Section A-Research paper

Antidiabetic Potential of Herbal DPP-4 Inhibitors- A Molecular Perspective

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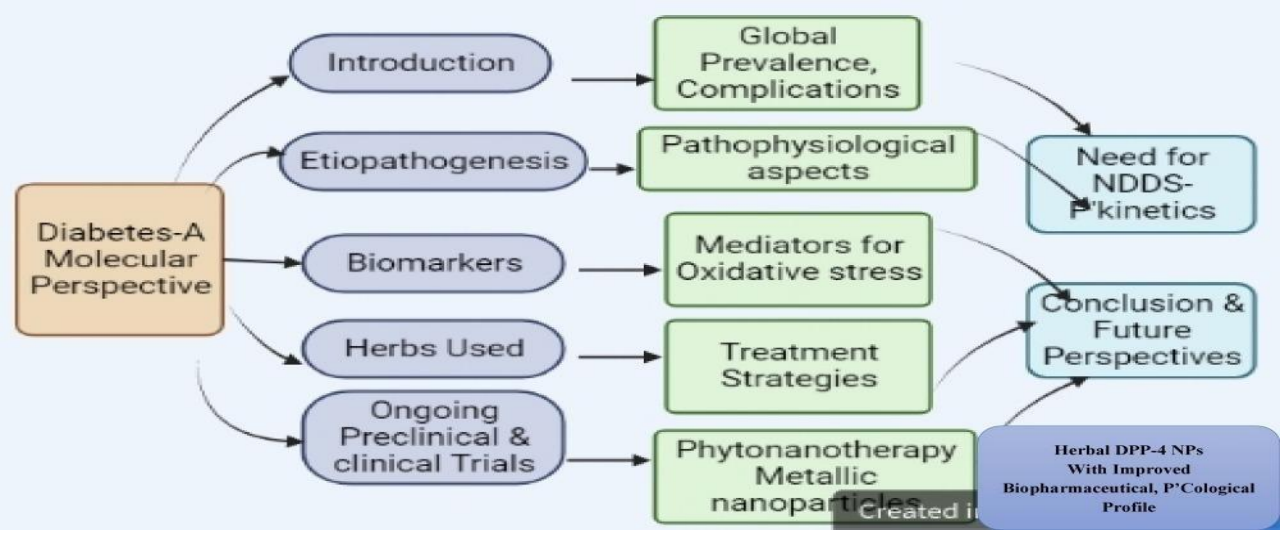
Abstract: Elevated plasma sugar is the foremost metabolic disorder around the globe, with an alarmingly rising mortality rate, and it exacerbates the patient's pathological condition. Following a research review, India had the world's greatest incidence of diabetes in 2000, with 31.7 million cases. Around 2030, the WHO forecasts that the global prevalence of diabetic instances might double. Multiple conventional hypoglycemic medications are adequate, yet they have a multitude of unpleasant side effects. Under the inclusion of numerous constituents in a plant with fewer negative impacts on peripheral organs, herbal novel formulations exhibit excellent synergistic efficacy. This study emphasizes on the biochemical constituents of medicinal herbs that inhibit Dipeptidyl peptidase-4 (DPP-4) enzymes which reduce blood glucose levels. The field of nanotechnology has an affordable price point and a higher safeguarding profile. The biosynthesis of herbal metal nanoparticles is one of the most promising approaches, with an outstanding pharmacokinetic profile, enhanced penetrability, and an environmentally friendly formulation. There are currently a handful of novel herbal formulations accessible on the market for sale. Regarding this, the authors of the present study investigated the molecular pharmacokinetic and pharmacodynamic profile status of medicinal herbs in numerous preclinical and clinical trials in future developments for their utility in treating this serious illness.

Keywords: Diabetes mellitus, Herbal drugs, Pharmacokinetic profile, Outstanding Pharmacodynamic status, DPP-4 inhibitors, Nanoparticles Formulations.

Graphical Abstract:



1. Introduction

Diabetes mellitus is a disorder in which the body is unable to produce or respond to the hormone insulin, resulting in abnormal metabolism of carbohydrates which elevate the levels of glucose in the blood. It is a non-communicable illness and the fourth most cause of mortality as it complicates the micro and macrovascular (cardiovascular) health of patients who need frequent hospitalization due to their associated risk factors [1] [2]. The most significant risk factors for diabetes are overweight and obesity. This is characterized by lots of symptoms like hyperglycemia, hypercholesterolemia, polyphagia, polydipsia, lactic acidosis, polyuria, etc [3]. Plants have always been a rich arsenal for controlling and treating diabetes problems and complication arising due to it. The increase in resistance and populations of patients at some risk, in conjunction with the restricted number of commercially available drugs for diabetes that still have many side effects and problems like unwanted hypoglycemic effects, are the cause to shift the research towards traditionally available medicine which have low side effect and wide range of bioactivity [4] [5]. These traditional treatments do not require laborious pharmaceutical synthesis and seem highly attractive. Dipeptidyl peptidase-4 (DPP-4) is one of the widely explored novel targets for Type 2 diabetes mellitus patients (T2DM). The goal of DPP-4 inhibitors is to preserve the endogenous glucagon-like peptide (GLP)-1 activity by inhibiting the DPP-4 action [6] [7]. The DPP-4 inhibitors are weight neutral, well tolerated, and give better glycaemic control over a longer duration of time compared to existing conventional therapies. The journey of DPP-4 inhibitors in the market started with the launch of sitagliptin in 2006 onwards on to vildagliptin in 2022. Along with helping to control blood sugar it also boosts weight loss, GLP-1s seem to have major benefits [8]. Research has also investigated that drugs in these groups may also lower the risk of heart diseases such as heart failure, stroke, and kidney disease [9]. Nanotechnology opens the possibility for a wide variety of biological research topics and medical uses at the molecular and cellular levels. The biosynthesis of nanoparticles has been proposed as a cost-effective and environmentally friendly alternative to chemical and physical methods. This innovative approach might significantly enhance diabetics' quality of life [10].

