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Mini-Review on Phytochemistry and Pharmacological Studies of *Piper regnellii* (Miq.) C.DC.

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Abstract: *Piper regnellii* (Miq.) C.DC. is an herbaceous plant that can be found in tropical and subtropical regions of the world and commonly employed in folk medicine for the treatment of wounds, swellings, and skin irritations. In particular, phytochemical studies on *P. regnellii* have yielded essential oils, benzofuran neolignans, and phenylpropanoids, while the extracts and compounds demonstrated a broad spectrum of pharmacological activities. The present study aims to provide a review of previously published studies conducted on both the phytochemistry and pharmacological activities of *P. regnellii*. Accordingly, the scientific journals used for this brief literature review were obtained from various electronic sources, including Science Direct, PubMed, Google Scholar, Scopus, and Web of Science. In particular, the outcome of this review is expected to support the therapeutic potential of *P. regnellii* further as well as provide convincing evidence to its future clinical applications in modern medicine. Overall, this is aimed to increase the amount of data that supports the application and exploitation of new drug development.

Keywords: *Piper regnellii*; Piperaceae; phytochemistry; pharmacology; neolignan; essential oil

1. Introduction

Over millions of years, the evolution of natural products has led to their unique chemical diversity, which tends to affect their biological activities and drug-like properties. Moreover, it should be noted that those products have become one of the most important resources in developing new lead compounds and scaffolds [1]. More importantly, natural products will continue to be used in meeting the urgent need of developing effective drugs, which further explains its leading role in the discovery of drugs to treat human diseases, especially critical diseases [2]. In addition, higher plants have served humankind as a source of natural products which act as medicinal agents since the earliest beginnings. In ancient times, a variety of chemical investigations as well as purifications of the extracts of plants with medicinal properties have yielded several purified compounds, which demonstrates its significance in the practice of modern medicine [3,4].

A search of the literature has shown that Piperaceae is one of the plant families which is believed to have high medicinal values due to its wide usage in an abundant amount of traditional medicines [5]. In particular, the *Piper* species belong to the Piperaceae family,

which leads it to be considered one of the most ancient flowering plants growing in tropical regions. Furthermore, it should be noted that the genus *Piper* consists of 700 species that grow in various parts of the world [6]. Essentially, these species are mostly shrubs, climbing herbs, or trees that are extensively distributed in several tropical regions such as Asia, Central and Western Africa, South and Central America, and Pacific Ocean Islands [7]. Apart from that, it is well known as the largest genus in the family with numerous medicinal and traditional uses. In traditional medicine, *Piper* species have been utilized worldwide to treat several diseases, including urological problems, skin, liver, and stomach ailments, wound healing, and antipyretic and anti-inflammatory agents [8-10]. On a more important note, the chemistry of the *Piper* species has been widely investigated in a considerable amount of phytochemical studies. Generally, the results of the studies have led to the isolation of numerous biologically active compounds such as alkaloids, lignans, neolignans, terpenes, steroids, kawapyrones, piperolides, flavonoids, followed by the effects of antioxidant, antimicrobial, anti-inflammatory, insecticidal, anti-hypertensive, antidiabetics, immunomodulatory, and antimutagenic [11-13].

Piper regnellii (Miq.) C.DC. is an herbaceous plant that grows in tropical and subtropical regions of the world and is popularly known in Brazil as '*pariparoba*' or '*caapeba*'. In a general sense, its traditional use is for the treatment of wounds, swellings, and skin irritations [14]. In addition, the leaf and root of *P. regnellii* are extensively adopted in the forms of crude extracts, infusions, or plasters in treating wounds and reducing swelling and skin irritations [15]. As previously mentioned, the phytochemical study of the leaves and roots of *P. regnellii* has shown the accumulation of several benzofuran neolignans and phenylpropanoids, which include conocarpan, eupomatenoid-3, eupomatenoid-5, and eupomatenoid-6. Accordingly, they are considered the most significant compounds that can be employed in potential pharmacological studies.

Hence, the current review aims to summarise the available information on the published studies of phytochemistry and pharmacology on *P. regnellii*. The literature used in the current review comprises scientific journals obtained from a variety of electronic sources, namely Science Direct, PubMed, Google Scholar, Scopus, and Web of Science. Accordingly, the present article is believed to provide a better understanding of *P. regnellii* and its properties. More importantly, this data may be valuable in planning future inspections for clinical preliminaries and creating new pharmaceuticals containing *P. regnellii* or its active constituent.

