EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 1
Year: 2026

NATURAL HERBAL AGENTS IN THE REGULATION OF BLOOD GLUCOSE: SCREENING ASSAYS AND THEIR DIVERSE PHARMACOLOGICAL ACTIONS

Shivam[1], Neelottama Kushwaha*[1], Swatantra Kumar Singh Kushwaha[1]

[1]Krishna Institute of Pharmacy and Sciences, Kanpur, India, 209217.

***Corresponding Author: Neelottama Kushwaha**

Krishna Institute of Pharmacy and Sciences, Kanpur, India, 209217.

DOI: https://doi.org/10.5281/zenodo.18150724

How to cite this Article: Shivam[1], Neelottama Kushwaha*[1], Swatantra Kumar Singh Kushwaha[1]. (2026). NATURAL HERBAL AGENTS IN THE REGULATION OF BLOOD GLUCOSE: SCREENING ASSAYS AND THEIR DIVERSE PHARMACOLOGICAL ACTIONS. European Journal of Biomedical and Pharmaceutical Sciences, 13(1), 220–229.

Article Received on 05/12/2025 **Article Revised on 25/12/2025** **Article Published on 05/01/2026**

ABSTRACT

Historically, symptoms that are today recognized as diabetes mellitus were treated with herbal remedies in various cultures. Determining the effectiveness, mechanisms, and safety of botanicals and their active ingredients in glycemic control has rekindled scholarly interest due to the rise in complementary and alternative medicines as well as the advancements in phytochemistry, pharmacology, and screening technologies. The current evidence on commonly studied antidiabetic herbs, the physiological and molecular pathways they control, the in vitro and in vivo testing used to screen and profile antidiabetic effects, and the difficulties in translating botanical drug candidates to the clinic are all summarised in this review. The primary focus is on agents with the best preclinical and clinical signals (such as Momordica charantia, Trigonella foenum-graecum, berberine-containing species, Gymnema sylvestre, Moringa oleifera, and Cinnamomum verum), assay cascade projects that combine cell-based, animal, in silico, and biochemical approaches, and practical considerations of standardisation, safety, and herb-drug interactions. The article concludes with clinical research priorities, quality and patient safety measures, and best practices for screening pipelines.

KEYWORDS: Herbal remedies, glycemic control, antidiabetic, safety, efficacy, clinical research.

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterised by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is a major global health concern, affecting millions of people worldwide and contributing significantly to morbidity, mortality, and healthcare costs. Based on current epidemiological statistics, the incidence of diabetes in the world has been on the increase especially in developing countries owing to the transformations in the lifestyles, the diet, and the ageing population. Although a number of classes of synthetic antidiabetic agents such as sulfonylureas, biguanides, thiazolidinedione as well as insulin analogs are available, these interventions have their drawbacks such as adverse effects, diminished effectiveness when used on a chronic or long-term basis, and cost considerations. These obstacles have revived the curiosity into alternative healing methods on natural products and medicinal plants as safer, less expensive and multi-functional therapy agents to combat diabetes.

The natural herbal agents have traditionally been core to the traditional medical systems in controlling the amount of glucose in the blood. The plants have a rich phytoconstituents such as alkaloids, flavonoid, saponins, terpenoids, glycosides, and polyphenols that help in reducing their antidiabetic and metabolic modulatory effects.[1] These compounds have numerous effects of action including the stimulation of insulin secretion, stimulation of peripheral glucose uptake and the modulation of carbohydrate-digesting enzymes, effects on b-cell activity and the alleviation of oxidative stress. It is due to the complex pathophysiology of diabetes and its related complications that herbal therapeutics are of particular importance as multi-factorial in their ability to treat the condition.

During the recent several decades, variety of in vitro and in vivo screening assays have been designed to test the hypoglycemic and antihyperglycemic effect of the natural products. More techniques sensitive techniques

like glucose uptake assays, the inhibition of a-amylase and a-glucosidase, studies of insulin secretion and animal models of chemically induced diabetes have been diverse in validating traditional allegations and in chiming a lead compound to drug formulation. Moreover, the phytochemical profiling and molecular docking have improved the comprehension of pharmacodynamic plants on the interactions of the plant-derived compounds and biological targets.

2. NATURAL HERBAL AGENTS IN THE REGULATION OF BLOOD GLUCOSE AND OTHER PHARMACOLOGICAL EFFECTS

Phyto-derived bioactive compounds have since been known to be useful in medicine due to varied therapeutic uses of such compounds in medicine. Several botanicals, including Trigonella foenum graecum (Fenugreek), Gymnema sylvestre (Gymnema), Moringa oleifera (Moringa), Cinnamomum verum and C. cassia (Cinnamon), Piper nigrum (Black Pepper), Momordica charantia (Bitter Melon), berberine-containing plants such as Berberis spp. and Coptis chinensis, Panax spp. (Ginseng), Nigella sativa (Black Cumin), and Aloe vera have shown great pharmacological effects. These have been greatly mediated by their rich composition in phytochemicals that comprise of alkaloids, saponins, flavonoids, polysaccharides, polyphenols, glycosides.[2]

2.1. Piper nigrum L. or black pepper is a well-known and widely recognised plant belonging to the family Piperaceae and it is widely recognised as the King of Spices. In addition to its food value, P. nigrum is characterized by a broad spectrum of pharmacological action due to its possession of a high level of phytochemical elements such as piperine, the major bioactive alkaloid. It also has other properties like chavicine which is known to contribute to its therapeutic properties as well as other constituents like piperettine, piperidine and essential oils. Significantly, antioxidant, anti-inflammatory, antidiabetic, antihyperlipidemic, antimicrobial, neuroprotective, hepatoprotective and bioavailability-enhancing properties of P. nigrum have been proven by extensive experimental and clinical studies.

