

Article

Phenolic Profile, Antioxidant and Antiproliferative Activity, and Acute Toxicity of *Bursera hindsiana* Engl

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Abstract

The aim of this study was to determine the phenolic compound profile, antioxidant activity, antiproliferative activity, and toxicity of *B. hindsiana*. Ethanolic extractions of *B. hindsiana* leaves and stems were performed. The content of phenolic compounds was determined by the Folin–Ciocalteu method, while the phenolic compound profile was determined by UPLC-DAD. The antioxidant activity was evaluated using the DPPH, ABTS, ORAC, and FRAP methods. Antiproliferative activity was determined by the MTT method against HeLa, A549, and ARPE-19 cell lines. Acute toxicity was determined in *Artemia salina*. The results showed that the *B. hindsiana* leaf extract had the highest concentration of phenolic compounds, with quercetin-3- β -glucoside, rutin, and chlorogenic acid being the major compounds. Regarding antioxidant activity, the leaf extract showed a greater capacity ($p < 0.05$) to stabilize free radicals and reduce metals. For antiproliferative activity, the leaf extract also showed a greater capacity ($p < 0.05$) to inhibit the proliferation cancer cell lines. Finally, the *B. hindsiana* extracts presented an LC₅₀ value greater than 100 μ g/mL in *A. salina*. Overall, the *B. hindsiana* extracts show promising biological potential, which may be associated with the phenolic compounds present, with low toxicity. This research is the first study reporting the phenolic compound profile and the leaf and stem biological activities from *B. hindsiana*.



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1. Introduction

Bursera hindsiana is a medicinal plant used in traditional Mexican medicine that has not been characterized. *B. hindsiana* is a shrub that can grow up to 4 m tall, its bark is reddish and resinous, and it thrives in semi-warm, semi-dry, and dry climates [1]. In Mexico, this plant is found in the states of Baja California, Baja California Sur, and Sonora, where it is known as copal or torote prieto [2]. The constituents of this plant such as stems and fruits through infusions are used in traditional Sonoran medicine to treat various

health conditions such as shortness of breath, inflammation, and cough [1]. Currently, the biological effects of this plant have been little explored, and there is no information on the profile of chemical compounds present or data on the plant's toxicity. Obtaining this information could help us understand the traditional uses of this plant and open the door to generating information on new biological effects, as well as identifying the chemical compounds associated with these effects and providing data on its safety.

Currently, it is well established that oxidative stress is a process associated with the development of several pathological conditions in humans. In this regard, the human body naturally owns endogenous antioxidant systems that help neutralize free radicals, thus maintaining homeostatic balance. However, when there is an overproduction of free radicals, the antioxidants are unable to neutralize them, generating a process known as oxidative stress [3]. This process can allow free radicals to react with the constituents of eukaryotic cells, such as lipids, proteins, and genetic material, which can lead to mutations [4]. In turn, these can develop into disorders such as Parkinson's disease, Alzheimer's disease, and cancer, the latter having the most repercussions [5,6].

Cancer is a major global public health problem, with high morbidity and mortality rates that have increased significantly in recent years, making it the second leading cause of death worldwide [7]. It is estimated that cancer causes approximately 10 million deaths annually, and this figure is projected to rise to over 18 million by 2050 [8]. This trend is associated with current high-risk factors, as well as the lack of timely detection. Treating this disease is becoming increasingly complex due to the declining effectiveness of current treatments, coupled with the adverse effects they can produce [9,10].

Given these complications, new alternatives for the treatment and management of cancer are required. In this regard, medicinal plants have been a strategy for managing health conditions since the dawn of humanity [11]. Currently, medicinal plants continue to be a widely used strategy worldwide for treating diseases [12]. Numerous studies focus on examining the biological potential of medicinal plants, which has resulted in the discovery of effective drugs used in the clinic [13]. Furthermore, studying the safety of medicinal plants is essential for advancing the development of new drugs.

Based on the above, the objective of the present research is to determine the phenolic profile of leaf and stem extracts of *B. hindsiana*, its antioxidant and antiproliferative activity, and its toxicity.

2. Materials and Methods

2.1. Plant Material and Extract Elaboration

Bursera hindsiana leaves and stems were collected in September of 2019 in Bahia de Kino (collection coordinates: 28.864415, −112.022894), Sonora, México, and were identified in the Herbarium of the Universidad de Sonora. Leaves and stems were cleaned to remove dust and soil particles. Afterward, leaves (whole) and stems (cut into 4–5 cm segments) were extracted with ethanol at a 1:10 *w/v* ratio for 4 days with occasional stirring. The ethanolic extracts were filtered (Whatman No. 4 filter paper), and the solvent was removed under vacuum at 40 °C. The obtained extracts were stored at −20 °C until their use.

2.2. Total Phenolic Content

B. hindsiana extracts at 1 mg/mL (10 µL) were mixed with 80 µL of distilled water, 40 µL of Folin–Ciocalteu reagent (0.25 N), 60 µL of sodium carbonate (5% in distilled water), and 80 µL of distilled water. The reactions were incubated at 25 °C for 1 h in darkness. The absorbance was measured at 750 nm using a microplate reader (Thermo Scientific Multiskan GO, Osterode, Germany). Obtained results are expressed as mg of gallic acid equivalent (GAE)/g dried weight (d.w.) [14].

