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INTEGRATING MODERN BIOTECHNOLOGICAL TOOLS TO STUDY ANTI-DIABETIC ACTIVITY OF INDIGENOUS PLANTS AND BLOOD BIOCHEMISTRY MODULATION

Bharat Kumar Anagani, Research Scholar, Sunrise University, Alwar

Dr. Neeraj Saxena, Professor, Sunrise University, Alwar

ABSTRACT

There is evidence that substances derived from living things, whether they be plants, animals, or microbes, may have positive effects on human and animal health. Eighty percent of the population in underdeveloped nations still relies on traditional or folk medicines, which are mostly made from plants, for illness prevention or treatment, according to the World Health Organization. There are less side effects, more successful therapeutic outcomes, and lower costs associated with traditional medicine derived from plant extracts compared to contemporary pharmaceuticals. The pharmaceutical industry's focus on the potential uses of phytochemical components of medicinal plants has grown substantially, according to published research. Steroids, alkaloids, phenolic, lignans, carbohydrates, glycosides, and many more plant-derived secondary metabolites have a wide range of useful biological effects for humans, including anti-inflammatory, anti-cancer, antimicrobial, antioxidant, and antidiabetic effects. Metabolic abnormalities in the β-cells of the pancreas leading to hyperglycemia constitute diabetes mellitus, a chronic illness.

KEYWORDS: Biochemistry, Anti-Diabetic Activity, Indigenous Plants, Diabetes mellitus

INTRODUCTION

Pakistan is endowed with a diverse landscape that includes vast irrigated plains, coastal areas, mountains with snow caps, and deserts that may be both hot and cold. In Pakistan's southern Punjab region is the vast Cholistan Desert, sometimes called Rohi. The total area it covers is 26,000 km^2. Extreme heat and a subtropical climate characterize the Cholistan Desert; the region receives little monsoon rains and experiences long, intermittent droughts, making it arid. The region's exceptionally powerful summer winds contribute to low humidity and high evaporation rates, which in turn reflect the unparalleled variety of plant life in the region. A large portion of the population's daily lives revolves on medicinal plants, which serve as the foundation for the treatment of several diseases. People involved in the production of herbal items and low-income field laborers also rely on them as a significant source of income. There hasn't been nearly enough study of plants despite the abundance of literature on their ethnobotanical, medicinal, and economic importance. However, in recent years, several institutions have conducted extensive study to investigate the medicinal plants' anti-oxidant, antibacterial, anti-inflammatory, and anti-cancer properties.

A chronic metabolic illness characterized by hyperglycemia, glycosuria, and negative nitrogen balance, diabetes mellitus is a complicated disease in and of itself. Reduced insulin production by pancreatic beta cells and inadequate insulin receptor responsiveness induce diabetes. About a quarter of the adult population is living with diabetes at this time. Roughly 150 million people are now impacted, and by 2025, that figure is expected to rise to 300 million. Presently present anti-diabetic medications do not provide a full cure for diabetes. Both the availability and affordability of these items are problematic in developing nations like Pakistan.

LITERATURE REVIEW

Sharma (2010) investigated the anti-diabetic activity of *Momordica charantia* using advanced biotechnological tools, including gene expression studies. Their research demonstrated the plant's ability to regulate genes associated with insulin sensitivity and glucose metabolism. The study highlighted the potential of molecular biology techniques, such as real-time PCR, to elucidate the mechanisms of action of indigenous plants and their role in modulating blood biochemistry.

Patel and Verma (2012) utilized proteomics to analyze the impact of *Trigonella foenum-graecum* (fenugreek) extracts on protein expression in diabetic animal models. Their findings showed that fenugreek modulates key proteins involved in oxidative stress and insulin signaling pathways. The research emphasized the importance of proteomic approaches in understanding how plant-based treatments influence blood biochemistry at the molecular level.

Khan (2013) explored the use of high-throughput screening techniques, such as metabolomics, to identify anti-diabetic compounds in *Azadirachta indica* (neem). Their analysis revealed the presence of bioactive metabolites, including flavonoids and terpenoids, that exhibited glucose-lowering effects. The study provided a framework for integrating metabolomics with biotechnological tools to study plant-based anti-diabetic therapies.

