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Review

Porophyllum Genus Compounds and Pharmacological Activities: A Review

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Abstract: The genus *Porophyllum* (family Asteraceae) is native to the western hemisphere, growing in tropical and subtropical North and South America. Mexico is an important center of diversification of the genus. Plants belong of genus *Porophyllum* have been used in Mexican traditional medicine to treat kidney and intestinal diseases, parasitic, bacterial, and fungal infections and anti-inflammatory and anti-nociceptive activities. In this sense, several trials have been made on its chemical and in vitro and in vivo pharmacological activities. These studies were carried on the extracts and isolated compounds and support most of their reported uses in folk medicine as antifungal, antileishmanial, anti-inflammatory, anti-nociceptive and burn repair activities, and as a potential source of new class of insecticides. Bio guided phytochemical studies showed the isolation of thiophenes, terpenes and phenolics compounds, which could be responsible for the pharmacological activities. However, more pre-clinical assays that highlight the mechanisms of action of the compounds involved in pharmacological function are lacking. This review discusses the current knowledge of their chemistry, in vitro and in vivo pharmacological activities carried out on the plants belonging to the *Porophyllum* genus.

Keywords: *Porophyllum*; phytochemical studies; bioactive compounds; pharmacological activities

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1. Introduction

A growing world-wide interest in the use of phytopharmaceuticals as complementary or alternative medicine, either to prevent or to ameliorate many diseases, has been noted in recent years. Furthermore, a great portion of the world's population uses plants as their primary source of medicinal agents [1]. Nowadays, medicinal plant's importance relies not only on their cultural richness but also on the scientific knowledge generated from ecological, geographical, cultural, pharmacological, and chemical analysis, which constitutes the current research context of traditional medicine.

Plants of the genus *Porophyllum* (family Asteraceae) are native to the western hemisphere, growing in tropical and subtropical areas from North and South America [2–7]. It consists of 25 species [8], 17 of which are found in Mexico, with Guerrero, Morelos, Puebla, and Hidalgo, the main states of large-scale production [2].

These are annual or perennial plants that possess developed green leaves with aromatic glands and a strong flavour. Some of these species are grown in family gardens

and are sometimes associated with tropical deciduous, sub-deciduous, sub-evergreen, evergreen, thorn, mesophyll mountain, oak, and pine forests [9–11].

Due to the strong flavour of its leaves, they are consumed in a fresh state or to spice some dishes, as well as being used as pesticides [1,12]. Mexican species, *Porophyllum linaria* (Cav.) DC. and *Porophyllum ruderale* (Jacq.) Cass. var. *macrocephalum* (DC.) R.R. Johnson. Known as 'papalos' or 'papaloquelites', particularly in central Mexico. Moreover, the infusions of some species of *Porophyllum* are used in traditional medicine because of activity against cramps and venereal diseases, as well as their antispasmodic, antibacterial, anti-inflammatory, antifungal, and insecticide properties, especially *Porophyllum gracile* Bent, *P. linaria*, *Porophyllum obscurum* (Spreng.) D.C., *P. ruderale*, *Porophyllum tagetoides*, *Porophyllum scoparia* A. Gray, and *Porophyllum riedelli* Baker [2,12].

The purpose of this review was to provide a comprehensive update on the status of the chemical, pharmacological in the treatment of multiple disorders of the extracts, oil, and active constituents from some plants belonging to the genus *Porophyllum*. This review also discusses the cellular and molecular mechanism by which *Porophyllum* active principles may exert their pharmacological effects.

2. Materials and Methods

An organized search for the ethnomedicinal use of the *Porophyllum* genus was carried out in terms of the pharmacological activities attributed to its compounds, as well as the preclinical studies carried out. The search was carried out systematically using MeSH (Medical Subject Headings) terms and "keywords". First, the related MeSH terms were defined: "Medicinal plants", "Ethnopharmacology", "Pharmacological action", "Bioactivity compounds", "Ethnobotany", "Antifungal", "Antiulcer", "Anti-inflammatory", "Insecticidal activity", and "Antileishmanial activity"; then, each term was combined with *Porophyllum*.

All articles found in the scientific information sources ScienceDirect, Pubmed, and Springer link were considered. A selection of titles was made, from which the abstracts were read and those that met the necessary characteristics were retrieved. The following criteria were included for the selection of documents. In the case of ethnomedicinal reports, the documents that exposed the use of the different parts of species of the genus *Porophyllum* were selected. On in vitro studies, articles were selected that mentioned in their methodology the type of test used, the species studied, and the type of extract or extracts used, as well as the compounds evaluated.

