

Chapter

Antioxidant Activity of Natural Products from Medicinal Plants

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Abstract

Ethnobotanical study is an important activity related to the research and development of drugs. The growing need to find alternatives for the treatment of chronic degenerative diseases, such as diabetes, hypertension, and metabolic syndrome, among others, justifies the study of medicinal plants used in traditional medicine. The therapeutic effects of plants are due to the content of different secondary metabolites such as essential oils, tannins, phenolic acids, sesquiterpenes, and flavonoids—for example, several reports about the beneficial effects of a wide range of plants to treat diabetes. In Mexico, most of the traditional knowledge about medicinal plants comes from pre-Hispanic times, and different ethnic groups still retain it.

Keywords: medicinal plants, oxidative stress, antioxidants, *Eryngium*, *Justicia*, *Potentilla*

1. Introduction

The ethnobotanical study is an important activity in the research and development of drugs. The growing need to find alternatives for the treatment of chronic degenerative diseases, such as diabetes, hypertension, and metabolic syndrome, among others, justifies the study of medicinal plants used in traditional medicine. The therapeutic effects of plants are due to the content of different secondary metabolites such as essential oils, tannins, phenolic acids, sesquiterpenes, flavonoids, among others [1]. In the literature are several reports about the beneficial effects of various plants in treating diabetes. In Mexico, most of the traditional knowledge about medicinal plants comes from pre-Hispanic times, and different ethnic groups still retain it. Also, the country's biodiversity regions range from semi-desert regions in Northern Mexico to tropical and rainy Southern regions with many plants that grow under different extreme climate conditions, producing many chemical compounds. Some plants, such as *Eryngium carlinae* F. Delaroche, commonly known as “Frog herb,” a perennial herb

plant that is distributed in forests of fir, pine and pine-oak hillsides, and canyons, deep soils rich in an organic matter [1]. The genus *Eryngium* (Picos, Eryngo, and Sea holly), spread throughout the world, representing one of the largest genera of the Apiaceae family [1], develops mainly in the pine-oak forest of the high parts of the country. It is frequently found in the open places on the edges of plots, around de houses, on degraded surfaces, and as weeds. There are eight species of *Eryngium* reported as medicinal in the central-western region of Mexico: *E. cymosum*, *E. longifolium*, *E. fluitans*, *E. beecheyanum*, *E. carlinae*, *E. comosum*, *E. heterophyllum*, and *E. nasturtiifolium*. The extracts contain various metabolites (e.g., tannins, phenolic acids, saponins, and terpenoids) that have shown biological activities such as hypoglycemic, hypocholesterolemic, renoprotective, anti-inflammatory, antibacterial, antioxidant, and others [2]. The hexanic extract of *Eryngium carlinae* possesses activities as an antioxidant, antilipidemic, hypoglycemic at the serum level, and in mitochondria from left ventricle increased nitric oxide levels and glutathione reduced, which may eventually reduce the risk of developing diabetic cardiomyopathy [3]. Also, this hexanic extract of *E. carlinae* reduced lipid peroxidation, protein carbonylation, and reactive oxygen species (ROS) in the liver, the kidneys, and the brain of streptozotocin-induced diabetes rats [4], and protection has been reported when cells of the yeast *Saccharomyces cerevisiae* reported were exposed to hydrogen peroxide-induced stress by reducing lipid peroxidation and protein carbonylation [4]. Under the organic solvent utilized, the chemical composition of the compounds identified, that is, in the hexanic extract of *E. carlinae*, was mainly identified (Z) β -farnesene and β -pinene [4].

Potentilla indica is a scientific synonym of *Fragaria indica* Andr. and *Duchesnea indica* Andr., is a plant belonging to the Rosaceae family, commonly known as “false strawberry,” “Indian strawberry,” or “wild strawberry.” It is an herbaceous perennial plant; it flowers from May to October, and the seeds ripen from July to October. Traditionally, *Potentilla indica* leaves are used as a decoction or applied externally as a poultice after the fresh leaves are crushed. The flowers are used in infusions, and the fruit is edible [2].

Justicia spicigera (Acanthaceae), Muicle or Mexican honeysuckle, has antioxidant properties due to significant concentrations of flavonoids [5]. It contains over 250 flowering plant species, commonly used as edible and medicinal plants in different countries. *Potentilla indica* is a perennial herb belonging to the Rosaceae family and native to Asia. It is widely used in traditional Asian medicine to treat leprosy, tissue inflammation, congenital fever, cancer, and diabetes mellitus [2]. *J. spicigera* stands out due to its high antioxidant capacity. Recent studies have demonstrated the therapeutic effects of this plant attributed to the phenolic secondary metabolites obtained with solvents of different polarities that can be used as a potential treatment in different pathologies such as cancer, diabetes, and hypertension. It should be noted that these effects may be due to the combination of compounds in the extracts, generating interactions that can be classified as antagonistic or synergistic [3], in which different mechanisms are involved that serve as points of opportunity for new research.

