results: Phytochemistry revealed the presence of several groups of special metabolism of the trunk bark of *Z. riedelianum*, and potential antifungal effect on *C. tropicalis*, *C. Guilliermondii* and *C. Krusei*. In addition, it showed good antibacterial activity against *E. coli* and *S. serovar Enteritidis*.

Conclusions: The ethanolic extract of the bark of the trunk of *Z. riedelianum* exhibited potential antifungal and antibacterial activity against strains of medical interest. These activities contrast with the numerous phytochemical groups present in the extract. Further studies should be conducted quantitatively evaluating phytochemical groups and other biological activities on ethanolic extract from the trunk bark of *Zanthoxylum riedelianum*.

Keywords: Genus *Zanthoxylum*; Escherichia coli; *Staphylococcus aureus*; Family *Rutaceae*; plant extract.

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Introduction

The genus *Zanthoxylum* belonging to the Rutaceae family encompasses a group of more than 250 species with a pantropical distribution, showing a high density of species in South America.[1,2] Among the species that include *Zanthoxylum*, we find in particular *Zanthoxylum riedelianum* Engl is commonly known in Brazil as "mamica de porca or mama de porca" and frequently found in the Midwest region[2], a species known for its pharmacological activities (anti-inflammatory and analgesic),[3] antinociceptive, cytotoxic and apoptotic[4] and biocides (insecticide).[5] The extracts and essential oils extracted from the leaves and stem bark present numerous phytochemical groups belonging to the special metabolism of this plant, making it an attractive natural source for new pharmacological, biological, biotechnological and agricultural studies.

Lara and others[2] found high antifungal activity against Sclerotinia sclerotiorum and Rhizopus stolonifer using the stem bark essential oil (*Z. riedelianum*), in addition, the researchers determined the major compounds by GC-MS where they found *E*-nerolidol with 67,21%, α- selinene with 14,94% and *β*-selinene with 7,41%, these being the volatile molecules responsible for the antifungal activity. Costa and collaborators[5] demonstrated that the essential oil of *Z. riedelianum* exhibited insecticidal activity through a repellent emulsion. Lima and collaborators[3] observed potential anti-inflammatory and analgesic action when studying the ethanolic leaf extract. *Pereira* and others[1] observed that the essential oil from the fruit of *Z. riedelianum* showed good insecticidal activity against *Bemisia tabaci*.

According Beirigo and collaborators[4] and Chen and collaborators[6] the plants belonging to this *Zanthoxylum* genus have phytochemical groups, especially alkaloids, aliphatic and aromatic amides, coumarins and lignans. The previous studies on *Z. riedelianum* have described the phytochemical metabolites, was well as alkaloids from the roots and lignans

from the stem bark. There is only one study that reported on cyclized peptides in the *Zanthoxylum* genus.

Although there are several studies characterizing the special metabolites of *Z. riedelianum*, this species still has potential for further studies evaluating the different types of extracts produced in all organs of this plant. To evaluate the qualitative phytochemical constitution and the antifungal and antibacterial activities of the ethanolic extract of the trunk bark of *Z. riedelianum*.

Methods

Plant material and ethanolic extract obtention

Fresh trunk bark (150g) of *Z. riedelianum* collected from the *Cerrado* domain at *Universidade de Rio Verde* (UniRV), Rio Verde, Goiás State, Brazil, in March 2022. A voucher specimens (HRV 3.177) was deposited in the Herbarium of the *Instituto Federal Goiano*, *Rio Verde*, *Goiás* State, Brazil. The ethanolic extract was obtained using 98% ethanol as a solvent and reflux in Soxlhet apparatus until exhausted. After filtering, both organic extract were concentrated at 45 °C and speed of 70 rpm in a rotary evaporator, then, stored in a freezer -18 °C. The *Z. riedelianum* trunk bark extract was then dried (yield 19.15%).

Phytochemical prospection

The phytochemical assay to detect presence of saponins, phenols, tannins, flavonoids, steroids, triterpenes, coumarins, quinones, organic acids, alkaloids, cardiac glycosides, carboxylic acids, aromatic and aliphatic compounds, azulenes were performed following the method described by Carvalho and collaborators[7]. The tests were based on the visual observation of color modification or precipitate formation after the addition of specific reagentes.

Antifungal activity assay

Were fungal acquired strains of the American Type Culture Collection (ATCC) used in this study, *Candida tropicalis* (ATCC2591-4), *C. albicans* (ATCC 2115-1), *C. krusei*

(ATCC 2047-3) and *C. guilliermondii* (ATCC 2018-2). The fungal strains belong to the first author's private mycological bank.

