ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 12, Issue 4, 2019

Online - 2455-3891
Print - 0974-2441

Review Article

AN UPDATED PHYTOCHEMICAL AND PHARMACOLOGICAL REVIEW ON *GYNURA PROCUMBENS*

KAMRAN ASHRAF[1,2]*

[1]Department of Pharmacology and Chemistry, Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia. [2]Atta-ur-Rahman Institute for Natural Products Discovery (AuRIns), Universiti Teknologi MARA, Puncak Alam Campus, Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia. E-mail: kamranashraf2@gmail.com

Received: 08 August 2018, Revised and Accepted: 29 October 2018

ABSTRACT

Nowadays, the use of medicinal plants increased significantly for the aim of producing more effective drugs with fewer side effects. *Gynura procumbens* (family Asteraceae) is a high value medicinal plant with different properties that are considered less, regardless of having great therapeutic potential in traditional medicine. Many pharmacological studies have established the ability of this plant to exhibit antimicrobial, antioxidant, hepatoprotection, antigenotoxic, antiplasmodial, cytotoxic, cardioactive, antidiabetic, anti-inflammatory, etc. The aim of this study was to review the updated phytochemical, pharmacological investigations as well as the traditional and therapeutic uses of *G. procumbens*. Important and different experimental data have been addressed along with a review of most of the phytochemicals identified in this plant.

Keywords: *Gynura procumbens*, Medicinal plant, Phytochemical, Pharmacological.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i4.28996

INTRODUCTION

Gynura procumbens belongs to family Asteraceae is a fast growing evergreen herb. In Malay, *G. procumbens* is called Sambung nyaw*a* 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, constipation, 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-dicaffeoilquinate methyl ester, terpenoid, tannin, alkaloid, saponin, and astragalinin (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 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.

Kaewseejan *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 CHCOOH 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

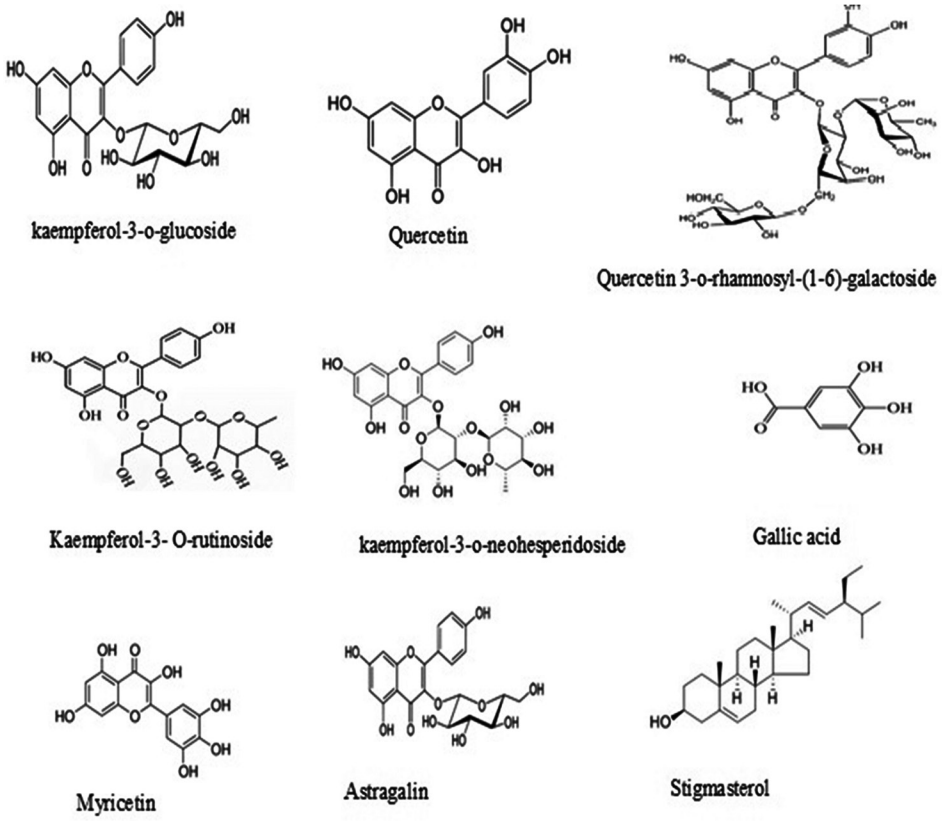

Fig. 1: Some of the important chemical constituents found in *G. procumbens*

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-Orutinosida, 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, CH2, and CH3 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 tropic 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 effects 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 procarcinogens 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 antireplicative 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 Vejanan *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 μg/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 [48,49]. *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 fibroflasts [10]. The results obtained could be associated with ROS scavenging activity of *G. procumbens* [46]**.** The details of most of the pharmacological activities of *G. procumbens* have shown in Table 1. A similar type of study and data collection was also done in previous research papers [64-67].

