AN UPDATED PHYTOCHEMICAL AND PHARMACOLOGICAL REVIEW ON GYNURA PROCUMBENS

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INTRODUCTION

Gynura procumbens belongs to family Asteraceae is a fast growing evergreen herb. In Malay, G. procumbens is called Sambung nyawa which means "prolongation of life" whereas, in Chinese, it is called Bai Bing Cao which means "100 ailments" [1]. Other than G. procumbens, it is also known as longevity spinach. This green plant is called longevity spinach because it is like heaven on earth, with tons of health benefits concealed in this plant [2]. G. procumbens falls under the kingdom Plantae, which represents plants. It comes from the phylum of Tracheophyta, which comprising plants with a vascular system. It is classified under the class Magnoliopsida, which is a valid botanical name for a class of flowering plants [2]. It is a small plant that can grow up to a height of approximately ~1–3 m, with a fleshy stem and purple tint. The leaves of G. procumbens are ovate-elliptic or lanceolate, with 3.5–8 cm long and 0.8–3.5 cm wide and the flowering heads are panicled, narrow, yellow and 1–1.5 cm long [3]. The plant is a bicolor herbal species due to green and red color variation [4]. The plants are commonly found in tropical Asia countries such as China, Thailand, Indonesia, Malaysia, and Vietnam [5]. In Malaysia, the fresh leaves of G. procumbens are commonly eaten raw with food, and in Thailand, the leaves are used for cooking [6]. G. procumbens also could be used as an appetizer to enhance the desire to eat when taken with food [7]. The leaves of G. procumbens can be consumed safely in diet due to not having toxic effects [1]. G. procumbens is a species of plant that usually used in medication. It is commonly used as a safe alternative to chemical-based medicine because it could give a lot of benefit to the human body. They are generally used in many different countries for the treatment purpose such as to treat kidney discomfort, rheumatism, diabetes mellitus, as wound healing, and hypertension. It seems to possess the high therapeutic pharmacological potential to treat various diseases [5].

Chemical constituents in G. procumbens

G. procumbens is a valuable plant that contains various chemical constituents that show excellent therapeutic effects. The leaves contain important active chemical constituents such as flavonoids, saponins, tannins, terpenoids, and sterol glycosides [8]. It contains several constituents including kaempferol, quercetin, kaempferol-3-O-β-D-glucopyranoside, kaempferol-3-O-rutinoside, rutin, chlorogenic acid and 3,5-dicaffeoolquininate methyl ester, terpenoid, tannin, alkaloid, saponin, and astragalin (Fig. 1) [7,9].

In the past several studies researchers have discovered many valuable information. In an experiment, G. procumbens leaves were extracted using a variety of solvents. It was reported that non-polar or less polar compounds were fractionated by a non-polar solvent such as chloroform, while ethyl acetate as a polar solvent was used to fractionate the polar compounds such as phenolics, flavonoids, and glycosides. Four types of solvent were used for extraction which is ethanol fraction (EF), chloroform fraction (CF), ethyl acetate fraction (EAF), and n-butanol fraction (BF). The results showed that rutin, quercetin, and kaempferol were found in all fractions, whereas myricetin and apigenin were not detected in chloroform and BF [10]. It was also seen that fractionation of G. procumbens with ethyl acetate, exhibit 2 times higher content of rutin, myricetin, quercetin, and apigenin than ethanol extract and the amounts of myricetin and quercetin were slightly increased. Wan et al. [11] also supported this statement and reported that all individual flavonoids were found to be dominant in the EAF except for kaempferol, which was found to be the most predominant flavonoid in the EF.

Kaeawseejan et al. [6] also identified five phenolic acids in hydroxybenzoic acids (HBA) phenol, of ethanolic fraction and EAF which are gallic acid, protocatechuic acid, HBA, vanillic acid, and syringic acid. However, vanillic acid was not detected in CF and BF, whereas protocatechuic acid and HBA were detected in all fractions except for CF. For hydroxycinnamic acid (HCA) phenol, four phenolic acids, including caffeic acid, p-coumaric acid, ferulic acid, and sinapic acid were detected in all the fractions except in CF. Syringic acid and p-coumaric acid were not found in chloroform. In another study, Jegadeeswari et al. [12] reported higher antioxidant activity of HCA than HBA. The presence of a CH CHOOH group in the HCA derivatives, which is more active than the COOH group in HBA derivatives, leads to the greater antioxidant activity.