Das and Roy (2014) conducted an in-vitro study using cell culture techniques to assess the impact of *Gymnema sylvestre* extracts on insulin secretion in pancreatic beta cells. Their research demonstrated that gymnemic acids stimulate insulin production and protect beta cells from oxidative damage. The study highlighted the role of biotechnological tools in bridging traditional medicine and modern pharmacology.

Gupta (2015) employed a combination of genomics and enzyme assays to investigate the anti-diabetic properties of *Syzygium cumini* (jamun). Their research showed that the plant extract inhibits alpha-glucosidase and alpha-amylase enzymes, reducing postprandial glucose levels. The genomic analysis also revealed its potential to regulate genes linked to carbohydrate metabolism, providing insights into its blood biochemistry modulation.

LATEST RESEARCHES ON THE MOLECULAR MECHANISMS AND PATHOGENIES OF DIABETES MELLITUS

Insulin insufficiency occurs in type 1 diabetes because CD4+ and CD8+ T lymphocytes and macrophages autoimmunely destroy the pancreatic b-cells (9, 10). Nearly eighty-five percent of patients have islet cell antibodies, the majority of which target the pancreatic b-cell glutamic acid decarboxylase (GAD) (9).

The immune system's attack on the pancreatic islets of Langerhans leads to a lack of insulin production, which in turn causes metabolic problems associated with type 1 diabetes mellitus. Not to mention that the metabolic abnormalities already brought on by insulin insufficiency are made more worse when pancreatic a-cells begin to operate improperly and emit an overly high quantity of glucagon in individuals with type 1 diabetes mellitus (11). The peripheral tissues' glucose metabolism is impaired due to an increase in free fatty acids in the circulation and an unchecked rate of lipolysis brought on by an insulin shortage (11). When insulin levels are too low, the liver's glucokinase enzyme and adipose tissue's GLUT-4 transporter protein are both reduced, making it so that insulin cannot ordinarily stimulate the target tissues.

The basic processes of the pathophysiology of type 2 diabetes include impaired secretion of insulin due to the death of insulin secreting b-cells and reduced insulin activity due to insulin resistance (9). Membranes that connect the mitochondria to the endoplasmic reticulum (MERs) are crucial for lipid exchange control, calcium signaling, cell survival, and metabolic equilibrium. Insulin signaling is facilitated by these MAM contacts, which are known to include many insulin signaling proteins, including AKT kinase, mTORC2, PP2A, and PTEN. More and more research is linking these MAMs to the development of type 2 diabetes

mellitus by influencing insulin resistance in peripheral tissues and malfunction of insulin-producing b cells (12). microRNAs (miRNAs) are short stretches of RNA that control processes such as cell proliferation, differentiation, apoptosis, death, and early development. They typically include 20–24 nucleotides. New research suggests that these microRNAs play a role in the development of type 2 diabetes mellitus and might be used as biomarkers in the future.

Because oxidative stress causes lipid peroxidation and reactive oxygen species affect chemical changes in every part of the cell,

