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Review Article

Ethnomedicinal uses, phytochemistry, and biological activity of plants of the genus *Gynura*

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ABSTRACT

Ethnopharmacological relevance: The genus *Gynura* (Compositae) includes around 46 species and is native to the tropical regions of Southeast Asia, Africa and Australia. Many species within this genus are used in ethnomedicine to treat various disorders including skin diseases, injuries, ulcers, wounds, burns, sores, scalds, as well as for the management of diabetes, hypertension, hyperlipidemia, constipation, rheumatism, bronchitis and inflammation.

Aim of the review: This review is an attempt to provide scientific information regarding the ethnopharmacology, phytochemistry, pharmacological and toxicological profiles of *Gynura* species along with the nomenclature, distribution, taxonomy and botanical features of the genus. A critical analysis has been undertaken to understand the current and future pharmaceutical prospects of the genus.

Materials & methods: Several electronic databases, including Google scholar, PubMed, Web of Science, Scopus, ScienceDirect, SpringerLink, Semantic Scholar, MEDLINE and CNKI Scholar, were explored as information sources. The Plant List Index was used for taxonomical authentications. SciFinder and PubChem assisted in the verification of chemical structures.

Results: A large number of phytochemical analyses on *Gynura* have revealed the presence of around 342 phytoconstituents including pyrrolizidine alkaloids, phenolic compounds, chromanones, phenylpropanoid glycosides, flavonoids, flavonoid glycosides, steroids, steroidal glycosides, cerebrosides, carotenoids, triterpenes, mono- and sesquiterpenes, norisoprenoids, oligosaccharides, polysaccharides and proteins. Several *in vitro* and *in vivo* studies have demonstrated the pharmacological potential of *Gynura* species, including antidiabetic, anti-oxidant, anti-inflammatory, antimicrobial, antihypertensive and anticancer activities. Although the presence of pyrrolizidine alkaloids within a few species has been associated with possible hepatotoxicity, most of the common species have a good safety profile.

Conclusions: The importance of the genus *Gynura* both as a prominent contributor in ethnomedicinal systems as well as a source of promising bioactive molecules is evident. Only about one fourth of *Gynura* species have been studied so far. This review aims to provide some scientific basis for future endeavors, including in-depth biological and chemical investigations into already studied species as well as other lesser known species of *Gynura*.

Keywords: *Gynura* species; compositae; ethnomedicinal uses; phytochemistry; phenolic compounds; pharmacological activity.

1. Introduction

The current number of vascular and flowering plants is estimated to be around 350,000 and 325,000, respectively. To date, only 25,791 of these plants (roughly less than 8%) have been recorded for their medicinal uses (Antonelli et al., 2020). Medicinal plants are known to produce a variety of bioactive phytochemicals that represent structurally-unique building blocks for the development of new drugs (Feher and Schmidt, 2003; McChesney, 1996; Swanson, 1998). This process of drug discovery commonly involves the biological screening of plant extracts and phytochemicals using *in vitro* and animal models (Bindseil et al., 2001; Kähkönen et al., 1999). The beneficial health effects of plants and their constituents are also valuable when used as functional foods, including in the management of chronic conditions (e.g. diabetes, hypertension and cancer) that also require a more diet-based treatment approach (Hemler and Hu, 2019).

The genus *Gynura* (Compositae) comprises 46 species widely distributed from tropical Africa to Australia and Southeast Asia, where the maximum diversity within this genus is found (The Plant List, 2013; Vanijajiva, 2009). From a botanical point of view, the presence of appendages to the style arms and of a basal tuber is a distinctive feature for this genus (Davies, 1980a). Phytochemical analyses of *Gynura* species have revealed the presence of diverse constituents including alkaloids, phenolic compounds (especially quinic acid derivatives), flavonoids, steroids, glycosides and terpenoids (Chandradevan et al., 2020; Do et al., 2020). Several *Gynura* spp. are used for culinary purposes and/or employed in traditional medicine for the treatment of migraine, fever, rashes, inflammation, rheumatism, herpes, constipation, hypertension, hemostasis, kidney disease, diabetes mellitus and cancer (Do et al., 2020; Hong et al., 2020; Lu et al., 2012; Xian and Juxian, 2002). The long historical use of consuming *Gynura* species, combined with their oral safety and their broad variety of phytochemicals, suggest that they are invaluable functional foods. This review aims to report on the ethnomedicinal uses of *Gynura* spp., and on previous phytochemical and biological studies on these species as a starting point for future work on this genus.

2. Methodology

An extensive literature search using the Google Scholar and PubMed databases was conducted to retrieve the information relevant to this review. The main keywords for the search were "*Gynura"*, "*Gynura* species", "ethnopharmacology", "ethnobotany", "chemical constituents", "phytoconstituents", "biological activity", "pharmacological activity" and "toxicology". The Web of Science, ScienceDirect, SciFinder, Scopus, Semantic Scholar, MEDLINE and CNKI Scholar were also used to collect the information. Our search yielded a total of 115 *Gynura*-related articles published between 1977-2020 in peer-reviewed journals worldwide. These articles were studied in detail in order to evaluate the authenticity and relevance of their data during the compilation and synthesis of information. Wherever appropriate, the data collected from the selected articles included the names of the authors, the plant species reported, the plant part(s) studied, the phytochemicals isolated from the species, the pharmacological investigations on each of the plant extract, the types of experiment conducted, the dose/concentration at which the experiment was performed, and the information related to toxicity studies. The retrieved information was categorized according to each subheading and described in detail. The Plant List (version 1.1, 2013) was used to confirm the identity of the *Gynura* species described in this review. All the chemical structures were validated with SciFinder and PubChem and drawn using ChemDraw Ultra 15.0.

3. Taxonomy and Distribution

The Compositae (also known as Asteraceae) family represents the largest family of angiosperms classified under the Magnoliopsida class and the Asterales order. The family covers over 27,773 species distributed under nearly 1,765 genera (The Plant List, 2013). The family name is derived from the composite arrangement of the flowers, which is a distinctive trait of the plants of this family. Except for the arctic regions, the family is widely distributed worldwide, especially in tropical and subtropical areas (Panero and Crozier, 2012; Stevens, 2001). The genus *Gynura* Cass. is well known for both its culinary and medicinal uses. Around 193 species ranks have been listed under this genus, among which 46 are accepted plant names (*i.e.*, the scientific name that should be preferably employed to identify the species) and another 125 names are synonymous (*i.e.*, recognized alternative names for plants for which accepted names have already been established) with different accepted names within the genus (The Plant List, 2013). Notably, accepted or synonymous plant names include the original author

name(s), original publication resource(s), and the International Plant Names Index (IPNI) identifier (The Plant List, 2013). The genus mainly includes herbs and subshrubs along with a few climbers and is distributed within the tropical regions of Asia, Africa and Australia. Plants generally have vertical or decumbent stems and fibrous or tuberous roots. The simple and alternately arranged leaves are characterized by an apiculate to acuminate apex, a cuneate, truncate or obtusely rounded base, along with some entire, crenate, minutely denticulate to coarsely dentate margins. Both the stems and leaves are of fleshy to succulent nature. The inflorescences termed as capitula comprise of homogamous florets which are arranged on a disc-like receptacle of flat, glabrous or epaleate shape along with eight to eighteen phyllaries. The florets commonly appear as yellow to orange, red or purple in some species. Within each flower, there are five stamens with linear anthers and two styles with branched, tapered style arms (Davies, 1980b, 1979, 1978; Vanijajiva, 2009). The complete taxonomical classification of the genus is provided given below (Classification for Kingdom Plantae Down to Genus *Gynura* Cass., 2013);

- Kingdom: Plantae (Plants)
- Subkingdom: Tracheobionta (Vascular plants)
- Superdivision: Spermatophyta (Seed plants)
- Division: Magnoliophyta (Flowering plants)
- Class: Magnoliopsida (Dicotyledons)
- Subclass: Asteridae
- Order: Asterales
- Family: Compositae/Asteraceae
- Genus: *Gynura* Cass.

4. Ethnomedicinal uses

Several *Gynura* spp. have a long history of use in traditional ethnomedicine to treat a range of ailments in Africa, Australia, Papua New Guinea, Nepal, Bhutan, Japan, China, Taiwan, India, Bangladesh, and countries in the Southeast Asian regions including Indonesia, Malaysia, Philippines, Myanmar (Burma), Thailand, and Vietnam. The individual ethnomedicinal uses of the main *Gynura* spp. are summarised in **Table 1**.

5. Chemical constituents

Gynura species are rich in pyrrolizidine alkaloids as well as phenolic and flavonoid constituents. A wide array of phenolic and flavonoid glycosides has also been isolated from the genus. Steroids, steroidal glycosides, carotenoids, triterpenes, sesquiterpenes, monoterpenes, oligosaccharides, polysaccharides, peptides, and several proteins have also been reported from *Gynura*. A comprehensive overview of the bioactive secondary metabolites isolated from *Gynura* spp. along with their sources and biological properties are discussed below and summarised in **Table 2** and **Figure 1-16**.

5.1. Pyrrolizidine alkaloids

Several *Gynura* spp. contain some ester-type pyrrolizidine alkaloids (PAs) which cause hepatotoxicity *in vivo*. The structure of these alkaloids features necine base, with two pentacylic rings fused together with a tertiary nitrogen atom as bridgehead (Fioeoen, 2000). Depending on the presence of unsaturation within the necine base and the oxidation state of the base, PAs are classified as the retronecine-type, otonecine-type and platynecine-type. Both the retronecine- and otonecine-type PAs contains a 1,2-double bond in the necine base and are hepatotoxic. The otonecine-type PAs differ from the retronecine-type by the presence of oxidation in the bridging carbon of the ring resulting in an octacyclic ring instead of fused pentacylic moieties. The platynecine-type PAs consist of a saturated necine base and are generally non-toxic or less toxic (Zhu et al., 2016). A total of twenty-six retronecine-type **(1-26)**, one otonecine-type **(27)** and three platynecine-type PAs **(28-30)**, have been isolated from *Gynura* spp. **(Figure 1)**. Senecionine **(6)** is the most abundant PA among different species including *G. bicolor* (Chen et al., 2017), *G. divaricata* (Chen et al., 2017), *G. elliptica* (Lin et al., 2000), *G. japonica* (Fang et al., 2014), *G. pseudochina* (Windono et al., 2012) and *G. segetum* (Liang and Roeder, 1984; Qi et al., 2009; Yang et al., 2009). The whole plant of *G. segetum* contains a maximum of sixteen PAs **(1-4, 6, 8, 9, 12, 15, 18, 22-26, 28)**. Eleven PAs **(6, 8, 9, 12, 14, 16, 18-22)** were isolated from the roots of *G. japonica* (Fang et al., 2014; Qi et al., 2009).

5.2. Phenolic compounds

Eight benzoic acid derivatives **(31-38)**, four cinnamic acid derivatives **(39-42)**, nine other phenolic constituents **(43-51) (Figure 2)** as well as twenty quinic acid derivatives **(52-71)** have been isolated from *Gynura* spp. Among the quinic acid derivatives, there are four mono-

substituted coumaroylquinic acids **(52-55)** and three mono-substituted feruloylquinic acid moieties **(69-71)**. Thirteen caffeoylquinic acid (chlorogenic acid) derivatives **(56-68)** reported from the genus include mono- and di-substituted caffeoylquinic acid moieties as well as methyl or ethyl esters of those acids **(Figure 3)**. With twenty-nine compounds **(31-33, 35, 37-41. 47. 50, 51, 52-64, 67, 69-71)**, *G. bicolor* has the highest number of phenolic constituents (Chao et al, 2015; Chen et al., 2015; Teoh et al., 2016). Chlorogenic acid **(56)** is the most abundant phenolic compound distributed among the species *G. bicolor* (Chao et al., 2015; Chen et al., 2015; Teoh et al., 2016), *G. divaricata* (Chen et al., 2015), *G. medica* (Tan et al., 2013), *G. nepalensis* (Yu et al., 2016), *G. procumbens* (Kaewseejan and Siriamornpun 2015) and *G. pseudochina* (Sukadeetad et al., 2018).

Four compounds **(72-75)**, isolated from the underground parts of *G. japonica* (Lin et al, 2003) and *G. elliptica* (Lin et al., 2000), bear the basic chromanone moiety in their structure **(Figure 4)**. Ten phenylpropanoids glycosides **(76-84)** have also been reported from the aerial parts of *G. cusimbua* (Ma et al., 2019) **(Figure 5)**. Multiple phenolic constituents including a caffeoyl group constitute the aglycone parts of these glycosides.

5.3. Flavonoids

Phytochemical investigations of *Gynura* spp. have revealed the presence of four flavones **(86-89)**, two flavanones **(90-91)**, two flavan-3-ols **(92-93)** and five anthocyanidins **(94-98)** **(Figure 6)**. Fourteen flavonoid glycosides **(99-112)** have also been reported **(Figure 7)**. The aglycone parts of these glycosides include eleven flavones **(99-109)** bonded to one or two monosaccharides or one disaccharide through *O*-glycosidic bonds, one flavone connected to a glucose moiety through a *C*-glycosidic linkage **(110)** as well as one flavanone **(111)** and one anthocyanidin **(112)** moieties with *O*-glycosidic linkages. Eleven flavonoids **(86-90, 93-98)** and eight flavonoid glycosides **(99-102, 106, 107, 109, 112)** have been isolated from *G. bicolor* (Chao et al, 2015; Chen et al., 2015; Teoh et al., 2016). Rutin **(107)** is distributed among the highest number of species including *G. bicolor* (Chao et al., 2015; Chen et al., 2015; Teoh et al., 2016), *G. divaricata* (Chen et al., 2009a; Chen et al., 2015; Wan et al., 2011b), *G. calciphila* (Anurukvorakun, 2013), *G. formosana* (Hou et al., 2005), *G. medica* (Liu et al., 2010; Tan et al., 2013), *G. procumbens* (Akowuah et al., 2002; Kaewseejan and Siriamornpun 2015), *G. pseudochina* (Siriwatanametanon and Heinrich, 2011; Sukadeetad et al., 2018) and *G. segetum* (Yuandani and Husain 2017).

5.4. Steroids

Twenty steroidal aglycones **(113-132) (Figure 8)** and seven steroidal glycosides **(133-139) (Figure 9)** have been reported from *Gynura* species. The most abundant steroids, β-sitosterol and β-stigmasterol, are present in *G. japonica* (Lin et al., 2003; Takahira et al., 1977), *G. segetum* (Zhu et al., 2013), *G. procumbens* (Hu et al., 2019; Rahman and Asad, 2013; Sadikun et al., 1996) and *G. pseudochina* (Gultom, 2016). All steroidal aglycones and glycosides, except for one **(123)**, have been isolated from the underground parts viz. rhizomes and roots of *G. japonica* (Lin et al., 2003; Takahira et al., 1977).

5.5. Cerebrosides

Cerebrosides are condensation products of long chain fatty hydroxy amines and fatty acids. Four cerebrosides **(140-144)** have been reported from the rhizomes of *G. japonica* (Lin et al., 2004) and one **(144)** from the aerial parts of *G. japonica* (Zhu et al., 2013). They all contained α-hydroxy amines connected to α-hydroxy acids by amide linkage. A glycosidic derivative **(145)** has also been isolated from the aerial parts of *G. divaricata* (Chen et al., 2009b) **(Figure 10)**.