Regarding preclinical studies, studies that described species of the genus *Porophyllum* and models to evaluate the different pharmacological activities (antileishmanial, antifungal, antimicrobial, insecticidal) including dose, reference drug, and possible mechanisms of action, as well as the main metabolites isolated from the plant, were included. Items that did not meet the requirements listed were discarded.

3. Results

3.1. Chemical Constituents Isolated from Plants of the Genus Porophyllum

Among all studied species, *P. gracile*, *P. linaria*, *P. obscurum*, *P. tagetoides*, and *P. ruderale* have received more phytochemical attention. Regarding the most investigated part of the plant, it has been observed that, in general, all vegetative parts are used since these species are often used in this way in folk medicine.

Although most compounds are chemically known, their pharmacological mechanism of action remains generally undetermined. In this context, different classes of organic compounds of medicinal interest have been reported, including sulphur compounds, such as bithiophenes, terpenes as well as, phenolics, aldehydes, and flavonoids (Table 1). However, it should be noted that monoterpenes, such as sabinene, β-pinene, α-phellandrene, terpinen-4-ol, and limonene, and other compounds, such as bithiophenes (Figure 1), are the most abundant compounds identified in this genus (Table 1).

An important factor that could explain the difference in the availability of secondary metabolites are the different environmental conditions that directly affect the chemical

constitution of plants, with nutrition being the most important factors that interfere with the content and variety of the bioactive substances [13].

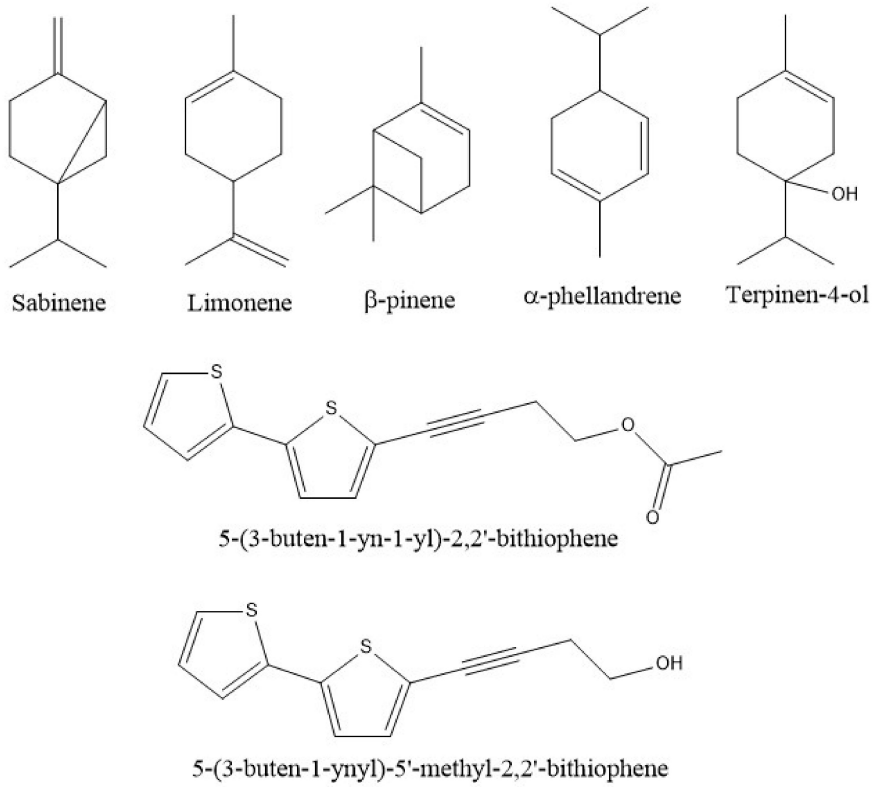

Figure 1. Major components isolated from species of the genus *Porophyllum.*

Another interesting aspect of phytochemical studies with the *Porophyllum* genus is the analysis of bioactivity of isolated compounds. Synergistic effects have been identified between some molecules present in plants that could be very useful if their mechanisms of action are thoroughly investigated for their possible use as medicinal plants. Some of the most important studies performed on the genus *Porophyllum* are detailed in the following sections.

