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Phytochemical and Biological Evaluation of Leaves, Stems, and Roots of *Schinus weinmanniifolia* Mart. Ex Engl.

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ABSTRACT

The genus *Schinus* L. includes plants used in folk medicine with important pharmacological effects. However, little is known about *Schinus weinmanniifolia* Mart. ex Engl. This study evaluated the antioxidant, photoprotective, antimicrobial, and cytotoxic activities of its ethanolic extracts and identified bioactive compounds. Phytochemical analysis confirmed saponins, alkaloids, phenolic compounds, flavonoids, and tannins in leaves, stems, and roots extracts. Syringic acid, epicatechin, and rutin were identified using ultra-performance liquid chromatography with a diode array detector. The leaves extract showed the lowest IC₅₀ in the DPPH method, and all extracts effectively scavenged ABTS radicals, outperforming BHT. All extracts demonstrated sun protection and antimicrobial action against Gram-positive bacteria and yeasts but lacked antiprotozoal activity. They showed no hemolytic potential or cytotoxicity in Vero cells at active concentrations. These findings highlight *S. weinmanniifolia* as a promising focus for future investigations aimed at further exploring its bioactive properties.

1 | Introduction

Medicinal plants have been used worldwide for the prevention and treatment of various diseases since ancient times. Their use represents an integral component of traditional and popular medicine across different cultures, with empirical knowledge transmitted through generations. Although medicinal plants are known to contain a wide diversity of bioactive compounds, many of their biological properties and therapeutic potentials remain insufficiently explored [1]. In this context, the investigation

and identification of natural bioactive compounds derived from medicinal plants have emerged as an important strategy for the development of new pharmaceuticals, cosmetics, and food supplements, while also contributing to biodiversity conservation, sustainability, and the preservation of local cultural knowledge [2].

The family Anacardiaceae comprises 81 genera and 800 species distributed in tropical, subtropical, and temperate regions. *Schinus* L. is one of the main genera of the 15 registered in Brazil

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[3, 4]. Of the 29 species originating in South America, this genus is distributed in five regions of Brazil and countries such as Peru, Chile, Argentina, and Paraguay and has records of cultivation in Egypt [4, 5]. *Schinus terebinthifolius* Raddi is a prominent species within the genus, and it is widely recognized for its therapeutic properties, such as antioxidant, anti-inflammatory [6, 7], photoprotective [8, 9], and antimicrobial [10, 11]. The extracts and essential oils of *S. terebinthifolius* are widely used to formulate herbal medicines. In Brazil, two herbal medicines, Kios (tablet for the treatment of gastritis) and Kronel (gel for the treatment of cervicitis, vaginitis, and cervicovaginitis), which are developed from extracts of the bark of *S. terebinthifolius* are registered with the Brazilian Health Regulatory Agency (ANVISA) and marketed [12, 13]. At the Brazilian National Institute of Industrial Property (INPI), patent deposits can be found for new herbal medicines that use extracts of *S. terebinthifolius* for antifungal and healing purposes [12, 14].

Schinus weinmanniifolia Mart. ex Engl., known as aroeira-do-campo, is native to the Alto Paraná and Cerrado forests, found in the Midwest, Southeast, and South regions of Brazil, and is predominant in Paraguay, Uruguay, and Argentina [15]. This species is a fast-developing subshrub that can withstand burning or removal of the aerial part, owing to the presence of an underground stems (xylopodium), which also contributes to its survival in nutrient-poor soils [16]. Owing to its morphological structure, it is often intended for making arrangements for decoration [15].

Regarding its popular use, there are reports in publications from the region of Mato Grosso do Sul that describe the medicinal use of this species as an analgesic, astringent, and emmenagogue [16]. However, information on the biological properties of *S. weinmanniifolia* is limited. Four studies with *S. weinmanniifolia* leaves are available in the literature: Velázquez et al. [17] verified the antioxidant potential of the methanolic fraction; Hernandez et al. [18] analyzed the chemical profile and antimicrobial potential of the essential oils; Ferreira et al. [19] reported the antimicrobial activity of the ethanolic extract; and Andrade et al. [20] evaluated the antifungal activity of the aqueous extract. Considering this gap in the literature and the premise of developing new herbal medicines, the present study aimed to investigate the antioxidant, photoprotective, antimicrobial, and cytotoxic activities of ethanolic extracts of *S. weinmanniifolia*, as well as to identify and quantify the bioactive compounds.

2 | Results and Discussions

2.1 | Spectral Scanning and Chemical Quantification

The scan indicated absorbance peaks of the three extracts at wavelengths ranging from 200 to 400 nm, characteristic of the UV region (Figure 1).

This study of the ethanolic extracts of the leaves, stems, and roots of *S. weinmanniifolia* directly contributes to the unprecedented characterization of this species, as well as the premise of new therapeutic applications. From the perspective of bioactive compounds, the three evaluated extracts showed more expressive

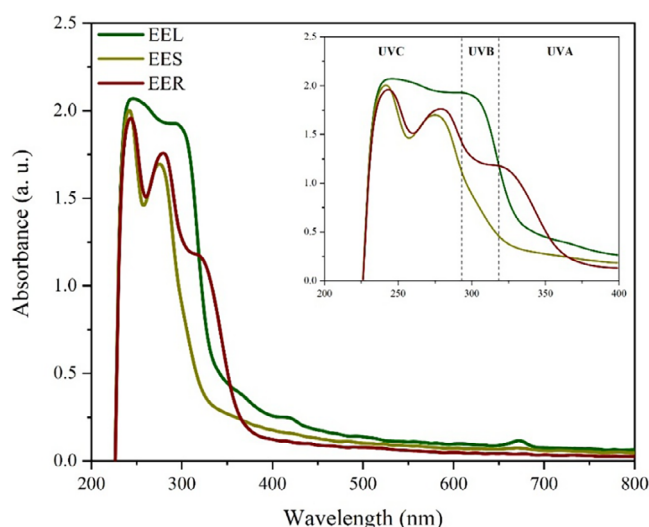


FIGURE 1 | Absorbance in the UV-vis region of ethanol extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl. Absorbance (absorbance unit), wavelength (nanometers).

