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# Review of in vitro and in vivo research on Gynura procumbens (Lour.) Merr.'s potential as an antidiabetic

**M Kishore Babu[1], P. Chandra Sekhar[2], S Chellaram[3], P. Gangi Reddy[4]**

1. Professor , Department of pharmaceutics , QIS College of pharmacy , Ongole , A.P
2. Assistant Professor , Department of Pharmaceutics , QIS College of pharmacy , Ongole , A.P
3. Assistant Professor , Department of Pharmaceutics , QIS College of pharmacy , Ongole , A.P
4. Assistant Professor , Department of Pharmaceutics , QIS College of pharmacy , Ongole , A.P

**ABSTRACT**

A chronic metabolic condition, diabetes mellitus (DM) affects around 10.5% of individuals globally. It causes serious side effects such cardiovascular disease, retinopathy, and nephropathy. Long-term usage of pharmaceutical medications, which may be expensive and have a number of negative consequences, is a common component of conventional therapy for diabetes mellitus. These difficulties have led to an increase in interest in complementary therapies, especially those made from herbal medications, in order to investigate their possible antidiabetic effects. According to scientific research, Gynura procumbens (Lour.) Merr. (GP) contains antioxidant qualities that significantly lower blood glucose levels and enhance lipid profiles. Therefore, the purpose of this study is to provide a thorough summary of the current understanding of GP's antidiabetic potential based on 12 in vivo investigations and four in vitro studies. With some trials indicating similar effectiveness to metformin in the treatment of diabetes, GP extract has encouraging promise as an antidiabetic drug at doses ranging from 50 mg to 3,000 mg. Furthermore, a variety of phytochemical metabolites have been identified by phytochemical investigations of GP, with a preponderance of polyphenolic metabolites—particularly phenolic acids and flavonoids—extracted from different solvents. The data is still conflicting, however, since other research has shown differing findings on GP's effectiveness in treating diabetes. This may be because there aren't enough clinical investigations, the extract preparation isn't standardized, and there isn't enough information on the bioactive metabolite causing the effects. Thus, more thorough research, including clinical trials, is required to elucidate the disparities in the results and show how GP helps to reduce DM. With these advancements, GP might provide patients with a safer, more comprehensive approach while supplementing conventional DM therapy.

**KEYWORDS**

**diabetes mellitus, antidiabetic plant, Gynura procumbens, hypoglycaemic, antioxidative, phytochemical**

- Corresponding Author
Kishore babu
kishorebabu@gmail.com

## Introduction

Persistent hyperglycemia brought on by decreased insulin production, action, or both is a hallmark of diabetes mellitus (DM), a chronic metabolic condition (Kharroubi and Darwish, 2015; Artasensi et al., 2020). Type 1 DM (T1DM) and type 2 DM (T2DM) are the two categories into which it falls. Ten percent of DM patients are T1DM, which is characterized by an extreme insulin shortage and often manifests as symptoms including thirst, weight loss, and polyuria (Sun et al., 2021). Conversely, type 2 diabetes is characterized by β-cell malfunction, insulin resistance in the target tissue, and relatively low insulin production, which often results in no symptoms (Nyenwe et al., 2011). Long-term consequences from diabetes mellitus impact the heart, blood vessels, kidneys, nerves, eyes, and other organs. Diabetes mellitus may be caused by a number of reasons, including genetic inheritance,

β-cells are destroyed by viral infections, bad

lifestyle choices, and other physical or chemical harm (Roglic, 2016).

According to Hossain et al. (2024), the incidence of diabetes mellitus is rising alarmingly globally and presents significant issues for healthcare systems everywhere. According to a recent research, if present trends continue, the prevalence of DM is expected to reach 700 million individuals worldwide by 2045, underscoring the urgent need for efficient treatment and preventative measures (Sun et al., 2022). According to a different research, DM is more common in low- and middle-income nations, where health systems are often ill-prepared to handle the disease's burden (Dendup et al., 2018). According to Weinberg Sibony et al. (2023), the primary goal of current conventional therapies for diabetes mellitus is blood glucose management with the use of pharmaceuticals like insulin, metformin, and other antidiabetic medications. They do not, however, address the disease's complex nature and often cause adverse effects. Long-term usage of certain drugs, for instance, may result in weight gain, gastrointestinal issues, and an elevated risk of cardiovascular events (Shurrab and Arafa, 2020). Furthermore, the fundamental causes of diabetes mellitus, such as insulin resistance and beta-cell dysfunction, are not sufficiently addressed by these therapies.

Consequently, the use of complementary and alternative treatments, such as herbal medications, to treat diabetes is becoming more popular. By focusing on many metabolic pathways implicated in the onset of diabetes mellitus, botanical medications provide a comprehensive strategy (Pang et al., 2019). They may provide further advantages including anti-inflammatory and antioxidant properties and are often thought to have minimal adverse effects (Adam et al., 2022). Additionally, in low- and middle-income nations, traditional antidiabetic medications may be too expensive or unavailable. Locally cultivated botanical drugs, in particular, are often thought to be more accessible and cost-effective (Mohan et al., 2020; Chaachouay and Zidane, 2024). Furthermore, in contemporary healthcare systems, integrative medicine—which blends traditional therapies with evidence-based complementary practices—is growing in significance. As a consequence, more study has been done on the antidiabetic qualities of many botanical medications, which have shown encouraging outcomes in preclinical and clinical trials (Vivó-Barrachina et al., 2022).