Table 1. Chemical constituents from plants of the genus *Porophyllum.*

Species	Common Name	Part of the Plant	Extraction System	Chemical Analysis Performed	Isolation/ Identification	Chemical Compounds and Yield (%)	Reference
P. gracile	"hierba del venado"	Aerial parts	Static head-space technique.	Gas chromatography (GC) with Flame Ionization Detector (FID)	Identification	α-pinene (17.7) Sabinene (3.5) Myrcene (62.7) β-cubenene (9.1)	[14]
P. linaria	"pipicha, pepicha o chepiche"	Leaves	Hidro-distillation using a Clevenger system equipped with a microwave set at 100% potency. Aromatic water recirculation system using a Clevenger-type apparatus adapted with a conventional microwave.	Gas Chromatography–Mass Spectrometry (GC–MS)	Identification	Phytol (25.50) Linoleic acid (29.50) β-myrcene (41.94) D-limonene (20.29) Estragole (20.03) 1-undecene (8.02) 3-(4-methyl-3-pentenyl)-furan (3.72) Terpinen-4-ol (8.51)	[5,15]
P.obscurum	"kilkina, pus-pus, quirquiña, ruda blanca, hierba de la gama, hierba del ciervo"	Aerial parts	Maceration with methanol Hhydro-distillation in an all-glass Clevenger-type apparatus Maceration with hexane	GC GC-MS Thin layer chromatography (TLC)	Identification and isolation	β-pinene (16.30) *trans*-sabinene hydrate (12.8) Undec-1-ene (12.4) 5-(3-buten-1-ynyl)-2,2′-bithiophene (0.018) 5-(4-acetoxy-1-butenyl)-2,2′-bithiophene (0.008) 5-(4-hydroxy-1-butenyl)-2,2′-bithiophene (0.010) 2,2′:5′,2″-terthiophene (0.039)	[16–18]
P.ruderale	"papaloquelite, pápalo"	Aerial parts	Maceration with Et_2O Modified Clevenger-type distillation Maceration with dichlorometane Hidro-distillation	^{1}H Nuclear Magnetic Resonance (NMR) GC-MS ^{1}H and ^{13}C NMR and MS	Identification and isolation	Myrcene (3.37) (Z)-β-ocimene (1.38) (E)-β-ocimene (93.95) β-pinene (0.27) α-terpineol (0.3) Terpinen-4-ol (10.3) 5′-acetoxymethylen-2-[4-acetoxy-but-3-inyl]-ditiophene (0.005) 5′-methyl-2-[4-acetoxy-but-3-inyl]-bitiophene (0.010) 3-but-1-en-3-inyldithyenil (0.003) 5,methyl-2,2′:5,2″-terthiophene (0.007) 5′-methyl-[5-4(4-acetoxy-1-butynyl)]-2,2′ bi-thiophene (0.018).	[19–22]

Table 1. *Cont.*

Species	Common Name	Part of the Plant	Extraction System	Chemical Analysis Performed	Isolation/ Identification	Chemical Compounds and Yield (%)	Reference
P. tagetoides	"pipicha"	Leaves and stems	Maceration with ethanol and water, oil emulsion	Headspace GC-MS	Identification	1-noneno (4.05) α-terpinene (0.52) Perilleno (6.49) Nonanal (1.88) 2-decenal (6.46) *p*-thymol (0.82) 8-phenyloctan-1-ol (1.10) Dodecyl hexanoate (1.01) β-myrcene (1.6) D-limonene (9.67) Nonanal (50.87) Decanal (19.52) (-)-trans-pineno (43.48) (Z)-8-dodecen1-ol (17.27)	[23]
P. scoparia	"jarilla, romerillo"	Root and aerial parts	Maceration with methanol/ether/petrolether, 1:1:1	^{1}H-NMR	Isolation	3-butyn-2-ol,4-[2,2′-bithiophene]-5-yl-1-chloro-2-acetate (0.002) 5-(3-buten-1-yn-1-yl)-2,2′-bithiophene (0.003) 5-(4-hydroxybut-1-ynyl)-2,2′-bithiophene (0.002) 2,2′:5′,2′′-terthiophene (0.002) 2,4,3-butyne-1,2-diol,4-[2,2′-bithiophene]-5-yl-1,2-diacetate (0.0006) 3-butyne-1,2-diol,4-[2,2′ bithiophene]-5-yl-isovalerate (0.0007) Sakuranetin (naringenin 7-methyl ether) (0.0007)	[24]
P. riedelli	Not specified	Aerial parts	Et_2O-petrol (1:2)	^{1}H-NMR	Isolation	5-(3-buten-1-yn-1-yl)-2,2′ bithiophene (0.005) 2,2′:5′,2′′-terthiophene (0.01) 2-methoxy-9-tygloyloxy-8,10-epoxy thymol isobutyrate (0.003) 2-methoxy-9- isobutyryloxy-8,10-epoxy thymol tiglate (0.003) 2-methoxy-9-tigloyloxy-8,10 epoxythymol tiglate (0.0002) 2-methoxy-9-isobutyryloxy-8,10-epoxythymol-isobutyrate (0.002) α-isocomene (0.003) β-isocomene (0.002) Modhephene (0.001) Squalene (0.014) Caryophyllene (0.001) Germacrene D (0.002) Bicyclogermacrene (0.0009)	[25]