Diabetes Mellitus and its Types

Diabetes can be divided into Type I and Type II based on their etiological factors. Low or very low levels of circulating insulin are the major issues in type-I diabetes mellitus (IDDM/Juvenile onset), which is brought on by autoimmune beta cell death in pancreatic islets [11]. Whereas, in Type- II diabetes, beta cells have an aberrant glucoceptor that only reacts to high glucose concentrations also called Non-Insulin Dependent Diabetes Mellitus (NIDDM/ Maturity Onset Diabetes Mellitus) [12]. The "Down Regulation" of insulin receptors, which reduces the sensitivity of peripheral tissues to insulin, is another name for this disorder. A defective insulin molecule, an increased concentration of circulating antagonists, and abnormalities in the target tissue all contribute to resistance to insulin action [13]. Insulin receptors sensitization and desensitization sometimes get altered due to some biochemical or cellular changes in the pancreas because of various etiological risk factors through GLUT-4 which have the task to remove and balence glucose from blood plasma (Figure -1).

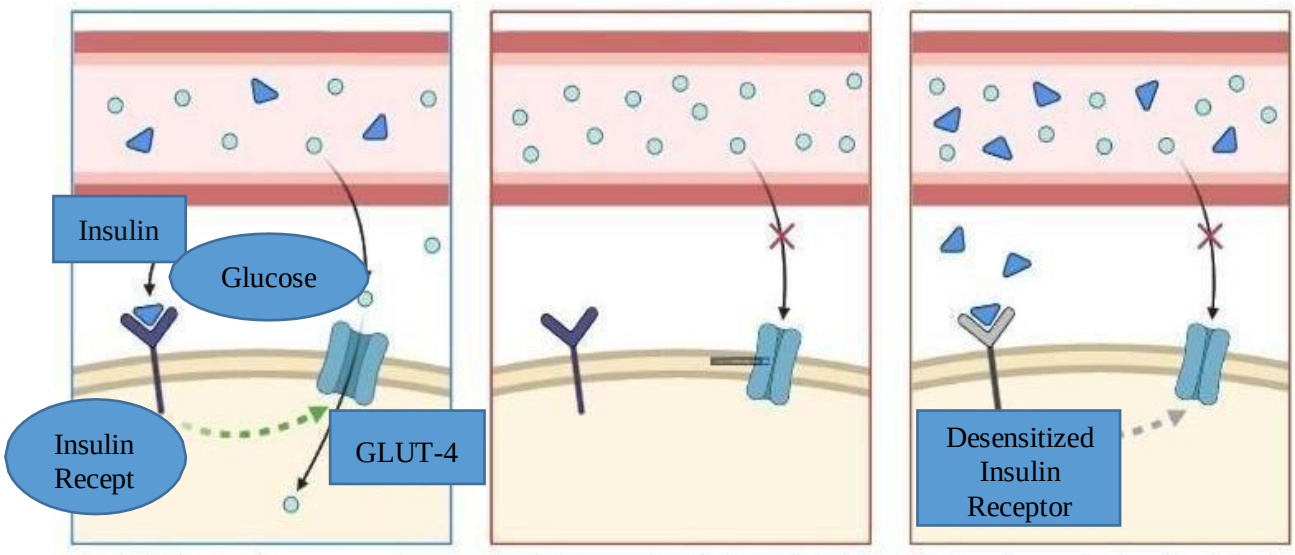


Figure No. -1 Pathogenesis of insulin receptor sensitization and desensitization in pancreatic beta cells to remove glucose from the bloodstream through GLUT-4 in a healthy person, Type-I and Type-II diabetic patients.

1. Healthy Person	2. Diabetes mellitus, type 1	3. Diabetes mellitus, type 2
Insulin binds to insulin receptors and triggers the opening of glucose transporters in fats/muscle cells, allowing glucose removal from the blood stream.	Insulin is not produced by beta cells in the pancreas and hence glucose is not removed fromthe bloodstream.	Prolonged overproduction of insulin leads to desensitizationof the insulin receptors and hence glucose is not removed from the bloodstream.

Etiopathogenesis

Different inflammatory mediators like Iκ- β, NF-κβ, TLR 4, MAPK, TNF, ROS, Macrophage, IL-1β and IL-6 are released in this disorder which complicate a wide range of painful and inflammatory consequences, like stroke, retinopathy, neuropathy, and nephropathy [14]. Figure 02 shows h o w oxidative stress, mitochondrial dysfunction, hepatic glucose production, glucose uptakes, vesicular insulin resistance, and neurotransmitter dysfunction all increase in diabetics. They also diminish incretin effects, moreover, several inflammatory mediators are generated, including IκB-NF, NF-κB, TLR 4, MAPK, TNF, ROS, Macrophage, IL-1, and IL-6 [15]. Numerous unpleasant and inflammatory effects are brought on by these inflammatory mediators, including retinopathy, neuropathy, nephropathy, coronary artery disease, and peripheral arterial disease, which can result in stroke (Figure -2).