Antifungal assay was performed as described by Menezes Filho and collaborators[8] adapted. The strains were resuspended in 25 mL os sterile Sabouraud Dextrose Broth (SDB). The suspension was shaken on a shaking table with incubation for 26 h at 36 °C. Starting from this culture inoculum containing approximately $1x10^8$ CFU mL^{-1} were prepared according to the turbidity in cuvette of 0.5 McFarland scale, in a UV-*Vis* spectrophotometer. The antifungal activity was carried out in a solid medium SDB using sterile filter paper discs with a 7 mm diameter. Four paper disks containing 50 µL in different concentrations of trunk bark extract concentration (100, 50, 25 and 12.5 mg mL^{-1}), diluted in ethanol and were added to each *Petri* dishes. As a negative control ethanolic was used, absence of interferents and, as a positive control, Ketoconazole concentration (50 µg mL^{-1}). Zones of inhibition were examined after 46 h, measured and recorded as the diameter (mm) of complete growth inhibition, obtained with the aid of a eletronic digital caliper. The minimum inhibition zone considered was 5 mm.

Antimicrobial activity assay

Escherichia coli (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Salmonella serovar* Enteritidis (ATCC 13076) and *Salmonella serovar* Typhimurium (ATCC 14028) assay was performed, in triplicate, according to Nascimento and collaborators[9] modified. Starting from this culture inoculum containing approximately $1x10^4$ CFU mL^{-1} were prepared according to the turbidity in cuvette of 0,5 McFarland scale, in a UV-*Vis* spectrophotometer. The bacteria test were grown in Petri dishes containing Müller-Hinton Agar II (MHA) in 7 mm diameter holes made in the nutrition agar. The ethanolic extract was assayed at concentration (10, 7, 5, 3 and 1 mg mL^{-1}/cavity). Dimethylsulphoxide (DMSO) concentration 5% (*v/v*) (-) and Cephalexin (30 µg disc) (+) and Azithromycin (15 µg disc) (+) were used as negative and positive controls, respectively. After, the plates were incubated at 36 °C for 24-36 h and the inhibition halo diameter was measured with a eletronic digital caliper. The minimum acceptable diameter was 5 mm.

Statistical analysis

The results are presented as the mean values (±) standard deviation. In order to determine the reproducibility of the measurement, each antifungal and antibacterial activities was

carried out in triplicate. Data were submitted to the analysis of variance (ANOVA) and the means of the treatments were evaluated by the Duncan's test at 5% significance level.

Resultados

Phytochemical prospection identified saponins, phenols, tannins, flavonoids, coumarins, alkaloids, quinones, organic acids, cardiac glycosides, carboxylic acids, aromatic compounds, purines, reducing sugars, no-reducing sugars, polysaccharides, amino acids, anthraquinones and resins. Steroids, triterpenes, azulenes, catechins and fatty acids were not detected by qualitative tests in the ethanolic extract of *Z. riedelianum* trunk bark (Table 1).

Table 1- Phytochemical screening of trunk bark extract of *Zanthoxylum riedelianum*

Special metabolites	Results
Hemolytic saponins	+
Foaming saponins	+
Phenols	+
Tannins	Green
Flavonoids	+
Steroids	-
Triterpenes	-
Coumarins	+
Quinones	+
Organic acids	+
Alkaloids	+
Cardiac glycosides	+
Carboxylic acids	+
Aromatic and aliphatic compounds	Aromatic
Azulenes	-
Purines	+
Reducing sugars	+
No-reducing sugars	+
Polysaccharides	+
Amino acids	+
Catechins	-
Anthraquinones	+
Resins	+
Fatty acids	-

*(-) Negative **(+) Positive ***(Green) = Condensed or catechins tannins.

The antifungal assay on *Candida* strains (Table 2) showed that for *C. tropical*, *C. krusei* and *C. guilliermondii* are sensitive to the ethanolic extract of the trunk bark of *Z. riedelianum* in most concentrations, showing a statistical difference between the commercial antifungal Ketoconazole and the extract. Among the highest concentrations 100-50 mg mL^{-1} there was no difference between them, except for *C. albicans* and *C. krusei*. Still in Table 2, *C. albicans*, *C. krusei* and *C. guilliermondii* showed to be resistant between 50-12.5 mg mL^{-1}.