2. Phytochemistry

A review of the literature revealed that the phytochemical properties of *P. regnellii* had been extensively investigated since 1999. As a result, a total of eighteen compounds have been isolated from the leaves and roots of *P. regnellii* in which the chemical structures are illustrated in Figure 1. Specifically, the species is reported to contain neolignans [14-21], phenylpropanoids [17], and essential oils [43-51]. Regarding this matter, Macedo *et al*. [16] have reported the presence of neolignans in various *Piper* species. For example, the first phytochemical investigation was carried out by Benevides *et al*. [17] on the species *P. regnellii*, which managed to discover the chemistry of neolignans. In addition, it is important to note the following isolated compounds that were obtained from the roots extracts of *P. regnellii*: neolignans conocarpan (**1**), eupomatenoid-3 (**2**), eupomatenoid-5 (**3**), and eupomatenoid-6 (**4**), together with (7*S*,8*R*)-4-hydroxy-4',7-epoxy-8,3'-neolignan-7'[*E*]-ene (**5**), (7*R*,8*R*)-3,4-methylenedioxy-4',7-epoxy-8,3'-neolignan-7'[*E*]-ene (**6**), methyl-(7*R*,8*R*)-4-hydroxy-8',9'-

dinor-4',7-epoxy-8,3'-neolignan-7'-ate (**7**), and (7*S*,8*R*)-4-hydroxy-8',9'-dinor-4',7-epoxy-8,3'-neolignan-7'-aldehyde (**8**). Nevertheless, the mentioned benzofuran neolignans (**1-4**) were also found in a considerable amount of studies [18-23]. Apart from that, Felipe *et al*. [14] successfully developed and validated the quantitative determination of neolignans found in the extracts of *P. regnellii*. Specifically, the procedure confirmed that the developed technique can produce a reliable analysis of the neolignans and appropriate for the quality control of the extracts as well as phytopharmaceutical preparations concerning *P. regnellii*.

