Anti-Diabetic Plants: Mechanisms and Applications

CHAPTER 14

AJWA[1*], MUHAMMAD AMEER QARIB NAQVI[1], FATMA HUSSAIN[1], SAADIYA ZIA[1], MUNIBA KARAMAT[1], IQRA SALEEM[1], SABA ZULFIQAR[2], JAVARIA HAFEEZ[1]

[1]Department of Biochemistry, University of Agriculture Faisalabad, Pakistan
[2]Department of Biochemistry, University Medical and Dental College, The University of Faisalabad, Faisalabad, Pakistan
[*]Corresponding author: ajwarana03@gmail.com

SUMMARY

There is a long history of using medicinal plants as the basis for potential therapeutic compounds that have been integrated into modern medical procedures. Plant-based remedies have been used to treat a variety of ailments since the beginning of human civilization. *Aloe barbadensis* Miller belongs to the Liliaceae family and *Gymnema sylvestre* belongs to Asclepiadaceae family and has highest potential against diabetes Numerous therapeutically active components, such as minerals, amino acids, enzymatic agents, sugars, nutrients, anthraquinones and saponins are found in these two plants. Phytochemicals isolated from these plants, such as phenolic compounds, phenols, alkaloids and terpenoids, play a role in diabetes management via a variety of mechanisms, including insulin secretion stimulation, insulin signaling improvement, glucose uptake enhancement, and gastrointestinal microbiota control. In addition to their diabetic potential, these herbs contain scar-filling, anti-inflammatory, antioxidant, antimicrobic, anticancer and cytotoxic effects.

INTRODUCTION

Hyperglycemia is characterized by a combination of autoimmune, metabolic and genetic diseases that lead to diabetes mellitus.DM is categorized into three types i.e. DM1, DM2 and gestational diabetes. DM1 can be either immune-mediated or idiopathic. Genetic abnormalities in insulin activity can also lead to dysfunctions: DM2 is due to insulin resistance and it leads to an increase the blood glucose (Egan & Dinneen, 2019).

Pakistan now has a 6.9% diabetes prevalence rate, but by 2040, it is expected to rise to 15%, making it the country with the fourth-highest incidence of diabetes globally. The frequency of prediabetes and diabetes in Pakistan has steadily increased in recent years. Diabetes prevalence is higher in Pakistan's rural Sindh and Khyber Pakhtunkhwa areas. The main reasons behind this were hypertension, obesity and filthy lifestyles (Akhtar et al., 2019). Types of diabetes mellitus (Fig. 1).

MEDICINAL PLANTS

Medicinal plants are defined as those with therapeutic qualities and significant pharmacological effects on human or animal bodies. Medicinal plants are utilized all throughout the world and men have long relied on their therapeutic qualities before the invention of artificial medications. According to the WHO, over 80% of the public of the world lives in underdeveloped regions, where they primarily depend on plants for their basic medical requirements (Ahvazi et al., 2012). Discovered on a Sumerian clay slab from Nagpur, the oldest reported written evidence of the application of plants for therapeutic use dates back approximately 5000 years. The use of herbs and phytomedicine has been historically an integral component of the medical therapy system. Across the world, botanical remedies are still used by an array of distinct cultures, people and ethnic communities. Various ethnomedical species of plants have applications in protecting against an extensive variety of life-threatening disorders (Poddar et al., 2020).

Many of the plants are utilized in treating various disorders and improving human health. Plants such as Malus domestica, Allium sepa and Fagopyrum esculantum contain quercetin in them, which help in combating SARS-CoV-2. Desert plants of Pakistan also have medicinal importance and are used in various therapeutic activities. Species like that of garlic and lemon are referred to as anti-bacterial and anti-diabetic agents. In curing wounds, many herbal remedies are used. Cicohoriun intybus is highly utilized to combat diabetes (Batool et al., 2023). Bidens pilosa is highly recognized as the anti-bacterial, anti-oxidant and anti-diabetic herb. The presence of pharmacological substances such as flavonoids and phenolic compounds make them efficient for improvement in human's health. Similarly, Syzgium cumini, Aloe barbedensis miller, *Gymnema sylvestre* are highly recognized as anti-diabetic plants and utilized in many regions of Asia in combating

How to Cite: Ajwa, MAQ Naqvi, F Hussain, S Zia, M Karamat, I saleem, S Zulfiqar & J Hafeez, 2024. Anti-diabetic plants: Mechanism and applications. In: Ethnopharmacology and Ethnobotany of Medicinal Plants (Sindhu ZuD, B Aslam, MN Faisal & W Majeed, eds): FahumSci, Lahore, Pakistan, pp. 100-107. ISBN: 978-627-7745-10-3. https://doi.org/10.61748/EEMP.2024/14