P. nigrum has had a lot of research on its antidiabetic value. Piperile enhances glucose homeostasis by promoting insulin secretion, promoting glucose uptake, and altering major carbohydrate metabolising enzymes; glucokinase, glucose-6-phosphatase and fructose-1, 6 bisphosphatase.[3] In addition, it has been demonstrated that glucocorticoid-lowering spots, glucocorticoid-raising spots and glucocorticoids have an effect on skeletal muscle and adipose tissue GLUT4 translocation, enhancing peripheral glucose utilisation. The efficacy in terms of reducing fasting blood glucose, HbA1c and serum lipid level has been proven in animal studies, which points to the potential of using it as a natural antidiabetic agent.

P. nigrum contains polyphenolic compounds, the presence of which is the main feature of the antioxidant activity of the product and scavenges reactive oxygen species (ROS), contributes to the activity of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These activities contribute towards the inhibition of cellular damage due to oxidative stress, hence forecasting the purpose of the activity towards the prevention of persistent metabolic and degenerative disorders.

Also, P. nigrum has significant anti-inflammatory properties, reducing pro inflammatory TNF-a, IL-1b and IL- 6 cytokines, as well as preventing the activation of the NF-kB and COX-2 pathways. All these effects help in rendering it therapeutic in inflammatory diseases like arthritis and colitis. Antimicrobial effect of black pepper has been reported to cause a very expansive number of pathogens such as; Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Candida albicans mainly through the membrane disruption and enzyme inhibitory abilities of piperine and essential oils.

In addition, P. nigrum has neuroprotective and cognitive-enhancing effects, which are achieved through altering cholinergic neurotransmission and oxidative damage of neural tissues. Its hepatoprotective effecticacies have been demonstrated in models of chemically induced liver injury, where, in a manner as evidenced, the piperazine encompasses the liver damage linked with the lipid peroxidation and the restoration of antioxidant defences, which constitute its functions.[4] Significantly, the biological activity of a variety of therapeutic agents, such as curcumin, resveratrol, as well as a variety of antibiotics, is also enhanced due to Chinese medicinal plants, including piperine, able to inhibit drug-metabolizing enzymes in the liver and intestine.

2.2. The family Lauraceae, of which Cinnamomum verum (true cinnamon) and Cinnamomum cassia (Chinese cinnamon) are the common examples, are aromatic medicinal plants with a broad potential to be used in traditional and modern medicine as a treatment. Cinnacoldehyde, cinnamic acid, eugenol, coumarin, and other polyphenolic compounds considered to be the bioactive constituents of cinnamon have been linked to the pharmacological activities of cinnamon such as; antidiabetic, antioxidant, anti-inflammatory, antimicrobial, lipid-lowering, and neuroprotective properties.

One of the pharmacological properties studied extensively about cinnamon is the antidiabetic effect. Polyphenols such as cinnamaldehyde promote phosphorylation of insulin receptor, translocation of glucose transporter 4 (GLUT 4), and the uptake of glucose at the periphery. Also, cinnamon can regulate the activity of major enzymes in carbohydrate metabolism, e.g. hexokinase, phosphofructokinase, and glucose-6-phosphatase, which is also associated with the

enhancement of insulin sensitivity and glycemic regulation. This has been proved in several clinical studies that Cinnamon has also been shown to have strong anti-inflammatory activity, which can principally be attributed to the inhibition of the pro-inflammatory cytokines (TNF-a, IL-1b, IL-6) and to the inhibition of the NF-kB signaling pathway. These are known to inhibit inflammatory process of long-term metabolic and autoimmune diseases. Moreover, C. verum and C. cassia both exhibit antimicrobial activity with a wide range of bacteria and fungi, such as Staphylococcus aureus, Escherichia coli, Candida albicans, and Aspergillus species due to the membrane disruptive effect of cinnamaldehyde and eugenol.[5]

The hypolipidemic and cardioprotective properties of cinnamon have been explained by the capacity to reduce total cholesterol, triglycerides and low-density lipoprotein (LDL) and increase the quantity of high-density lipoprotein (HDL) levels. Also, new findings were neuroprotective and hepatoprotective based on the regulation of oxidative and inflammatory processes.

2.3. Momordica charantia L., commonly known as bitter melon or bitter gourd, belongs to the family Cucurbitaceae and has been widely used in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine, and Unani for the management of diabetes mellitus. The plant's fruits, seeds, and leaves possess potent hypoglycemic properties attributed to its rich phytochemical composition, including charantin, polypeptide-P, vicine, momordicosides, and various triterpenoids and flavonoids. Hypoglycaemic responses have been preclinically indicated by augmented insulin discharge, augmented peripheral glucose uptake, AMPK signalling and gluconeogenesis repression. The size and nature of the clinical trials is small and heterogeneous; the evidence base contains a number of small clinical trials, which point into the potential benefit of glucose-lowering in T2D, but no large and well-controlled trials exist in the evidence base.[6] The plant exhibits significant antidiabetic, antioxidant, anti-inflammatory, anticancer, antimicrobial, hepatoprotective, lipid-lowering, and immunomodulatory activities, attributed to its rich phytochemical composition.

The antidiabetic potential of M. charantia is well documented and primarily associated with the presence of bioactive compounds such as charantin, vicine, and polypeptide-p. All these components are insulin-mimetic and insulin-secretagogue agents enhancing the functioning of pancreatic b-cells, activating glucose absorption in the pancreas by GLUT4 translocation, and suppressing intestinal glucose uptake. Moreover, the plant alters major carbohydrate metabolizing enzymes, which enhances the glucose homeostasis and insulin sensitivity.

The antioxidant as well as anti-inflammatory activity is regulated by increasing the expression of endogenous antioxidant enzymes, including superoxide dismountable (SOD), catalase (CAT), and glutathione peroxidase (GPx) and inhibiting the production of pro inflammatory cytokines, such as TNF-a, IL-6, and NF-kB. Such measures lead to the reduction of oxidative stress and inflammatory damage, which are a usual prevalence of metabolic diseases.[7]

Moreover, the study of M. charantia shows anticancer activity through the apoptosis-indcing effect, cell proliferation suppression, and the regulation of essential cellular processes of MAPK, PI3K/Akt, and AMPK. The antimicrobial activity of the plant on bacterial, fungal and viral pathogens further increases its therapeutic interest. Furthermore, hepatoprotective effect has been described against chemically induced liver injury, this is mainly by suppressing lipid peroxidation as well as reinstatement of antioxidant defence mechanisms.

