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Review Paper

Wound healing, hyperpigmentant and antitumor activity of *Pyrostegia venusta*

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Abstract

***Pyrostegia venusta* (Ker Gawl.) Miers is a plant species of the family Bignoniaceae, which is originally endemic to Brazil. It is presently a well-known garden species. It is cultivated on account of its outstanding ornamental features and on its important therapeutic properties. It has been commonly used in the traditional Brazilian medicine as a general tonic, treating many diseases such as skin diseases. Ethnomedicinal research has recently been recognized to investigate bioactive plant components in modern scientific lines of phytochemical analysis, pharmacological screening and clinical trials. This study reviews the published literature on wound healing, hyperpigmentant and antitumor activity of *P. venusta* which has folklore tradition of medicinal uses. Therefore, the present review could constitute a good basis for further investigation in the potential therapeutic effects of *P. venusta* which could provide useful information for future research.**

Keywords: *Pyrostegia venusta,* skin diseases, wound healing, hyperpigmentant, antitumor activity

Introduction

Pyrostegia venusta (Ker Gawl.) Miers (Bignoniaceae) is a popular ornamental plant with cascades of orange flowers (Figure 1). It is generally grown throughout the tropical, subtropical areas and in mild Mediterranean climates. It is a native woody vine widely spread in Brazil. It is popularly known as “flame vine” or “cipó-de-são-joão”, this plant is cultivated in different areas on account of outstanding ornamental features and on its important therapeutic properties [1]. Its leaves and stems are used in native folk medicine of *Brazil* as a tonic and for the treatment of diarrhea, while its flowers are used in the treatment of white patches on the body, such as leucoderma and vitiligo. In addition, it is used in cough and common diseases of the respiratory system linked to infections, such as bronchitis, flu and cold [2-4]. The extracts of flowers and roots of this species contain significant amounts of phytochemicals with antioxidative properties that could act as inhibitors or scavengers of free radicals [5]. Furthermore, this plant demonstrates anti-inflammatory, analgesic, antinociceptive, hepatoprotective, spasmolytic, antipruritic, anticancer, antiangiogenic, antiallergic, wound healing and antimicrobial activity [2-5]. No genotoxic effect was observed for *P. venusta* extracts on bone marrow of mice using the micronucleus and chromosome aberration assay [6].

It is hoped that research on various plant species will continue to discover other new natural active compounds and to find other active natural molecules with potent therapeutic action devoid or less toxic than the synthetic ones [7]. The present review could constitute a good basis for further investigation in the potential discovery of new natural bioactive compounds, and could offer preliminary information for future research. Therefore, the aim of this study is to review the published literature on wound healing, hyperpigmentant and antitumor activity of *P. venusta* in order to support

its popular uses in disease treatments. This plant could be exploited as a potential source for plant-based pharmaceutical products.

Figure 1: *Pyrostegia venusta* (Ker Gawl.) Miers

Traditional uses

P. venusta is a neotropic evergreen vine. It has been widely used in the traditional Brazilian medicine. It could be exploited as a potential source for plant-based pharmaceutical products. It contains phyto-chemicals such as triterpenes, iridoid glucosides, alkaloids, naphthoquinones, flavones, tannins, polyphenols, oleanolic acid, allo-tannic acid, seed oils, acacetin-7-O-β-glucopyranoside, glycoside bellericanin and β-sitosterol. Its extracts possess a wide range of pharmacological activities. Native Brazilians utilize *P. venusta* to treat flu and cough. Its decoction is orally administered as a general tonic and also as an infusion for the treatment of diarrhoea, jaundice and vitiligo [2-4]. Tonics made from its stems are useful for the treatment of diarrhoea, while flower preparations have been demonstrated to attenuate vomiting [4].

In general, the plant has been found to be effective against skin disorders, genital infections, respiratory ailments and a number of bacterial and fungal pathogens. Various parts of *P. venusta* display anti-inflammatory, antioxidant, hepatoprotective, antitumor, spasmolytic, antipruritic, antiangiogenic, analgesic, antinociceptive, antiallergic, wound healing, antimicrobial and is useful in the treatment of disorders that induced sickness behavior, such as flu and cold [2,4,5,8,9].