3.2. Insecticidal Activity

It has long been based on traditional medicine, that the beneficial medicinal action of infusion of some species of plants of the genus *Porophyllum* could be associated, at least in part, with insecticidal and antifungal activities. In this regard, the insecticidal activity of essential oil obtained from flowers and leaves of the species *P. ruderale* against *Aedes aegypti* larvae has been reported. The oil exhibited a LC_{90} value of 240.87 ppm, and its chemical analysis showed that the biological activity was directly associated with the content of monoterpenes, such as (E)-β-ocimene (93.95%), myrcene (3.37%), and β-pinene (0.27%) (Figure 2) [22]. Terpenes, like 1,8-cineole, anisole, limonene, β-pinene, linalool, menthone, α-pinene, pulegone, and myrcene, are capable of inhibiting acetylcholinesterase and produce neurotoxic intoxication, which is generated when acetylcholine is released from nerve terminal vesicles in nerve impulse transmission, causing the depolarization of the membrane; this neurotransmitter binds to postsynaptic receptors prolonging electrical transmission, as a result, an extreme excitation is generated causing insect death [26–29].

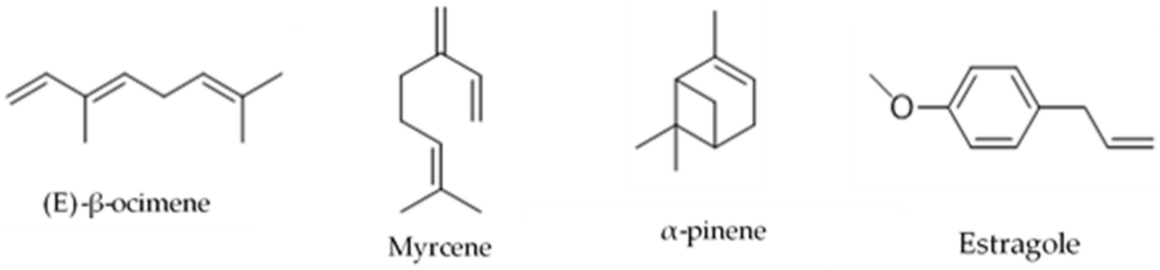

Figure 2. Isolated compounds from *P. ruderale* and *P. gracile* with insecticidal activity.

Also relevant are findings demonstrating that the volatile compounds emitted from the aerial parts of *P. gracile* and *P. ruderale* exert a synergistic effect on the insecticidal properties of α-terthienyl (commercial insecticide). The insecticidal effect of *Porophyllum* spp. is related to the presence of monoterpenes sabinene, myrcene, and limonene in *P. ruderale* leaves, and α-pinene, sabinene, and myrcene in *P. gracile* leaves (Figure 2). In addition, the synergism between volatile monoterpenes and α-terthienyl in reducing the relative growth rate of *Ostrinia nubilalis* (a pest of cereals, specifically corn), is due to a nearly two-fold increase in α-terthienyl concentration when larvae are exposed to the volatile compounds emitted from plant leaf secretory cavities [14].

Furthermore, other monoterpene compounds with insecticidal activity have been isolated and characterized in the essential oil of *P. linaria*, including β-myrcene, D-limonene, and estragole (Figure 2) [15]. Insecticidal activity of *Sitophilus zeamais* essential oil was derived from the toxic effects of β-myrcene, D-limonene, and estragole, compounds attributed to a reversible competitive inhibition mechanism acetylcholinesterase, by occupying the hydrophobic site of the active centre of the enzyme, thus, avoiding the growth of insects [30].