2. Diabetes mellitus and oxidative stress

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia and alterations in the metabolism of carbohydrates, lipids, and proteins because of defects in the secretion or action of insulin or a combination of both [6]. The prevalence of DM is growing exponentially worldwide being one of

the main challenges for health systems [7], in fact, according to IDF data [6], it is estimated that there are 537 million people with DM worldwide, and by 2045 the figure will increase to 783 million. There are different types of diabetes: type 1 DM (T1DM), type 2 DM (T2DM), and gestational diabetes. T1DM represents approximately 5–10% of all cases, the pathophysiology of this type of diabetes results from the destruction of pancreatic beta cells, resulting in decreased insulin levels [8]. T2DM is the most prevalent type of diabetes, accounting for 90% of all cases and is associated with both deficiency and tissue resistance to insulin [9]. Gestational diabetes is caused by hormonal variation during pregnancy, which results in the appearance of chronic hyperglycemia [10].

Chronic hyperglycemia in non-insulin-dependent tissues causes a higher glycolytic rate, which leads to a greater conversion of pyruvate to acetyl-CoA, which feeds the Krebs cycle, and this, in turn, produces a greater amount of NADH y FADH₂ than they donate their electrons to mitochondrial electron transport chain (ETC), and this causes an increase in the leak of electrons resulting in greater generation of reactive oxygen species (ROS) [11]. In this sense, the main source of ROS in the cell is the mitochondria, specifically complex I and III of ETC [12]. Chronic hyperglycemia, in addition, increases the activity of other metabolic pathways that together lead to the increase in generation of ROS and consequently the development of oxidative stress [13]. Among these, pathways related to hyperglycemia is overactivation of protein kinase C (PKC) due to the increase in *de novo* synthesis of diacylglycerol (DAG), and due to a higher availability of glycolytic intermediate glyceraldehyde-3-phosphate, this activation results in the increase of several pro-oxidant enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) [14]. The polyol pathway metabolizes approximately 30% of total glucose during hyperglycemia, the rate-limiting step is the reduction of glucose into sorbitol catalyzed by aldose reductase, using NADPH as a cofactor, this reaction decreases the cytosolic NADPH/NADP⁺ ratio, NADPH depletion leads to a decrease in the reduced/oxidized glutathione (GSH/GSSG) ratio, and GSH reduction contributes to oxidative stress [15]. Hexosamine pathway is activated by the increase in concentration of glycolytic intermediate fructose-6-phosphate and results in the synthesis of N-acetylglucosamine, which is a potent protein glycosylation agent [16]. Excess ROS leads to a decrease/alteration in the activity of the enzymes of antioxidant system and in turn damage to cellular macromolecules, such as respiratory chain complexes or membrane lipids, thus culminating in oxidative damage [17–19]. This imbalance between overproduction of ROS and the inability of the antioxidant system leads to a state of oxidative stress that exacerbates the complications and damage caused by DM per se [20, 21].

2.1 *Eryngium carlinae* F. Delaroche

Currently, different drugs are available for the treatment of diabetes [22]. However, these drugs only act by reducing glucose levels and not oxidative stress, and furthermore, there are different drawbacks to their use such as severe hypoglycemia, weight gain, lower therapeutic efficacy, ineffective dosage, solubility and permeability problems, low potency, and altered side effects due to drug metabolism [23]; due to these effects, the use of medicinal plant extracts that can exert hypoglycemic and antioxidant effects is of importance in the research of effective therapies against DM and oxidative stress.

Among the compounds that have been isolated from *E. carlinae* and have demonstrated antioxidant activity *in vivo* are gallic acid, protocatechuic acid, rutin,

epicatechin, and quercetin, for this reason, *E. carlinae* is a plant that has great potential to be used as a treatment against DM and oxidative stress [24].