2.3. UPLC-DAD Analysis

The phenolic compound profile of *B. hindsiana* extracts were identified and quantified through an UPLC™ system (Acquity, Waters Co., Milford, MA, USA) equipped with a photodiode array extended λ (PDA e λ) detector, an Acquity UPLC™ BEH C18 VanGuard precolumn (130 Å, 1.7 μ m, 2.1 mm $\times$ 5 mm), and a UPLC™ BEH C18 column (1.7 μ m, 3.0 $\times$ 100 mm) with a column temperature of 60 °C and an auto sampler set at 5 °C. The mobile phase was constituted by 0.5% formic acid in water (solvent A) and methanol (solvent B). The elution was performed under different conditions: 0 min, flow 0.4 mL/min, 80% solvent A; 0.25 min, flow 0.150 mL/min, 80% solvent A; 5 min, flow 0.200 mL/min, 80% solvent A; 12 min, flow 0.180 mL/min, 55% solvent A; 25 min, flow 0.100 mL/min, 0% solvent A; 26 min, flow 0.200 mL/min, 60% solvent A; 27 min, flow 0.400 mL/min, 80% solvent A; 30 min, flow 0.400 mL/min, 80% solvent A. The detection of phenolic compounds was analyzed using the standard retention time. The absorption spectrum at 240 nm (protocatechuic acid, catechin, and chlorogenic acid), 280 nm (vanillic acid, p-coumaric acid, gallic acid, ellagic acid, catechol, cinnamic acid, and epigallocatechin gallate), 320 nm (caffeic acid, apigenin, and chlorogenic acid), 360 nm (rutin, kaempferol-3- β -glucoside, quercetin-3- β -glucoside, and kaempferol) and 380 nm (quercetin) was analyzed. Quantification of phenolic compounds was analyzed using standard calibration curves. Results are reported as μ g/g d.w [15].

2.4. DPPH Assays

The DPPH assay was analyzed using the modified method described by Usia et al. [16]. *B. hindsiana* extracts (100 μ L) were combined with DPPH solution at 300 μ m (100 μ L) in a microplate. The microplates were incubated at 25 °C for 30 min in the dark. The samples were read on a microplate reader at 517 nm (ThermoScientific Multiskan GO, Osterode, Germany). Results are expressed as IC₅₀ (μ g/mL). The inhibition percentage was calculated using the following formula:

$$\text{DPPH scavenging activity (\%)} = (A_0 - A_1)/A_0 \times 100$$

where A_0 is the absorbance of the control, and A_1 is the absorbance of the sample.

2.5. TEAC Assay

The TEAC assay was performed according to the methodology previously described by Re et al. [17] with some modifications. Initially, ABTS^{•+} was performed by reacting ABTS, 7 mm (5 mL), with potassium persulfate, 0.139 mm (88 μ L), for 16 h in darkness. Afterward, the radical absorbance was adjusted to 0.700 ± 0.02 at 754 nm. Subsequently, 5 μ L of *B. hindsiana* extract was reacted with the adjusted radical (245 μ L). Finally, samples were incubated for 5 min, and the absorbance was measured at 754 nm (Fluostar Omega microplate reader, BMG Labtech, Ortenberg, Germany). Results are expressed as IC₅₀ (μ g/mL). The inhibition percentage was calculated using the following formula:

$$\text{ABTS scavenging activity (\%)} = (A_0 - A_1)/A_0 \times 100$$

where A_0 is the absorbance of the control, and A_1 is the absorbance of the sample.

2.6. ORAC Assay

The ORAC assay was performed using the modified method described by Ou et al. [18]. The AAPH reagent generated peroxy radicals, and fluorescein was used as the fluorescent indicator. Initially, we mixed fluorescein at 10 nm (150 μ L), phosphate buffer (75 mm, pH 7.4) (25 μ L) as a blank, and *B. hindsiana* extracts at 50 μ g/mL (25 μ L). Subsequently,

AAPH was added at 240 μ M and incubated (37 °C). Finally, fluorescence was read every 90 s for 1.5 h at an excitation wavelength of 485 nm and an emission wavelength of 530 nm using a microplate reader (Fluostar Omega, BMG Labtech, Ortenberg, Germany). Results are reported as μ M Trolox Equivalent (TE)/g dried weight (d.w.).

2.7. FRAP Assay

The FRAP assay was performed as described by Benzie and Strain [19]. Initially, FRAP reagent was elaborated by reacting acetate buffer pH 3.6 (300 mM), TPTZ (dissolved in 40 mM HCl), and ferric chloride (20 mM) in a proportion 10:1:1. Afterward, *B. hindsiana* extract (20 μ L) was reacted with FRAP reagent (280 μ L). The samples were incubated at 25 °C for 30 min in the dark, and absorbance was measured at 630 nm using a microplate reader (Thermo Scientific Multiskan GO, Osterode, Germany). Results are expressed as μ M of Fe(II)/g d.w.