A large and priceless source of bioactive metabolites, many of which have a variety of pharmacological characteristics, may be found in botanical medications. They are a promising research route with great potential to improve the overall treatment of diabetes mellitus because of their varied methods of action and typically decreased risk of side effects. In 2023, Yedjou et al. A herbal plant high in bioactive metabolites, Gynura procumbens (Lour.) Merr. (GP) may have therapeutic uses for a variety of illnesses. The Asteraceae family includes this perennial evergreen plant (Tan et al., 2016). It is referred to as "bai bing cha" by Chinese and Malay populations (Murugaiyah et al., 2018), "Sambung Nyawa" or Sabungai in Malay (Jobaer et al., 2023), and "pyar-hmee" in Myanmar (Aung et al., 2021). "Longevity spinach" is another name for it (Jobaer et al., 2023). According to Tan et al. (2016), this green vegetable usually grows tiny and reaches a height of one to three meters. Additionally, it has ovate-elliptical or lanceolate leaves that are 3.5–8 cm long and 0.8–3.5 cm broad, as well as yellow, thin, panicle-shaped flower heads that are 1–1.5 cm tall. There are large populations of this edible herbaceous plant in China, Malaysia, Indonesia, Thailand, and Vietnam. According to Kaewseejan et al. (2015), GP leaves are a popular vegetable in Thailand that are used in a wide range of culinary inventions. They are used in salads, soups, curries, chilli paste, and other meals and may be eaten raw or cooked. It is often eaten raw with rice in Malaysia and added to salads and ulam (Hew and Gam, 2011).

Diabetes, hyperlipidemia, kidney disease, hypertension, fever, constipation, skin irritation, migraine, rheumatism, hemorrhoids, and colon cancer have all been treated with this plant for a long time in traditional medicine (Zhang and Tan, 2000; Rosidah et al., 2009; Hassan et al., 2010; Mohamed et al., 2023). According to Iskander et al. (2002), Kim et al. (2011), Algariri et al. (2013), Hew et al. (2013), Jarikasem et al. (2013), Jeon and Kwon (2016), and others, this plant possesss a wide range of medicinal qualities, including anti-hyperlipidaemic, anti-inflammatory, antibacterial, antifungal, antihypertensive, antioxidant, and anticancer effects. Compared to synthetic medications that are sold commercially, this natural substance is a superior choice with less adverse effects. GP is a substantial alternative to contemporary medicine since it is easily accessible and reasonably priced, which is crucial for a

population that is very impoverished. Furthermore, because of the expanding markets for herbal raw materials and processed goods, GP has the potential to be grown commercially and used to produce organic products as a result of its rising popularity as a natural treatment.

Thus, the purpose of this review is to provide an overview of the most recent data from in vitro and animal models on the possible health advantages of GP in DM and its complications. This plant's promise as a supplementary therapy for the treatment of diabetes mellitus is highlighted by both its historic usage in folk medicine and scientific confirmation.

## 1 Nutritional and Phytochemistry of *Gynura procumbens* (Lour.) Merr

The nutritional analysis of GP leaves revealed that they contain 13.59% crude fibre and 16.92% ash. Its nutritional properties, especially the high fibre content and low glycaemic profile, increase the antidiabetic potential of GP and make it a promising candidate for dietary intervention for the prevention or treatment of T2DM (Nath et al., 2023). In addition, GP leaves contain a low composition of protein (6.2%), moisture (6.2%), carbohydrate (0.4%), and fat (0.07%) (Nath et al., 2023). This is important as it can help reduce the risk of various chronic diseases, such as type 2 diabetes by improving insulin sensitivity, regulating blood glucose levels, and reducing the risk of developing diabetes (Jobaer et al., 2023). The nutritional contents of the GP extract are listed in Table 1.

TABLE 1 Proximate nutritional contents of GP extract.

| Component | Content | References |
|---|---|---|
| Proximate analysis (%) | | Nath et al. (2023) |
| Ash | 16.92 | Nath et al. (2023) |
| Moisture | 6.2 | Nath et al. (2023) |
| Carbohydrate | 0.4 | Nath et al. (2023) |
| Protein | 6.2 | Nath et al. (2023) |
| Fat | 0.07 | Nath et al. (2023) |
| Crude fiber | 13.59 | Nath et al. (2023) |

Meanwhile, phytochemical studies of GP have revealed a diverse phytochemical metabolite, with a predominance of polyphenolic metabolites, especially phenolic acids and flavonoids, extracted from various solvents. Of the phenolic acids, gallic acid, protocatechuic acid, p-hydroxybenzoic acid, vanillic acid and syringic acid, which belong to the hydroxybenzoic acid subclass were consistently detected. They can be detected in the aqueous, ethanolic and ethyl acetate fractions of the leaves (Kaewseejan et al., 2015; Liu et al., 2019). Caffeic acid, p-coumaric acid, ferulic acid and sinapic acid, which belong to the hydroxycinnamic acids, can be found in both polar (aqueous, methanol) and semi-polar (ethyl acetate) extracts, indicating their solubility in

a range of solvents (Kaewseejan et al., 2015; Alam et al., 2016; Liu et al., 2019; Kim et al., 2021). In addition, phenolic acids have been shown to lower blood glucose levels and protect against chronic diseases caused by hyperglycaemia through antioxidant protection (Deka et al., 2022). Important flavonoids such as rutin (a quercetin glycoside), quercetin, myrricetin, kaempferol, apigenin and luteolin have been found in several extracts, reflecting their richness and structural diversity within the plant matrix (Kaewseejan et al., 2015; Liu et al., 2019; Kim et al., 2021). These metabolites act on multiple diabetes targets and regulate key signalling pathways that improve both the symptoms and complications of T2DM (Dhanya, 2022). Furthermore, chlorogenic acid, a biologically active caffeoylquinic acid ester, was exclusively detected in the methanolic extract. This indicates its preferential solubility in more polar organic solvents (Kim et al., 2021).

In addition to polyphenols, the methanolic extract of GP also contained considerable amounts of non-phenolic bioactive metabolites, including coumarins such as oxypeucedanin and isoimperatorin, which are known for their anti-inflammatory and vasodilatory effects (Kim et al., 2021; Flores-Morales et al., 2023; Kubrak et al., 2025). Indole-derived compounds such as indole-3- carboxylic acid and kynurenic acid, a tryptophan metabolite with neuroprotective properties, have also been identified and broaden the pharmacological spectrum of the plant (Kim et al., 2021).