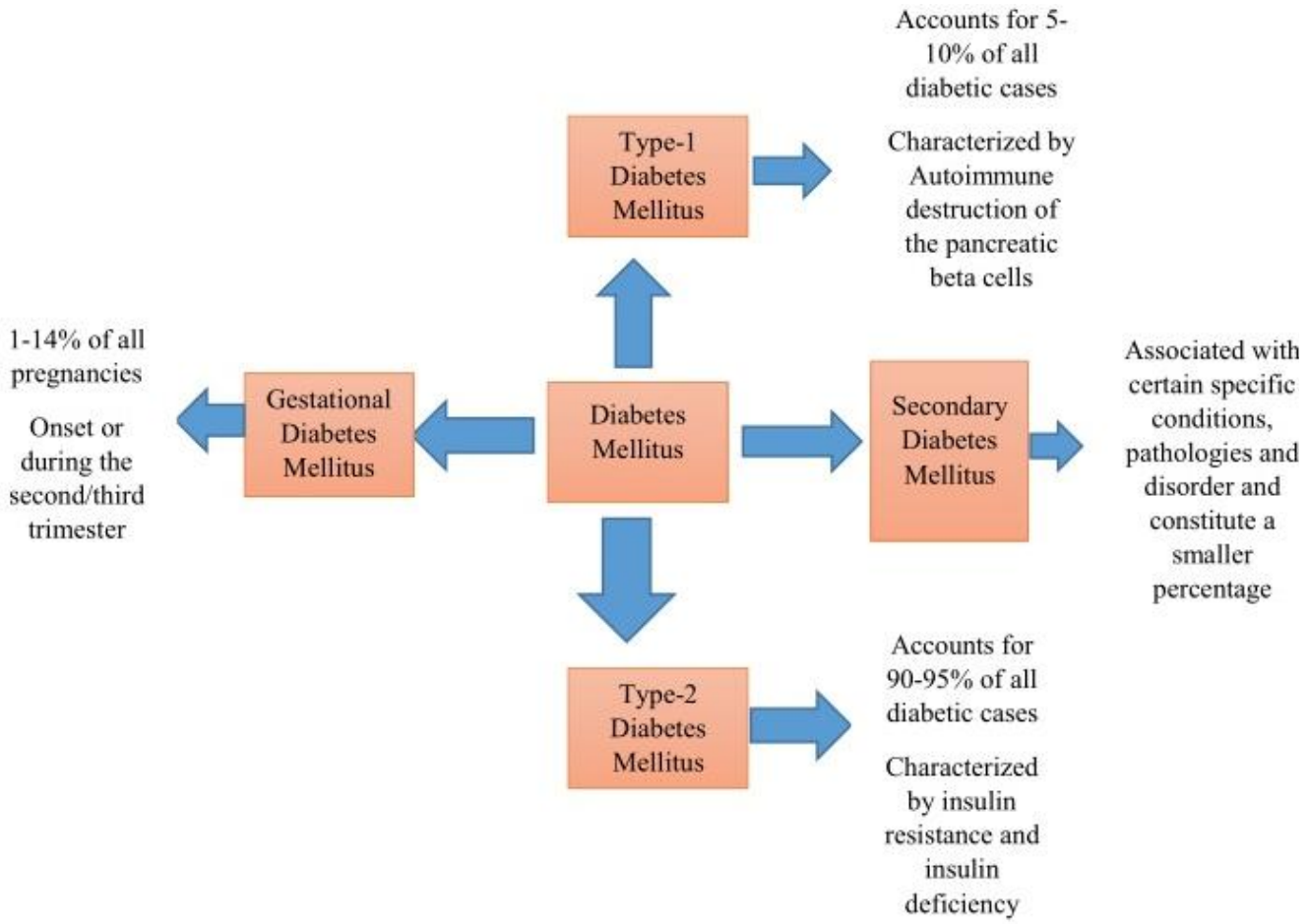

Fig 1. Classification of diabetes mellitus

diabetes. Drimia Indica is highly recognized as anti-inflammatory, anti-diabetic and anti-oxidant herb. In this way, different herbs are being used in combating various diseases (Nxumalo et al., 2023). A graphical representation for the formation of a novel drug from medicinal plants is shown in Fig. 2.

ANTI-DIABETIC PLANTS

Aloe barbadensis miller

There are four hundred xerophyte plant species in the genus Aloe, which is a member of the Xanthorrhoeaceae family and grows worldwide. Because of its numerous components, including polyphenols, vitamins, minerals, peptides, polysaccharides, and tannins, *Aloe vera* (Fig. 3) is regarded as an essential plant in traditional medicine for the treatment of a variety of ailments. The inner leaf of *Aloe vera* gel contains polysaccharides, which are carbohydrates with a variety of biological properties, including anti-tumor, antibacterial, antioxidant, anti-inflammatory, and anti-diabetic properties (Kang et al., 2014). *Aloe vera* gel comprises around 75 physiologically active elements and is largely composed of water approximately 98.5 - 99.5%. Additional active ingredients found throughout the entire plant include carbohydrates, minerals, vitamins, amino acids, and enzymes. The phytochemicals that exist comprise anthrones, lectins, polymannans, acetylated mannans, sterols, resins, saponins, tannins and flavonoids. Anthraquinones, lignin, enzymes, chromones and salicylic acid are additional active components. One of the strongest immune-boosting substances in plants, acemannan, is its most significant polysaccharide (Jangannanavar et al., 2021).

For thousands of years, the medical properties of A. barbadensis Miller have been utilized by the ancient cultures of China, Greece, India, Rome and Egypt. It was thought to have beneficial effects on wound healing, inflammation, radiation damage, gastrointestinal issues, skin conditions and act as an anti-ulcer and anti-diabetic agent. It is regarded as a crucial component in functional meals, nutritional drinks, curd, and beverages in the food sector. *Aloe vera* gel offers an extensive variety of health-promoting characteristics, such as antibacterial, anti-inflammatory, antioxidant, antidiabetic and gastrointestinal tract protection. The toiletries and cosmetic sectors historically utilized *Aloe vera* as a key and essential component in soaps, shampoos, lotions and other goods. It has been applied in the healthcare sector to produce capsules and pills, along with ointments, lotions and balms (Gorsi et al., 2019).

Gymnema sylvestre

Asclepiadaceae is the family of plants that includes the herb *Gymnema sylvestre*. It is significantly spread in Malaysia,