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 aorticring by AngI and AngII. Potentiation of vasorelaxant effect and blood pressure dropping effect of bradykinin *in vivo*.	[19]
	Ethanolic leaf extract (Aqueous fraction)	Lessened mean arterial pressure of hypertensive and normotensiverats as well as inhibition of ACE activity.	[57]
	Ethanolic leaf extract (aqueous)	It causes vasorelaxation of isolated aorta, negative ionotropic effects in the left atrium, negative chronotropic effect 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 as 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]
	Ethanolic leaf extract	It shows decreased DMBA-induced breast cancer development in rats.	[33]
	Ethanolic leaf extract	It causes blockade of VEGF receptor through inhibition of COX-2, tyrosine kinase, and MMP activity.	[32]
	Ethanolic leaf extract	It reduces COX-1activity, tyrosine kinase, and MMP activity.	[30]
	Ethanolic leaf extract (ethyl acetate fraction)	It acts to inhibit colon cancer cells proliferation and potentiated efficacy of 5-FUbutantagonism effect with cisplastin.	[34]
	Ethanolic leaf extract	Chick CAM embryo: Inhibition of angiogenesis	[31]
Anti-inflammatory	Ethanolic leaf extract	T cells: Increased proliferation B cells: Decreased proliferation.	[43]
	Ethanolic leaf extract	It causes to increase in T cells proliferation.	[42]
	Ethanolic leaf extract	It enhanced wound healing rate: Less inflammatory cells at granulation tissue, more collagen with angiogenesis.	[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 indiabetic 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]
	Methanolic leaf extract and butanol fraction	Fasting blood glucose levels get reduced indiabetic rats.	[64]
Antimicrobial	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 againstHSV-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: Cyclooxygenase-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.

ACKNOWLEDGMENT

Kamran Ashraf would like to acknowledge Universiti Teknologi MARA for the financial support under the reference number 600-IRMI/MyRA 5/3/LESTARI (079/2017).

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.