2.2 Antioxidant, hypoglycemic, and hypolipidemic effects of *E. Carlinae* extracts

Pérez-Ramírez et al. [25] obtaining an aqueous decoction from the flowers, performed the phytochemical identification using the HPLC-ESI/MSD technique, where the presence of phenolic acids, flavonoids, phytosterols, and saponins was found. The main components of this extract were ellagic acid (38.3 ± 1.8 mA), campesteryl β -D-glucopyranoside (28.9 ± 1.4 mA), and caffeic acid (20.3 ± 1.5 mA); administration of this decoction in obese male Wistar rats induced with a high fat and fructose diet (13% protein, 18% lipids [6% saturated fat] and 43% carbohydrates [14% fructose]) at a dose of 0.6 g/day; this treatment reduces oxidative stress in kidneys because lipid peroxidation and protein carbonylation decreased by 29 and 18%, respectively, in the treated obese group compared to the control obese group. Trejo-Hurtado et al. [26] from an ethyl acetate extract from the inflorescences, carried out the identification and quantification of secondary metabolites where the main compounds were rosmarinic acid (3473.79 ± 146.18 μ g/g of dried extract), chlorogenic acid (64.92 ± 1.24 μ g/g of dried extract), and kaempferol-3-O-glucoside (50.42 ± 1.72 μ g/g of dried extract); oral administration of this extract in streptozotocin-induced (45 mg/kg of body weight) diabetic male Wistar rats at a dose of 30 mg/kg of body weight for 60 days; this treatment did not show hypoglycemic effect; however, antioxidant effects were observed in the liver since the treated group showed a two-fold decrease in ROS generation and lipid peroxidation compared to diabetic group. These results were related to the restoration of the activity of antioxidant enzyme catalase in the treated group. Noriega-Cisneros et al. [27] identified the compounds present in the ethanolic extract of aerial part by gas chromatography/mass spectrometry (GC/MS), which were β -selinene (26.04% of abundance), α -selinene (17.54% of abundance), and stearic acid (14.54% of abundance); oral administration of this extract in streptozotocin-induced (45 mg/kg of body weight) diabetic male Wistar rats at a dose of 30 mg/kg of body weight for 40 days; this treatment showed hypolipidemic activity since it significantly decreased the levels of total cholesterol from 74 ± 7 to 55 ± 4 mg/dl, triglycerides from 224 ± 40 mg/dl, and non-HDL cholesterol from 61 ± 7 to 35 ± 4 mg/dl in the serum of the diabetic group with respect to the group administered respectively. Peña-Montes et al. [4] obtained a hexanic extract of inflorescences where identified the main compounds by GC/MS that were (Z) β -Farnesene (38.79% of abundance), β -pinene (17.53% of abundance), and calamenene (13.3% of abundance); oral administration of this extract in streptozotocin-induced (45 mg/kg of body weight) diabetic male Wistar rats at two doses of 3 and 30 mg/kg of body weight for 7 weeks; only the group treated with the dose of 30 mg/kg body weight showed antioxidant and protective activity against oxidative damage in brain, liver, and kidney because it significantly decreased lipid peroxidation, protein carbonylation, and ROS generation with respect to diabetic group, and blood glucose levels also decreased from 503.3 mg/dl in the diabetic group to 410 mg/dl in the group treated with the 30 mg dose. Furthermore, García-Cerrillo et al. [3] obtained a hexanic extract of inflorescences oral administration of this extract in streptozotocin-induced (45 mg/kg of body weight) diabetic male Wistar rats at a dose of 30 mg/kg of body weight for 7 weeks; this treatment showed hypoglycemic and hypolipidemic effects in serum because it significantly decreased glucose levels from 355.2 to 120 mg/dl and triacylglycerides from 274.8 to 111.8 mg/dl in the diabetic group compared with respect to administered group, respectively.

On the other hand, in recent years, nanoformulations have presented a new therapeutic alternative in DM treatment. Nanoparticles increase several key pharmacological characteristics of drugs such as solubility, rapid onset of action, controlled release, increased half-life, and optimized bioavailability [28]. Among all nanoparticle synthesis techniques is the green synthesis technique. This technique is based on the reduction of mono- or divalent metal ions, nucleation, and stabilization using biological species, such as fungi and bacteria, especially plant extracts [29]. The advantage of this method is that the compounds of the extract used first carry out the synthesis of nanoparticles, and subsequently these metabolites remain attached to the surface of these nanoparticles; this characteristic allows nanoparticles to increase the pharmacokinetic characteristics of secondary metabolites when they are administered in a biological system [30]. Lemus de la Cruz et al. [31], using an aqueous extract of aerial part of *E. carlinae*, synthesized silver nanoparticles (AgNPs) through green synthesis technique from which they obtained structures with a spherical morphology and an approximate size of 10–100 nm. They also carried out the qualitative characterization of secondary metabolites present in the extract where it was found that the most abundant metabolites were flavonoids. After oral administration for 45 days of both the extract and extract-AgNPs combination at a dose of 30 mg/kg body weight in streptozotocin-induced diabetic rats, both treatments showed antioxidant activity in mitochondria isolated from the brain since they significantly decreased ROS generation and lipid peroxidation, also restored the activity of antioxidant enzymes SOD2 and glutathione peroxidase (GPx), and also restored the activity of complexes I, II, and III of respiratory chain; these results were related to presence of flavonoids in both treatments. On the other hand, only the extract-AgNPs combination had hypoglycemic and hypolipidemic activity in serum, which was associated with the biological activity of AgNPs per se.

3. *Potentilla indica* (Andrews) Th.Wolf

Potentilla indica, which has scientific synonymy with *Fragaria indica* Andr. and *Duchesnea indica* Andr., is a plant belonging to the Rosaceae family, commonly known as “false strawberry,” “Indian strawberry,” or “wild strawberry.” It is an herbaceous perennial plant; it flowers from May to October, and the seeds ripen from July to October. This species grows in temperate biomes, humid, and semi-shady areas, and presents a height of 10 cm, the foliage is semi-deciduous with trifoliate leaves, leaflets with serrated edge, and a petiole up to 5 cm long. Its flowers are yellow with five nonoverlapping petals, and its fruits are red, which are ovoid or globose, 1 to 1.5 cm in diameter with a great similarity to strawberries (**Figure 1**) [32].

