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Sesbania grandiflora (L.) Pers.: A review of its phytochemistry, molecular pharmacology, and clinical potential

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ABSTRACT

Sesbania grandiflora (L.) Pers. is a valuable medicinal herb with numerous traditional uses, yet its contribution to an evidence-based therapeutic potential is incomplete. This comprehensive review focuses on the current state of knowledge, the mechanistic analysis of its activities, pharmacokinetics, pharmacodynamics, and clinical validation. It also reveals a rich phytochemical profile of compounds such as isoflavonoids (medicarpin), triterpenes (betulinic acid), and unique 2-arylbenzofurans with significant anti-tubercular activity. Mechanistic studies validate its anticancer activity modulating κBI3K/Akt signalling pathways and the induction of mitochondrial-mediated apoptosis. Its apoptotic activity is linked to the inhibition of key carbohydrate-metabolizing enzymes. However, clinical translation is impeded by significant challenges, including the poor bioavailability of key lipophilic compounds, genotoxicity, and safety concerns. Still, robust clinical trial evidence provided that the first randomized controlled trial evaluated a standardized extract in improving heart health. In conclusion, while *S. grandiflora* confirms the confirmatory potential, its future as a modern botanical medicine depends on systematically managing the identified gaps in pharmacokinetics and long-term safety to develop standardized and efficacious formulations.

1. INTRODUCTION

Nature has been a remarkable source of medicine, and plants have been crucial for sustenance and nourishment. Medicinal plants are the source of bioactive compounds that can help treat a wide range of disorders, and they have been utilized for thousands of years to treat illnesses. The World Health Organization reports that over 21,000 plant species are used worldwide. 10% of the world's population relies on medicinal plants for both their health and means of subsistence. *Sesbania* belongs to the clan Robinieae, Papilionoideae – subfamily, and family – Fabaceae. Fabaceae is the third-largest family of flowering plants and is most economically significant [1]. Many Fabaceous plants, especially those belonging to the Papilionoideae subfamily, are commonly used as traditional medicines to cure various ailments, including fever, diarrhea, diabetes, coughing, urinary issues, eye and lung diseases, toothaches, and other infections. About 60 species are found in the genus, primarily in tropical climates worldwide. *Sesbania* species are mainly annual and perennial herbs, shrubs, and trees. They are mainly divided into four subgenera of their pods: Daubentonia, Pterosesbania, *Sesbania*, and Agati. *Sesbania grandiflora*, famous as the *Agati grandiflora* L., West Indian pea, and vegetable-hummingbird, is a fast-growing plant species belonging to the *Sesbania* genus. *Sesbania grandiflora* is native to Malesia and New Guinea [2]. It is grown and naturalized in Colombia. It grows mainly in the wet tropical environment. Since it cannot confirm the taxon's native place, *S. grandiflora* is classified as the IUCN Red List of endangered species, which was last updated in 2023 list. This rapidly growing tree is prized for its many applications. Southeast Asian traditional meals frequently use their edible flowers, leaves, and pods. Different parts of the plant are utilized in Ayurveda and conventional medicine to treat ailments such as respiratory problems, pain,

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and inflammation. The species name "*grandiflora*" describes its huge, flashy blossoms, while "*Sesbania*" comes from the Sesban tribe. The tree helps to enhance the soil fertility and promote nitrogen fixation that is sustainable for agriculture. It is one of India's most widely consumed green vegetables with deeply rooted in traditional medicine and regional cuisines [3]. In a more recent investigation, *S. grandiflora* leaf supplementation was also demonstrated to have a significant hypolipidemic impact against rats Triton-induced hyperlipidemia [4].

Modern pharmacological studies have shown that various parts of this plant, as well as its biologically active constituents, exert a wide range of pharmacological activities, such as antibacterial, antifungal, antidiabetic, and antitumorigenic properties, have been reported for *S. grandiflora* – in both *in-vitro* and *in-vivo* studies. Due to the lack of lipophilicity and bioavailability, the bioactive constituents are less explored. Nano-based drug delivery system helps to overcome this problem. Future researchers can focus on to identify the key lead molecules of this plant for incorporation in the modern system of medicine.

This review aims to draw attention to the medicinal properties of *S. grandiflora* by focusing on its botany, phytochemical constituents, ethnomedicinal uses, extracts' pharmacological activities, and unreported clinical trials. This will help the plant gain significant use in the future.

2. BOTANICAL IDENTITY AND TRADITIONAL SIGNIFICANCE

2.1. Taxonomy, morphology, and global distribution

Sesbania grandiflora belongs to the Kingdom—Plantae, Subkingdom—Tracheobionta, Superdivision—Spermatophyta, Order—Magnoliales, Subclass—Rosidae, Family—Fabaceae (Leguminosae), Genus—*Sesbania*, Species—*grandiflora* (L.) Pers [5]. *Sesbania grandiflora* can grow up to 4–10 m. The root system is typically shallow but spreading. It is heavily nodulated with nitrogen-fixing bacteria, contributing to soil fertility [6]. The bark is naturally furrowed deeply and develops corky, thick, grayish, pink, or whitish plates. It is slightly bitter to taste. Leaves are alternate, pinnate, and compound, 15–40 cm long. They are narrower at the ends of the rachis than in the middle. Both surfaces of the leaflets can have dense, appressed purplish-brown glands and are appressed villous but glabrescent. Its leaves are pinnately compound, 15–40 cm long, bearing 20–60 pairs of oblongs, rounded leaflets. Leaves are at the tips of the branches and become bright yellow before they fall. Inflorescences are 4–7 cm-long pendulous racemes with 2–5 large pink, red, yellowish, or white flowers. Flowers are 5–10 cm long, curved, and approximately 3 cm wide when closed. The bell-shaped calyx is 2 cm long, faintly two-lobed with five shallow teeth. Fruit pods are long (20 to 60 cm), narrow (6 to 9 mm), hanging, flat, septate, with approximately 15–50 swollen margins bearing red-brown seeds. Petiole is 7–15 mm long, and the leaf's midrib (rachis) is terete, densely appressed pubescent when young and glabrescent at maturity. Calyx is campanulate (bell-shaped), 15–29 mm long, with the basal part persistent in the fruit. The corolla consists of five white or red fleshy petals: a standard petal oblongs-obovate to broadly ovate, 50–75 mm long and 35–50 mm wide, reflexed at anthesis (at flowering); two curved wings 50–105 mm long and 20–30 mm wide; and two united curved inside petals. Seeds are ellipsoid to subreniform (almost kidney shaped), 5–6.5 mm long and 2.5–4 mm wide [7,8].

2.2. Role in ethnomedicine and regional cuisines

In many parts of Southeast Asia, *S. grandiflora* has traditionally been used as food and medicine. In particular, the flowers are consumed in Northern Thailand and Malaysia either fresh, boiled, or steamed. This traditional use confirms with scientific findings on plants nutritional value and biological activities. In the modern era, the bioactivity of *S. grandiflora* extends beyond its traditional uses. Its rich protein fraction and high amino acid profile make it a valuable herbal-based protein source for the growing market as a neutraceutical. The bioactive phytomolecules in *Sesbania grandiflora* also present a new possibility for use in functional foods and nutraceuticals [9]. The leaves have remarkably multifunctional applications, used to treat conditions such as epilepsy, night blindness, and bronchitis, and topically used as a poultice for rheumatic swellings, sprains, and wounds. Leaves are diuretic and laxative, and the juices of leaves are also consumed as a remedy to treat diarrhea and dysentery. The flowers are used in traditional practices for headaches, colds, and various inflammatory conditions, with the juice applied for eye sinus and congestion diseases. The decoction of bark is used for the treatment of smallpox, diarrhea, colic, and fever, and is applied topically for relieving rheumatic pain and gout. The roots are applied externally to alleviate inflammation and rheumatic swelling [10].