2.8. Cell Cultures

Cell lines were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 5% heat-inactivated serum of fetal bovine serum (By Productos S.A. de C.V., Guadalajara, Jalisco, Mexico) and penicillin (Sigma-Aldrich, Saint Louis, MO, USA) (100 U/mL) in 25 cm² culture dishes. The cultures were stored in an Isoterm incubator (5% of CO₂ at 37 °C and 95% of relative humidity) (Fischer Scientific, Pittsburgh, PA, USA). Non-small-cell lung cancer cells (A549) and human cervical cancer, HPV-positive (HeLa), were purchased from the American Type Culture Collection (ATCC; Rockville, MD, USA).

2.9. Antiproliferative Assay

The MTT assay was used to determine the antiproliferative activity of *B. hindsiana* extracts [20,21]. Initially, on a microplate (Costar, Corning, NY, USA), a cell suspension (2 $\times$ 10⁵ cells/mL, 50 μ L) was incubated for 24 h. Afterwards, in the microplates, the *B. hindsiana* extracts at different concentrations (50 μ L) were incubated (48 h). The *B. hindsiana* extracts were dissolved in DMSO and re-suspended in DMEM to obtain a final DMSO concentration of 0.25% (which showed no interference with the growth of the cell lines). Subsequently, the cells were washed with PBS and incubated with MTT (5 mg/mL) for 4 h. The formazan crystals were resuspended in acidic isopropanol, and absorbance was measured at 570 and 630 nm in a microplate reader (iMark microplate absorbance reader, Bio-Rad Laboratories, Mexico City, Mexico). The obtained results are expressed as IC₅₀ (μ g/mL) values.

2.10. Acute Toxicity in *Artemia salina*

Acute toxicity was assessed according to the method previously described by Chávez-Magdaleno et al. [22]. An Erlenmeyer flask was adapted to a system of aeration and artificial lighting. Once the equipment was set up, 250 mL of sterile seawater was placed in the flask, along with 30 g of *A. salina* eggs (White Mountain, Great Salt Lake, Utah, EUA). These were incubated at 25 °C for 24 h to allow the nauplii to hatch. Afterwards, the *A. salina* nauplii were divided into groups of 10 and placed into test tubes containing sterile seawater and the *B. hindsiana* extracts at different concentrations. As controls, seawater and DMSO were used. The tubes were kept under light for 24 h. Finally, the number of surviving nauplii was counted, and the results are reported as a survival percentage (%).

2.11. Statistical Analysis

The obtained results were analyzed by one-way ANOVA using the NCSS software (2007). Differences among treatments were determined with the Tukey–Kramer test ($p < 0.05$).

3. Results and Discussion

3.1. Phenolic Compounds

The study of the chemical composition of understudied medicinal plants plays an important role in natural product chemistry, since it allows one to understand the biological effects these plants may exhibit, as well as the possible mechanisms of action involved for each of the biological activities observed. Some of the most widely distributed chemical compounds in plants are phenolic compounds, which have been attributed with a broad spectrum of biological activities [23].

The phenolic compound content of leaf and stem extracts of *B. hindsiana* is shown in Table 1. The leaf extract showed a concentration 2.09 times higher ($p < 0.05$) than that of the stem extract. Subsequently, UPLC-DAD analysis was performed to identify the specific phenolic compounds present in the extracts (Table 2, Figures 1 and 2). Overall, the total concentration of identified phenolic compounds is 97% higher in the leaf extract compared to the stem extract. Seven compounds were identified in the leaf extract, with quercetin-3- β -glucoside, rutin, and chlorogenic acid being the most abundant, with concentrations of 47%, 38%, and 9%, respectively. Furthermore, five compounds were identified in the stem extract, with quercetin being the most abundant, followed by quercetin-3- β -glucoside and vinylic acid. These compounds represented 54%, 26%, and 14% of the total compounds identified.

Table 1. Phenolic content and antioxidant activity of *Bursera hindsiana* extracts.

Method	Extract	
	Leaves	Stems
Total phenols (mg GAE/g)	160.0 $\pm$ 13.0 ^b	76.4 $\pm$ 7.7 ^a
DPPH (IC ₅₀ , μ g/mL)	42.8 $\pm$ 2.2 ^a	152.8 $\pm$ 8.0 ^b
ABTS (IC ₅₀ , μ g/mL)	12.2 $\pm$ 1.9 ^a	44.9 $\pm$ 3.8 ^b
ORAC (μ m TE/g)	3055.17 $\pm$ 120.07 ^b	966.46 $\pm$ 28.85 ^a
FRAP (μ m Fe(II)/g)	1492.7 $\pm$ 70.9 ^b	574.3 $\pm$ 46.0 ^a

Data are presented as the mean $\pm$ standard deviation of three independent experiments. ^{a,b} Different superscripts in each method indicate significant differences ($p < 0.05$).

Table 2. Phenolic profile of *Bursera hindsiana* extract.

Compound	Extract (μ g/g)	
	Leaves	Stems
Protocatechuid acid	396.27 $\pm$ 6.36	NI
Catechin	2753.91 $\pm$ 28.67	NI
Chlorogenic acid	9362.66 $\pm$ 20.64	NI
Vanillic acid	NI	402.96 $\pm$ 3.21
p-Coumaric acid	NI	25.09 $\pm$ 0.40
Quercetin-3- β -glucoside	46,434.90 $\pm$ 27.25	777.42 $\pm$ 18.26
Rutin	37,735.20 $\pm$ 18.26	NI
Kaempferol-3- β -glucoside	718.04 $\pm$ 0.48	NI
Quercetin	1400.61 $\pm$ 32.18	1584.96 $\pm$ 1.59
Kaempferol	NI	123.57 $\pm$ 0.74
Total	98,801.59	2914.00

NI: compound not identified.

