

# Pyrostegia Genus: An Update Review of Phytochemical Compounds and Pharmacological Activities

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**Abstract:** The *Pyrostegia* genus of the Bignoniaceae family. This genus consists of four species and is indigenous to South America. The plants of this genus are being applied in traditional uses in Brazil. This review of the scientific work about *Pyrostegia* genus was highlighting and updating their traditional uses, phytochemical compounds, pharmacological activities, genotoxicity tests, and toxicity studies. The information was systematical with the scientific literature database, including Elsevier, Google Scholar, PubMed, Science Direct, and Scopus, and Springer. The literature survey showed various traditional uses of *Pyrostegia* genus, such as drugs to therapy diarrhea, coughing, vitiligo, jaundice, and respiratory system-related diseases, i.e., colds, coughs, and bronchitis. Phytochemical compounds from the *Pyrostegia* genus have shown the presence of flavonoids, phenolic compounds, phenylpropanoids, phenylethanoid glycosides, triterpenes, and sterols. The extract of *Pyrostegia* genus has a variety of pharmacology actions, i.e., antioxidant, antimicrobial, antifungal, anti-inflammatory, wound healing activities, antinociceptive, analgesic, vasorelaxant activities, antitumor, cytotoxic, hepatoprotective, antitussive, anthelmintic, hyperpigmented, treatment of sickness behavior, estrogenic, antihypertensive, and immunomodulatory. *Pyrostegia* genus is considerably used in traditional medicines and has various pharmacological activities. However, most species of *Pyrostegia* genus must be further researched concerning its chemical constituents and pharmacological activities.

**Keywords:** *Pyrostegia*; Bignoniaceae; traditional uses; phytochemical compounds; pharmacological activities; toxicology.

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## 1. Introduction

*Pyrostegia* C. Presl, a genus is indigenous to South America, one of the Bignoniaceae family (consists of about 120 genera and 800 species [1]) in the major group's Angiosperms [2]. This genus is a small genus with only 4 species that originate in South America [3]. The name of *Pyrostegia* is established by C. Presl (1845). *Pyrostegia* genus is lianas and has leaves with a terminal tendril and two leaflets. The calyx is campanulate shaped. Flowers with narrow corollas that lobes valvate basally and has four stamens. It has linear capsules (parallel with the septum) and thin bialate seeds. Most of the *Pyrostegia* species are pollinated by hummingbird (related extrafloral nectaries (ENFs) in *Pyrostegia venusta* [4]) and have flowers that are very identical with reddish-orange color; corollas are cramped tubular-infundibular [2]. Pollen of *Pyrostegia* genus was heterobrochate and duplicolumellate reticulum [5]. *Pyrostegia* genus has the axillary buds triangular shape, hexagonal shape stems, 2- or 3-foliolate, and pellucid-

punctate leaves with the terminal leaflet often replaced by a trifid tendril, inflorescences arranged in corymbose cymes, and exceptional corolla lobe arrangement [6]. The corolla lobes are valvate in the bud and then shift to imbricate at apices [2].

In *Bignoniaceae* family, only four genera are characterized by having pellucid glands: *Amphilophium*, *Pithecoctenium*, *Pyrostegia*, and *Stizophyllum* [7]. *Pyrostegia* species are distributed in Brazil, Amazonas, Manaus, Guyana, Suriname, Peru, Venezuela, Colombia, Bolivia, Para, Maranha, Paraguay, and Argentina [3] and is utilized in traditional medicine by genuine Brazilians [8,9].

The principal chemical compounds known in the *Bignoniaceae* family are alkaloids, polyphenols, flavones, tannins, triterpenes, naphthoquinones, iridoid glucosides, and seed oils [3]. The flavonoids in leaf and petal of *Bignoniaceae* exposed that many flavonoids are flavones subgroup and a little flavonols subgroup [10]. The major classes of secondary metabolites familiarized in *Pyrostegia* genus are flavonoids, phenolic compounds, phenylpropanoids, phenylethanoid glycosides, triterpenes, and sterols.

Even though being applied in traditional medicine, only one species of *Pyrostegia* genus was investigated for its phytochemical compounds and pharmacological activities. *P. venusta* (Ker Gawler) Miers was among the most attractive and widely cultivated of all tropical ornamental vines, which grown on the pH range of 5.4-7.4 [11,12]. *P. venusta* has complete chloroplast genome sequences for phylogenetic analysis [13].

In traditional Brazilian remedy, *P. venusta* is applied as an infusion or decoction and given per oral as a tonic, a drug to therapy diarrhea, coughing, vitiligo, and infectious diseases on the respiratory system, such as cold, flu, and bronchitis. Vitiligo, diarrhea, and jaundice are treated using its infusions [3,14]. Flowers can be used to decrease vomit, while tonic of the stem had anti-diarrhea [9].