Phytochemical studies have found out that it has triterpenoids, alkaloids, flavonoids, saponins, and glycosides that are all presently contributing towards its broad pharmacological spectrum. Altogether, Momordica charantia can be a perspective natural therapeutic compound with a complex of pharmacological activities, especially in the treatment of diabetes and related metabolic disorders.

2.4 Trigonella foenum-graecum L., that is also referred to as fenugreek is a genus of Trigonaceae, a broadly grown plant due to its medicinal, nutritional, and pharmacological characteristics. It has been commonly used in other medicine systems such as the Ayurveda and Unani, in the treatment of metabolic and inflammatory conditions. Fenugreek has been found to have high phytochemical components which explain its pharmacological effects: steroidal saponins (diosgenin, yamogenin), alkaloids (trigonelline), flavonoids, and polyphenols, coumarins and galactomannan fibers. It has a variety of pharmacological effects such as antidiabetic, hypolipidemic, antioxidant, anti inflammatory, hepatoprotective, gastroprotective and neuroprotective effects as a result of these bioactive compounds. T. foenum-graecum has been widely studied with regard to antidiabetic property. Grains of fenugreek have got soluble fiber (galactomannan) that retards the emptying of products in the stomach and absorption of glucose, which leads to better postprandial glycemic regulation. Additionally, the compounds, 4-hydroxyisoleucine and trigonelline, are insulin secretion stimulants, peripheral glucose usage stimulants as well as regulators of key carbohydrate metabolic enzymes, hexokinase, glucose-6 phosphatase. The experimental and clinical findings have showed that due to supplementation of fenugreek, the level of fasting blood glucose, glycated haemoglobin (HbA1c) and the ability to tolerate glucose are significantly reduced in diabetic subjects.[8]

The presence of phenolic and flavonoid compounds determines the antioxidant power of fenugreek that

captures the free radicals and expands the activities of endogenous antioxidant enzymes, e.g., superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This antioxidative effect is involved in the mechanism of prevention of oxidative stress-induced cellular injury especially in diabetes and cardiovascular diseases.

Fenugreek also demonstrates pronounced anti-inflammatory activity and this is mediated by the inhibition of the pro-inflammatory mediators like TNF-a, IL-1b, IL-6, and also suppression of COX-2 and NF-kB signalling pathways. It has been clearly proven to have hypolipidemic and cardioprotective properties, and it has been shown that fenugreek lowers serum total cholesterol, triglycerides and low-density lipoprotein (LDL) concentrations with positive effects on high density lipoprotein (HDL) levels. This is because of the occurring of saponins and dietary fibre, which disrupt the absorption of the intestinal cholesterol and facilitates the excretion of the bile acids.

Also, T. foenum-graecum proved to have hepatoprotective effects curing the hepatic antioxidant defense system and lowering lipid peroxidation in toxin-induced liver injury models. It has also been reported to have neuroprotective and memory enhancing effects probably because of the antioxidant and anti inflammatory effects that protect the integrity of the neuron.[9] In addition, fenugreek has antimicrobial and gastroprotective properties, which justify its application in traditional medicine in the heavy and infectious diseases of the gastrointestinal tract.

2.5 Plants Berberis spp. and Coptis chinensis are enriched with berberine that is an active isoquinoline alkaloid with multifunctional pharmacological effects. This drug Berberine has a wide range of anti-diabetic, anti-lipid, anti-oxidant, anti-inflammatory, anti-microbial, hepatoprotective, and cardioprotective as well as anti-cancer properties and these kinds of plants are useful in both traditional and modern treatment.

The antidiabetic effect of berberine is beyond doubt, and it has several mechanisms. Berberine enhances insulin sensitivity, promotes the uptake of glucose through the GLUT4 translocation and chimes the important carbohydrate metabolic enzymes such as glycogen synthase, AMP-activated protein kinase (AMPK), and glucose-6 phosphatase. Clinical and preclinical researchers have shown that berberine is effective in lowering the level of fasting blood glucose, postprandial glucose and HbA1c level of patients with type 2 diabetes mellitus.

Also, berberine has hypolipidemic reactions through the control of cholesterol and triglyceride metabolism. It decreases serum total cholesterol, low-density lipoprotein (LDL), triglycerides and increases high-density lipoprotein (HDL) concentrations, mostly by increasing LDL receptors and activating AMPK signaling pathways. All these outcomes have led to its cardioprotective properties in the advancement of lipid profiles and atherosclerotic risks.[10]

In vivo mechanisms of action Berberine has an antioxidant and anti-inflammatory effect that is mediated through reactive oxygen species (ROS) scavenging and pro-inflammatory mediator inhibitions like TNF- a, IL-6, IL-1b and NF-kB signaling. These effects assist to alleviate the oxidative stress and inflammatory reactions linked with the metabolic, cardiovascular and neurodegenerative diseases. Besides, berberine has been demonstrated to protect the brain, and to affect gut microbiota, indicating its extended therapeutic use.

2.6. Gymnema sylvestre R. Br., which is also sometimes referred to as Gymnema is a species of the family Apocynaceae which has been well identified as having therapeutic value in metabolic syndrome especially the diabetes mellitus.[11] The bioactivity of antidiabetic, anti-obesity, antioxidant, anti-inflammatory, lipid-lowering, along with his hepatoprotective effects have been ascribed to a combination of pharmacological activities of G. sylvestre, namely: gymnemic acids, gymnemasaponins, flavonoids and triterpenoids, among them.