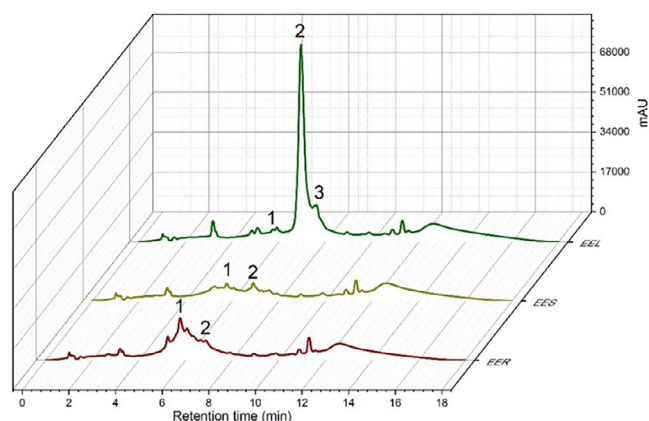


FIGURE 2 | UPLC-DAD ($\lambda = 271$ nm) of ethanol extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl. Epicatechin (1), syringic acid (2), and rutin (3).

peaks in the region from 200 to 400 nm in the spectral scan, which is characteristic of the better absorption of phenolic compounds, according to Castro et al. [21] and Souza et al. [22]. Some phenolic compounds can have antioxidant, antimicrobial, anticancer, and photoprotective activities, indicating their potential applications from different perspectives related to health [23, 24]. The three extracts analyzed contained saponins and alkaloids in the qualitative evaluation. Phenolic compounds, flavonoids, and tannins were found in greater quantities in EEL than in EES and EER (Table 1). However, a gap in the literature exists regarding the quantification and identification of phenolic compounds and other secondary metabolites in *S. weinmanniifolia*.

Epicatechin (1), syringic acid (2), and rutin (3) (Figure 2) were identified by ultra-performance liquid chromatography using a diode array detector.

The quantification of these compounds is presented in Table 2. Epicatechin was more abundant in the EER and EES. EEL

TABLE 1 | Quantification of bioactive compounds of ethanol extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl.

Analysis	EEL	EES	EER
Phenolic compounds (mg GAE/g $\pm$ SD)	317.80 $\pm$ 2.36 ^a	308.47 $\pm$ 1.15 ^b	301.80 $\pm$ 1.76 ^c
Flavonoids (mg RE/g $\pm$ SD)	84.79 $\pm$ 0.97 ^a	46.73 $\pm$ 1.12 ^b	14.50 $\pm$ 0.39 ^c
Tannins (mg TAE/g $\pm$ SD)	132.29 $\pm$ 0.99 ^a	121.18 $\pm$ 1.46 ^b	124.51 $\pm$ 0.50 ^c

Note: Different letters indicate significant differences according to Tukey's test ($p < 0.05$).

Abbreviations: mg GAE/g, milligrams of gallic acid equivalent per gram of extract; mg RE/g, milligrams of rutin equivalent per gram of extract; mg TAE/g, milligrams of tannic acid equivalent per gram of extract; SD, standard deviation.

TABLE 2 | Content (mg/g) of compounds identified by UPLC-DAD of ethanolic extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl.

Compound	EEL	EES	EER
Epicatechin	18.03 $\pm$ 1.63	36.07 $\pm$ 1.31	96.18 $\pm$ 4.53
Syringic acid	146.93 $\pm$ 4.48	3.99 $\pm$ 0.50	14.39 $\pm$ 0.87
Rutin	8.14 $\pm$ 0.26	ND	ND

Note: ND, Not detected; content $\pm$ standard deviation.

showed a higher syringic acid content. Rutin was identified only in the EEL. The presence of rutin just in the leaves are interesting, because they metabolomic synthesis pathway is directly related to the photosynthetic system. As a glycosylated flavonol derived from quercetin, rutin is primarily synthesized in photosynthetic tissues, where high carbon availability and light-regulated expression of phenylpropanoid and flavonoid biosynthetic enzymes favor its accumulation [25]. Transcriptomic and metabolomic analysis in *Cinnamomum camphora* (L.) revealed that rutin and other flavonoids were significantly more abundant in leaves and stems than in roots, and that key flavonoid biosynthesis genes (e.g., PAL, CHS, F3H) showed differential expression patterns correlated with this tissue-specific accumulation [26].

The identified probably had an important role in the sun protection factor (SPF), considering DAD signal (Figure 2) reveals absorption of radiation near the UVB region (280–315 nm) for syringic acid (279 nm) and epicatechin (275 nm), but the rutin probably have a role to highlight the SPF of the EEL, present in identifiable quantities just in the leaves and present absorption around the UVB region (250–350 nm). It is important to mention that the observed profile in the extracts are result of synergism and/or antagonism of the compounds present in the extract (Figure 3).

Syringic acid, identified at high levels in the leaves extract, is a biologically active molecule against oxidative stress, with antibacterial, antiproliferative, antidiabetic, and anti-inflammatory properties [27, 28]. This compound was also found in a study by El-Massry et al. [10] in *S. terebinthifolius* extracts. In addition, epicatechin and rutin (compounds identified only in EEL) are associated with therapeutic activities of considerable interest because of their antioxidant, antimicrobial, and antitumor properties [29, 30]. The aqueous extract of *S. weinmanniifolia* exhibited different compounds, such as shikimic acid, gallic acid,

and methyl gallate [20]. This variation may be associated with the extraction method and the solvents employed [31].

The synthesis of secondary metabolites are associate with biological adaptation to biotic and abiotic environmental conditions, such as solar radiation and microbial infections [32]. In this way, the composition and concentration of secondary metabolism are different depending on the plant organ, because of the function and the temperature faced. The higher concentration of phenolic compounds with antioxidant potential and UV absorption in leaves may be associated with high exposure to solar radiation [33]. In addition, this behavior is recurrent in the literature [34–37].

Other relevant aspects that can be associated with the higher concentration of phenolic compounds in the leaves. The leaves are more susceptible to herbivory compared to the stems and roots because they are palatable and easily digestible [38]. Leaves may exhibit greater phenolic content compared to stems and roots as a result of enhanced carbon flux through the phenylpropanoid pathway, which is supported by the high photosynthetic capacity of foliar tissues that provides abundant precursors for secondary metabolite synthesis [35]. All this goes against the optimal defense theory, that define allocating of secondary metabolites preferentially to organs that contribute more to overall fitness and are more vulnerable to herbivory and other stresses [39].