On the other hand, the methanolic extract of GP also contained numerous lipophilic metabolites. These include lutein, a potent antioxidant involved in chlorophyll biosynthesis and known for its antimicrobial properties. Several triterpenoids such as lupeol, β-amyrin and friedelanol acetate, which are associated with antidiabetic, anti- inflammatory, anticancer and hepatoprotective activities have also been detected in the methanolic extract of GP (Szakiel et al., 2012; Saha and Bandyopadhyay, 2020; Kim et al., 2021; Jobaer et al., 2023; Dalimunthe et al., 2024). In addition, phytosterols such as stigmasterol and a mixture of stigmasterol and β-sitosterol have also been identified, which are known for their cholesterol-lowering effect as well as their cytoprotective potential and reduced hyperglycaemic effects (Vezza et al., 2020; Jobaer et al., 2023). The antidiabetic effect of stigmasterol may be due to the regeneration of the pancreatic β-cells of Langerhans and thus the secretion of insulin, which controls blood glucose levels (Eidi et al., 2006; Nualkaew et al., 2015).

However, the non-specific bioactivity of natural products is often a hurdle in their bioassay evaluation, including GP (Baell, 2016). Some of its metabolites can behave as pan-assay interference compounds (PAINS), causing false positive signals in various assays and thus complicating their interpretation. For example, the pyrrolizidine alkaloids in GP are known to cause interference in a variety of bioassays due to their reactive nature and the formation of DNA adducts (Ji et al., 2019). Lupeol, stigmasterol and β-sitosterol can interfere with enzyme assays and receptor binding studies due to their structural similarity to endogenous steroids and thus bind non-selectively to other non-endogenous targets (Jobaer et al., 2023). In addition, polyphenolic metabolites such as chlorogenic acid, caffeic acid and various flavonoids could also interfere with redox-based assays (Kim et al., 2021). In addition, some pharmacological profiles of GP may also correspond to mechanisms typical of PAINS. For example, its anti-inflammatory activities have been shown to inhibit the NF-κB signalling pathway and downregulate the expression of pro- inflammatory cytokines such as IL-1β and TNF-α (Wong et al., 2015; Tan et al., 2022). These activities, which involve multiple signalling pathways, are often considered characteristic of PAINS. Nonetheless, the

potential for interference by PAINS does not undermine the medical value of GP. Evidence from a wide range of *in vitro* and *in vivo* studies, as well as from thousands of years of traditional use, has provided a solid basis for its efficacy and safety. This evaluation can be further enhanced by modern analytical and computational techniques. High-resolution techniques, in particular UHPLC-QTOF-MS/MS and HPLC-MS, and the use of computational tools such as molecular docking and molecular dynamics simulations enable the prediction of binding affinities and target interactions. These strategies are particularly useful for the identification of compounds with high promiscuity and thus potential PAINS properties (Tithi et al., 2023). By integrating such approaches, researchers can minimise concerns about assay interference and detect consistent, target-specific biological effects across multiple experimental platforms.

Table 2 provides an overview of the phytochemical metabolite found in GP.

TABLE 2 Phytochemical metabolites found in GP leaves.

| Classification | Phytochemical metabolites | Extraction methods | References |
|---|---|---|---|
| Polyphenol | Gallic acid | Aqueous extract; ethanolic extract; ethyl acetate fraction | Liu et al. (2019) |
| Polyphenol | Protocatechuic acid | Aqueous extract; ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015), Liu et al. (2019) |
| Polyphenol | *p*-Hydroxybenzoic acid | Ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015) |
| Polyphenol | Vanillic acid | Ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015) |
| Polyphenol | Syringic acid | Ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015) |
| Polyphenol | Caffeic acid | Aqueous extract; ethanolic extract; ethyl acetate fraction; methanolic extract | Liu et al. (2019), Kim et al. (2021) |
| Polyphenol | *p*-coumaric acid | Aqueous extract; ethanolic extract; ethyl acetate fraction; methanolic extract | Liu et al. (2019), Kim et al. (2021) |
| Polyphenol | Ferulic acid | Ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015) |
| Polyphenol | Sinapic acid | Ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015) |
| Polyphenol | Rutin | Aqueous extract; ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015), Liu et al. (2019) |
| Polyphenol | Myricetin | Aqueous extract; ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015), Liu et al. (2019) |
| Polyphenol | Quercetin | Aqueous extract; ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015), Liu et al. (2019) |
| Polyphenol | Apigenin | Aqueous extract; ethanolic extract; ethyl acetate fraction | Liu et al. (2019) |
| Polyphenol | Kaempferol | Aqueous extract; ethanolic extract; ethyl acetate fraction | Kaewseejan et al. (2015), Liu et al. (2019) |
| Polyphenol | Chlorogenic acid | Methanolic extract | Kim et al. (2021) |
| Coumarins | Oxypeucedanin | Methanolic extract | Kim et al. (2021) |

| | | | |
|---|---|---|---|
| Coumarins | Isoimperatorin | Methanolic extract | Kim et al. (2021) |
| Indolecarboxylic acids and derivatives | Indol-3-Carboxylic acid | Methanolic extract | Kim et al. (2021) |
| Tryptophan metabolite | Kynurenic acid | Methanolic extract | Kim et al. (2021) |
| Carotenoid | Lutein | Methanolic extract | Kim et al. (2021) |
| Polyphenol | Luteolin | Methanolic extract | Kim et al. (2021) |
| Diterpenoid | Phytol | Methanolic extract | Jobaer et al. (2023) |
| Triterpenoid | Lupeol | Methanolic extract | Jobaer et al. (2023) |
| Phytosterol | Stigmasterol | Methanolic extract | Jobaer et al. (2023) |
| Triterpenoid | Friedelanol acetate | Methanolic extract | Jobaer et al. (2023) |
| Triterpenoid | β-amyrin | Methanolic extract | Jobaer et al. (2023) |
| Phytosterol | Mixture of stigmasterol and β-sitosterol | Methanolic extract | Jobaer et al. (2023) |