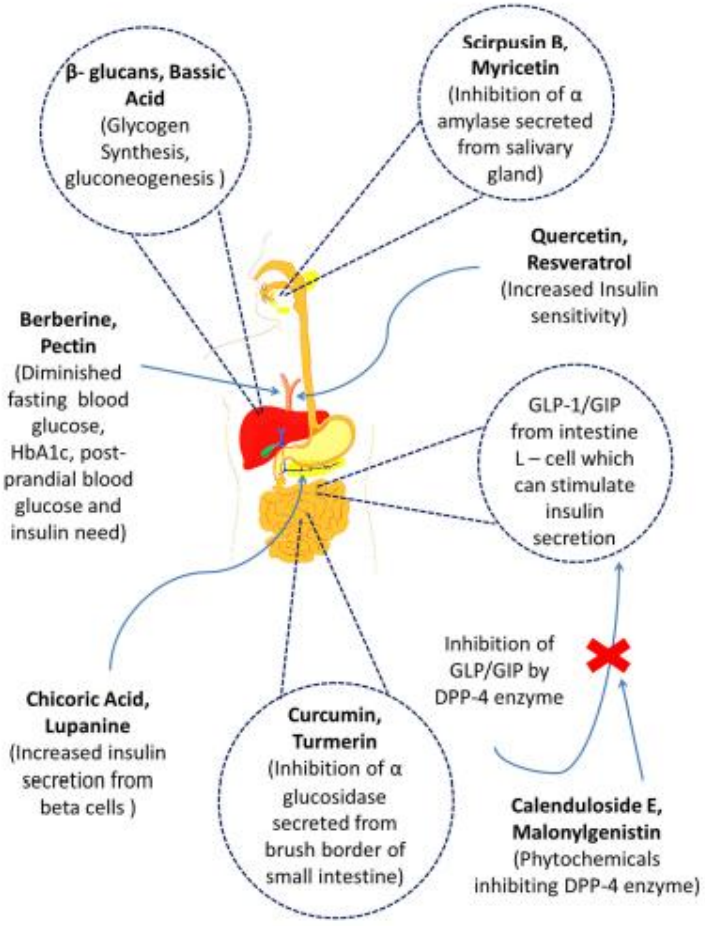


FIGURE 1 | The mechanisms of action of several prospective bioactive secondary metabolites (phytochemicals) obtained from different medicinal plants.

Type 2 diabetes mellitus is caused by stress as well. This means that lipid peroxidation is a major contributor to T2DM (14). Excessive levels of hydrogen peroxide (H2O2) cause substantial damage to lipids, DNA, and RNA. The primary enzyme that controls hydrogen peroxide levels is catalase (CAT), which converts the reactive oxygen species (ROS) to water and oxygen. Overproduction of reactive oxygen species (ROS) and oxidative stress makes pancreatic islet-cells more vulnerable to catalases (CAT) deficiency, which in turn causes pancreatic islet dysfunction and obvious type 2 diabetes mellitus (15). Plasma levels of oxidized low-density lipoprotein (oxLDL) are higher in several disease conditions where oxidative stress is a major contributor, including obesity and diabetes (16). One of the most significant stress-signaling pathways involves nuclear factor kappa B (NF-B), NH2-terminal Jun kinases, and p53 MAPK; oxidative stress contributes to the onset of type 2 diabetes mellitus by influencing these pathways.

A sedentary lifestyle, low levels of physical activity and exercise training, and heightened markers of chronic systemic inflammation are all associated with type 2 diabetes mellitus (17). In this particular case, metabolic inflammation is caused by the production of proinflammatory molecules into the circulation and into certain organs. These molecules include interleukin 6 (IL-6), C-Reactive Protein (CRP), tumor necrosis factor-alpha (TNF-), and interleukin 1 (IL-1) (18). Insulin-like growth factor 1 (IL-1) plays a role in the pancreatic autoimmune response by lowering -cell activity and activating the NF-B transcription factor, which in turn inhibits -cell function and induces cell death.

Recent research has shown that dysbiosis may raise the risk of type 2 diabetes mellitus (19), adding to the mounting evidence that the gut microbiota plays a significant role in diabetes development. A high-fat diet may triple the production of lipopolysaccharide (from Gram-negative bacteria), which can lead to low-grade inflammation and insulin resistance, according to animal model experiments. The generation of short-chain fatty acids, which are essential for the integrity of the gut barrier, the proliferation of pancreatic cells, and insulin manufacture, may be hindered by intestinal dysbiosis. Glucose homeostasis and type 2 diabetes mellitus may be disturbed when dysbiosis affects the generation of branched amino acids and trimethylamine, among other metabolites. To further understand the connection between gut bacteria and type 2 diabetes mellitus, more research is necessary, and the clinical implications of the gut microbiome are currently being investigated.

Bioactive Compounds from Plants Having Type 2 Antidiabetic Activity

There is solid evidence that several plants used traditionally as antidiabetic treatments have hypoglycemia and antidiabetic properties, and these plants' hypoglycemic activity mechanisms have been thoroughly investigated. The process of traditional herbal and natural medicines derived from traditional medicinal plants for the treatment of diabetes is the main topic of this study.