2.3. Comprehensive nutritional profile

Sesbania grandiflora is a good source of plant protein because of its well-documented high protein content. As reported, it has a much higher crude protein content (25.24%) than other tree fodders and shrubs. Its high nutritional value as feedstuff is due to its high protein and lower crude fiber content of 8.43%. *Sesbania grandiflora* seed nutritional composition was even more remarkable [11]. Seeds have a crude protein content of 37.78%, a total carbohydrate content of 34.91%, and a total lipid content of 5.2%, as reported by research. This indicates that *S. grandiflora* seeds may be a good energy and protein source. Further analysis of the protein content of the seed showed that globulin: 4.24% *S. grandiflora* seeds may supply a balanced amino acid content, making them a high-quality protein source in animal and human nutrition [12].

Sesbania grandiflora is also a rich source of essential micronutrients besides macronutrients. Specifically, the leaves of *S. grandiflora* have a high concentration of vitamins and minerals. In one investigation, the leaves were seen to have the following contents: Vitamin C:145 mg/100 g, Calcium:666 mg/100 g. Notably, the high level of Vitamin C adds not only to the antioxidant activity but also to the nutritional value of the plant. With its high calcium content, *S. grandiflora* could also be a significant plant source of the essential mineral, which is important to provide healthy bones. The presence of other minerals, such as potassium and sodium, also supplements

the nutrient quality of *S. grandiflora*. The presence of such electrolytes would then mean that *S. grandiflora* could play the function of fluid balance regulation and facilitate various physiological processes [8].

This robust nutritional profile not only justifies its role as an edible herb but also contributes to the overall health benefits attributed to it in the traditional medicine system.

3. THE PHYTOCHEMICAL PROFILE OF SESBANIA GRANDIFLORA

Sesbania grandiflora has various secondary metabolites that may have therapeutic and nutritional uses. The plant synthesizes an array of bioactive compounds, such as alkaloids, flavonoids, tannins, saponins, terpenoids, and phenolics, with the highest levels of lipids and alkaloids occurring in the summer season. The leaves are abundant in these compounds compared to the bark and wood.

3.1. An inventory of bioactive constituents

The pharmacological activities of *S. grandiflora* are mainly due to its rich composition of various bioactive phytochemical constituents. Among these constituents, alkaloids, flavonoids, tannins, saponins, and sterols are the important constituents that play an important role behind the biological activities [10]. That includes anti-cancer, anti-inflammatory, and anti-diabetic activities. It acts both as a traditional medicine and nutraceutical. A total of 69 metabolites were identified from *S. grandiflora,* out of which Sesbagrandiflorain A, Sesbagrandiflorain B, and Sesbagrandiflorain C are the main active profiles of this herb. This comprehensive metabolite profile highlights the plants potential as a source of various bioactive constituents.

- **Benzofurans:** Are a class of biologically active chemical compounds having a benzofuran structure and an aryl group. They have shown multiple health benefits, such as anti-hypertensive, estrogenic, anti-cancer, and antioxidant properties. From the stem bark of 4 Benzofuran have been discovered and published, namely Sesbagrandiflorain A, Sesbagrandiflorain B, Sesbagrandiflorain C, and 2-arylbenzofuran [11,12].
- **Phenol:** Four phenols, namely Antiarol, 3, 5-di-t-Butylphenol, Gallic acid, Chlorogenic acid, Neochlorogenic acid, have been reported [13].
- **Fatty acid:** A total of six fatty acids have been isolated and reported, namely, Erucic acid, Nonanoic acid, 6-Octadecenoic acid, Hexadecanoic acid, methyl ester, and Linolenic acid from the leaves and seeds [13].
- **Flavonoid:** Nine flavonoids have been isolated and reported, namely**,** Sativan, Quercetin, Myricetin, Kaempferol, Cyanidin, Leucocyanidin, Chrysin-dimethylether, Dendroinfundin A, and Rutin have been found in the aerial parts and seeds [1].
    - **Flavonoid glycosides:** A total of eight Flavonoid glycosides have been isolated and reported, namely, kaempferol-3–2G-rhamnosylrutinoside, Panasenoside, Isoquercitrin, Tricin 7-O-(600-(E)-Sinapoyl)-B-D glucopyranoside, Luteolin-7-O-B-Glucopyranoside, Keampferol-5-O-Arabinoside, Kaempferol-3-O-B-D-Glucopyranosyl-(1!2)-B-D-Galactopyranoside, and Astragalin from the leaves and twigs [1].
    - **Isoflavonoid**s: Two isoflavonoids have been isolated and reported, namely, Isovestitol, and Medicarpin from the roots of *S. grandiflora* [14].
    - **Terpenoids:** Two terpenoids have been isolated and reported, namely, Vomifoliol, and (6S, 7E) 6, 9-dihydroxy-10-(20hydroxyethoxy) 4,7-megastigmadien-3-one, from the leaves and twigs of *S. grandiflora* [15].
    - **Glycoside:** Six glycosides have been isolated and reported, namely, 3-oxo-α-ionol β-D-glucoside, 11-O-b-D-glucopyranoside-abscisic alcohol, 3, 6'-di-O-feruloylsucrose, Choushenoside A, Scarbroside, and 7-megastigmadien-3-one-9-O-b-Dglucopyranoside from the leaves and twigs of *S. grandiflora* [16].
    - **Sesquiterpene lactone:** Three Sesquiterpene lactones have been isolated and reported, namely, 8b-isobutyryloxycumambranolide, Britanin, and Callitrin from the leaves and twigs of *S. grandiflora* [1].
    - **Ester:** Two esters have been isolated and reported, namely, Ethyl 3-hexyl ester and 4-Ethoxy ethyl benzoate, from the leaves of *S. grandiflora* [17].
    - **Carboxylic acid:** Two carboxylic acids have been isolated and reported, namely, Malonic acid and Benzoic acid from the leaves of *S. grandiflora* [18].
- **Triterpene:** Two triterpenes have been isolated and reported, namely, Lupane and Betulinic acid from the roots of *S. grandiflora* [19].

3.2. Characterization of key compounds: medicarpin, betulinic acid, and novel isolates

Among the richness of phytochemicals in *S. grandiflora*, several compounds have been explored for their potent and specific biological potential, making them subjects of deeper scientific interest.

- **Medicarpin:** This isoflavonoid has been mainly extracted from the roots of *S. grandiflora*, but it is a phytoalexin, that is, produced on pathogenic attack. Its pharmacological profile is strong. It has been shown to effectively exhibit anti-tubercular activity against *Mycobacterium tuberculosis*, having a minimum inhibitory concentration (MIC) of 50 µg/ml. More recently, it has been postulated using molecular docking that the anti-biofilm potential of medicarpin to inhibit the enzyme responsible for *Pseudomonas aeruginosa*, the production of which serves to regulate the formation of biofilm c-di-GMP phosphodiesterase. Medicarpin's ability to cross the blood-brain barrier, postulated in *in silico* models, may also hold promise of neuroprotective applications, but this should be further explored [20].