The use of G. sylvestre as antidiabetic has been well-established. The glucose-lowering effects of gymnemic acids include the inhibition of intestinal absorption of glucose by the prevention of sugar transporters, the increase of the insulin secretion and the healing of the pancreatic b -cells. Moreover, Gymnema regulates major carbohydrate-metabolizing enzymes, such as glucokinase, glucose-6-phosphatase and glycogen synthase, which promotes glycemic regulation and infertility to insulin. Preclinical and clinical trials have shown that there is a great decrease in fasting blood glucose, postprandial glucose, and glycated hemoglobin (HbA1c) after taking the gymnema.

G. sylvestra has also been shown to have anti-obesity and lipid-lowering properties such as the decrease of postprandial sugar absorption, body weight reduction, and improvements in serum lipid profile, i.e., total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels and a rise in high-density lipoprotein (HDL) levels. Its antioxidant effects are facilitated by scavenging of the reactive oxygen species and by increase in the activity of endogenous antioxidant enzymes e.g. superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx).

Moreover, Gymnema has anti-inflammatory effects through inhibition of pro inflammatory cytokines (TNF-a, IL-6, IL-1b) and inhibition of NF-kB signaling, which leads to the diminished chronic inflammation related to the metabolic illnesses. The plant is also hepatoprotective in nature guarding against liver tissues

against oxidative stress and remedying the liver enzymes.[12]

Moringa oleifera Lam., also referred to as the drumstick tree or the horseradish tree, is a nutritional plant and a widespread plant in terms of medical benefits as it belongs to the family Moringaceae.

M. oleifera exhibits potent antioxidant activity, scavenging reactive oxygen species (ROS) and enhancing endogenous antioxidant defences, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This antioxidative effect adds up to the prevention of oxidative stress-related injury in the metabolic, hepatic, and neurodegenerative conditions.

The plant also has important anti-inflammatory properties due to the inhibition of pro-inflammatory cytokines and other activities, including activation of the NFkB pathway, exonerating it as useful in immune diseases and metabolic dysfunctions. M. oleifera is hepatoprotective and decreases lipid peroxidation and restores liver enzyme functions in intoxicated liver damage models.[13]

Other pharmacological effects are cardioprotective action by altering lipid profiles and blood pressure, neuroprotective action by reducing oxidative stress in neural tissue, antimicrobial action by killing bacterial and fungal pathogens and anticancer effect by causing cell apoptosis and eliminating the growth of different cancer cell lines.

2.7. Panax ginseng (Asian ginseng) and Panax quinquefolius is a genus of the family Panaxaceae. (American ginseng) are plants of the family Araliaceae and are one of the most widely spread. researched the traditional and modern pharmacological tradition of medicine through study of medicinal plants. Their pharmacological the effects are mainly known to be due to ginsenosides: a family of steroidal saponins, heteropolymers, polymerized proteins, polyacetylenes and polyacetylpenics.[14]

These bioactive constituents bring about a broad spectrum of therapeutic actions, one of which is adaptogenic. Firstly, it has antidiabetic, antioxidant, anti-inflammatory, immunomodulatory, neuroprotective, cardioprotective, hepatoprotective, and anticancer properties. The Panax spp. have the antidiabetic activity that is well documented. Insulin is improved by ginsenosides secretion, enhance peripheral glucose intake, and control important carbohydrate-metabolizing, enzymes glucokinase and glucose -phosphatase. Moreover, ginseng is a modulator. The action of AMP-activated protein kinase (AMPK) signalling enhancing insulin sensitivity and glucose homeostasis. Preclinical and clinical trials have indicated the decline of fasting blood glucose Values of postprandial glucose, and HbA1c after the use of ginseng.

Ginseng has strong antioxidant properties, as it scavenges the reactive oxygen species (ROS). increasing antioxidant enzymes that are also endogenous, such as superoxide dismutase (SOD), Such enzymes include catalase (CAT), and glutathione peroxidase (GPx). It is used to prevent oxidative by these activitiesmetabolic, cardiovascular, and neurodegenerative disorder damage caused due to stress.

The anti-inflammatory and immunomodulatory action of ginseng is meditated with inhibition of pro-inflammatory cytokines (TNF-a, IL-1b, IL-6), inhibition of NF-kB As well as modulating the innate and adaptive immune responses, signaling improves them. This dual action plays a role in its therapeutic ability in chronic inflammatory and infections.

Ginseng too has strong neuroprotective properties such as improving. cognitive effect, suppression of neural injury, and decrease of neuroinflammation, which can be ascribed to the action of the cholinergic pathways, and oxidative stress. It causes improvements in lipid profiles, blood reduction which reflects cardioprotective effects (pressure) and anti-inflammatory and anti-oxidative protection of myocardial injury mechanisms. In addition, ginseng displays hepatoprotective as well as anticancer effects, involving induction of apoptosis, cell proliferation inhibition, and signaling. signaling pathways (PI3K/Akt, MAPK and AMPK).

2.8. Nigella sativa L., otherwise referred to as black cumin or black seed is a species in the family Ranunculaceae and it has mostly been made use of in traditional medicine because of its therapeutic property. The pharmacological properties of N. sativa are primarily attributed to its bioactive constituents, including thymoquinone, nigellone, α-hederin, flavonoids, saponins, and essential oils, which collectively confer antidiabetic, antioxidant, anti inflammatory, hepatoprotective, neuroprotective, antimicrobial, immunomodulatory, and anticancer activities.

N. sativa has good antidiabetic properties. Thymoquinone and other active components can better regulate glucose, which increases insulin secretion and glucose absorption in peripheral tissues as well as carbohydrate-metabolising enzyme processes of glucokinase and glucose-6-phosphatase.[15] There have been clinical and preclinical studies of decreases in fasting blood glucose, intake of glucose after meals, and glycated haemoglobin (HbA1c) when N. sativa extracts or oil are taken.

N. sativa exhibits significant antioxidant activity, scavenging reactive oxygen species (ROS) and enhancing endogenous antioxidant defence systems,

including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). The actions prevent the damage of tissues caused by oxidative stress in metabolic, hepatic and neurodegenerative diseases.