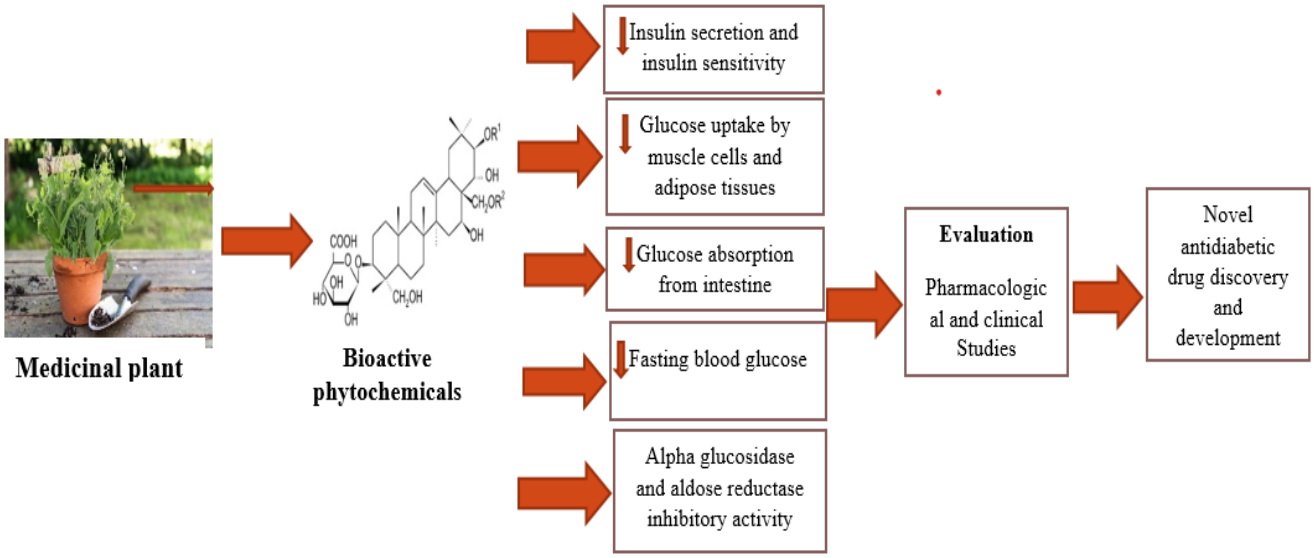

Fig 2. Graphical abstract of isolated phytochemicals from medicinal plants for the discovery and development of a new anti-diabetic drug

Indonesia, Srilanka, India and Pakistan. This is usually called as Gurmar in Hindi. In English, it is also referred to Periploca of the woods. Gymnema, whose name is taken from the Hindu term "Gurmar," which means "sugar destroyer," is believed to equalize the excess sugar that cause diabetes mellitus in the body. *G. sylvestre* is an herb found around the world. The plant's leaves are commonly used in medicine for their diuretic medication and to treat diabetes (Karande et al., 2022).

Gymnemic acid is the primary active component of *G. sylvestre*. The plant's benefits include anti-inflammatory, digestive, diuretic, antihelmentic and hypoglycemic properties. It is used to treat hemorrhoids, asthma, jaundice, constipation, bronchitis, leukoderma, dyspensia and cardiopathy. The plant's pharmacological activities include antidiabetic, hypolipidemic, antibacterial, free radical scavenging, anti-obesity along with anti-inflammatory properties. *G. sylvestre*'s leaves have triterpene saponins classified as oleanane and dammarene. Oleanane saponins include gymnemasaponins and gymnemic acid, whereas dammarene saponins are gymnemasides. Administering plant leaf extract to diabetic patients stimulates the pancreas, leading to increased insulin release. These compounds were linked to increased cholesterol excretion through feces (Saneja et al., 2010).

PHYTOCHEMICALS IN ANTI-DIABETIC PLANTS

Plants like *G. sylvestre* and A. barbadensis miller may have been utilized historically to make medicines. Ethnobotanical data suggests that about 800 plants may possess anti-diabetic qualities. Because traditional plant medicines for diabetes are safe, effective, and have few to no side effects, the World Health Organization has recommended that they be examined. They are also excellent candidates for oral treatment. The effectiveness of medicinal plants in decreasing blood sugar levels has been demonstrated by scientific validation of multiple plant species (Teoh & Das, 2018).

According to studies on the possible usefulness of medicinal plants against diabetes, phytochemicals play an important role in diabetes treatment. "Phytochemicals" encompasses a broad category of chemical compounds found in nature that are bioactive and may have significant physiological effects on humans, such as polyphenols, steroids, flavonoids, and saponins (Rex et al., 2018). Active ingredients in diabetes treatments are compounds that are isolated from different plant species and have different structures but the same therapeutic effect. Using these plants and phytoconstituents may, through several mechanisms, control metabolic abnormalities and halt the advancement of diabetes-related issues. Moreover, several phytochemicals

Fig 3. *A. barbadensis Miller* plant

from plants that have been linked to anti-diabetic effects have been discovered recently. Numerous phytoconstituents derived from diverse plant sources, including amino acids, dietary fibers, polysaccharides, glycolipids, alkaloids, glycosides, flavonoids, and saponins, are potent hypoglycemic agents (Gaikwad et al., 2014).

Phenolic Compounds

Phenolic chemicals are extracted from medicinal plants. The most common class of polyphenols are called flavonoids. Flavonoids are made up of 15 carbon atoms that contain two benzene rings, these two benzene rings joined through heterocyclic pyrane rings. Numerous pharmacological actions, such as antidiabetic, antiviral, anti-inflammatory anticancer, antihistaminic, antioxidant, and hepatoprotective, have been demonstrated for flavonoids. By binding to glucose transporter 1(GLUT1) and peroxisome proliferator-activated receptor γ (PPARγ), these flavonoids increase glucose absorption and improve lipid metabolism, thus having a hypoglycemic effect. In diabetic animals and humans, peroxisome proliferator-activated receptor γ activation enhances lipid metabolism, insulin stimulation glucose absorption, and glucose tolerance (Rebhun et al., 2015).

Alkaloids

Alkaloids are classified as complex, heterocyclic, high-molecular-weight molecules that have at least two carbons and nitrogen attached to them. Originally, the term "alkaloid" was used to refer to N-containing compounds that were distinctly basic and derived from plants. This phrase is now being used much more broadly. Alkaloids are a broad class of natural N-containing chemical molecules generated by plants, microorganisms, marine creatures, and fungi. Protoberberine alkaloids-containing plants are reportedly used as sedatives, analgesics, antiseptics, and antidiabetic drugs. Similar herbs are used as antiseptics, sedatives, stomatics, and uterine muscle relaxants in Indian and Pakistani medicine and are also used for the treatment of hemorrhage and eye ailments. Numerous biological and therapeutic effects of quaternary alkaloids and their tetrahydro derivatives have been reported; for instance, in vitro, antimalarial activity has been demonstrated for palmatine, jatrorrihizine, and tetrahydropalmatine. In China, tetrahydropalmatine is used as an analgesic and has been shown to cause sedation, bradycardia and hypotension (Gonzales et al. 2015).