This species is native to East Asia; however, it is widely distributed in the Asian, European, and American continents, which converts it into a plant with a favorable environmental adaptability.

The use of plants as a complementary therapy is an ancestral practice that nowadays continues to spread all over the world. Traditionally, *Potentilla indica* leaves are used as a decoction or applied externally as a poultice after the fresh leaves are crushed. The flowers are used in infusions, and the fruit is edible. The plant has been widely used in traditional Asian medicine, mainly for the treatment of leprosy, burns, congenital fever, tissue inflammation, hematemesis, diarrhea, cancer, diabetes, among other uses [33].

Medicinal plants have been of great interest to different research groups as they may represent an important natural source of bioactive compounds for the



Figure 1.
Potentilla indica plant.

development of new and promising drugs in the search for an effective treatment with a lower degree of side effects for various diseases. These plant-derived bioactive compounds can exert their therapeutic effects through different mechanisms that may include, in general terms, their interaction with cytoplasmic membrane receptors, resulting in the modulation of distinct signaling cascades with the activation/inhibition of different regulatory kinases. Also, through their ability to regulate gene expression in target cells or by interacting directly with the aggressor agent.

It has been documented that the different extracts of *Potentilla indica* present a great variety of pharmacological effects associated with antioxidant, anti-inflammatory, immunomodulatory, anticancer, and antimicrobial activity [32, 34–36] whose effects are attributed precisely to the content of secondary metabolites (SM) that it presents.

3.1 Antioxidant effect of *Potentilla indica*

It is well documented that oxidative stress represents a determinant factor in the development and evolution of multiple chronic degenerative diseases such as diabetes, metabolic syndrome, cardiovascular disease, cancer, Alzheimer’s, and Parkinson’s disease, and its incidence has been increasing exponentially in recent years [37]. Therefore, it is necessary to search for and implement drugs with antioxidant properties as a therapeutic strategy. In this sense, numerous studies have reported a potent antioxidant activity exhibited by different extracts of certain parts of *Potentilla indica* due to their phytochemical composition. In 2009, compounds of phenolic nature were identified in the fruit by HPLC-MS/MS, comprising three anthocyanins: cyanidin 3-O-ruthinoside, peonidin 3-O-ruthinoside, and petunidin 3-O-ruthinoside [38]. Anthocyanins are phenolic compounds pertaining to a subgroup of flavonoids, which are characterized by being water-soluble pigments responsible for the range of colors in flowers, fruits, and leaves, and in addition, they have shown promising antioxidant properties directly related to their structure due to the presence of hydroxyl groups in the B ring, as well as the oxonium ion in the C ring; thus, they are phytochemicals with a great capacity to neutralize free radicals [39]. Moreover, in 2019 Shan et al.

[40] demonstrated that *Potentilla indica* fruit possesses potent antioxidant activity by neutralizing the DPPH radical and H_2O_2 , which may be correlated to its high content of phenolic compounds. In addition, a neutral polysaccharide obtained from *Potentilla indica* has also been reported to exhibit *in vitro* antioxidant and anti-inflammatory activity [32]. Additionally, it was demonstrated that the methanolic extract of *Potentilla indica*, in which ellagic acid was identified as the major SM by HPLC, exhibits antioxidant activity at a concentration of 200 $\mu\text{g/mL}$ in human skin fibroblast cells (CCD-986Sk) and at 100 μg by topical application to mouse skin. Another *in vitro* study identified two compounds (2,4-dichloro-6-hydroxy-3,5-dimethoxytoluene and 2-methyl-6-(4-methylphenyl)-2-hepten-4-one) isolated from an ethyl acetate fraction of *Potentilla indica* by their mass and $^1\text{H-NMR}$, which showed potent antioxidant activity by neutralizing the DPPH radical, in addition to significant antidiabetic activity by inhibiting α -amylase and α -glucosidase enzymes [41].