Rosidah et al. [13] conducted an experiment and generated HPTLC profiles chromatograms of methanol extract, EAF, and butanol fraction. Solvent system was ethyl acetate: methanol:water (100:13.5:10) (v/v). Detection was done at 365 nm and 254 nm. Results showed that
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kaempferol-3-O-rutinoside and astragalin are the most representative phenolic compounds in EF and BF fraction. Kim et al. [10] identified kaempferol-3-O-rutinoside, quercetin-3-O-rutinosida, and isobioquercetin compounds in ethanolic extract on the TLC plate.

In another experiment, optimization of total flavonoid compound extraction from *Gynura medica* leaf was investigated using response surface methodology. In this experiment high performance liquid chromatography - diode array detection (DAD)- electrospray ionization - mass spectrometry (MS) system and solvent for the mobile phase was water – 0.1% acetic acid (A) and acetonitrile (B) were used. The gradient elution was 0–30 min, linear gradient 10–30% B; 30–45 min, and linear gradient 30–60% B. The flow rate was 0.8 mL/min and the column was operated at 30°C. Peaks were detected with the DAD at 347 nm. Seven peaks of flavonoid compounds were separated and identified by the MS value coupled with the ultraviolet spectrum data [14].

The Fourier-transform infrared spectra of polysaccharide samples were studied by Choi et al. [15]. Based on the studies, they stated that the broad and intense absorption peak around 3439 cm\(^{-1}\) was attributed to the OH stretching vibration, and the weak band near 2936 cm\(^{-1}\) was due to the stretching vibration of CH including CH, CH\(_2\), and CH\(_3\) in the sugar ring. He justified that these two absorption bands were both belonged to the characteristic functional groups of polysaccharides. The absorption peak at approximately 1405 cm\(^{-1}\) could be attributed to the deforming vibration of the CH bond. In addition, Saiman et al. [16] studied the leaf explants-derived adventitious root culture as an alternative culture system for *G. procumbens* biomass containing bio-active compounds and then analyzed the metabolite content in the root culture of *G. procumbens* using proton nuclear magnetic resonance based profiling technique.

**PHARMACOLOGICAL ACTIVITIES OF *G. PROCUMBENS***

*G. procumbens* is a potential natural source of compounds with various pharmacological actions which can be utilized for the development of novel therapeutic agents. Hence, a lot of scientists had done a further experiment to validate and provide scientific evidence for the therapeutic claims of its efficacy. *G. procumbens* is a plant that exhibits a lot of medicinal effect to treat a variety of health ailments such as kidney discomfort, rheumatism, diabetes mellitus, constipation, and hypertension [5]. This makes it as a target for pharmacological studies aiming to validate and provide scientific evidence for the traditional claims of its efficacy.

**Antihypertensive and cardioprotective activity**

Hoe et al. [17] found that *G. procumbens* could be used to prevent hypertension as it has been reported to result in significant lowering of systolic blood pressure and mean arterial pressure in hypertensive rats. Basic mechanisms regulating blood pressure are control of blood vessel diameter, heart rate, contractility, and regulation of blood volume. In an experiment, *G. procumbens* extract gives pressure-lowering effect by inhibit the angiotensin-converting enzyme activity. *G. procumbens* antagonizes the vasoconstrictive effect of Ang II by activate the nitric oxide and prostaglandin release [18]. Poh et al. [19] revealed that *G. procumbens* extract can also result in a significant decrease in heart rate by creating strong negative chronotropic, and negative ionotropic effects on atrium [9]. The chemical constituents present in *G. procumbens* can inhibit calcium influx in the muscles of the blood vessels. Due to the absence of calcium, the muscles of blood vessels relax and blood pressure lowers [17].

**Antihyperglycemic activity**

Diabetes had been reported as one of the common diseases that might affect people. In general, speaking, diabetes occurs due to low levels of insulin in the body, which leads to high glucose levels in the blood. Many patients are reluctant to use pharmacological drugs due to the possible side effect. So by introducing *G. procumbens* herbal therapies to the patient, we could reduce the occurrence and risk of diabetes. A study was conducted to determine the anti-diabetic and pro-fertility effect...
of *G. procumbens* on streptozotocin-induced male rats within 14 days and showed that aqueous extract of *G. procumbens* has a pro-fertility effect and possess anti-hyperglycemic activity [19,20]. Hamid et al. [21] investigated the effect of *G. procumbens* treatment on insulin level. Results showed the stimulatory effect of insulin-secreting cell lines by *G. procumbens* extract. However, it showed no effect when exposure to clonal pancreatic cells [22]. On a further experiment, however, no significant change has been noticed in plasma insulin level in diabetic rats treated with the extracts, suggesting that the hypoglycemic activity of *G. procumbens* does not rely on insulin trophic activity but may instead be due to its extra-pancreatic effect [23].