REFERENCES

1. Yam MF, Sadikun A, Asmawi MZ, Rosidah. Antioxidant potential of *Gynura procumbens*. Pharm Biol 2008;46:616-25.
2. Keng CL, Yee LS, Pin PL. Micropropagation of *Gynura procumbens* (Lour.) Merr. An important medicinal plant. J Med Plants 2009;3:105-11.
3. Rahman AF, Asad MS. Chemical and biological investigations of the leaves of *Gynura procumbens*. Int J Biosci 2013;3:36-43.
4. Abidin ZZ, Mohamad WN, Samad M. Optimization of chlorophyll extraction from *Gynura procumbens*. Malays J Anal Sci 2016;6:1421-8.
5. Tan HL, Chan KG, Pusparajah P, Lee LH, Goh BH. *Gynura procumbens*: An overview of the biological activities. Front Pharmacol 2016;7:52.
6. Kaewseejan N, Sutthikhum V, Siriamornpun S. Potential of *Gynura procumbens* Leaves as source of flavonoid-enriched fractions with enhanced antioxidant capacity. J Funct Foods 2015;12:120-8.
7. Saeed MA, Meng K, Sadikun A, Murugaiyah V, Asmawi M, Ismail Z. Stability study of *Gynura procumbens* extracts using high performance liquid chromatography. J Pharm Res 2014;8:822-7.
8. Hoe SZ, Lee CN, Mok SL, Kamaruddin MY, Lam SK. *Gynura procumbens* Merr. Decreases blood pressure in rats by vasodilatation via inhibition of calcium channels. Clinics 2011;66:143-50.
9. Abrika OS, Yam MF, Asmawi MZ, Sadikun A, Dieng H, Hussain EA, *et al*. Effects of extracts and fractions of *Gynura procumbens* on rat atrial contraction. J Acupunct Meridian Stud 2013;6:199-207.
10. Kim J, Lee CW, Kim EK, Lee SJ, Park NH, Kim HS, *et al*. Inhibition effect of *Gynura procumbens* extract on UV-B-induced matrix-metalloproteinase expression in human dermal fibroblasts. J Ethnopharmcol 2013;137:427-33.
11. Wan C, Yu Y, Zhou S, Tian S, Cao S. Isolation and identification of phenolic compounds from *Gynura divaricata* Leaves. Pharmacogn Mag 2011;7:101-8.
12. Jegadeeswari P, Daffodil ED, Mohan VR. Quantification of total phenolics, flavonoid and *in vitro* antioxidant activity of *Aristolochia bracteata* Retz. Int J Pharm Pharm Sci 2014;6:747-52.
13. Rosidah, Yam MF, Sadikun A, Ahmad M, Akowuah GA, Asmawi MZ, *et al*. Toxicology evaluation of standardized methanol extract of *Gynura procumbens*. J Ethnopharmacol 2009;123:244-9.
14. Liu W, Yu Y, Yang R, Wan C, Xu B, Cao S, *et al*. Optimization of total flavonoid compound extraction from *Gynura medica* Leaf using response surface methodology and chemical composition analysis. Int J Mol Sci 2010;11:4750-63.
15. Choi SI, Park MH, Han JS. *Gynura procumbens* extract alleviates postprandial hyperglycemia in diabetic mice. Prev Nutr Food Sci 2016;21:181-6.
16. Saiman MZ, Mustafa NR, Schulte AE, Verpoorte R, Choi YH. Induction, characterization, and NMR-based metabolic profiling of adventitious root cultures from leaf explants of *Gynura procumbens*. Plant Cell Tissue Organ Cult 2012;109:465-75.
17. Hoe SZ, Lee CN, Mok SL, Kamaruddin MY, Lam SK. *Gynura procumbens* Merr. Decreases blood pressure in rats by vasodilatation via inhibition of calcium channels. Clinics 2011;66:143-50.
18. Kaur N, Kumar R, Yam MF, Sadikun A, Sattar AM, Asmawi MZ. Antihypertensive effect of *Gynura procumbens* water extract in spontaneously hypertensive rats. Int J Appl Res Nat Prod 2013;6:20-7.
19. Poh TF, Ng HK, Hoe SZ, Lam SK. *Gynura procumbens* causes vasodilation by inhibiting angiotensin II and enhancing bradykinin actions. J Cardiovasc Pharmacol 2013;61:378-84.
20. Akmara KK, Mahanem MN. Profertility and antidiabetic properties of *Gynura procumbens* on streptozotocin induced male rats. AIP Conf Proc 2016;1784:020027.
21. Hamid M, Saufi M, Musaadah NM. Study on antidiabetic properties of *Gynura procumbens* Merr. In 18 Seminar of the Malaysian Natural Products Society (Kota Kinabalu: Universiti Malaysia Sabah); 2004.
22. Hassan Z, Ahmed M, Yosof P, Naidu S, Kumar G, Umachigi S. Hypoglycemic effect of aqueous extract of *Gynura procumbens*. Pharmacologyonline 2008;1:30-50.
23. Lee HW, Hakim P, Rabu A, Sani HA. Antidiabetic effect of *Gynura procumbens* Leaves extracts involve modulation of hepatic carbohydrate metabolism in streptozotocin-induced diabetic rats. J Med Plants Res 2012;6:796-812.
24. Bohari M, Pauliena S, Hamid M, Shaari K, Lajis N. Glucose uptake: Stimulatory activity of *Gynura procumbens* in 3T3-F442A adipocytes. In: Malaysian Medicinal Plant: Chemistry and Biological Activity. Sarawak: UNIMAS and Malaysian Natural Products Society; 2006.
25. Hassan Z, Yam MF, Ahmad M, Yusof AP. Antidiabetic properties and mechanism of action of *Gynura procumbens* water extract in streptozotocin-induced diabetic rats. Molecules 2010;15:9008-23.