Bioactive Compounds Act as Insulin

Momordica charantia (Bitter Melon)

One of the most prevalent tropical vegetables is Momordica charantia (MC), which is native to Southeast Asia, East Africa, Vietnam, China, India, and South and North Asia as well as Central and South America. Common names for this plant include bitter melon and bitter gourd, and it belongs to the Cucurbitaceae family (Figure 2). In addition to its culinary usage, MC has traditional medicinal uses as a herbal remedy. Its bioactivities, include its anti-diabetic, anti-inflammatory, anti-oxidant, anti-viral, anti-cancer, anti-bacterial, and so on.

Figure 2 Pictures show the morphological characteristics of the Momordica charantia (MC): (a) whole plant and (b) unripe fruit

Phytochemistry

A large body of research suggests that bitter melon's active ingredients may help with the management of type 2 diabetes. Steroids, momordicosides (A, B, C, D, E, G, F1, F2, I, K, L), acyl glucosyl sterols, fatty acids, amino acids, alkaloids, phenolic compounds, steroidal saponin, vitamins, carbohydrates, minerals, and many more phytochemicals are found in plants. The antidiabetic activity of Momordica charantia was shown in tests conducted on rats, gerbils, langurs, and humans. This was due to the presence of insulin-like proteins in the plant's fruits, seeds, and callus, which are similar to human insulin. For a long time, people in China and India thought that MC could cure diabetes. Its anti-hyperglycemic properties have recently been the subject of a great deal of scientific investigation. Figure 3 shows that its bioactivities drop dramatically in blood glucose levels, as established in several study studies. Researchers found that bitter melon improved glucose tolerance in both healthy and diabetic mice, in addition to people. A large body of research has shown that the bioactive components of MC provide potent antidiabetic effects (Table 1)

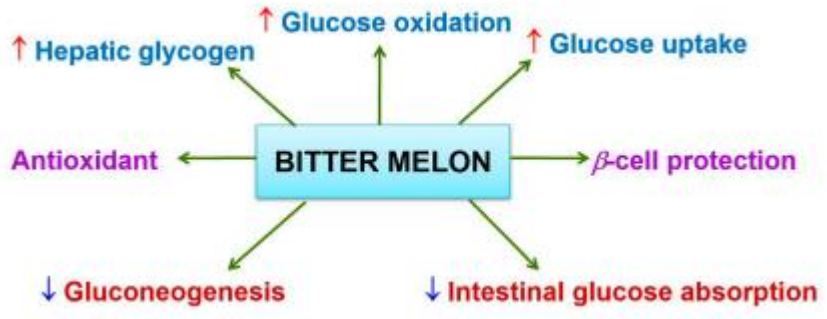


Figure 2 The mechanism in decreasing blood glucose levels of M. charantia

Table 1 Bioactive compounds and their effects in Momordica charantia

Bioactive Compounds	Antidiabetic Effects
Polypeptide-p	Act as Insulin-like protein, decrease blood glucose level
Momordicosides	Enhance the uptake of glucose
Saponins	Stimulate insulin secretion, a lower blood glucose level
Conjugated linolenic acid	Release intestinal GLP-1
Momordin	PPAR δ activation
9c, 11t, 13t conjugated linolenic acid	PPAR α activation

Charantin, vicine, and polypeptide-p were found in the ethanolic extract of MC fresh green whole fruit. According to Akhtar N et al., these components function as insulin-like proteins. When administered to alloxan-induced diabetic rabbits at a dose of 200 mg/kg b.w., these proteins reduced blood glucose levels, stimulated insulin secretion and tissue glucose uptake, decreased hepatic gluconeogenesis, stimulated glucose uptake and utilization, and inhibited intestinal glucose absorption. By evaluating insulin secretion activity, the in vitro insulin secretion test demonstrated that Momordicoside U (3β,7β-Dihydroxycucurbita-5,23(E)-dien-19-al-25-O-β-d-glucopyranoside) might improve glucose absorption. In a study conducted by Singh N et al., it was shown that rats with diabetes caused by alloxan could have their β-cells from the pancreatic islets of Langerhans restored with oral administration of 25 mg, 50 mg, and 75 mg dosages of an alcoholic extract of the whole fruit [54]. When administered to alloxan diabetic albino rats at dosages of 25 mg, 50 mg, and 75 mg of extract over the course of 8 to 30 days, this fruit power's acetone extract