In addition to the fruit, other parts of the plant have been subjected to research and have been shown to possess antioxidant activity, both *in vitro* and in different experimental models. In 2015 Zhu et al. identified by HPLC-ESI-MS/MS and ESI-IT-MS (ion trap MS) 27 phenolic compounds in an ethanolic extract of the aerial part (stems and leaves) of *P. indica*, which comprised ellagitannins, ellagic acid and ellagic acid glycosides, hydroxybenzoic acid, hydroxycinnamic acid derivatives, and flavanols, such as quercetin 3-O-glucuronide and kaempferol, which have been shown in various studies to possess potent antioxidant activity [33]. Quercetin is a considerably prominent flavonoid due to the extensive pharmacological effects it has been demonstrated to possess as an antioxidant, antimicrobial, antidiabetic, anti-inflammatory, and anticarcinogenic. However, among the various biological properties of quercetin and its conjugated metabolites, the most remarkable property is undoubtedly the antioxidant aspect, which is directly associated with its chemical structure, where the hydroxyl groups at the 3, 5, 7, 3', 4' position of the A and B rings, the double bond between the second, and third carbon and the carbonyl group of the fourth carbon play a fundamental role in its antioxidant properties [42]. In the same way, Liaquat et al. [43] determined the *in vitro* antioxidant activity of extracts of different polarity of different parts of *Potentilla indica* (whole plant, leaves, stems, and root) where they showed that the aqueous and methanolic extract of all plant parts evaluated in the study and exhibit potent antioxidant activity and in which they determined a high content of phenolic compounds through spectrophotometric methods. In another study, Landa-Moreno et al. [2] demonstrated that ethyl acetate extract from the leaves and stems of the plant exhibited antioxidant activity *in vitro* and in renal mitochondria in an animal model of streptozotocin-induced type 1 diabetes after oral administration for 60 days at a dose of 25 mg/kg, and in which phenolic acids, such as ferulic acid, vanillic acid, and t-cinnamic acid, were identified by UPLC-MS/MS as the major phytochemicals. Ferulic acid is a phytochemical derived from cinnamic acid that has been shown to possess a pharmacological effect on different diseases related to oxidative stress such as neurodegenerative diseases, diabetes and its complications, cardiovascular diseases, cancer, inflammation, and even bacterial and viral infections [44]. Ferulic acid and its derivatives have demonstrated significant antioxidant activity due to their structural features attributed to their phenolic ring and unsaturated side chain. The free radical reacting with ferulic acid easily abstracts a hydrogen atom leading to the formation of the phenoxyl radical, which is rapidly stabilized by resonance, as the unpaired electron can either remain on oxygen or delocalize throughout the molecule [45]. Therefore, the generated phenoxyl radical is unable to initiate or propagate a radical chain reaction, and thus condenses with another ferulate radical to

form dimerized compounds, such as curcumin [45, 46]. The curcumin dimer, whose structure presents a second phenolic hydroxyl group, can enhance antioxidant activity due to increased resonance stabilization and o-quinone formation. Additionally, ferulic acid can increase the activity of antioxidant enzymes and inhibit oxidative enzymes, which converts it into a potent natural antioxidant [45].

In 2019, ferulic acid was demonstrated to activate Nrf2 protein, a factor involved in the positive transcriptional regulation of cellular antioxidant response, *via* the PI3K signaling pathway in human umbilical vein endothelial cells (HUVEC) [47]. Furthermore, ferulic acid exerts a renoprotective effect on methotrexate-induced nephrotoxicity in rats by activation of the Nrf2/ARE/HO-1 and PPAR γ pathway and suppression of NF- κ B/NLRP3 inflammasome axis [47]. Chowdhury et al. [22] demonstrated that an oral treatment with ferulic acid (50 mg/kg) for 8 weeks exerts a renoprotective effect in streptozotocin-induced diabetic rats *via* modulation of the MAPK pathway (p38, JNK and ERK 1/2), NF- κ B, mitochondria-dependent and -independent apoptosis, as well as induction of autophagy. In addition, it exerts a protective effect on methotrexate-induced hepatotoxicity in mice by decreasing oxidative stress and inflammation [48]. Thus, plants containing ferulic acid as a chemical constituent, including *Potentilla indica*, show promising potential in the treatment of different diseases associated with oxidative stress.

3.2 Anti-inflammatory effect of *Potentilla indica*

There is accumulating evidence that dysregulation of inflammatory pathways is closely linked to the development and progression of various chronic diseases [49]. Several investigations have been reported an anti-inflammatory effect of *Potentilla indica* in different study models. In 2021, Ullah et al. [50] demonstrated that the 18-hour exposure to ethanolic extract of *Potentilla indica* leaves and stems at different concentrations (12.5, 25, 50, y 100 μ g/mL) potentially attenuates coal fly ash-induced inflammation in murine alveolar macrophages by inhibiting the proinflammatory NF- κ B signaling pathway, where the major SM identified in the extract by UPLC-QTOF-MS was ellagic acid. Ellagic acid is a phenolic acid well recognized for its high therapeutic potential since it has been shown in several studies to possess pronounced antioxidant, anti-inflammatory, antiproliferative, antimicrobial, antifibrotic, and antidiabetic properties [39]. This compound has been the secondary metabolite mostly identified in alcoholic extracts of *Potentilla indica*. In 2022, Lee et al. [51] demonstrated that the oral administration of ethanolic extract of the *Potentilla indica* (100 and 300 mg/kg) in which ellagic acid was identified by UPLC as the major component, ameliorates LPS-induced septic shock in mice and decreases the levels of inflammatory markers in the serum of mice in a chronic sepsis model by suppressing NF- κ B translocation to the nucleus of lung cells in a dose-dependent manner. Similarly, in 2008, Zhao and colleagues [34] demonstrated that ethanolic extract of *Potentilla indica* (whole plant) displayed anti-inflammatory activity in an inflammatory cell model by addition of lipopolysaccharide (LPS, 10 ng/mL) in the RAW264.7 cell line in the presence of 10, 5, and 1 μ g/mL concentrations of the extract for 24 h, blocking NF- κ B activation.