2.2 | Antioxidant Potential

The concentration capable of inhibiting 50% of the free radicals (IC₅₀) was lower for the ethanolic leaves extract (3.55) than for the AA (4.04) and BHT (5.24) controls in the DPPH assay. However, in the ABTS assay, the three extracts showed better IC₅₀ values than the BHT control (Table 3).

Many studies have sought alternatives to natural antioxidants to complement or replace conventional synthetic antioxidants. From this perspective, highlighting the potential of the EEL, EES, and EER of *S. weinmanniifolia* is important. Compared to the AA standard, EEL showed better antioxidant potential in the DPPH assay. In relation to the BHT compound, EEL requires concentrations 1.47 and 3.12 times lower to inhibit 50% of the DPPH and ABTS free radicals, respectively. Compared with the IC₅₀ (12.32 μ g/mL) of the methanolic extract of *S. terebinthifolius* leaves in the DPPH assay described by Silva et al. [7], EEL was also prominent in inhibiting the same free-radical at a concentration 3.55 times lower. The aqueous extract of *S. weinmanniifolia*

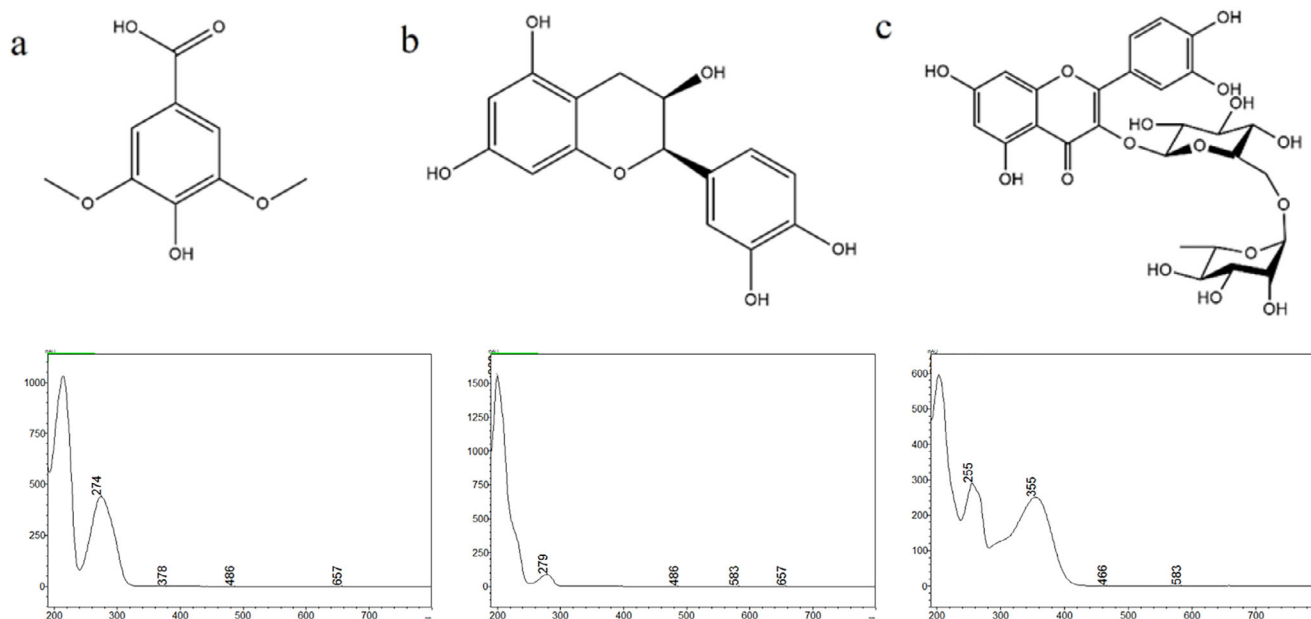


FIGURE 3 | Chemical structure of epicatechin (a), syringic acid (b), and rutin (c) identified by UPLC-DAD of ethanolic extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl. and their respective DAD profiles.

TABLE 3 | Antioxidant potential of ethanol extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl. and standard antioxidants ascorbic acid (AA) and butylated hydroxytoluene (BHT).

Sample	IC ₅₀ (μg/mL)	
	DPPH	ABTS
AA	4.04 ± 0.24	1.92 ± 0.10
BHT	5.24 ± 0.30	6.62 ± 0.16
EEL	3.55 ± 0.21	2.12 ± 0.11
EES	7.40 ± 0.20	2.50 ± 0.10
EER	5.12 ± 0.12	2.22 ± 0.12

Note: IC₅₀, Concentration in g/mL capable of inhibiting 50% of free radicals in the reaction ± standard deviation.

exhibited similar antioxidant potential values, with 5.51 in the DPPH assay and 1.52 in the ABTS assay [20]. Even when different solvents are employed for extract preparation, this species consistently demonstrates high antioxidant activity, which may be associated with the presence of specific bioactive compounds. In this context, the occurrence of gallic acid in the aqueous leaves extract of *S. weinmanniifolia* may contribute to the pronounced antioxidant activity observed [20], while the detection of rutin and epicatechin in the evaluated ethanolic extracts may similarly be associated with their high antioxidant performance [29, 30]. According to the adopted classification criteria, the antioxidant activity of the analyzed extracts is considered very strong [40].

2.3 | Photoprotective Potential

The photoprotective potential was evaluated from the perspective of antioxidant action and its possible applications, and the SPF of

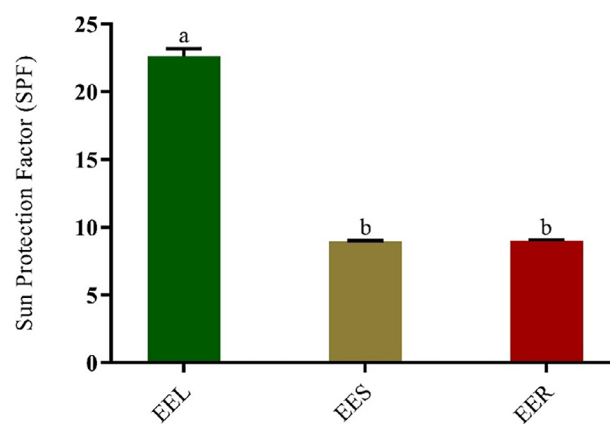


FIGURE 4 | Photoprotective potential of ethanol extracts from the leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl. Different letters indicate a significant difference by Tukey's test ($p < 0.05$).