- **Betulinic acid:** A famous pentacyclic compound, betulinic acid is also present in *S. grandiflora* roots. It is one of the most examined natural products with potential cancer therapy. It is famous for inducing apoptosis in many cancer cell lines, especially in melanoma, but largely with minimal toxicity to the normal ones. That its anti-TB activity is maximized, having an MIC of 100 µg/ml, only further reinforces its therapeutic potential. Nevertheless, its low aqueous solubility and bioavailability have been a serious obstacle to clinical development of betulinic acid, a task in which scientists are currently engaged through the development of more soluble derivatives [16,17].
- **Sesbagrandiflorains A and B:** These compounds are amongst the most structurally new and exciting findings of *S. grandiflora*. They are dimers of 2-arylbenzofuran obtained by isolation of the stem bark. Both were demonstrated to have anti-TB, the Sesbagrandiflorain B being highly active with an MIC of 12.5 µg/ml against *M. tuberculosis*. This is much more active than Sesbagrandiflorain A (MIC = 200 µg/ml), which was attributed to a free hydroxyl group at C-6 in compound B. This observation presents an excellent structure-activity relationship principle since this particular structural aspect was critical towards its elevated anti-TB activity and identifies the plant as a source of new chemical scaffolds in drug discovery efforts [21].

Table 1 below summarizes the essential phytochemicals isolated from *S. grandiflora* and their key reported bioactivities. Table 2 summarizes the Synergistic effects of phytochemical interactions of *Sesbania grandiflora.*

4. MOLECULAR PHARMACOLOGY AND MECHANISMS OF ACTION

The wide range of applications of *S. grandiflora* is being progressively confirmed by contemporary pharmacological research, discovering both the specific action pathways and the individual components of *S. grandiflora* phytochemical complex by which their action works. The complex interaction probably accounts for its effectiveness against multiple diseases. It suggests that its usefulness as a therapeutic agent may best be exploited using well-characterized, multicomponent extracts and not using single isolated molecules.

4.1. Anti-cancer properties: from cytotoxicity to signaling pathway modulation

Sesbania grandiflora, or hummingbird tree, has gained valuable interest due to its potential role in oncology. Researchers have studied how its extracts and isolated compounds suppress cancer cell growth through various mechanisms.

4.*1.1. Induction of apoptosis via the intrinsic pathway*

The primary mechanism by which *S. grandiflora* unveils its anti-cancer effects is the induction of apoptosis, or apoptotic cell death. Numerous studies have shown that its fractions and extracts can trigger this process in different cancer cell lines, including those of the breast (MCF-7), lung (A549), colon (SW-480), and leukemia (U937) [24]. The evidence clearly shows the activation of the apoptosis's intrinsic, or mitochondrial, pathway. Apoptosis mechanisms that have been observed include:

- **Mitochondrial disruption and cytochrome C release:** Permeabilizing the mitochondrial outer membrane is the critical step in the intrinsic pathway. Active metabolites from *S. grandiflora*, such as the cyclic peptide sesbanimide obtained from the seeds and a protein fraction (SF2) from the flowers, can directly disrupt mitochondrial function. The key signal that commits the cell to apoptosis is the disruption, which leads to the release of cytochrome C from the mitochondria to the cytoplasm. Apoptosis was demonstrated in both human colon cancer cells and murine ascites cells [21].
- **Activation of caspase cascade:** The cytochrome C release triggers the formation of the apoptosome, which activates the cascade of cysteine proteases. Studies have shown that treatment with *S. grandiflora* active constituents leads to the activation of caspases, including caspase-9, caspase-3, and caspase-8. The SF2 protein fraction causes a 4.4-fold increase in caspase-3 enzymatic activity in Daltons Lymphoma Ascites cells [22].

Table 1. Major phytochemicals of *Sesbania grandiflora.*

Compound Name	Chemical class	Plant Part(s)	Key reported bioactivity(ies)	References
Medicarpin	Isoflavonoid	Roots	Anti-TB	
Isovestitol	Isoflavonoid	Roots	Anti-TB	[18]
Betulinic acid	Triterpene	Roots	Anti-TB, anti-cancer, anti-inflammatory	
Sesbagrandiflorain A and B	2-Arylbenzofuran	Stem bark	Anti-TB, antiproliferative	[1]
Quercetin	Flavonoid	Stem bark	Antioxidant, anti-proliferative, enzyme inhibition	[10]
Kaempferol	Flavonoid	Leaves, flowers	Antioxidant, anti-diabetic	
Vomifoliol	Terpenoid (ionone)	Leaves, twigs	Enzyme inhibition (α-amylase/α-glucosidase), anti-inflammatory	[3]
Loliolide	Terpenoid (ionone)	Leaves, twigs	Enzyme inhibition (α-amylase/α-glucosidase)	
Sesbanimide	Cyclic peptide	Seeds	Potent cytotoxic (anti-cancer)	[1]
Gallic acid	Phenolic acid	Leaves, bark	Antioxidant, anti-microbial	[1]

Note: All MIC/IC_{50} values are expressed in µg/ml.

Table 2. Synergistic effects of phytochemical interactions of Sesbania grandiflora.

Sr No.	Key phytochemicals	Synergistic effects	References
1	Tannins + Gum	Increases antidiarrheal activity	[19]
2	Medicarpin + Betulinic acid	Increases anti-inflammatory activity and neuroprotection	[22]
3	Sesbanimide + Saponins	Increases immunomodulatory activity	[1]
4	Kaempferol + oleanolic acid	Increases hepatoprotective activity	[23]
5	Oleanolic acid + Quercetin	Increases anticancer activity	[15]

- **Cleavage of PARP:** Activated caspase-3 cleaves the cellular substrates, leading to apoptosis. Its primary targets are the Poly (ADP-ribose) polymerase (PARP), a DNA repair enzyme. PARP cleavage is a recognized characteristic of apoptosis and apoptosis in cells treated with the SF2 protein fraction and methanolic leaf extracts, indicating induction of the apoptotic program [25]. Figure 1 illustrates the complex anti-cancer mechanisms of *S. grandiflora* through four different pathways [20–22].

4.1.2. Modulation of key cancer signaling pathways

Beyond the direct induction of apoptosis, compounds from *S. grandiflora* have been shown to interfere with critical signaling pathways that control cancer cell proliferation, inflammation, and survival.

- **NF-κB pathway:** A 2014 study has demonstrated that a methanolic extract of *S. grandiflora* leaves significantly reduced the activation of the NF-kappa B in A549 cells from human lung cancer. This suppression decreases the levels of cyclin D1, a downstream/signal target of NF-κB essential to cell cycle progression between G1 and the S phase [1,21]. This finding suggests that the plant's anti-cancer effect is mediated by suppressing this key pro-survival and pro-proliferative pathway, a mechanism shown by many plant-derived anti-cancer agents [21].
- **PI3K/Akt/mTOR pathway:** Another key signalling pathway that often becomes hyperactivated due to alterations in cancer cells is the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway, which facilitates cell growth, proliferation, and survival and suppresses apoptosis. Four studies have also started correlating the anti-cancer activity of *S. grandiflora* to this pathway. It is hypothesized that fatty acid components of the flowers and leaves of the plant that contain elements such as oleic acid and palmitic acid can inhibit tumour growth through interference with PTEN/Akt/mTOR and PI3K/Akt pathways. While this research is still in its early stages, it opens up a new avenue for understanding the plant's complex anti-cancer mechanisms [21].