3.3 Anticancer effect of *Potentilla indica*

Cancer is one of the leading causes of mortality worldwide [52]. Cancer cells frequently experience resistance to chemotherapeutic drugs; however, it has

been reported in different cellular models that several phytochemicals are able to increase the sensitivity and efficacy to chemotherapy through different mechanisms; therefore, they may contribute considerably to decrease the mortality of this disease [53]. In this context, it has been reported in different studies that *Duchesnea indica* has anticancer activity. This effect can be attributed to epicatechin gallate (ECG) and derivatives, which are phenolic compounds that have been shown in several studies to possess potent antiproliferative and antioxidant activity in different tumor models [54, 55] and have been identified in extracts of *Potentilla indica*. In 2017, Chen et al. [56] demonstrated that *Potentilla indica* leaves extract, whose main secondary metabolite identified by HPLC was ECG and exhibits antitumor activity by significantly reducing tumor growth in a BALB/c nude mouse xenograft model orally administered with the extract (500 mg/kg). Likewise, it inhibits highly metastatic cells by reducing extracellular matrix metalloproteinase-2 (MMP-2) and urokinase-type plasminogen activator secretions. This study also demonstrated that *Potentilla indica* negatively regulates N-cadherin, fibronectin, and vimentin and increases E-cadherin expression, decreasing cell adhesion capacity. Phenolic extracts of this plant have also been shown to significantly inhibit SKOV-3 ovarian cancer cell proliferation and *in vitro* and *in vivo* cervical cancer growth through induction of apoptosis *via* mitochondrial pathway and cell cycle arrest [57, 58]. It has also been reported that an extract of *Potentilla indica* possesses antimetastatic effects on oral squamous cell carcinoma through the inhibition of the MMP-2 activity by down-regulating the MEK/ERK pathway [36].

3.4 Antimicrobial effect of *Potentilla indica*

Currently, infectious diseases caused by different pathogenic microorganisms represent one of the main global threats to public health. Additionally, in recent decades, drug resistance to commercially available synthetic compounds has increased considerably [59], and natural products could represent a promising source to satisfy this demand. In this context, *Potentilla indica* has been demonstrated to possess effective activity against pathogenic microorganisms. In 2021, Liaqat et al. [60] demonstrated a significant antimicrobial activity of extracts of different polarity (aqueous, chloroform, n-hexane, and methanolic) of *Potentilla indica* (whole plant, leaves, stems, and root) against *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, *Klebsiella pneumoniae*, *Bacillus subtilis*, *Vibrio cholera*, and *Saccharomyces cerevisiae* and in which they determined a high content of phenolic compounds by quantitative spectrophotometric methods. The potent antimicrobial capacity of plant-derived phenolic compounds toward different microorganisms has been reported in multiple studies [61]. This antimicrobial effect has been associated to different mechanisms promoted by these phytochemicals, which include the inhibition of virulence factors; membrane disruption; inhibition of efflux pump; biofilm inhibition; inhibition of virulence enzymes: neuraminidase, sortase, coagulase, and urease y protease; cell envelop synthesis inhibition, nucleic acid synthesis inhibition, and bacterial motility inhibition [61].

On the other hand, 25 compounds have been identified by GC–MS in the essential oil of *Potentilla indica*, whose main constituents were carvacryl acetate, valencene, nona hexacontanoic acid, aistalone, dehydroaromadendrene, eicosane, 2-hexadecanol, and aromadendrene, which have been demonstrated to possess antimicrobial activity [62].

3.5 Perspectives and limitations of using of *Potentilla indica*

The administration of the plant for specific therapeutic purposes may present some limitations in medical practice since years of clinical research are required for the establishment of a therapeutic dose with controlled studies to validate its efficacy and safety. However, no toxic side effects of *Potentilla indica* have been documented. Additionally, it is worth mentioning that thanks to the different lines of research directed to the study of medicinal plants and their effects in different experimental models, as well as the possible molecular mechanisms involved in such effect, and we can infer that these plants, among them *Potentilla indica*, contain bioactive compounds with promising therapeutic properties that can contribute significantly as adjuvant therapy to the treatment and prophylaxis of multiple chronic degenerative diseases that currently represent a public health problem worldwide, such as diabetes, metabolic syndrome, infectious diseases, cancer, among others, and may also represent an important natural source for the pharmaceutical industry for the discovery and development of new drugs with a high therapeutic potential, a wide margin of safety and fewer side effects. Further. Research in this direction is required to consolidate this pharmacological application.

4. *Justicia spicigera* Schltdl

Justicia spicigera corresponds to the kingdom Plantae, division Tracheophyta, class Magnoliopsida, order Lamiales, Family Acanthaceae, Genus *Justicia* L., and *spicigera* species Schltdl [63]. It is known by the names of “Muicle,” “Mouij,” “Stone indigo,” “purple grass,” “limanin,” “micle,” “mohuite,” “muele,” “muecle,” “muille,” “muite,” “muitle,” among others [64] and is widely distributed in Latin American countries such as Mexico, Belize, Costa Rica, and Honduras where there are optimal conditions for its development, such as dry or semi-dry, temperate climates warm, and semi warm, from 0 to 3000 meters above sea level [65, 66]. Likewise, this species of *Justicia* is specified as a perennial subshrub that can reach between 0.5 and 1.5 meters in height, its leaves are petiolate with an entire leaf margin approximately 0.02 meters long, and it produces orange inflorescences arranged in spikes with a bilobed rear lip. And anterior three-lobed, two stamens, a capsule with four seeds, and a sterile basal portion that are grouped at the end of the union of the stem and the leaf [65, 67].