These results show a significantly higher concentration of phenolic compounds in the leaf extract compared to the stem extract. This difference could be attributed to the location of each component within the plant. Leaves are naturally located on the outermost part of the plant, covering the stems. Solar radiation is known to be a key factor in the synthesis of

phenolic compounds, as these act as a protective agent against radiation [24,25]. Therefore, leaves may be exposed to greater radiation, which would explain the results observed in this study.

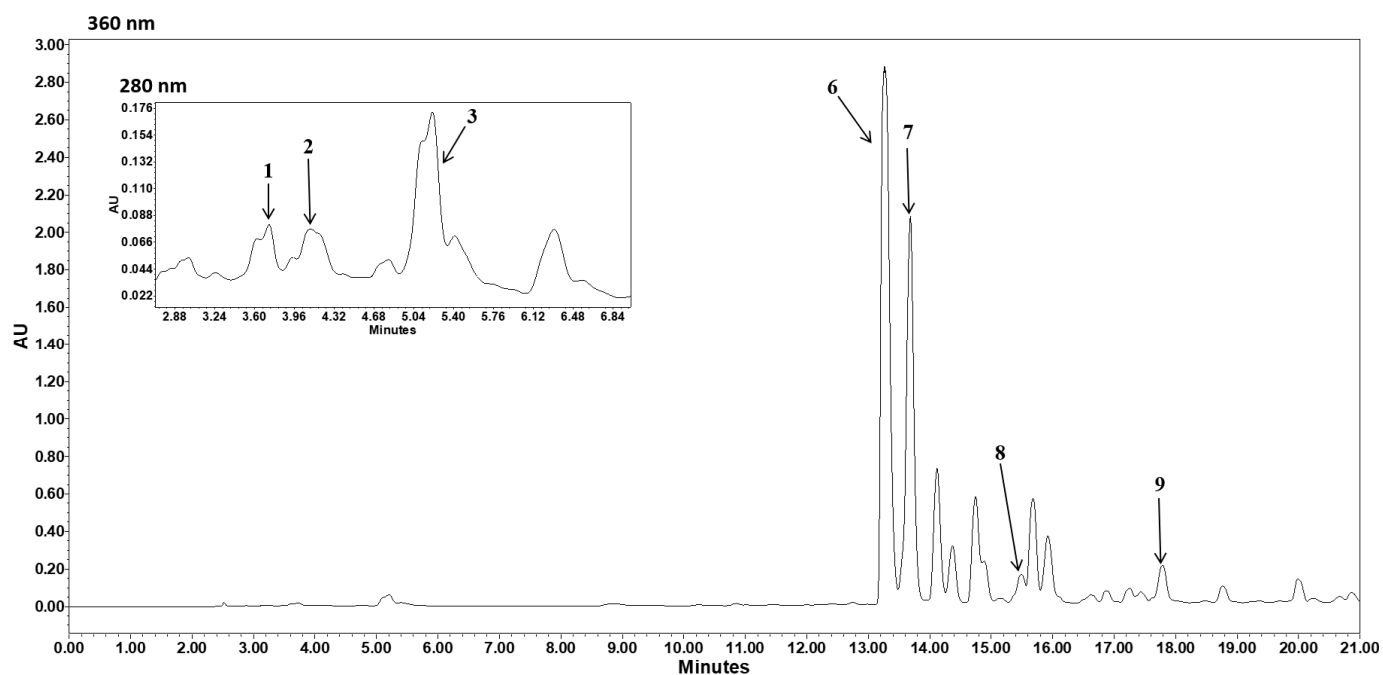


Figure 1. Chromatogram obtained from *B. hindsiana* leaf extract recorded at 280 and 360 nm. 1. Proto-catechuic acid, 2. catechin, 3. chlorogenic acid, 6. quercetin-3- β -glucodise, 7. rutin. 8. kaempferol-3- β -glucoside, and 9. quercetin.