Terpenoids

Another important class of bioactive substances that are widely distributed in many natural products are called terpenoids. Studies have indicated that some terpenoids have anti-diabetic properties. A few of them are undergoing different stages of preclinical and clinical development to become medications that treat diabetes. These substances mainly function as inhibitors of the enzymes that cause insulin resistance to develop and insulin and plasma glucose levels to return to normal. Additionally, they have a major impact on glucose metabolism by obstructing several pathways linked to diabetes and related issues (Rivera et al., 2019).

Bioactive terpenoids have been demonstrated in numerous research to have antidiabetic potential. Medicinal plants such as *G. sylvestre* and A. barbedensis miller contain different terpenoid compounds like betulinic acid, caryophyllene, carvacrol, α-humulene camphene, myrcene, limonene, α-phellandrene, carvone, spathulenol that have antidiabetic potential. Other plants such as Foeniculum vulgare, Matricaria chamomilla contain germacrene D, α-pinene, β-caryophyllene, phytol, hexa-hydrofarnesyl acetone, with antidiabetic activity, and have also other therapeutic activities (Popova et al., 2021). Instead of antidiabetic properties other therapeutic properties of both plants are shown in Table 1 and Table 2.

MECHANISMS OF ACTION

Since ancient times, plants have been a significant source of medicinal drugs. Medicinal herbs are the foundation of traditional medicine. It has been demonstrated that the diverse family of phytochemicals known as polyphenols, which include phenol rings, has antidiabetic qualities. They are divided into four groups: lignans, stilbenes, phenolic compounds and flavonoids (Kim et al. 2016). Their potential to regulate glucose metabolism has led to research into their potential anti-diabetic effects. Genes that regulate glucose metabolism, insulin release and function, antioxidant impact, inflammation, vascular functions and other possible pathways are among those hypothesized to be expressed more frequently as type 2 diabetes develops. The growing popularity of traditional herbal therapy (Ayurveda) in India and Pakistan has led to the resuscitation of ancient medicinal practices. The metabolic pathways that bioactive compounds use to regulate diabetes are described in the sections that follow (Sayem et al., 2018).

Stimulation of Insulin Secretion

The only hormone that lowers blood glucose levels is insulin, whose production is strictly regulated, which is mainly responsible for maintaining glucose homeostasis. The pancreatic b-cells sense higher glucose concentrations and make insulin as needed at that time. To maintain stable blood glucose levels, insulin increases cellular glucose absorption and controls the metabolism of proteins, fats and carbohydrates (Komatsu et al., 2013).

The cell goes through a sequence of events that are started when insulin attaches to the insulin receptor. By enhancing glucose transport into the cell, it increases glucose absorption via GLUT in skeletal muscles, adipocytes and hepatocytes. Additionally, insulin controls metabolism by increasing the liver's and muscles' synthesis of glycogen, preventing lipolysis and enhancing lipid synthesis (lipid metabolism), and stimulating protein synthesis while suppressing protein breakdown (Kellera et al. 2011). Momordicine I and II, linalool, aloin, isobarbaloin, barbaloine, aloetic acid, acetogenin, gymnenic acid, linalool, eugenol, gurmarin, carvacrol, chlorogenic acid, quercetin and ginsenosides are among the different types of polyphenols that have been demonstrated to stimulate insulin secretion present in plants like alovera and gurmar. These compounds should be given according to a certain dosage. Insulin secretion is increased

Table 1. Active Phytoconstituents of *A. barbadensis Miller* and their pharmacological activity

Isolated Phytochemical	Pharmacological activity	Reference
Lophenol (Phytosterols)	Anti-hyperglycemic activity with a protective effect on pancreas, liver and small intestine.	Sahare, 2007
Anthraquinones	purgative effect, antimicrobial activity	
Salicylic acid	Antidiabetic property by enhancing glucose uptake to the cells	Dat et al., 2012
Barbaloin	Antioxidant, ant proliferative property	Boudreau et al., 2017
p-coumaric acid	used as antioxidants, singlet oxygen quenchers and reducing agents	Liu et al., 2019
Acemannan	Antibacterial, antifungal activity	
Ascorbic acid	Help in collagen synthesis and in muscle tissue	Sonawane et al., 2021
Malic acid	Involved in enzymatic degradation, antimicrobial activity	
Aloin	Anticancer activity	

Table 2. Active constituents of *G. sylvestre* and their pharmacological activities

Isolated phytochemicals	Pharmacological Activity	References
Gymnenic acid Saponins	Anti-hyperglycemic effect, Anti-diabetic activity	Padgilwar, 2014
Triterpene saponins	Antioxidant activity	Liu et al., 2016
Gymnemosides	Antibacterial activity	Yoshikawa et al., 2017
Pentahydroxytriterpene	Wound healing property	
Flavonol glycoside	Anticancer activity, anti-inflammatory activity	Khan et al., 2019
Gymnemasins	Antitumor	Sahu et al., 2020
pentahydroxyolean-12-ene	Anticancer	

when pancreatic and hepatic tissues are protected by oxymatrine and vitellogenin (Shehadeh et al., 2021). The mechanism of insulin stimulation is shown in Fig 4.

Enhancement of Glucose Uptake

The process by which cells take in glucose is known as glucose absorption. This happens by facilitative diffusion, which is made possible by the membrane transport protein family's glucose transporters, also referred to as Glut (SLC2A) proteins. In the cell membrane GLUT proteins are found, where they help the transportation of glucose into the cell. It is commonly known that the regulatory and kinetic characteristics of GLUTs 1-4 contribute to the homeostasis of glucose in cells and organisms (Hajiaghaalipour et al., 2015). In fat and muscle cells, the CAP/Cb1/TC10 and PI3K/AKT signaling pathways cooperate to enhance insulin-induced GLUT-4 translocation. GLUT4 in cells is activated by Phytocompounds present in antidiabetic plants i-e Aloe vera and *G. sylvestre* such as iridoid, catalpol, specioside and verminoside, which promotes intracellular glucose uptake. Protocatechuic acid and cyanidin-3-O-b-glucoside increase GLUT4 translocation and adiponectin synthesis, which raises PPAR- γ activity (Sayem et al., 2018).

