

***Alangium salviifolium* fruits a traditional medicinal plant used in Diabetes Management: A Phyto-therapeutic Hypothesis**

Vishal Goldar¹, Ved Pal^{2*}

^{1,2*}Department of Pharmacognosy, ISF College of Pharmacy, Moga, Punjab, India. 142001.

ABSTRACT

Alangium salviifolium (L.f.) Wangerin, a traditionally important medicinal plant, has recently gained attention for its potential role in diabetes management due to its rich phytochemical composition and diverse pharmacological activities. This study proposes a novel phytotherapeutic hypothesis integrating *in vitro*, *in vivo*, and molecular evidence supporting its antidiabetic potential. Phytochemical investigations reveal the presence of bioactive constituents such as flavonoids, alkaloids, tannins, and terpenoids, which are known to exert antihyperglycemic, antioxidant, and anti-inflammatory effects. *In vitro* studies demonstrate significant inhibition of carbohydrate-digesting enzymes, including α -amylase and α -glucosidase, along with enhanced glucose uptake and antioxidant capacity. *In vivo* evaluation using the Streptozotocin-induced diabetes model confirms its efficacy in reducing blood glucose levels, improving lipid profiles, and restoring pancreatic architecture. At the molecular level, the extract is hypothesized to modulate key signaling pathways such as PI3K/Akt and AMPK, enhance insulin secretion, and attenuate oxidative stress and inflammatory mediators. The integration of these multi-target mechanisms suggests that *Alangium salviifolium* may act as a promising phytotherapeutic agent for diabetes management. However, further studies including bioactive compound isolation, mechanistic validation, and clinical evaluation are required to substantiate its therapeutic potential.

Keywords: *Alangium salviifolium*, Diabetes mellitus, Phytotherapy, Antidiabetic activity, Streptozotocin-induced diabetes, α -glucosidase inhibition, Antioxidant activity.

INTRODUCTION

Diabetes mellitus is a chronic heterogeneous metabolic disorder that alters the metabolism of carbohydrates, proteins and lipids and is a severe global health concern. It is caused by a lack of insulin secretion, activity, or both (1). The worldwide incidence of diabetes is increasing at an alarming rate, demanding the study of safer and more effective treatment options, particularly from natural sources (2). In recent years, medicinal plants have attracted significant interest as prospective antidiabetic medications due to their multi-targeted mechanisms, decreased toxicity, and cost-effectiveness when compared to synthetic pharmaceuticals (3). *Alangium salviifolium*, often known as sage-leaved alangium, is a medicinal flowering plant that is native to the Indian subcontinent and other tropical countries. Ayurveda and folk medicine use it to treat a variety of ailments

(Shown in Fig.1) (4). Phytochemical study of *Alangium salviifolium* shows the presence of several bioactive compounds, such as alkaloids, flavonoids, glycosides, terpenoids, tannins and phenolics. These substances are often linked to pharmacological value, e.g. antioxidant (3). In particular, recent research (2024-2026) indicated the existence of structurally varied isoquinoline alkaloids and other secondary metabolites, which may play a major role in its biological impact (5). Preclinical studies have shown that extracts of *Alangium salviifolium* dramatically lower blood glucose levels, improve lipid profiles, and increase insulin secretion in experimental diabetic animals, showing its promising antidiabetic potential (6). The processes are hypothesized to include pancreatic β -cell protection, insulin release stimulation, antioxidant activity, and regulation of key metabolic enzymes involved in glucose homeostasis (2, 6). Despite these promising results,

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the bulk of existing data is restricted to in vitro and animal studies, with a lack of well-defined molecular

pathways and clinical validation, emphasizing a key gap in translational research (6).