5.6. Terpenoids

Two triterpenes, named lutein **(146)** and zeaxanthin **(147),** have been isolated from the leaves of *G. bicolor* [30,47] **(Figure 11)**. Eleven triterpenes **(148-158)** have been isolated from the aerial parts of *G. segetum* and the rhizomes of *G. japonica* (Lin et al., 2004; Lin et al., 2003) **(Figure 12)**. Several mono- and sesquiterpenes, of both non-volatile and volatile nature, have also been reported from *Gynura* species. Eight non-volatile mono- and sesquiterpenes **(159-166)** have been identified in the aerial parts of *G. bicolor* (Chen et al., 2012b) and *G. procumbens* (Zhang et al., 2014) **(Figure 13)**. Eighty-nine volatile constituents **(167-255)** from various *Gynura* spp. **(Figure 14)** have been detected using gas chromatography-mass spectrometry (GC-MS) and gas chromatography-flame ionization detector (GC-FID) techniques (Chen et al., 2012a; Jiangseubchatveera et al., 2015; Lin et al., 2003; Lin et al., 2000; Rana and Blazquez, 2007; Shimizu et al., 2009). Four megastigmane-type norisoprenoids **(256-259)** have been isolated from the aerial parts of *G. bicolor* (Chen et al., 2012b) **(Figure 15)**.

5.7. Carbohydrates

Five fructo-oligosaccharides **(260-264)** have been reported from the aerial parts of *G. divaricata* (Chou et al., 2012) **(Figure 16)**. Besides, nine polysaccharides **(265-273)** of variable monomers have been isolated from *G. divaricata* (Liu et al., 2011), *G. medica* (Li et al., 2016) and *G. procumbens* (Li et al., 2017).

5.8. Peptides and proteins

A large number of biologically-active peptides and proteins **(274-342)** have been isolated from the leaves of *G. procumbens* (Hew et al., 2011). One has also been reported from the leaves of *G. pseudochina* (Chaichana et al., 2019).

6. Pharmacological properties

Pharmacological investigations on crude extracts and phytochemicals isolated from different parts of *Gynura* species have revealed diverse pharmacological properties including, antidiabetic, anti-oxidant, anti-inflammatory, antimicrobial, cardioprotective and anticancer activity. Since *G. japonica* and *G. segetum* are synonymous, with the former being the accepted name (The Plant List, 2013), their pharmacological activities have been described under the title of *G. japonica.* The key pharmacological properties of extracts and phytochemicals of major *Gynura* species are summarized in **Table 3**.

6.1. Antidiabetic/hypoglycemic activity

6.1.1. G. bicolor

The aqueous extract of *G. bicolor,* when incorporated into the diet of male BALB/cA mice at concentrations of 0.5% and 1%, induced a significant reduction in the plasma glucose level and increase in the insulin level. It also reduced the plasma protein C and anti-thrombin III levels as well as increased the plasma plasminogen activator inhibitor-I and fibrinogen levels. It decreased the plasma triglycerides level and reduced the oxidative and inflammatory stress commonly associated with diabetes. The extract also enhanced the glutathione concentration, activated glutathione peroxidase, glutathione reductase and catalase, and reduced the production of reactive oxygen species in the heart and kidneys. It diminished the release of pro-inflammatory mediators including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α and the mRNA expression of inflammatory precursors including p38 and nuclear factor kappa (NF-κ) B (Pai et al., 2019). The aforementioned information suggests that the antidiabetic activity

of *G. bicolor* is mediated in an insulin-dependent manner and future investigations are required in order to ascertain the efficacy of this species in insulin-resistant *in vivo* systems.

6.1.2. G. divaricata

The antidiabetic properties of the aqueous extract of *G. divaricata* leaves, and its different fractions, were investigated *in vitro*. Potent hypoglycemic activity was reported for the aqueous extract as well as the ethyl acetate fraction. This was attributed to their capacity to inhibit α-amylase and α-glucosidase in a dose-dependent manner. The concentrations required for 50% inhibition of α-amylase (IC_{50} value) were 1.36 ± 0.11 and 0.0475 ± 0.0036 mg/mL for the aqueous extract and the standard drug acarbose, respectively. In the case of α-glucosidase, the IC_{50} values were calculated as 2.17 ± 0.09 and 0.27 ± 0.03 mg/mL for the aqueous extract and acarbose, respectively (Wu et al., 2011). A study in mice further demonstrated the hypoglycemic effect of *G. divaricata*. The latter reduced the fasting plasma glucose level, enhanced glutathione peroxidase and total superoxide dismutase activity, diminished plasma triglycerides and cholesterol levels, and improved glycogen accumulation in the liver. At the cellular level, the extract enhanced the genetic and protein expression of protein kinase B (PKB, also known as AKT), phosphatidylinositol 3-kinase (PI3K) and 3-phosphoinositide-dependent protein kinase 1 (PDK1). This study also showed an amelioration of insulin level in diabetic mice (Xu et al., 2015). The aqueous extract of *G. divaricata* (at doses of 5 and 10 mg/mL) also improved dexamethasone-induced insulin resistance in HepG2 cells by enhancing glucose uptake and metabolism. The extract minimized fat accumulation in the liver and pancreatic islets, leading to a reduced total body weight as opposed to the net increase in body weight of diabetic mice treated with pioglitazone and a high-fat diet (Li et al., 2018). Phytochemical analysis of *G. divaricata* showed the presence of polysaccharides capable of minimizing intestinal disaccharidases activities as well as of caffeoylquinic acid derivatives with prominent α-glucosidase inhibitory activity (Chaichana et al., 2019; Hew et al., 2011). In streptozotocin-induced diabetic rats, disaccharidase enzymes like maltase, sucrase and lactase have an enhanced level of activity. A polysaccharide-containing preparation from *G. divaricata* demonstrated a noteworthy decrease in maltase and sucrase activity in all three segments of the small intestine. Lactase activity was attenuated in the duodenum only. This polysaccharide preparation reduced fasting plasma glucose concentration and improved the plasma insulin level to a significant extent (Deng et al., 2011). 3,4-Dicaffeoylquinic acid **(61)**, methyl 3,4-dicaffeoylquinate **(62)**, 4,5-dicaffeoylquinic acid **(66)** and methyl 4,5-dicaffeoylquinate **(67)** showed prominent α-glucosidase inhibitory activity, as evident from their IC_{50} values of 187.2

± 12.9, 12.23 ± 0.64, 130.8 ± 10.3 and 13.08 ± 0.86 μM, respectively, when compared to acarbose (IC_{50} value 867.4 ± 76.2 μM). 3,5-Dicaffeoylquinic acid **(63)** and 4,5-dicaffeoylquinic acid **(66**) as well as the standard seramin exerted comparable inhibitory activities (41.6, 58.2 and 44.6%, respectively) against protein tyrosine phosphatase 1B (PTP1B), a down-regulator of insulin receptor signal transduction (Chen et al., 2014). Although the antidiabetic activity of both *G. divaricata* extract and its individual constituents have been thoroughly characterized through enzymatic interactions, *in vivo* reciprocation of the data is necessary along with adequate structure-activity relationship analysis in order to identify potential antidiabetic lead molecules.

6.1.3. G. medica

Multiple studies have demonstrated that *G. medica* reduced the plasma glucose level and improved glucose tolerance in adrenaline-glucose-induced diabetic mice. This effect was attributed to an enhanced secretion of insulin from the islet cells and a sustained high plasma insulin level (Ji et al., 2009; Liu et al 2005; Zheng-dong and Wen-shu, 2008). Whilst these results are interesting, further studies using insulin resistant models should be carried out in in order to ascertain the complete antidiabetic potential of this species. Phytochemical investigation followed by *in vitro* antidiabetic assay revealed prominent activity for several constituents isolated from the ethanol extract of this plant. Compared to the standard acarbose (IC_{50} value 0.99 ± 0.02 mg/mL), methyl 3,5-dicaffeoylquinate **(64)**, quercetin **(88)**, kaempferol-3-*O*-β-D-glucoside **(99)**, kaempferol-3-*O*-rutinoside **(101)** and rutin **(107)** demonstrated significant α-glucosidase inhibitory activity in yeasts (IC_{50} values of 0.53 ± 0.02, 1.67 ± 0.05, 1.46 0.03, 0.38 ± 0.03 and 0.10 ± 0.01 mg/mL, respectively) (Tan et al., 2013).

6.1.4. G. procumbens

G. procumbens is gaining popularity as the "Insulin plant" or "Diabetes plant" as it has been demonstrated to be effective in limiting the requirement of insulin in diabetic patients. Its antidiabetic activity follows a biguanide (metformin)-like mechanism of action. This species significantly lowers the plasma glucose, cholesterol and triglycerides levels in streptozotocin-induced diabetic rats. At doses of 150 mg/kg body weight, the ethanol extract showed a maximum reduction of the plasma glucose concentration (15.8%) 2h after a glucose load (Zhang and Tan, 2000). The aqueous extract, at doses of 500 and 1000 mg/kg body weight, significantly lowered the fasting plasma glucose level in rats. *G. procumbens* extract enhanced the uptake of glucose by abdominal muscle cells, thus improving the plasma glucose regulation.

In the absence of insulin, the aqueous extract enhanced the glucose uptake (3.77 ± 0.43 mg per g tissue weight) compared to the control group (1.76 ± 0.35 mg per g tissue weight). A similar, yet more prominent effect, was observed with concomitant administration of insulin (100 mU/mL) (glucose uptake of 5.77 ± 0.32 mg per g tissue weight) (Hassan et al., 2010). The aqueous extract enhanced the translocation of the glucose transporter type 4 to the plasma membrane of skeletal muscle by increasing the phosphorylation of AMP-activated protein kinase. The extract also reduced the rate of gluconeogenesis in the liver by down-regulating glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (Choi et al., 2016a). The antidiabetic activity of the aqueous and ethanol extract, as well as their different fractions, has been linked to an enhanced activity of glycogen synthase kinase (GSK3β) and subsequent boost in the assimilation of glycogen in the liver. The increased activity of glycolytic enzymes viz. liver hexokinase, phosphofructokinase and fructose-1,6-bisphosphatase in *G. procumbens*-treated mice, also suggested a greater degree of glucose breakdown in the liver (Gansau et al., 2012; Lee et al., 2012). *G. procumbens* has been reported to directly suppress postprandial hyperglycemia. This was attributed to the inhibition of α-glucosidase and α-amylase *in vitro*. In the case of α-glucosidase, the aqueous extract exerted a comparable inhibition to that of acarbose (IC_{50} values of 0.092 ± 0.018 and 0.075 ± 0.006 mg/mL, respectively). The extract also inhibited α-amylase (IC_{50} value of 0.084 ± 0.027 mg/mL) (Choi et al., 2016b). The cellular mechanism and biochemical implications of different *G. procumbens* extracts have been adequately characterized. This confirms the suitability of this species as a traditional antidiabetic remedy.

6.2. Anti-oxidant activity

6.2.1. G. bicolor

The ethyl acetate extract of *G. bicolor* showed a high phenolic content (10.87 mg of gallic acid equivalents per gram (GAEs/g) of extract) and prominent anti-oxidant activity (IC_{50} value 0.53 ± 0.01 mg/mL) in a DPPH scavenging activity assay (Teoh et al., 2013). Its aqueous and ethanol extracts also showed high phenolic contents (14.28 and 15.69 GAEs/g of extract, respectively). Both extracts exerted prominent protection against oxidative stress in HUVE cells (Chao et al., 2015).

6.2.2. G. divaricata

The total phenolic content and total flavonoid content of the 45% aqueous ethanol extract of *G. divaricata* were determined under different extraction procedures and at varying

temperatures. Extraction at 100 °C showed a maximum phenolic content of 36.68 ± 0.62 GAEs/g of dry plant material and a maximum flavonoid content of 47.52 ± 0.21 mg kaempferol equivalent/g of dry material. The extract obtained at 100 °C also exhibited maximum radical scavenging potential (89.67 ± 0.06% inhibition of DPPH and 68.27 ± 1.36% inhibition of 2,2-azinobis-3-ethylbenzothiazoline-6-sulphonic acid (ABTS) radicals (Wan et al., 2011a). However, no IC_{50} values were reported, which makes it difficult to compare its anti-oxidant potential with that of other species.

6.2.3. G. formosana

The ethyl acetate extract of *G. formosana* showed significant radical scavenging activity in the DPPH and ABTS assays, with IC_{50} values of 11.17 ± 1.83 and 21.82 ± 0.88 µg/mL, respectively. Its anti-oxidant potential was associated with an enhanced level of catalase, superoxide dismutase and glutathione activity and a reduced lipid peroxidation rate in rat liver when administered at doses of 250 and 500 mg/kg body weight (Ma et al., 2019). Its phenolic constituents such as caffeic acid **(40)** and quercetin 3-*O*-rutinoside **(107)** possessed anti-oxidant activity by scavenging DPPH, superoxide and hydroxyl radicals *in vitro*. In the DPPH assay, the aforementioned compounds exhibited IC_{50} values of 6.7 and 7.7 µM, respectively (Hou et al., 2005).

6.2.4. G. japonica

Both the ether and ethyl acetate extracts of *G. japonica* showed potent anti-oxidant activity (Su et al., 1986). The methanol extract showed moderate dose-dependent activity with 36.8 ± 0.4% inhibition at 500 µg/mL in a DPPH scavenging assay and 89.5 ± 0.6% inhibition at 1000 µg/mL in a β-carotene–linoleic acid assay (Seow et al., 2014b). It is possible that further bioassay-guided fractionation of this extract might have produced better results.

6.2.5. G. procumbens

The ethyl acetate fraction derived from the methanol and ethanol extracts of *G. procumbens* exhibited the potent activity in the hydroxyl radical, hydrogen peroxide, DPPH ($IC_{50,}$ 0.22 ± 0.01 mg/mL), ABTS ($IC_{50,}$0.06 mg/mL) scavenging assays and in the β-carotene–linoleic acid and xanthine oxidase inhibition assays. This anti-oxidant potential was attributed to a high phenolic and flavonoid content (24.36 ± 1.11 mg GAE/g dry fraction and 17.33 ± 1.39 mg catechin equivalent/g dry fraction, respectively) and to inhibition of lipid peroxidation (Kaewseejan and Siriamornpun, 2015; Lee et al., 2012; Tan et al., 2013). A comparative

investigation, using DPPH scavenging and ferric reducing anti-oxidant power assays, revealed that the roots were richer in phenolics and flavonoids than other plant parts and had stronger anti-oxidant activity (Krishnan et al., 2015).

6.2.6. G. pseudochina

The 40% aqueous ethanol extract showed a strong DPPH radical scavenging activity owing to its high phenolic content (94.24 ± 0.1552 mg GAE/g of dry sample) (Krisyanella et al., 2016). This potent free radical scavenging activity was further confirmed in another study using a 2,4-dinitrophenylhydrazin (DNPH) assay (Suhartono et al., 2016). However, the absence of IC_{50} values limits comparison with other species.

6.3. Anti-inflammatory activity

6.3.1. G. bicolor

The ether extract of *G. bicolor*, administered at doses of 30, 60 and 120 µg/mL to RAW 264.7 cells, showed a dose-dependent inhibition of the lipopolysaccharide (LPS)-induced inflammatory response. This activity was attributed to the capacity of the extract to inhibit the inducible NO synthase (iNOS) and the cyclooxygenase (COX)-2 responsible for the synthesis of the pro-inflammatory mediators nitric oxide (NO) and prostaglandin E_2 (PGE_2), respectively. Compared to the control group, the extract at a dose of 120 µg/mL showed a maximum of 30% and 72% reduction in NO and PGE_2 production, respectively. The underlying mechanism in this anti-inflammatory response involved a prominent reduction in the expression of the cytosolic phosphorylated (p)-IκBa and nuclear p65 proteins and a subsequent inactivation of the nuclear factor kappa B (NF-κB) (Wu et al., 2013).