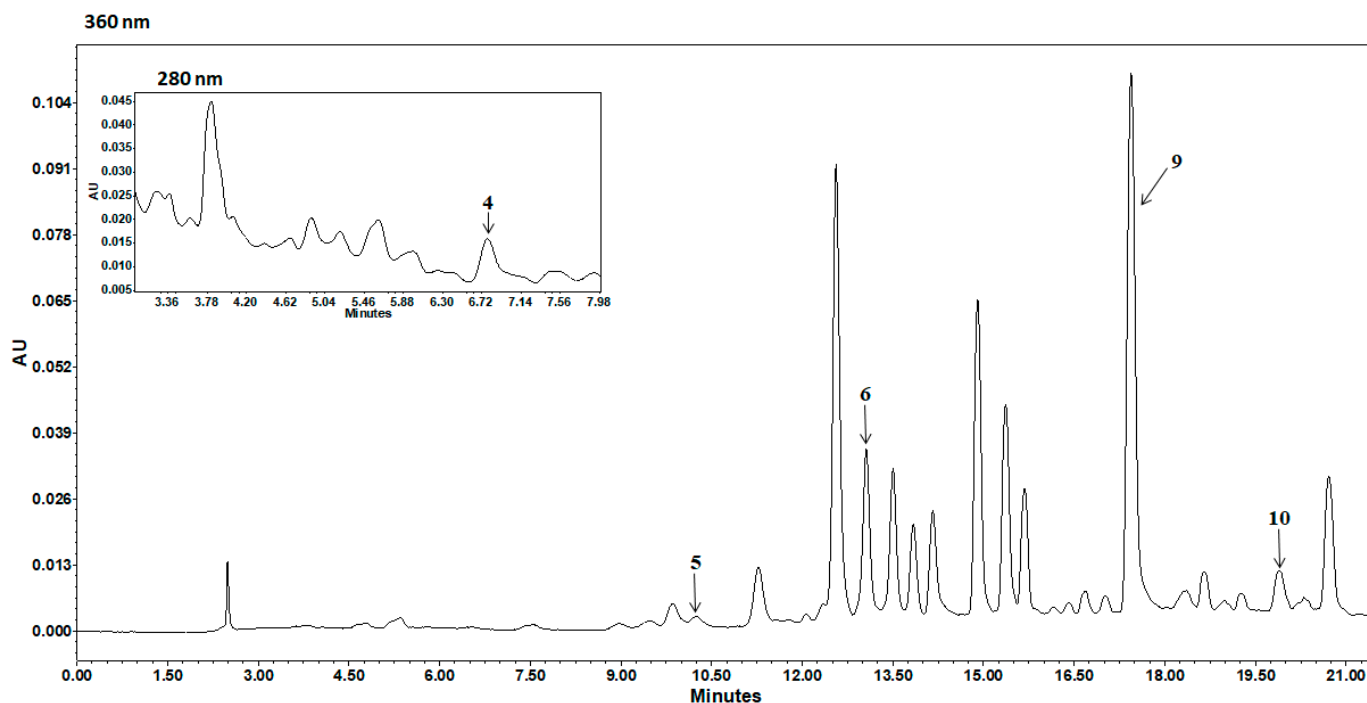


Figure 2. Chromatogram obtained from *B. hindsiana* stem extract recorded at 280 and 360 nm. 4. Vanillic acid, 5. p-coumaric acid, 6. quercetin-3- β -glucoside, 9. quercetin, and 10. kaempferol.

This research is the first study to report the presence of flavonoids and phenolic acids in *B. hindsiana*, with a total of 10 compounds. This information is relevant because it could help us understand and explain the biological effects this plant may exhibit.

3.2. Antioxidant Activity

One of the most widely explored biological activities in natural products is their antioxidant activity due to its practicality and reproducibility. The antioxidant activity of the leaf and stem extracts of *B. hindsiana* is shown in Table 1. In the DPPH assay, the leaf extract showed an IC₅₀ value 3.7 times lower ($p < 0.05$) than that of the stem extract. A similar result was observed in the ABTS assay, where the leaf extract required a concentration 3.8 times lower ($p < 0.05$) to inhibit 50% of the radical compared to the stem extract. Regarding the capacity to stabilize the peroxyl (ORAC assay), the leaf extract was 3.2 times more effective ($p < 0.05$) than the stem extract was. Finally, regarding the reducing effect, it was observed that the leaf extract showed a reducing effect 2.8 times greater ($p < 0.05$) than that shown by the stem extract.

The results described above demonstrated that bioactive compounds in *B. hindsiana* extracts were able to transfer hydrogen atoms and electrons, providing an antioxidant effect. Through DPPH and ABTS methods, it is possible to prove the capability of compounds to transfer hydrogen or electron and remove DPPH· and ABTS·⁺, respectively [26]. Additionally, the capability of compounds to transfer hydrogen due to peroxyl radical removal (ORAC assay) is proven [27]. Furthermore, extract compounds showed a reducing potential by electrons transferring through ferric ion reduction to ferrous by FRAP [26]. These last findings confirm that extract compounds are suitable to react with free radicals and metals, suggesting their potential application as therapeutics agents.

This study reveals novel information about the biological potential of *B. hindsiana*, which can be considered of high antioxidant potential based on its capacity to stabilize free radicals and reduce metals [28,29]. The antioxidant potential of leaves and stems of *B. hindsiana* had not been previously demonstrated.

The results showed that *B. hindsiana* exhibits a promising antioxidant effect aimed at avoiding or stopping oxidative stress, which is known to play a significant role in the development of chronic degenerative diseases. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species and the body's ability to neutralize or eliminate them [30]. This overproduction can lead to alterations at the cellular level, which may lead to genetic mutations [31]. Then, the ability of *B. hindsiana* extract to stabilize synthetic and biological free radicals, as well as reduce metals, suggests that this plant source could initially neutralize free radicals, preventing the occurrence of oxidative stress, or interrupt the oxidative process once initiated, preventing excessive cellular damage. However, further studies are needed to demonstrate its safety and efficacy at the biological level.