4.2. Anti-diabetics: targeting key metabolic enzymes and pathways

The traditional use of *S. grandiflora* in treating diabetic conditions is strongly supported by preclinical studies that have identified several well-defined molecular mechanisms through which it can help control blood glucose levels and mitigate diabetic complications.

4.2.1. Inhibition of carbohydrate-digesting enzymes

An important strategy for managing type 2 diabetes is to reduce postprandial hyperglycemia by slowing down the hydrolysis of carbohydrates [26]. *Sesbania grandiflora* has unveiled significant potential in this area through the inhibition of two key enzymes in the small intestine:

- **α-Amylase:** This enzyme primarily breaks complex carbohydrates into smaller oligosaccharides.
- **α-Glucosidase:** This enzyme is in the intestinal brush border of the intestine, responsible for the final breakdown of oligosaccharides and disaccharides into monosaccharides that can be absorbed into the bloodstream.

Methanolic extracts also indicated up to 81% inhibition of alpha-amylase and an IC_{50} value of 50.95 µg/ml, comparable to the standard drug acarbose. Similarly, the novel nanoparticle formulation developed using plant materials has been reported to have a significant inhibitory effect on enzymes, α-amylase, and α-glucosidase. A study went further by performing bio-guided fractionation to identify the specific compounds responsible for this activity. The study isolated 14 primary metabolites and found, for the first time, that the terpenoids vomifoliol (IC_{50} = 64.5 mM) and loliolide (IC_{50} = 388.48 mM), along with the well-known flavonoid quercetin (IC_{50} = 17.45 mM), were potent inhibitors of α-glucosidase [27].

4.2.2. Enhancement of insulin action and pancreatic function

- **Improved insulin secretion and β-cell function:** The flower extracts of *S. grandiflora* have been reported to have therapeutic effects in diabetic rats on the level of insulin and C-peptide. Moreover, the pancreatic islets have been partially preserved and restored in the pancreas of rats histopathologically. This also indicates that the extract is protective or even regenerative of the β-cells of the insulin-producing pancreatic islet injured in diabetes [27].
- **Enhanced glucose utilization:** The extracts have been demonstrated to replenish hepatic glycogen, indicating that the body can store excess glucose in the liver. This is allied with regulating the main carbohydrate metabolic enzymes associated with glycolysis and gluconeogenesis, thus enhancing the stability of glucose levels in the body's environment [27].
- **Inhibition of advanced glycation end-products (AGEs):** Nanoparticle formulations derived from *S. grandiflora* have shown a significant ability to inhibit the formation of AGEs, an effect featured in bioactive compounds like hydroxymethoxybenzaldehyde and the inherent anti-oxidant properties of the nanoparticles themselves [28]. Figure 2 illustrates the anti-diabetics activity of *S. grandiflora*, em-

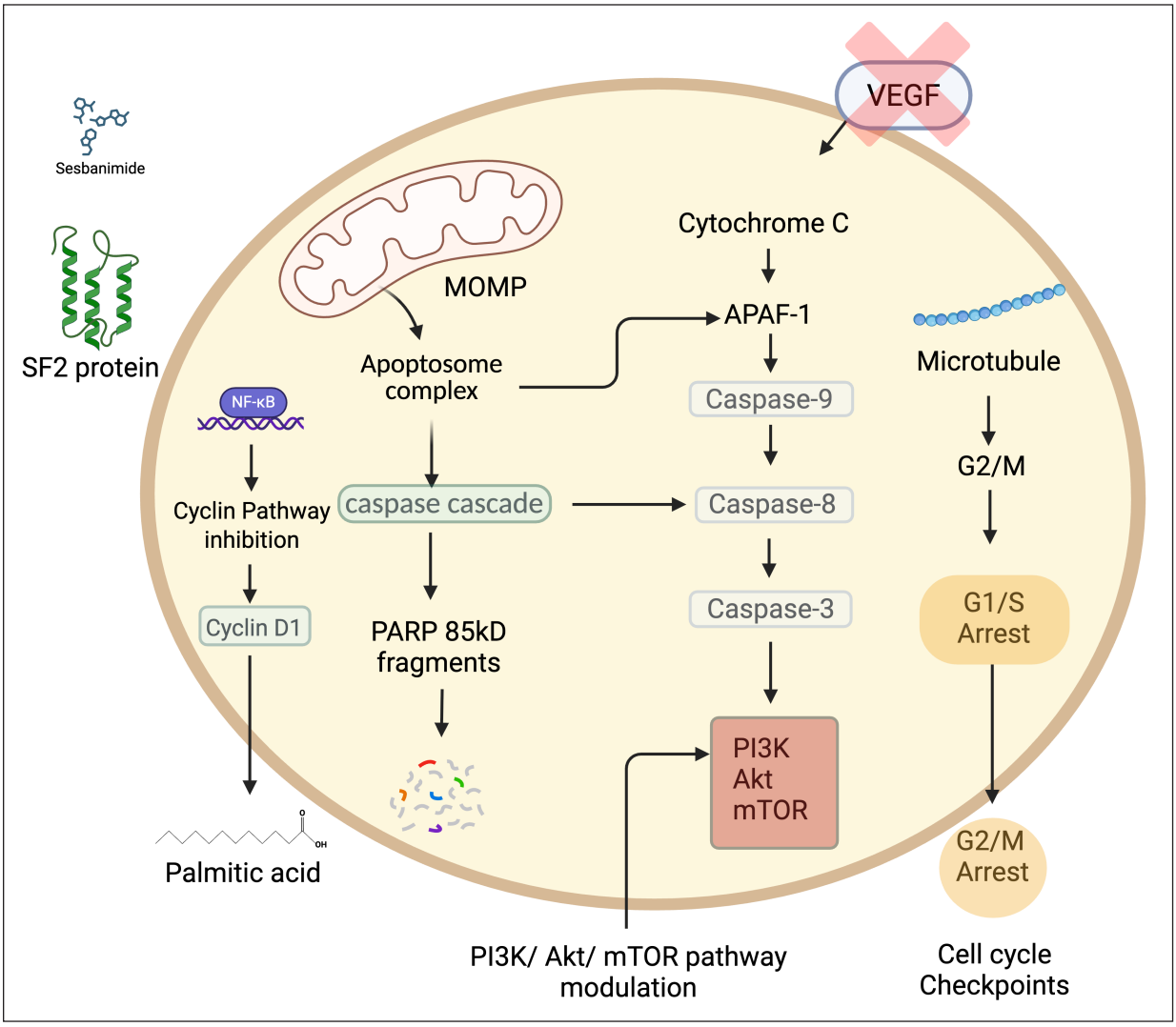

Figure 1. A complex anti-cancer mechanism of *Sesbania grandiflora* through four different pathways. (A) Mitochondrial-Mediated MOMP driven Apoptosis in sesbanimide and SF2 protein, which promotes the release of cytochrome C, formation of apoptosome, and activation of caspase cascade that results in PARP cleavage to 85 kDa fragments; (B) NF-κB Pathway inhibition indicating the inactivation of nuclear translocation as well as cyclin D1 downregulation for cell cycle regulation; (C) PI3K/Akt/mTOR Modulation by oleic acid and palmitic acid influencing PTEN/PI3K/Akt signaling for the reprogramming of metabolism; and (D) Additional Mechanisms such as G1/S and G2/M cell cycle checkpoints, VEGF-mediated anti-angiogenic activities, and microtubule dynamics disruption (adapted from [7,21]).

phasizing its roles in enhancing glucose uptake, improving insulin secretion and sensitivity, inhibiting carbohydrate digestion and absorption, and suppressing gluconeogenesis.