*P. venusta*, one of four of *Pyrostegia* genus, is an evergreen, woody vine authentic from Brazil that generates one of the beautiful flowers in the world [15]. Bioactive compounds expressed from of *Pyrostegia* genus plants have previously demonstrated many pharmacological activities such as antioxidant, antimicrobial, antifungal, anti-inflammatory, wound healing activities, antinociceptive, analgesic, vasorelaxant activities, antitumor, cytotoxic activity, hepatoprotective, antitussive, anthelmintic activity, hyperpigmentation activity/melanogenic activity, treatment of sickness behavior, estrogenic activity, antihypertensive activity, and immunomodulatory. This review structurally described the usage of *Pyrostegia* genus in traditional medicine, chemical constituents, and pharmacological activities information, which may be useful for research of new drug development in the future.

## 2. Materials and Methods

Data in this article are collected from literature study international scientific journals in PubMed, Google Scholar, Science Direct, Elsevier, Springer, and Scopus portal using meta-analysis based PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis).

## 3. Results and Discussion

### 3.1. Traditional uses of *Pyrostegia* genus.

*Pyrostegia* C. Presl was a genus that contains 4 species that are original from South America. *Pyrostegia* genus consists of *P. cinerea* Bureau ex. K. Schum; *P. dichotoma* Miers

ex. K. Schum; *P. millingtonioides* Sandwith, Kew Bull.; and *P. venusta* (Ker Gawl.) Miers [2,16]. There are some properties that given by *Pyrostegia cinerea*, which diverge from the other *Pyrostegia*. Specifically, *Pyrostegia cinerea* has cylindrical shape stems, simple tendrils, and interpetiolar glands, whereas other *Pyrostegia* species have hexagonal shape stems, trifold tendrils, and lack of glands [17].

In Southeast Asia, *P. venusta* (Flame vine) is used as an ornamental and medicinal plant. In traditional Brazilian medicine, the *P. venusta* is utilized as an infusion or decoction as a tonic, a drug to treat diarrhea, coughing, vitiligo, and infectious diseases of the respiratory system, such as colds, coughs, and bronchitis which given orally [3]. The leaves and stems of the *P. venusta* are applied in traditional Brazilian medicine as a tonic and diarrhea treatment, while the flowers for leucoderma and vitiligo treatment. Vitiligo is a skin disease common progressive depigmentation of the epidermis that destroys melanocytes in the depigmented parts of the skin, mucous membrane, and retinal wall [18]. The *P. venusta* flowers can stimulate melanogenesis so that they can be utilized to treat vitiligo [19,20]. Extracts of *P. venusta* leaves and flowers stimulated cellular melanogenesis at low concentrations after 4 days of incubation on melanoma cells. Therefore, both extracts of *P. venusta* may be a possible option for the treatment of hypopigmentation diseases such as vitiligo [20,21]. Besides, the flower is applied in general diseases of the respiratory system associated with infections, such as bronchitis, flu, and colds [8,9].

*P. venusta* is utilized in traditional medicine for vitiligo, dysentery, menstrual flow, genital infections, uterine infections, and diseases in the respiratory system [14,19,22]. This therapeutic effect is connected with the existence of phenolic substances, mainly flavonoids, established in the stems and leaves [19,22,23]—the hydroalcoholic extracts of *Pyrostegia* genus, which could be used for the treatment of infections [24].

The *P. venusta* flowers extract increases epithelialization, fibroplasia, and neovascularization after treatment [25]. Topical formulations of *P. venusta* are commonly used for the treatment of vitiligo that. The herb seems to be effective for its melanogenic, anti-inflammatory, and antioxidant properties [26]. These biological activities are correlated to phenolic compounds, mainly flavonoids [27]. The content of flavonoids and sterols in *P. venusta* have estrogen-like biological activity. The flavonoid and sterols related to a low incidence of diseases estrogen-dependent, such as cardiovascular illness, osteoporosis, and cancers [28].

### 3.2. Phytochemical compounds of *Pyrostegia* genus.

Phytochemicals are a chemical compound that occurs naturally in plants. Phytochemicals may have preventive or treatment disease properties. Phytochemical screening results from roots and flowers methanol extract of *P. venusta*, one of *Pyrostegia* genus, showed steroids, terpenoids, alkaloids, tannins, and saponins [29]. Compounds identified in the phytochemistry research of *P. venusta*, components were characterized as triterpenes, flavonoids, carbohydrates (meso-inositol), nitrogenous compounds (allantoin), n-alkanes (n-hentriacontane), choline chloride, fatty acids, and sterols [3]. *P. venusta* contained phytochemical compounds, such as triterpenes, polyphenols, flavones, acacetin-7-O- $\beta$ -glucopyranoside, iridoid glucosides, bellericanin glycosides, alkaloids, naphthoquinones, tannins, allo-tannic acids, oleanolic acid, seed oils, and  $\beta$ -sitosterol [30]. Several factors affect the botanical composition of plants, such as climatic conditions and the phenological variation of the vegetative species [31].