In addition, this study showed that the *B. hindsiana* leaf extract exhibits a greater antioxidant effect. This behavior can be attributed to the higher content of phenolic compounds present in the leaf extract, which was 2.09 times greater than that of the stem extract. In this regard, several studies have demonstrated a close relationship between phenolic compounds and the antioxidant activity of natural products, with these bioactive compounds having the greatest impact [32].

Likewise, the results presented in this study are consistent with other published studies. Balaji et al. [33] observed that *Ocimum tenuiflorum* leaf extract exhibited a greater antioxidant effect compared to the stem extract. Similarly, Brij and Arun [34] observed that *Solanum indicum* leaf extract was more effective in stabilizing free radicals compared to the stem extract. This behavior may be associated with the constituent's source of the

plants analyzed. In this regard, it is well known that plant stems contain high amounts of cellulose, hemicellulose, and lignin, which can decrease the quantity and concentration of free phenolic compounds [35,36]. Conversely, the leaves exhibit a higher content of free phenolic compounds, which may contribute to their biological activities, particularly antioxidant activity [37].

Although there is currently no information on the antioxidant mechanism of *B. hindsiana*, it is possible that it is associated with the bioactive compounds identified in the chemical characterization performed in this study. For the leaf extract, two of the major compounds identified were quercetin-3- β -glucoside and rutin, while in the stem extract, the major compound was quercetin. In this regard, various studies have demonstrated that these compounds possess a similar chemical structure (they only differ in the hydroxyl group or carbohydrate residue present at position 3 of ring C) and a strong antioxidant effect [38,39]. The effect is associated with the hydroxyl groups present at positions 3 and 4 of ring B of the phenolic structure (all three compounds), and at position 3 of ring C (only quercetin), which can release a proton or electron to stabilize free radicals or reduce metals. Furthermore, the double bond present in ring C (all three compounds) helps stabilize the generated phenolic radicals [40–42]. In addition, other unidentified compounds could also influence the antioxidant effect of *B. hindsiana* due to chromatograms from both extracts, which exhibited an important amount of unidentified compounds, particularly in the stem extract. Thus, a large phenolic compound database would be useful in identifying more compounds as well as their association with different biological activities from this plant.

3.3. Antiproliferative Activity

Another widely explored biological activity in natural products is their antiproliferative effect, which is evaluated to determine their potential as agents with anticancer activity. In this regard, Table 3 shows the antiproliferative effect of *B. hindsiana* against two cancer cell lines and one non-cancerous cell line. The IC₅₀ values range between 24.7 and >200 μ g/mL. It can be observed that the leaf extract was more active ($p < 0.05$) than the stem extract, as it was 44% and 27% more effective in inhibiting 50% of cell proliferation in the cervical and lung cancer cell lines, respectively. Furthermore, the extracts showed selectivity against the evaluated cancer cell lines, since the IC₅₀ value for the non-cancerous cell line was higher than the maximum concentration evaluated (200 μ g/mL).

Table 3. Antiproliferative activity of *Bursera hindsiana* extracts.

Extract	IC ₅₀ (μ g/mL)		
	HeLa	A549	ARPE-19
Leaves	24.7 $\pm$ 1.7 ^a	41.4 $\pm$ 5.3 ^a	>200
Stems	43.8 $\pm$ 1.8 ^b	56.7 $\pm$ 3.8 ^b	>200

Data are presented as the mean $\pm$ standard deviation of three independent experiments. ^{a,b} Different superscripts in each extract indicate significant differences ($p < 0.05$).

Previous studies have reported the antiproliferative effect of resins and stems of *B. hindsiana* against HeLa and A549 cancer cell lines and showed IC₅₀ values between 90 and 500 μ g/mL [43,44]. In contrast, this is the first time that the antiproliferative activity of *B. hindsiana* leaves has been reported, proving that the leaf extract is more active than the other constituents previously reported. This may guide future studies of this plant to identify the chemical compounds responsible for the antiproliferative effect. The difference observed between the present research and previous studies may be associated with various factors, such as the collection site, collection date, the part of the plant analyzed, and the biotic and abiotic factors to which the plants were exposed. It has been reported that these factors

impact the synthesis of chemical compounds within the plant and directly affect their biological potential and constituents [45,46].

An important finding in this study is that the *B. hindsiana* leaf extract can be classified as highly cytotoxic against the HeLa cell line as it exhibits an IC₅₀ value below 30 µg/mL, the threshold established by the U.S. National Cancer Institute for extracts with potential cytotoxicity against cancer cell lines [47]. Furthermore, the values against the A549 cell line are close to this threshold, suggesting that this plant source can be further explored to identify fractions or compounds with greater antiproliferative effects.

Cancer is known to be one of the main public health issues and one of the leading causes of death worldwide. In 2022 alone, it is estimated that there were nearly 20 million new cases and more than 9 million deaths from this disease [48]. Lung cancer has the highest mortality rate globally, with more than 1.8 million deaths annually [49]. Similarly, cervical cancer shows a high mortality rate among women worldwide, causing more than 350,000 deaths annually [50]. In addition, the number of deaths has increased in recent years, associated with various factors, such as the stage of disease identification or the limited effectiveness of administered procedures or treatments [51,52]. In this sense, it has been observed that antineoplastic therapy can sometimes be ineffective due to the ability of cancer cells to develop chemoresistance [53]. It has been observed that antineoplastic therapies often have low selectivity against cancer cells, which can damage healthy cells in an organism, leading to adverse effects [54,55]. The selectivity of *B. hindsiana* extracts against cancer cell lines reported in the present study constitutes an interesting finding for the development of new antineoplastic therapies. However, it is certain that further experiments are needed to ensure safe application in humans.