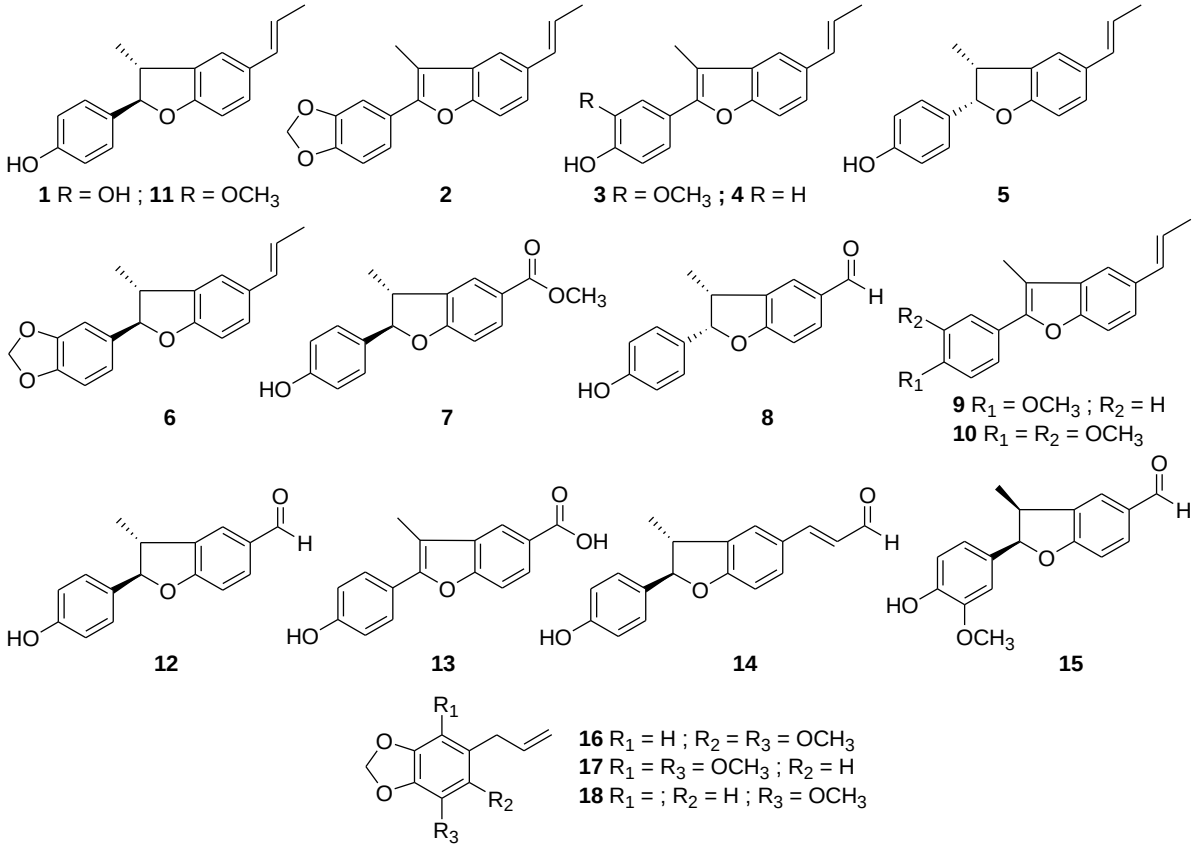

Figure 1. Chemical structures of isolated compounds from *P. regnellii.*

Meanwhile, research by Pessini *et al*. [18] successfully isolated 4'-(methoxyphenyl)-3-methyl-5(*E*)-propenyl benzofuran (**9**), 2-(4',5'-dimethoxyphenyl)-3-methyl-5(*E*)-propenyl benzofuran (**10**), and (2*R*,3*R*)-2,3-dihydro-2-(4'-methoxyphenyl)-3-methyl-5(*E*)-propenylbenzofuran (**11**), including compounds (**1-4**). Other than that, Ramos *et al*. [24] reported the isolation of decurrenal (**12**), 2-(4-hydroxyphenyl)-3-methyl-5-benzofuranylcarboxylic acid (**13**), 3-[(2*R*,3*R*)-2,3-dihydro-3-(methyl)-2-(4-hydroxyphenyl)-5-benzofuranyl]-(2*E*)-propenal (**14**), and (2*R*,3*R*)-2,3-dihydro-2-(3-methoxi-4-hydroxyphenyl)-3-methyl-5-benzofurancarboxaldehyde (**15**), through the biotransformation of compounds (**1-4**) performed by the beetles. In this case, compounds (**1-3**) underwent oxidative cleavage of the ozonolysis type, followed by selective oxidation at the terminal methyl of the alkyl group for their respective aldehyde (**12**, **14**, and **15**) as well as the acid (**13**) during their metabolism in *Naupactus bipes*. More importantly, previous phytochemical investigations demonstrated that Piper species is a very rich source of phenolic compounds comprised of phenylpropanoids [25-27]. Nevertheless, in the case of *P. regnellii*, only in the study of Benevides *et al.* [17] that the phenylpropanoids were successfully identified. Specifically, they managed to isolate apiol (**16**), dillapiole (**17**), and myristicin (**18**) from the roots part of *P. regnellii.* On another note,

the *Piper* genus is an extremely well-known and widely distributed pantropical taxon of aromatic plants.

3. Essential oils

The essential oils of plant origin have been used since ancient times. Essential oils are composed of secondary metabolites commonly concentrated in aromatic plants' leaves, bark, or fruit. As produced by aromatic plants, essential oils are commonly used in beverages, food, pharmaceutical, and cosmetics industries due to their documented medicinal properties. These oils are responsible for both the aroma and biological properties of medicinal plants. Researchers have pointed out that the volatile oils of different plant organs possess antitumorigenic, insecticidal, antifungal, anticarcinogenic, antibacterial, anti-inflammatory, antiparasitic, antiviral, and antioxidant properties [28-42]. As previously mentioned, the chemistry of *P. regnellii* essential oils, mainly from Brazil [43-51] has been extensively studied, as listed in Table 1. In the first study of essential oil from Brazilian *P. regnellii*, the occurrence of β-caryophyllene, (*E*)-nerolidol, spathulenol, and globulol in the aerial parts was reported [43]. On a similar note, Anderson *et al*. [51] reported that the highest percentage of a sesquiterpene, germacrene D was detected in *P. regnellii* leaves oil. In addition, Costantin *et al*. [44] described the presence of monoterpene from leaves with a predominance of myrcene, followed by other studies that reported the presence of myrcene as the major component [45-47,49]. Regarding this matter, Ramos *et al*. [48] recorded the presence of monoterpene known as β-pinene, while the richness of phenylpropanoids was detected in the leaves, flowers, and stem oils of *P. regnellii*, which are respectively characterized as apiole, anethole E, and dillapiole [49]. In a general sense, it can be understood that essential oils are rich in all classes of volatile chemical compounds. However, the composition for both inter and intra is highly variable, which further suggests that the differences are dependent on the polymorphism, plant part, geographical differences, environmental conditions, and chemotypes [52,53].