Enhancement of Insulin Signaling

Insulin sensitivity improved after administering methylswertianin and bellidifolin phytochemicals. These phytochemicals are found in plants such as *Aloe vera* and gurmar. The way these phytochemicals function is by boosting the synthesis of proteins implicated in insulin signaling pathways, such as PI3K, IRS-1 and IR. Additionally, both phytochemicals can raise the activity of glucose-6-phosphatase (G6Pase) and decrease the activity of glucokinase (GK), which promotes the production of insulin by pancreatic beta cells (Gurung et al., 2020).

OTHER THERAPEUTIC ACTIVITIES OF ANTI-DIABETIC PLANTS

Anti-Oxidant Activity

Free radicals are unpaired electrons in atoms, molecules, or ions that become extremely reactive during chemical processes. Within biological systems, reactive oxygen, nitrogen and sulfur species are created. These species can interact with DNA, proteins and lipids to cause permanent oxidative damage. Oxidative stress is caused by an imbalance in living cells characterized by a high concentration of free radicals and a low number of antioxidants. Antioxidant phytochemicals, such as flavonoids and natural polyphenols, scavenge and neutralize free radicals. It is known that naturally occurring phenolic chemicals are potent antioxidants (Reza Nazifi et al., 2019). At all tested dosages, *Aloe vera* polysaccharides show significant antioxidant activity in scavenging superoxide, 2,2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide (NO) and hydrogen peroxide. More so, *Aloe vera* polysaccharides significantly alleviate the cardiotoxicity during a 14-day therapy period caused by doxorubicin. Catalase (CAT), superoxide dismutase (SOD), cardiac thiobarbituric acid reactive substances (TBARS) and serum lactate dehydrogenase levels all significantly have their levels reduced due to this protective action. Moreover, a dose-dependent increase in blood and tissue levels of reduced glutathione creates the possibility that *Aloe vera* possesses antioxidant properties (Kaithwas et al., 2014).

A few examples of this are antioxidants like polyphenols and flavonoids, which are fit for scavenging free radicals and hence neutralize these highly active species. *Aloe vera* is a medicinal herb containing naturally occurring phytochemicals like polyphenols, along with a range of biological properties; the most prominent one being its antioxidant capacity. Emodipine is a phenolic compound with an anthraquinone

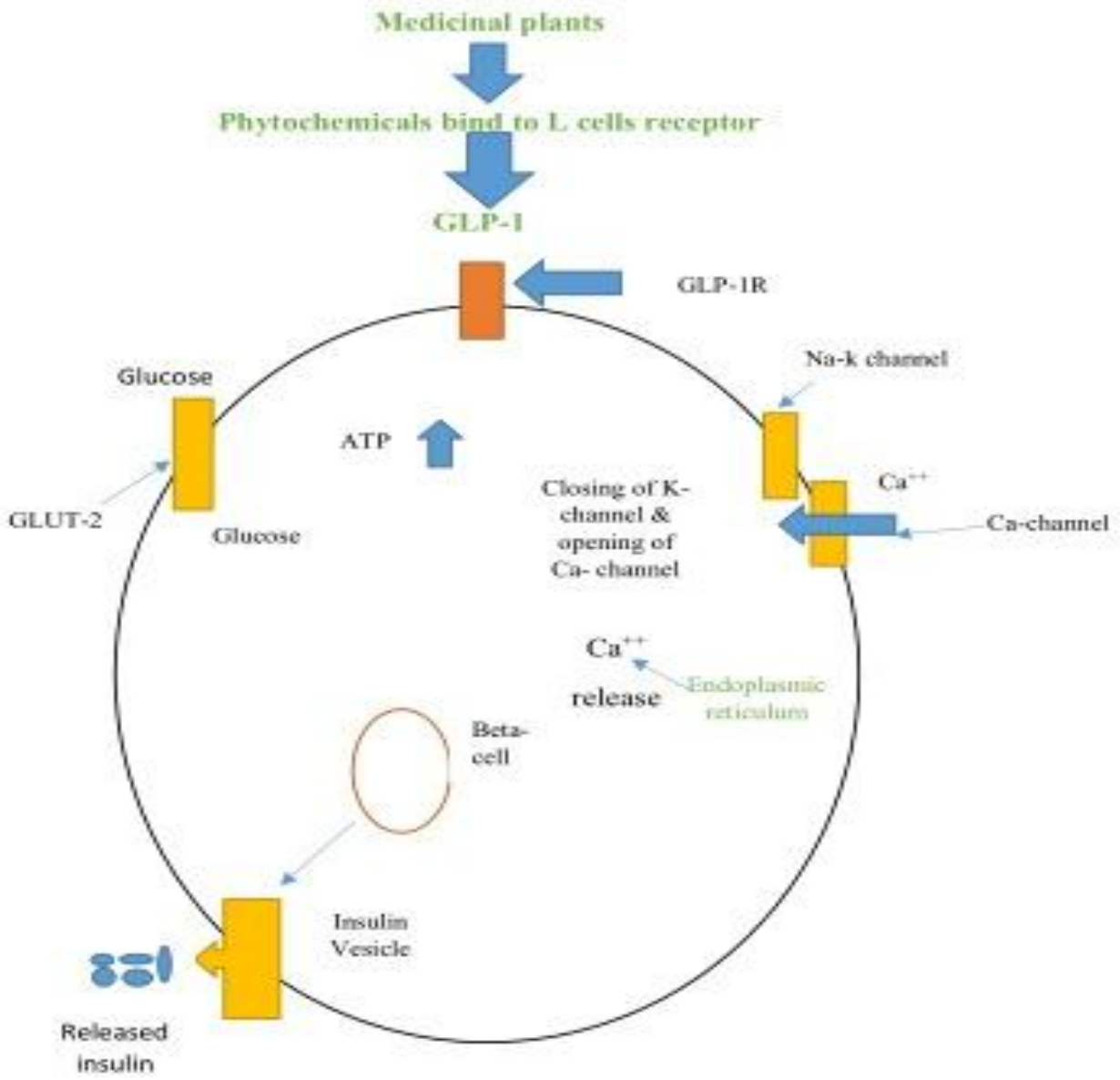

Fig 4. Mechanism of insulin secretion; GLP-1= Glucagon like peptide 1, GLP-1R= Glucagon like peptide-1 receptor, GLUT-2= glucose transporter 2, ATP= Adenosine triphosphate