Recent studies show that phenolic compounds strongly inhibit the growth of cancer cell lines [56]. Furthermore, in vivo studies have shown that phenolic compounds, or natural sources rich in these compounds, reduce the incidence and development of cancer in animals [57]. The mechanisms of action associated with these compounds include decreased angiogenesis and inflammation, inhibition of the MAPK, ERK 1/2, and PI3K/Akt pathways, induction of apoptosis and, cell cycle arrest [58,59]. This last mechanism provides evidence to consider this plant as a natural source of potential antineoplastic agents.

The antiproliferative mechanism of stem and leaf extracts of *B. hindsiana* has not been explored. However, considering the present chemical characterization of the extracts, it is suggested that this effect may be associated with the major compounds identified in both extracts, which have shown antiproliferative effects in HeLa and A549 cancer cell lines in previous studies. For example, quercetin, when evaluated in the HeLa cell line, decreases cell viability by inducing cell cycle arrest in the G2/M phase, as well as mitochondrial apoptosis through a p53-dependent mechanism. This resulted in changes in nuclear morphology, externalization of phosphatidylserine, mitochondrial membrane depolarization, and interference with the regulation of cell cycle regulatory proteins and members of the NF-κB family. It also led to overexpression of pro-apoptotic proteins of the Bcl-2 family, cytochrome C, Apaf-1, and caspases, and dysregulation of the anti-apoptotic proteins Bcl-2 and survivin [60]. Similarly, quercetin-3-glucoside exhibited high cytotoxicity against HeLa cells. The mechanism was associated with cell cycle arrest in the S phase and induction of apoptosis with chromosomal DNA degradation and increased production of reactive oxygen species. Furthermore, activation of caspases 3 and 9 was observed, along with downregulation of the expression of the anti-apoptotic protein Bcl-2 and upregulation of Bcl-2-associated protein X [61]. Similarly, when evaluated in the HeLa cell line, rutin decreased cell viability with subsequent cell cycle arrest in the G0/G1 phase. Furthermore, rutin decreased the expression of the E6 and E7 oncogenes, leading to an increase in the expression of p53 and pRB. In addition, an increase in Bax expression and a decrease in

Bcl-2 expression were observed, resulting in the release of cytochrome C into the cytosol and subsequent activation of caspases 3, 8, and 9 [62]. On the other hand, organic fractions of ethyl acetate obtained from extracts of *Achillea millefolium* and *Cassia fistula* showed a high concentration of chlorogenic acid (the second major compound). *A. millefolium* induced apoptosis and cell cycle arrest in the G2/M phase when evaluated against the HeLa cell line [63]. Finally, *C. fistula* caused apoptosis in HeLa by inducing phosphatidylserine externalization [64].

Furthermore, in the A549 cell line, a similar behavior has been observed, since quercetin, rutin, quercetin 3-glucosium and chlorogenic acid decrease cell viability by inducing cell cycle arrest and apoptosis and altering the function of proteins (Bax, Bcl-2 and caspases) and genes associated with this process (cIAP2 and cIAP2), in addition to increasing the production of reactive oxygen species, affecting cell adhesion and migration [65–68].

Derived from this information, it could be suggested that the antiproliferative effect of *B. hindsiana* is related to the mechanisms previously described, due to the high concentration of phenolic compounds identified in the extracts (quercetin, quercetin-3- β -glucoside, rutin, and chlorogenic acid). Nevertheless, other groups of bioactive compounds could also influence the antiproliferative potential. For this reason, it seems feasible to continue exploring the chemical composition of this natural source.

3.4. Acute Toxicity

The results for acute toxicity of the leaf and stem extracts of *B. hindsiana* are shown in Figures 3 and 4. It can be observed that the leaf extract (Figure 3) showed no toxicity at the evaluated doses (0–100 $\mu\text{g/mL}$), as a survival rate greater than 96% was observed at all doses. This indicates an LC_{50} value greater than 100 $\mu\text{g/mL}$. Regarding the stem extract, an LC_{50} value greater than the maximum evaluated dose of 300 $\mu\text{g/mL}$ is expected. Similarly, the survival percentage in *A. salina* ranged from 100% to 80% at concentrations of 150 and 300 $\mu\text{g/mL}$, exhibiting the highest acute toxicity ($p < 0.05$) in *A. salina*, respectively.