26. Pramono S, Nugroho A. Effect of herbal combination of *Andrographis paniculata* (Burm. f) Ness and *Gynura procumbens* (Lour.) Merr ethanolic extracts in alloxan-induced hyperglycemic rats. Int Food Res J 2015;22:1332-7.
27. Sunarwidhi AL, Sudarsono S, Nugroho AE. Hypoglycemic effect of combination of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Lour.) Merr. Ethanolic extracts standardized by rutin and quercetin in alloxan induced hyperglycemic rats. Adv Pharm Bull 2014;4:613.
28. Shwter AN, Abdullah NA, Alshawsh MA, Alsalahi A, Hajrezaei M, Almaqrami AA, *et al*. Chemoprevention of colonic aberrant crypt foci by *Gynura procumbens* in rats. J Ethnopharm 2014;151:1194-201.
29. Afandi A, Sadikun A, Ismail S. Antioxidant properties of *Gynura procumbens* extracts and their inhibitory effects on two major human recombinant cytochrome P450s using a high throughout luminescence assay. Asian J Pharm Clin Res 2014;7:36-41.
30. Ghofur A, Hamid IS, Listyorini D. Anti-carcinogenic activity of *Gynura procumbens* extract through cytochrome P450 and glutathione stransferase. Int J PharmTech Res 2015;8:24-9.
31. Hamid IS, Wati WK, Mustofa I, Plumeriastuti H. Activity test of *Gynura procumbens* Leaves extract as antiangiogenic on chick embryo chorioallantoic membrane induced by basic fibroblast growth factor (bFGF). Vet Med 2011;4:105-10.
32. Jenie RI, Meiyanto E, Murwanti R. Antiangiogenic effect of Sambung nyawa leaves (*Gynura procumbens* (Lour.) Merr.) Ethanolic extract on chick embryo chorioallantoic membrane (CAM). Indones J Pharm 2006;17:50-5.
33. Hamid I, Dewi R, Nazar D, Ratnani H. Effectivity of *Gynura procumbens* extract to inhibit vascular endothelial growth factor (VEGF) expression on new blood vessels of chorioallantoismembran (CAM) chicken embryonal. Vet Med 2013;6:27-32.
34. Meiyanto E, Jenie RI. Co-chemotherapy of sambungnyawa (*Gynura procumbens* (Lour.) Merr.) Leaves ethanolic extract and doxorubicin on breast cancer cell. Indones J Pharm 2007;18:81-7.
35. Nurulita NA, Meiyanto E, Matsuda E, Kawaichi M. *Gynura procumbens* modulates the microtubules integrity and enhances distinct mechanism on doxorubicin and 5-flurouracil-induced breast cancer cell death. Orient Pharm Exp Med 2012;12:205-18.
36. Nurulita NA, Meiyanto E, Sugiyanto S, Matsuda E, Kawaichi M. The ethyl acetate fraction of *Gynura procumbens* sensitizes widr colon cancer cell line against 5-fluorouracil but shows antagonism with cisplatin. Int J Phytomed 2011;3:392-405.
37. Rohin MA, Jumli MN, Ridzwan N, Baig AA, Latif AZ, Hadi NA. Effects of *Gynura procumbens* extracts on anti-proliferative activity and its associated morphological changes of human glioblastoma multiforme cell line (U-87). Pharmacogn J 2018;10:492-6.
38. Jarikasem S, Charuwichitratana S, Siritantikorn S, Chantratita W, Iskander M, Frahm AW, *et al*. Antiherpetic effects of *Gynura procumbens*. Evid Based Comp Alt Med 2013;2013:394865.
39. Kaewseejan N, Sutthikhum V, with enhanced antioxidant capacity. J Funct Foods 2015;12:120-8.
40. Nasir NN, Khandaker MM, Mat N. Bioactive compound and therapeutic value of some Malaysia medicinal plants: A review. J Agron 2015;14:319-30.
41. Vejanan V, Latip J, Chin LP, Embi N, Sidek HM. *In vitro* and *in vivo* anti-plasmodial activities of *Gynura procumbens*. Sains Malays 2012;41:1535-42.
42. Wiart C. Medicinal Plants of Asia and the Pacific. Boca Raton, FL: CRC Press.
43. Zahra AA, Kadir FA, Mahmood AA, Al Hadi AA, Suzy SM, Sabri SZ, *et al*. Acute toxicity study and wound healing potential of *Gynura procumben*s Leaf extract in rats. J Med Plant Res 2011;5:2551-8.
44. Dwijayanti DR, Rifa'i M. Immunomodulator testing on ethanol extract of *Gynura procumbens* Leaves to *Mus musculus* adaptive immune system: *In vitro* study. J Exp Life Sci 2014;4:10-4.
45. Dwijayanti DR, Riffs M. *Gynura procumbens* ethanolic extract promotes lymphocyte activation and regulatory T cell generation *in vitro*. J Trop Life Sci 2015;5:14-9.
46. Mahmood A, Mariod AA, Al-Bayaty F, Abdel-Wahab SI. Anti-ulcerogenic activity of *Gynura procumbens* Leaf extract against experimentally-induced gastric lesions in rats. J Med Plants Res 2010;4:685-91.
47. Habibipour S, Oswald TM, Zhang F, Joshi P, Zhou XC, Dorsett MW, *et al*. Effect of sodium diphenylhydantion on skin wound healing in rats. Plast Reconstr Surg 2003;112:1620-7.
48. Shukla A, Rasik AM, Dhawan BN. Asiaticoside-induced elevation of antioxidant levels in healing wounds. Phytother Res 1999;13:50-4.
49. Getie M, Gebre-Mariam T, Rietz R, Neubert RH. Evaluation of the