It is a plant that has been used in Mexico since pre-Hispanic times as a source of natural pigment to dye fabrics and crafts [68]. Furthermore, in traditional Mexican medicine, *Justicia spicigera* leaves are commonly used as an infusion, mainly for the treatment of headaches, hypertension, epilepsy, stomach pain, diarrhea, dysentery, constipation, and in the treatment of chronic degenerative diseases, such as diabetes and hypertension. On the other hand, the branches of the leaves and flowers are used as therapy for dermatological conditions, tumors, or pimples that are difficult to cure [5, 67, 69]. These effects are related to the presence of different compounds in the plant, among which are phenolic secondary metabolites, such as kaempferitrin and kaempferol triamnoside that have been extracted from the leaves or tannins that have been extracted from the branches and flowers [65].

Currently, various studies have been carried out aimed at the use of *J. spicigera* extracts obtained with solvents of different polarities to identify the nature and effect of the secondary metabolites present in the plant for the treatment of various pathologies.

4.1 Anticancer activity

Recent research has shown that extracts of dried plant material of *Justicia spicigera* obtained with polar solvents present cytotoxic activity in certain cell lines [70]. In a study conducted in 2020 [9], it was reported that methanolic extract of *J. spicigera* 1:10 (w/v) decreased the viability of HEP-G2 hepatocellular carcinoma cells with a mean inhibitory concentration (IC₅₀) of 2.92 µg/mL. In addition to the above, in 2023, [70] it was shown that the 1:20 (w/v) methanolic extract inhibits the growth of tumor cells from murine lymphoma L5178Y-R at an IC₅₀ of 29.10 µg/mL. In the same study, the presence of coumarins, quinones, and tannins in the extract was determined, to which these effects are attributed. In both experiments, the Probit test was used to calculate the IC₅₀ values.

On the other hand, it was found that the ethanolic extract of *J. spicigera* also exerts cytotoxic effects on MCF-7 cells (IC₅₀ = 28 µg/mL) and HeLa (IC₅₀ = 17 µg/mL), which was calculated by regression analysis (% of survival versus logarithmic concentration), where it is highlighted that an effective dose ≤30 µg/mL for plant extracts is considered cytotoxic [71]. Likewise, it was found that the hydroalcoholic extract (water: ethanol; 50:50) of *J. spicigera* obtained by evaporation under reduced pressure and lyophilization, reduces the proliferation of androgen-dependent LNCaP prostate cancer cells by 62% ± 1.7% (IC₅₀ = 3026 ± 421 µg/mL) without affecting cell viability, that is, it was found that there is a cytostatic mechanism on the part of the extract, which prevents progression to mitosis in the cell cycle. These effects could be related to the presence of different compounds present in the plant determined by qualitative methods, where the presence of flavonoids, sterols, steroids, and steroidal sapogenins has been reported [72].

4.2 Hypoglycemic activity

In previous reports, the potential hypoglycemic effect present in the ethanolic extract of dried plant material of *J. spicigera* has been documented. In a study carried out by Ramírez and collaborators [73], reported that the ethanolic extract (60%) of *J. spicigera* 1:10 (w/v) inhibits alpha glucosidase in tests carried out in vitro by 0.4 ± 1.5% at a concentration of 1 mg/mL. Similarly, Ortiz-Andrade and collaborators [67] carried out in vivo tests, where they demonstrated that the ethanolic extract of *J. spicigera* at a dose of 100 mg/kg significantly reduces the glucose levels obtained in an oral tolerance test after its administration in male rats of the Wistar strain, induced to type 2 diabetes with streptozotocin (65 mg/kg) and nicotinamide (100 mg/kg). These effects were attributed to the presence of kaempferitrin, which was determined by the reverse phase HPLC method in water 2795; In this study, one-way analysis of variance (ANOVA) with Tukey's post hoc test (sample versus control) was performed. Finally, in a recent study, the effect of the ethanolic extract of fresh leaves of *J. spicigera* 1:10 (w/v) was evaluated in a treatment for 30 days at a dose of 100 mg/kg in male Wistar rats, induced to diabetes with streptozotocin (50 mg/kg), showing a significant decrease in blood glucose levels in the group treated with the extract (219 mg/dL) when compared to the control diabetic group (427.3 mg/dL) [74], which could be related to the presence of kaempferitrin.