6.3.2. G. formosana

The ethyl acetate extract of *G. formosana* inhibited the cotton pellet-induced granuloma formation (inflammatory response) in rats by decreasing the plasma levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα) and interleukin-1β (IL-1β). It showed a dose-dependent anti-inflammatory activity at a dose of 250 mg/kg body weight, equivalent to that observed for indomethacin used at 4 mg/kg (Ma et al., 2019).

6.3.3. G. japonica

The methanol and chloroform extracts (50 µg of extract/disc) demonstrated significant anti-inflammatory activity (76.82 ± 2.10% and 70.76 ± 1.77% inhibition of inflammation,

respectively) in the Hen's egg test chorioallantoic membrane (HET-CAM) assay (Seow et al., 2014a). In the cotton pellet-induced inflammatory assay in rats, *G. japonica* at doses of 250 and 500 mg/kg body weight, significantly reduced the plasma levels of TNFα (62.9 ± 5.5 and 72.2 ± 3.5%, respectively). The extract also inhibited the production of IL-1 (89.2 ± 1.2%). Compared to the complete inhibition of COX-1 by aspirin, the methanol extract only showed 55.0 ± 0.6% inhibition at a dose of 200 µg/mL. On the other hand, the extract potently inhibited COX-2 activity, even better than celecoxib (86.8 ± 1.5 and 43.3 ± 1.7% inhibition, respectively) (Seow et al., 2014b).

6.3.4. G. nepalensis

The ethanol extract of *G. nepalensis* showed strong anti-inflammatory activity in the carrageenan-induced paw oedema and xylene-induced ear oedema assays in mice. The extract, at doses of 250 and 500 mg/kg body weight, inhibited the paw oedema to a maximum of 77.8 and 94.4%, respectively. In the ear oedema assay, the extract at the dose of 500 mg/kg showed a comparable inhibition (36.32%) to that of the standard (38.84%). It also produced significant peripheral analgesia by inhibiting acetic acid-induced writhing and formalin-induced paw licking of mice. The extract, at doses of 250 and 500 mg/kg, showed 58.98 and 58.28% inhibition of writhing, respectively (Rahman et al., 2018). Further studies should aim to ascertain the possible mechanism of such activity, particularly unravelling whether the extract from this species interferes with cyclooxygenase enzymes.

6.3.5. G. procumbens

The ethanol extract of *G. procumbens* as well as its hexane and toluene extracts demonstrated topical anti-inflammatory properties as potent as hydrocortisone in the croton oil-induced mouse ear inflammation model. The ethanol extract (0.75 mg per ear) and hydrocortisone (6 mg per ear) showed similar activity (65.2 and 64.8% inhibition, respectively). The hexane and toluene extracts (0.75 mg/ear) showed 44.6 and 34.8% inhibition, respectively. Hydrocortisone (4 mg per ear) showed comparable activity (35.0%) (Iskander et al., 2002). The ethanol extract of *G. procumbens* suppressed the production of TNF-α and interferon γ (IFN-γ) but promoted the production of the anti-inflammatory interleukin IL-10 (Wong et al., 2015).

6.4. Antimicrobial activity

6.4.1. G. divaricata

The methanol extract of *G. divaricata* at 20 mg/mL exhibited moderate activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (zones of inhibition of 11.0 ± 0.50 and 15.0 ± 0.26 mm, respectively) compared to gentamicin (35.0 ± 0.30 and 27.0 ± 0.50 mm at 75 µg/mL, respectively). It also showed moderate activity against *Aspergillus flavus* and *Candida albicans* (10.0 ± 0.42 and 13.0 ± 0.26 mm, respectively) compared to ketoconazole (25.0 ± 0.50 and 37.0 ± 0.40 mm at 250 µg/mL, respectively). The methanol and the dichloromethane extracts inhibited the growth of *Trichophyton mentagrophytes* (14.0 ± 0.40 and 13.0 ± 0.26 mm at 75 µg/mL, respectively) compared to ketoconazole (16.0 ± 0.20 mm) (Jiangseubchatveera et al., 2015). It is possible that further bioassay-guided fractionation of the methanol extract might have produced better results.

6.4.2. G. japonica

The ethyl acetate soluble fraction of *G. segetum* (*G. japonica*) at 50 mg/mL showed strong *in vitro* inhibitory activity on the growth of *S. aureus, Bacillus subtilis, Enterobacter aerogenes, P. aeruginosa, Escherichia coli* and *Proteus mirabilis* (zones of inhibition of 20.0 ± 1.0, 18.3 ± 1.2, 13.0 ± 1.0, 23.3 ± 2.0, 17.0 ± 1.0 and 20.7 ± 0.6 mm, respectively). The extract at the same concentration was also active against *C. albicans* (13.0 ± 1.0 mm) as comparable to that of amphotericin (15.3 ± 0.6 mm at 500 ppm dose) (Seow et al., 2012).

6.4.3. G. procumbens

The methanol extract of *G. procumbens* showed potent inhibitory activity against the regular (H37Rv) and a multidrug resistant strain of *Mycobacterium tuberculosis*. The minimum inhibitory concentration (MIC) was 500 ppm compared to that of the standard ofloxacin at 1 ppm (Isrul et al., 2018). The methanol extract also showed antibacterial activity against *S. aureus*, *B. subtilis*, *Klebsiella pneumoniae*, and *P. aeruginosa*. At 400 mg/mL, the extract displayed zones of inhibition of 10.5 ± 0.06, 10.0 ± 0.0, 9.7 ± 1.5 and 9.0 ± 0.0 mm, respectively (Nawi et al., 2019).

The aqueous and the ethanol extract exerted potent *in vitro* activity against *Plasmodium falciparum* 3D7 (IC_{50} values of 25.69 ± 4.34 and 42.23 ± 7.19 µg/mL, respectively) and *P. berghei* NK65 (IC_{50} values of 12.4 ± 6.02 and 14.38 ± 7.53 µg/mL, respectively). An *in vivo* study in mice demonstrated that *G. procumbens* reduced the population of *P. berghei* within erythrocytes. Both extracts, administered at doses of 25, 50 and 100 mg/kg/day for four days,

exerted a dose-dependent inhibition of parasitaemia and showed a maximum inhibition of the parasitic population (93.06 ± 5.46 and 84.73 ± 3.18%, respectively) at 250 mg/kg body weight. *G. procumbens* extracts improved survivability in *P. berghei*-infected mice (mean survival time of 21 days after treatment) (Vejanan et al., 2012; Wong et al., 2015).

The ethanol extract of *G. procumbens* also exhibited potent virucidal activity against Herpes Simplex Virus (HSV), inhibiting viral replication within host cells (Jarikasem et al., 2013). Bioactivity-guided fractionation of these extracts and their subsequent phytochemical investigation is essential in order to identify the constituent(s) responsible for the antiplasmodial and antiviral activities.

6.4.4. G. pseudochina

G. pseudochina inhibited the growth of *C. albicans* on an acrylic resin denture base (Rahman, 2020). However, the data can be considered limited in absence of suitable standards.

6.5. Cardioprotective activity

6.5.1. G. divaricata

An *in vitro* study of the aqueous extract of *G. divaricata* reported its ability to inhibit the Angiotensin Converting Enzyme (ACE) significantly, which further suggested some potential antihypertensive properties for this species. The extract, at a dose of 1.25 mg/mL, exhibited a maximum inhibition of 85.2% with an IC_{50} value of 370.0 ± 70.0 µg/mL, compared to captopril (IC_{50}, 0.0027 ± 0.0002 µg/mL) (Wu et al., 2011). A recent *in vivo* study confirmed the antihypertensive potential of *G. divaricata* in a two-kidney one-clip (2K1C) renovascular hypertensive rat model. The aqueous extract at the dose of 200 mg/kg/day, significantly improved vasodilation in acetylcholine-, sodium nitroprusside- and atrial natriuretic peptide-treated rats (97.72, 76.4 and 54.64%, respectively). The extract also enhanced endothelial nitric oxide synthase expression, which in turn, boosted the concentration of vasodilator nitric oxide. Moreover, the extract was found to counteract hypertension-induced ventricular hypertrophy as well as the expression of cardiac dysfunction biomarkers (i.e. brain natriuretic peptide and troponin T). The antihypertensive activity of *G. divaricata* was further associated with its renoprotective capacities *in vivo.* The extract significantly reduced urinary volume while increasing the concentration of sodium, potassium and chloride in urine. The aldosterone and angiotensin activity was also restrained along with higher level of creatinine clearance in extract-treated animals (Hong et al., 2020).

6.5.2. G. procumbens

The aqueous extract of this species administered at a dose of 500 mg/kg/day over a period of 4 weeks, lowered the systolic blood pressure in spontaneously hypertensive rats. Mean blood pressure values of 191.7 ± 13.2 and 172 ± 14.6 mm Hg were reported for the control and for the extract-treated group, respectively. This finding was attributed to the fact that *G. procumbens* increased the concentration of the vasodilator molecule nitric oxide by a margin of 60.7%. A decrease in the serum activity of lactate dehydrogenase and creatine phosphate kinase (up to 34 and 48%, respectively) was also observed (Kim et al., 2006). Another study linked the hypotensive effect of *G. procumbens* with its ability to inhibit the angiotensin converting enzyme *in vitro* and *in vivo* (Hoe et al., 2007). Multiple studies have showed that *G. procumbens* could lead to vasodilation through direct enhancement of bradykinin activity as well as antagonism of angiotensin II and calcium channel mediated vasoconstriction (Hoe et al., 2011; Poh et al., 2013). Another study suggested that the plant caused vasodilation owing to its ability to increase prostacyclin production and open potassium channels (Ng et al., 2013).

6.5.3. G. japonica

The antiplatelet activity of *G. japonica* extract and pure compounds was tested using a turbidimetric method where platelet aggregation was induced by thrombin (0.1 U/mL), arachidonic acid (100 μM), collagen (10 μg/mL) and platelet activating factor (2 ng/mL). In the case of arachidonic acid-induced aggregation, the chloroform fraction (100-500 μg/mL) showed 8.1-98.4% inhibition compared to that of aspirin (100% inhibition at both 50 and 100 μg/mL doses). The extract also inhibited collagen- and platelet activating factor-induced aggregation (88.1 and 53.8%, respectively). 6-Acetyl-2,2-dimethylchroman-4-one (**74**) and vanillin (**167**) were among the isolated compounds, which at the dose of 100 μg/mL effectuated complete inhibition of arachidonic acid induction in a similar manner as aspirin (Lin et al., 2003). This, in turn, suggests that their activity may be mediated predominantly through the inhibition of the cyclooxygenase enzyme.

6.6. Cytotoxic/anticancer properties

6.6.1. G. bicolor

The hot water extract of *G. bicolor* exhibited cytotoxic properties by prompting apoptosis in HL60 leukemia cells (Hayashi et al., 2002). Its ethyl acetate extract showed cytotoxicity against HCT-116 and HCT-15 colon cancer cells, mediated through apoptosis and necrosis. After a treatment period of 24 h, the IC_{50} values obtained for the extract were of 16.0 ± 4.5

μg/mL in the HCT-116 cell line (cisplatin, IC_{50} of 12.0 ± 0.7) and 12.8 ± 5.3 μg/mL in the HCT-15 cell line (cisplatin, IC_{50} of 6.2 ± 0.4) (Teoh et al., 2013). Chlorogenic acid **(56)** and 3,5-dicaffeoylquinic acid **(63)** isolated from this species showed selective cytotoxicity against HCT-116 cells (IC_{50} values of 79.7 ± 4.5 and 79.3 ± 3.1 μg/mL, respectively) (Teoh et al., 2016).

6.6.2. G. cusimbua

Several phenylpropanoid glycosides isolated from the *n*-butanol extract of *G. cusimbua* were investigated for their anti-angiogenic properties. Two compounds, namely α-L-rhamnopyranosyl-(1→2)-β-D-[4″-(8E)-7-(3,4-dihydroxyphenyl)-8-propenoate,1″-O-(7S)-7-(3,4-dihydroxyphenyl)-7-methoxyethyl]-glucopyranoside **(82)** and spicaoside **(83),** significantly suppressed vascular endothelial growth factor (VEGF)-stimulated cell proliferation in human umbilical vascular endothelial cells (HUVEC) *in vitro*. Their IC_{50} values (12.65 ± 0.06 and 14.09 ± 0.78 μM, respectively) were comparable to the standard axitinib (4.57 ± 0.92 μM). Three more compounds viz. β-hydroxy-verbascoside **(77)**, betonyoside A **(80)** and 3′,9,9′-trihydroxy-3,5-dimethoxy-8-*O*-4′-neolignan-4-O-β-D-glucopyranoside **(84)** exhibited moderate cytotoxicity (IC_{50} values of 52.43 ± 0.51, 21.52 ± 0.24, and 33.25 ± 0.62 μM, respectively). A similar effect was observed i*n vivo* where all five compounds suppressed vascular formation in the wild-type zebrafish (IC_{50} values of 3.1 ± 1.3, 3.3 ± 1.5, 13.2 ± 5.1, 11.3 ± 4.8 and 15.7 ± 6.9 μM, respectively) compared to the standard semaxanib (2.9 ± 1.4 μM) (Ma et al., 2019). The cytotoxic potential of these lead molecules investigated through both *in vitro* and *in vivo* methods warrant further clinical investigation.

6.6.3. G. divaricata

The essential oil from *G. divaricata* showed cytotoxicity against the oral cancer KB, breast cancer MCF-7, and lung cancer NCI-H187 cell lines (IC_{50} values of 5.79 ± 0.04, 47.44 ± 0.19 and 17.65 ± 0.13 μg/mL, respectively). This contained cubenol **(205)** which exhibited an IC_{50} value of 45.37 ± 2.94 μg/mL (Jiangseubchatveera et al., 2015). The aqueous extract inhibited cellular proliferation as well as tumor growth in Huh7, Mahlavu and Hep3B liver cancer cells to a moderate degree (< 70 % cytotoxicity). At a dose of 250 μg/mL, the extract potentiated the anticancer property of cisplatin (7.36-fold increase in activity), 5-flurouracil (4.03-fold) and doxorubicin (2-fold) *in vivo* (Yen et al., 2018). Gynuraoside **(145)**, a cerebroside isolated from the ethanol extract of the aerial parts of *G. divaricate*, dose-dependently inhibited the proliferation of L1210 leukemia cells (95% inhibition at 20 μg/mL) (Chen et al., 2009b).

629

630 ***6.6.4. G. formosana***

631 The ethyl acetate extract of *G. formosana* showed activity against HeLa, HepG2, and MCF-
632 7 cells (IC_{50} values of 81.47, 100.94, and 104.76 μg/mL, respectively) (Ma et al., 2018). Its
633 cytotoxicity was attributed to an inhibition of autophagy-mediated cell proliferation. Further
634 studies should include comparative screening using multiple standards and a characterization
635 of the biochemical markers affected by this extract in order to ascertain the molecular
636 mechanism of action.

637

638 ***6.6.5. G. japonica***

639 Different *G. segetum* (*G. japonica*) extracts showed potent anti-angiogenic activity by
640 reducing the size and the number of blood vessels in a chick embryo chorioallantoic membrane
641 (CAM) assay. Compared to the standard suramin (50 μg per disc), the chloroform extract
642 exhibited the highest activity, followed by the petroleum ether and the methanol extract, each
643 at concentrations of 100 μg per disc (Seow et al., 2011). Further studies using cell lines and
644 suitable standards are required to strengthen these observations.

645

646 ***6.6.6. G. medica***

647 *G. medica* is rich in kaempferol **(87)** which showed strong dose-dependent cytotoxicity
648 against the human breast cancer MCF-7 cell line. This flavonoid, at concentrations of 20, 40
649 and 80 μM, showed 26.3%, 49.7% and 77.3% inhibition of cellular growth, respectively.
650 Kaempferol **(87)** also induced apoptosis by up-regulating the pro-apoptotic protein Bax and
651 down-regulating the anti-apoptotic protein Bcl2 (Yi et al., 2016).