EEL, EES, and EER were determined. The ethanolic extract of the leaves showed better potential (22.88 SPF), followed by the ethanolic extracts of the stems (8.99 SPF) and roots (9.04 SPF). The results and statistical comparisons are shown in Figure 4.

In the context of antioxidant potential tests, the SPF is directly associated with defense mechanisms against oxidative stress of reactive oxygen and nitrogen species caused by UVA and UVB radiation in contact with the human skin [41]. This type of skin exposure can reduce the natural production of antioxidants, cause burns, aging, and changes in DNA levels, which can trigger the onset of cancer. Additionally, synthetic sunscreens may be associated with low stability, toxicity, and biological changes when released into the environment [42].

The Brazilian Health Regulatory Agency (ANVISA), through RDC N°. 30 of June 1, 2012, recommends that sunscreens have

TABLE 4 | Minimum inhibitory concentration ($\mu\text{g/mL}$) of ethanol extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl. against Gram-positive and Gram-negative bacteria.

Microorganism	EEL	EES	EER	AMP
<i>Bacillus cereus</i>	250	250	125	32
<i>Staphylococcus aureus</i>	125	250	250	0.06
<i>Staphylococcus epidermidis</i>	125	250	250	64
<i>Staphylococcus saprophyticus</i>	125	250	250	0.125
<i>Klebsiella pneumoniae</i>	>1000	>1000	>1000	>128
<i>Salmonella typhimurium</i>	>1000	>1000	>1000	1

Note: AMP, ampicillin.

an SPF equal to or greater than 6 [43]. The evaluated extracts had an SPF greater than 6, especially EEL, which showed better photoprotective activity. Considering the applicability levels related to SPF, EEL fits into the average protection parameter with indications for moderately sensitive skin and sunburns [43]. The search for new natural extracts that can be incorporated into photoprotective phytocosmetics to reduce the amount of synthetic substances is of interest because the secondary metabolites of plants can play a fundamental role in antioxidant action, UV radiation protection, and other potential bioactives, as well as better interactions with the ecosystem due to the absence of synthetic compounds [44, 45].

2.4 | Antibacterial Activity

The MIC of the EEL, EES, and EER extracts against the tested bacterial strains are listed in Table 4. The three extracts showed antibacterial activity against Gram-positive microorganisms. The leaves extract showed higher activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus*, with an MIC of 125 $\mu\text{g/mL}$. The minimum bactericidal concentration (MBC) of the three extracts for *S. epidermidis* was 1000 $\mu\text{g/mL}$.

The MBC of EEL, EES, and EER for other microorganisms was >1000 $\mu\text{g/mL}$. The extracts did not show inhibitory activity against Gram-negative bacteria (*Klebsiella pneumoniae* and *Salmonella typhimurium*).

The extracts of *S. weinmanniifolia* showed antibacterial activity against Gram-positive microorganisms, classified as active according to the description by Saraiva et al. [46]. Among the bacteria evaluated, it is important to highlight the activity of EEL against *S. aureus* as this microorganism is present on human skin and is associated with different infections in humans and can manifest itself opportunistically in the imbalance of immunity or by contamination in different environments, especially hospitals [47]. Furthermore, the inhibitory activity extends to *S. epidermidis* and *S. saprophyticus*, which have a higher incidence in hospital environments, aggravating the recovery of immunocompromised patients and causing bacteremia and infections in exposed wounds [48].

TABLE 5 | Minimum inhibitory concentration ($\mu\text{g/mL}$) of extracts of leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. Ex Engl. against the yeasts.

Microorganism	EEL	EES	EER	FLU
<i>Candida albicans</i>	0.97	1.95	1.95	2
<i>Candida glabrata</i>	0.48	0.97	0.48	8
<i>Candida krusei</i>	0.48	0.97	0.48	—
<i>Candida tropicalis</i>	0.97	1.95	1.95	1
<i>Candida parapsilosis</i>	0.97	1.95	0.97	2
<i>Cryptococcus gattii</i>	0.97	1.95	1.95	8
<i>Cryptococcus neoformans</i>	250	250	250	8

Note: FLU, fluconazole. *Candida* spp. strains with MIC ≥ 8 $\mu\text{g/mL}$ are considered fluconazole resistant. Except for *C. glabrata*, where the MIC ≥ 64 $\mu\text{g/mL}$ is characterized as fluconazole-resistant. *Candida krusei* is intrinsically fluconazole-resistant (—).

This activity may be associated with the presence of syringic acid, which provides a detailed description of the mechanisms of action and inhibitory activity against *S. aureus* [28]. Minich et al. [49] reported that syringic acid has antimicrobial potential against *S. epidermidis* by directly inhibiting poly-*N*-acetyl-D-glucosamine (PNAG) and quorum sensing (QS). According to Al-Shabib et al. [50], another important compound with antibacterial activity is rutin, which inhibits the production of exopolysaccharides (EPS) and is associated with the resistance of microorganisms to available drugs. The presence of saponins and alkaloids also corroborated antibacterial activities, mainly in the development of *S. aureus* and *S. epidermidis* [51, 52]. The lack of activity in Gram-negative bacteria is possibly because these microorganisms have a structure with a double layer of lipopolysaccharide-phospholipids, production of specific enzymes, and performance of efflux pumps, hindering the action of the compounds present in the extracts [53]. El-Massry et al. [10] and Uliana et al. [11] found that the ethanolic extract of *S. terebinthifolius* leaves had an MIC against *S. aureus* of 750 and 500 $\mu\text{g/mL}$, respectively. In the case of potentiated infections and bacterial resistance, the activities of *S. weinmanniifolia* extracts were superior to *S. terebinthifolius*, indicating possible pharmacological applications.