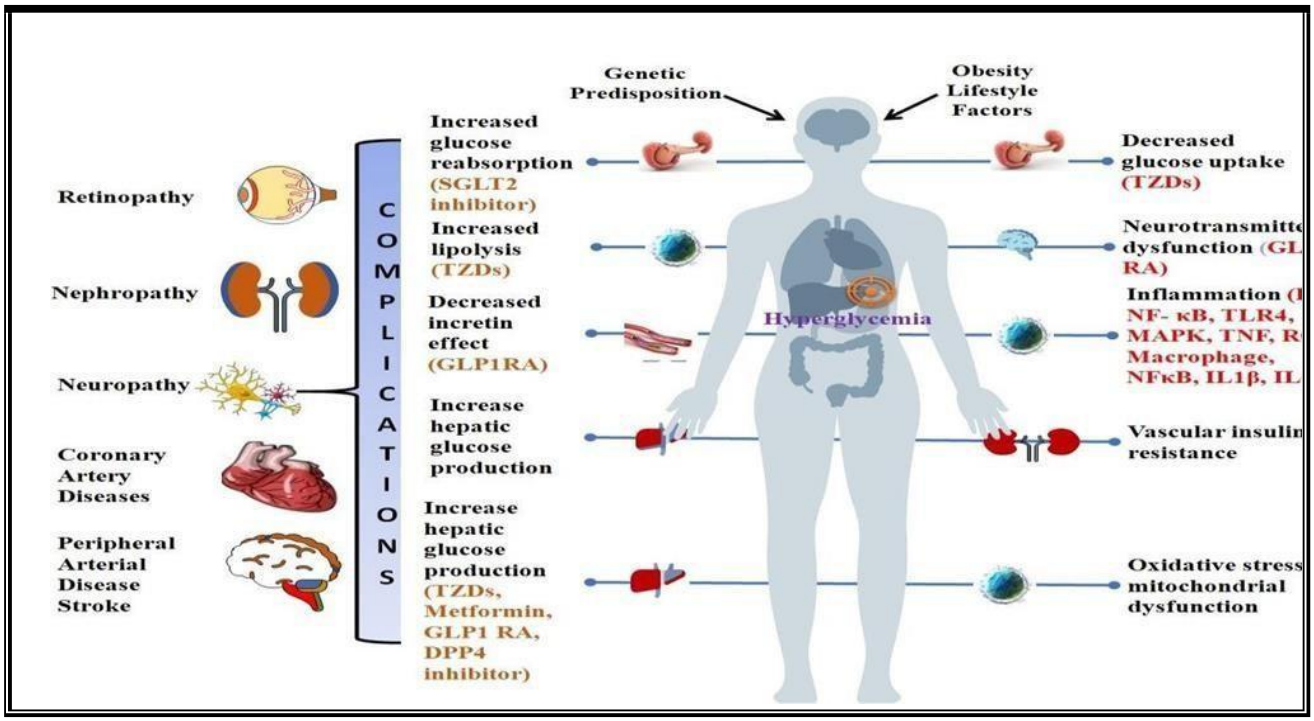


Figure -2 Pathophysiology of diabetes mellitus, risk factors, biomarkers, complications, targeted drugs, and their mechanism of action.

The primary factors for oxidative stress and mitochondrial dysfunction are genetic predisposition and obesity lifestyle, which increase glucose reabsorption, decrease incretin effects, increase hepatic glucose production, decrease glucose uptakes, vesicular insulin resistance, and neurotransmitter dysfunction [16].

Free radicals are implicated in the pathogenesis of diabetes [5] and, more importantly, in the onset of diabetic complications [17]. Free radicals are capable of causing damage to cellular molecules, DNA, proteins, and lipids, altering cellular functions. Acute or chronic hyperglycemia in diabetes increases ROS production and activates beta-cell apoptosis [18]. Under physiological conditions such as hypertension, ischemic heart disease, and diabetes, as well as during the aging process, reactive oxygen species (ROS) play a role in intracellular signal transduction of oxidative stress [19]. Numerous pathological processes involving protein and lipid peroxidation and DNA damage are well-known to be induced by oxidative stress [20]. Calcium cycling between the sarcoplasmic reticulum (SR) and the cytosol via the sarco-/endoplasmic reticulum Ca-ATPase (SERCA) pump, inositol-1,4,5-triphosphate receptor (IP3R), and Ryanodine receptor (RyR), plays a major role in agonist-induced intracellular calcium dynamics in vascular smooth muscle cells (VSMC) of diabetic patients [21]. The ATP-sensitive K+ channel (K ATP channel) detects metabolic alterations in the beta-cell of the pancreas, coupling metabolism to electrical activity and, ultimately, insulin secretion. When K ATP channels open, beta-cells hyperpolarize and suppress insulin secretion [22]. Ca2+ ion is an essential signaling molecule for the function of pancreatic beta-cells. Ca2+ is also essential for multiple beta-cell pathways, including insulin secretion, transcription, metabolism, endoplasmic reticulum function, and stress response. A novel approach could substantially improve diabetics' quality of life [23].

The below-mentioned diagram (Figure -3) depicts the interactions of insulin receptors and their route in controlling blood serum concentrations. It also depicts how oxidative stress and reactive

oxygen species inside beta islet cell becomes the etiological cause of Diabetes mellitus by some biochemical changes at a molecular level.