The flowers contained carotenoids, meso-inositol, acacetin-7-O- $\beta$ -glucopyranoside, verbascoside, n-hentriacontane, and  $\beta$ -sitosterol [10,32,33]. Carotenoids cause orange and yellow petal colors in *P. venusta* [3]. The methanolic extracts of the flower of *P. venusta* revealed the existence of myo-inositol, adipic acid, linoleic acid, oleic acid, arabipyranose, acetophenone, diazoprogestrone, propanoic acid, stigmasteryl tosylate, pentamethyldisilanyl ester, trans-3-hexenedioic acid, and methyl oleic [3,29]. The methyl oleic (synonym-9-Octadecenoic acid (Z)-methyl ester) role-play as an antioxidant [34].

The leaves contained rutin [35], also phenolic compounds, flavonoids like quercetin, catechin, biochanin, syringyl groups, and sterols (cholesterol,  $\beta$ -sitosterol, stigmasterol) [28,29,35,36]. The phenolics in the leaves of *P. venusta* had different biological activities, which their production was enhanced in the callus cultures [27,28]. In callus cultures, phloem differentiates to mature phloem explants and xylem to mature xylem explants [37].

The stem bark of *P. venusta* contained lupeol, betulin, betulinic acid, and choline chloride [3]. In the methanolic extracts of the roots of *P. venusta* was found flavonone hesperidin, 3-b-b-D-glycopyranosyl sitosterol, steroids, and allantoin [29]. In roots also had been identified  $\beta$ -sitosterol [28]. The ethanol extract of the roots of *P. venusta* had allantoin,  $\beta$ -sitosterol, 3 $\beta$ -O- $\beta$ -D-glupyransylsitosterol, and hesperidin [8]. Allantoin,  $\beta$ -sitosterol, hesperidin had antioxidant, antimicrobial, anti-inflammatory, and healing properties [38,39].

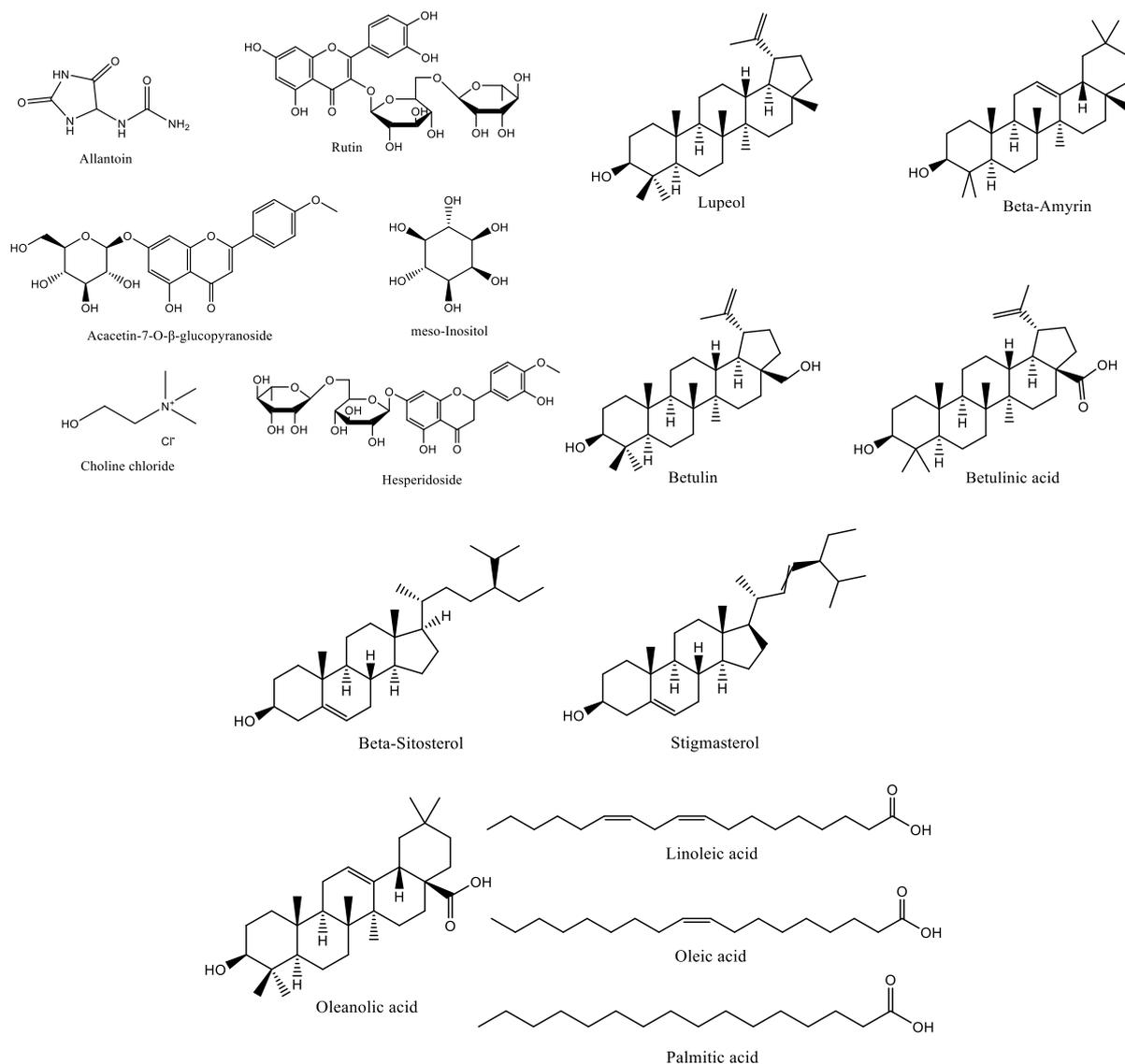
The flowers of *P. venusta* have been evaluated in phytochemical and GC-MS analyses. These analyses showed many phytochemicals compounds and pharmacological activities, which can be seen in Table 1. Chemical structures of compounds isolated from the *Pyrostegia* genus can be seen in Figure 1 [3,14,29,40].