2.5 | Antifungal Activity

The evaluated extracts were notable for their antifungal properties. EEL showed better activity than the commercial antifungal fluconazole, with an MIC <1 $\mu\text{g/mL}$ for the five strains of *Candida* and *Cryptococcus gattii* (Table 5).

EES and EER obtained MIC values from 0.48 to 1.95 $\mu\text{g/mL}$ (Table 5). The three extracts and the antifungal agent fluconazole were characterized as fungistatic because they did not exhibit fungicidal activity at the evaluated concentrations.

From the perspective of antifungal activity, notably, *Candida albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, and *Candida krusei* have a higher incidence of invasive candidiasis. They are associated with multiple public health

problems, mainly due to their resistance to azole antifungals [54]. In the tests conducted with these microorganisms, EEL, similarly to the aqueous extract of *S. weinmanniifolia*, despite containing different compounds, showed a lower MIC than the commercial drug fluconazole and can be classified as highly active against *Candida* species, according to the descriptions by Saraiva et al. [46] for plant extracts. *S. weinmanniifolia* extracts also showed antifungal activity against *C. gattii*, which, unlike *Cryptococcus neoformans*, can infect immunocompromised or immunocompetent patients, is associated with resistance to azoles and has an early mortality rate of 10%–25% [55]. Few studies have sought to evaluate new compounds of natural origin for the treatment of *C. gattii* infections [56, 57]. Thus, the results obtained in this study can be used in future research for the treatment of infections caused by yeasts of clinical interest.

Regarding the possible mechanisms of action that may be associated with antifungal activity, Mendoza et al. [58] evaluated syringic acid alone and in combination with laccase and aniline against the fungus *Botrytis cinerea* and observed that the heterodimeric compound induced damage to the cell wall of the fungus studied. No records were found regarding the anti-*Candida* activity of syringic acid. The presence of alkaloids in *S. weinmanniifolia* extracts may be related to their activity against *C. gattii*. Cruz et al. [59] reported that derivatives of alkaloids act on extracellular alterations of nucleotides of *C. gattii*. In addition, the presence of tannins in the analyzed extracts may also be associated with the observed antifungal potential against different yeast species [60].

2.6 | Antiprotozoal Activity

The EEL, EES, and EER extracts did not show considerable antiprotozoal activity against *Trypanosoma cruzi* CL Brener, *Leishmania amazonensis* or *Acanthamoeba castellanii* at the tested concentrations (MIC > 250 µg/mL). Chagas disease and leishmaniasis are neglected diseases that affect thousands of people, with *T. cruzi* and *Leishmania* spp. as the etiological agents. These microorganisms have life cycles and complex structures with enzymes that differ from those of other eukaryotes. Drugs available for these diseases have low efficacy, strong side effects, and mechanisms of action without a complete definition, making it important to search for new bioactive compounds for the treatment of these protozooses [61–63].

2.7 | Hemolytic Activity and Cytotoxicity

Considering all the bioactive potentials evaluated and the unprecedented findings, pharmacological safety is an important parameter to be considered in studies of natural extracts as it provides an initial screening for toxicity and elucidates different paths of applicability [64, 65]. In this context, the cytotoxicity was evaluated in human red blood cells and Vero cells. The three extracts did not present a concentration capable of causing 50% hemolysis in human erythrocytes, with an IC₅₀ greater than 500 µg/mL (Table 6). EES showed the same performance in the cytotoxicity test in Vero cells, followed by the leaves (IC₅₀ 77.11 µg/mL) and roots (IC₅₀ 33.15 µg/mL).

TABLE 6 | Hemolytic activity on human erythrocytes and cytotoxicity in Vero cells of ethanolic extracts of the leaves (EEL), stems (EES), and roots (EER) of *Schinus weinmanniifolia* Mart. ex Engl. (µg/mL).

Sample	Hemolytic activity (IC ₅₀) ^a	Cytotoxicity (IC ₅₀) ^b
EEL	>500	77.11 ± 5.31
EES	>500	>500
EER	>500	33.15 ± 5.05

Note: ±standard deviation.

^aConcentration in µg/mL capable of causing 50% hemolysis in human erythrocytes.

^bConcentration in µg/mL capable of causing 50% cytotoxicity in Vero cells.

As a result, Costa-Lotufo et al. [66] determined that IC₅₀ of natural extracts greater than 200 µg/mL can be considered non-hemolytic. Based on this interpretation, EEL, EES, and EER were characterized as non-hemolytic, significantly expanding the limits of pharmacological safety and highlighting the biological potential found in this study.

The leaves and stems extracts of *S. weinmanniifolia* did not show cytotoxicity in Vero cells at concentrations with antifungal and antioxidant activities. On the contrary, EER showed the highest cytotoxic potential against Vero cells. This may be associated with the production of phytotoxins in the roots of different plant species owing to the allelopathic interactions that they perform as a form of defense [67]. Notably, this result regarding the cytotoxicity of EER is of considerable value, as it evidently demonstrates that the aerial parts (leaves and stems) of this species are the most promising for future studies and applications, guaranteeing the integrity of the roots, which is reflected in the appreciation and preservation of this species with limited investigated.

Through a broad observation of the identified compounds, their bioactive potentials, and cytotoxicity profiles, it was possible to determine important ways of applying these extracts. In terms of selectivity and applicability, the use of a concentration of 62.5 µg/mL of EEL or EES (aerial parts) would confer high antifungal activity against the five species of *Candida* and *C. gatti* (i), would not affect the resident and transient microbiota of the skin, as it would not be active against *Staphylococcus* species (ii), it would be attributed to a high antioxidant potential with a photoprotective profile (iii), and low cytotoxicity (iv).

Considering the scientific studies and pharmaceutical use of *S. terebinthifolius*, the results obtained for *S. weinmanniifolia* highlight this species as an underexplored source of bioactive compounds within the genus. The biological activities observed in different plant parts support its relevance for further phytochemical and biological investigations, particularly in the context of phytotherapeutic and phytocosmetic research.