In summary, the available experimental data strongly support the view that distinct structural classes of naturally occurring secondary metabolites, present in the leaves, stems, and roots of some species of plants belonging to the genus *Porophyllum*, such as the afore mentioned monoterpene compounds like α and β pinene, α-terpineol and myrcene; they act as synergists of insecticides synthetics by inhibiting the activity of some enzymes detoxifying, this inhibition or stimulation of these enzymes involved in mechanisms of detoxification to insecticides in insects, produce an imbalance hormonal, impaired growth and finally the death of the insect, after being exposed to compounds from these plants, supporting the development of commercial pesticides. Therefore, the isolated constituents of some *Porophyllum* spp. may constitute a relevant and important basis for the development of a potentially new class of insecticides to replace synthetic products that are traditionally used [14,15,26–29].

3.3. Antifungal Activity

Some species of plants belonging to the genus *Porophyllum*, especially *P. obscurum* and *P. linaria*, are widely used in traditional medicine as a potent antifungal agent. Photosensitive antifungal activity, against *Candida albicans* ATCC 10231 strain of 16 extracts of different polarity (hexane, dichloromethane, ethyl acetate, and methanol) were obtained from aerial parts of *P. obscurum* in four phenological stages. The results obtained in these tests showed that the hexane extract was the most active after UV-A radiation with a minimum fungicide concentration (MFC) value of 0.98 μg/mL, followed by the dichloromethane extract (7.81 μg/mL); however, these were inactive in experiments without irradiation. Those responsible for this antifungal activity were sulphur compounds, specifically thiophenes, with 2,2′:5′,2″-terthiophene and 5-(4-hidroxy-1-butenyl)-2,2′-bithiophene (Figure 3) being the most potent (0.24–3.90 μg/mL) [11]. There are studies on the mechanism of action of a thiophene, α-terthienyl, with a similar structure to those identified in *P. obscurum*, which under ultraviolet light promotes the generation of singlet O_2, a molecule extremely toxic to fungal membranes [31,32]. Although the mechanism by which it causes fungal cell death is not clear, the results showed that hexane extract of *P. obscurum* does not induce apoptosis, so it could occur by another mechanism, such as necrosis or autophagy, and it is also important to note that it did not cause damage to the erythrocyte membrane, which decreases the possibility of haemolysis [18].

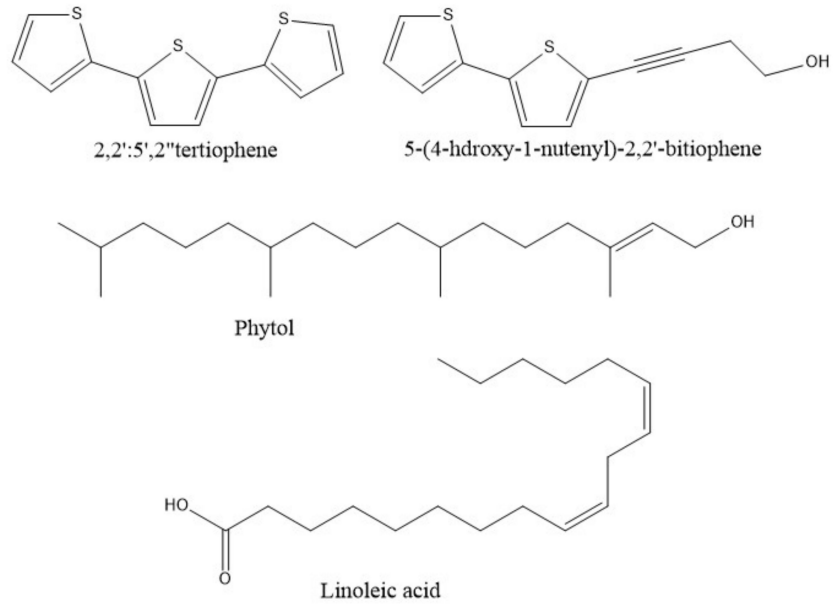

Figure 3. Components isolated from *P. linaria* and *P. obscurum* with antifungal activity.