group that might be responsible for antioxidant properties. Speaking of the phenolic compounds of *Aloe vera*, one is Aloesone; being a chromone moiety, this might be responsible for its antioxidant action. Another phenolic compound found in *Aloe vera* includes the compound known as Isoeleutherol represented by a Naphtafuranone Scaffold (Reza Nazifi et al., 2019). Antioxidants found in *G. sylvestre* include cinnamic acid, butyric acid, flavonoids, tannins, tartaric acid, alkaloids, phenols, folic acid and ascorbic acid. Another antioxidant is a type of unsaturated hydrocarbons called terpenoids. It is formulated from terpenes with oxygenated functional groups. Flavonoids contain a structure of a carbon skeleton that includes a hetero-cycle ring (C) and two phenyl rings (A and B). Another antioxidant found in *G. sylvestre* is folic acid. It is also known as a vitamin. Also known as pteroglutamic acid and the phenolic acids. Ascorbic acid can be considered not only as an antioxidant but equally as a hypoglycemic agent due to its superoxide and hydroxyl radical scavenging action. Terpenoids, flavonoids, cinnamic acids, tannins and phenols are other antioxidants present within *G. sylvestre* (Kim et al., 2016).

Total anthocyanin content, ferric reducing power and total antioxidant activity of *G. sylvestre* represent the antioxidant ability of the plant. The antioxidant attributes of the leaf extract suggest that *G. sylvestre* leaves are characterized by a higher content of TPC and anthocyanin. All this justifies the powerful antioxidant properties of *G. sylvestre*'s aqueous extract (Abhiram et al., 2023).

Anti-cancer Activity

The anticancer activity of *Aloe vera* is hypothesized to be related to the antiproliferative and immunomodulatory properties it holds. In contrast, antiproliferative activity is attributed to Aloe latex, formed in the central layer of the Aloe leaves, in addition to anthracene and anthraquinone, whereas immunomodulatory properties are attributed to Aloe polysaccharides and acemannan (Majumder et al., 2019; Unlu et al., 2016).

A. barbadensis Miller contains bioactive compounds such as barbaloin, aloe-emodin, aloin, aloesin, and lectin, among others, that have shown antioxidant, antimutagenic, antiapoptotic, antiproliferative and antimetastatic properties against a wide variety of malignancies. Aloe-emodin has been involved in the induction of apoptosis in cervical and hepatocellular cancer cell lines through upregulating the levels of BAX, caspases (Sanders et al., 2018; Hussain et al., 2015). Aloe-emodin has powerful cytotoxic effects on leukemia, lymphoma, Merkel cell carcinoma, and oral, gastric, colon, nasopharyngeal, bladder cancer, as well as on glioma (Manirakiza et al., 2021). Aloin, an anthraquinone found in Aloe, reduces angiogenesis by blocking VEGF. In a clinical experiment, 240 patients with metastatic tumors received chemotherapy as well as a daily oral dose of 10 mg of *Aloe vera*. The combination effect of chemotherapy and *Aloe vera* dramatically boosted the patients' three-year survival rate (Lissoni et al., 2009). Chrysophanol, an anthraquinone contained in *Aloe vera*, reduced cancer cell proliferation by decreasing NFκB, inducing apoptosis, increasing oxidative stress leading to ROS production, releasing cytochrome C, and stimulating necrosis (Majumder et al., 2019). *Aloe vera* gel has been shown to reduce insulin resistance, normalize impaired fasting glucose, and lower fasting blood glucose and triglyceride levels alone or in conjunction with glibenclamide (Noor et al., 2017).

Numerous saponins derived from the *G. sylvestre* plant, including soyasaponins, saikosaponins, and ginsenosides, have been shown to have powerful anticancer effects. It was discovered that the isolated bioactive component gymnemagenol greatly inhibited the proliferation of cancer cells. Furthermore, under in vitro conditions, these saponins exhibited no negative effects on the growth of healthy cells. The herbal composition shows potential as a cancer treatment considering the growing prevalence of cancer in individuals (Tiwari et al.,2014). An ethanol extract from *G. sylvestre*'s leaves showed exceptional antitumor efficacy against A375 cells. It can break nuclear DNA and then can upregulate expression in the mRNA of genes that are related to apoptotic signals, such as cytochrome C, Bax, noticeable PARP activity in houses, and caspase 3, and it has mRNA downregulating expressions in ICAD, EGFR, and on the anti-apoptotic gene Bcl2. This signifies the potential of its application as a palliative remedy for cancer patients (Kishore et al., 2014).

CONCLUSION

The immense medicinal power of *Aloe vera* and *G. sylvestre* in diabetes treatment accrues from the myriads of bioactive components found in them. Essentially, it is the high content of polysaccharide, anthraquinones and lectin in *Aloe vera* that are regarded as positively antidiabetic. *Aloe vera* eases blood sugar reduction, enhances insulin sensitivity and guards against oxidative stress. Glymnemic acids are found in *G. sylvestre*, known as the "sugar destroyer" plant. Glymnemic acids contribute to the plant's antidiabetic properties. These acids are reported to increase insulin secretion, lower the intestinal absorption of sugar and suppress the taste of sweetness. The *G. sylvestre* also restores the beta cells in the pancreas destroyed by a normal insulin factor. Both *Aloe vera* and *G. sylvestre* have therapeutic effects that are quite beneficial to patients with diabetes. These plants can be an adjunct to diabetes management, supplementing conventional therapies by stimulating an approach that improves patient outcomes and quality of life. Phytochemicals are natural sources of materials for the development of new drugs, which will be more efficient against diabetes mellitus. This is of particular essence in that even the first-line pharmacotherapy for T2D, metformin, presents adverse gastrointestinal side effects such as abdominal pain, diarrhea and flatulence. Further clinical studies shall be conducted to fully understand their mechanisms for full clinical applications in diabetic care.