2.9. Aloe Vera (L.) Burm. f. is a commonly used medicinal plant which belongs to the family Asphodelaceae, which may be used as a medicine or cosmetic. The pharmacological effects of A. vera are explained by the presence of an abundant phytochemical composition with such effects as wound healing, antioxidant, anti-inflammatory, immunomodulatory, antidiabetic, hepatoprotective, antimicrobial and anticancer.

Experimental and clinical trials show that A. vera can be used as an antidiabetic because it improves insulin secretion, enhances peripheral glucose uptake, and the regulation of carbohydrate-metabolising enzymes that lead to a reduction in fasting blood glucose, postprandial glucose level and glycated haemoglobin (HbA1c).

The wound healing and dermatological actions of the A. vera are properly reported. Acemannan and amylaceous polysaccharides enhance the proliferation of fibroblasts, collagen synthesis and angiogenesis, which promote.[16]

Premiere restitution and healing. Also, the presence of anthraquinones helps in the antimicrobial effect which helps in preventing wound infection.

The ability of A. vera in reducing oxidative stress involves scavenging reactive oxygen species (ROS), increasing endogenous antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)) thus alleviating the adverse effects of oxidative stress in metabolic (liver) and skin diseases.

The plant demonstrates potent anti-inflammatory effects by inhibiting pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and modulating NF-κB signalling pathways, making it beneficial in chronic inflammatory and dermatological conditions.

Other pharmacological properties include hepatoprotective effects, mediated by reduction of lipid peroxidation and restoration of liver enzyme function; immunomodulatory activity, enhancing both innate and adaptive immune responses; antimicrobial activity against bacteria, fungi, and viruses; and anticancer potential, involving apoptosis induction, inhibition of proliferation, and modulation of signalling pathways such as PI3K/Akt and MAPK.

3. ANTIDIABETIC SCREENING, BOTANICAL AND DRUG DISCOVERY PIPELINE

It is an intensive herbal screening pipeline of antidiabetic discovery that incorporates several steps to determine bioactive compounds. It starts with ethnobotanical prioritisation to choose promising plants, then moves onto phytotransformational screening so as to characterise active components. The biochemical high-throughput assays are used to determine the inhibition of the enzymes, whereas the cell-based functional studies are used to measure the secretion of insulin and the uptake of glucose.[17]

In vivo efficacy is supported by animal models, targets, and optimisation of leads are predictable by computational methods, such as molecular docking and network pharmacology, which create a holistic structure of herbal drug discovery. Before the biological screening, the phytochemical screening-qualitative and quantitative analysis of alkaloids, flavonoids, saponins, terpenoids, and phenolics with the chromatographic (HPLC, UPLC, GC-MS) and spectroscopic (NMR, MS) methods) is performed on extracts. The batch-to-batch consistency can be done through fingerprinting and standardisation with the help of markers as a necessary condition in order to achieve reproducible bioactivity results.

3.1. In vitro biochemical assays

Biochemical assays are widely employed for the preliminary evaluation of antidiabetic potential, as they offer cost-effective, rapid, and reproducible methods for screening natural compounds and plant extracts. These assays are instrumental in identifying agents capable of modulating key enzymes or biochemical pathways involved in glucose metabolism. Common examples include the α-amylase inhibition assay, α-glucosidase inhibition assay, glucose uptake assay, glycation inhibition assay, and DPP-4 enzyme inhibition assay, which collectively help elucidate the mechanisms by which herbal extracts influence glycemic regulation.[18]
α-Glucosidase, α-amylase inhibition: Two types (colourimetric and fluorimetric) of assays are used to assess the capacity of plant extracts or compounds to inhibit enzymes (carbohydrate-hydrolysing enzymes) (α-amylase and αglucosidase). These are easy, quick and high-throughput assays, which enable screening of large numbers of samples easily to detect potential antidiabetic compounds that can regulate the postprandial glucose levels.

3.1.1. Protein tyrosine phosphatase 1B (PTP1B) is an inhibitor that suppresses the action of insulin to decrease insulin sensitivity. PTP1B inhibition increases the insulin receptor, enhances downstream PI3K-AKT signalling and enhances glucose uptake in peripheral tissues. Inhibiting PTP1B is thus viewed as a potential option for enhancing insulin sensitivity and controlling insulin resistance in diabetes.[19]

3.1.2. Screening in Dipeptidyl peptidase-4 (DPP-4). One such way of finding compounds that can lengthen the effect of incretin-like growth hormone (GLP-1) and glucagon-insulin-peptide (GIP) is through DPP-4 inhibition, which causes the stimulation of glucose-contingent insulin secretion. These agents prevent insulin breakdown that stimulates the secretion of the hormone,

improves post prandial glucose and reduces the amount of glucose in the bloodstream. This test is applicable in the identification of potential antidiabetic agents that have incretin pathways.

3.1.3. Hepatic glucose metabolic enzymes refers to an Enzyme-based assays of the primary hepatic enzymes, such as glucose- 6-phosphatase and fructose- 1, 6-bisphosphatase, which help in the establishment of compounds that control gluconeogenesis. The fact that the activity of these enzymes can be measured using plant extracts or bioactive compound enables the researchers to determine the capacity of the enzyme in reducing the endogenous glucose production, increasing the process of hepatic glucose metabolism and offering some aid to the process of glycemic control in the management of diabetes.[20]

3.2. Cell-based functional assays

Cell-based functional assays, which lie between physiology and biochemical research, offer further information on the cellular pathways of antidiabetic effect. The assays test the impact of natural compounds or extracts on insulin secretion, glucose intake, lipid metabolism and cell signalling pathways associated with glucose homeostasis. The most commonly used types are insulin secretion in the assays of pancreatic b-cell (INS-1, MIN6), glucose uptake in the adipocyte or muscle cells (3T3-L1, L6, or C2C12), and hepatic glucose production assays.[21] Through such studies, there is an elucidation of how the herbal agents can be able to regulate cellular responses that lead to the resultant improvement of glycemic control.