**Table 1.** Phytochemical compound and pharmacological activities based on the GC/MS analysis of *P. venusta*.

Name of compound	Pharmacological activity
Cyperene	Antimalarial, antiplasmodial
Methyl linoleate (Synonym- Linoleic Acid)	Anti-inflammatory, hepatoprotective, antihistaminic, hypocholesterolemic, anticoronary, 5-Alpha reductase inhibitor, antiproliferative activity, cancer preventive, antieczemic, antiacne, antiandrogenic, antiarthritic
Methyl oleate	Anti-inflammatory, antileukotriene-D4 (Anti-platelet activating factor), allergenic, hypocholesterolemic, anemiagenic, anticancer, anti-alopetic, 5-Alpha reductase inhibitor, Alpha- Reductase-Inhibitor, antiandrogenic, dermatitogenic, cancer-preventive, choleric, percutaneostimulant, irritant
Acetophenone	Antibacterial, hypnotic
Methyl palmitate (Synonym- Palmitic Acid)	Antioxidant, 5-Alpha reductase inhibitor, antiproliferative activity, anticancer, hypocholesterolemic, anti-androgenic, hemolytic
Trimethylsilyl-meso-inositol	Antidepressant, used in panic disorders, liver problems, and diabetes
Stigmasteryltosylate	Antioxidant, anti-inflammatory, antihepatotoxic, estrogenic, antiophidic, sedative

### 3.3. Pharmacological activities of *Pyrostegia* genus.

Phytochemical compounds reported from plants of *Pyrostegia* genus have previously demonstrated many pharmacological activities such as antioxidant, antimicrobial, antifungal, anti-inflammatory, wound healing activities, antinociceptive, analgesic, vasorelaxant activities, antitumor, cytotoxic activity, hepatoprotective, antitussive, anthelmintic activity, hyperpigmentation activity/melanogenic activity, treatment of sickness behavior, estrogenic activity, antihypertensive activity, and immunomodulatory.



**Figure 1.** A representative of chemical structures of compounds isolated from the *Pyrostegia* genus.

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#### 3.3.1. Antioxidant activity.

The antioxidant activity was linked to the presence of phenolic compounds such as flavonoids and coumarins. These compounds were present in the crude extract based on phytochemical tests [41]. The antioxidant activity of *P. venusta* was described in the previous study [29], which correlated with the presence of flavones (polyphenol) [29,30] and the presence of rutin in the leaves [35,41]. The antioxidant activity of the phenolics due to the catechol group and conjugated double bonds structurally [38]. *P. venusta* is natural antioxidants due to a large number of flavonoids and phenylpropanoids [42].

The antioxidant in vitro test was conducted with various methods, such as 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging, 2'-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and ferric reducing antioxidant power (FRAP) assays. According to the other research [29], showed the antioxidant activity of the flowers and roots of *P. venusta* which was tested using 2,2-Diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid (ABTS), and ferric reducing antioxidant power (FRAP) assays. The antioxidant activity of methanolic flower extracts at 0.1 mg/ml (95%) and roots (94%) in DPPH radicals was proportional to ascorbic acid, and butylated hydroxytoluene BHT was 98.9% and 97.6%, respectively. The inhibitory effect of flower extracts and root extracts expressed by IC<sub>50</sub>, i.e., 0.018 ± 0.69 mg/ml and 0.026 ± 0.94 mg/ml in ABTS free radicals. The reducing ability of root extracts (3046.98 ± 60.87 µm Fe(II)/g) and flower extracts (112.49 ± 37.11 µm Fe(II)/g), compared to BHT 63.56 ± 2.62 µm Fe(II)/g, catechins (972.02 ± 0.72 µm Fe(II)/g) and quercetin (3208.27 ± 31.29 µm Fe(II)/g) [29]. All DPPH, ABTS, and FRAP methods showed the antioxidant activity of *P. venusta* flower extract was higher than of *P. venusta* root extract.