4.3. Antioxidant and anti-inflammatory effects

The potent antioxidant and anti-inflammatory properties of *S. grandiflora* are central to its other therapeutic effects, including its cardioprotective, hepatoprotective, and anti-cancer activities. The mechanisms behind these properties are well-documented.

- **Mechanisms of radical scavenging:** The leaves and flowers of the plant are particularly rich in phenolic and flavonoid compounds, which are potent antioxidants. Extracts have demonstrated robust free radical scavenging activity in various *in vitro* assays, including the DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)), as well as Ferric Reducing Antioxidant Power (FRAP). This ability to neutralize reactive oxygen species (ROS) helps protect cells and tissues from oxidative damage, a main factor of aging and many chronic diseases [29].
- **Cytokine inhibition:** The anti-inflammatory property of the plant is also achieved through its inhibitory effect on the production or synthesis of major pro-inflammatory cytokines. Research has found that extracts can block the release of Tumor Necrosis Factor-alpha (TNF-alpha) and Interleukin-6 (IL-6), which are also primary patrons in the inflammatory cascade process [30].

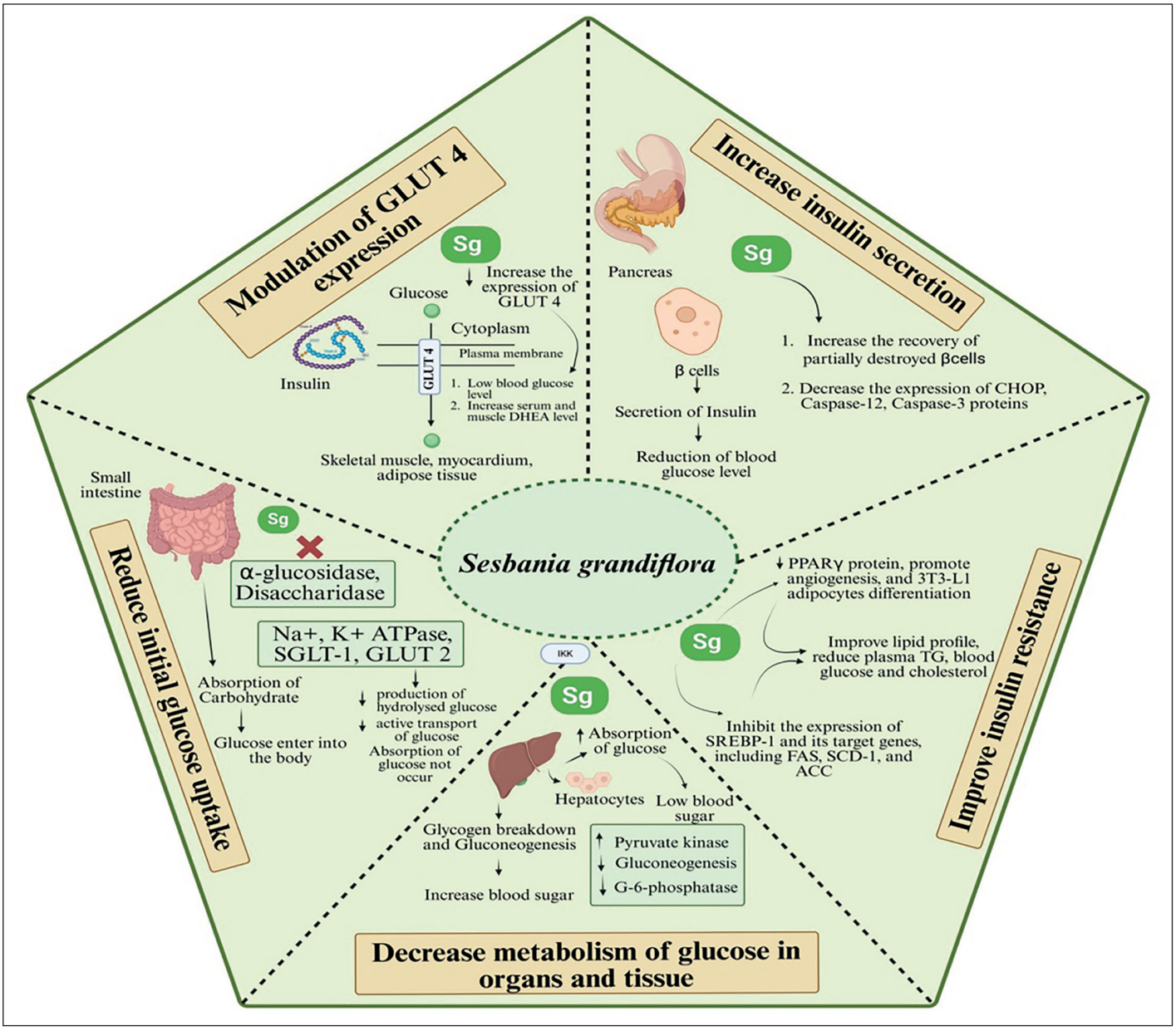

Figure 2. Schematic representation of the anti-diabetic mechanisms of *Sesbania grandiflora*, illustrating its multifaceted actions: (1) modulation of GLUT4 expression in skeletal muscle, myocardium, and adipose tissue to enhance glucose uptake; (2) stimulation of insulin secretion through pancreatic β-cell recovery and reduced expression of ER stress-related proteins (CHOP, Caspase-12, Caspase-3); (3) improvement of insulin resistance via PPARγ activation, lipid profile enhancement, and suppression of SREBP-1 mediated lipogenesis; (4) reduction of initial glucose uptake by inhibiting carbohydrate-hydrolyzing enzymes (α-glucosidase, disaccharidase) and glucose transporters (SGLT-1, GLUT2); and (5) decreased metabolism of glucose in organs and tissues through suppression of gluconeogenic enzymes. Together, these pathways contribute to lowering blood glucose levels and improving metabolic health (adapted from [8,41]).

- **Membrane stabilization:** A specific measure of anti-inflammatory activity of any product is that *S. grandiflora* extracts also exhibit high levels of membrane-stabilizing activity. They can suppress hemolysis (rupture) of human red blood cells caused by hypotonic solutions or heat, a conventionally utilized *in vitro* system to measure anti-inflammatory activity. This suggests that the active metabolite will protect cell membranes from damage during inflammatory processes [31]. Figure 3 illustrates how *S. grandiflora* downregulates oxidative stress–induced signaling pathways—including NF-κB, AP-1, PI3K-Akt, and Mitogen-Activated Protein Kinase cascades—thereby attenuating TLR4/MyD88-mediated inflammation.

4.4. Cardioprotective and hepatoprotective activities

The heart and liver protective properties of *S. grandiflora* are mainly a consequence of its excellent antioxidant and anti-inflammatory properties.