REFERENCES

Abhiram G, A Briyangari & R Sivakanesan, 2023. The antioxidant activity, total phenolic and monomeric anthocyanin content of *Gymnema sylvestre* leaf aqueous extract. Journal of Dry Zone Agriculture 9:26-44. https://doi.org/10.4038/jdza.v9i1.68

Ahvazi M, F Khalighi-Sigaroodi, MM Charkhchiyan et al., 2012. Introduction of medicinal plants species with the most traditional usage in Alamut region. The Iranian Journal of Pharmaceutical Research 11:185-94.

Akhtar S, JA Nasir, T Abbas et al., 2019. Diabetes in Pakistan: A systematic review and meta-analysis. Pakistan Journal of Medical Sciences 35:1173-77. https://doi.org/10.12669/pjms.35.4.194

Batool Z, K Singh & S Gairolaet, 2023. Medicinal plants traditionally used in the health care practices by the indigenous communities of the Trans-Himalayan region of Ladakh. Indian Journal of Ethnopharmacology 317:1-19. https://doi.org/10.1016/j.jep.2023.116837

Boudreau GR, VP Olson, MS Tryndyak, et al., 2017. Beland from the cover: aloin, a component of the *Aloe vera* plant leaf, induces pathological changes and modulates the composition of microbiota in the large intestines of male rats. The Journal of Toxicological Sciences 158:302-18. https://doi.org/10.1093/toxsci/kfx105

Dat AD, F Poon, KBT Pham et al., 2012. *Aloe vera* for treating acute and chronic wounds. Cochrane Database of Systematic Reviews 2:1-24. https://doi.org/10.1002/14651858.CD008762.pub2

Egan AM & SF Dinneen, 2019. Diabetes and its types. Medicine 47:1-4. https://doi.org/10.1016/j.mpmed.2018.10.002

Gaikwad S, G Krishna Mohan & M Sandhya Rani, 2014. Phytochemicals for diabetes management. Pharmaceutical Crops 5:1-5. https://doi.org/10.2174/2210290601405010011

Gonzales GB, G Smagghe & C Grootaert, 2015. Flavonoid interactions during digestion, absorption, distribution and metabolism: a sequential structure-activity/property relationship-based approach in the study of bioavailability and bioactivity. Drug Metabolism Reviews 47:175-90. https://doi.org/10.3109/03602532.2014.1003649

Gorsi FI, T Kausar & M A Murtaza, 2019. Evaluation of antibacterial and antioxidant activity of *Aloe vera* (*Aloe barbadensis* Miller) gel powder using different solvents. Pure and Applied Biology 8:1265-70. https://doi.org/10.19045/bspab.2019.80068

Gurung M, H You, R Rodrigues et al., 2020. Role of gut microbiota in type 2 diabetes pathophysiology. BioMedicine 51:1-5. https://doi.org/10.1016/j.ebiom.2019.11.051

Hajiaghaalipour F, M Khalil pourfarshbafi & A Arya, 2015. Modulation of glucose transporter protein by dietary flavonoids in type 2 diabetes mellitus. International Journal of Biological Sciences 11:508-15. https://doi.org/10.7150/ijbs.11241

Hussain A, C Sharma, S Khan et al., 2015. *Aloe vera* inhibits proliferation of human breast and cervical cancer cells and acts synergistically with

cisplatin. Asian Pacific Journal of Cancer Preview 16:2939-46. https://doi.org/10.7314/APJCP.2015.16.7.2939

Jangannanavar VD, MK Patil, L S Chougala et al., 2021. Biogenic synthesis and characterization of ZnO nanoparticles from *Aloe barbadensis* miller leaf extract. In Macromolecular Symposia 400:1-9. https://doi.org/10.1002/masy.202100177

Kaithwas, G., P. Singh & D. Bhatia, 2014. Evaluation of in vitro and in vivo antioxidant potential of polysaccharides from *Aloe vera* (Aloe barbadensis Miller) gel. Drug and Chemical Toxicology 37:135-43. https://doi.org/10.3109/01480545.2013.834350

Kang MC, 2014. In Vitro and in vivo Antioxidant Activities of Polysaccharide Purified from *Aloe Vera* (*Aloe Barbadensis*). Carbohydrate Polymers 99:365-71. https://doi.org/10.1016/j.carbpol.2013.07.091

Karande SS, DN Vikhe & RS Jadhav, 2022. Gynmema sylvestre A potentional medicinal herb. Research Journal of Science and Technology 14:193-96. https://doi.org/10.52711/2349-2988.2022.00032

Kellera AC, J Ma, A Kavalier et al., 2011. Saponins from the traditional medicinal plant Momordica charantia stimulate insulin secretion in vitro. Phytomedicine 19:32-7. https://doi.org/10.1016/j.phymed.2011.06.019

Khan F, MMR Sarker, LC Ming et al., 2019. Comprehensive review on phytochemicals, pharmacological and clinical potentials of Gymnema sylvestre. Frontiers in Pharmacology 10:1223-25. https://doi.org/10.3389/fphar.2019.01223

Kim HJ, SH Hong, SH Chang et al., 2016. Effects of feeding a diet containing Gymnema sylvestre extract: Attenuating progression of obesity in mice. Asian Pacific Journal of Tropical Medicine 9:437-44. https://doi.org/10.1016/j.apjtm.2016.03.037

Kishore L, N Kaur & R Singh 2014. Role of Gymnema sylvestre as alternative medicine. Journal of Homeopathy and Ayurveda Medicine 3:172-80.

Komatsu M, M Takei, H Ishii et al., 2013. Glucose-stimulated insulin secretion: a newer perspective. Journal of Diabetes Investigation 4:511-16. https://doi.org/10.1111/jdi.12094

Lissoni, P, F Rovelli & F Brivio, 2009. A randomized study of chemotherapy versus biochemotherapy with chemotherapy plus *Aloe arborescens* in patients with metastatic cancer. In Vivo 23:171-5.