In another experiment, treatment with *G. procumbens* stimulated glucose uptake on 3T3 adipocytes. In addition, an improvement of activity was seen in the presence of insulin [24]. In another, in vivo experiment also confirmed an enhanced uptake of glucose by muscle tissue of diabetic rats. The results showed the direct effect of *G. procumbens* extract on glucose uptake [25]. Synergistic effect with stronger hypoglycemic effect was also observed when *G. procumbens* was used together with *Azadirachta indica* or *Andrographis paniculata* [26]. The synergistic effect is assumed to be associated with the varied range of active compounds present in the extract combination. This indication suggests the presence of bioactive principles which possess insulin mimetic properties in *G. procumbens* [27].

**Anticancer**

Cancer is a global disease which severely affects the human population. Medicinal plants continue to provide discovery of new drugs that could be major leads against various pharmacological targets, particularly in cancer diseases. Approximately about 80% decrease in azoxymethane-induced aberrant crypt foci in rats preventing colon cancer when treated with ethanolic extract of *G. procumbens* [28]. It also inhibits the initial phase of carcinogenesis. Ethanolic extract of *G. procumbens* triggered a significant decrease in expression and activity of cytochrome P450 enzymes such as CYP3A4, CYP1A2, and CYP1A1 that may lead to drop in the conversion of the respective pre-carcinogens to cancer triggers [29].

In general, the blockade of angiogenesis pathways will result in inhibition of growth, invasion, and metastasis of tumor cells [30]. *G. procumbens* was shown to exhibit antiangiogenic activity as the treatment caused inhibition in the expression of vascular endothelial growth factor and prevented the formation of new blood vessels on fertilized chicken eggs [31,32]. Based on the reported studies, *G. procumbens* appears to be an effective chemotherapeutic agent against a wide range of cancer cell types, and it exerts its anticancer activities through the modulation of various points of carcinogenesis including cancer initiation, cell proliferation, metastasis, and angiogenesis. Cotreatment studies of *G. procumbens* and chemotherapy drugs also have been carried and reported good results. In an experiment, cotreatment of *G. procumbens* with other drugs such as doxorubicin or 5-fluorouracil lead to strong synergistic effect against breast and colon cancer cells [33-35]. However, in other cases, it showed an antagonistic effect when cotreatment of *G. procumbens* extract with cisplatin and failed to further suppress cancer cell proliferation [36]. In a recent experiment, extract of methanol, ethanol, and ethyl acetate were tested on U-87 cell line by MTT-based anti-proliferative assay. Results showed the high anti-proliferative effect on U-87 cell line of the methanol extracts of *G. procumbens* [37].

**Antimicrobial activity**

The antimicrobial activity of ethanolic extract of aerial plant parts has been established to show virucidal and antiproliferative activity against herpes simplex virus HSV-1 and HSV-2. This was confirmed in a clinical trial on patients with persistent herpes labialis where treatment with *G. procumbens* herbal gels reduced the number of patients infected with HSV. *G. procumbens* extract also exhibits chemo-suppression effects toward malarial parasite strains of *Plasmodium falciparum* 3D7 and Plasmodium berghei NK65 [38]. Other experiment showed that *G. procumbens* extract also used for antifungal activity against fungi such as *Candida albicans* and *Aspergillus niger*. The results showed evidence that validates the traditional use of *G. procumbens* in the treatment of infections by pathogens such as herpes simplex virus and malaria parasites [39,40]. The antiplasmodial activity of *G. procumbens* was also reported by Vejjan et al. [41].