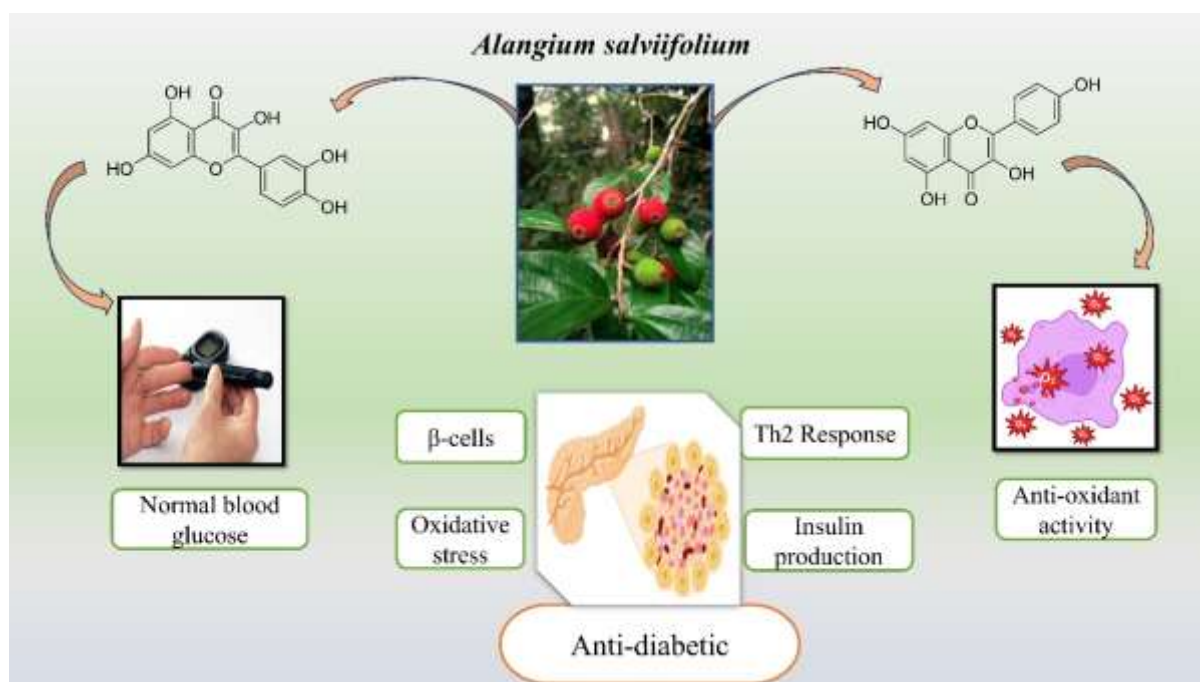


Fig. 1 Representation of the antidiabetic potential of *Alangium salviifolium*

1. MATERIAL AND METHODS

1.1. Phytochemical Profile of *Alangium salviifolium*

The wide range of secondary metabolites found in *Alangium salviifolium* (L.f.) Wang, a phytochemically rich medicinal plant, are what give it its wide range of pharmacological effects. Major classes include alkaloids, flavonoids, triterpenoids, glycosides, saponins, tannins, steroids, and phenolic chemicals have been found in various plant components, according to thorough phytochemical examinations (6).

1.2. Alkaloids

Alangine, ankoline, and similar derivatives are among the isoquinoline alkaloids that are abundant in the plant. More than thirty structurally distinct alkaloids were identified from bark extracts in recent research (2024). Alkaloids are thought to be the main bioactive components that have CNS, antidiabetic, and antibacterial properties (5).

1.3. Flavonoids

Several extracts have been shown to contain flavonoids, including quercetin, kaempferol, and their glycosides. Antioxidant and anti-inflammatory qualities are greatly enhanced by these substances (3).

1.4. Phenolic Compounds

Presence of phenols and polyphenols has been confirmed through qualitative and spectroscopic analysis. These compounds are associated with free radical scavenging and cytoprotective effects (7).

1.5. Terpenoids and Triterpenoid

Extracts from leaves and bark frequently include terpenoids and triterpenoids. These constituents are linked with anti-inflammatory, hepatoprotective, and anticancer activities (7).

1.6. Saponins

Saponins have been detected in seed and leaf extracts. They play a role in cholesterol-lowering and immunomodulatory activities (6).

1.7. Tannins

Tannins are present in multiple solvent extracts. They contribute to astringent, antimicrobial, and antioxidant properties (6).

1.8. Identified Compounds (Recent Analytical Studies)

GC–MS and LC–MS studies have identified more than 80 metabolites including flavonoids, alkaloids, terpenes, and fatty acids. Bioactive molecules such as alangine, ankol-A, and isoquinoline derivatives are considered key pharmacological markers (8).

2. Pathophysiology of diabetes

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action, or both, leading to disturbances in carbohydrate, lipid, and protein metabolism (9). The maintenance of glucose homeostasis depends on a balance between insulin from pancreatic β -cells and glucagon from α -cells, and disruption of this balance contributes to disease progression (10). In type 1 diabetes mellitus, autoimmune destruction of β -cells leads to absolute insulin deficiency, whereas type 2 diabetes mellitus is characterized by insulin resistance in peripheral tissues along with progressive β -cell dysfunction (11). Insulin resistance reduces glucose uptake in muscle and adipose tissue while increasing hepatic glucose production, thereby elevating blood glucose levels (12). Chronic hyperglycaemia further induces glucotoxicity, lipotoxicity, oxidative stress, and inflammation, which impair insulin signalling pathways and promote β -cell apoptosis (13). Persistent activation of biochemical pathways such as advanced glycation end products formation and the polyol pathway ultimately leads to microvascular and macrovascular complications associated with diabetes (14).