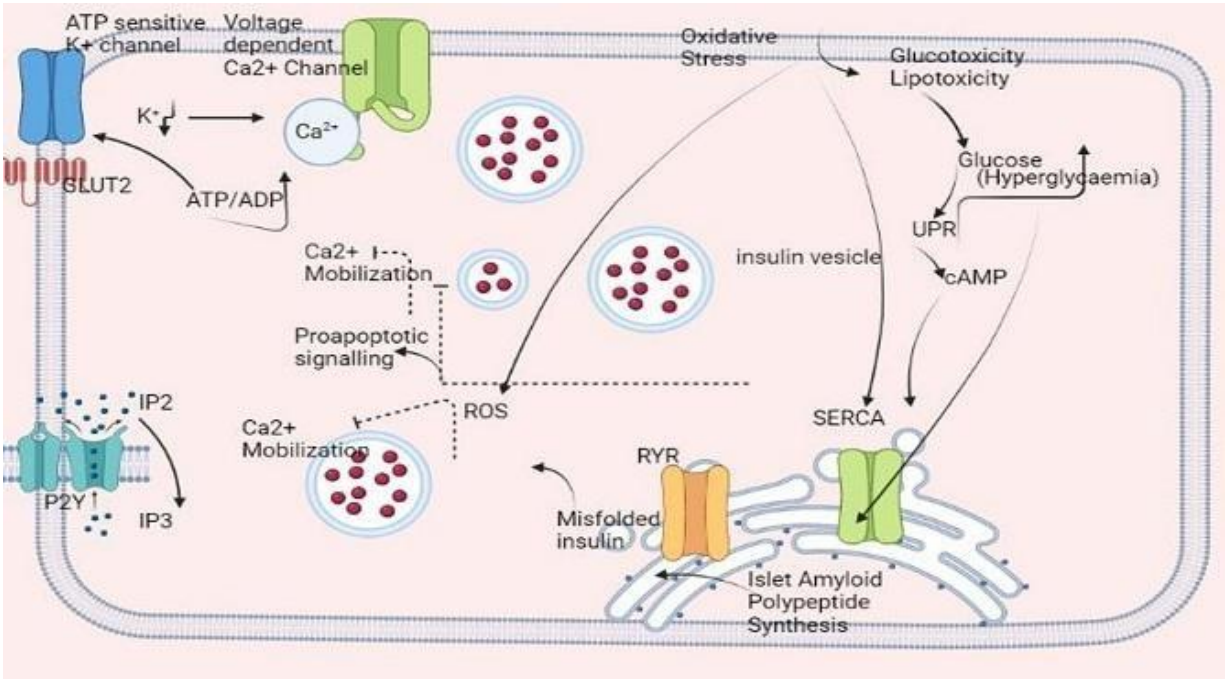


Figure -3 Pancreatic β-cell dysfunctioning results in the manifestation of Hyperglycaemia. Biochemical changes induced by oxidative stress up to ion

Risk Factors

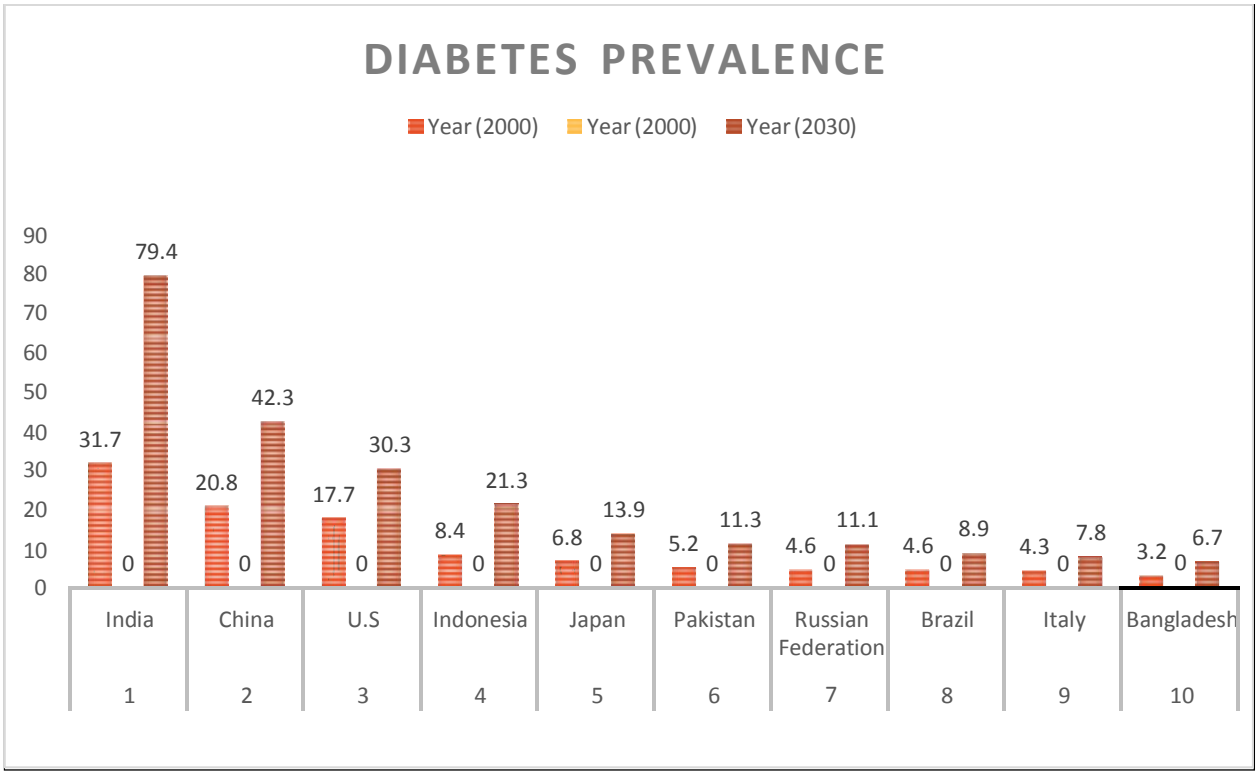
Family history, polycystic ovarian syndrome (PCOS), low HDL, hypertension, age, ethnicity, diet, physical activity, overweight, and smoking are the risks associated with this metabolic disorder (Figure -4). In women age, waist, body mass index (BMI), hypertension, low education, and living environment; in men age, BMI, and hypertension were independently associated with an increased prevalence of diabetes [24]. Numerous risk factors contribute to the development of diabetes mellitus are diet, family history, overeating or obesity, smoking, ethnicity, genetics, and hypertension [25].

Figure 4: Risk Factors Accountable in a Diabetic Victim.

Global Prevalence

Diabetes-related deaths accounted for 3.1 percent of all deaths in India in 2016, up from 0.98 percent in 1990. A recent study found that diabetes mortality will double in the upcoming five years and these patients in India invest for their care total of approximately 10,000 rupees in urban areas and 6260 rupees in rural regions per year [26]. It was found that around 462 million individuals have TD2, and by 2025, this figure may probably rise up to 600 million. It was also analyzed that between the age group of 20 and 79 years, 537 million people (or 1 in 10) have diabetes mellitus [27]. This number may be projected to be 643 million by 2030 and 783 million by 2045. China is the country with the highest rate of diabetic cases in the world, where about 141 million people are affected [28]. Table Chart 1 lists the nations with the greatest estimated incidence of diabetes, and it was shown that Bangladesh has the fewest while India has the most incidences of diabetes.