3 | Conclusions

In an unprecedented manner, this study identified and quantified bioactive compounds in the ethanolic extracts of leaves, stems,

and roots of *S. weinmanniifolia* Mart. ex Engl., highlighting the high content of syringic acid in the leaves extract. The extracts exhibited relevant in vitro antioxidant, photoprotective, antibacterial, and antifungal activities.

Notably, the aerial parts (leaves and stems) showed no cytotoxic effects at biologically active concentrations, indicating a favorable preliminary safety profile. Overall, these findings provide initial evidence supporting the biological relevance of *S. weinmanniifolia* and establish a foundation for future studies, including in vivo evaluations, to further validate its pharmacological potential.

4 | Experimental Section

4.1 | Plant Material Collection and Preparation of the Ethanol Extracts

Botanical materials from *S. weinmanniifolia* Mart. ex Engl. (leaves, stems, and roots) were collected in February 2025 in the municipality of Dourados—Mato Grosso do Sul, near the Cural de Arame and Campo Beli farms (22°11'14" S, 54°55'14" W). This plant was identified by Dr. Augusto Giarretta de Oliveira of the Federal University of Grande Dourados (UFGD, Brazil). A specimen of this species was deposited in the DDMS-UFGD herbarium under registration number 8856. It is registered with the Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado (SisGen) under registration A9BE079.

The leaves, stems, and roots were dried in a circulation oven (72 h) at 40°C. After drying, the plant material was crushed and extracted using 10 % (w/v) PA ethanol. The samples were stirred continuously for 72 h at room temperature in the dark. After continuous agitation, extraction was performed by sonication for 45 min, followed by filtration. The solvent was then evaporated in a fume hood for 72 h. The extract was collected and stored at 4°C. The ethanolic extracts of leaves, stems, and roots were named EEL, EES, and EER, respectively.

4.2 | Spectral Scanning in the UV Region

The extracts were diluted to a concentration of 200 µg/mL in water with 2% dimethyl sulfoxide (DMSO), and the absorbance was read between wavelengths of 200 and 400 nm with a resolution of 5 nm using a UV-vis spectrophotometer. The assay was performed in triplicates.

4.3 | Qualitative Analysis of Secondary Metabolites

4.3.1 | Saponins

The samples were diluted in water containing 2% DMSO. The sample was vigorously agitated, and persistent foam formation indicated the presence of saponins [68].

4.3.2 | Alkaloids

For the qualitative evaluation of alkaloids, 1 mL of Dragendorff's reagent was added to 2 mL of extract already diluted in water with 2% DMSO at a 1000 µg/mL concentration. The instantaneous formation of an orange-red precipitate demonstrated the presence of alkaloids in the samples [69].

4.3.3 | Quantification of Phenolic Compounds, Flavonoids, and Tannins

A solution of *S. weinmanniifolia* extract (1000 µg/mL in ethanol) was used for the assays. Phenolic compound and flavonoid contents were determined according to the method described by Djeridane et al. [70]. To quantify the phenolic compounds, the equation of the straight line of a calibration curve with a gallic acid standard was used, and the results were expressed in milligrams of gallic acid equivalent per gram of extract (mg GAE/g).

Flavonoids were quantified using a calibration curve based on the rutin standard. The results were expressed in milligrams of rutin equivalent per gram of extract (mg RE/g). Total tannin content was determined using the Folin–Denis spectrophotometric method described Pansera et al. [71]. An analytical curve with tannic acid standards was used to calculate the tannin concentration. The results were expressed in milligrams of tannic acid equivalent per gram of extract (mg TAE/g).

4.3.4 | Identification and Quantification of Compounds by UPLC-DAD

The chromatographic profile of the extracts was determined on an ultra-performance liquid chromatography (UPLC) coupled to a diode array detector (DAD), using a 2 × 75 mm Shim-pack XR-ODS column packed with C18 with 2.2 µm particles. An injection volume of 1 µL was used at a flow rate of 0.15 µL/min. The mobile phase in a gradient system was water with 0.1% formic acid (A) and methanol (B). The elution gradient used was as follows: 0–4 min (10%–70%), 4–7 min (70%–90%), 7–8 min (90%–100%), 8–15 min (100%–10%), and 15–18 min (10%). The DAD detector monitored the spectral range from 200 to 600 nm. The samples were prepared at a 1 mg/mL concentration. The standards of caffeic acid, chlorogenic acid, ferulic acid, gallic acid, *p*-coumaric acid, sinapic acid, syringic acid, vanillic acid, epicatechin, luteolin, naringenin, rutin, quercetin, and vanillin (Aldrich-Sigma, USA, purity >99.9%) were prepared and injected at a concentration of 0.67 mg/mL. Compound identification was performed by comparing the retention times and DAD spectral profiles of the peaks obtained for the standards and the sample.

Based on the results of the preliminary analysis of the presence of compounds, standard curves were prepared for each compound identified in the samples (Table 7). 1 µL of the standards was injected in concentrations between 1 and 300 µg mL⁻¹, and the analytical curve was building calculating the mass in ng corresponding to the area of the peak. In this way, the quantification of

TABLE 7 | Standard curve information of phenolic compounds identified by UPLC-DAD.

RT (min)	Compounds (CAS)	λ (nm)	R^2	Linear range (ng)	LOQ (ng)	LOD (ng)
5.77 $\pm$ 0.03	Epicatechin (490-46-0)	279 nm	0.99982	160 to 850	53.3	16
6.64 $\pm$ 0.02	Syringic acid (530-57-4)	275 nm	0.99915	160 to 850	53.3	16
7.60 $\pm$ 0.04	Rutin (153-18-4)	350 nm	0.9996	25 to 160	8.3	2.5

Abbreviations: λ , quantification wavelength; LOD, limit of detection; LOQ, limit of quantification; RT, retention time.

the concentration of the compound in the sample was performed by relating the ng of compounds present in the sample and the injected volume of the sample [72]. The result was expressed in mg of the identified compound per g of dry extract.