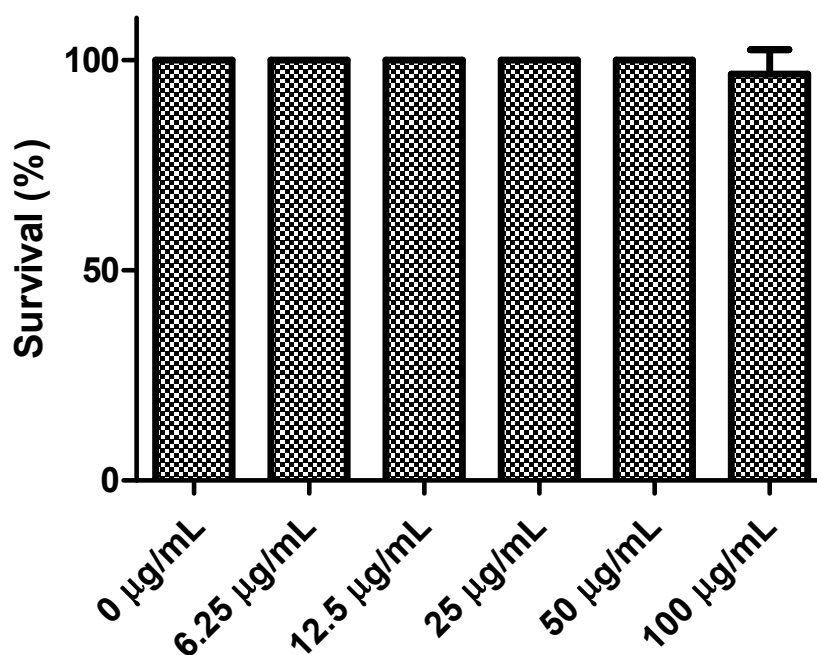


Figure 3. Acute toxicity of *Bursera hindsiana* leaf extract. Data are presented as the mean $\pm$ standard deviation of three independent experiments.

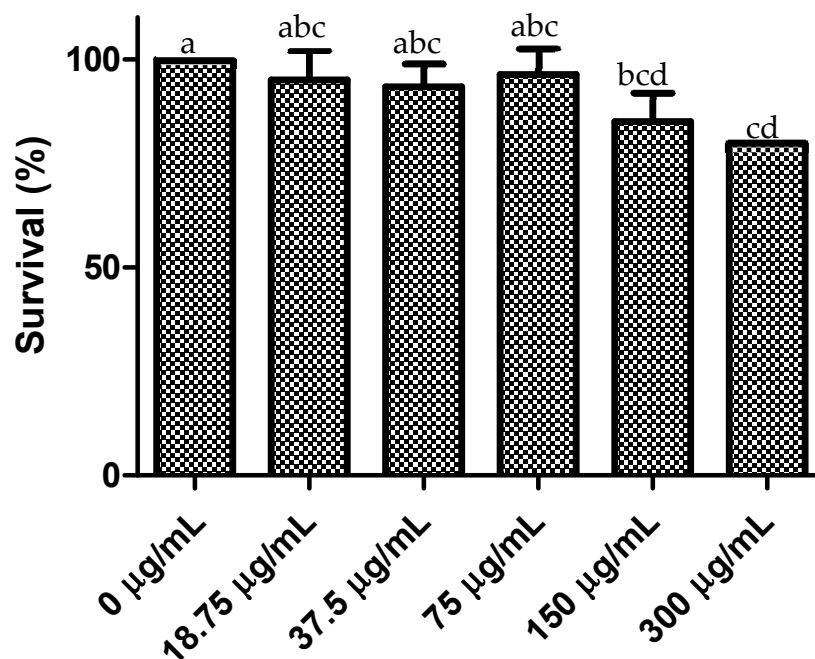


Figure 4. Acute toxicity of *Bursera hindsiana* stem extract. Data are presented as the mean $\pm$ standard deviation of three independent experiments. ^{a–d} Different superscripts in each bar indicate significant differences ($p < 0.05$).

These results report for the first time the acute toxicity of *B. hindsiana* extracts and indicate that the extracts obtained from this plant source so far do not present high toxicity, since the LC_{50} values are greater than 100 $\mu\text{g/mL}$ [69].

An important aspect when exploring potential applications of medicinal plant extracts in humans or animals is ensuring their safety to prevent risks during consumption or application [10]. In addition to in vitro assays using cell lines, in vivo analyses can be used to assess toxicity. The *A. salina* assay is a simple and easily reproducible analysis in vivo. This assay provides an initial indication of the potential toxicity of an extract or treatment and is widely used to determine acute toxicity as *A. salina* is a highly sensitive system to changes in its environment that can lead to damage or death [70].

Together, the results show that the IC_{50} of antioxidant and antiproliferative activity are significantly lower than the LC_{50} values obtained in the toxicity assay. Therefore, it is possible to continue investigating this plant source to further analyze its safety and efficacy and potentially develop drugs to address the aforementioned health problems.

4. Conclusions

The results of this research provide novel and original information about the chemical composition of the plant, identifying for first time several phenolic compounds in *B. hindsiana*. Furthermore, this plant is observed to be a natural source with promising biological potential, particularly its high antioxidant and antiproliferative effects. In addition, *B. hindsiana* exhibited low cytotoxicity against healthy cells, as well as low acute toxicity. This indicates the possibility to continue studying this natural source, including the isolation of the chemical compounds responsible for its biological effects and the determination of their respective mechanisms of action. This could lead to the use of this natural source for the development of new therapeutic agents; however, product safety must be analyzed.

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Abbreviations

The following abbreviations are used in this manuscript:

GAE	Gallic acid equivalent.
TE	Trolox equivalent.
DMEM	Dulbecco's Modified Eagle Medium.
DMSO	Dimethyl sulfoxide.
IC ₅₀	Half maximal inhibitory concentration.

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