652

653 ***6.6.7. G. procumbens***

654 The cytotoxic properties of the ethanol extract of *G. procumbens* were investigated in a
655 squamous cell carcinoma induced in the tongue cells of mice by the carcinogenic agent 4-
656 nitroquinoline 1-oxide (4NQO). Significant inhibition of dysplastic changes in the tongue cells
657 suggested that this species displayed potent anticancer properties (Agustina et al., 2006). The
658 ethanol extract, at doses of 50 and 100 μg/mL, inhibited the cellular proliferation of fetal bovine
659 serum-activated mesangial cells by reducing the expression of platelet-derived growth factor
660 (PDGF-BB), transforming growth factor (TGFβ1) and cyclin dependent kinase (CDK1 and
661 CDK2) (Lee et al., 2007). It suppressed the 7,12-dimethylbenz(a)anthracene (DMBA)-induced
662 mammary carcinoma in Sprague Dawley rats (up to 60 % at 250 mg/kg of body weight)

(Meiyanto et al., 2007). The same extract, at doses of 300 and 750 mg/kg body weight, also exhibited significant anti-proliferative activity against DMBA-induced hepatic carcinoma in Sprague Dawley male rats (Nisa et al., 2012). The ethyl acetate extract of this species suppressed the nuclear translocation of NF-κB as well as the ribosomal expression of the NF-κB p65 protein leading to a reduced cellular proliferation and metastasis of U2-OS osteosarcoma cells. The extract, administered at concentrations ranging from 10 to 80 μg/mL, inhibited cellular proliferation in a dose- and time-dependent manner. When applied at 80 μg/mL over 24 h, the extract led to apoptosis in 37.94% of cells (Wang et al., 2013). The cytotoxic effect of *G. procumbens* could be attributed to the activation of CD4+ T lymphocyte cells as a result of an increased expression of certain interleukins viz. IL-2, IL-4, and IL-12) by helper T cells (Takanashi et al., 2019). This was supported by the fact that *G. procumbens* could activate CD4+ T cells by enhancing the expression of CD25 molecules and suppressing the expression of CD26L molecules (Dwijayanti and Rifa'i, 2015). The ethyl acetate extract enhanced the anti-proliferative effect of doxorubicin and 5-flurouracil in MCF-7 and T47D breast cell lines. In MCF-7 cells, the combination therapy induced c-PARP mediated apoptosis leading to cell death (Nurulita et al., 2012). One study reported the cytotoxic properties of protein fractions against MDA-MB-231 breast cancer cells (Hew et al., 2013). The anticancer activity of *G. procumbens* extracts has been well characterized through in-depth studies, but extensive phytochemical investigations are now warranted to identify the constituent(s) responsible for such activity and develop new anticancer drug leads.

6.6.8. G. pseudochina

Anticancer activity against human gastric KATO-III cells was reported for the peptide gynurin **(301)** isolated from *G. pseudochina* rhizomes (Chaichana et al., 2019). Bioactivity-guided fractionation revealed a fraction with an IC_{50} value of 100 μg/mL. Further investigation on this fraction yielded gynurin (IC_{50} value of 100 μM). This compound had a minimal cytotoxic effect on normal cells at the same potency. Structural modification of this active compound might be necessary in order to obtain molecules with better activity.

7. Safety and toxicity studies

Few systematic studies have been conducted on the safety and toxicity of *Gynura* species. The methanol extract of *G. bicolor* was investigated for acute oral toxicity in healthy male Sprague-Dawley rats at doses of 0.3, 2 and 5 g/kg of body weight over a period of 14 days. The

absence of any visual and behavioural signs of toxicity suggested that this species was relatively safe for oral consumption (Teoh et al., 2013).

An extract of *G. japonica,* and its PAs, were evaluated for oral toxicity in a mice model at a dose of 50 mg/kg of body weight. Profound hepatic damage characterized by a breakdown of hepatocytes, clot formation within hepatic sinusoids and penetration of inflammatory cells into hepatic lobules was observed for both samples. These histological changes, along with increased levels of hepatic markers viz. alanine aminotransferase, aspartate aminotransferase, total bilirubin and total bile acids, led to a hepatic sinusoidal obstruction syndrome (Xiong et al., 2019).

Studies on the acute oral toxicity of *G. procumbens* at doses of 1 and 5 g/kg body weight administered were conducted in BALB/c mice for a period of 7 days. A similar characterization of the hepatic microsomal P450 contents between the control and extract-treated group as well as the absence of any neural or respiratory side effects, showed that this extract was safe when taken orally at both doses (Zhang et al., 2000). Another study evaluating the acute and sub-chronic toxicity of *G. procumbens* in male and female Sprague Dawley rats at doses of 1.25, 2.5 and 5 mg/kg of body weight revealed no noticeable changes in physical, behavioural, hematological and histological parameters. This demonstrated the oral safety of this species (Yam et al., 2009). However, more preclinical data need to be produced, conducting in-depth toxicity and pharmacokinetic studies of all the species, before further clinical trials.

8. Critical assessment and perspectives

The major species of the genus *Gynura* in ethnomedicine are used mainly in the treatment of diabetes, cancer and hypertension. Prominent antidiabetic properties have been reported for *G. bicolor*, *G. divaricata*, *G. medica* and *G. procumbens* through *in vitro* and *in vivo* studies. This has yet to be demonstrated in case of *G. formosana*, *G. japonica*, *G. nepalensis* and *G. pseudochina*, which are employed in diabetes. Specific constituents responsible for the reported antidiabetic properties have been identified from *G. divaricata* and *G. medica*, but remain to be isolated from *G. bicolor* and *G. procumbens*. Several phytoconstituents of *G. divaricata,* namely 3,4-dicaffeoylquinic acid (**61**), methyl 3,4-dicaffeoylquinate (**62**), 3,5-dicaffeoylquinic acid (**63**), 4,5-dicaffeoylquinic acid (**66**) and methyl 4,5-dicaffeoylquinate (**67**), with prominent antidiabetic activity *in vitro*, have also been reported wholly or partly in *G. bicolor*, *G. nepalensis*, *G. procumbens* and *G pseudochina*. All or some of the antidiabetic constituents of *G. medica* namely quercetin (**88**), kaempferol-3-O-β-D-glucoside (**99**), kaempferol-3-O-

729 rutinoside (**101**) and rutin (**107**), have also been identified in *G. bicolor*, *G. formosana* and *G.*
730 *procumbens*. Therefore, bioactivity-guided phytochemical investigations are warranted into *G.*
731 *bicolor* and *G. procumbens*, to evaluate if the aforementioned compounds form the basis of the
732 antidiabetic properties of these plants. In-depth antidiabetic and phytochemical screenings of
733 *G. formosana* and *G. nepalensis* are also required to assess their potential as antidiabetic
734 remedies. The similarity in terms of phytoconstituents is also reflected in the underlying
735 mechanism of these plants in exerting antidiabetic activity. Four plants viz. *G. bicolor*, *G.*
736 *divaricata*, *G. medica* and *G. procumbens* exert their antidiabetic activity through inducing
737 hypoglycemia. To that end, *G. bicolor*, *G. divaricata* and *G. medica* enhanced insulin secretion
738 while carbohydrate digesting enzymes were inhibited by *G. divaricata*, *G. medica* and *G.*
739 *procumbens*, reducing carbohydrate digestion and intestinal absorption. Moreover, both *G.*
740 *divaricata* and *G. procumbens* can enhance cellular glucose uptake and subsequent glycolysis,
741 as well as increase the rate of liver glycogenesis. The multiplicities of mechanisms supporting
742 the antidiabetic properties of different Gynura spp. are illustrated in **Figure 17**.
743 All the species mentioned in this review possess prominent anticancer activity. Although
744 most of the studies were performed on specific cancer cell lines, this was not the case for *G.*
745 *japonica* which employed a chick embryo chorioallantoic membrane assay to ascertain anti-
746 angiogenic activity (Seow et al., 2011). The translation of *in vitro* cytotoxicity into *in vivo*
747 anticancer activity is often unattainable due to the lack of selectivity and subsequent unwanted
748 interactions. *In vivo* cytotoxicity was only demonstrated for *G. cusimbua* (Ma et al., 2019) and
749 *G. procumbens* (Meiyanto et al., 2007; Nisa et al., 2012) in wild-type zebrafish and Sprague
750 Dawley rats, respectively. The cellular mechanisms of action and the selectivity were only
751 outlined for *G. procumbens* extract and *G. medica*-derived kaempferol (**87**). Therefore, future
752 in-depth investigations into the *Gynura* spp. are required to establish their *in vivo* selectivity,
753 interactions, and anticancer potential. Individual phytoconstituents with significant cytotoxic
754 activity have been isolated from *G. bicolor*, *G. cusimbua*, *G. divaricata*, *G. medica* and *G.*
755 *pseudochina*. One or all of the cytotoxic compounds of *G. bicolor* namely senecionine (**6**),
756 chlorogenic acid (**56**) and 3,5-dicaffeoylquinic acid (**63**), have also been reported from *G.*
757 *divaricata*, *G. medica*, *G. nepalensis*, *G. japonica*, *G. procumbens* and *G. pseudochina*, further
758 reinforcing their anticancer potential. Further bioactivity-guided phytochemical investigations
759 are required into these species to identify any additional cytotoxic secondary metabolites.
760 Whilst *G. bicolor*, *G. formosana*, *G. japonica*, *G. nepalensis* and *G. procumbens* have
761 displayed substantial anti-inflammatory activity, the same cannot be said for *G. divaricata* and
762 *G. pseudochina* (despite being both used ethnomedicinally to treat inflammation and

763 inflammation-associated conditions). It should be added that the detailed mechanisms involved
764 in the anti-inflammatory effect of *G. bicolor* and *G. nepalensis* are yet to be explored. Further
765 bioactivity-guided phytochemical investigations into these plants are also required. All species,
766 except for *G. nepalensis*, exert their anti-inflammatory activity by decreasing the levels of
767 TNF-α and pro-inflammatory interleukins. *G. japonica* and *G. bicolor* have also demonstrated
768 a common ability to inhibit cyclooxygenase-2 enzyme. *G. bicolor* and *G. procumbens*
769 suppressed nuclear factor Kappa B. This was further attributed to the anti-inflammatory activity
770 of *G. bicolor* and the anticancer activity of *G. procumbens*. Future investigations may be
771 targeted to extend the anti-inflammatory properties of *G. bicolor* to potential anticancer activity
772 and vice-versa. **Figure 18** illustrates the shared mechanisms involved when the aforementioned
773 species exert their anti-inflammatory effect.
774 Ethnomedicinal records have reported the use of *G. bicolor*, *G. divaricata*, G. *formosana*,
775 *G. japonica* and *G. nepalensis* for the treatment of hypertension. Such a claim was only
776 substantiated in the case of *G. divaricata*. Interestingly, *G. procumbens* demonstrated
777 antihypertensive properties although not reported as a traditional antihypertensive remedy.
778 Both *G. divaricata* and *G. procumbens* act on the cardiovascular system in a comparable
779 manner, inhibiting the ACE and lowering the plasma triglycerides and cholesterol levels
780 (**Figure 17)**. The traditional use of *G. japonica* for its anti-platelet effect has been validated
781 pharmacologically, including the identification of pure compounds responsible for such action
782 (Lin et al., 2003). Future *in vivo* experimentations are warranted in order to reciprocate such
783 action. Future work should also endeavor to assess the antihypertensive potential of other
784 *Gynura* species.
785 All major *Gynura* species, except for *G. cusimbua* and *G. medica,* possess noticeable anti-
786 oxidative potential demonstrated through one or more *in vitro* assays. This has only been
787 replicated *in vivo* for *G. bicolor* and *G. formosana*. The anti-oxidant activity of *G. bicolor*, *G.*
788 *divaricata*, *G. procumbens* and *G. pseudochina* has been associated with the presence of
789 several phenolics and flavonoids (**Table 2)**.
790 The antimicrobial activity of *G. divaricata* and *G. japonica*, demonstrated through *in vitro*
791 assays, reinforces their ethnomedicinal claims. Further *in vivo* studies are necessary,
792 particularly to support the ethnomedicinal use of *G. divaricata* for bronchitis and tuberculosis.
793 The traditional reports of *G. cusimbua* being employed against infections also require
794 validation through appropriate pharmacological studies. The antimicrobial and antiplasmodial
795 properties demonstrated for *G. procumbens* might extend its traditional applications.

Despite the variety of pharmacological studies already carried out to support the traditional uses of *Gynura* spp., many more traditional uses are yet to be substantiated. This includes the renoprotective potential of *G. procumbens*, the anti-herpetic potential of *G. pseudochina* and the uterine-associated effects of *G. bicolor*. The use of *Gynura* species in the treatment of burns, wounds, bruises, bleeding, ulcers, boils and scalds as well as to improve gastric conditions such as constipation and discomfort also requires further pharmacological investigations.

Most of the experimental studies using mice models reported in this review followed the conventional practice of using $1/10^{th}$ of the maximum non-lethal dose as the highest concentration to be administered (common maximum doses of 400 or 500 mg/kg). Some studies extended this limit to 750 mg/kg (Meiyanto et al., 2007; Nisa et al., 2012) and 1000 mg/kg (Hassan et al., 2010). In such cases, further toxicological studies are/or the re-evaluation of the experimental parameters using lower doses are required. Further *in vivo* work as well as detailed oral toxicity studies are warranted to establish the safety profile of *G. divaricata*, *G. formosana*, *G. medica*, *G. nepalensis* and *G. pseudochina* for traditional use.

9. Concluding remarks

The genus *Gynura*, which has a long history of use in traditional medicine, has demonstrated a wide variety of biological effects that support many of its uses. *Gynura* species have already afforded a broad spectrum of phytoconstituents and further bioactivity-guided phytochemical analyses of these plants could generate promising leads for new drugs. In light of the renewed worldwide interest towards herbal medicine, *Gynura* spp. represent an interesting alternative to conventional treatments for a range of disorders, especially diabetes, hypertension, cancer, inflammation and related disorders. Many *Gynura* species are also used as nutritional food and deemed safe to be consumed occasionally. Further studies should establish conclusively the efficacy and long-term safety of regular consumption of these plants.