4.4 | Antioxidant Potential

4.4.1 | Radical Scavenging 2,2-Diphenyl-1-picrylhydrazyl (DPPH)

The antioxidant activity was measured using the DPPH free radical scavenging test. The applied methodology followed the descriptions of Yao et al. [73] with modifications. A quantity of 1800 μ L of methanolic solution of DPPH (0.11 mM) was incubated with 200 μ L of positive controls, ascorbic acid (AA), and butylated hydroxytoluene (BHT), as well as the extracts EEL, EES, and EER in concentrations of 0.24–125 μ g/mL diluted in 80% methanol. An 80% methanol solution with the tested concentrations of the extracts was used as a negative blank such that the color of the extract did not alter the interpretation of the results.

A DPPH solution without contact with the samples was used as a control. After 30 min of incubation at room temperature (protected from light), the absorbance was measured at 517 nm using a spectrophotometer. The absorbance of each sample was transformed into the percentage of free radical inhibition using the following formula:

$$\% \text{ DPPH inhibition} = (\text{Abs control} - \text{Abs sample}) / \text{Abs control} \times 100.$$

The results were expressed as the percentage of total DPPH free radical inhibition at a concentration capable of inhibiting 50% of the DPPH free radicals (IC_{50}).

4.4.2 | Radical Scavenging 2,2-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS)

To verify the antioxidant potential through the capture of the ABTS free radical, the methodology described by Xiao et al. [74] was adapted. The ABTS stock solution was prepared using potassium persulfate 16 h before the experiment and stored at room temperature in the dark. Subsequently, the ABTS radical was diluted in 80% ethanol to an absorbance of 730 nm and incubated for 6 min with EEL, EES, and EER extracts or positive controls (AA and BHT) at concentrations from 0.24 to 125 μ g/mL.

For the reaction, volumes of 1980 μ L of ABTS and 20 μ L of samples or positive controls were used.

Ethanol (80%) at the concentrations of the extracts was used as a negative blank, and the ABTS solution without contact with the samples was used as a control. Absorbance was measured at 730 nm using a spectrophotometer. The results were expressed as a percentage of ABTS radical inhibition, using the following formula:

$$\% \text{ ABTS inhibition} = (\text{control Abs} - \text{sample Abs}) / \text{control Abs} \times 100.$$

In addition, the results were expressed as the total percentage of ABTS free radical inhibition at a concentration capable of inhibiting 50% of the ABTS free radicals (IC_{50}).

4.4.3 | Analysis of Photoprotective Potential

The photoprotective potential of the extract was evaluated through a preliminary in vitro spectrophotometric assay using the method proposed by Mansur et al. The extract was diluted in an appropriate solvent to obtain a final concentration of 200 μ g/mL. An initial exploratory spectral scan was performed over the range of 200–600 nm, with a 1 nm interval, using a UV-vis spectrophotometer in order to assess the general absorption profile of the sample [75].

Subsequently, absorbance readings were recorded in the UVB region (290–320 nm) at 5 nm intervals, as recommended for SPF estimation by the Mansur method. The SPF was calculated according to the equation proposed by Mansur et al. [76].

$$\text{SPF} = \text{CF} \times \sum [\text{EE}_{\lambda} \times \text{I}_{\lambda} \times \text{Abs}_{\lambda}] \quad (1)$$

where, SPF = sun protection factor; CF = correction factor (=10), determined according to two known SPF sunscreens; EE_{λ} = erythemogenic effect of wavelength (λ) radiation; I_{λ} = sunlight intensity at the wavelength (λ); Abs_{λ} = spectrophotometric reading of the absorbance of the sunscreen solution at the wavelength (λ). The values used for $\text{EE}_{\lambda} \times \text{I}_{\lambda}$ were previously described by Sayre et al. [77].

This assay was conducted exclusively as an in vitro screening tool, aiming to provide an initial indication of UVB absorption capacity. Therefore, the results do not substitute standardized in vivo SPF determination, nor do they address photostabil-

ity or comparative performance against commercial sunscreen formulations.

4.5 | Antibacterial and Antifungal Activities

4.5.1 | Microorganisms

Standard strains of bacteria and yeasts were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA). Bacteria: *Bacillus cereus* (ATCC 11778), *S. aureus* (ATCC 25923), *S. epidermidis* (ATCC 12228), *S. saprophyticus* (ATCC BAA 750), *S. typhimurium* (ATCC 14028), and *K. pneumoniae* (ATCC 13883). Yeasts: *C. albicans* (ATCC 90028), *C. glabrata* (ATCC 2001), *C. krusei* (ATCC 6258), *C. tropicalis* (ATCC 750), *C. parapsilosis* (ATCC 22019), *C. gattii* (ATCC 56990), and *C. neoformans* (ATCC 32045).

4.6 | Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentrations of the extracts were determined using the broth microdilution method, according to the Clinical and Laboratory Standards Institute guidelines M07-A9 [78] for bacteria and M27-A3 [79] for yeasts, with adaptations for natural products. Bacteria and yeast were suspended in sterile saline solution (0.9% NaCl), and the suspensions were standardized using a spectrophotometer at 625 nm for bacteria and 530 nm for yeast. The extracts were diluted in 2% DMSO and subjected to successive dilutions (1:2) in 96-well microplates with Mueller–Hinton broth for bacteria and RPMI-1640 for yeast. The extract concentrations (EEL, EES, and EER) were 0.24–1000 µg/mL.

Negative sterility controls of the culture medium and extracts, as well as positive controls, were prepared to verify the viability of the microorganisms. Ampicillin and fluconazole were used as the standard antibiotic and antifungal, respectively. Temperatures and incubation times were 37°C for 24 h (bacteria), 35°C for 24 h (*Candida* strains), and 35°C for 48–72 h (*Cryptococcus* strains). For bacteria, visual reading was performed with the addition of 50 µL of triphenyl tetrazolium chloride (TTC) solution at 0.1%, the MIC being determined as the concentration at which there was no color change in the wells. The reading was performed visually for yeasts, and the MIC was determined as the lowest concentration that reduced 50% of fungal growth for both fluconazole and the extracts compared to the positive control [80]. The assays were performed in duplicate three different times.

4.7 | Minimum Bactericidal and Fungicidal Concentration (MBC and MFC)

After MIC interpretation, a 5 µL aliquot of the wells that showed MIC was transferred to plates with the Mueller–Hinton agar for the bacterial assay and Sabouraud agar for the yeast assay. Plates were incubated at 37°C for 24 h (bacteria) and at 35°C for 24–48 h (yeast). The lowest concentration at which there was no colony-forming unit (CFU) growth was determined as the MBC or MFC [81].