Table 1. Chemical components isolated from Brazillian *P. regnellii* essential oils

Parts	Total identified	Major components
Aerial parts	28, 96.5%	β-Caryophyllene (23.4%), (*E*)-nerolidol(13.7%), spathulenol (11.1%), globulol (6.1%) [43]
Leaves	25, 98.7%	Myrcene (52.60%), linalool (15.89%), β-caryophyllene (8.50%)[29,30]
Leaves	*nm	Myrcene (70%) [46]
Leaves	19, 91.51%	Myrcene (15.45%), β-pinene (13.34%), bicyclogermacrene (9.66%), (*E*)-nerolidol (8.37%), aromadendrene (8.27%), spathulenol (7.80%), β-caryophyllene (7.21%) [47]
Leaves	30, 83.1%	β-Pinene (54.9%), linalool (5.9%) [24]
Leaves	61, 99%	Myrcene (21.97%), anethole E (16.01%), dillapiole (14.5%), bicyclogermacrene (9.43%), junicedranol (8.93%) [49]
Stems	64, 99%	Dillapiole (30.15%), myrcene (14.9%), anethole E (13.42%), junicedranol (7.91%) [49]
Flowers	61, 99%	Anethole E (28.24%), myrcene (23.04%), bicyclogermacrene (9.60%), γ-muurolene (7.23%) [49]
Leaves	*nm	Apiole (42.0%), dillapiole (16.7%) [50]
Leaves	28, >90%	Germacrene D (45.6%), α-chamigrene (8.9%), β-caryophyllene (8.2%) [51]

*not mentioned

4. Pharmacological studies

A search of the literature revealed the occurrence of biological activities, including antimicrobial, antifungal, anticancer, anti-inflammatory, antileishmanial, wound healing, antiviral, and anti-biofilm activities. As can be observed, the bioactivities of the isolated compounds (**1**-**4**) [54-60] have been widely investigated, as listed in Table 2.

4.1. Antimicrobial activity.

In the study conducted by Marçal *et al*. [56], the ethyl acetate extract presented a good activity against *Staphylococcus aureus* MRSA with minimal inhibitory concentration (MIC) as well as minimal bactericidal concentration (MBC) of 16 µg/mL. Accordingly, the leaves, roots, and stems extracts demonstrated good activity against *Staphylococcus aureus* and *Bacillus subtilis,* with MIC recorded between 31.25 - 62.5 µg/mL. Moreover, the hydroalcoholic extract of the leaves was found to be more active than the stems and roots extracts despite the insignificant differences. Other than that, all extracts of *P. regnellii* in the anti-yeast assay displayed good activity against *Candida tropicalis* (MIC of 62.5 µg/mL), followed by a moderate response against *Candida albicans* (MIC of 250 µg/mL) [61]. In another case, the essential oil and ethanolic leaves/roots extracts of *P. regnellii* reported a weak anti-candida activity against *Candida albicans* CBMAI 0475 with MIC of >2 µg/mL [62]. Similarly, a weak activity against *Candida albicans* (MIC of 125 µg/mL) was found in the aerial part extract as published in a study conducted by Johann *et al*. [63]. In addition, Holetz *et al*. [64] reported that *P. regnellii* extract exhibited activity against the yeasts *Candida krusei* (MIC of 125 µg/mL) and *Candida tropicalis* (MIC of 500 µg/mL). More importantly, the ethanolic leaves extract of *P. regnellii* showed strong activity against the bacteria *Staphylococcus aureus* (MIC of 7.8 µg/mL) as well as *Bacillus subtilis* (MIC of 15.6 µg/mL). However, the aqueous extract displayed a weak activity against *Staphylococcus aureus* and *Bacillus subtilis* with MIC and MBC of 1000 µg/mL. In addition, the ethyl acetate extract in a study of Pessini *et al*. [18] presented a good activity against *S. aureus* and *B. subtilis* with MIC and MBC at 15.62 µg/mL.