Morphology of the plant

P. venusta is a liana (a vigorous, woody climber) that makes a beautiful ornamental plant with cascades of orange flowers [10]. It is commonly grown in tropical, subtropical regions and in mild Mediterranean climates. *P. venusta* forms dense masses, growing up trees, over rocks or on walls. It is covered with flowers in the cool, dry season. It carries cascades of bright orange tubular flowers. It blossoms in the winter through late spring. This plant is fairly drought tolerant but does need well drained soil. The compound leaves are arranged in pairs opposite each other on the stem. The center leaflet is commonly modified into a coiled, three-parted tendril. The margins of leaves are ovate, with pinnate venation, evergreen. The plant branches generously and climbs by clinging with its tendrils. The orange color, tubular flowers showed dichasial cymes inflorescence. The long orange stamens and style extends beyond the tube. Its fruits are found in an elongated shape with dry capsules [9-11].

Taxonomical classification

Kingdom : Plantae
Class : Equisetopsida
Subclass : Magnoliidae
Superorder : Asteranae
Order : Lamiales
Family : Bignoniaceae
Genus : *Pyrostegia*
Species : *venusta*
Scientific name : *Pyrostegia venusta* (Ker Gawl.) Miers

P. venusta has many common names in different languages. For example, Its English common names include flame vine, golden shower, flame creeper, flame flower, flame flower vine, flaming trumpet, flaming trumpet vine, golden shower vine, orange creeper and orange trumpet vine. Its Brazilian native names include cipó-de-são-joão, flor-de-são-joão, cipó- de-cesto, cipó-de-fogo, cipó-delagartixa, cipó-pé-de-lagartixa and cipó- delagarto [9-11].

Phytochemistry

Phytochemical screening of *P. venusta* demonstrated the presence of terpenoids, steroids, saponins, alkaloids and tannins [5]. Compounds identified upon deeply phytochemical study constituents were classified as sterols, triterpenes, carbohydrates, fatty acids, nitrogenous compounds, *n*-alkanes, flavonoids and choline chloride. From the flowers, the compounds β-sitosterol, acacetin-7-O- β-glucopyranoside, n-hentriacontane and meso-inositol have been isolated [4]. Ferreira *et al.* [2] isolated allantoin, β-sitosterol, 3β-O-β-Dglupyranosylsitosterol and hesperedin from *P. venusta* ethanol root extract. Their structures were identified on the basis of spectral data. Other studies have shown the presence of carotenoids in the flowers [12] and rutin in the leaves [13-14]. Orange and yellow petal colors in this species were due to carotenoids, and not to 3-deoxyanthocyanins [13].

In addition, gas chromatography-mass spectroscopy (GC-MS) studies were undertaken to assess the phytochemical composition of the flower methanol extracts. GC-MS study on HP-5 MS column showed the presence of linoleic acid, oleic acid, myoinositol, diazoprogesterone, arabipyranose, hexadecanoic acid, stigmasteryl tosylate, propanoic acid, pentamethyldisilanyl ester, *trans*-3-hexenedioic acid, acetophenone and 9-octadecenoic acid (Z)-methyl ester in the flower extracts [5]. GCMS analysis of flower extract has demonstrated the presence of many compounds [14]. It has been revealed that the compounds acacetin-7-O-β-glucopyranoside and β-sitosterol showed anti-inflammatory activity [5,15]. The Dr. *Duke's* phytochemical and ethnobotanical databases [16] have indicated several of these compounds to be useful in different medicinal complications. Dinda *et al.* [17] reported isolation of four known compounds betulin, lupeol, betulinic acid and choline chloride from *P. venusta* stem bark.

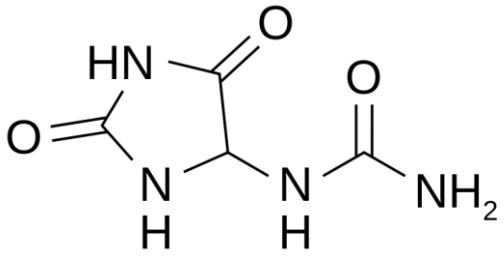

Figure 2: The chemical structure of Allantoin

Allantoin (Figure 2) has been commonly described in the literature to have several pharmacological activities, such as antipsoriase, and immunostimulant, it is widely employed in dermatology [2], stimulation of cell mitosis [18], analgesia [19], keratolytic activity [20], and anti-inflammatory [21]. Araujo et al. [22] suggest that allantoin modulates the inflammatory reaction, probably by hindering the chemotaxis of inflammatory cells in wound site, thus inhibiting the release of reactive species responsible for the oxidative stress and tissue damage. In addition, allantoin treatment led to significant reduction in the levels of IgE and Th2-type cytokines in bronchoalveolar lavage fluid. Because allantoin is a compound with several pharmacological activities, including in processes of

skin ailments. It is possible that allantoin could participate in the melanogenic action of *P. venusta*. Moreira et al. [23] determined allantoin content in the hydroalcoholic extracts of leaves and flowers of *P. venusta*, and results demonstrated low amounts in both extracts.