release profiles of flavonoids from topical formulations of the crude extract of the leaves of *Dodonea viscosa* (Sapindaceae). Pharmazie 2002;57:320-2.
50. Martin A. The use of antioxidants in healing. Dermatol Surg 1996;22:156-60.
51. Akowuah G, Ahmad M, Fei YM. Effects of *Gynura procumbens* Leaf extracts on plasma lipid peroxidation and total antioxidant status in CCl4-treated rats. Nat Prod J 2012;2:247-51.
52. Akowuah GA, Mariam A, Chin JH. The effect of extraction temperature on total phenols and antioxidant activity of *Gynura procumbens* Leaf. Pharmacogn Mag 2009;4:81-5.
53. Afandi A, Sadikun A, Ismail S. Antioxidant properties of *Gynura procumbens* extracts and their inhibitory effects on two major human recombinant cytochrome P450s using a high throughout luminescence assay. Asian J Pharm Clin Res 2014;7:36-41.
54. Maw SS, Mon MM, OO ZK. Study on antioxidant and antitumor activities of some herbal extracts. World Acad Sci Eng Technol 2011;75:450-5.
55. Rosidah, Yam M, Sadikun A, Asmawi M. Antioxidant potential of *Gynura procumbens*. Pharm Biol 2008;46:616-25.
56. Luerang A, Thammasarn K, Sittiwet C, Naowaratwattana W, Chaichanadee S, Puangpronpitag D, *et al*. Evaluation of nutritional value and antioxidative properties of the medicinal plant *Gynura procumbens* extract. Asian J Plant Sci 2010;9:146-51.
57. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. Sci World J 2013;2013:16.
58. Krishnan V, Ahmad S, Mahmood M. Antioxidant potential in different parts and callus of *Gynura procumbens* and different parts of gynura bicolor. Biomed Res Int 2015;2015:1-7.
59. Hoe SZ, Lam SK. Hypotensive activity of an aqueous fraction of *Gynura procumbens* and possible mechanisms of action (hypertension, basic 1 (H), The 69th annual Scientific meeting of the Japanese circulation society). Circ J 2005;69:348.
60. Gofur A, Hamid IS, Listyorini D. Gene p53 mutations after the induction of 7,12-dimethylbenz(a)anthracene (DMBA) and administration of anti-carcinogenesis properties of *Gynura procumbens* in sprague dawley rats. Biomed Eng 2015;1:53-7.
61. Nisa F, Hermawan A, Murwanti R, Meiyanto E. Antiproliferative effect of *Gynura procumbens* (lour.) Merr. Leaves etanolic extract on 7,12dimethylbenz(a)antracene induced male rat liver. Adv Pharm Bull 2012;2:99-106.
62. Hamid IS, Meiyanto E, Widyarini S. CYP1A1and GSTμexpression of hepatocytes induced by 7,12-dimethylbenz(a)anthracene and the influence of ethanolic extract of *Gynura procumbens*. Indones J Pharm 2009;20:198-206.
63. Kang YH, Kim TW, Kim KK, Choe M. Effect of *Gynura procumbens* water extract on enzymes activities related with glucose metabolism in HepG2 cell. FASEB J 2015;29:730.
64. Algieri K, Atangwho IJ, Meng KY, Asmawi MZ, Sadikun A, Murugaiyah V. Antihyperglycaemic and toxicological evaluations of extract and fractions of *Gynura procumbens* Leaves. Trop Life Sci Res 2014;25:75-93.
65. Algariri K, Meng KY, Atangwho IJ, Asmawi MZ, Sadikun A, Murugaiyah V, *et al*. Hypoglycemic and anti–hyperglycemic study of *Gynura procumbens* Leaf extracts. Asian Pac J Trop Biomed 2013;3:358-66.
66. Akowuah G, Sadikun A, Mariam A. Flavonoid identification and hypoglycaemic studies of the butanol fraction from *Gynura procumbens*. Pharm Biol 2002;40:405-10.
67. Ashraf K, Sultan S. Comprehensive review on *Curcuma longa* Linn.: Phytochemical, pharmacological and molecular study: A review. Int J Green Pharm 2017;11:1-15.
68. Ashraf K, Sultan S, Ali SA. Phychemistry, phytochemical, pharmacological and molecular study of *Zingiber officinale* Roscoe: A review. Int J Pharm Pharm Sci 2017;9:8-16.
69. Pujiyanto S, Lestari Y, Suwanto A, Budiarti S, Darusman LK. Alpha-glucosidase inhibitor activity and characterization of endophyticactinomycetes isolated from some Indonesian diabetic medicinal plants. Int J Pharm Pharm Sci 2012;4:327-33.