## 2 Pharmacokinetics of *Gynura procumbens* (Lour.) Merr

The pharmacokinetics of GP have significant implications for its potential therapeutic use; however, they are far from clear. The antidiabetic effect of GP, which is attributed to increased glucose uptake and improved insulin sensitivity, may also be associated with metabolic interactions (Hassan et al., 2010; Guo W. et al., 2021).There are also scants *in vivo* reports on the absorption, distribution, metabolism and excretion profiles of GP and its active fractions. However, useful information can be extrapolated from the known phytochemical profile of this plant and pharmacokinetic studies on structurally related metabolites.

It has been hypothesised that the absorption of polyphenolic metabolites extracted from GP may be poor. The flavonoids and phenolic acids generally have low oral bioavailability due to a high degree of first-pass metabolism (Xin et al., 2011; Ye et al., 2023). However, there is evidence that the presence of other molecules in GP can increase its absorption. For example, chlorogenic acid (CA), a predominant phenolic metabolite of GP, was found to increase intestinal absorption and improve bioavailability when combined with other phytochemicals in plants, with the improvement increasing from 6.7% (CA alone) to 16.0% (Wang et al., 2022). Pharmacokinetic analyses of the total extract are also not available, and the distribution of GP metabolites in the body remains unknown. However, similar flavonoids and phenolic acids have been found to accumulate in metabolically active organs such as adipose tissue, intestine, liver, kidneys and lungs (Ye et al., 2023). These results are in line with previous studies that have shown that GP molecules are widely distributed in numerous tissues, possibly leading to hepatoprotective and nephroprotective effects (Tahsin et al., 2022).

In addition, the metabolites of GP are generally expected to undergo phase I and phase II metabolism, namely, oxidative, reductive, hydrolytic, glucuronidated and sulphated, and methyl-mediated metabolic reactions, which mainly occur in the liver and gastrointestinal tract (Xin et al., 2011; Wang et al., 2022; Ye et al., 2023). Flavonoids and phenolic acids from GP are also likely to be metabolised via these pathways, leading to the formation of conjugated metabolites that can be detected in plasma after oral administration. Such modulating effects may also contribute to its antidiabetic effect. Although the excretion patterns of GP metabolites are not well studied, it is assumed that, like other plant

polyphenols, they are mainly excreted via the kidneys and bile (Ye et al., 2023).

Overall, the data available to date indicate that the biological effects of GP are significantly influenced by its low bioavailability, extensive metabolism and wide tissue distribution. Further studies are needed to clarify this involvement and to translate the molecular understanding to the clinical level of GP-targeted therapy.

## 3 Effects of *Gynura procumbens* (Lour.) Merr. on diabetes mellitus

Previous studies have documented the potential antidiabetic effect of GP, which is characterised by a reduction in blood glucose levels and improved glucose tolerance in DM. A total of 16 studies were found including four *in vitro* studies and 12 *in vivo* studies.

### 3.1 *In vitro* studies

The mechanisms behind GP's antidiabetic effects have been clarified by in vitro research. The molecular processes and signaling pathways involving many cell types were disclosed by the in vitro investigations. Merz and Thurmond (2020) and Aung et al. (2021) found that the aqueous extract of GP caused the GLUT4 membrane to translocate into 3T3-L1 adipocytes, while both the aqueous and ethanolic extracts caused the GLUT4 membrane to translocate into C2C12 muscle cells, which is a crucial location for insulin-stimulated glucose uptake. It's interesting to note that GP affected GLUT4 membrane translocation more strongly in C2C12 muscle cells than in 3T3-L1 adipocyte cells. Tissue-specific variations in sensitivity or responsiveness to the plant extract may be the cause of the observed effect. Both cells also showed an increase in AMP-activated protein kinase (AMPK) phosphorylation. A known therapeutic target for metabolic diseases including type 2 diabetes, AMPK is a crucial regulator of cellular energy balance (Kim et al., 2016; Aydin et al., 2025). Similar to how metformin works, AMPK activation promotes glucose uptake and fatty acid oxidation while suppressing lipogenesis and gluconeogenesis (Ke et al., 2018; O'Neill, 2013; Hasanvand, 2022).

Similarly, the ethanolic extract of GP reduces insulin resistance and restores glucose uptake by activating the PI3K/Akt signaling pathway, a key mechanism in the control of glucose homeostasis (Guo S. et al., 2021; Fontana et al., 2024). The Akt, PI3K, and GLUT4 genes were shown to be upregulated by gene expression analysis, whereas the GS and GSK genes were significantly downregulated.

3β genes. Protein analysis corroborated these gene results, showing that the GP-treated group had greater levels of PI3K, Akt, p-GSK 3β, p-Akt, GLUT4, p-GS, and p-PI3K than the control group. On the other hand, the expression of the GS and GSK 3β proteins was significantly downregulated. Following treatment with varying dosages of GP, the research demonstrated a considerable improvement in both glucose content and glucose absorption. The therapeutic potential of GP in reducing insulin resistance and encouraging efficient glucose utilization is shown by this dose-dependent improvement. All things considered, these molecular and biochemical results demonstrate that GP's ethanolic extract can alter the PI3K/Akt signaling pathway and related downstream targets, supporting its potential as a natural treatment option for insulin resistance and hyperglycemia (Feng et al., 2024).