Therapeutic effects

P. venusta demonstrates antioxidant, anti-inflammatory, antimicrobial, antiviral, antibacterial, antifungal, antihelmintic, hepatoprotective, spasmolytic, antipruritic, anti-angiogenic, antiallergic, immunomodulatory, wound healing**,** hyperpigmentant and antitumor. This plant is a natural source of important phytochemicals [2,5,8,9].

Wound healing

In developing countries, wound infections are difficult to deal with due to poor hygienic circumstances. Furthermore, chronic wounds affect more than 6 million patients in the USA. It is presumed that this number will increase worldwide as a result of the increase in age-related ailments. While present therapeutic agents have usually insufficient effectiveness and several serious effects, many plants have been used in medicine since ancient times and are well known for their abilities to enhance wound healing and prevent infection without serious side effects. Therefore, herbal therapy may be an alternative strategy for treatment of wounds. Budovsky et al. [24] reviewed the data on the medicinal plants with wound healing activity including the biologically active substances belonging to these herbal preparations and described in detail the different cellular and molecular mechanisms of their actions.

The bacteria *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae, Pseudomonas aeruginosa* and *Klebsiella pneumonia* are some important microorganisms of wound infection [25]. *P. venusta* methanol extract was examined for its antibacterial activity against *Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus, Escherichia coli*, *Shigella sonnei, Bacillus cereus* **and** *Klebsiella pneumoniae*. *P. venusta* extract showed antibacterial activity against all bacteria tested according to the results of the agar diffusion assay [26].

Flavonoids, alkaloids, saponins and phenolic compounds were active constituents present in a variety of herbs facilitating wound closure. Glycosides and proteolytic enzymes were among the main active components [27]. Roy et al. [8] examined wound healing and antimicrobial activity of *P. venusta* flower extract, including in vivo antioxidant activity. Methanolic extracts of *P. venusta* flowers were investigated for wound healing efficiency along with its effect on pro-inflammatory and anti-inflammatory cytokines was tested using excision and incision model of wound repair in Wistar rats. The wound healing mechanism could be attributed to increased contraction, tensile strength, hexosamine, hydroxyproline, cytokine content, antioxidative and antimicrobial activities. These healing properties could be linked with activities of isolated compounds from *P. venusta*, such as oleanolic acid, which has demonstrated wound healing activities in tests performed *in vivo*. In addition, antimicrobial activity of the flower extract against twelve microorganisms was assessed. In vivo antioxidant activity was achieved to understand the mechanism of wound healing potency. Their results showed that the extract has potent wound healing capacity as evident from the wound contraction and increased tensile strength. Furthermore, hydroxyproline and hexosamine expression were correlative with the healing pattern observed. The extract showed moderate antimicrobial activity against the microorganisms: *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus pyogenes*, *Bacillus subtilis*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Candida albicans*, *Candida tropicana, Aspergillus niger*, *Enterobacter aerogenes* and *Salmonella typhi.* In early wound healing phase, TNF-α and IL-6 level were found to be up regulated by *P. venusta* treatment. They concluded that increased wound contraction and tensile strength, increased hexosamine and hydroxyproline content along with antioxidative activity and moderate antimicrobial activity support the early wound healing exhibited by the flower extract. Cytokine production is possibly one of the mechanisms involved in accelerating the wound healing. These results suggest that this species may be useful in the tropical management of wound healing. The study offers scientific basis for the traditional use in wound treatments. However, precise mechanisms and the active principles need further investigation.