Juarez et al. [5] demonstrated the antifungal capacity of the essential oil of *P. linaria* on 11 strains, *Aspergillus amylovorus* (NRRL 5813), *A. flavus* (NRRL 3518), *A. nomius* (NRRL 13137), *A. ostianus* (NRRL403), *Eurotium halophilicum* (NRRL 2739), *Eupenicillum hirayamae* (NRRL 3587), *E. hyrayamae* (NRRL 3588), *E. hyrayamae* (NRRL 3589), *E. hyrayamae* (NRRL 3591), *Penicillium cinnamopurpureum* (NRRL 3118), and *P. viridicatum* var. ii (NRRL 5571). All strains were susceptible to *P. linaria* essential oil (MIC = 0.92 to 0.0069 μg/mL), with the greatest effect observed on *Aspergillus amylovorus* (MIC = 0.0069 g/mL), and the least on *A. flavus* (MIC = 0.92 g/mL). The authors attributed the effect to the presence of phytol and linoleic acid (Figure 3), which can cause damage irreversible to the cell wall, cell membrane, and cell organelles of fungi [33].

The results shown in these studies verified the synergistic effect that these compounds have once combined. Based on these results, it would be possible to continue with studies of the fungicidal activity of essential oils of plants that present these compounds, to support

the use of these essential oils, thus, providing a viable alternative to the use of synthetic chemical fungicides.

3.4. Antileishmanial Activity

Plants of the genus *Porophyllum* have long been used in traditional medicine for the treatment of intestinal infections, parasitic diseases, and bacterial diseases [3,4,34]. Leishmaniasis is an infection caused by protozoa of the genus *Leishmania*, showing several clinical forms: cutaneous (CL), mucocutaneous (MCL), and visceral (VL) leishmaniasis. The drugs used in leishmaniasis treatment present several problems, including high toxicity and many adverse effects; pharmaceutical research on natural products represents a major opportunity for discovering and developing new drugs and plant-based remedies that represent lower risk and decrease complications [35–40].

Many studies suggest promising beneficial effects of plants belonging to the genus *Porophyllum* for the treatment of leishmaniasis. Takahashi et al. [21] reported that dichloromethane extract from the aerial parts of *P. ruderale* affect the growth of *Leishmania amazonensis* (60.3 μg/mL) inhibited 50% of the growth of promastigote and axenic amastigote forms after 72 h of incubation. The activity was directly correlated with two compounds isolated by chromatographic separation of the dichloromethane extract of aerial parts of *P. ruderale*, which were identified by their analysis with Mass Spectrometry (MS) and Nuclear Magnetic Resonance (NMR) spectra as thiophene derivatives: 5-methyl-2,2′:5′,2″-terthiophene and 5′-methyl-[5-(4-acetoxy-1-butynyl)]-2,2′-bitiophene (Figure 4). The mechanism of action of these compounds in antileishmanial activity has focused on alterations in the mitochondrial membrane, followed by changes in mitochondrial potential, indicating a cell death mechanism, like apoptosis [41]. In summary, the use of these bioactive compounds can help the development of new agents against these diseases of great importance for public health.

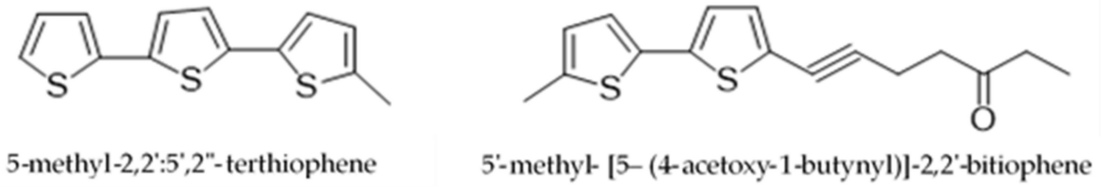

Figure 4. Components isolated from *P. ruderale* with antileishmanial activity.

3.5. Antinociceptive and Anti-Inflammatory Activities

Pain is a sensory modality, which, in many cases, represents the only symptom for the diagnosis of various diseases, in addition to the fact that it can represent a protective function. Over time, many forms of therapy have been used for pain relief, including some medicinal herbs that are noted for their wide popular use [42]. Lima et al. [4] reported that the aqueous extract of aerial parts of *P. ruderale*, administered orally in volumes of 0.1 mL/10 g, significantly inhibited the acetic acid induced twisting in mice in a dose-dependent way; the highest effect (94.8% inhibition) was obtained at a dose of 400 mg/kg. Likewise, such extracts had an effect on the second phase of pain induced by formalin at 1% (34.4% inhibition at 400 mg/kg of extract) but not on the first phase, which suggests that the anti-nociceptive and anti-inflammatory effect may be due to a peripheral effect. These results support the hypothesis of *P. ruderale* compounds have participation in the inhibition of prostaglandin synthesis since the nociceptive mechanism involves the processing or release of arachidonic acid metabolites through cyclooxygenase (COX) and prostaglandin biosynthesis during acetic acid induced abdominal twisting [20].