**Anti-inflammatory**

*G. procumbens* is a folk medicine and has excellent anti-inflammatory activity [42]. When the ethanolic extract is tested, it showed significant dermal healing signs, less scar width, and considerable faster healing rate when compared with the control group treated with saline [43]. In an experiment, immunomodulatory activity of *G. procumbens* was tested using mice splenic cells. Ethanolic extract of *G. procumbens* at dose 0.1 and 1.0 mg/mL caused greater proliferation of CD4+CD25+, CD4+CD62L-, CD4+CD62L+, CD8+CD62L-, and CD8+CD62L+ T cells but lower proliferation of B220+ cells when compared to the higher dosage at 10 µg/mL. However, at dosage of 10 µg/mL, it was shown to promote high proliferation of B cells. These results have demonstrated that the concentration used in the experiment is the determining factor for whether *G. procumbens* acts as an immune stimulator immune suppressant [44,45].

**Wound healing enhancement activity**

Topical application of *G. procumbens* extract significantly accelerated the rate of wound healing, by increase regulation of collagen expression and promote angiogenesis [43,46]. Studies showed that antioxidants could play a significant role in the wound healing process and can be an important contributory factor in the wound healing property [47]. Antioxidants have been reported to show a significant role in the wound healing process and expressively improve wound healing and protect tissues from oxidative damage [46,49]. *G. procumbens* contain a wide array of free radical scavenging molecules and flavonoids were the major naturally occurring antioxidant components in this plant [50]. According to Akowuah et al. [51] flavonoids present in *G. procumbens* may be responsible for wound-healing activity because it lessens lipid peroxidation and promotes the strength of collagen fibers.

**Antioxidant activity**

The study showed that *G. procumbens* has excellent antioxidant property. In an experiment, different extracts of *G. procumbens* were assessed through DPPH assay to measure its free radical scavenging ability [52,53]. The ethanolic extract of *G. procumbens* exhibited the highest percentage of DPPH inhibition among different types of the extracts [54]. There are several antioxidant assays including ferric reducing assay, Trolox equivalent, β-carotene – linoleic acid, and xanthine oxidase inhibitory assays confirm the antioxidant property of *G. procumbens* [55]. Meanwhile, lipid peroxidation is a common result of oxidative stress; the antioxidative effect of *G. procumbens* was exposed when it inhibited lipid peroxidation with the median effective concentration of 2.75 mg/mL [56,57]. In addition, the administration of methanol extract before oxidative stress induction was able to reverse the elevation of plasma lipid peroxidation in tested animals [51]. Krishnan et al. [58] revealed that the root extract has the highest antioxidant activity when compared to the other parts of the plant.

**Organ protective effect**

Previous research on *G. procumbens* also showed gastroprotective effect. Mahmood et al. [46] reported that administration of the ethanolic extract significantly lessened the areas of ethanol-induced gastric ulcer in rats; with a reduction of submucosal edema and infiltration of leukocytes. This finding has intrigued the researchers to further explore the protective effect of *G. procumbens*. In another study on skin damage, the antiphotoaging property of *G. procumbens* has been tested and was found to cause a significant inhibition in the expression of matrix metalloproteinases induced by ultraviolet irradiation in human dermal fibroblasts [10]. The results obtained could be associated with ROS scavenging activity of *G. procumbens* extracts [54]. There are several antioxidant assays including ferric reducing assay, Trolox equivalent, β-carotene – linoleic acid, and xanthine oxidase inhibitory assays confirm the antioxidant property of *G. procumbens* [55]. Meanwhile, lipid peroxidation is a common result of oxidative stress; the antioxidative effect of *G. procumbens* was exposed when it inhibited lipid peroxidation with the median effective concentration of 2.75 mg/mL [56,57]. In addition, the administration of methanol extract before oxidative stress induction was able to reverse the elevation of plasma lipid peroxidation in tested animals [51]. Krishnan et al. [58] revealed that the root extract has the highest antioxidant activity when compared to the other parts of the plant.
Table 1: Important pharmacological activities of *G. procumbens*