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Tables

Table 1. Ethnomedicinal uses of major species of *Gynura*

Accepted names	Synonyms	Geographical location	Plant part used	Traditional uses	References
Gynura bicolor (Roxb. ex Willd.) DC.	*Cacalia bicolor*	India, Nepal, Bhutan, Japan, China, Taiwan, Myanmar and Thailand	Leaves, roots and aerial parts	Diabetes, cancer, inflammation, hypertension, post-labor recovery, dysmenorrhea, hemoptysis, improvement of blood circulation.	(Davies, 1980b, 1979; Shimizu et al., 2010; Teoh et al., 2013; Xian and Juxian, 2002; Vanijajiva, 2009)
Gynura cusimbua (D.Don) S.Moore	*Cacalia cusimbua*	Bangladesh, India, Nepal, Bhutan, China, Myanmar and Thailand	Leaves and aerial parts	Wounds healing, bleeding, headache, sedative, fever, various infection, constipation and other GIT discomforts.	(Ma et al., 2019; Rana and Blazquez, 2007; Vanijajiva, 2009)
Gynura divaricata (L.) DC.	*Cacalia hieracioides, Cacalia incana, Cacalia ovalis, Gynura auriculata, Gynura hemsleyana, Gynura incana, Gynura ovalis*	China, Vietnam and Taiwan	Leaves, aerial parts and whole plant	Diabetes, cancer, inflammation, hypertension, bronchitis, pulmonary tuberculosis, pertussis, sore eye, toothache, rheumatic arthralgia, uterine bleeding, traumatic injury, fracture, wound, bleeding, mastitis, boils, leg ulcer, burns and scald.	(Davies, 1980b, 1979; Roeder et al., 1996; Xian and Juxian, 2002; Xu et al., 2015)
Gynura formosana Kitam.		North, south and east coastal region of Taiwan, China	Whole plant	Diabetes, inflammation, cancer, cerebral infarction and hypertension.	(Hou et al., 2005; Ma et al., 2017)

Gynura japonica (Thunb.) Juel	*Gynura segetum* (most commonly used), *Arnica japonica, Cacalia pinnatifida, Gynura aurita, Gynura flava, Gynura pinnatifida, Gynura truncata, Gynura vaniotii, Kleinia japonica, Porophyllum japonicum, Senecio japonicus.*	Nepal, Tibet, Japan, China, Taiwan and Thailand	Roots, rhizomes and aerial parts	Diabetes, cancer, hypertension, hemostasis, inflammation, snake bite, different skin afflictions, bleeding wounds, ulcerous wounds, bruises, sores, septic nails, burns and scalds.	(Davies, 1980b, 1979; Lin et al., 2003; Seow et al., 2012)
Gynura nepalensis DC.	*Gynura dielsii, Gynura foetens, Gynura nudibasis, Senecio nudibasis.*	Nepal, Bangladesh, India, Bhutan, China, Myanmar, Malaysia and Thailand	Leaves	Wounds, indigestion, diabetes and hypertension.	(Davies, 1980, 1979; Yu et al., 2016; Vanijajiva, 2009)
Gynura procumbens (Lour.) Merr.	*Cacalia cylindriflora, Cacalia finlaysoniana, Cacalia procumbens, Cacalia reclinata, Cacalia sarmentosa, Crassocephalum latifolium, Gynura affinis,*	Bangladesh, India, China, Myanmar, Vietnam, Thailand, Malaysia, Philippines, Indonesia and Papua New Guinea	Leaves and whole plant.	Inflammation, rheumatism, viral diseases of skin, kidney diseases, rashes, diabetes, hyperlipidemia, cancer, constipation and hemorrhoids, fever and migraine.	(Davies, 1980a, 1980b, 1979; Nurulita et al., 2012; Perry and Metzger, 1980; Vanijajiva, 2009)

	Gynura agusanensis, *Gynura cavaleriei,* *Gynura clementis,* *Gynura latifolia,* *Gynura lobbiana,* *Gynura piperi,* *Gynura pubigera,* *Gynura sarmentosa,* *Gynura scabra.*				
Gynura pseudochina (L.) DC.	*Cacalia bulbosa,* *Gynura biflora,* *Gynura bodinieri,* *Gynura bulbosa,* *Gynura eximia,* *Gynura miniata,* *Gynura nudicaulis,* *Gynura purpurascens,* *Gynura rusisiensis,* *Gynura sagittaria,* *Gynura somalensis,* *Gynura variifolia,* *Senecio biflora,* *Senecio pseudochina.*	India, Vietnam, Laos, Cambodia, Bhutan, Myanmar, Sri Lanka, China, Thailand, Malaysia, Indonesia and Australia	Leaves, roots, rhizome and whole plant.	Inflammation, herpes infection, burning pain, ulcer and abscesses, pain, fever, eruptive fever, detoxification, bleeding, rash, diabetes and cancer.	(Davies, 1980a, 1980b, 1979; Nurulita et al., 2012; Siriwatanametanon and Heinrich, 2011; Vanijajiva, 2009)

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1252 **Table 2.** Phytoconstituents from the genus *Gynura*

No.	Compounds	Sources	Plant part(s)	References
Pyrrolizidine alkaloids				
1	Retronecine-7-$C_5H_9O_2$	*G. segetum*	Whole plant	(Qi et al., 2009)
2	Retronecine-9-$C_5H_9O_2$	*G. segetum*	Whole plant	(Qi et al., 2009)
3	Retronecine-7-$C_5H_9O_2$ N-oxide	*G. segetum*	Whole plant	(Qi et al., 2009)
4	Retronecine-9-$C_5H_9O_2$ N-oxide	*G. segetum*	Whole plant	(Qi et al., 2009)
5	Nilgirine	*G. bicolor*	Aerial parts	(Fioeoen, 2000)
6	(+)-Senecionine/ Senecionine	*G. bicolor*	Aerial parts	(Chen et al., 2017)
		G. divaricata	Aerial parts	(Chen et al., 2017)
		G. elliptica	Roots	(Lin et al., 2000)
		G. japonica	Roots	(Fang et al., 2014)
		G. pseudochina	Tuber	(Windono et al., 2012)
		G. segetum	Whole plant, root tubers	(Liang and Roeder, 1984; Qi et al., 2009; Yang et al., 2009)
7	Retrorsine	*G. bicolor*	Aerial parts	(Chen et al., 2017; Fioeoen, 2000)
		G. divaricata	Aerial parts	(Chen et al., 2017)
8	Seneciphylline	*G. bicolor*	Aerial parts	(Chen et al., 2017)
		G. divaricata	Aerial parts	(Chen et al., 2017)
		G. japonica	Roots	(Chen et al., 2017)
		G. segetum	Whole plant, root tubers	(Qi et al., 2009; Yang et al., 2009)
9	Seneciphyllinine	*G. japonica*	Roots	(Fang et al., 2014)
		G. segetum	Whole plant	(Qi et al., 2009)
10	Gynuramine	*G. scandens*	Whole plant	(Wiedenfeld, 1982)
11	Acetylgynuramine	*G. scandens*	Whole plant	(Wiedenfeld, 1982)
12	Senecionine N-oxide	*G. japonica*	Roots	(Fang et al., 2014)

		G. segetum	Whole plant, roots, tuber.	(Qi et al., 2009; Yang et al., 2009)
13	Retrorsine N-oxide	*G. bicolor*	Aerial parts	(Chen et al., 2017)
14	Seneciphylline N-oxide	*G. bicolor*	Aerial parts	(Chen et al., 2017)
		G. divaricata	Aerial parts	(Chen et al., 2017)
		G. japonica	Roots	(Fang et al., 2014)
15	Seneciphyllinine N-oxide	*G. segetum*	Whole plant	(Qi et al., 2009)
16	Integerrimine	*G. bicolor*	Aerial parts	(Chen et al., 2017; Fioeoen, 2000)
		G. divaricata	Aerial parts	(Chen et al., 2017; Roeder et al., 1996)
		G. japonica	Roots	(Fang et al., 2014)
17	Usaramine	*G. bicolor*	Aerial parts	(Fioeoen, 2000)
		G. divaricata	Aerial parts	(Roeder et al., 1996)
18	Spartioidine/ (E)-Seneciphylline	*G. bicolor*	Aerial parts	(Chen et al., 2017)
		G. divaricata	Aerial parts	(Chen et al., 2017)
		G. japonica	Roots	(Fang et al., 2014)
		G. segetum	Whole plant	(Fioeoen, 2000)
19	(E)-Seneciphyllinine	*G. japonica*	Roots	(Fang et al., 2014)
20	Integerrimine N-oxide	*G. japonica*	Roots	(Fang et al., 2014)
21	(E)-Seneciphylline N-oxide	*G. japonica*	Roots	(Fang et al., 2014)
22	(E)-Seneciphyllinine N-oxide	*G. japonica*	Roots	(Fang et al., 2014)
		G. segetum	Whole plant	(Qi et al., 2009)
23	Yamataimine	*G. segetum*	Whole plant	(Qi et al., 2009)
24	Jacoline	*G. segetum*	Whole plant	(Qi et al., 2009)
25	Sennecicannabine (or stereoisomer)	*G. segetum*	Whole plant	(Qi et al., 2009)
26	Sennecicannabine (or stereoisomer) N-oxide	*G. segetum*	Whole plant	(Qi et al., 2009)
27	(+)-Senkirkine	*G. bicolor*	Aerial parts	(Chen et al., 2017)
		G. divaricata	Aerial parts	(Chen et al., 2017)
		G. elliptica	Roots	(Lin et al., 2000)

		G. pseudochina	Tuber	(Windono et al., 2012)
28	Tetrahydrosenecionine	*G. segetum*	Whole plant	(Qi et al., 2009)
29	Petasinine	*G. bicolor*	Aerial parts	(Fioeoen, 2000)
30	Macrophylline	*G. bicolor*	Aerial parts	(Fioeoen, 2000)
Phenolic compounds				
31	Benzoic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
		G. japonica	Rhizomes	(Lin et al., 2003)
32	3-Hydroxybenzoic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
33	4-Hydroxybenzoic acid	*G. bicolor*	Aerial parts, leaves	(Chen et al., 2015; Teoh et al., 2016)
		G. divaricata	Aerial parts	(Chen et al., 2015)
		G. japonica	Rhizomes	(Lin et al., 2004)
34	Methyl 4-hydroxybenzoate	*G. japonica*	Rhizomes	(Lin et al., 2004)
35	Protocatechuic acid	*G. bicolor*	Aerial parts, leaves	(Chao et al., 2015)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
36	Vanillic acid	*G. procumbens*	Leaves	(Kaewseejan and Siriamornpun, 2015)
		G. segetum	Aerial parts	(Zhu et al., 2013)
37	Gallic acid	*G. bicolor*	Aerial parts, leaves	(Chao et al., 2015; Chen et al., 2015)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
		G. segetum	Leaves	(Yuandani and Husain; 2017)
38	Syringic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
		G. segetum	Aerial parts	(Zhu et al., 2013)
39	*p*-Coumaric acid	*G. bicolor*	Aerial parts, leaves	(Chao et al., 2015; Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)

		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
		G. pseudochina	Leaves	(Sukadeetad et al., 2018)
40	Caffeic acid	*G. bicolor*	Aerial parts, Leaves	(Chao et al., 2015; Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
		G. formosana	Whole plant	(Hou et al., 2005)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
		G. pseudochina	Leaves	(Sukadeetad et al., 2018)
41	Ferulic acid	*G. bicolor*	Leaves	(Chao et al., 2015)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
42	Sinapic acid	*G. procumbens*	Leaves	(Kaewseejan and Siriamornpun, 2015)
43	4-Hydroxy benzaldehyde	*G. japonica*	Rhizomes	(Lin et al., 2004)
44	Syringaldehyde	*G. elliptica*	Roots	(Lin et al., 2000)
45	Gynunol	*G. elliptica*	Roots	(Lin et al., 2000)
46	(+)-Gynunone	*G. elliptica*	Roots	(Lin et al., 2000)
47	4-Hydroxy phenyl pyruvic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
48	4,5,4′-Trihydroxy-chalcone	*G. segetum*	Leaves	(Yuandani and Husain; 2017)
49	8,8′-(Ethene-1,2-diyl)-dinaphtalene-1,4,5-triol.	*G. segetum*	Leaves	(Yuandani and Husain; 2017)
50	Ellagic acid	*G. bicolor*	Leaves	(Chao et al., 2015)
51	Rosmarinic acid	*G. bicolor*	Leaves	(Chao et al., 2015)
Quinic acid-based phenolic derivatives				
52	3-*O*-*p*-Coumaroylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
53	4-*O*-*p*-Coumaroylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
54	Methyl 4-*O*-*p*-coumaroylquinate	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)

55	5-*O*-*p*-Coumaroylquinic acid	*G. bicolor*	Aerial parts, leaves	(Chen et al., 2015; Teoh et al., 2016)
		G. divaricata	Aerial parts	(Chen et al., 2015; Chen et al., 2014)
56	Chlorogenic acid/ 3-*O*-Caffeoylquinic acid	*G. bicolor*	Aerial parts, leaves	(Chao et al., 2015; Chen et al., 2015; Teoh et al., 2016)
		G. divaricata	Aerial parts	(Chen et al., 2015; Chen et al., 2014)
		G. medica	Leaves	(Tan et al., 2013)
		G. nepalensis	Leaves	(Yu et al., 2016)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
		G. pseudochina	Leaves	(Sukadeetad et al., 2018)
57	Methyl 3-*O*-caffeoylquinate	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
58	4-*O*-Caffeoylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
59	5-*O*-Caffeoylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015; Chen et al., 2014)
		G. pseudochina	Leaves	(Siriwatanametanon and Heinrich, 2011)
60	Methyl 5-*O*-caffeoylquinate	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015; Chen et al., 2014)
61	3,4-Dicaffeoylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015; Chen et al., 2014)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Chen et al., 2014, Wan et al., 2011)
		G. nepalensis	Leaves	(Yu et al., 2016)
62	Methyl 3,4-dicaffeoylquinate	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Chen et al., 2014)
		G. nepalensis	Leaves	(Yu et al., 2016)

63	3,5-Dicaffeoylquinic acid	*G. bicolor*	Aerial parts, leaves	(Chen et al., 2015; Teoh et al., 2016)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Chen et al., 2014, Wan et al., 2011)
		G. nepalensis	Leaves	(Yu et al., 2016)
		G. pseudochina	Leaves	(Siriwatanametanon and Heinrich, 2011)
64	Methyl 3,5-dicaffeoylquinate	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Chen et al., 2014)
		G. medica	Leaves	(Tan et al., 2013)
		G. nepalensis	Leaves	(Yu et al., 2016)
65	Ethyl 3,5-dicaffeoylquinate	*G. nepalensis*	Leaves	(Yu et al., 2016)
66	4,5-Dicaffeoylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Chen et al., 2014, Wan et al., 2011)
		G. nepalensis	Leaves	(Yu et al., 2016)
		G. pseudochina	Leaves	(Siriwatanametanon and Heinrich, 2011)
67	Methyl 4,5-dicaffeoylquinate	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015; Chen et al., 2014)
		G. nepalensis	Leaves	(Yu et al., 2016)
68	Ethyl 4,5-dicaffeoylquinate	*G. divaricata*	Aerial parts	(Chen et al., 2014)
69	3-*O*-Feruloylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
70	4-*O*-Feruloylquinic acid	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
71	5-*O*-Feruloylquinic acid	*G. bicolor*	Leaves	(Chen et al., 2015)
Chromanones				
72	(-)-*Gynura*one	*G. japonica*	Rhizomes	(Lin et al., 2003)
73	6-Hydroxy-2,2-dimethylchroman-4-one	*G. elliptica*	Roots	(Lin et al., 2000)
74	6-Acetyl-2,2-dimethylchroman-4-one	*G. elliptica*	Roots	(Lin et al., 2000)

		G. japonica	Rhizomes	(Lin et al., 2003)
75	6-Acetyl-2-hydroxymethyl-2'-methylchroman-4-one	*G. japonica*	Rhizomes	(Lin et al., 2003)
Phenylpropanoid glycosides				
76	Verbascoside	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
77	β-Hydroxy-verbascoside	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
78	Isoacteoside	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
79	Forsythoside A	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
80	Betonyoside A	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
81	Echinacoside	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
82	α-L-rhamnopyranosyl-(1↔2)-β-D-[4″-(8E)-7-(3,4-dihydroxyphenyl)-8-propenoate,1″-O-(7S)-7-(3,4-dihydroxyphenyl)-7-methoxyethyl]-glucopyranoside	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
83	Spicaoside	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
84	3′,9,9′-Trihydroxy-3,5-dimethoxy-8-O-4′-neolignan-4-O-β-D-glucopyranoside	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
85	Cuneataside E	*G. cusimbua*	Aerial parts	(Ma et al., 2019)
Flavonoids				
86	Apigenin	*G. bicolor*	Leaves	(Chao et al., 2015)
		G. calciphila	Whole plant	(Anurukvorakun, 2013)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
87	Kaempferol	*G. bicolor*	Aerial parts	(Chao et al., 2015; Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015; Chen et al., 2009a)
		G. medica	Leaves	(Liu et al., 2010; Yi et al., 2016)
		G. procumbens	Leaves, stems	(Hu et al., 2019; Kaewseejan and Siriamornpun 2015)
88	Quercetin	*G. bicolor*	Leaves	(Chao et al., 2015)
		G. calciphila	Whole plant	(Anurukvorakun, 2013)
		G. medica	Leaves	(Tan et al., 2013)