Table 2 - Antifungal activity of the ethanolic extract of the trunk bark of *Zanthoxylum riedelianum* on *Candida strains*

Fungal strains	**Inhibition zone (mm) Concentration mg mL^{-1}**			
	100	50	25	12.5
C. tropicalis	13.01 ± 0.07b	11.90 ± 0.03b	7.14 ± 0.21c	5.3 ± 0.12d
C. albicans	6.55 ± 0.13b	-c	-c	-c
C. krusei	9.67 ± 0.09b	6.03 ± 0.11c	-d	-d
C. guilliermondii	10,10 ± 0.15b	8.64 ± 0.15b	5.10 ± 0.04c	-d

*(-) not detectable. **Ketoconazole = *C. tropicalis* 25,2 mm a, *C. albicans* 24,6 mm a, *C. krusei* 27,4 mm a and *C. guilliermondii* 27,3 mm a. ***Equal letters on the same line show no statistical difference by the Duncan's test at 5% significance.

Results obtained in the study of antibacterial activity (Table 3) were satisfactory for the strains *E. coli* showed to be highly sensitive to the ethanolic extract of the trunk bark of *Z. riedelianum* between the highest and lowest concentrations, except at the concentration of 1 mg mL^{-1} where it did not show growth inhibition. Although it showed important bacterial activity, the results indicated that it was inferior to the reference antibacterials. Statistically, between 10-7 and 5-3 mg mL^{-1} did not differ statistically.

Another important pathogenic bacteria *S. serovar* Enteritidis proved to be sensitive between concentrations of 10-5 mg mL^{-1}, showing a statistical difference between the reference antibacterial and the concentrations of the ethanolic extract of *Z. riedelianum*. *S. aureus* did not exhibit any growth inhibition activity, demonstrating to be highly resistant at the usual concentrations, and finally, the *S. serovar* Typhimurium strains only showed sensitivity at the highest concentration, also showing a difference between the reference antibacterial and the extract ethanolic.

Table 3- Antibacterial activity of the ethanolic extract of the trunk bark of *Zanthoxylum riedelianum* on *Escherichia*, *Staphylococcus* and *Salmonella sp*

Bacterial strains	Inhibition zone (mm) Concentration mg mL^{-1}				
	10	7	5	3	1
E. coli	15,08 ± 0,11b	14,43 ± 0,08b	9.17 ± 0,08c	7,03 ± 0,12c	-d
S. aureus	-b	-b	-b	-b	-b
S. Enteritidis	14,05 ± 0,04b	11,78 ± 0,06c	7,33 ± 0,05d	-e	-e
S. Typhimurium	5,83 ± 0,07b	-c	-c	-c	-c

*(-) not detectable. **Cephalexin (30 µg disc) = *S. aureus* 23.1 mm a, *S. serovar* Typhimurium 27.7 mm a, *S. serovar* Enteritidis 26.7 mm a. ***Azithromycin (15 µg disc) = *E. coli* 26.8 mm a. ****Equal letters on the same line show no statistical difference by the Duncan's test at 5% significance.

Discussion

The Rutaceae family comprises a set of exuberant plant species, mainly in the tropics and especially in South America. As previously discussed, the *Zanthoxylum* genus exhibit pharmacological potential mainly with antifungal, antibacterial, antioxidant and cytotoxic activities[10,11,12]. *Zanthoxylum* sp. shares among species the presence of common special metabolites such as alkaloids, coumarins, lignans, flavonoids, terpenes, steroids, alkylamides.[12]

The phytochemical prospection component demonstrated numerous chemical groups of medical, biological and agricultural relevance, as well as biotechnology. In agreement with this study, Ombito[13] and Okagu and collaborators[14] in a phytochemical review on the *Zanthoxylum* genus described 500 new phytochemical compounds included in the special metabolism in several species belonging to this genus, such as alkaloids, amides, lignans and neolignans, coumarins, peptides, terpenoids, phenolic acids and flavonoids. Several of these representative molecules have formidable antifungal, antibacterial, analgesic, anti-inflammatory activities and, as observed in Table 1, the presence of purines that are used in th[15]e production of drugs that reflect neurological action.