### 3.3.2. Antimicrobial activity.

The antimicrobial activity has been reported of several phenolic compounds and can act directly on the bacterium or suppress virulence factors. Phenolic compounds can disturb or increase the cytoplasmic membrane permeability, depriving the substrates important for microbial growth, inhibit enzymes, and form chelates [38].

In general, *P. venusta* plants have been proven effective in skin disorders, genital infections, respiratory diseases, some bacteria, and pathogenic fungi [30]. *P. venusta* methanol extract has an antimicrobial effect, using the agar well diffusion method towards *Bacillus cereus*, *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella typhimurium*, *Shigella sonnei*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [43].

According to the results of Roy *et al.* (2012), methanol extracts of the *P. venusta* flowers exhibited moderate antimicrobial activity. The antimicrobial activity against the organisms such as *Aspergillus niger*, *Bacillus subtilis*, *E. coli*, *Enterobacter aerogenes*, *Micrococcus luteus*, *P. aeruginosa*, *S. aureus*, *Staphylococcus epidermidis*, *Staphylococcus pyogenes*, and *Salmonella typhi* [39].

### 3.3.3. Antifungal activity.

Ethanollic extracts from *P. venusta* were tested by bioautography on thin-layer chromatography (TLC) for their antifungal effects against pathogenic *Fusarium verticillioides*. To determine the antifungal activity of each extract, direct bioautography was done on thin-layer chromatography (TLC). Each extract dissolved in ethanol was applied on TLC plates at the volume needed to reach a final dose of 0.01- 2.0 mg/spot. Controls with and without ethanol were also used. The fungicide mancozeb was used as a positive control. Minimum Inhibitory Concentrations (MICs) were determined as the lowest extract concentration showing no visible fungal growth on spots. The extracts of *P. venusta* has Minimum Inhibitory Concentrations (MICs) of >2 mg/spot was effective in inhibiting fungal growth. Thus, ethanollic extracts of *P. venusta* inhibited *F. verticillioides* growth at Minimum Inhibitory Concentrations (MICs) of >2 mg/spot [44].

The results of Roy *et al.* (2012) indicated that methanol extracts of the *P. venusta* flowers exhibited moderate antifungal activity against the organisms such as *Candida albicans* dan *C. tropicalis* [39]. The research Pereira *et al.* (2014) has evaluated the antimicrobial activity of the extracts against *Candida* strains (*C. albicans*; *C. krusei* ATCC 6258; and the clinical isolate strains of *Candida* sp. *C. albicans*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and *C. guilliermondii*). The *P. venusta* flower extracts displayed antimicrobial activities. The semi-purified fraction of the *P. venusta* flower extract and the phenylpropanoid glycoside verbascoside exhibited activity similar to that of amphotericin B, which denoted that they are potentially applicable as anticandidal agents in the pharmaceutical industries [45].

#### 3.3.4. Anti-inflammatory activity.

The compounds acacetin-7-O- $\beta$ -glucopyranoside,  $\beta$ -sitosterol, meso-inositol, and n-hentriacontane in *P. venusta* showed anti-inflammatory activity [29,46,47]. The acacetin inhibited the induction of cyclooxygenase-2 (COX-2) and nitric oxide synthase (NOS) in macrophages that were induced with lipopolysaccharide (LPS) with action inhibiting the transcriptional activation [14,46,48]. Flavonoids and tannin could overcome the inflammation, infection, and oxidative process, as well as and enhance would cause contraction, fibroblasts proliferation, angiogenesis, and collagen synthesis [38] - the potential degrees of anti-inflammatory and analgesic activity correlated with the presence of flavonoids and phenolic compounds. Appropriately mechanisms related to antinociceptive and anti-inflammatory actions of the *P. venusta* extract yet know completely [14].

The anti-inflammatory activity can also be improved by the enhanced bioavailability or uptake of each other, so that synergistically boost antioxidant capacity and the different target cells [38]. The presence of acacetin-7-O- $\beta$ -glucopyranoside and  $\beta$ -sitosterol [46,49,50] figured anti-inflammatory activity [38]. Acacetin, a flavonoid compound, had anti-peroxidative and anti-inflammatory effects [49]. The  $\beta$ -sitosterol has potent anti-inflammatory and antipyretic activities. The anti-inflammatory activity is independent of the pituitary-adrenal system. Moreover,  $\beta$ -sitosterol had a wide margin of safety with minimum ulcerogenic activity [46].

According to research Gupta *et al.* (1980),  $\beta$ -sitosterol has shown anti-inflammatory and antipyretic activities [46]. The  $\beta$ -sitosterol showed meaningful anti-inflammatory activity towards carrageenan-induced edema and in granulation tissue formation induced by cotton pellet implantation. The  $\beta$ -sitosterol had antipyretic activity similar to acetylsalicylic acid [46].