Additionally, prior research has shown that the regulation of important enzymes involved in insulin signaling pathways, including glycogen synthase kinase three beta (GSK3β), may underlie the antihyperglycaemic actions of GP. This process is believed to include kaempferol, a bioactive flavonoid metabolite of GP that inhibits GSK3β activity (Wong et al., 2015; Yang et al., 2022). As dysregulation of GSK3 activity is linked to insulin resistance and hyperglycemia, the study demonstrated that HepG2 cells treated with the aqueous extract of GP showed increased phosphorylation of GSK3β (Ser9), which in turn caused an increase in glucose (Henriksen, 2010; Liu and Yao, 2016). In hyperglycemic HepG2 cells, GP was also shown to enhance glucose absorption in a concentration-dependent manner, suggesting that it may be used as a natural medicinal drug to lower blood glucose levels.

However, a research using β-cells in T1DM rats' islets of Langerhans revealed no increase in cell viability after the injection of GP water extract (Hassan et al., 2010). In the pancreatic tissue of T1DM rats, however, significant alterations were seen in the distribution pattern of insulin-positive cells, with a notable reduction in the quantity of insulin-positive cells. This decline implies that GP

extract has no protective or regenerative effects on pancreatic insulin-secreting cells and is consistent with the autoimmune destruction of β-cells that defines type 1 diabetes (T1DM) (Roep et al., 2021; Atkinson and Mirmira, 2023). RIN-5F cell treatment, the cloned pancreatic β-cells, with different concentrations of GP water extract also did not lead to a significant increase in insulin levels or an improvement in cell viability. This indicates that the hypoglycaemic effect of the extract is not dependent on insulin secretion. The study concluded that the ability of GP to enhance or mimic insulin action at the cellular level may be related to the insulin-like properties of the active ingredient contained in the extract. Therefore, further studies are needed to identify the active ingredient in GP extract that may play a role in these insulin-like properties which could contribute to the development of new therapies to combat insulin resistance.

### 3.2 *In vivo* studies

Several *in vivo* studies have demonstrated the beneficial blood glucose-lowering effect of DM, which is consistent with traditional claims of its therapeutic use and indicates its potential for diabetes management. For example, repeated oral administration of 250 mg/kg body weight/day of the methanolic extract and its various soluble fractions (SF), including aqueous (AQSF), chloroform (CSF), ethyl acetate (EASF), and petroleum ether (PESF), was found to lower blood glucose levels in T1DM rats for 21 days. AQSF, CSF and PESF showed a greater decrease in blood glucose levels than the other fractions (Jobaer et al., 2023). Similarly, in a 28-day dietary experiment in T1DM rats, administration of dry GP leaf powder was shown to decrease blood glucose levels, increase body weight, decrease triglycerides, cholesterol and low-density lipoproteins (LDL), and increase high-density lipoproteins (HDL) (Nath et al., 2023). These changes reflect the lipid-lowering and cardioprotective potential of GP, which is particularly beneficial for diabetics, who are at increased risk of cardiovascular complications. Furthermore, in a T2DM model using eight-week-old male C57BL/ 6JJL mice fed a high-fat diet (HFD), administration of dried GP powder resulted in a significant reduction in fasting and 2-h blood glucose levels in HFD mice after 3 months and maintained this effect for up to 5 months (Aung et al., 2021).

A previous study has shown that administration of the ethanolic extract of GP at different doses (500, 750 and 1,000 mg/kg) over a treatment period of approximately 42 days led to an increase in body weight in rats with T1DM and showed dose-dependent hypoglycaemic effects (Tahsin et al., 2022). In rats receiving higher doses, the reduction in blood glucose levels was more pronounced, suggesting that the antihyperglycaemic effect of GP is concentration-dependent and possibly related to the better bioavailability of the active phytochemicals at higher doses (Alfahel et al., 2023). Similarly, repeated administration of 50, 150 and 300 mg/kg body weight of an ethanolic GP extract to T1DM rats over a 7-day period resulted in an increase in body weight, a decrease in serum total cholesterol levels and a decrease in triglycerides in these rats. This indicates that GP is able to improve glucose tolerance in STZ-induced T1DM rats but not in normal rats (Zhang and Tan, 2000). The improvement in glucose tolerance could be due to an improvement in insulin sensitivity or modulation of hepatic glucose production and the antidiabetic activity of GP could be more strongly activated under hyperglycaemic conditions. (Li et al., 2022).

The study on the effect of GP also shows acute antihyperglycaemic activity and 14-day antihyperglycaemic activity in T1DM rats. This study showed a significant reduction in blood glucose levels of 25% ethanol extract (EE) and all GP fractions (ethyl acetate fraction (EAF), n-butanol fraction (n-BF) and aqueous fraction (AF)), with the EAF significantly lowering blood glucose levels at 3 and 5 h (Algariri et al., 2014). Further analysis showed that the n-BF and AF fractions of GP exhibited antihyperglycaemic effects comparable to those of metformin, suggesting that it could affect glucose metabolism via similar pathways such

as modulating AMPK activity, altering insulin signalling or increasing the expression of glucose transporters (Entezari et al., 2022; Lee et al., 2022). In addition, the 14-day antihyperglycaemic activity showed a significant reduction in blood glucose levels, with the n-BF fraction showing the most potent effect. The efficacy of this fraction could be related to the presence of flavonoids and other phytoconstituents known for their insulin-mimetic or insulin-sensitising properties (Vinayagam and Xu, 2015; Zanzabil et al., 2023).

Meanwhile, Hassan et al. (2010) showed a significant reduction in body weight and fasting blood glucose levels as well as improved glucose tolerance and marked improvement in glucose utilisation 15–120 min after glucose loading in T1DM rats after 14-day of administration of 500 or 1,000 mg/kg GP water extract (Hassan et al., 2010). In addition, the isolated abdominal muscle of T1DM rats showed a significant increase in glucose uptake. This finding suggests a peripheral mechanism of action likely mediated by increased glucose transporter activity or enhanced intracellular glucose metabolism in skeletal muscle, which plays an important role in glucose utilisation (Chang et al., 2004; Chadt and Al-Hasani, 2020). The same study also concluded that GP inhibits endogenous insulin production and does not stimulate insulin secretion. In another study using different fractions of GP (n-butanol, hexane and ethyl acetate), a significant decrease in blood glucose levels was observed in T1DM rats, with the ethyl acetate fraction showing the most significant effect compared to the other fractions (June et al., 2012). The study also found that GP inhibits GSK3β, suggesting that the hypoglycaemic effect of the GP fractions may be due to direct or indirect effects on the activities of one or more components upstream of the insulin signalling pathway.