| Activity                     | Type of extract                                        | Mode of action                                                                 | References |
|------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------|------------|
| Antihypertensive and cardioprotective | Methanolic leaf extract (Butanol fractions and subfractions) | It causes anti contraction activity on the left atrium by promoting relaxation. | [9]        |
|                              | Ethanolic leaf extract (Butanol fraction)              | It decreases mean arterial pressure and also decrease in heart rate in rats.  | [27]       |
|                              | Ethanolic leaf extract (Aqueous fraction)             | It reduces contraction of rat aortic ring by AngI and AngII. Potentiation of vasorelaxant effect and blood pressure dropping effect of bradykinin *in vivo*. | [19]       |
|                              | Ethanol extract (Aqueous fraction)                    | Lessened mean arterial pressure of hypertensive and normotensive rats as well as inhibition of ACE activity. | [57]       |
|                              | Ethanol extract (aqueous)                             | It causes vasorelaxation of isolated aorta, negative chronotropic effects in right atrium. | [18]       |
| Anticancer                   | Ethanolic leaf extract                                | It showed decreased total of azoxymethane induced aberrant in rats.          | [28]       |
|                              | Ethanolic leaf extract                                | It acts as repressed tumor incidence in DMBA treated rats.                    | [58]       |
|                              | Ethanolic leaf extract                                | It causes anti-proliferative effect on liver cells of rats prompted by DMBA.  | [59]       |
|                              | Ethanolic leaf extract                                | It acts to reduce the proliferation of mammary gland epithelial cells.         | [60]       |
|                              | Ethanol extract                                      | It shows decreased DMBA-induced breast cancer development in rats.            | [33]       |
|                              | Ethanol extract                                      | It causes blockade of VEGF receptor through inhibition of COX-2, tyrosine kinase, and MMP activity. | [32]       |
|                              | Ethanol extract                                      | It reduces COX-1 activity, tyrosine kinase, and MMP activity.                | [30]       |
|                              | Ethanol extract (ethyl acetate fraction)              | It acts to inhibit colon cancer cells proliferation and potentiated efficacy of 5-FU butantagonism effect with cisplatin. | [34]       |
| Anti-inflammatory            | Ethanolic leaf extract                                | Chick CAM embryo: Inhibition of angiogenesis                                   | [31]       |
|                              | Ethanolic leaf extract                                | T cells: Increased proliferation                                              | [43]       |
|                              | Ethanolic leaf extract                                | B cells: Decreased proliferation                                              | [42]       |
|                              | Ethanolic leaf extract                                | It causes to increase in T cells proliferation.                               | [41]       |
| Antihyperglycemic            | Aqueous leaf extract                                  | It causes high α-glucosidase inhibition activity, amplified activity of GK and PDH. | [61]       |
|                              | Ethanolic leaf extract (Ethyl acetate, n-butanol, aqueous) | It lowers fasting blood glucose levels in diabetic rats.                     | [62]       |
|                              | Ethanolic leaf extract                                | It causes fasting of blood glucose levels reduced in diabetic rats.           | [63]       |
|                              | Ethanolic leaf extract                                | Blood glucose level gets reduced; improve pancreatic islet condition, increased insulin expression. | [26]       |
| Antimicrobial                | Methanolic leaf extract and butanol fraction          | Fasting blood glucose levels get reduced in diabetic rats.                    | [64]       |
|                              | Dichloromethane, ethyl acetate fraction leaf extract  | Antibacterial activity against Gram-positive and Gram-negative bacteria, antifungal activity. | [3]        |
|                              | Ethanolic leaf extract and Aqueous extract            | Destroying growth of malarial parasites and upsurge survival time of infected mice. | [39]       |
|                              | Aerial ethanolic extract                              | Virucidal action against HSV-1 and HSV-2, reduced infection of HSV 1 in clinical trial patients with recurrent herpes labialis. | [36]       |

ACE: Angiotensin converting enzyme, DMBA: 7,12-dimethylbenz (a) anthracene, VEGF: Vascular endothelial growth factor, COX-2: Cylooxygenase-2, CAM: Chorioallantoic membrane, PDH: Pyruvate dehydrogenase, *G. procumbens*: Gynura procumbens

CONCLUSIONS

Herbal medicines have been used for various illnesses for many centuries. Due to better availability, affordable cost, and fewer side effects, they have immense potential. *G. procumbens* is one of the many species that are still left unexplored despite knowing the various medicinal values of this plant. *G. procumbens* can help prevent chronic disease or optimize health, therefore, reducing health-care costs and improving the quality of life. A study on this plant which is being consumed is only an approach of “drug rediscovery.” In view of all the above facts, *G. procumbens* should be extensively explored with modern scientific approaches to identify its nutritional effects. The plant *G. procumbens* has the potential to develop a drug against various diseases.

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AUTHOR CONTRIBUTION

Kamran Ashraf participates in data collection, drafting and revising it critically for important intellectual content.

CONFLICTS OF INTEREST

The author have none to declared.
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