Pereira et al. [28] examined the *in vitro* anticandidal and antioxidant activities of phenolic compounds detected in *P. venusta* flower extracts. Using the HPLC technique, one flavonoid (quercetin-3-O-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-galactopyranoside) and two phenylpropanoid glycosides (verbascoside and isoverbascoside) were purified. The antimicrobial activity of the extracts was assessed against five *Candida* strains (*C. albicans, C. krusei* ATCC 6258, and clinical isolates strains of *Candida sp*: *C. albicans, C. krusei*, *C. tropicalis, C. parapsilosis* and *C. guilhermondii*). The antimicrobial and antioxidant activities were proved in extracts. Semi-purified fraction and verbascoside demonstrated similar activity to amphotericin B.

Hyperpigmentant activity

Skin diseases are numerous and commonly occurring health problems affecting all ages. Maintaining healthy skin is vital for a healthy body. Many people might develop skin diseases ranging from rashes to terrible skin cancer. Several wild plants are commonly used to treat these diseases. Their use is as old as the mankind. Natural treatment is cheap and assumed to be safe. Furthermore, it is suitable for raw material production of new synthetic agents[29].

Pigmentation disorders can result from abnormalities of melanocytes migration from the neural crest to the skin during embryogenesis, from immunologic or toxic destructions of melanocytes[30]. More than 100 genes are involved in the melanogenesis process, encoding vital structural, enzymatic and regulatory proteins[31]. Tyrosinase is recognized to play a significant role in the melanogenesis regulation[32], as it is responsible for melanin synthesis which begins with the hydroxylation of l-tyrosine to l-dihydroxyphenylalanine (DOPA), which is followed by the oxidation of DOPA to DOPA quinine[33]. The DOPA quinone conjugated is progressively transformed into reddish-yellow pheomelanins or to create brownish-black eumelanins. At that time, the melanin is packaged in vesicles called melanosomes and then transferred to keratinocytes through the dendritic tips of melanocytes, resulting in melanin distribution throughout the epidermis. Any impairment of melanosome transfer to keratinocytes may lead to abnormal skin pigmentation[30].

Vitiligo is the most common hypopigmentant skin disorder, which is an autoimmune-induced depigmentation disease [34]. Vitiligo affects 1–2% of the world population. It causes the destruction of melanocytes that promotes the formation of white patches in the normally pigmented skin which generally starts on the hands and feet and then spreads to other parts of the body [34,35]. Moreover, vitiligo causes a profound effect on people quality of life [36,37]. Symptoms such as depression, anxiety, sleep disturbances and suicidal thoughts are typical in affected individuals [38]. This disease is chiefly treated with corticosteroids, immunomodulators, ultraviolet radiation, lasers, alternate therapy, depigmentation and camouflage. When standard treatments fail, surgical procedures with melanocytes transplantation can be performed. Other methods, such as topical or systemic tyrosine, cysteine, vitamins, clofazimine and traditional herbal medications, have been also tested [39].

P. venusta has been traditionally used as a remedy for treating white patches and infections on the skin. It has different uses in traditional Brazilian folk medicine including the treatment of vitiligo. Nevertheless, its effectiveness on melanogenesis is not yet well elucidated. Moreira et al. [23] investigated the melanogenic activity of hydroalcoholic extracts from *P. venusta* leaves and flowers on murine B16F10 melanoma cells. They evaluated different concentrations of the hydroalcoholic extracts of flowers and leaves of this plant in trials of spontaneous melanin content (4 days), and cell viability by the MTT assay in murine B16F10 cells, and in the mushroom tyrosinase activity in vitro. Both extracts, leaves (0.1, 0.3, 1 and 3 µg/mL) and flowers (0.03 and 0.1 µg/mL) increased the melanin content in a concentration dependent manner after 4 days of incubation on melanoma cells. Leaves extract promoted melanogenesis enhancement with maximum effect of 33.3% (3 µg/mL), and the flower extract increased in 23.4% (0.1 µg/mL). The cell viability test using MTT demonstrated that in the same tested concentrations of both extracts no cell death was detected. In fact, either extract was not able to cause any change in the tyrosinase activity. HPLC analysis of the extracts found 0.09% and 1.08% of allantoin on leaves and flowers extracts. Therefore, *P. venusta* leaves and flowers extracts stimulate B16F10 melanogenesis at very low concentrations. These results support the folk medicinal use of this plant for the treatment of hypopigmentation diseases like vitiligo.