The research Veloso *et al.* (2011) has investigated the anti-inflammatory effects of *P. venusta* hydroethanolic extract (PvHE) in paw edema and peritonitis in Swiss male mice induced by carrageenan and lipopolysaccharide. The results showed that PvHE at doses of 30-300 mg/kg peroral cause an anti-inflammatory effect. PvHE decreased paw edema caused by carrageenan and inhibited leukocyte mobilization into the peritoneal cavity [50].

The research Veloso *et al.* (2014) investigated the effects of the treatment of inflammatory and metabolic dysfunction induced by a high-refined-carbohydrate (HC) diet from the hydroethanolic extract of *P. venusta* flowers (PvHE). The results demonstrated that PvHE increased glucose intolerance, reduce adipocyte area, serum triacylglycerol levels, and systemic inflammatory cells. Moreover, it reduced several inflammatory mediators levels in adipose tissue and liver. Thus, PvHE had useful effects such might treat inflammatory and metabolic dysfunction caused by the HC diet [51].

Moreover, an aqueous extract of *P. venusta* decreased bronchial hyperresponsiveness, lung, and airway inflammation. In preclinical trials, *P. venusta* may have the possibility of asthma treatment [52].

#### 3.3.5. Wound healing activities.

Wounds were physical injuries result in an opening or impairment of the skin. Wound healing was the stage that is done by the body and delayed the occasion of microbial infection [53]. The wound healing process had several steps that included coagulation, inflammation, the formation of granulation tissue, matrix formation, remodeling of connective tissue, collagenization, and the result of wound strength [54]. Wound healing was a dynamic and complex process of substituting impaired cellular structures and missing tissue layers. Wound healing in the human often consists of three phases, i.e., inflammatory, proliferative, and remodeling phases [55].

The mechanisms of different targets of *P. venusta* are also concerned with the synergistic interaction to increase healing [38]. The phenolic compounds might build a suitable environment for the healing process and affected one or more phases of healing [38]. The wound healing potential of flower extract of *P. venusta* gave preferable-wound closure and increased tissue regeneration on the infected Wistar rat model. The study provided a scientific reason for wound treatments in traditional use [14].

According to results, Roy *et al.* (2012) indicated that extracts of methanol of the *P. venusta* flowers had effective wound healing activity, obvious from the increased tensile strength and wound contraction that evaluated utilizing cutting and incision model in Wistar rats. In experimental, expressed hydroxyproline and hexosamine were also related to the healing. Moreover, TNF- $\alpha$  and IL-6 levels were found to be up-regulated by *P. venusta* treatment during wound healing early phase [39].

#### 3.3.6. Antinociceptive effect.

The research Veloso *et al.* (2011) has evaluated the antinociceptive effect of *P. venusta* hydroethanolic extract (PvHE). In experiments, the nociceptive model using writhing and paw-licking that caused by acetic acid and formalin, respectively, in Swiss male mice. The extracts expressed antinociceptive activity in both writhing and paw-licking action. Thus, PvHE has antinociceptive action in mice [50].

#### 3.3.7. Analgesic.

The research Veloso *et al.* (2011) had evaluated the analgesic effects of *P. venusta* hydroethanolic extract (PvHE). In experiments, paw edema and peritonitis in Swiss male mice induced by carrageenan and lipopolysaccharide, respectively. The results displayed that PvHE decreased paw edema and inhibited leukocyte mobilization into the peritoneal cavity [50].

#### 3.3.8. Vasorelaxant activities.

According to research Martinez *et al.* (2019), has been founded the metabolites in the compact callus of *P. venusta*. Callus from *P. venusta* gained from the plant tissue culture technology as an alternative to obtaining a constant production of secondary metabolites. The compounds identified from *P. venusta* related mainly to phenylethanoid glycosides, which

showed vasorelaxant activity in isolated rat aorta rings. Verbascoside, isoverbascoside, and leucosceptoside A are phenylethanoid glycosides (PhGs) including water-soluble polyphenolic compounds has identified in the compact callus of *P. venusta*. The callus from *P. venusta* has metabolites presented vasorelaxant activity about 65 to 100% [56-58].

### 3.3.9. Antitumor activity.

In tumor cells, microtubules were an important therapeutic target. Agents that bind to microtubules was part of the pharmacopeia of anticancer treatment for decades [59]. The hydroalcoholic *P. venusta* extract has significant antitumor activity and moderate cytotoxicity [14, 60].

The research Silva *et al.* (2012) have identified the antitumor activities of hydroalcoholic extract *P. venusta* flowers. The result showed that *P. venusta* extract has antitumor activity in the *Artemia salina* test [61].

### 3.3.10. Cytotoxic activity.

Cytotoxicity might be related to cytotoxic naphthoquinones, which phytochemicals compound in *P. venusta*. The cytotoxicity on Vero cells (CC50) of ethanol extract from *P. venusta* leaves and stems was >200 µg/ml [62].

The research Silva *et al.* (2012) have identified the cytotoxicity activities of hydroalcoholic extracts *P. venusta* flowers. The result stated that the *P. venusta* flower extracts did not display significant cytotoxic activity in the *Artemia salina* test [61].