Table Chart 1. List of nations where diabetes is thought to be most prevalent



DPP-4 Inhibitors

DPP-4 inhibitors, a class of oral diabetic medications, inhibit the DPP-4 enzyme, which is a unique enzyme present on the cell surface and deactivates the maximum number of polypeptides (GLP-1) and glucose-dependent insulinotropic polypeptides [29]. DPP-4 inhibitors are superior therapies based on the GLP-1 receptor; they reduce stomach emptying and food intake, increase insulin secretion dependent on blood glucose, and suppress glucagon post-meal release. GLP-1 (glucagon-like peptide 1) is an intestinal hormone produced in response to diet by inducing hypoglycemia and stimulating insulin secretion from the pancreas. DPP-4 inhibitors may be used as monotherapy in patients who are intolerant to metformin or have contraindications to its use, such as those with chronic renal disease and a significant risk for hypoglycemia [30].

The contraption of DPP-4 Inhibitors is explained in Figure-5 below, which shows how, after eating, our GI Track is employed to block or release GLP-1 from pancreatic beta cells, which activate and release insulin. DPP IV hydrolyzes incretin, a key regulatorof postprandial insulin secretion. This hormone aids diabetics in controlling their blood sugar. A DPP-4 inhibitor, sitagliptin boosts insulin production and lowers the overproduction of glucose in the liver. Raising the levels of active incretins, it prolongs the effect of GLP-1 and GIP. It prevents the DPP-4 enzyme from increasing the activity of GLP-1 and GIP hormones, which causes insulin secretion to longer lasting [31].

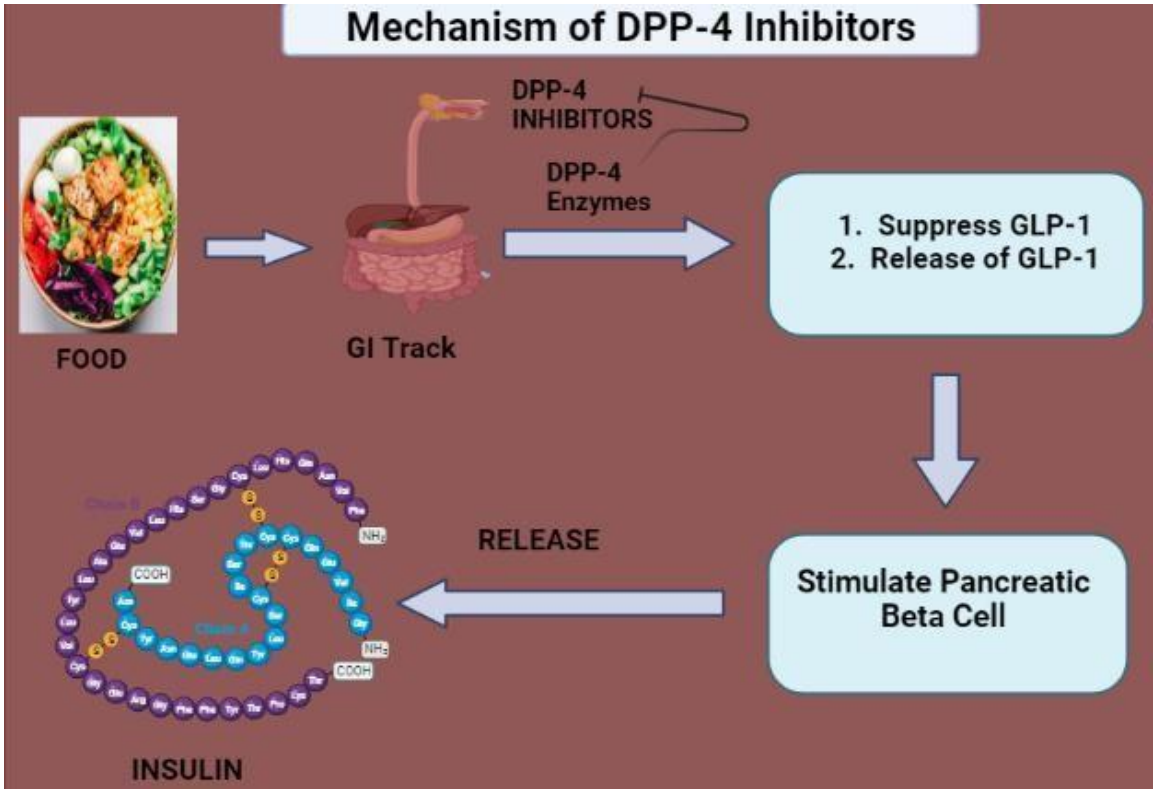


Figure -5: Sitagliptin's mechanism of action is depicted in a figure along with other DPP-4 inhibitor medications and GLP-1.

The best quality of DPP-4 inhibitors is even their adverse effect is also helpful as it leads to weight loss in victims. Therefore, in this review, we have focused on the pharmacokinetic and pharmacodynamic status of DPP-4 inhibitor herbal drugs both in animal and human patient research studies.

Whereas, Sulfonylurea (Biguanides) primarily attempts to block ATP-sensitive K+ channels in the plasma membrane of beta cells shown in Figure -6 to start a series of events in the pancreas. Insulin is released when sulfonylurea binding changes the resting potential of the cell and causes calcium influx [32]. Sulfonylureas and other conventional hypoglycaemic drugs have 2numerous adverse effects like hypotension, increase hunger, weight gain, dizziness, confusion, heartburn, stomach upset etc [33].