Table 2. Pharmacological studies of isolated compounds from *P. regnellii.*

Compounds	Bioactivities	Description
Conocarpan (**1**)	Anti-biofilm	Exhibited a good activity against *Staphylococcus aureus* MRSA and *S. aureus* MSSA with MIC of 50 µg/mL and MBC of 100 µg/mL [54]
	Antiproliferative	Presented considerable activity against epimastigote forms of *Trypanosoma cruzi* with IC_{50} of 8.0 mg/mL [20]
	Antibacterial	Presented quite active against *S. aureus* and *B. subtilis* with MIC of 6.25 µg/mL [18]
	Antifungal	Exhibited a strong activity against *C. albicans, C. krusei, C. parapsilosis,* and *C. tropicalis* with MIC value 6.3, 12.5, 25, and 6.3 µg/mL, respectively [19]
	Anti-tuberculosis	Exhibited a strong activity against *Mycobacterium tuberculosis* with MIC of 15.6 µg/mL [55]
Eupomathenoid-3 (**2**)	Antimicrobial	Presented MIC of 16 µg/mL against *S. aureus* MRSA [56]
	Antifungal	Exhibited a strong activity on *Trichophyton rubrum* with MIC of 50 µg/mL [15]
		Exhibited a moderate activity against *C. albicans, C. krusei, C. parapsilosis,* and *C. tropicalis* with MIC value >100 µg/mL, each [19]

Compounds	Bioactivities	Description
	Anti-tuberculosis	Displayed weak activity against *Mycobacterium tuberculosis* with MIC of 250 µg/mL [55]
Eupomathenoid-5 (**3**)	Anti-tuberculosis	Exhibited a strong activity with MIC of 1.9 µg/mL on *Mycobacterium tuberculosis* H37Rv and a good selectivity index of 20.0 [55]
	Anti-biofilm	Exhibited a good activity against *S. aureus* MRSA and *S. aureus* MSSA with MIC of ≤6.25 µg/mL and MBC of <25 µg/mL [54]
	Anticancer	Exhibited a strong activity against kidney, ovary, prostate, and breast cell lines, with TGI values of 1.93, 5.50, 6.17, and 6.24 µg/mL, respectively [22]
	Antiviral	Inactive against bovine herpesvirus-1 (BHV-1) and poliovirus viruses with EC_{50} value >50 µg/mL [57]
	Antibacterial	Exhibited a good activity against *S. aureus* and *B. subtilis* with MIC of 3.12 µg/mL, each [18]
	Antiproliferative	Presented considerable activity against epimastigote forms of *Trypanosoma cruzi* with IC_{50} of 7.0 mg/mL [20]
		Exhibited activity against trypomastigotes, the infective form of *Trypanosoma cruzi* (EC_{50} of 40.5 mM), leading to ultrastructural alteration and lipoperoxidation in the cell membrane [58]
	Antileishmanial	The compound shows the incubation of *Leishmania amazonensis* promastigotes for 3 and 24 h resulted in a 16% increase in the proportion of cells in the sub-G0/G1 phase at the lower concentration (30 µM) and a 28% increase at the higher concentrations (85 and 170 µM) [59]
		Exhibited a dose-dependent activity during 72 h of treatment with IC_{50} of 9.0 µg/mL and 13.0 µg/mL for promastigote and axenic amastigote forms, respectively, and IC_{50} of 5.0 µg/mL for intracellular amastigote forms of *Leishmania amazonensis* [60]
	Antifungal	Exhibited a strong activity on *Trichophyton rubrum* with MIC of 6.2 µg/mL [15]
		Displayed a moderate activity against *C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* with MIC value >100 µg/mL, each [19]
Eupomathenoid-6 (**4**)	Antiproliferative	Presented considerable activity against epimastigote forms of *Trypanosoma cruzi* with IC_{50} of 7.5 mg/mL [20]
	Antibacterial	Displayed a good activity against *S. aureus* (MIC of 1.56 µg/mL) and *B. subtilis* (MIC of 3.12 µg/mL) [18]
	Antifungal	Displayed moderate activity against *C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* with MIC value >100 µg/mL [19]