### 3.3.11. Hepatoprotective.

The study had indicated the relationship presence of potential antioxidant and hepatoprotective molecules, nevertheless needed to be established preclinical study in rats induced hepatitis [14].

### 3.3.12. Antitussive.

The flavonoid, cyanogenic glycoside, tannin, and phenol in *P. venusta* exhibited significant antitussive activity. Nevertheless, the lack of research studies that support [14].

### 3.3.13. Anthelmintic activity.

Helminths are parasitic that infectious agents to humans and can produce disease, including malaria. Methanol and chloroform extracts of *P. venusta* have anthelmintic activity significantly. However, this extract takes more time to remove helminths more than piperazine citrate. This extract was free from the side effects of synthetic drugs [14].

The research Nisha *et al.* (2012) have evaluated the anthelmintic activity of chloroform extract and methanol extract from stems and leaves of *P. venusta* towards *Pheretima posthuma* as a test helminths model. Five different concentrations, such as 2.5, 5.0, 7.5, 10.0, and 12.5 mg/ml of methanol and chloroform extracts were used to establish their effect as measuring the time is taken to paralysis and to induce death in the worms. The results showed that chloroform extract tested at 12.5 mg/ml concentration has effective anthelmintic activity with paralysis time and death time was 23 min and 44 min, respectively. The methanolic extract tested at 12.5 mg/ml concentration has significant anthelmintic activity with paralysis time and death time was 34 min and 78 min, respectively. Thus, research expressed that chloroform extract was more effective compared to methanolic extract in anthelmintic activity towards *P. posthuma*

helminths. But both extracts were less effective compared with the piperazine citrate standard [60].

#### 3.3.14. Hyperpigmentation activity/melanogenic activity.

Melanin was a pigment found in skin, hair, and eyes, roles to the protection of cells towards skin injury caused by ultraviolet irradiation and other environmental effects. Melanogenesis is organized by three main enzymes, i.e., tyrosinase, tyrosinase-related proteins 1 (TRP 1), and 2 (TRP 2). Tyrosinase has a role catalyzes a rate-limiting step for melanin synthesis [63].

The hydroalcoholic extracts of leaves and flowers of *P. venusta* at low concentration showed anti vitiligo (hyperpigmentation) activity [61]. Vitiligo is characterized by depigmented spots on the surface skin. The antioxidant properties could be beneficial towards vitiligo symptoms, which are related to the accumulation of reactive oxygen species in the skin [19,64].

Generally, leaves of *P. venusta* are used to therapy vitiligo. The research Moreira *et al.* (2015) has identified the anti-inflammatory and hyperpigmented activities of hydroethanolic (HE) extract of *P. venusta* leaves on animal models of vitiligo that croton oil and monobenzene-induced. The results presented that orally and topically administrations of *P. venusta* have anti-inflammatory and hyperpigmentation effects significantly. This result presented topical effects has different from systemic effects. Besides increasing pigmentation and melanin components, HE extracts of *P. venusta* leaves have a prospect for the therapy of vitiligo [19].

The research Moreira *et al.* (2012) have identified the melanogenic activity on murine B16F10 melanoma cells from hydroalcoholic leaves and flower extracts of *P. venusta*. The results exhibited that leaves and flowers extract enhanced the melanin content on melanoma cells after 4 days of incubation (concentration-dependent). Leaves extract showed an increase of melanogenesis with a maximum effect of  $33.3 \pm 3\%$  (3  $\mu\text{g/ml}$ ). Flower extract showed an increase of melanogenesis of  $23.4 \pm 3\%$  (0.1  $\mu\text{g/ml}$ ). Therefore, leaves and flower extracts of *P. venusta* with very low concentrations can stimulate B16F10 melanogenesis. These results supported the traditional use of *P. venusta* on the therapy of hypopigmentation diseases, i.e., vitiligo [20]. *P. venusta* are well-known as melanogenesis stimulators [65,66].

#### 3.3.15. Treatment of sickness behavior.

The research Veloso *et al.* (2010) has evaluated the effects of a hydroethanolic extract of flowers of *P. venusta* on sickness behaviors in mice lipopolysaccharide (LPS)-induced. The results found that *P. venusta* extract decreased the depressive-like and exploratory behaviors caused by LPS. Thus, it corresponded to prior claims of the benefits of these plants in ethnopharmacology and can be beneficial in the therapy of disorders that induced sickness behavior, i.e., flu and cold [9].

#### 3.3.16. Estrogenic activity.

The herbal from *P. venusta* has been used to decrease the symptoms of menopause. These are related to content flavonoids and sterols in *P. venusta* that have estrogen-like biological activity. Epidemiologically, the consumption of flavonoids and sterols decreases menopausal symptoms, including hot flashes. However, the active compounds in *P. venusta* extract were displayed in rather low concentration. On the other hand, a higher concentration

of metabolites can be gained from plant tissue culture as a choice for the enhancement of plant extracts effect [28].