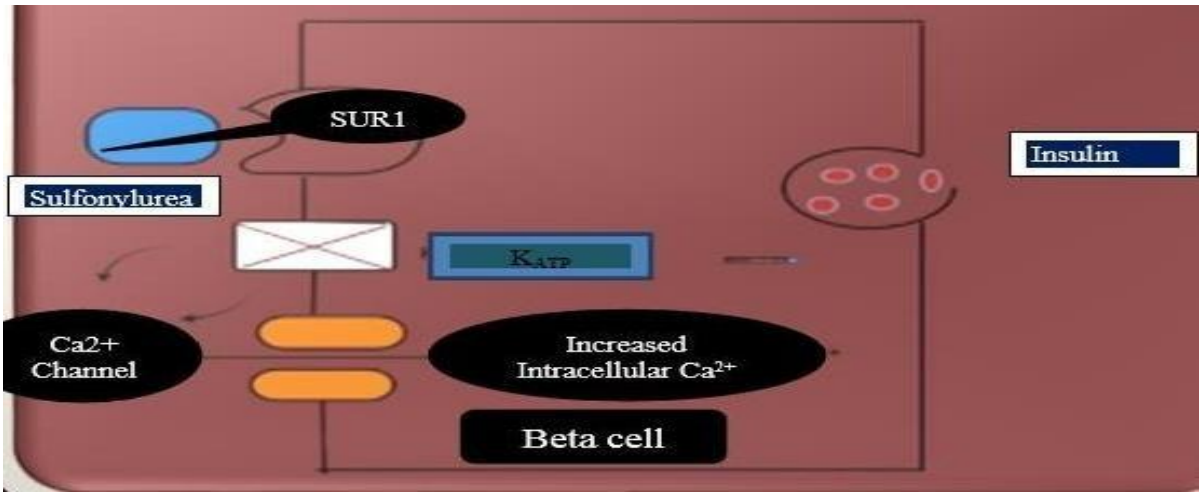


Figure -6 Diagram illustrating the operating procedure of Sulfonyl Urea in Pancreatic β- Cell by deliverance of insulin through the actuation of ATP-sensitive K^+ and Ca^{2+} ion channels inside pancreatic islets.

Herbal Drugs

In contrast to conventional medicine, the use of botanicals for the treatment and prevention of diseases, including diabetes, has a long history. Herbal medicine has been utilized for centuries to treat a variety of health conditions. If someone wishes to avoid prescription medications and invasive treatments as much as possible, herbal medicine may be a suitable alternative [34]. There are several benefits to using herbal medicine to treat diabetic illness, including reduced adverse effects, lower costs, improved overall health, and self-healing [35]. However, the selection of botanicals may depend on many variables, such as the stage of progression of diabetes, the categories of comorbidities the patients have, their availability, affordability, and their safety profile [36]. Numerous herbal treatments are recommended for diabetes and diabetic complications. However, there are very few herbal treatments for diabetes on the market, so more research is required to demonstrate their efficacy and ensure their safety [37].

Nanotechnology

The conventional treatment options for type 2 diabetes mellitus (T2DM) are extensive. However, conventional medications have some disadvantages that can impact the treatment's efficacy. Low bioavailability and immediate drug release are the primary disadvantages of the ground in the development of novel delivery modalities that could enhance the efficacy of anti-diabetic regimens [38]. Pharmacies and other medical corporations use nanotechnology applications worldwide in a range of biotechnology, bioengineering, and biomechanics disciplines, replacing the current scenario of researchers pursuing this field as an alternative drug delivery system [38]. As a result, nanotechnology is now one of the most intriguing academic disciplines. Nanomedicine and Nano delivery utilize nanoscale materials as diagnostic instruments for the targeted delivery of therapeutic agents. This field makes it possible to design biomaterials with the desired Nanoscale size, shape, and morphology due to increased bioavailability, prolonged release, and decreased dosing, thereby improving patient compliance [39]. This novel approach could significantly improve diabetics' quality of life. Existing oral treatments for T2DM

necessitate an increase in administration frequency. In tandem with the onset of adverse side effects, patient adherence to treatment decreases. Nanotechnology has found favor in recent years [40].

This review gives a thorough update to address the worldwide crisis, stressing the global situation and the statistical incidence. It became a need for future diabetic laypeople, as it ranks the fourth most prevalent cause of death in the nation. So there should be more and more research and production of novelherbal medicines in this era.

Biomarkers

The acronym biomarker pertains to a trait that may be objectively tested and assessed as a predictor of pathogenic biological processes, healthy biological processes, pharmacological reactions to therapeutic interventions, or chemicals that seem to be biological manifestations of a disease. Understanding the illness spectrum is made easier by biomarkers [41, 42]. Biomarkers are generally utilized in epidemiological research to understand the risk factors and problems linked to illnesses, identify the etiological and pathophysiological variables, and diagnose the disease early [43].

Many blood indicators for diabetic pathology are present. Blood analysis is necessary to determine the pathological and physiological aspects of the illness [44, 45]. The acute phase response is triggered by two crucial pro-inflammatory cytokines, TNF-α and IL-6, which boost the production of CRP and AGA among other proteins. TNF-α serum and urine concentrations are greater in DM3 patients compared to normoalbuminuric subjects or healthy controls. According to recent studies, serum TNFR1 and TNFR2 concentrations may be utilized to predict how diabetics' renal illness may develop in the future [46, 47].