GP has also been reported to have an insulinomimetic effect due to its high content of flavonoids and glycosides. GP has been found to inhibit gluconeogenesis in the liver, stimulate glycogenesis, stimulate hepatic glucose and lower hepatic endogenous glucose (Lee et al., 2012; Sok Yen et al., 2021). This contributes to better glycaemic control. In a study on the T1DM rat model, administration of ethanolic and aqueous extracts of GP led to an increase in liver glycogen content, but not to an increase in plasma insulin concentration (Lee et al., 2012). Interestingly, there was a decrease in fasting blood glucose and HbA1c levels. These findings suggest that the glucose-lowering and glycogen-promoting effect of GP is not mediated by increased insulin secretion, but may be due to insulin-independent mechanisms (Panahi et al., 2020). Thus, the ethanolic extract has the potential as an adjunct treatment in the treatment of DM due to its antidiabetic effect, which is comparable to that of metformin. However, further studies are needed to investigate the mechanism of action, long-term efficacy and safety profile.

On the other hand, in-depth studies at the molecular level revealed several potential signalling pathways associated with the role of GP in alleviating T2DM. The ethanolic extract of GP was found to strongly

TABLE 3 Summary of the effects of GP on DM.

| Type of model | Treatment dosage | Treatment duration | Findings | References |
|---|---|---|---|---|
| *In vitro* studies | | | | |
| C2C12 muscle cells 3T3-L1 adipocytes | GP water extract (100 μg/mL) and ethanolic extract (100 μg/mL) | 24 h | ↑ AMPK phosphorylation in both cells Water extract induced GLUT4 membrane translocation in 3T3-L1 adipocytes Both extracts induced GLUT4 membrane translocation in C2C12 muscle cells GLUT4 membrane translocation was more prominently in the C2C12 cells than in 3T3-L1 cells | Aung et al. (2021) |
| HepG2 cells | 0.0391–1.2500 mg/mL ethanolic extract | 24 h | ↑ Akt, PI3K and GLUT4 genes ↓ GS and GSK 3β genes ↑ PI3K, Akt, p-GSK 3β, p-Akt, GLUT4, p-GS, and p-PI3K proteins ↓ GS and GSK 3β proteins Regulated glucose metabolism and insulin resistance via PI3K/Akt signalling pathway | Guo et al. (2021a) |
| HepG2 cells | 0.1 μg/mL aqueous extract | 24 h | ↑ glucose consumption by 51% ↑ phosphorylations of GSK3β | Wong et al. (2015) |
| β-cells in the islet of Langerhans of diabetic rats Insulin-positive cells in the pancreas of diabetic rats RIN-5F cells | 1, 5 or 10 mg/mL water extract | 72 h 72 h 4–5 days for insulin secretion | No improvement in β-cells viability ↓ insulin-positive cells ↑ insulin levels in RIN-5F cells ↑ RIN-5F cells viability | Hassan et al. (2010) |
| *In vivo* studies | | | | |
| Wistar albino rats induced T1DM by 120–150 mg/kg | 250 mg/kg BW/day methanolic extract and its soluble | 21 days | ↓ blood glucose level AQSF, CSF and PESF showed a greater reduction in glucose | Jobaer et al. (2023) |

| | | | | |
|---|---|---|---|---|
| alloxan | fractions: AQSF, CSF, EASF and PESF | | levels compared to the other fractions | |
| Female Swiss albino mice induced T1DM by 150 mg/kg alloxan monohydrate | 0.5% and 1.0% dry GP leaf powder | 28 days | ↓ glucose level<br>↑ body weight<br>↑ HDL level<br>↓ triglycerides, cholesterol, and LDL levels | Nath et al. (2023) |
| Male C57BL/6JJL mice induced T2DM by fed with a high-fat diet (HFD-60) | 1% dried GP powder | 1, 3 and 5 months | ↓ fasting and 2-h blood glucose levels | Aung et al. (2021) |
| Adult male Wistar rats induced T1DM with 150 mg/kg alloxan | 500, 750 and 1,000 mg/kg BW/day ethanolic extract | 42 days | Hypoglycemic activities in a dose-dependent manner<br>↑ body weight | Tahsin et al. (2022) |
| Male Sprague-Dawley induced T1DM by 60 mg/kg body weight STZ | 50, 150 and 300 mg/kg BW/day ethanolic extract | 7 days | ↑ body weight<br>↓ serum glucose level<br>↓ triglyceride<br>↓ serum cholesterol level | Zhang and Tan (2000) |
| Male and female Sprague Dawley rat, induced T1DM by 55 mg/kg STZ | Acute antihyperglycemic activity: 500, 1,000 and 2000 mg/kg BW/day of 25% EE, EAF, n-BF and AF<br>14-day period antihyperglycemic activity: 500 and 1,000 mg/kg BW/day of 25% EE, EAF, n-BF and AF | 14 days in total | Acute antihyperglycemic activity<br>↑ body weight, but insignificant compared to the control group EAF fraction ↓ blood glucose level comparable to metformin after 3 and 5 h<br>14-day period antihyperglycemic activity<br>↑ body weight<br>↓ glucose levels n-BF fraction showed the highest efficacy in reducing glucose levels in a dose-dependent manner | Algariri et al. (2014) |

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TABLE 3 (*Continued*) Summary of the effects of GP on DM.