3.2.1. Adipocytes and myocytes glucose uptake The researchers determine insulin dependent and insulin-independent glucose uptake in cultured cells using glucose analogues labelled with radiolabels or fluorescence. Enhanced models are 3T3-L1 adipocytes, L6 myotubes, and C2C12 myotubes. The tests will determine the effects of compounds or extracts on the uptake of glucose in the cells which are indicative of insulin sensitivity and potential antidiabetic effect.

3.2.2. The insulinotropic potential of plant extracts or bioactive compounds is determined by the insulin secretion of b-cells INS-1 and MIN6 pancreatic b- cells lines. Insulin secretion response and glucose level at basal and glucose stimulated concentration can be measured on the cells and this can be utilized to ascertain the effect of compounds on the b-cells directly and the effects of the compounds on glucose stimulated release of insulin and their action in potential antidiabetic effect.[22]

3.3. Hepatocyte assays

Immortalized or primary culture of hepatocytes is a useful in vitro study of glucose metabolism in the liver. These systems enable the researcher to determine the effects of natural compounds or plant extracts on the transcription of gluconeogenic genes, the production of glycogen and net hepatic glucose production. This type of assays gives important information to the processes through which bioactive agents work to avert liver functioning, regulate endogenous glucose production and general glycemic homeostasis. Hepatocyte-based assays convert molecular targets to glucose regulation in the body by simulating major processes of hepatic metabolism.[23]

3.4. Assays of inflammation and oxidative stress

Assays of cell inflammation and oxidative stress using cells are valuable in the mechanistic study of insulin resistance and dysfunction of the b-cell in diabetes. They are usually the measurement of the generation of proinflammatory cytokines, the stimulation or suppression of nuclear factor-kappa B (NF-kB), or the production of reactive oxygen species (ROS) in appropriate cell models. NF-kB signal, cytokine expression, and intracellular ROS concentrations Australian and Chinese researchers can use these variables to understand the anti-inflammatory and antioxidative properties of bioactive compounds or herbal extracts. Moreover, dose-response analysis in such cellular models can facilitate characterization of mechanistic pathways (by pathway inhibitors) and give information on cytotoxicity or safety profiles, which in turn would be a complete assessment of the therapeutic potential of the compounds in reducing the effects of oxidative and inflammatory stress induced by diabetes.[24]

3.5. In vivo Assay

The model animals are necessary in studying the system pharmacology, pharmacodynamics and safety of the prospective antidiabetic drugs. These models are very useful to understand the complicated interactions in physiology that is not completely replicated in a test tube. Some of the most used models of diabetes are chemically induced diabetic models (alloxan-induced diabetes, streptozotocin induced diabetes in rodents) and genetic models (ob/ob mice, db/db mice, Zucker diabetic fatty rats), and diet-induced insulin resistance and type 2 diabetes models. These in vivo models play a crucial role in evaluating the effectiveness, action mechanism of action and long-term metabolic effects of natural products and herbal formulations on a physiologically relevant model.

3.6 In silico approaches

Network pharmacology, virtual screening and molecular docking are computational techniques which are very important in current antidiabetic drug discovery. The approaches are used to identify and prioritize candidate molecules to be tested experimentally because they predict molecular targets, affinities of binding, ligand-ligand interactions and off-target effects.[25] The in silico analysis is difficult to increase the speed with which the screening is conducted as well as enriches the knowledge of the mechanistic interactions between

phytoconstituents and the biological pathways of glucose regulation.

4. TRANSLATIONAL/METHODOLOGICAL PROBLEMS

Although preclinical evidence relating to the use of most botanical candidates as antidiabetic agents is found in large amounts, few of these compounds are advanced to clinical stages. The cause of this discrepancy is due to constant translational and methodological differences such as the variability of plants, absence of standardised extracts, inadequate bioavailability, low pharmacokinetic characterisation, and inappropriate experimental design. Also, disparities in efficacy and safety outcomes could also arise due to differences among in vitro, in vivo, and human physiology, whereas the lack of regulatory barriers and the absence of sufficiently rigorous clinical trial data only contributes to the inability to transform any promising herbal agent into available therapeutic provision.

4.1. Change in extract composition

The chemotypes, harvesting conditions, extraction solvents and extraction methods in plants can also vary considerably between plants, and this can result in large changes in phytochemical composition and bioactivity. This variability has an impact on the consistency, potency, and reproducibility of herbal extracts, which is why standardization is important in order to achieve consistent therapeutic effects in the research and clinical practices.[26]

4.2. Dose standardization

The absence of agreement on what should be equivalent dose in preclinical models and human beings makes it difficult to generalize the study results. Human studies have difficulties in determining safe and effective doses based on animal studies due to variations in metabolism, bioavailability and physiological reactions. To achieve reproducibility, optimality of therapeutic activities, and ease of clinical use of bioactive compounds, standardised dosing guidelines are a necessity.

4.3. Bioavailability and pharmacokinetics

A high number of promising phytochemicals are poorly absorbed orally, are highly metabolised during the first-pass, and/or rapidly excreted, which limits their in vivo activities. In an effort to solve these issues, it is important to use nanoencapsulation, liposomes or bioenhancers as specialized formulation strategies to enhance the stability, absorption and bioavailability.[27] These pharmacokinetic properties should be improved in order to obtain therapeutic effects in clinical practice.

4.4. Quality and contamination

Some herbal products have been reported to be adulterated with pharmaceutical substances or contaminated with heavy metals and microbial pathogens and this is dangerous to the safety of the users. This contamination may cause toxicity, adverse reactions and unfavourable efficacy. In order to preserve the therapeutic reliability of herbal remedies and ensure that the health of consumers is not jeopardised, it is essential to ensure high-quality control and adequate sourcing and manufacturing practices.