		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
89	Myricetin	*G. bicolor*	Leaves	(Chao et al., 2015)
		G. procumbens	Leaves	(Kaewseejan and Siriamornpun, 2015)
90	Naringenin	*G. bicolor*	Leaves	(Chao et al., 2015)
91	Hesperitin	*G. calciphila*	Whole plant	(Anurukvorakun, 2013)
92	Catechin	*G. calciphila*	Whole plant	(Anurukvorakun, 2013)
93	Epicatechin	*G. bicolor*	Leaves	(Chao et al., 2015)
94	Cyanidin	*G. bicolor*	Leaves	(Chao et al., 2015)
95	Petunidin	*G. bicolor*	Leaves	(Chao et al., 2015)
96	Pelargonidin	*G. bicolor*	Leaves	(Chao et al., 2015)
97	Peonidin	*G. bicolor*	Leaves	(Chao et al., 2015)
98	Malvidin	*G. bicolor*	Leaves	(Chao et al., 2015)
Flavonoid glycosides				
99	Kaempferol-3-*O*-β-D-glucoside	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Chen et al., 2009a; Wan et al., 2011b)
		G. medica	Leaves	(Liu et al., 2010; Tan et al., 2013)
		G. procumbens	Leaves	(Akowuah et al., 2002)
100	Kaempferol-3-*O*-β-D-galactoside	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015; Wan et al., 2011b)
101	Kaempferol-3-*O*-rutinoside/ Kaempferol-3-*O*-rhamnosyl-1→6-glucoside	*G. bicolor*	Aerial parts	(Chen et al., 2015; Teoh et al., 2016)
		G. divaricata	Aerial parts	(Chen et al., 2015, 2009a; Wan et al., 2011b)
		G. formosana	Whole plant	(Hou et al., 2005)
		G. medica	Leaves	(Liu et al., 2010; Teoh et al., 2016)
		G. procumbens	Leaves	(Akowuah et al., 2002)
102	Kaempferol-3-*O*-robinobioside	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Wan et al., 2011b)
		G. formosana	Whole plant	(Hou et al., 2005)

		G. medica	Leaves	(Liu et al., 2010)
103	Kaempferol-3,7-di-*O*-β-D-glucoside	*G. divaricata*	Leaves	(Wan et al., 2011b)
		G. medica	Leaves	(Liu et al., 2010)
104	Kaempferol-3-*O*-rutinoside-7-*O*-β-D-glucoside	*G. divaricata*	Leaves	(Wan et al., 2011b)
105	Kaempferol-3-*O*-robinobioside-7-*O*-β-D-glucoside	*G. divaricata*	Leaves	(Wan et al., 2011b)
106	Quercetin-3-*O*-β-D-glucoside	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Wan et al., 2011b)
		G. medica	Leaves	(Liu et al., 2010)
107	Rutin/ Quercetin-3-*O*-rutinoside/ Quercetin-3-*O*-rhamnosyl-1→6-glucoside	*G. bicolor*	Aerial parts, leaves	(Chao et al., 2015; Chen et al., 2015; Teoh et al., 2016)
		G. divaricata	Aerial parts, leaves	(Chen et al., 2015; Wan et al., 2011b)
		G. calciphila	Whole plant	(Anurukvorakun, 2013)
		G. formosana	Whole plant	(Hou et al., 2005)
		G. medica	Leaves	(Liu et al., 2010; Tan et al., 2013)
		G. procumbens	Leaves	(Akowuah et al., 2002; Kaewseejan and Siriamornpun, 2015; Siriwatanametanon and Heinrich; 2011)
		G. pseudochina	Leaves	(Sukadeetad et al., 2018)
		G. segetum	Leaves	(Yuandani and Husain, 2017)
108	Quercetin 3-*O*-rhamnosyl-1→2-galactoside	*G. procumbens*	Leaves	(Akowuah et al., 2002)
109	Isorhamnetin 3-*O*-rutinoside	*G. bicolor*	Aerial parts	(Chen et al., 2015)
		G. divaricata	Aerial parts	(Chen et al., 2015)
110	Homoorientin	*G. procumbens*	Stems	(Hu et al., 2019)
111	Eriocitrin,	*G. procumbens*	Stems	(Hu et al., 2019)
112	Kuromanin	*G. bicolor*	Leaves	(Hu et al., 2019)
Steroids				
113	β-Sitosterol	*G. japonica*	Rhizomes	(Lin et al., 2003)
		G. procumbens	Leaves, stems	(Hu et al., 2019; Sadikun et al., 1996)
		G. pseudochina	Whole plant, Leaves	(Ferlinahayati et al., 2017; Gultom, 2016)

		G. segetum	Leaves	(Yuandani and Husain; 2017)
114	7-Hydroxy-sitosterol	*G. japonica*	Rhizomes	(Lin et al., 2004)
115	7-Oxo-sitosterol	*G. japonica*	Rhizomes	(Lin et al., 2004)
116	β-Sitosterone	*G. japonica*	Rhizomes	(Lin et al., 2003)
117	6-Hydroxy-sitosterone	*G. japonica*	Rhizomes	(Lin et al., 2004)
118	β-Stigmasterol	*G. japonica*	Rhizomes	(Lin et al., 2003)
		G. procumbens	Leaves, stems	(Hu et al., 2019; Rahman et al., 2013; Sadikun et al., 1996)
		G. pseudochina	Leaves	(Ferlinahayati et al., 2017)
		G. segetum	Aerial parts, Leaves	(Yuandani and Husain, 2017; Zhu, 2013)
119	7-Hydroxy-stigmasterol	*G. japonica*	Rhizomes	(Lin et al., 2004)
120	7-Oxo-stigmasterol	*G. japonica*	Rhizomes	(Lin et al., 2004)
121	Stigmasterone	*G. japonica*	Rhizomes	(Lin et al., 2003)
122	6-Hydroxy-stigmasterone	*G. japonica*	Rhizomes	(Lin et al., 2004)
123	5α-Stigmastan-3-one	*G. procumbens*	Stems	(Hu et al., 2019)
124	Stigmast-3-one	*G. japonica*	Rhizomes	(Lin et al., 2004)
125	Stigmast-22-en-3-one	*G. japonica*	Rhizomes	(Lin et al., 2004)
126	Stigmasta-1,4-dien-3-one	*G. japonica*	Rhizomes	(Lin et al., 2003)
127	Stigmasta-1,4,22-trien-3-one	*G. japonica*	Rhizomes	(Lin et al., 2003)
128	Cholest-3-one	*G. japonica*	Rhizomes	(Lin et al., 2004)
129	Ergost-3-one	*G. japonica*	Rhizomes	(Lin et al., 2004)
130	5,8-Epidioxy-ergost-6,22-dien-3-ol	*G. japonica*	Rhizomes	(Lin et al., 2004)
131	3-*epi*-Ruscogenin	*G. japonica*	Roots	(Takahira et al., 1977)
132	3-*epi*-neo-Ruscogenin	*G. japonica*	Roots	(Takahira et al., 1977)
Steroid glycosides				
133	Daucosterol/ 3-*O*-β-D-Glucopyranosyl-β-sitosterol	*G. japonica*	Rhizomes	(Lin et al., 2003)
		G. procumbens	Leaves, stems	(Hu et al., 2019; Sadikun et al., 1996)
134	β-Sitosteryl glucoside-6'-*O*-heptadecoicate	*G. divaricata*	Aerial parts	(Chen et al., 2009a)

135	7-Oxositosteryl-3-*O*-β-D-glucopyranoside	*G. japonica*	Rhizomes	(Lin et al., 2004)
136	3-*O*-β-D-Glucopyranosyl stigmasetrol	*G. japonica*	Rhizomes	(Lin et al., 2003)
		G. procumbens	Leaves	(Sadikun et al., 1996)
137	7-Oxostigmasteryl-3-*O*-β-D-glucopyranoside	*G. japonica*	Rhizomes	(Lin et al., 2004)
138	3-*epi*-Diosgenin-3-*O*-β-D-glucopyranoside	*G. japonica*	Roots	(Takahira et al., 1977)
139	3-*epi*-Sceptrumgenin-3-*O*-β-D-glucopyranoside	*G. japonica*	Roots	(Takahira et al., 1977)
Cerebrosides				
140	*Gynura*mides I/ (2S,3S,4R,8E)-2-[(R)-2-hydroxypentacosanoylamino]-8-en-1,3,4-octadecanetriol	*G. japonica*	Rhizomes	(Lin et al., 2004)
141	*Gynura*mides II/ (2S,3S,4R,8E)-2-[(R)-2-hydroxytetracosanoylamino]-8-en-1,3,4-octadecanetriol	*G. japonica*	Rhizomes	(Lin et al., 2004)
142	*Gynura*mides III/ (2S,3S,4R,8E)-2-[(R)-2-hydroxytricosanoylamino]-8-en-1,3,4-octadecanetriol	*G. japonica*	Rhizomes	(Lin et al., 2004)
143	*Gynura*mides IV/ (2S,3S,4R,8E)-2-[(R)-2-hydroxydocosanoylamino]-8-en-1,3,4-octadecanetriol	*G. japonica*	Rhizomes	(Lin et al., 2004)
144	(2S, 3S, 4R, 8E)-2-[(2R)-2 Hydroxypalmitoylamino]-8-octadecene-1, 3, 4-triol	*G. segetum*	Aerial parts	(Zhu et al., 2013)
145	*Gynura*oside/ 1-*O*- β - D-Glucopyranosyl-(2S,3S,4R,10E)-2-[(2'R)-2' -hydroxydocosanoyl-amino]-10-octadecene-1,3,4-triol	*G. divaricata*	Aerial parts	(Chen et al., 2009b)
Terpenoids (Carotenoids)				
146	Zeaxanthin	*G. bicolor*	Leaves	(Chao et al., 2015)
147	Lutein	*G. bicolor*	Leaves	(Chao et al., 2015)
Terpenoids (Triterpenes)				

148	Arborinol	*G. segetum*	Aerial parts	(Zhu et al., 2013)
149	Isoarborinol	*G. segetum*	Aerial parts	(Zhu et al., 2013)
150	α-Amyrin	*G. japonica*	Rhizomes	(Lin et al., 2004)
151	β-Amyrin	*G. japonica*	Rhizomes	(Lin et al., 2004)
152	Friedelan-3-ol	*G. japonica*	Rhizomes	(Lin et al., 2004)
153	Friedelan-3-one	*G. japonica*	Rhizomes	(Lin et al., 2004)
154	Lupeol	*G. japonica*	Rhizomes	(Lin et al., 2004)
155	Cycloarta-24(31)-en-3-ol	*G. japonica*	Rhizomes	(Lin et al., 2004)
156	α-Tocospiro A	*G. japonica*	Rhizomes	(Lin et al., 2004)
157	α-Tocospiro B	*G. japonica*	Rhizomes	(Lin et al., 2004)
158	(-)-α-Tocospirone	*G. japonica*	Rhizomes	(Lin et al., 2003)
Terpenoids (Non-volatile sesquiterpenes)				
159	Loliolide	*G. bicolor*	Aerial parts	(Chen et al., 2012)
160	Ficusic acid	*G. bicolor*	Aerial parts	(Chen et al., 2012)
161	4β,10α-Aromadendranediol	*G. procumbens*	Leaves	(Zhang et al., 2014)
162	Schensianol A	*G. procumbens*	Leaves	(Zhang et al., 2014)
163	Negunfurol	*G. procumbens*	Leaves	(Zhang et al., 2014)
164	Muurol-4-ene-1β,3β,10β -triol	*G. procumbens*	Leaves	(Zhang et al., 2014)
165	Muurol-4-ene-1β,3β,10β-triol 3-*O*-β-D-glucopyranoside	*G. procumbens*	Leaves	(Zhang et al., 2014)
166	Muurol-4-ene-1β,3β,15-triol 3-*O*-β-D-glucopyranoside	*G. procumbens*	Leaves	(Zhang et al., 2014)
Terpenoids (Volatile mono- and sesquiterpenes)				
167	Vanillin	*G. elliptica*	Roots	(Lin et al., 2000)
		G. japonica	Rhizomes	(Lin et al., 2003)
168	α-Pinene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)

		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
169	β-Pinene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a; Jiangseubchatveera et al., 2015)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
170	Sabinene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
171	α-Thujene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
172	β-Elemene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
173	Bicycloelemene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
174	α-Cubebene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
175	β-Cubebene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
176	α-Copaene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a; Jiangseubchatveera et al., 2015)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
177	β-Copaene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
178	β-Yalangene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
179	Cyclosativene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)

		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
180	α-Muurolene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
181	γ-Muurolene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
182	α-Cadinene	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
183	δ-Cadinene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
		G. divaricata	Leaves	(Jiangseubchatveera et al., 2015)
184	γ-Cadinene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
		G. bicolor	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
185	α-Selinene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
186	7-*epi*-α-Selinene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
187	β-Selinene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
188	Menthol	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
189	*p*-Menth-2-en-1-ol	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
190	Menthone	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)

191	α-Terpinene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
192	γ-Terpinene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
193	α-Terpineol	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
194	Terpinen-4-ol	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
195	Terpinolene	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
196	Limonene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
197	α-Phellandrene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
198	β-Phellandrene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
199	Carvone	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
200	3-Cyclohexen-1-one, 2-isopropyl-5-methyl-	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
201	*o*-Cymene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)

		G. medica	Leaves	(Chen et al., 2012a)
202	*p*-Cymene	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
203	*p*-Cymen-7-ol	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
204	α-Cadinol	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
205	Cubenol	*G. divaricata*	Leaves	(Jiangseubchatveera et al., 2015)
206	α-Calacorene	*G. divaricata*	Leaves	(Jiangseubchatveera et al., 2015)
207	δ-3-Carene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
208	4-Carene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
209	Germacrene D	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
210	Bicyclo-germacrene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
211	α-Humulene/ α-Caryophyllene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
		G. divaricata	Leaves	(Chen et al., 2012a; Jiangseubchatveera et al., 2015)
		G. medica	Leaves	(Chen et al., 2012a)
212	β-Caryophyllene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
213	Caryophyllene oxide	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. japonica	Rhizomes	(Lin et al., 2003)

		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
214	Dihydro-actinidiolide	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
215	Toluene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
216	Benzaldehyde	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
217	Benzene acetaldehyde	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
218	Styrene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
219	2,6-Dimethyl-pyridine	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
220	2-Butylfuran	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
221	*p*-Benzoquinone	*G. cusimbua*	Aerial parts	(Jiangseubchatveera et al., 2015)
222	Cuminaldehyde	*G. cusimbua*	Aerial parts	(Jiangseubchatveera et al., 2015)
223	Methyl salicylate	*G. medica*	Leaves	(Chen et al., 2012a)
224	Viridiflorene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
225	Viridiflorol	*G. divaricata*	Leaves	(Jiangseubchatveera et al., 2015)
226	Spathulenol	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a; Jiangseubchatveera et al., 2015)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)