4.3 Antioxidant activity

Various *in vitro* and *in vivo* studies have been carried out to evaluate the antioxidant capacity of the extracts obtained from the plants. Antioxidant activity can be

determined by electron transfer methods for the reduction of a compound such as the 2,2-diphenyl-1-picrylhydrazyl (DPPH•) radical scavenging assay or by scavenging free radicals by donating from a hydrogen atom to another compound, as is the case of ABTS• + (2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid) [75]. In a previous study using *in vitro* tests carried out with powdered leaf and stem extracts of *J. spicigera*, it was shown that the content of phenolic compounds depends on the extraction conditions influenced by the solvent used (water, ethanol, glycerol, and propylene glycol), pH (3.5, 5.5 and 7.4), temperature (25 and 60°C) and storage time (20 days). The results obtained indicated that the polar extracts have greater inhibitory activity of DPPH• and ABTS•+ [76]. According to above, a study demonstrated that the ethanolic extract of *J. spicigera*, where the majority presence of kaempferitrin was determined, presents a mean effective concentration (EC₅₀) of 180 µg/mL in the ABTS test and 100 µg/mL in the DPPH• assay [67]. In contrast, a study showed that the CH₂Cl₂: MeOH 1:1 extract in the DPPH• and ABTS• + assays present an EC₅₀ of 35.5 and 15.7 µg/mL [77]. On the other hand, a decrease in oxidative stress markers has been observed in experiments carried out *in vivo*. Awad and collaborators in 2015 [78] found that the ethyl acetate fraction of *J. spicigera*, administered two times a week at a dose of 500 mg/kg for 6 weeks in rats induced liver fibrosis with CCl₄ (0.5 mL/Kg; via I.P.) improves liver functions and levels of oxidant stress markers, attributed to the phenolic compounds identified in this extract, mainly Peonidin 3,5-diglucoside.

4.4 Lipid-lowering and anti-inflammatory activity

Obesity is a proinflammatory disease that is related to certain chronic degenerative diseases such as type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), and cancer [79]. Real-Sandoval [80], administered the ethanolic extract of *J. spicigera* powder 1:100 (w/v) at a dose equivalent to 250 µg/kg of weight daily for 8 weeks and observed a decrease in the percentage of accumulated fat and triglycerides, as well as their participation in the negative modulation of the expression of proinflammatory genes such as Tlr4, Tnf-α, Nlrp3, Caspase-1, Il-18, Il-1β, Srebp-1c, Ppar-γ, and Ucp2, in addition to the overexpression of Ppar-α in a model of obesity-induced with a high-fat diet in male rats of the Wistar strain. These effects were attributed to the presence of kaempferitrin, which was determined by the reverse phase HPLC method.

4.5 Antihypertensive activity

The effect of extracts of dry plant material of *J. spicigera* obtained with nonpolar solvents such as chloroform has been evaluated, where the majority presence of hesperidin, naringenin, and kaempferol was identified by reverse phase HPLC, compounds to which an effect is attributed antihypertensive at a dose of 150 mg/kg in male Wistar rats induced with L-NAME at 75 mg/kg in drinking water [81].

4.6 Antimicrobial activity

Recent studies have shown that *J. spicigera* compounds extracted with CH₂Cl₂: MeOH 1:1 inhibit the growth of *E. faecalis* with a minimum inhibitory concentration (MIC) of 0.06 mg/mL, which is considered a sensitive strain and *P. aeruginosa* with a MIC of 0.5 mg/mL, that is, it presents medium sensitivity to the extract, which showed the presence of alkaloids, flavonoids, phenols, carbohydrates, and triterpenes that were determined by qualitative methods [77].

In another sense, *J. spicigera* biomolecules have been used in foods, bioproducts, dyes, and materials synthesis [65].

In summary, Mexico is a country with a great diversity of medicinal plants, among which *J. spicigera* stands out due to its high antioxidant capacity. Recent studies have demonstrated the therapeutic effects of this plant attributed to the phenolic secondary metabolites obtained with solvents of different polarities that can be used as a potential treatment in different pathologies such as cancer, diabetes, and hypertension. It should be noted that these effects may be due to the combination of compounds in the extracts, generating interactions that can be classified as antagonistic or synergistic [82], in which different mechanisms are involved that serve as points of opportunity for new research.

5. Conclusions

According to the research on these medicinal plants, *Eryngium* native plant of Mexico, *Potentilla* widely in Asian traditional medicine, and *Justicia* distributed in Latin American, all represent an important natural source of bioactive compounds. Flavonoids it is the major compound in all plants and help improve lipid profiles, blood pressure, insulin resistance, and systemic inflammation and have important effects on various chronic degenerative diseases. However, seasonality, water, light supply, temperature, herbivory and microbes, and soil factors can be influenced by climate and can result in up to 50% increased or decreased content of secondary plant metabolites. It is for that reason that further studies need to be done to characterize new active compounds with the objective of making science and evidence-based hard claims for the functionality and efficacy of the phytonutrient blend. Synergistic activity in the compounds is what makes them have a beneficial effect because they contain each of the compounds in specific quantities demonstrating the claimed biological functionality and health benefit as specifically to the mixture of active compounds. However, such molecular blends are difficult to reproducibly generate and formulate it is because regulatory authorities are more in favor of approving single or few active principles rather than complex blends.

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Conflict of interest

The authors declare no conflict of interest.

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