4.5. Heterogeneity of clinical trials

The small size of samples, short duration of studies, and heterogeneous endpoints are limiting factors of clinical conclusions of herbal therapies that limit reliability and generalizability. Uneven standardisation of herbal preparations also leads to changes in phytochemical content and herbal activities, and thus it is hard to come to conclusive and reproducible findings about the effectiveness and safety of using such herbal preparations in the management of diabetes.[28]

4.6. Safety and interactions

Conventional drugs may have a clinically significant interaction with botanicals (e.g. by inhibiting CYP enzymes, altering the absorption of drugs); they are often not well investigated. To seal these gaps, there is a need to resort to common methods, open disclosures and multidisciplinary collaborations between ethnobotany and analytical chemistry, pharmacology, and clinical trial design.

5. SUGGESTIONS AND CLINICAL EVIDENCE

In meta-analyses and systematic reviews it is often determined that certain botanicals contain an insignificant but significant glucose-lowering effect (e.g., cinnamon, fenugreek, berberine) but they note the heterogeneity and low quality of the trials available.[29] The recommendations to the clinicians are:

5.1. Consider the power of evidence: There are very limited herbal therapies which have undergone large, high-quality randomized controlled trials (RCT) that can be compared directly with conventional antidiabetic drugs. Adjunctive herbal therapy use thus should be taken cautiously. Such treatments are suggested to be backed by strong scientific data and standard preparations in order to guarantee similar effectiveness, security, and dependability, reducing dangers of negative results or variability in effects when applied with standard drugs.

5.2. Close monitoring: In cases where patients are taking herbal products with antidiabetic drugs, close attention should be given to the glycemic control. Specific emphasis is to be made on the risk of hypoglycemia, particularly in the case of insulinotropic herbs which stimulate the secretion of insulin. It entails monitoring blood glucose routinely, educating patients and cooperation with medical practitioners that are going to offer the combination therapy its safety and effectiveness and minimize negative effects.[30]

5.3. Investigate interactions: Evaluate concomitant medications and potential herb drugs interactions of the

patients with particular consideration to the herbs, which alter hepatic enzymes or drug transporters.[31] Such interactions have the potential of resulting in changes in metabolism, absorption or clearance of traditional drugs and this impacts on efficacy and safety. Close observation will also enable the prevention of any adverse outcomes and ensure the greatest treatment outcome in case of using pharmaceutical and herbal therapy.

5.4. Market quality: Patients need guidance to choose herbal products that are manufacturing by reputed companies that undergo tests of the third party to establish the purity and safety of the quality. The standardization (i.e., active compounds, extract ratios, labeling etc.), and ensures consistent clinical effects and minimizes the risk of contamination, adulteration, or variability and are safely and reliably used alongside common antidiabetic therapeutic agents.[32]

6. CONCLUSION

The natural herbal agents have a potential in management of diabetes mellitus because of their multi-faceted pharmacological properties such as glucose metabolism regulation, insulin sensitivity, antioxidant and anti-inflationary effects, and pancreatic b-cell protection. The ethnobotanical evidence alongside traditional knowledge has led to the identification of several plant species with antidiabetic potential of which many have been confirmed using in vitro, in vivo, and in silico screening procedures. The assays can be utilized for mechanistic information, target identification and optimization of bioactive compounds to therapeutic use. Although preclinical data has very much been available, clinical development still suffers due to challenges like variability in plant extracts, low bioavailability and differences in experimental testing models and human physiology. Addressing these methodological limitations, along with standardised extract preparation and rigorous pharmacokinetic evaluation, is essential to fully realize the therapeutic potential of herbal antidiabetic agents.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

1. Bhandari, S., Trivedi, Rahul, Maheshwari, R. A.; Besh, S.; Mahant, M.; Patil, S.; Garg, V.; & Singh, R. Diabetes: Exploring the intersection of metabolic disorders, lifestyle factors and herbal remedies: A review. Pharmacognosy Research, 2025; 17(1): 11-17. https://doi.org/10.5530/pres.20251951ahul
2. Bhatt, S. M.; Sharma, N. The potential of various herbal plants for potential therapeutic treatment for diabetes management. Annals of National Academy of Medical Sciences, 2025; 61: 213-223. https://doi.org/10.25259/ANAMS_70_2024
3. Gautam, P. K.; Gautam, S.; Yadav, V.; Jain, A., Bharti, A.; Ahirwar, A.; Ahirwar, N.; Herbal medicinal plants in diabetes management: insights from in vitro studies and future directions. Indo American Journal of Pharmaceutical Sciences, 2024; 11(01): 67-72. https://zenodo.org/records/10556184
4. Hawky, E. M. Advances in natural products application for diabetes management: A comprehensive review. Egyptian Russian University Journal, 2025; 4(2): 2400-2428. https://doi.org/10.21608/erurj.2025.304238.1169
5. Singh, R. K., & Sharma, K. A comprehensive review on the therapeutic potential of herbal plants in diabetes and diabetes-associated problems. Journal of Disease and Global Health, 2025; 18(1): 7-27. https://doi.org/10.56557/jodagh/2025/v18i19088
6. Yedjou, C. G.; Grigsby, J.; Mbemi, A.; Nelson, D.; Mildort, B.; Latinwo, L.; & Tchounwou, P. B. The management of diabetes mellitus using medicinal plants and vitamins: current evidence and future prospects. International Journal of Molecular Sciences, 2023; 24(10): 9085. https://doi.org/10.3390/ijms24109085
7. Rahman, M. M.; Islam, M. R.; Shohag, S.; Hossain, M. E.; Rahaman, M. S.; Islam, F.; Ahmed, M.; Mitra, S.; Khandaker, M. U. The multifunctional role of herbal products in the management of diabetes and obesity: a comprehensive review. Molecules, 2022; 27(5): 1713. https://doi.org/10.3390/molecules27051713
8. Usai, R.; Ncube, B.; & others. Natural products for the treatment and management of diabetes mellitus in Zimbabwe review. Frontiers in Pharmacology, (2022), https://doi.org/10.3389/fphar.2022.980819
9. Omale, J.; Akpanabiatu, M. I.; Macrow, C.; Ogunleye, T.; Nagarajan, S.; Lorimer, S.; Gould, G. W. A systematic analysis of anti-diabetic medicinal plants from cells to clinical trials, 2023; PeerJ, 11: e14639. https://doi.org/10.7717/peerj.14639\
10. Khan, A; Safdar, A.; Ali Khan, M. M.; Khattak, K. N.; & Anderson, R. A. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care., 2003; 26(12): 3215-3218. https://doi.org/10.2337/diacare.26.12.3215
11. Sabu, M. C.; & Kuttan, R.; Antidiabetic activity of medicinal plants and its relationship with their antioxidant property. Journal of Ethnopharmacology, 2002; 81(2): 155-160. https://doi.org/10.1016/S0378-8741(02)00034-X
12. Pang, B. Application of berberine on treating type 2 diabetes mellitus. BioMed Research International, 2015; 905749. https://doi.org/10.1155/2015/905749