| Type of model | Treatment dosage | Treatment duration | Findings | References |
|---|---|---|---|---|
| Sprague Dawley rats induced T1DM by 55 mg/kg STZ | 0, 25, 50, 75% and 95% (ethanol in water) | Up to 120 min, 7 h and 14 days for each treatment | ↑ body weight after 14 days<br>95%, 25% and 0% extracts exerted significant effects on blood glucose from 15 to 120 min<br>25% ethanol extract demonstrated the most fasting blood glucose-lowering effect in acute/single oral administration and the 14-day study | Algariri et al. (2013) |
| Male Sprague-Dawley rats, induced T1DM by 65 mg/kg body weight STZ | 500 or 1,000 mg/kg BW/day of water extract | 14 days | ↓ body weight<br>↓ fasting blood glucose level<br>↑ glucose tolerance<br>↑ glucose disposal<br>↑ muscle glucose uptake No glucose absorption | Hassan et al. (2010) |
| Male Sprague-Dawley rats induced T1DM by 45 mg/kg body weight STZ (i.v) | Hexane, ethyl acetate and n-butanol fractions at 250 mg/kg BW/day | 2 weeks | ↓ blood glucose level<br>↑ liver glycogen contents GSK3β was phosphorylated | June et al. (2012) |
| C57BL/KsJ-db/db mice (db/db mice were derived from autosomal recessive inheritance of an C57BL/ KsJ inbred strain used as T2DM model) | 3 g/kg BW/day ethanolic extract | 5 weeks | ↑ protein expression of AKT, eNOS, iNS and MAPK<br>↓ expression of caspase-8 and caspase-3 ameliorated insulin resistance and sensitivity via PI3K/Akt and AGE-RAGE signalling pathway | Guo et al. (2021b) |

| | | | | |
|---|---|---|---|---|
| Male and female C57BL/KsJ db/db mice (used as T2DM model) | 3 g/kg BW/day ethanolic extract | 5 weeks | ↓ water and food intake<br>↓ body weight<br>↓ blood glucose levels after 2 h and fasting blood glucose level<br>↓ serum TC and TG levels ameliorated insulin resistance and sensitivity via PI3K/Akt signalling pathway | Guo et al. (2021a) |
| Male Sprague Dawley rats induced T1DM by 55 mg/kg body weight STZ | 50, 100 and 150 mg/kg BW/day aqueous and ethanolic extract | 42 days | ↓ HbA1c and fasting blood glucose levels<br>↑ liver glycogen content Ethanolic extract showed better improvement than aqueous extract in a dose-independent manner and comparable to metformin<br>Liver hexokinase activity<br>↑ in 100 mg/kg body weight of aqueous extract<br>↓ in 100 and 150 mg/kg body weight of ethanolic extract<br>Liver phosphofructokinase activity<br>↑ in 100 and 150 mg/kg body weight of ethanolic extract led<br>↑ in 100 mg/kg body weight of aqueous extract<br>Liver fructose-1,6-bisphosphatase activity<br>↓ in all dosages of aqueous extract showed a decrease in diabetic rats<br>↓ in 100 and 150 mg/kg body weight of ethanolic extract | Lee et al. (2012) |

affect key proteins and markers in the two disease-related protein signalling pathways, such as phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) and receptor for advanced glycation end products (AGE- RAGE) (Guo W. et al., 2021). Genetic analysis of the study using the T2DM rat model revealed that the genes for eNOS, AKT, MAPK and iNS were significantly upregulated in the GP group compared to the model group, while the genes for caspase-8 and caspase-3 were downregulated. This study also showed

the involvement of two ther metabolic pathways: retinol metabolism and glycerol phosphate metabolism. Further genetic and protein analyses in the T2DM rat model also showed the effect of the ethanolic extract of GP in upregulating GLUT4, Akt and PI3K genes by GP, along with downregulation of GS and GSK 3β genes (Guo S. et al., 2021). This suggest that GP promotes glycogen synthesis and facilitates glucose uptake via insulin-mimetic or insulin-sensitising mechanisms (El- Ashmawy et al., 2022).

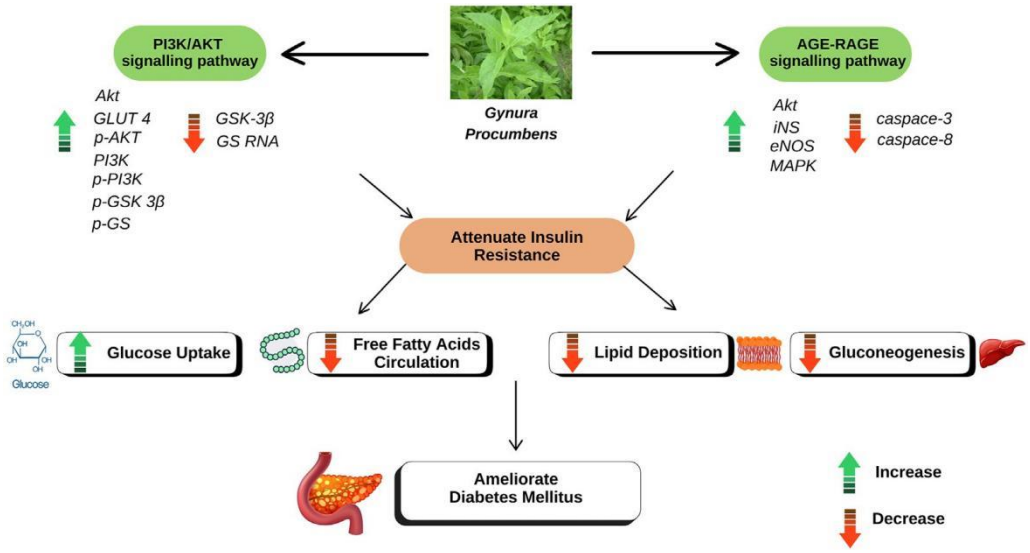


FIGURE 1
The proposed mechanism of action of GP in ameliorating DM.