4.8 | Antiprotozoal Activity

The extracts were also evaluated for their antiprotozoal activity in 96-well microplates, as described by Baek et al. [82], with some modifications. The evaluated protozoa were *T. cruzi* CL Brener (COLPROT 005), *Leishmania amazonensis* (MHOM/BR/77/LTB0016), and *A. castellanii* (COLPROT 928), which were available from the Fiocruz Rio de Janeiro Protozoan Collection (COLPROT).

Epimastigotes of *T. cruzi* CL Brener and promastigotes of *Leishmania amazonensis* and *A. castellanii* were quantified by light microscopy in a Neubauer chamber, totaling 1.0×10^6 cells/mL in the exponential phase of cell growth. The media used were liver infusion tryptose (LIT) for *T. cruzi* CL Brener, Grace for *L. amazonensis*, and PYG for *A. castellanii*.

The extract concentrations (EEL, EES, and EER) were 0.24–250 µg/mL. The microplates were incubated at 28°C for 48 h. Growth was compared with that of control wells containing untreated cells. The 0.5 mM resazurin dye was used to identify the MIC in tests with protozoa, and the cells were visualized under an optical microscope (400× magnification for *T. cruzi* CL Brener and *L. amazonensis* and 100× for *A. castellanii*). The assays were performed in duplicate three different times.

4.9 | Hemolytic Activity

Hemolytic activity was assessed according to the method described by Dhonnar et al. [83], with some modifications. This study was authorized by the Research Ethics Committee involving human beings of the Federal University of Grande Dourados (Dourados, MS), opinion no. 5588196. Five milliliters of human blood from a healthy donor were collected and transferred to an EDTA vacuum tube. Subsequently, the blood sample was centrifuged for 10 min at 1600× rpm and 20°C. The supernatant was removed, and the pellet was treated with potassium phosphate buffer solution (PBS) at three alternating times with centrifugation. Erythrocytes at a concentration of 1% were used for the tests.

We used 1000 µL of erythrocyte solution with 1000 µL of EEL, EES, and EER extracts at concentrations of 0.24–500 µg/mL. In addition, 0.1% Triton-X was used as the positive and negative controls, respectively. Samples were incubated at 37°C with continuous agitation for 60 min. After the incubation period, they were centrifuged for 10 min at 1600× rpm and 20°C, and the supernatant was collected and read in a spectrophotometer at 540 nm. Hemolytic activity was calculated according to the following equation:

$$\text{Hemolytic activity (\%)} = \frac{(\text{Abs sample} - \text{Abs negative control})}{(\text{Abs Triton} - \text{Abs negative control})} \times 100.$$

Therefore, the results were expressed as concentrations capable of causing 50% hemolysis in human erythrocytes (IC₅₀).

4.10 | Cytotoxicity in Vero Cells

To evaluate cytotoxicity in mammalian cells, the Vero strain (ATCC CCL-81) from the African green monkey kidney was used as described by Kischkel et al. [84]. When 80% of cell confluence was verified, they were suspended by the action of trypsin, and the concentration was adjusted to 2×10^5 cells/mL in Dulbecco's modified Eagle medium containing 10% fetal bovine serum, 1% penicillin/streptomycin, and amphotericin B, added to a 96-well microplate, incubated in an oven at 37°C and 5% CO₂. After 24 h, the wells were washed with potassium phosphate buffer (PBS, 0.1 M, pH 6.8), and the compounds were added in a sequence of 12 concentrations (0.24–500 µg/mL) with DEMEM culture and incubated for 24 h.

Then, the wells were washed with PBS, and 20 µL of neutral red dye solution at a concentration of 0.5 mg/mL and 180 µL of DEMEM medium without phenol red were added. The plate was incubated for 3 h. Subsequently, the dye incorporated into the lysosomes was extracted with a solution of acetic acid and ethanol (1% acetic acid in 50% absolute ethyl alcohol), and the absorbance was performed in a spectrophotometer at 540 nm [85]. With the values obtained, the cytotoxic concentration capable of killing 50% of the cells (IC₅₀) was determined according to International Organization for Standardization (ISO) guideline ISO/EN 10993-5 [86].

4.11 | Statistical Analysis

The results were statistically analyzed using ANOVA followed by Tukey's test. Differences were considered statistically significant at $p < 0.05$. Statistical analyses, graphs, and determination of IC₅₀ were performed using the software GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA).

Author Contributions

João Andrade: conceptualization, data curation, formal analysis, investigation, methodology, roles/writing – original draft and roles, writing – original draft. **Adriana Araújo de Almeida-Apolonio:** conceptualization, data curation, formal analysis, supervision, validation, visualization; roles/writing – original draft, writing – review and editing. **Fabiana Gomes da Silva Dantas:** conceptualization, data curation, formal analysis, supervision, validation, visualization, roles/writing – original draft, writing – review and editing. **José Irlan da Silva Santos:** investigation, methodology. **Andréia Sangalli:** investigation, methodology. **Melyssa Negri:** formal analysis, investigation, methodology. **Deisiany Gomes Ferreira:** investigation, methodology. **Claudia Andrea Lima Cardoso:** investigation, methodology. **Thiago Luis Aguayo de Castro:** investigation, methodology. **Aline dos Santos Garcia Gomes:** investigation, methodology. **Rhagner Bonono:** investigation, methodology. **Liliana Fernandes:** formal analysis, visualization, writing – review and editing. **Maria Elisa Rodrigues:** formal analysis, visualization, writing – review and editing. **Mariana Contente Rangel Henriques:** formal analysis, visualization, writing – review and editing. **Kelly Mari Pires de Oliveira:** conceptualization, formal analysis, funding acquisition, project administration, resources, supervision, validation, visualization, roles/writing – original draft, writing – review and editing.

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Ethics Statement

The hemolysis assay involving human blood was conducted in accordance with ethical standards and approved by the Research Ethics Committee involving human beings of the Federal University of Grande Dourados (Dourados, MS) (protocol number: 5588196). Informed consent was obtained from all donors prior to sample collection.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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