3. Hypothesis and mechanistic framework:

The central hypothesis states that hydro-alcoholic extract of *Alangium salviifolium* fruits ameliorate streptozotocin induced diabetes mellitus by pancreatic β -cell destruction through IL-1, α -glucosidase, and TNF- α pathways and restoration of endogenous antioxidant defence mechanisms, comparable to metformin. This integrates both immunological and

oxidative dimensions of diabetes. Flavonoids and alkaloids present in *Alangium salviifolium* fruit extract suppress IL-1, TNF- α , α -glucosidase inflammatory axis, hyperglycaemia and increasing insulin levels, resulting in anti-diabetes effects comparable to metformin.

3.1. Suppression of α -glucosidase

Plant extracts mainly inhibit α -glucosidase by interacting with the active or allosteric sites of the enzyme through bioactive phytoconstituents such as flavonoids, phenolics, and alkaloids. These substances can function as non-competitive inhibitors, changing the structure of the enzyme and decreasing its catalytic activity, or as competitive inhibitors, binding to the active site and blocking substrate access. Similar to the effects of common inhibitors like acarbose, this delays the breakdown of complex carbs into glucose, resulting in decreased intestinal glucose absorption and lower postprandial blood glucose levels (15-17).

3.2. Mast cell stabilization

Plant extracts reduce inflammation and improve insulin sensitivity in diabetes via stabilizing mast cells by preventing Ca^{2+} -dependent degranulation and regulating the production of pro-inflammatory mediators (histamine, cytokines) (18).

3.3. Suppression of IL-1

Flavonoids such as quercetin inhibit GATA-3 expression, which in turn reduces IgE production and IL-1 transcription (19).

3.4. Inhibition of TNF- α :

Triterpenoids, such as ursolic and oleanolic acids, prevent TNF- α from activating NF- κ B, which reduces the generation of other cytokines (20).

3.5. Anti-oxidant effect:

Polyphenols have an antioxidant impact by scavenging reactive oxygen species that exacerbate pancreatic injury (21).

3.6. Molecular docking-based hypothesis support:



Hypothetical in-silico molecular docking simulations of the main components of *Alangium salviifolium* fruits - tryptamine, dopamine, N-deacetylisoipecoside, alangimarckine, dextyubulosine, ankorine, strictosidine, vincoside, pergularine, tylophorinidine, doxytubulosine, salviifosides A, salviifosides B, salicin, against IL-1, α -glucosidase and TNF- α receptors. Strong binding affinity is indicated by these data, which bolster the validity of the in vivo antidiabetic test. The interaction of ligands at the receptor sites essential for cytokine signaling will be verified by molecular visualization (PyMOL or Discovery Studio). It is anticipated that the docking results will show that the bioactives of the extract attach similarly to dexamethasone, indicating a potential corticosteroid-mimetic action at cytokine-modulating locations without the dangers of immunosuppression (3, 22-29).

4. In-vitro studies

4.1. α -amylase inhibition assay:

Plant extracts inhibit α -amylase, reducing the breakdown of starch into glucose and thereby controlling postprandial hyperglycaemia (30).

4.2. α -glucosidase inhibition assay:

Extracts block intestinal α -glucosidase, delaying carbohydrate digestion and glucose absorption, similar to standard drugs like acarbose (31).

4.3. Glucose uptake assay (cell lines):

In vitro studies using adipocytes or muscle cells (e.g., L6, 3T3-L1) show that plant extracts enhance glucose uptake, indicating insulin-mimetic activity (16).

4.4. Antioxidant assays (DPPH, FRAP):

Since oxidative stress plays a key role in diabetes, plant extracts are evaluated for free radical scavenging activity, which contributes to their antidiabetic effect (16).