In a brief review, it is possible to cite the main molecules found in *Zanthoxylum*, such as neohesperidin, hesperidin, eriocitrin and quercetin in *Z. zanthoxyloides* extracted from the roots and trunk; hyperoside, quercetin-3-*O*-glucopyranoside, datiscin and quercetin no extrato foliar[15]. Tine and collaborators found hexadecanoic acid, germacrene D and decanal while pellitorine for the essential oil of *Z. zanthoxyloides* as major compounds in the roots and trunk bark. *Z. zanthoxyloides* include atanine, hesperetin, isoplatydesmine, *N*-methylplatydesminium cation, myrtopsine, ribalinine, *N*-methylatanine, *Trans*-fagaramide, zanthoamides G-I, (+)-sesamin, skimmianine and hesperidin from the fruits described by the study Tamdem[16]; 4′-(4″-hydroxy-3″-methylbutyloxy)-2-phenylethanol,

hydrocuspidiol, cuspidiol, 4′-(3″-methylbut-2″-enyloxy)-3-phenylpropanol, dihydrocusidiol, lupeol, 8-acetonyldihydrochelerythrine, *N*-isobutyl-(*2E,4Z*)-deca-2,4-dienamide, (+)-sesamin[17]; burkinabins A, B and C, *N*,*N*-dimethyllindicarpin, 1,8-di-*O*-(3-methoxy-4-hydrobenzoyl)-3,6-dihydroxycyclooctane-2,7-endoperoxide, hesperidin, fagaronine, and norchelerythrine, and from the root bark; and flavonoids (rutin and quercetin) and phenolic acids (caffeic and chlorogenic acids) as the major constituents of the stem bark[18]; 8-acetonyldihydrochelerythrine in *Z. paracanthum*, *Z. zanthoxyloides* and *Z. gilletii* por Kaigongi e colaboradores.[19]

This large number of compounds provides different biological activities mainly in the fight against pathogenic microorganisms such as fungi and Gram-positive and Gram-negative bacteria. Although our results have show antifungal and antibacterial potential, the reference antifungal and the two antibacterials, even if synthetic, is still the best option, however, it is observed that the *Candida* genus has been showing resistance to Ketoconazole and Fluconazole, thus opening the possibility of introducing molecules of plant origin as a means of interaction promoting, through synergism, the biochemical inhibition of this genus of yeasts of medical interest. Thus, comparing the antibiosis results obtained in this study on the antifungal and antibacterial effects, demonstrates that the *Zanthoxylum* genus is a possible candidate with biomolecules capable of being possible new drug candidates. This is confirmed by observing other *Zanthoxylum* species such as *Z. nitidum* where the alcoholic extract demonstrated antifungal and antibacterial activity against *S. aureus*, *E. coli*, *C. albicans*, *Pseudomonas aeruginosa* and MRSA.[20] Huang and collaborators[21] also obtained high antibacterial and antifungal potential in extracts of *Z. nitidum* in different solvent polarities (70% ethanol extract, ethyl acetate portion, *n*-butanol portion and water portion) on *E. coli*, *Salmonella*, *Bacillus subtilis*, *S. aureus* and *C. albicans*. Not only do the extracts present a formidable antibiosis action against a large number of pathogenic microorganisms for humans, animals and plants, where many are of commercial interest, Wang and collaborators,[22] evaluating the essential oil of *Z. bungeanum* incorporated in a starch-based biopolymer, also found antibacterial action against *E. coli*, *S. aureus* and *L. monocytogenes*. In a study, Lara and collaborators[2] described a high inhibition capacity of the essential oil of *Z. riedelianum* on *R. stolonifer* (> 80%) and (> 72%) for *Sclerotinia sclerotiorum*. Chen and collaborators[6] suggest that the high inhibition potential of the essential oil of *Z. riedelianum* is due to the major compound *E*-nerolidol on *Colletotrichum fructicola*.

It concludes that the ethanolic extract of *Zanthoxylum riedelianum* has potential for in vitro and in situ studies, as well as quantification of the phytochemical compounds present in the trunk bark. In addition, the species can be studied throughout the seasons, thus observing variations in biological activities, phytochemical quantification and other actions of pharmacological, agricultural and biological interest.

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Author contributions

Conceptualiztion: Antonio Carlos Pereira de Menezes Filho.

Writing (original draft): Antonio Carlos Pereira de Menezes Filho; Matheus Vinicius Abadia Ventura and Cinthia Alves Porfiro.

Formal analysis: Antonio Carlos Pereira de Menezes Filho and Matheus Vinicius Abadia Ventura.

Investigation: Carlos Frederico de Souza Castro; Marconi Batista Teixeira and Frederico Antônio Loureiro Soares.

Translation: Antonio Carlos Pereira de Menezes Filho and Cinthia Alves Porfiro.

Writing (review and editing): Antonio Carlos Pereira de Menezes Filho and Matheus Vinicius Abadia Ventura.

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