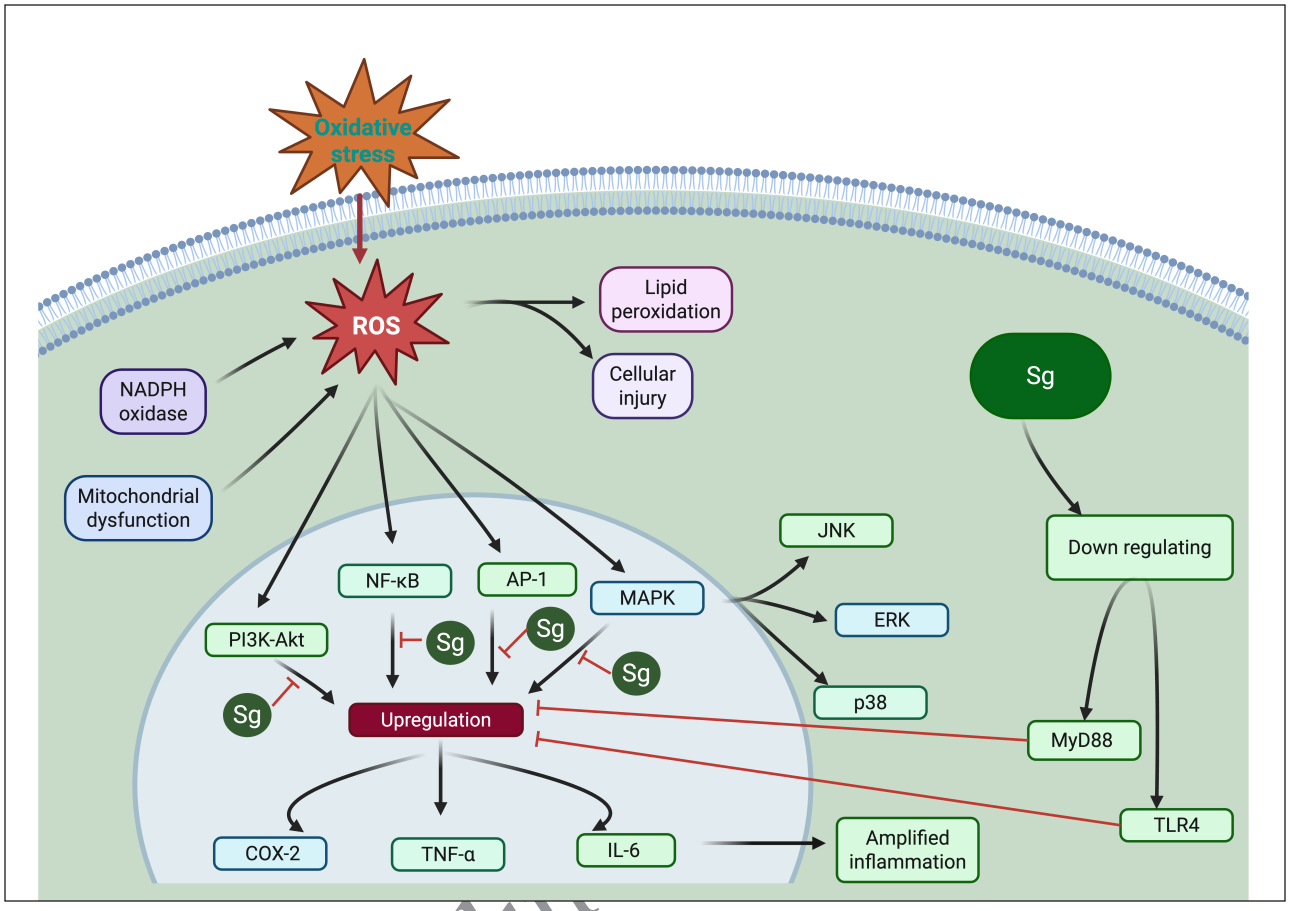

Figure 3. Mechanistic overview of how *Sesbania grandiflora* (Sg) counters oxidative stress–induced inflammatory signaling by downregulating NF-κB, AP-1, PI3K-Akt, MAPK, and TLR4/MyD88 pathways. *Sesbania grandiflora* acts as an antioxidant and anti-inflammatory agent in the human body in a complex mechanism associated with direct free radical scavenging, modulation of enzymes, and inhibition of pro-inflammatory pathways. When exposed to oxidative stress like oxidative stress generated by environmental toxins or metabolic imbalance, reactive oxygen species (ROS) is produced through NADPH oxidase and mitochondrial dysfunction which result in the lipid peroxidation and cell damage. These ROS causes the activation of the MAPK (Mitogen-Activated Protein Kinase) signalling cascade, comprising of p38 (p38 Mitogen-Activated Protein Kinase), JNK (c-Jun N-terminal Kinase) and ERK (Extracellular Signal-Regulated Kinase), thereby stimulating the pro-inflammatory mediators e.g. TNF-alpha (Tumor Necrosis Factor-alpha), IL-6 (Interleukin-6), COX-2 (Cyclooxygenase-2) in an upregulated process. This inflammation process is still enhanced by this transcription factors such as NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) and AP-1 (Activator Protein-1) that stimulate the production of cytokines and the gathering of immune cells. Meanwhile, the PI3K (Phosphoinositide 3-Kinase) -Akt (Protein Kinase B) axis and TLR4 (Toll-Like Receptor 4) -MyD88 (Myeloid Differentiation Primary Response 88) pathway preserve chronic inflammation and cell survival, which increases tissue degeneration and disease progression. The protective effect by *Sesbania grandiflora* decreases the expression of TLR4 and MyD88 and breaks the inflammatory cascade. Its high flavonoid and phenolic content too stimulates the Nrf2 (Nuclear Factor Erythroid 2–Related Factor 2)-ARE (Antioxidant Response Element) pathway, and this improves expression of endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). The two functions not only reduce oxidative damage but also inhibit inflammatory mediators which enable the cellular intactness and tissue repair (adapted from [25]).

- **Cardioprotection:** In the following content, we discuss the various mechanisms of action through which *S. grandiflora* appears to exert cardioprotective effects through multiple biochemical and physiological adaptation processes. Flavonoids and phenolic compounds in the plant have been shown to reduce oxidative stress by scavenging free radicals and preventing lipid peroxidation. *Sesbania grandiflora* possesses antioxidant potential, as suggested by its ability to suppress ROS generation while potentiating the upregulation of endogenous anti-oxidant enzymes like superoxide dismutase and catalase, thereby fortifying cardiac tolerance to oxidative stress. *In vivo* experiments have shown that it can replenish the activities of important endogenous antioxidant enzymes such as glutathione peroxidase, catalase (CAT), and superoxide dismutase. It may also improve endothelial functioning by increasing endothelial nitric oxide synthase and subsequent production of nitric oxide, a vasodilator and an anti-inflammatory agent that reduces vascular inflammation [32,33].
- **Hepatoprotection:** The liver is a vital organ responsible for metabolism in the body. Endogenous or exogenous substances are continually being converted by it; any anomaly could produce free radicals, which would cause oxidative stress, necrosis, and cell death. Liver marker en-

zymes are essential for determining the extent of hepatic damage. The hepatoprotective potential of the aqueous extract of leaves was investigated in carbon tetrachloride-induced hepatotoxicity in albino rats [34].