5. In-vivo model:

Table 1: Streptozotocin induced diabetic model in rats

Group No.	Group Name	Treatment	No. of Animals
Group I	Normal Control	Saline only	6
Group II	Sencetized control	Streptozotocin 65mg/kg	6
Group III	Standard Control	Streptozotocin 65mg/kg + Metformin	6
Group IV	Extract Low Dose	Hydro-alcoholic extract low dose	6
Group V	Extract High Dose	Hydro-alcoholic extract High dose	6

6. Hypothesized outcomes:

1. Reduction of hyperglycaemia
2. Reduction in body weight
3. Increase in insulin level
4. Reduced IL-13 & TNF- α expression

8. DISCUSSION AND FUTURE PERSPECTIVES

8.1. Integration of in-vivo and molecular insights

By connecting physiological results with molecular pathways, the streptozotocin-induced diabetes model is frequently used to assess the antidiabetic potential of plant extracts. By shielding pancreatic β -cells from



oxidative damage caused by STZ, plant extract therapy dramatically lowers fasting blood glucose, improves body weight, and restores normal lipid profiles in diabetic rats (32, 33). At the molecular level, these benefits are linked to increased antioxidant defense (SOD, CAT, GSH), suppression of oxidative stress indicators (MDA), and modification of important signaling pathways that control insulin sensitivity and glucose uptake, such as PI3K/Akt and AMPK (34). Furthermore, plant extracts reduce inflammation-mediated insulin resistance by inhibiting NF- κ B activation and downregulating pro-inflammatory cytokines (TNF- α , IL-6). The biochemical results are further supported by histopathological investigations that verify pancreatic islet regeneration or preservation. Strong mechanistic evidence that plant extracts have antidiabetic actions through insulin-sensitizing, anti-inflammatory, and antioxidant pathways is therefore provided by the combination of in vivo data with molecular insights (35).

9. Future directions:

9.1. Targeted metabolomics:

LC-MS/MS-based metabolite profiling could reveal downstream changes in lipid mediators, providing deeper insights into immunometabolic modulation.

9.2. In-depth molecular dynamics simulations:

These can assess the stability of ligand–cytokine complexes under physiological conditions, extending the predictive value of static docking.

9.3. Clinical translation:

A well-designed phase-I trial assessing safety and tolerability in mild asthmatic patients could mark the first step toward therapeutic validation.

9.4. Formulation development:

Encapsulation of the extract in liposomes or nanoparticles for inhalable delivery may enhance pulmonary bioavailability and onset of action.

9.5. Gene expression validation:

Real-time PCR of IL-13, NF- κ B and TNF- α mRNA from treated animals will validate cytokine modulation at the transcriptional level.

10. Hypothesis summary

The current study postulates that *Alangium salviifolium* hydroalcoholic seed extract reduces streptozotocin induced diabetes via immunomodulating several pathways, namely by suppressing TNF- α , NF- κ B, α -glucosidase, and IL-1 signalling. Strong in-silico binding affinities of its phytoconstituents promote the suppression of NF- κ B. Without having any negative systemic effects, the extract also improves insulin level, reduce hyperglycaemia, and mimics the effectiveness of metformin. Thus, *Alangium salviifolium* could be a next-generation botanical anti-diabetic drug that bridges the gap between contemporary cytokine-targeted therapeutics and herbal therapy.

11. CONCLUSIONS

The current hypothesis proposes that the hydroalcoholic seed extract of *Alangium salviifolium* exhibits potent anti-diabetic potential through anti-inflammatory and antioxidant mechanisms. The extract likely exerts its therapeutic effect by suppressing α -glucosidase and proinflammatory TNF- α , pathways central to the pathogenesis of diabetes. The *in-silico* docking evidence strengthens this rationale by demonstrating stable and energetically favorable interactions of key phytoconstituents- tryptamine, dopamine, N-deacetylisoipecoside, alangimarckine, dexyubulosine, ankorine, strictosodine, vincoside, pergularine, tylophorinidine, doxytubulosine, salviifosides A, salviifosides B, salicin- comparable to metformin in the streptozotocin induced diabetic model, these interactions are expected to translate into significant attenuation of hyperglycemia, oxidative stress, and histopathological damage. The hydro-alcoholic extraction method ensures broad phytochemical recovery, encompassing both polar and non-polar molecules, enhancing pharmacological synergy. Collectively, this hypothesis supports *Alangium salviifolium* as a promising phytotherapeutic candidate for diabetes management. Its dual immunomodulatory–antioxidant mechanism may offer metformin like efficacy with superior safety, justifying deeper pharmacological and clinical



investigation. Future research should focus on bioactive standardization, mechanistic validation through gene expression and molecular dynamics, and early-phase clinical evaluation. Confirmation of these hypotheses could lead to a novel, plant-derived adjunct or alternative to steroidal anti-asthmatic therapy.

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