#### 3.3.17. Antihypertensive activity.

The potential antihypertensive activity of *P. venusta* was evaluated in vitro test. *P. venusta* has the ability to inhibit the angiotensin-converting enzyme (ACE). Extracts of *P. venusta* stems gave angiotensin-converting enzyme (ACE) inhibitory activity about  $31.6 \pm 30.8$  % [67].

#### 3.3.18. Immunomodulatory.

The methanol extract of *P. venusta* flowers and leaves displayed an increase in the immune system. Moreover, it supports a rise in anti-inflammatory and suppresses of proinflammatory cytokines [14].

#### 3.4. Genotoxicity test.

The research Magalhães *et al.* (2010) had evaluated the genotoxic effect of extracts of ethanol of the *P. venusta* utilizing the micronucleus (MN) and chromosome aberration tests (CA) in mice. The experimental groups received different concentrations (50, 100, and 200 mg/kg body weight) orally. The frequency of micronucleated polychromatic erythrocytes (MNPCE) of experimental controls was lower significantly when compared with the negative control group receiving water, but was statistically lower than the positive control group receiving Cyclophosphamide. Thus, *P. venusta* didn't show genotoxicity activity [68].

The research Magalhães *et al.* (2010) had tested the genotoxic effect of extracts of ethanol of the *P. venusta* using the micronucleus (MN) and chromosome aberration tests (CA) in mice. The experimental groups received different concentrations by orally. The result showed the amount of micronucleated polychromatic erythrocytes (MNPCE) of experimental controls was lower significantly when compared with the negative control group that received water, but was statistically lower than the positive control group that received Cyclophosphamide. Thus, *P. venusta* didn't denote genotoxicity activity [68].

According to research Viel *et al.* (2019), ethanolic extract of *P. venusta* flowers did not present genotoxic effects. However, the extract of *P. venusta* showed antigenotoxic potential, possibly due to the different flavonoid compounds present in its extract [69]. In conclusion, both types of research have shown that ethanolic extracts from *P. venusta* didn't present genotoxic effects.

#### 3.5. Toxicity study.

According to research Viel *et al.* (2019), ethanolic flowers extract of *P. venusta* extract does not present reproductive toxicity. Based on the toxicological analysis, *P. venusta* has no negative effect significantly on reproductive and cellular levels. Thus, *P. venusta* extract does not show reproductive toxicity [69]. Approximate LD<sub>50</sub> of  $\beta$ -sitosterol in mice was more than 3 g/kg intraperitoneally [46]. The  $\beta$ -sitosterol is one of most compounds of *P. venusta*.

Phytochemical constituents and pharmacological activities in the *Pyrostegia* genus can be applied as drug candidates. Therefore, the drug discovery process should be continued. The drug discovery process for treating disease initiates with the identification of medical needs

and consideration of the adequacy of available therapies. Next, assessing the up to date knowledge about the target disease, make hypotheses future about how to probably increase and repair therapy, i.e., efficacy, safety, or novel improvements (mechanistically), which will enhance the method of treatment for patients with the target disease. For stages in the drug discovery process were consist of preclinical studies and clinical studies. Preclinical studies consist of the formation of a research team and objectives set; novel chemicals synthesized; chemicals tested for efficacy and safety (*in vitro* with test tubes and *in vivo* with animals), which results are used to the choice drug candidate. The next steps are formulation, stability scale-up synthesis, and chronic safety in animals. Finally, the company files an Investigational New Drug (IND) application with the Food and Drug Administration (FDA). After the preclinical studies, clinical studies are performed, which consist of Phase I: studies in healthy humans (toleration), Phase II: studies in patients (efficacy), Phase III: large clinical trials in many patients. Then the company files New Drug Application (NDA), FDA reviews the NDA, and finally, drug is approved for the market [70].

#### 4. Conclusions

The *Pyrostegia* genus has proven to be rich in phytoconstituents, mainly consisting of flavonoids, phenolic compounds, phenylpropanoids, phenylethanoid glycosides, triterpenes, and sterols. Also, the *Pyrostegia* genus has shown significant pharmacological potential and promising activities such as antioxidant, antimicrobial, antifungal, anti-inflammatory, wound healing activities, antinociceptive, analgesic, vasorelaxant activities, antitumor, cytotoxic, hepatoprotective, antitussive, anthelmintic, hyperpigmented, treatment of sickness behavior, estrogenic, antihypertensive, and immunomodulatory activities. These results make the traditional uses rational and highlight the importance of the *Pyrostegia* genus. Based on the literature review expressed the traditional uses, chemical compounds, and pharmacological activities of the *Pyrostegia* genus. The literature study showed that the *Pyrostegia* genus is used as a traditional medicine in South America, such as Brazil, Argentina, and Paraguay. Most of the pharmacological activities studies about *Pyrostegia* genus were limited to the in-vitro screening and few preclinical studies. Nevertheless, the *Pyrostegia* genus can be used as a natural medicinal source and enhance the importance of further studies.

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#### Conflicts of Interest

The authors declare no conflict of interest.

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