4.2. Antifungal activity.

Research by Johann *et al*. [65] showed that the leaves extracts of *P. regnelli* had strong antifungal activity against pathogenic fungus *Paracoccidioides brasiliensis* with MIC of 7.8 µg/mL. Meanwhile, a similar result of strong activity was found in the hydroalcoholic leaves extract of *P. regnellii* against the dermatophyte fungi *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, and *Microsporum gypseum* with their respective MICs of 15.62, 15.62, 15.62, and 62.5 µg/mL [15]. On a similar note, the same authors conducted another study two years later and reported that the dichloromethane and chloroform extracts showed strong activity against *Trichophyton rubrum* with MIC of 7.8 µg/mL [66]. Research by Lemos *et al*. [23] reported that the leaves extract of *P. regnellii* showed strong activity against *Trichophyton mentagrophytes* and *Trichophyton rubrum* at 40ºC and 25 MPa

with the MIC of 7.8 µg/mL. Meanwhile, Pessini *et al*. [19] recorded a significant activity in the EtOAc extract against *Candida albicans* with MIC of 125 µg/mL, while moderate activity was detected against both *C. krusei* and *C. parapsilosis* with MIC of 500 µg/mL. However, it is important to note that *Candida tropicalis* is not able to be inhibited by this extract at a concentration as high as 1000 µg/mL.

4.3. Anticancer activity.

In vitro studies conducted by Longato *et al*. [22] revealed that *P. regnellii* dichloromethane extract was effective against almost all human tumor cell lines, including melanoma (UACC-62) (TGI of 26.45 µg/mL), breast (MCF7) (TGI of 39.58 µg/mL), kidney (786–0) (TGI of 21.93 µg/mL), lung (NCI-H460) (TGI of 20.39 µg/mL), prostate (PC-3) (TGI of 10.97 µg/mL), ovary (OVCAR-3) (TGI of 12.05 µg/mL), colon (HT29) (TGI of 42.09 µg/mL), and leukemia (K-562) (TGI of 158.44 µg/mL) cell lines.

4.4. Anti-inflammatory activity.

A study by Schmidt *et al*. [67] examined the anti-inflammatory activity against NF-kB DNA binding, p38α, and TNF-α release in whole blood. In NF-kB DNA binding, the hexane extract showed strong inhibition (>70%) of DNA binding at 100 µg/mL, whereas the ethanol extract was found inactive (<30%). In the case of p38α assay, the hexane and ethanol extracts recorded the inhibition percentage of 61.88% and 48.63%, respectively. Next, the hexane extract in TNF-α assay showed weak activity with an inhibition percentage of 5.98%.

4.5. Antileishmanial activity.

In the case of antileishmanial activity, the leaves extract of *P. regnellii* showed a high percentage of growth inhibition at 98.2% and 96.8% against axenic amastigote and promastigote forms of *Leishmania amazonensis*, respectively. In addition, the extract showed strong inhibition against epimastigote forms of *Trypanosoma cruzi* with the inhibition growth of 89.7% at a concentration of 100 µg/mL [68].

4.6. Wound healing (scratch) activity.

Schmidt *et al*. [67] conducted a study to investigate the influence of the extracts on fibroblasts' migration and proliferation into the wounded monolayer of the scratch assay against swiss 3T3 mouse fibroblasts. The ethanolic extracts of *P. regnellii* at a 10 µg/mL concentration showed a weak activity with the percentage stimulation of 22.11%, whereas the hexane extract was found inactive.

4.7. Antiviral activity.

Research by Bertol *et al*. [57] detected antiviral activity in hexane, chloroform, chloroform/ethyl acetate (19:1), and chloroform/ethyl acetate (9:1) fractions against bovine herpesvirus-1 (BHV-1). Similarly, the chloroform, chloroform/ethyl acetate (19:1), chloroform/ethyl acetate (9:1), chloroform/ethyl acetate (1:1), and ethyl acetate fractions were found to be active against poliovirus.

4.8. Anti-biofilm activity.

The dichloromethane leaves extract of *P. regnellii* showed a good effect against the isolated methicillin-sensitive *S. aureus* biofilms (MIC of 15.6 μg/mL) as well as *S. aureus* planktonic cells (MIC of <12.5 μg/mL) [54].

6. Conclusions

The overall review of the literature revealed neolignans in *P. regnellii* as the major class, which is rich in conocarpan, eupomatenoid-3, eupomatenoid-5, and eupomatenoid-6. Meanwhile, it is important to note that the overall biological investigations of *P. regnellii* have not been well investigated except for some preliminary works regarding in vitro screenings. Hence, the isolated compounds could only be found in various pharmacological studies. Accordingly, this seems to suggest valuable potential constituents for drug development. In conclusion, in-depth investigations of *P. regnellii* are recommended, especially concerning both the in vivo and in vitro pharmacological evaluations of the extracts and constituents deemed valuable and encouraging.

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Conflicts of Interest

The authors declare no conflict of interest.

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