Biomarkers in Body Fluids

Many biomarkers that show pancreatic beta-cell dysfunction and disease development may be identified in blood plasma, blood serum, and urine. These biomarkers include Lipoprotein Lipase, LDL, VLDL, IDL, Apo proteins, leptin, TNF-, and IL [48]. All of the biomarkers for diabetes mellitus are included in Table 02 below, along with their mediators, molecules, samples, and methodologies [49]. The diverse biomolecule levels in the various bodily fluids, such as blood plasma, serum, and urine, become unbalanced in diabetes mellitus, a liver and pancreatic condition [50]. Also, table 2 lists the adverse responses as well as the clinical result and numerous problems. Elevated TNF- and IL-6 impair the body's system and contribute to diabetic nephropathy and other cardiovascular risk factors [51]. The table describes the biomolecules and mediator changes in various biofluid samples using various methodologies. According to the results of the available literature, diabetic beta cell dysfunction is characterized by an imbalance in the levels of lipoprotein lipase, apolipoproteins E, cholesterol, and TNF- [52].

Since the metabolism of amino acids is significantly affected in pre-diabetes and continues to change as T2DM progresses, amino acids have been suggested as potential diagnostic indicators [53]. Due to greater blood concentrations in T2DM patients, tryptophan and branched-chain amino acids (BCAAs, which include valine, leucine, and isoleucine) may be particularly helpful as T2DM biomarkers [54]. In T2DM/pre-diabetes patients and healthy controls, there were statistically equal amounts of LPC (C18:2), palmitic acid (C16:0), alanine, citrulline, glutamate, glycine, isoleucine, leucine, lysine, phenylalanine, proline, serine, tyrosine, and valine amino acids [55]. Pre-diabetes and T2DM are very different from one another, showing that different disease stages are connected to unique and distinct metabolic biomarker profiles [56].

Table 2:- Biomarkers of Diabetes mellitus along with their mediators, molecules, sample, and their methodology

Sr. No.	**Biomarkers (Biofluids)**	**Mediators**	**Molecules**	**mples**	**Methods**	**Comments**	**Reference**
1.	Bloodplasma	Leptin system, Monoclonal sandwich	Soluble leptin-R, Interleukin (IL-6), Hs- CRP, C-Peptide, HbA1C	Blood Plasma	ELISA Immunol turbidime tricassay	Biomarkers correlation structure was disturbed before the clinical diagnosis	[57]
2.	Blood serum	Lipids, proteins for lipids metabolism	Lipo protein lipase, Apolipoprotein E, Apolipoprotein A1, A2, Apolipoprotein B, Cholesterol l esters transferase, proteins	Blood serum	-	An increase in Copolipoprotein develops coronary artery disease, MI	[58]
			nicroglobulin (α1 m)	erum, urine	-	plicate liverdisease	[59]
		Cytokine related proteins	tin, TNF-α,IL-6	Blood serum	-	-	[60] [61]
		mmune-related proteins	MCP-1	Blood serum	-	-	[62] [63]
3	Urine	Defense response	α1- Complement factor, Alpha-1, antichymo trypsin precursors, Antithrombin-III, α-2, Glycoprotein-I, Vitronectin Precursors			Urine	[64] [65] [66] [67] [68]

		n-codingRNA	21-23 Nucleotides	iRNA	-	Mi-RNA progression from prediabetes to T2DM	[71] [72] [73] [74] [75]
		Glomerular	Transferrin Type- IV Collgen	Urine	-	Elevation complicates diabetic nephropathy	[76] [77] [78] [79] [80]
		Inflammato Ry	TNF-α	Urine /serum	-	TNF- α elevation & IL-6 ccomplicate diabetic nephropathyy	[81] [82] [83] [84]
		Genotype	HLA-DR/-DQ	Blood plasma	-	Immunological biomarkers lead to the development& progression of T1DM	[85] [86] [87] [88]
		Proteomic	GAD IGRP IL-6 SOB-R	Blood plasma	-	-	[89] [90]

Principles of Preclinical Studies

Before a trial on humans, medications must first undergo preclinical testing on animals. To be able to establish the pharmacological and toxic effects of a therapeutic molecule, preclinical testing utilizes the advantages of both in-vitro and in-vivo testing [91]. Preclinical research is intended to ascertain the initial dosage, safe dose, adverse drug responses, and toxicity of a drug product, which often includes a novel medical device, prescription medications, and diagnostics [92] [93]. The effects of synthetic drug compounds evaluated on rats are listed in Table 3; their effects and treatment results are noted for various time horizons (7 days, 21 days, 8 weeks, etc.) [94].

Table 3: Preclinical studies, their effects, treatment, and results are noted for various time horizons

Sr. No.	Herbal Drugs	Animals	Dose	Duration of study	Side effects	Mechanism/ Molecular Targets	Reference
1.	Acacia arabica	36 female albino	100, 200	21 days	Unpleasant mouth sensation,	Hypoglycaemia by initiating release of insulin from pancreatic	[95]

		rats	mg/kg		morning sickness, slight diarrhea, and bloating.	β cell, Reduction in blood glucose, TC and LDL	
2.	Aegle marmelosa (Methanolic extract)	Wistar rats	250, 500 mg/kg	21 days	Diarrhea, indigestion, constipation and dysentery	Weight gain, blood sugar, lipid profile, C-Peptide, HbA1c, insulin secretion, and pancreatic insulin levels are all affected by the decline in beta cell density and disturbance of the normal architecture of the pancreatic beta cell.	[96]
3.	Allium cepa	Rats	300 mg/kg	45 days	Indigestion, bleeding disorders	Reduce levels of blood sugar, elevate insulin levels, and lessen the production of advanced glycation end products (AGE) Regulate cholesterol levels, blood sugar, and the liver's hexokinase, glucose-6-phosphatase, and HMG-co-A-reductase enzymes	[97]
4.	Allium sativum	Rabbits	Aqueous homogenate of garlic 10ml/kg/day	2 months	Bad breath. Body odor. Burping. Heartburn. Upset stomach	Extremely reduced AST, urea, uric acid, total cholesterol, and other blood markers Hypoglycemia, increased hepatic metabolism, insulin release, hepatic glycogen, and free amino acids	[98]
5.	Aloe vera and barbedensis	Mice	200 mg/kg	2 weeks	skin irritation, hives, cramping, and diarrhea	Boosts the body's tissues' receptivity to insulin, increasing the effectiveness of the hormone. encourage the pancreas to produce or release more insulin	[99]
6.	Azadirachta indica (hydroalcoholic extract)	Rats	400 mg/kg	30 days	death, vomiting, abdominal pain, sleepiness, blood disorders, seizures, loss of consciousness, coma, brain diseases, and brain disorders	adjusted the changing concentrations of GLUT4 proteins, serum insulin, lipid profile, blood sugar, and insulin signaling molecules. Method to increase glucose absorption and glycogen synthesis in the rat hemi diaphragm	[100]
7.	Caesalpinia bondcella (85% ethanolic	Rats	250, 500 mg/kg	8 weeks	abdominal pain, colic, leprosy, fever	By restoring free radical scavenging capacity, blocking glucose absorption causes hypoglycaemic and hypolipidaemic activity, which	[101]