shown the capacity to restore beta cells of the pancreatic islets of Langerhans. In a study on streptozotocin-induced diabetic rats, researchers found that MC fruit juice had antidiabetic effects. At a dose of 10 mL/kg/day for 14 days, the herb improved insulin secretion from pancreatic β-cells, raised serum insulin levels, improved β-cell function, decreased insulin resistance, and increased glucose utilization. In pancreatic cells, Momordica charantia may promote insulin secretion by repairing damaged cells or even regenerating them.

In addition, an in vitro investigation revealed that pancreatic β-cells were protected by an aqueous ethanolic extract of MC seeds. Research on rats with type 1 diabetes mellitus produced by streptozotocin has shown that MC extract may potentially enhance beta cells in pancreatic islets. Concerning type 1 diabetes, polypeptide-p has shown physiological activity comparable to that of human insulin; hence, it has the potential to serve as a plant-based insulin substitute for those afflicted with this condition. The potential of MC extracts to inhibit diabetes-related enzymes like alpha-glucosidase and alpha-amylase has been the subject of some other research.

Panax ginseng C.A Meyer

Figure 3 shows that ginseng has long been the most well-known traditional herb utilized in folk medicine in Korea. A member of the Araliaceae family, ginseng is a member of the Panax genus.

Figure 3 Panax ginseng C.A Meyer

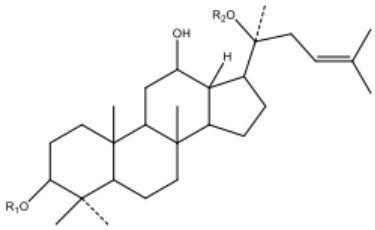
Phytochemistry

Triterpene glycosides, panaxans, vanillic acid, salicylates, and saponins, sometimes called ginsenosides (Table 2), are among the bioactive substances found in this plant's root. Vitamins B1 and B2, among other active components, are present in every part of the plant. Other components include alkaloids, phenols, proteins, polypeptides, and amino acids.

Antidiabetic Activity

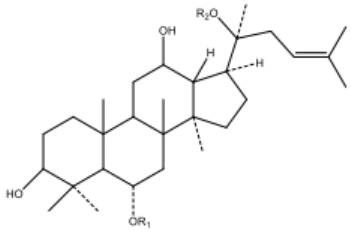
Therapeutic drugs should be used to improve insulin resistance, enhance glucose absorption, decrease blood glucose concentration, and protect or regenerate β-cells from pancreatic islets, since these are the characteristics of diabetes mellitus. In vitro and in vivo studies on the root of Panax ginseng have been extensively studied for its potential anti-diabetic effects. Ginsenosides, a class of saponins unique to Panax ginseng, are the plant's most significant phytochemicals. The component that reduced blood glucose levels the most effectively in streptozotocin-induced diabetic rats was ginsenosied Rb2.

Table 2 Structure of ginsenosides (ginseng-specific saponins)



A. Protopanaxadiol

$R_2 = Ra_1, Ra_2, Ra_3, Rb_1, Rb_2, Rb_3, Rc, Rd, Rg_2, Rg_3, Rs_1, Rs_2$, etc.



B. Protopanaxatriol

$R_2 = Re, Rf, Rg_1, Rg_2, Rh_1$, etc.

CONCLUSION

Patients, their families, and society as a whole bear the financial burden of diabetes mellitus. Chronic consequences of diabetes, including blindness, renal failure, and heart failure, are significant when the disease is not treated. Researchers are looking at potential novel antidiabetic drugs as a means to lessen this issue. Many traditional treatments have gained attention due to the negative consequences of contemporary therapy. In addition, combinatorial therapy including plant extracts and conventional medications are becoming more feasible. Low blood sugar and diabetic problems may be better managed with the help of the active components found in each plant.

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