227	α-Gurjunene	*G. divaricata*	Leaves	(Chen et al., 2012a)
228	Aromadendrene	*G. divaricata*	Leaves	(Jiangseubchatveera et al., 2015)
229	α-Farnesene / (E,E)-α-Farnesene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. medica	Leaves	(Chen et al., 2012a)
230	(Z,E)-α-Farnesene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
231	*trans*-β-Farnesene	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
232	Citronellal	*G. medica*	Leaves	(Chen et al., 2012a)
233	Nonanal	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
234	3-Nonene	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
235	Linalool	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a; Jiangseubchatveera et al., 2015)
		G. cusimbua	Aerial parts	(Jiangseubchatveera et al., 2015)
236	*cis*-Linalool oxide	*G. cusimbua*	Aerial parts	(Jiangseubchatveera et al., 2015)
237	Myrcene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
238	(E)-β-Ocimene / *trans*-Ocimene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
		G. cusimbua	Aerial parts	(Jiangseubchatveera et al., 2015)
239	*cis*-Ocimene	*G. cusimbua*	Aerial parts	(Jiangseubchatveera et al., 2015)
240	Ethyl caproate	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)

241	Sulcatone	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
242	Dodecyl acrylate	*G. cusimbua*	Aerial parts	(Jiangseubchatveera et al., 2015)
243	Phytol	*G. divaricata*	Leaves	(Jiangseubchatveera et al., 2015)
244	1-Tridecene	*G. bicolor*	Leaves	(Shimizu et al., 2009)
245	1-Undecene	*G. bicolor*	Leaves	(Chen et al., 2012a; Shimizu et al., 2009)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
246	1-Octen-3-yl acetate 1	*G. bicolor*	Leaves	(Chen et al., 2012a)
247	Octanal	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
248	Heptanal	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
249	(Z)-2-Heptenal	*G. bicolor*	Leaves	(Chen et al., 2012a)
250	1-Hexanol	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
251	(E)-2-Hexenol / 2-Hexen-1-ol	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
		G. cusimbua	Aerial parts	(Rana and Blazquez, 2007)
252	3-Hexen-1-ol	*G. cusimbua*	Aerial parts	(Rana and Blazquez, 2007)
253	Hexanal	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)

254	(E)-2-Hexenal	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
255	(E,E)-2,4-Hexadienal	*G. bicolor*	Leaves	(Chen et al., 2012a)
		G. divaricata	Leaves	(Chen et al., 2012a)
		G. medica	Leaves	(Chen et al., 2012a)
Terpenoids (Megastigmane-type norisoprenoids)				
256	Vomifoliol	*G. bicolor*	Aerial parts	(Chen et al., 2012b)
257	Dehydrovomifoliol	*G. bicolor*	Aerial parts	(Chen et al., 2012b)
258	Boscialin	*G. bicolor*	Aerial parts	(Chen et al., 2012b)
259	(6S,9S)-Roseoside	*G. bicolor*	Aerial parts	(Chen et al., 2012b)
Fructo-oligosaccharides				
260	β-D-Fructofuranose	*G. divaricata*	Aerial parts	(Chou et al., 2012)
261	Sucrose	*G. divaricata*	Aerial parts	(Chou et al., 2012)
262	1-kestose	*G. divaricata*	Aerial parts	(Chou et al., 2012)
263	Nystose	*G. divaricata*	Aerial parts	(Chou et al., 2012)
264	1-β-Fructofuranosyl nystose	*G. divaricata*	Aerial parts	(Chou et al., 2012)
Polysaccharides				
265	GDPs-1	*G. divaricata*	Leaves	(Liu et al., 2011)
266	GDPs-2	*G. divaricata*	Leaves	(Liu et al., 2011)
267	GDPs-3	*G. divaricata*	Leaves	(Liu et al., 2011)
268	GMP	*G. medica*	Whole plant	(Li et al., 2016)
269	GMP-1	*G. medica*	Whole plant	(Li et al., 2016)
270	GPP-20	*G. procumbens*	Leaves	(Li et al., 2017)
271	GPP-40	*G. procumbens*	Leaves	(Li et al., 2017)
272	GPP-60	*G. procumbens*	Leaves	(Li et al., 2017)
273	GPP-80	*G. procumbens*	Leaves	(Li et al., 2017)
Peptides and proteins				

274	Actin	*G. procumbens*	Leaves	(Hew and Gam, 2011)
275	Aldolase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
276	Alpha-L-fucosidase 2 precursor	*G. procumbens*	Leaves	(Hew and Gam, 2011)
277	ATS1 (Arabidopsis thaliana Seed gene 1)	*G. procumbens*	Leaves	(Hew and Gam, 2011)
278	ATGSTU20 (glutathione S- transferase TAU 20)	*G. procumbens*	Leaves	(Hew and Gam, 2011)
279	ATP synthase beta subunit	*G. procumbens*	Leaves	(Hew and Gam, 2011)
280	ATP synthase CF1 alpha subunit	*G. procumbens*	Leaves	(Hew and Gam, 2011)
281	ATP synthase beta subunit	*G. procumbens*	Leaves	(Hew and Gam, 2011)
282	ATP synthase gamma chain	*G. procumbens*	Leaves	(Hew and Gam, 2011)
283	Auxin-induced protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
284	Catalase 4	*G. procumbens*	Leaves	(Hew and Gam, 2011)
285	Catalase Energy and metabolism	*G. procumbens*	Leaves	(Hew and Gam, 2011)
286	Chlorophyll a/b-binding protein C (cab-C)	*G. procumbens*	Leaves	(Hew and Gam, 2011)
287	Chlorophyll a/b-binding protein type I	*G. procumbens*	Leaves	(Hew and Gam, 2011)
288	Chlorophyll a/b binding protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
289	Chlorophyll a/b binding protein 215	*G. procumbens*	Leaves	(Hew and Gam, 2011)
290	Chlorophyll a/b binding protein precursor	*G. procumbens*	Leaves	(Hew and Gam, 2011)
291	Chloroplast chlorophyll a/b binding protein 8	*G. procumbens*	Leaves	(Hew and Gam, 2011)
292	Citrate binding protein Growth and division	*G. procumbens*	Leaves	(Hew and Gam, 2011)
293	Cysteine synthase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
294	Elongation factor Tu	*G. procumbens*	Leaves	(Hew and Gam, 2011)
295	Ferredoxin-NADP reductase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
296	Fructose-bisphosphate aldolase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
297	F-box family protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
298	Glutamine synthetase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
299	Glyceraldehyde-3-phosphate dehydrogenase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
300	Quinone-oxidoreductase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
301	Gynurin (monomeric sequence: LNCCNLLL)	*G. pseudochina*	Rhizomes	(Hew and Gam, 2011)

302	Harpin binding protein 1	*G. procumbens*	Leaves	(Hew and Gam, 2011)
303	Heat-shock protein 60-3A	*G. procumbens*	Leaves	(Hew and Gam, 2011)
304	Heat-shock protein Secondary metabolism	*G. procumbens*	Leaves	(Hew and Gam, 2011)
305	Hydin-like protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
306	Light-harvesting complex	*G. procumbens*	Leaves	(Hew and Gam, 2011)
307	Miraculin homologue	*G. procumbens*	Leaves	(Hew and Gam, 2011)
308	Maturase K	*G. procumbens*	Leaves	(Hew and Gam, 2011)
309	Malate dehydrogenase Transport	*G. procumbens*	Leaves	(Hew and Gam, 2011)
310	Nucleic acid synthesis	*G. procumbens*	Leaves	(Hew and Gam, 2011)
311	Nucleoside diphosphate kinase B Protein destination and storage	*G. procumbens*	Leaves	(Hew and Gam, 2011)
312	Osmotin-like protein I	*G. procumbens*	Leaves	(Hew and Gam, 2011)
313	Oxygen-evolving enhancer protein 2	*G. procumbens*	Leaves	(Hew and Gam, 2011)
314	Oxygen-evolving enhancer protein 1	*G. procumbens*	Leaves	(Hew and Gam, 2011)
315	PAG1;endopeptidase/peptidase/threonine-type endopeptidase Signal transduction	*G. procumbens*	Leaves	(Hew and Gam, 2011)
316	Protein kinase family protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
317	Protein synthesis	*G. procumbens*	Leaves	(Hew and Gam, 2011)
318	Peroxidase 12	*G. procumbens*	Leaves	(Hew and Gam, 2011)
319	Peroxidase 67	*G. procumbens*	Leaves	(Hew and Gam, 2011)
320	PSI type III chlorophyll a/b binding protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
321	PS II stability/assembly factor HCF136	*G. procumbens*	Leaves	(Hew and Gam, 2011)
322	Probable peroxisomal (S)-2-hydroxy-acid oxidase 2	*G. procumbens*	Leaves	(Hew and Gam, 2011)
323	Photosynthetic electron transfer-like protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
324	Phosphoglycerate kinase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
325	Phosphate translocator-related	*G. procumbens*	Leaves	(Hew and Gam, 2011)
326	Putative kinesin-like protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
327	Putative peroxidase	*G. procumbens*	Leaves	(Hew and Gam, 2011)

328	Putative blue light receptor	*G. procumbens*	Leaves	(Hew and Gam, 2011)
329	PUR5; ATP binding/ phosphoribosylformylglycinamidinecyclo-ligase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
330	3-Mercaptopyruvate sulfurtransferase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
331	Ribulose 1,5-bisphosphate carboxylase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
332	60S Ribosomal protein L13-2	*G. procumbens*	Leaves	(Hew and Gam, 2011)
333	RuBisCo large subunit	*G. procumbens*	Leaves	(Hew and Gam, 2011)
334	RuBisCo-activase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
335	Ribulose-phosphate 3-epimerase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
336	Ribosomal protein L4	*G. procumbens*	Leaves	(Hew and Gam, 2011)
337	RNA polymerase II second largest subunit	*G. procumbens*	Leaves	(Hew and Gam, 2011)
338	mRNA-binding protein CSP41 precursor	*G. procumbens*	Leaves	(Hew and Gam, 2011)
339	Sedoheptulose-1,7-bisphosphatase	*G. procumbens*	Leaves	(Hew and Gam, 2011)
340	Small ribosomal protein 4	*G. procumbens*	Leaves	(Hew and Gam, 2011)
341	Thylakoid lumen 18.3 kDa protein	*G. procumbens*	Leaves	(Hew and Gam, 2011)
342	Type I (26 kD) CP29 polypeptide	*G. procumbens*	Leaves	(Hew and Gam, 2011)

1260 **Table 3.** Pharmacological activities of different species of *Gynura*

Species	Activity	Preparation types	Types of study	Testing subjects/ methods	Administered Dose	Effects	References
Gynura bicolor	Antidiabetic	Aqueous extract	*In vivo*	Male BALB/cA mice	0.5 & 1% (w/w) of GAE diet	↓ Plasma glucose concentration. ↑ Insulin level in plasma.	(Pai et al., 2019)
	Anti-oxidant	Methanol extract	*In vitro*			Prominent activity in DPPH scavenging assay.	(Teoh et al., 2013)
	Anticancer	Methanol extract	*In vitro*			Cytotoxicity against HCT 116 and HCT-15 colon cancer cells.	(Teoh et al., 2013)
	Anticancer	(+)-Senecionine/ Senecionine	*In vitro*	Cell viability assay in HepG2 cells	0.335 mg/mL	Significant cytotoxicity.	(Chen et al., 2017)
	Anticancer	Chlorogenic acid/ 3-*O*-Caffeoylquinic acid	*In vitro*	MTT assay on cell viability on HCT 116 cancer cells	79.3±3.1 µg/mL	Selective cytotoxic activity.	(Chao et al., 2015; Chen et al., 2015; Teoh et al., 2016)
	Anti-oxidant	Aqueous and ethanol extract	*In vitro*		2 and 4 %	↓ Reactive oxygen species formation.	(Chao et al., 2015)
	Anti-inflammatory	Aqueous and ethanol extract	*In vitro*		2 and 4 %	↓ Production of interleukin-6, tumor necrosis factor-alpha and prostaglandin E2 and cyclooxygenase-2 activity.	(Chao et al., 2015)

	Anti-inflammatory	Ether extract	*In vitro*	Immuno-blots and Electro-phoresis mobility Shift assays		↓ LPS-induced inducible NO synthase (iNOS).	(Wu et al., 2013)
	Anticancer	Hot water extract	*In vitro*			↑ Apoptosis in HL60 leukemia cells.	(Hayashi et al., 2002)
Gynura cusimbua	Anticancer	Ethanol extract	*In vivo*	HUVECs and wild-type zebrafish		Exceptional antiangiogenic activity.	(Ma et al., 2019)
	Antiangiogenic activity	β-Hydroxy-verbascoside, Betonyoside A, 3′,9,9′-Trihydroxy-3,5- dimethoxy-8-*O*-4′- neolignan-4-*O*-β-Dglucopyranoside, α-L-rhamnopyranosyl-(1↔2)-β-D-[4″-(8E)-7- (3,4-dihydroxyphenyl)-	*In vitro* and *In vivo*	Inhibition of VEGF mediated cell proliferation in human umbilical vascular endothelial cells and Quantitative endogenous alkaline phosphatase (EAP) assay in	10 ng/mL	Significant antiangiogenic activity.	(Ma et al., 2019)

		8-propenoate,1″-*O*-(7S)- 7-(3,4-dihydroxyphenyl)-7- methoxyethyl]-glucopyranoside and Spicaoside		wild-type (Zebrafish			
Gynura divaricata	Anti-hypertensive	Aqueous extract	*In vitro*		1.25, 0.625 and 0.3125 mg/mL	↓ Angiotensin-I converting enzyme (ACE) activity.	(Wu et al., 2011)
	Antidiabetic	Aqueous extract	*In vitro*		1.25, 0.625 and 0.3125 mg/mL	↓ α-amylase and α-glucosidase enzymes activity.	
	Antidiabetic	Lyophilized powder	*In vivo*	Male imprinting control region mice	1.2 and 4.8 % of GD diet	↑ Insulin resistance. ↑ Glycogen synthesis. ↓ Fasting plasma glucose level.	(Xu et al., 2015)
	Hypoglycemic	5-*O*-p-Coumaroylquinic acid, 3,5-Dicaffeoylquinic acid and 4,5-Dicaffeoylquinic acid	*In vitro*	PTP1B inhibition assay	10 mg/mL	Hypoglycemic activity	(Chen et al., 2015; Chen et al., 2014)

Hypoglycemic	3,4-Dicaffeoylquinic acid, 4,5-Dicaffeoylquinic acid and Methyl 4,5-dicaffeoylquinate	*In vitro*	Yeast α-glucosidase inhibition assay	10 mg/mL	Hypoglycemic activity.	(Chen et al., 2015; Chen et al., 2014)
Hypoglycemic	Nystose and 1-β-Fructofuranosyl nystose	*In vitro*	Hexose transport assay via uptake of 2-deoxyD-[3H] glucose in 3T3-L1 cells	5 mg/mL	Hypoglycemic activity.	(Chou et al., 2012)
Anti-oxidant	Lyophilized powder	*In vivo*	Male imprinting control region mice	1.2 and 4.8 % of GD diet	↑ Glutathione peroxidase.	(Xu et al., 2015)
Antidiabetic	Aqueous extract	*In vivo*	Male Kunming (KM) mice	100 mL/kg	↓ Fasting serum glucose level.	(Li et al., 2018)
Anticancer	Aqueous extract	*In vitro*			Exhibited low toxicity through MTT assay.	(Li et al., 2018)
Anticancer	(+)-Senecionine/ Senecionine	*In vitro*	Cell viability assay in HepG2 cells	0.335 mg/mL	Cytotoxicity was shown.	(Chen et al., 2017)