4.5. Anti-microbial, anti-biofilm, and anti-tubercular activities

Sesbania grandiflora has been shown to have a wide range of anti-microbial action, with the anti-tubercular being quite remarkable.

- **Anti-bacterial and Anti-biofilm:** The leaf and flower extracts have been reported to have activity against various human pathogens, including Gram-positive *Staphylococcus aureus* and *P. aeruginosa*, and fish pathogens. A rather interesting discovery of the plant is that it could fight bacterial biofilms, otherwise immune to regular antibiotics. Molecular docking has determined that isoflavonoid medicarpin in *P. aeruginosa* can be a possible inhibitor of the c-di-GMP phosphodiesterase enzyme [35].
- **Anti-tubercular and anti-inflammatory activities:** Root extracts and several isolated compounds have demonstrated good potency against the virulent H37Rv strain. The isoflavonoids medicarpin, isovestitol (MIC = 50 µg /ml), and triterpene betulinic acid (MIC = 100 µg /ml) are active. Nevertheless, the most active compound is the new 2-arylbenzofuran dimer, Sesbagrandiflorain B, whose MIC is 12.5 µg/ml. It is proposed that the mechanism of action is that the gyrase is targeted, which is fundamental to the survival of bacteria, and that the RNA polymerase is targeted, which is required since it is an essential part of bacteria replication [18].

5. PHARMACOKINETICS, BIOAVAILABILITY, AND TOXICOLOGY

The preclinical pharmacological profile of *S. grandiflora* is strong and positive. Still, the imminent transition to clinical use requires knowledge of its absorption, distribution, metabolism, and excretion (ADME) and establishment of its safety profile. This section tackles these essential features, including the opportunities and significant problems heading towards modern medicine and traditional remedies.

5.1. ADME profiles of key phytochemicals: insights from *in silico* and *in vivo* studies

Very little data is available on the pharmacokinetics of *S. grandiflora* constituents, and this is a significant gap, producing latent effects on knowledge. Nevertheless, *in silico* and *in vivo* analysis methods have started illuminating some of the ADME properties of some of its principal compounds, particularly the isoflavonoid medicarpin.

***In silico* predictions (pkCSM):** A 2024 study used the pkCSM web server to explain the ADME properties of medicarpin and other active compounds of *S. grandiflora* [36]. The key predictions for medicarpin are:

- **Absorption:** The model indicated that the compound was potentially well-absorbed with high intestinal absorption and is predicted to show good permeability in Caco-2 cell monolayers (a model of the intestinal wall), indicating that the compound should be well-absorbed following administration as an oral dose. Nevertheless, it had low skin permeability.
- **Distribution:** Medicarpin was predicted to cross the blood-brain barrier and penetrate the central nervous system, a property not shown by other active compounds from the plant. This suggests that it may have the potential to act on neurological targets.
- **Metabolism:** The expected results showed the possibility of high drug-drug interactions. It was postulated that medicarpin is a substrate of the most critical metabolic enzyme CYP3A4 and an inhibitor of such other vital cytochrome P450 enzymes as CYP1A2, CYP2C19, CYP2C9, and CYP3A4. This implies that it can significantly affect the metabolism and clearance of different drugs that these enzymes metabolize.
- **Toxicity:** The model raised a potential safety concern, predicting that medicarpin could be positive in the AMES test for assessing the mutagenic potential [36].

***In vivo* metabolism (Medicarpin):** A Previous study on a rat model explained the metabolic fate of medicarpin after oral administration. The findings reported extensive and rapid metabolism. One hundred sixty-five metabolites were found in many tissues and fluids, indicating that the parent compound is rapidly metabolized in the body. The processes involved phase I, such as demethylation and hydroxylation, and then focused on extensive phase II conjugation, primarily glucuronide and sulfate conjugation. Medicarpin glucuronide was the most prevalent metabolite in most organs, consistent with the possibility that medicarpin is quickly conjugated to facilitate its biliary excretion. Such widespread metabolism implies that the biological activity *in vivo* may be a result more of the metabolite than the parent compound itself [1].

5.2. The bioavailability hurdle: solubility and absorption challenges of lipophilic triterpenes

A major obstacle to clinical development of *S. grandiflora* constituents is the lack of bioavailability of the key lipophilic constituents, most importantly, the anti-cancerous triterpenoid betulinic acid [17]. Betulinic acid is a prototypical example of a brick dust molecule, a highly potent compound with dreadful water solubility. This poor solubility significantly hinders digestion in the gastrointestinal system, resulting in poor oral bioavailability with very low absorption [37]. This renders that, even when high oral doses are administered, only a minimal part of the compound ends up in the systemic circulation to bring forth the therapeutic effect, and, as a result, it is ineffective mainly within a feasible scenario. Realizing this severe shortcoming, researchers have sought to improve its pharmacokinetics. A potentially satisfying direction is the semi-synthesis of more soluble analogs. A study in 2023 has described the synthesis of 28-O-succinyl betulin (SBE). SBE is a semi-

synthetic derivative of betulinic acid, modified by attaching a water-soluble succinyl group to the parent betulin backbone. The results were excellent: SBE was substantially more soluble in different solvents than the initial compound. Most significantly, this was reflected in a substantial enhancement of pharmacokinetics in rats. Oral bioavailability SBE was found to be 9.49, a highly significant increase that shows that the bioavailability barrier could be overcome through chemical modification [38]. These formulation and derivatization approaches will be crucial in gaining therapeutic benefits of betulinic acid and other forms of lipophilic compounds of *S. grandiflora*.

5.3. A comprehensive safety evaluation: acute, sub-acute, and genotoxicity data

Safety is a significant concern for any potential therapeutic agent and should be appropriately evaluated. The safety of *S. grandiflora* is complicated because, on the one hand, there is a long tradition of its use as a food source, and, on the other hand, scientific evidence exists that is creating specific concerns.

- **Acute and sub-acute toxicity:** In line with its long history of use as an edible plant, *S. grandiflora* demonstrates a very high safety margin in conventional toxicity studies. Multiple studies in rodent models investigate various extracts (including hydroalcoholic leaf, ethyl acetate root, and methanolic root extracts). In these studies, administration of even very high single or repeated doses (up to 5,000 mg/kg daily for 28 days) did not result in mortality or significant adverse effects on body weight, organ weight, or key hematological and biochemical markers have consistently reported a median lethal dose (LD_{50}) of greater than 2,000 mg/kg [35].
- **Genotoxicity:** An essential contrast to this overall safety picture is provided by a 2021 analysis of the genotoxic potential of a methanolic flower extract using an extremely sensitive mouse bone-marrow micronucleus test as performed *in vivo* in mice. This genotoxic potential may be associated with specific phytochemical components in the methanolic flower extract (e.g., uncharacterized phenolics or terpenoids), and future studies should isolate and test individual compounds to identify the causal agent. This test specifically looks for damage to chromosomes or the mitotic apparatus. Although the extract was not cytotoxic (it did not kill bone marrow cells), it did cause a statistically significant increase in frequency of micronucleated polychromatic erythrocytes at 40 and 90 mg/kg. This suggests that the extract is genotoxic, which may cause chromosomal aberrations *in vivo* [39]. It is important to note that the observed genotoxicity may depend on factors such as extraction method (e.g., methanol *vs*. aqueous solvents), extract purity, or specific phytochemical fractions. Future studies should investigate whether nongenotoxic extracts can be obtained by adjusting extraction parameters.
- **General cytotoxicity:** Contrary to the exclusive genotoxicity result, the overall cytotoxicity is relatively poor. In an *in vitro* brine shrimp lethality bioassay, the aqueous and ethanolic extracts exhibited LC_{50} values that were very high (12,773 and 10,313 µg /ml, respectively), which indicated low toxicity by these two extracts relative to the cytotoxic drug, cyclophosphamide (LC_{50} = 110 µg/ml) [30].