Although the study of Moreira et al.[23] obviously showed the melanogenic effect of *P. venusta* extracts in melanoma cells, important questions remain unclear like its in vivo efficacy. Many other melanogenesis stimulators actually found in the in vitro studies failed to show in vivo efficacy, possibly

because they could not reach or enter skin cells because of the stratum corneum barrier. Further studies are required to directly investigate whether *P. venusta* can enhance human skin pigmentation under physiologically relevant conditions. Therefore, in a recent study on *P. venusta* leaves which are popularly used to treat vitiligo. Moreira et al.[40] evaluated the antiinflammatory and hyperpigmentant activities of hydroethanolic extract of *P. venusta* leaves in animal models of vitiligo induced by croton oil and monobenzone. Their data showed that topical and oral uses of *P. venusta* have significant antiinflammatory and hyperpigmentant activities, revealing different topical and systemic activities in two animal models. These models are also capable to mimic several features of vitiligo. Thus the results support the ethnopharmacological use of this plant.

Genotoxic activity

The genotoxic effect of *P. venusta* extracts was investigated in mice, using the micronucleus (MN) and chromosome aberration tests (CA). The experimental groups received orally different concentrations (50, 100, and 200 mg/kg body weight). Frequency of micronucleated polychromatic erythrocytes (MNPCE) of experimental controls was significantly lower than that of negative control group receiving water. It was also statistically lower than that of positive control group receiving Ciclophosphamide®. Thus, *P. venusta* did not demonstrate genotoxicity activity[6].

Antitumor activity

Silva *et al.* [41] investigated the antitumor and cytotoxicity activities of *Kielmeyera coriacea* and *P. venusta* extracts. They prepared hydroalcoholic extracts of *P. venusta* flowers and *Kielmeyera coriacea* leaves. They found that both extracts showed antitumor activity but did not show significant cytotoxic activity in *Artemia salina* test. Figueiredo *et al.* [42] evaluated the antitumor activity of *P. venusta* extracts against melanoma. The cytotoxic activity and tumor induced cell death of heptane extracts from *P. venusta* flowers were investigated against murine melanoma B16F10-Nex2 cells *in vitro* and in a syngeneic model *in vivo*. They revealed that heptane extract induced apoptosis in melanoma cells by disturbance of mitochondrial membrane potential, initiation of reactive oxygen species and late apoptosis verified by plasma membrane blebbing, cell reduction, chromatin compression and DNA fragmentation, exposure of phosphatidylserine on the cell surface and activation of caspase-2,-3,-8,-9. Moreover, the heptane extract was protective against singeneyc subcutaneous melanoma. The extract compounds were also able to induce cell cycle arrest at G2/M phases on tumor cells. On fractionation of heptane extract in silica gel they isolated a cytotoxic fraction that contained a mixture of saturated hydrocarbons identified by ^{1}H NMR and GC-MS analyses. Chief compounds were octacosane ($C_{28}H_{58}$ - 36%) and triacontane ($C_{30}H_{62}$ - 13%), which individually demonstrated significant cytotoxic activity against murine melanoma B16F10-Nex2 cells *in vitro* and a very promising antitumor protection against subcutaneous melanoma *in vivo*. Their findings suggest that the components of the heptane extract, chiefly octasane and triacontane, which demonstrated antitumor activities in experimental melanoma upon regional administration. Furthermore, they might also be therapeutic in human cancer and as an adjuvant treatment to surgical excision.

Conclusion

P. venusta is internationally one of the most popular and beautiful flowering climbers. It has been utilized in Brazil as a traditional medicine throughout history. It is a natural source of antioxidants that could serve as inhibitors or scavengers of free radicals. *P. venusta* extracts have been utilized in the treatment of various diseases such as skin diseases. It may be useful in the management of wound healing and cancer. *P. venusta* can be also used in the treatment of hypopigmentation diseases such as vitiligo by stimulation of melanogenesis. This plant may supply us with pharmaceutical preparations for the treatment of common diseases related to infections. Because active ingredients may be found in low concentrations, recently, plant tissue culture can bring the solution, this can assist us explore more pharmacological activities. This species could be an important source for pharmaceutical products, and could form a good basis for further research in the potential discovery of new natural bioactive compounds. These compounds need to be explored scientifically and their utilization for therapy. Therefore, *P. venusta* has obviously significant pharmacological potential and promising activities, particularly in the field of skin problems. It may serve as a vital natural bioactive medicinal source, and encourage a great interest in further studies.

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