3.6. Burn Repair Activity

There are available animal studies suggesting a burn repair property of extracts from *Porophyllum* plants. The activity of *P. ruderale* on healing burns in rats was evaluated using a hydroalcoholic extract (ethanol:water 70:30 *v*/*v*) from the leaves of the plant. Among

the results obtained, *P. ruderale* extract at 10%, administered at a dose of 1 mL/day *p.o.*, was effective in decreasing the presence of granulocytes during the cell repair process (21.3 ± 2.4 to 8.1 ± 2.2 granulocytes n/10^4 μm^2), but it showed no effect on the production of fibroblasts. Likewise, it generated an increase in the expression of TGFβ-1 during the first 7 days of treatment but later it decreased, which could be attributed to flavonoids present in the extract that favoured the release of this protein at this stage of the healing process. The extract maintained the expression of vascular endothelial growth factors (VEGF) during the whole experimental process, a very important protein since it participates in wound healing [43].

3.7. Toxicological Studies

In a study to evaluate the toxic effects of two bithiophenes isolated from *P. ruderale*, both compounds showed low levels of toxicity to human cells, even at the highest concentrations (hemolytic index < 10% at 500 μg/mL) [42]. Moreover, other species of *Porophyllum* were also evaluated for their toxicological potential. For example, the toxicity of *P. linaria* essential oil showed a low toxicity on TPH-1 macrophages and *Artemia salina* LD_{50} = 10.90 and 2301.07 μg/mL, respectively [15].

4. Discussion

Although current ethnopharmacological investigations of traditional medicines have achieved important contributions to plant-derived medicines, as well as the advancement of pharmacology, drug discovery from medicinal flora is more complex than is generally recognized because plants are applied for different therapeutic indications within and between cultures [44–52].

Many plants of the genus *Porophyllum* have been used in folk medicine as remedies to treat a wide variety of human pathologies, particularly those related to digestive disorders. Of all the known species of this genus, the specie *P. ruderale* is the most investigated, however, there are few studies focused on the pharmacological activity of its compounds.

In vitro and in vivo studies performed with the purified extracts and compounds of these plants support most of their reported uses in folk medicine for the treatment of a wide variety of pathological conditions, including its use as an antifungal agent and insecticide [4,14,15,22,26,29]. In addition, some studies in animals have shown antinociceptive properties for some of the pure constituents of these plants [4]. It is important to mention that there are very few studies on its toxicity, which indicates that plants of this genus are well tolerated for human consumption.

The compounds of the *Porophyllum* genus have been of great interest due to the large number of biological activities they present [53]. In plants, these compounds fulfil chemical defence functions against environmental stress, as well as wound and injury repair mechanisms. The compounds present in the genus have been evaluated for their antibacterial and insecticidal activities [14,21,22,26,29,54–57]. This effects could be mediated by the activation of the Mucosal-associated invariant T (MAIT) cells in charge of recognizing the antigens sent by non-polymorphic MR1, MAIT cells are activated by a metabolic precursor of riboflavin (present in the genus *Porophyllum*) synthesis presented by MR1 and, therefore, respond to many bacteria and some fungi. Despite their broad antibacterial properties, their functional role in persistent viral infections is poorly understood, and several studies have reported that MAIT cells recognize only bacterial- and yeast-derived antigens presented via MR1 and that they do not have antiviral specificity [2,58,59]. There is accumulating evidence suggesting that terpene compounds like myrcene, limonene, linalool and caryophyllene are a promising target for use as real alternatives that can be applied in vector-borne disease control programs, for their considerable potential as repellents and larvicides, their low level of toxicity to mammals, and their limited environmental impact [29]. In the study carried out by Fontes-Jr et al. [22], it was found that the larvae of *A. aegypti* were susceptible to the composition of essential oil from the flowers and leaves of *P. ruderale*; the main compounds identified in the oil were (E)-β-ocimeno (93.95%),

myrcene (3.37%), (Z)-β-ocimeno (1.38%), and β-pinene (0.27%). The responsibility of this biological activity has been studied, showing that the lipophilicity of monoterpene compounds is related to the production of neurotoxic intoxication, in addition to the fact that components of essential oils act to block octopamine receptors, producing serious neurological alterations with harmful effects on insects [56] octopamine and tyramine are distinguished by the presence or absence of a hydroxyl group at the β position [57]. These structurally closely-related amines regulate intracellular cAMP levels in opposite directions, i.e., up and down regulation, by acting on different G protein-coupled receptors. Based on the evaluation of compounds for endocrine disruptor activity using a reporter gene assay, three-dimensional quantitative structure activity relationships were analysed to elicit responses through androgen receptors [60]. Therefore, findings regarding the structures of the binding sites of natural biomolecules, such as terpene compounds found in the *Porophyllum* genus, would be useful to design new insecticidal molecules with a novel mode of action in addition to lower production cost and effective insecticidal activity.