The collective safety data paints a complex picture. The plant is clearly safe from an acute toxicity perspective, supporting its traditional food use. However, the positive genotoxicity result cannot be ignored. It indicates that the plant is potentially safe under limited culinary consumption, but its use as a regular medicine or supplement should be considered cautiously. This observation illustrates that the safety of a botanical is not absolute and is dose-dependent, duration of use-dependent, extract-dependent, and endpoint-dependent. The genotoxicity findings raise a massive red flag that should be considered and eliminated before long-term clinical usage can be widely encouraged.

6. CLINICAL EVIDENCE AND COMMERCIAL LANDSCAPE

The validation of any traditional remedy in terms of its therapeutic potential is the final examination by high-standard human clinical trials. With *S. grandiflora*, transitioning from preclinical promise to clinical proof will be a new beginning. A new research publication, however, has opened the door to a more practical transformation to a modern use case, predominantly for nutraceutical and cosmeceutical products. According to the current Indian patent application (No. 06/2024) entitled *S. grandiflora: A treasure trove of therapeutic compounds* mainly focuses on the identification of flavonoids, alkaloids, and its potential antioxidant activity using the column chromatography method. The formulation gave high importance on the plant's capacity to develop antioxidant-rich therapeutic agents. The application is waiting for examination. Table 3 summarizes the available marked products of *S. grandiflora.*

6.1. Human clinical trials: analysis of a randomized, placebo-controlled study

The validation of any traditional remedy in terms of its therapeutic potential is the final examination by high-standard human clinical trials. With *S. grandiflora*, transitioning from preclinical promise to clinical proof will be a new beginning. A

Table 3. Available marked products of *S. grandiflora.*

Sl.No	Product name	Formulation	Activity	Manufacturer
1	Bharat Herbal *Sesbania* Extract Powder	Powder	Dietary supplement	Bharat Herbal
2	*Sesbania grandiflora* flower Powder	Powder	Improves digestion and strength	Sidhara betta herbals
3	*Sesbania grandiflora* extract tablet	Tablet	Promote hair and skin health	Growequal
4	Azani biotin	Capsules	Promote hair and skin health	Relentless Sports Pvt Ltd

new research publication, however, has opened the door to a more practical transformation to a modern use case, predominantly for nutraceutical and cosmeceutical products [40].

- **Study design and intervention:** The study chose 51 healthy adult individuals who self-identify as having poor hair quality. The active or placebo treatment was assigned to the participants and continued fully with no interruptions over 56 days. The intervention was SesZen-Bio [SesZen-Bio®, a proprietary extract of *S. grandiflora* developed by Zenherb Labs, Mumbai, India], 250 mg capsules, and standardized to have 0.5 natural biotin. They were divided into doses of one capsule orally twice a day.
- **Primary outcomes and efficacy:** The findings were statistically significant and clinically meaningful. In 56 days, the SesZen-Bio® extract receiving group had significant improvements in comparison to the placebo group:
    - **Hair density:** An instrumental analysis through a phototrichogram evaluation resulted in a 25% mean increase in hair density ($p < 0.0001$).
    - **Hair thickness:** The average thickness also increased significantly, with an average improvement of 16.94% ($p < 0.0001$).
    - **Serum ferritin:** A key mechanistic outcome was a 27% increase in serum ferritin in the treatment group. As low ferritin is recognized to contribute to hair loss, this implies that the extract's health-giving properties may play out, at least in part, via a nutrient-related pathway linked to the enhancement of iron balance.
- **Safety and conclusion:** The study concluded that the *S. grandiflora* extract was well-tolerated and acted as an efficient daily supplement for improving hair health. It provided the first robust, evidence-based validation for its use in a human population [40].

It was a wise strategic decision to aim at the cosmeceutical/nutraceutical market as a first clinical validation. It is a long, costly, and risky process to develop a prescription medication to treat serious diseases such as cancer or diabetes, coupled with the pharmacokinetic and, potentially, genotoxicity issues raised with *S. grandiflora*. Instead, the health of the hair market is a vast, consumer-focused space in which supplements, supported by provable scientific evidence, can quickly become a successful product. Standardization of the extract to a commonly known vitamin in hair health, biotin, the product addresses what consumers see as a conflict between the familiar, natural, and traditional botanicals against a scientifically proven ingredient. The supporting evidence of increased serum ferritin further anchors the mechanism in a plausible nutritional context. This approach represents a pragmatic and successful model for translating traditional plant knowledge into a modern commercial product, suggesting that the most immediate and viable future for *S. grandiflora* lies in developing well-characterized, evidence-backed supplements for the wellness and beauty from within sectors.

The recent clinical trial data for *S. grandiflora* are limited to nutritional support, with no trials targeting chronic diseases such as diabetes, tuberculosis, and cancer. Future studies should focus on well-designed clinical trials to evaluate the plant's therapeutic effectiveness in these areas.

7. CONCLUSION AND FUTURE PERSPECTIVES

Sesbania grandiflora has transitioned from a traditional remedy to a scientifically recognized source of diverse bioactive compounds, including flavonoids, terpenoids, phenolics, 2-arylbenzofurans, and cytotoxic peptides. Modern research confirms its multitarget, multicomponent synergy as the basis for its potent anticancer, antidiabetic, anti-inflammatory, and antimicrobial effects. Human clinical trials are scarce, with only one notable study, highlighting the need for stringent randomized controlled trials, particularly for type 2 diabetes, chronic inflammation, and traditional indications. Pharmacokinetic data for many of the major compounds are lacking, and the poor bioavailability of specific lipophilic actives emphasizes the importance of advanced delivery systems. The role of synergistic phytochemical interactions is largely undiscovered, and long-term safety concerns, especially a positive genotoxicity finding, require thorough investigation. A phased research strategy is proposed: in the short term (1–3 years), develop and clinically validate standardized extracts for nutraceutical and cosmeceutical applications; in the medium term (3–7 years), conduct detailed pharmacokinetic studies, enhance bioavailability, explore phytochemical synergy, and address safety issues; and in the long term (7+ years), observe prescription therapeutics for diabetes, inflammation, and tuberculosis through large-scale clinical trials. By following this roadmap, *S. grandiflora* can be advanced into a new generation of safe, effective, and evidence-based botanical therapeutics.

The great potential of *S. grandiflora* for treating various diseases is due to the vast array of phytochemical composition. Future researchers can focus on developing a nano-based drug delivery system to improve the solubility and bioavailability of lipophilic compounds such as betulinic acid, which could help the treatment be more effective. Structural modifications can improve the antitubercular activity of the lead compound Sesbagrandiflorain B. To confirm the safety and effectiveness of *S. grandiflora,* large-scale randomized controlled trials for treating type 2 diabetes and tuberculosis should be conducted.

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9. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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12. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

13. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

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The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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