13. Och, A.; Berberine, a herbal metabolite in the metabolic syndrome. Molecules, 2022; 27(4): 1351. https://doi.org/10.3390/molecules27041351
14. Willcox, M. L.; Effectiveness of medicinal plants for glycaemic control in type 2 diabetes: systematic overview of meta-analyses. Frontiers in Pharmacology, 2021; 12: 777561. https://doi.org/10.3389/fphar.2021.777561
15. Zenab, F Rampura.; Singh Shailendra Panwar; Herba antidiabetics: An evidence-based review of medicinal plants used in type 2 diabetes. Journal of Pharmacognosy & Phytochemistry, 14(5): 250-257. https://doi.org/10.22271/phyto.2025.v14.i5d.15582
16. Al-Ishaq, R. K.; Abotaleb, M., Kubatka, P.; Kajo, K.; & Büsselberg, D. Flavonoids and their anti-diabetic effects: Cellular mechanisms and effects to improve blood glucose levels. Biomolecules, 2019; 9(9): 430. https://doi.org/10.3390/biom9090430
17. Benzie, I. F. F.; & Strain, J. J. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay. Analytical Biochemistry, 1996; 239(1): 70-76. https://doi.org/10.1006/abio.1996.0292
18. Antar,S.A.; Ashour, N.A.; Marawan, M.E.; Al-Karmalawy, A.A.; Fibrosis: Types, Effects, Markers, Mechanisms for Disease Progression, and Its Relation with Oxidative Stress, Immunity, and Inflammation, Int. J. Mol. Sci., 2023; 24(4): 4004, https://doi.org/10.3390/ijms24044004. 49)
19. Fujioka K. Pathophysiology of type 2 diabetes and the role of incretin hormones and beta-cell dysfunction. JAAPA, 2007; 3-8.
20. International Expert Committee International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care, 2009; 32: 1-8. https://doi.org/10.2337/dc09-S001
21. Yoon, K.H.; Lee, J.H.; Kim, J.W.; Cho, J.H.; Choi, Y.H.; Ko, S.H.; Epidemic obesity and type 2 diabetes in Asia. Lancet, 2006; 368(9548): 1681-1688. https://doi.org/ 10.1016/S0140-6736(06)69703-1
22. Cassidy S.; Thoma C.; Houghton D.; and Trenell M. I., High-Intensity Interval Training: A Review of Its Impact on Glucose Control and Cardiometabolic Health, Diabetologia, 2017; 60(1): 7–23. https://doi.org/10.1007/s00125-016-4106-1
23. Hurtado, M.D.; Vella A. What is type 2 diabetes? Medicine, 2019; 47: 10–5. doi:10.1016/j.mpmed.2018.10.010
24. Forbes, J.M.; Cooper, ME. Mechanisms of diabetic complications. Physiol Rev., 2013; 93: 137–88. doi:10.1152/physrev.00045.2011
25. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2020, Diabetes Care, 2020; 43: S14–31. doi: 10.2337/dc20-S002
26. Leslie, R.D.; Palmer, J.; Schloot N.C.; Lernmark A. Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment. Diabetologia, 2016; 59: 13–20. doi: 10.1007/s00125-015-3789-z
27. Bharti, S.K.; Krishnan, S; Kumar, A; Kumar, A; Antidiabetic phytoconstituents and their mode of action on metabolic pathways. Ther Adv Endocrinol Metab., 2018; 9: 81-100. doi: 10.1177/2042018818755019
28. Sansome, D.J.; Xie, C.; Veedfald, S.; Horowitz, M.; Rayner, C.K.; Wu ,T. Mechanism of glucose-lowering by metformin in type 2 diabetes: Role of bile acids. Diabetes Obes Metab., 2020; 22: 141–8. doi: 10.1111/dom.13869
29. Kaur, R.; Dahiya, L.; Kumar, M.; Fructose-1,6-bisphosphatase inhibitors: A new valid approach for management of type 2 diabetes mellitus. Eur J Med Chem., 2017; 141: 473–505. doi: 10.1016/j.ejmech.2017.09.029
30. Tran, N.; Pham, B.; Le, L. Bioactive compounds in anti-diabetic plants: from herbal medicine to modern drug discovery. Biol (Basel), 2020; 9: 252. doi: 10.3390/ biology9090252
31. Kumar, A.; Nirmal, P.; Kumar, M.; Jose, A.; Tomer, V.; Oz, E. Major phytochemicals: Recent advances in health benefits and extraction method. Molecules, 2023; 28: 887. doi: 10.3390/molecules28020887
32. Nagpal, R.; Kumar, A.; Kumar, M.; Behare, P.V.; Jain, S.; Yadav, H. Probiotics, their health benefits and applications for developing healthier foods: a review. FEMS Microbiol Lett., 2012; 334: 1–15. doi: 10.1111/j.1574-6968.2012.02593.x