Other monoterpenic compound of pharmacological importance is α-terpineol, whose antihypertensive activity has been studied, mainly mediated by the release of Nitric Oxide (NO) and the subsequent activation of the NO-cGMP pathway (cyclic guanosine 3′,5′-monophosphate). This activity is linked to a reduction in calcium influx that occurs through voltage sensitive CavL channels, resulting in a decrease in vascular resistance attributed to α-terpineol that leads to the induction of hypotension [61].

Regarding antinociceptive activity, monoterpenic compounds have been identified to produce significant analgesic effects in formalin and writhing tests, which are related to the inhibition of PGE2 and PGF2α levels in the peritoneal fluid and to the inhibition of the release of substance P and other inflammatory molecules. However, the activity of these compounds has also been linked to a selective inhibition of COX-2 (0.69 mM), so this type of compound could potentially be used in the development of new drugs for the treatment of diseases painful and/or inflammatory [62]. Thiophenes are a class of heterocyclic compounds that contain sulphur and are found in both natural and synthetic products, displaying several different pharmacological properties, including anti-inflammatory, antiulcer [63], antimicrobial [64], antifungal [65], and anticancer [66] effects. Natural thiophenes are characteristic secondary metabolites of plants belonging to the Asteraceae family, among which *Porophyllum* is a genus [67]. The interest in the bioactivity of these compounds is due to their properties that can be developed synthetically or used naturally for the design of new drugs, using thiophenes as raw material.

These compounds have not yet been thoroughly studied, specifically the mechanisms of action of the pharmacological activities attributed to them, however, some authors such as Takahashi et al. [21,42] have shown that the extract in dichloromethane from aerial parts of *P. ruderale* exhibit strong activity against *L. amazonensis*, making it a potent antileishmanial compound. Those responsible for these pharmacological activities were bithiophenes and terthiophenes, whose biocidal activities were attributed primarily to the decrease in mitochondrial membrane potential in promastigotes [68].

Conversely, it was observed that treatment with a hexane extract of the aerial parts of *P. obscurum* (PoHex) showed photosensitive activity against a panel of twenty-five *Candida* strains isolated from patients with head and neck cancer undergoing radiotherapy with MFC values between 0.98 and 1.95 μg/mL, which were resistant to multiple drugs [11]. The mechanism of the antifungal activity of the thiophenes contained in PoHex can be classified as photodynamic, considering that thiophenes are excellent producers of singlet oxygen but are not precursors in electron transfer reactions, understanding that oxygen singlets have high chemical reactivity, which leads to rapid death in microorganisms and in lower concentrations than other biocides, in addition to not affecting nearby cells or organs [69].

Terthiophenes present in this genus have also been associated with HIV-1 protease inhibitory activities with an IC_{50} value of 58 μM, but did not show any activity towards HIV-1 integrase [70].

Among these effects, its anticancer activity has been highlighted, which has been linked to the induction of cell death by apoptosis, through an increase in the activity of caspase 3 and in the expression levels of the apoptotic proteins Bak and Bim, as well as a decrease in the antiapoptotic proteins Bcl-2 and Bcl-xL. On the other hand, it has been seen that these compounds cause a blockage of the cell cycle in the G2/M phase, decreasing the expression of the regulatory proteins of this phase, cyclins A and b1 and the kinase Cdk1 [71].

5. Conclusions

The genus *Porophyllum* represents one of the most widely used pre-Hispanic species in traditional medicine for the treatment of various diseases. The data presented here show the great potential represented by the compounds contained in their different species. Important pharmacological activities of isolated *Porophyllum* compounds has been found. Those compounds can be used in the synthesis of some phytopharmaceuticals, including terpenic and azufraid compounds, such as thiophenes, which may even develop synergism among the compounds containing these plants and increase their pharmacological potency. However, a great deal of information remains to be discovered about the mechanisms of action of these molecules, as well as preclinical studies that check these gender and its compounds could be safely used as treatments for different pathologies.

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