In particular, RAGE, a molecule from the immunoglobulin superfamily, acts as a receptor for advanced glycation end products (AGEs) (Ong et al., 2018). AGEs are formed by non-enzymatic glycation and protein oxidation, especially in the presence of elevated blood glucose levels (Twarda-Clapa et al., 2022). Consequently, RAGE is considered a key player in the accumulation of various ligands in diabetic tissues (Ramasamy et al., 2011). In addition, PI3K/Akt also plays an important role in cell physiology by regulating the transmission of growth factor signals during important cellular processes and organismal growth, including glucose homeostasis and metabolism (Huang et al., 2018; Savova et al., 2023). The PI3K/AKT signalling pathway controls lipid and glucose metabolism under the guidance of insulin. Under normal circumstances, insulin is released immediately after food intake, which triggers activation of the PI3K/AKT signalling pathway. In T2DM, however, there is a reduced response to insulin which disrupts the activity of the PI3K/AKT signalling pathway. This can lead to reduced insulin secretion by the pancreas, impaired glucose utilisation, increased release of free fatty acids in adipose tissue, decreased lipid accumulation in the body, increased gluconeogenesis in the liver and muscles, and a loss of fine regulation of lipid and glucose metabolism (Huang et al., 2018; Petersen and Shulman, 2018; Feng et al., 2024). A summary of the antidiabetic properties of GP can be found in Table 3 and the proposed mechanism of action of GP is shown in Figure 1.

## 4 Safety of *Gynura procumbens* (Lour.) Merr

Preclinical studies have generally shown that GP is safe for consumption at various doses. For example, the study by Algariri et al. (2014) showed that the maximum dose of the extract of 2000 mg/kg in an acute toxicity test did not result in any treatment-related mortality during the 14-day observation period

(Algariri et al., 2014). In addition, the acceptable daily intake (ADI) was set at 700 mg/kg/day. At the same time, the growth rate and indices of liver, kidney and haematopoietic function were also unaffected, indicating that the extract is safe and no acute toxicity was observed, as the LD50 for female rats is above 2000 mg/kg.

Furthermore, administration of 2 and 4 g/kg GP to rats in a 14- day toxicity trial did not cause any abnormalities in serum biochemical parameters (liver and kidney) or the structure of their organ tissues, with a zero-mortality rate even after the experimental period (Jabbar et al., 2023). The possibility of safe therapeutic use is supported by the absence of adverse effects on organ function, biochemical parameters and histological structures. These results may indicate that GP is a safe candidate of complementary therapy for the treatment of DM, as it has a wide safety margin. Despite the encouraging preclinical results, long-term toxicity, reproductive safety and human clinical studies are still scarce. To ensure the safety of the extract for long-term use in DM, these factors still need to be thoroughly investigated.

## 5 Future direction

Despite these encouraging data on the potential antidiabetic properties of GP, the evidence for its efficacy in the treatment of DM is still inconsistent. Future experimental research should focus on the testing of plant extracts for which comprehensive phytochemical fingerprints should be established according to the ConPhyMP guidelines to improve reproducibility and transparency in phytochemical pharmacology (Heinrich et al., 2022). This includes comprehensive taxonomic authentication using voucher specimens, comprehensive reporting of collection and extraction conditions, and the use of more than one orthogonal analytical technique, such as UHPLC-QTOF-MS/MS, HPLCMS, GCMS and In addition, the lack of standardisation of the extract preparation can lead to different concentrations of the bioactive metabolites, which poses a major challenge for reproducibility and efficacy. For example, aqueous extracts can have different pharmacological effects compared to ethanolic extracts due to differences in solubility and stability of the active metabolites. Thus, standardising the extraction method and ensuring a consistent phytochemical profile is crucial to improve the reproducibility of results and demonstrate the clinical utility of GP in the treatment of DM.

In addition, the bioactive compound responsible for the observed effects was not clearly identified and quantified in some studies. The different study designs and the lack of clinical trials may also contribute to some inconsistencies and limit the generalisability of the results. To clarify these issues, more comprehensive studies are needed to identify the bioactive compounds and molecular targets as well as the mechanisms of action and to assess long- term safety. Potential risks that may be associated with prolonged use of GP, such as hepatotoxicity, nephrotoxicity and other systemic effects, also need to be carefully assessed. An understanding of the pharmacokinetics and pharmacodynamics of GP will also support its integration into current treatment regimens.

However, studies on the safety and efficacy, dose and long-term

effects of GP in humans in clinical trials are very limited. Most current studies are conducted to investigate the underlying mechanisms and pharmacodynamics in controlled laboratory settings that have not yet been translated to the clinical. Accordingly, the lack of comprehensive clinical data on this product has greatly hindered

its inclusion in evidence-based medical systems and practises. Therefore, clinical studies need to be conducted to assess safety, tolerability and dose in healthy humans. This will allow the identification of relevant biomarkers that should be useful not only for monitoring the efficacy of the therapy, but also for the early detection of signs of toxicity. These studies should also include long-term use to detect any chronic toxicities or late-onset adverse effects.

## 6 Conclusion

GP has an impact similar to that of metformin and has encouraging promise as an antidiabetic drug. GP may help lower insulin resistance and boost insulin production by focusing on the AGE-RAGE and PI3K/AKT signaling pathways. The data is still conflicting, however, since other research has shown differing findings on GP's effectiveness in treating diabetes. This may be because there aren't enough clinical trials, the extract preparation isn't standardized, and there isn't enough information on the bioactive ingredient causing the effects. Thus, more thorough research, including clinical trials, is required to elucidate the disparities in the results and show how GP helps to reduce DM. With these advancements, GP might provide patients with a safer, more comprehensive approach while supplementing conventional DM therapy.

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