Liu H, F Kiuchi & Y Tsuda, 2016. Isolation and structure elucidation of gymnemic acids, antisweet principles of Gymnema sylvestre. Chemical and Pharmaceutical Bulletin 40:1366-75. https://doi.org/10.1248/cpb.40.1366

Liu, CY Cui, F Pi et al., 2019. Extraction, purification, structural characteristics, biological activities and pharmacological applications of acemannan, a polysaccharide from *Aloe vera*: A Review. Molecules 24:1-9. https://doi.org/10.3390/molecules24081554

Majumder, RCK Das & M Mandal, 2019. Lead bioactive compounds of *Aloe vera* as potential anticancer agent. Pharmacological Research 148:1-8. https://doi.org/10.1016/j.phrs.2019.104416

Manirakiza, A., L Irakoze & S Manirakiza, 2021. Aloe and its effects on cancer: A Narrative Literature Review. The East African Health Research Journal 5:1-5. https://doi.org/10.24248/eahrj.v5i1.645

Noor A, S Gunasekaran & MA Vijayalakshmi, 2017. Improvement of insulin secretion and pancreatic β-cell function in streptozotocin-induced diabetic rats treated with *Aloe vera* extract. Pharmacognosy Research 9:99-104. https://doi.org/10.4103/pr.pr_75_17

Nxumalo KA, AO Aremu & OA Fawole, 2023. Metabolite profiling, antioxidant and antibacterial properties of four medicinal plants from Eswatini and their relevance in food preservation. The South African Journal of Botany 162:719-29. https://doi.org/10.1016/j.sajb.2023.10.008

Padgilwar S, 2014. Traditional uses, phytochemistry and pharmacology of Oroxylum Indicum: A Review. International Journal of Pharmaceutical and Phytopharmacological Research 3:483-6.

Poddar S, T Sarkar, S Choudhury et al., 2020. Indian traditional medicinal plants: A concise Review. International Journal of Botany Studies 5:174-90.

Popova VT, TA Ivanova, MA Stoyanova et al., 2021. The Leaves and Stems of Cape Gooseberry (*Physalis peruviana* L.) as an Alternative Source of Bioactive Substances. Material Science and Engineering 1031:1-9. https://doi.org/10.1088/1757-899X/1031/1/012094

Rebhun JF, KM Glynn & SR Missler, 2015. Identification of glabridin as a bioactive compound in licorice (*Glycyrrhiza glabra* L.) extract that activates human peroxisome proliferator-activated receptor gamma (PPARc). Fitoterapia 106:55-61. https://doi.org/10.1016/j.fitote.2015.08.004

Rex JRS, NMSA Muthukumar & PM Selvakumar, 2018. Phytochemicals as a potential source for antimicrobial, antioxidant and wound healing A Review. Bioorganic and Organic Chemistry 2:61-70. https://doi.org/10.15406/mojboc.2018.02.0058

Reza Nazifi, SMMH Asgharshamsi, MM Dehkordi, et al., 2019. Antioxidant properties of *Aloe vera* components: a density functional theoretical evaluation. Free Radical Research 53:922-31. https://doi.org/10.1080/10715762.2019.1648798

Rivera SM, A Andrade-Cetto & G Sánchez-Villaseñor, 2019. Phytochemical Composition and Chronic Hypoglycemic Effect of Bromelia Karatas on STZ-NA-Induced Diabetic Rats. Evidence Based Complement. The Journal of Alternative Medicine 1:1-8. https://doi.org/10.1155/2019/9276953

Sahare AY, 2007. Hypericum perforatum: A Medicinal plant. Plant Archives 7:463-8.

Sahu NP, SB Mahato, SK Sarkar et al., 2020. Triterpenoid saponins from *Gymnema sylvestre*. Phytochemistry 41:1181-5. https://doi.org/10.1016/0031-9422(95)00782-2

Sanders B, AM Ray, S Goldberg et al., 2018. Anti-cancer effects of aloe-emodin: A Systematic Review. Journal of Clinical and Translational Research 3:283-6.

Saneja A, C Sharma, KR Aneja et al., 2010. Gymnema sylvestre (Gurmar): A review. Der Pharmacia Lettre 2:275-84.

Sayem AS, A Arya, H Karimian et al., 2018. Action of phytochemicals on insulin signaling pathways accelerating glucose transporter (GLUT4) protein translocation. Molecules 23:258-63. https://doi.org/10.3390/molecules23020258

Shehadeh MB, GA Suaifan & AM Abu-Odeh, 2021. Plants secondary metabolites as blood glucose-lowering molecules. Molecules 26:4333. https://doi.org/10.3390/molecules26144333

Sonawane SK, JS Gokhale, MZ Mulla et al., 2021. A comprehensive overview of functional and rheological properties of *Aloe vera* and its application in foods. Journal of Food Science and Technology 58:1217-26. https://doi.org/10.1007/s13197-020-04661-6

Teoh SL, & S Das, 2018. Phytochemicals and their effective role in the treatment of diabetes mellitus: A Short Review. Phytochemistry Reviews 17:1111-28. https://doi.org/10.1007/s11101-018-9575-z

Tiwari P, BN Mishra & NS Sangwan, 2014. Phytochemical and pharmacological properties of Gymnema sylvestre: an important medicinal plant. Biomedicine Research International 2014:1-8. https://doi.org/10.1155/2014/830285

Unlu A, E Nayir, H Ay et al., 2016. *Aloe vera* and cancer. Turk Onkoloji Dergisi. Turkish Journal of Oncology 31:1-5. https://doi.org/10.5505/tjo.2016.1433

Yoshikawa M, M Kadoya, Y Li et al., 1997. Medicinal foodstuffs. The inhibitors of glucose absorption from the leaves of Gymnema sylvestre. (Asclepiadaceae): Structures of gymnemosides A and B. Chemical and Pharmaceutical Bulletin 45:1671-6. https://doi.org/10.1248/cpb.45.1671