Cytotoxic	Gynuraoside/ 1-*O*-β-D-Glucopyranosyl-(2S,3S,4R,10E)-2-[(2'R)-2' -hydroxydocosanoyl -amino]- 10-octadecene-1,3,4-triol	*In vitro*	Cell viability assay on L1210 leukemia cell line	2-20 µg/mL	Significant cytotoxicity.	(Chen et al., 2009b)
Cytotoxic	Cubenol	*In vitro*	Cell viability assay on KB, MCF-7 and NCIH187 cancer cell lines	50 µg/mL	Mild cytotoxicity.	(Jiangseubchatveera et al., 2015)
Antidiabetic	Polysaccharides	*In vivo*	Male Sprague–Dawley rats	400mg/kg	↓ Intestinal disaccharidases enzyme.	(Deng et al., 2011)
Antidiabetic	Aqueous- alcoholic extract	*In vitro*	Yeast		↓ α-glucosidase and Protein Tyrosine Phosphatase 1B (PTP1B) enzyme activity.	(Chen et al., 2014)

	Antibiotic	Essential oil, n-hexane, dichloro-methane and methanol extract	*In vitro*			Significant antibacterial activity .	(Jiangseubchatveera et al., 2015)
	Anticancer	Essential oil, n-hexane, dichloro-methane and methanol extract	*In vitro*			↓ Growth of KB, MCF-7 and NCI-H187 cancer cell lines.	(Jiangseubchatveera et al., 2015)
	Anti-oxidant	Aqueous (45%)-ethanol extract	*In vitro*			Significant activities were shown.	(Wan et al., 2011a)
	Anticancer	Aqueous extract	*In vitro & In vivo*	Huh7 xenograft mice	300 mg/kg	↓ Cellular proliferation as well as tumor growth in Huh7 liver cancer cells.	(Yen et al., 2018)
Gynura formosana	Anti-oxidant	70% aqueous acetone extract	*In vitro*			Exerting antioxidative activity.	(Hou et al., 2005)
	Anti-oxidant	Ethyl acetate extract	*In vitro*			↑ DPPH and ABTS radicals scavenging properties.	(Li et al., 2018)
	Anti-oxidant	Caffeic acid, Kaempferol-3-Orutinoside/	*In vitro*	DPPH assay, superoxide anion and	0.997-500 µg/mL	Exerting antioxidative activity.	(Hou et al., 2005)

		Kaempferol3-*O*-rhamnosyl-1→6-glucoside, Kaempferol-3-*O*-robinobioside and Rutin/ Quercetin-3-Orutinoside/ Quercetin-3-*O*-rhamnosyl-1→6-glucoside		hydroxyl radical scavenging assay			
	Anti-inflammatory	Ethyl acetate extract	*In vivo*	Sprague-Dawley rats	100, 250 & 500 mg/kg	↓ Tumor necrosis factor-α (TNFα) and interleukin-1β (IL-1β) level in plasma.	(Li et al., 2018)
	Anti-oxidant	Ethyl acetate extract	*In vivo*	Sprague-Dawley rats	100, 250 & 500 mg/kg	↑ Catalase, superoxide dismutase and glutathione level.	(Li et al., 2018)
	Anticancer	Ethyl acetate	*In vitro*			↓ HeLa cervical cells, HepG2 liver cells, and MCF-7 breast cells line growth.	(Ma et al., 2018)
Gynura japonica	Anti-oxidant	Ether and ethyl acetate extract	*In vitro*	Thiocyanate method		Exerted potent antioxidative activity.	(Su et al., 1986)
(Gynura segetum)	Anti-oxidant	Methanol extract	*In vitro*	DPPH assay & β-carotene–		Strong activity was observed.	(Seow et al., 2014b)

			linoleic acid method			
Anti-inflammatory		*In vivo*	Male Sprague Dawley rats	125, 250 and 500 mg/kg	↓ Plasma levels of TNFα, IL-1 and cyclooxygenase activity specially that of COX-2.	(Seow et al., 2014b)
Anti-inflammatory	Methanol extract	*In vitro*	Hen's egg test chorioallantoic membrane (HET-CAM) assay		Significant anti-inflammatory activity was observed.	(Seow et al., 2014a)
Antiplatelet aggregation activity	6-Acetyl-2,2-dimethylchroman-4-one and Vanillin	*In vitro*	Arachidonic acid induced platelet aggregation assay	150 µg/mL, 100 µg/mL	Prominent antiplatelet aggregation activity.	(Lin et al., 2003)
Immuno-suppressive activity	Gallic acid, 4,5,4′-Trihydroxychalcone, 8,8′-(Ethene-1,2-diyl)- dinaphtalene-1,4,5- triol, Rutin/ Quercetin-3-Orutinoside/ Quercetin-3-*O*-	*In vitro*		3.125-100 µg/mL	↓ Phagocytosis, lymphocyte proliferation, cytokine release and nitric oxide production from phagocytic cells.	(Yuandani and Husain; 2017)

		rhamnosyl-1→6-glucoside and β-Sitosterol				
	Antibiotic	Ethyl acetate fraction of methanol extract	*In vitro*	Agar well-diffusion method	↓ *S. aureus, B. subtilis, E. aerogenes, P. aeruginosa, Escherichia coli, P. mirabilis* and *C. albicans* growth.	(Seow et al., 2012)
	Anticancer	Methanol extract and its fraction	*In vitro*	Chick embryo chorioallantoic membrane (CAM) assay	Showed potent anti-angiogenic property.	(Seow et al., 2011)
Gynura medica	Antidiabetic	Ethanol extract	*In vivo*	Adrenaline-glucose-induced diabetic mice	↓ Plasma glucose level. ↑ Glucose tolerance.	(Ji et al., 2009; Liu et al., 2005; Zheng-dong and Wen-shu, 2008)
	Antidiabetic	Methyl 3,5-dicaffeoylquinate, quercetin, kaempferol-3-*O*-β-D-glucoside, kaempferol-3-*O*-rutinoside and rutin.	*In vitro*	α-Glucosidase inhibitory assay	↓ α-Glucosidase enzyme activity.	(Tan et al., 2013)

Anti-oxidant	GMP and GMP-1	*In vitro*	DPPH and ABTS radicals scavenging assay	1.6 mg/mL	Prominent antioxidant activity.	(Li et al., 2016)
Hypoglycemic	Chlorogenic acid/ 3-OCaffeoylquinic acid, Methyl 3,4-dicaffeoylquinate, Quercetin, Kaempferol-3-*O*-β-D-glucoside, Kaempferol-3-*O*-rutinoside/ Kaempferol-3-*O*-rhamnosyl-1→6-glucoside and rutin.	*In vitro*	Yeast α-glucosidase inhibition assay	0.125-2 mg/mL	Strong hypoglycemic activity was observed.	(Tan et al., 2013; Liu et al., 2010; Teoh et al., 2016)
Hypoglycemic	GMP	*In vitro*	Yeast α-glucosidase inhibition assay	1 mg/mL	Significant hypoglycemic activity.	(Li et al., 2016)
Anticancer		*In vitro*	MCF-7 Human breast cancer cell line		↓ Anti-apoptotic protein Bcl2. ↑ Pro-apoptotic protein Bax.	(Yi et al., 2016)

	Cytotoxic	Kaempferol	*In vitro*	Cell viability assay in MCF-7 cell line	20-80 µM	Significant cytotoxic activity.	(Liu et al., 2010; Yi et al., 2016)
Gynura nepalensis	Anti-inflammatory	Ether extract	*In vivo*	Swiss albino mice	250 & 500 mg/kg	↓ Paw and ear edema.	(Rahman et al., 2018)
	Analgesic	Ether extract	*In vivo*	Swiss albino mice	250 & 500 mg/kg	↓ Acetic acid induced writhing and formalin induced paw licking.	(Rahman et al., 2018)
Gynura procumbens	Antidiabetic	Aqueous extract	*In vivo*	Male ICR mice	300 mg/kg	↓ α-glucosidase and α-amylase.	(Choi et al., 2016b)
	Antidiabetic	Ethanol extract	*In vivo*	Male Sprague-Dawley rats	250 mg/kg	↑ Glycogen levels in liver.	(Gansau et al., 2012)
	Antidiabetic	Aqueous ethanol extract	*In vivo*	Male Sprague Dawley rats	50, 100, 150 mg/kg	↑ Glucose metabolism. ↑ Liver hexokinase, phosphofructokinase and fructose-1,6-bisphosphatase. ↓ Gluconeogenesis.	(Lee et al., 2012)
	Antidiabetic	Aqueous extract	*In vitro*	RIN-5F cell study		↑ Glucose uptake by abdominal muscle cells.	(Hassan et al., 2010)
	Antidiabetic	Aqueous extract	*In vivo*	Male C57BL/KsJ-db/db mice	0.5% w/w	↑ Insulin sensitivity. ↓ Insulin resistance.	(Choi et al., 2016a)
	Anti-oxidant	Methanol extract	*In vitro*	β-carotene–		Significant activity shown by ethyl acetate fraction.	(Rosidah et al., 2008)

			linoleic acid model system, DPPH scavenging assay, reducing power and xanthine oxidase inhibitory activity			
Anti-oxidant	Ethanol extract	*In vitro*	DPPH, $ABTS^{+}$, OH and H_2O_2 scavenging assay.		↓ Lipid peroxidation and oxidative protein damage.	(Kaewseejan and Siriamornpun, 2015)
Anti-oxidant	Aqueous extract	*In vitro*	DPPH assay and ferric reducing antioxidant power assay		↑ Anti-oxidative capacity.	(Krishnan et al., 2015)
Anti-oxidant	GPP-20, GPP-40, GPP-60 and GPP-80	*In vitro*	Reducing power, DPPH and hydroxyl anion scavenging assay	78.1-5000 µg/mL	Prominent anti-oxidant activity.	(Li et al., 2017)

Anti-inflammatory	Ethanol extract	*In vivo*	BALB /c white mice	0.75 mg	Potent topical activity in croton oil-induced mouse ear inflammation model.	(Iskander et al., 2002)
Anti-inflammatory	Ethanol extract	*In vivo*	Male BALB/c mice		↓ Pro-inflammatory TFN-α and interferon γ (IFN-γ). ↑ Anti-inflammatory interleukin IL-10.	(Wong et al., 2015)
Antibiotic	Methanol extract	*In vitro*		500 ppm	Prominent antimycobacterial activity.	(Isrul et al., 2018)
Antibiotic	Methanol and hexane extract	*In vitro*	Disc diffusion method	50, 100, 200, 400 mg/mL	Strong activity against *S. aureus, B. subtilis, K. pneumoniae,* and *P. aeruginosa.*	(Nawi et al., 2019)
Antiviral	Ethanol extract, water-methanol, methanol and ethyl acetate fraction	*In vitro*	Plaque reduction assay	Vero cell line	Potent virucidal and antireplicative activity against herpes simplex virus HSV-1 and HSV-2.	(Jarikasem et al., 2013)
Anti-hypertensive	Aqueous extract	*In vivo*	Male SHR rats		↑ Concentration of vasodilator Nitric oxide.	(Kim et al., 2006)
Anti-hypertensive	Ethanol extract	*In vivo*	SHR and control normotensiveWistar-Kyoto (WKY) rats	10 mg/kg	↓ Angiotensin Converting Enzyme.	(Hoe et al., 2007)

		In vitro	Thoracic aortic rings of rat	0-10 mg/kg		
Anti-hypertensive	Butanol fraction	*In vivo*	Adult male albino Sprague-Dawley (SD) rats	2.5-20 mg/kg	↑ Vasodilation ↓ Calcium influx through voltage-dependent calcium channels.	(Hoe et al., 2011)
Anti-hypertensive	Purer aqueous fraction	*In vitro*	Thoracic aortic rings of rat		↑ Bradykinin activity. ↑ Nitric oxide and prostaglandins.	(Poh et al., 2013)
		In vivo	Adult male albino Sprague-Dawley (SD) rats			
Anti-hypertensive	Butanol fraction and different sub-fraction	*In vitro*	Adult male SD rats		↑ Vasodilation. ↑ Potassium channel opening. ↑ Prostacyclin production.	(Ng et al., 2013)
Anticancer	Ethanol extract	*In vivo*	Male Sprague Dawley rats	3.5 g dry leaves/kg	↓ Dysplastic changes.	(Agustina et al., 2006)
Anticancer	Aqueous extract	*In vitro*			↓ DNA synthesis by reducing the expression of platelet-derived growth factor (PDGF-BB), transforming growth factor (TGFβ1) and cyclin dependent kinase (CDK1 and CDK2).	(Lee et al., 2007)

	Anticancer	Ethanol extract	*In vivo*	Sprague Dawly Rats	250, 500 & 750 mg/kg	↓ Tumor growth.	(Meiyanto et al., 2007)
	Anticancer	Ethanol extract	*In vivo*	Sprague Dawly male Rats	300 & 750 mg/kg	Significant anti-proliferative properties against DMBA-induced hepatic carcinoma.	(Nisa et al., 2012)
	Anticancer	Ethanol extract	*In vitro*			↓ Nuclear translocation of NF-κB. ↓ Ribosomal expression of NF-κB p65 protein. ↓ Cellular proliferation.	(Wang er al., 2013)
	Anticancer	Ethanol extract (30%)	*In vitro*			↑ IL-2, IL-4, and IL-12 expression. ↑ CD4 + T cell activation.	(Takanashi et al., 2019)
	Anticancer	Ethanol extract	*In vitro*			↑ CD4 + T cell activation. ↓ CD62L molecule. ↑ CD25 molecule.	(Dwijayanti and Rifa'I, 2015)
	Anticancer	Ethyl acetate extract	*In vitro*			Cytotoxic activity against MCF-7 and T47D breast cell lines.	(Nurulita et al., 2012)
	Anticancer	Protein fraction	*In vitro*			↓ Expression of Ki67, PCNA and CCL2 in the MDA-MB-23 breast cancer cells.	(Hew et al., 2013)
Gynura pseudochina	Anti-oxidant	Water extract	*In vitro*			Potent free radical scavenging property.	(Suhartono et al., 2016)
	Anti-oxidant	Aqueous-ethanol extract	*In vitro*			Prominent activity with high phenolic content.	(Krisyanella et al., 2016)

	Antibiotic	Ethanol extract	*In vitro*			Potent antifungal properties.	(Rahman, 2020)
	Anticancer	Gynurin (monomeric sequence: LNCCNLLL)	*In vitro*	Cell viability assay on KATO-III cancer cells	0-400 μM	Significant cytotoxicity.	(Hew and Gam, 2011)

1261 Note: '↑' sign represents upregulation/stimulation; '↓' sign represents downregulation/suppression/inhibition

Figures legends

Figure 1. Pyrrolizidine alkaloids from the genus *Gynura.*

Figure 2. Phenolic compounds from the genus *Gynura.*

Figure 3. Quinic acid based phenolic derivatives from the genus *Gynura.*

Figure 4. Chromanones from the genus *Gynura.*

Figure 5. Phenylpropanoid glycosides from the genus *Gynura.*

Figure 6. Flavonoids from the genus *Gynura.*

Figure 7. Flavonoid glycosides from the genus *Gynura.*

Figure 8. Steroidal compounds from the genus *Gynura.*

Figure 9. Steroid glycosides from the genus *Gynura.*

Figure 10. Cerebrosides from the genus *Gynura.*

Figure 11. Carotenoids from the genus *Gynura.*

Figure 12. Triterpenes from the genus *Gynura.*

Figure 13. Non-volatile sesquiterpenes from the genus *Gynura.*

Figure 14. Volatile mono- and sesquiterpenes from the genus *Gynura* (Continued).

Figure 15. Megastigmane-type norisoprenoids from the genus *Gynura.*

Figure 16. Fructo-oligosaccharides from the genus *Gynura.*

Figure 17. Downstream mechanisms leading to antidiabetic activities of different *Gynura* species.

Figure 18. Intracellular mechanisms of the anti-inflammatory and anticancer properties of different *Gynura* species.