	extract)					reduces oxidative stress in pancreatic cells.	
8.	Coccinia indica	Rats	500 mg/ kg	6 weeks	None	restore lipoprotein lipase, lower lactate dehydrogenase, glucose-6-phosphatase, and severe hypoglycemia Alloxan increases superoxide dismutase, decreases oxidative stress, and increases lipid levels in the RBS, kidney, and heart.	[102]
9.	Eugenia jambola na (Decocti on extract of jamun pulp)	Rats	400mg/ kg	2 weeks	bodily pains, fever, phlegm buildup in the lungs, and coughing	free radical scavenging, as shown by increased oxidative stress, raised catalase, glutathione peroxidase, glutathione-s-transferase, and SOD activity, a 73.5% decrease in sugar, a rise in blood insulin levels, and an inhibition of insulinase activity in the liver and kidney	[103]
10.	Mangfer a indica (oral aqueous extract)	Rats	200 µg/mL	30 min.	stomach pain, indigestion and diarrhoea	boost muscle and liver glycogen stores, significantly reduce alpha-amylase activity, and significantly improve glucose absorption in diabetic groups to affect the glycogen production pathway.	[104]
11.	Momord ica charantia (extract of fruit pulp, seeds)	Langurs (s.c.)	200 mg/kg	21 days	boost muscle and liver glycogen stores, significantly reduce alpha-amylase activity, and significantly improve glucose absorption in diabetic groups to affect the glycogen production pathway.	enhancing the sensitivity of insulin, Sugar, amino acids, TC, TG, and total lipids are all reduced Hepatic fructose-1,6-biphosphatase, glucose-6-phosphatase, and glucose-6-phosphate dehydrogenase activities are all inhibited.	[105]
12.	Ocimum sanctum (aqueous extract of leaves)	Rats	200mg/ kg	30days	severe headache, hallucinations, convulsions, irregular heartbeat, and extreme dizziness	substantial reductions in fasting and postprandial blood glucose levels, improved pancreatic beta-cell activity, and insulin secretion Skeletal muscle and hepatic glycogen levels decline by 68 and 75%, respectively, but renal	[106]

						glycogen content increases tenfold.260	
13.	Phyllanthus amarus (methanolic extract of plant)	Rats	600 mg/kg	21 days	increased risk of bleeding	extract improved adipogenesis in 3T3-L1 fat cells and raised deoxyglucose absorption in C2C12 muscle cells. strong antioxidant effects and a reduction in sugar levels	[107]
14.	Pterocarpus marsupium (Tannates extract	Male albino rats	250, 1000 mg/kg	10 days	None	stimulated the insulin secretion and glucose uptake Pancreatic beta cells regranulation, hypolipidaemics, stimulate oxygen uptale in fats cells and tissues, increase glycogen content of rat diaphragm	[108]
15.	Trigonella foenum graecum	Wistar male rats	1.6 g/kg	60 min	Dizziness and headaches are sporadic, along with symptoms of the digestive system such as diarrhea and nausea.	Limit the activity of fructose-1,6-bisphosphate, glucose-6-phosphatase, and the liver Reduce blood sugar levels in both healthy and diabetic rats while enhancing glucose metabolism normalize the levels of liver, skeletal muscle, and cardiac CK in these tissues	[109]
16.	Tinospora cordifolia (Guduchiroot extract)	Rats	200, 400 mg/kg	30 days	headache or nasal pain	Strengthening the liver's ability to store glycogen or reducing its ability to release glucose. decrease in blood sugar and triglycerides, hypoglycemic activity, and improvement in glucose tolerance	[110]
17.	Urtica diocia	Wistar male rats	100, 200, 300 mg/kg	21 days	minor stomach discomfort, bloating, diarrhea, perspiration, and hives or rash	Leaves have insulin secretagogue, PPAR gamma agonistic, and alpha-glucosidase inhibitory effects Reduction in fasting insulin resistance index and increase sensitivity of tissues	[111]
18.	Anacardium occidentale leaves extract	Rats	100 mg/kg	30 days	bloating, constipation, weight gain, and joint swelling	levels of glycated hemoglobin, insulin, fasting blood sugar, and lipid markers have decreased. a decrease in fasting sugar, a rise in serum insulin, and an improvement in skeletal muscle glycogenesis	[112]

19.	S. cochinchinesis	Mouse	1000 mg/kg	28 days	constipation and excessive urination	significantly decreased fasting blood glucose Decrease homeostatic model score on insulin resistance index, increase sensitivity of tissues	[113]
20.	Helicterus angustifolia (ethanol extract)	Rats	200, 400 mg/kg	28 days	hepatotoxicity, nephrotoxicity and hypersensitivity	enhancing microcirculation, raising insulin secretion, controlling glycemic metabolism, lowering cholesterol, removing free radicals, and all of the above Lower HOMA-IR and blood sugar levels, higher insulin levels	[114]
21.	Pleurotus ostseatus (aqueous extract)	Rats	100, 200, 400 mg/kg	4 weeks	hives, fever, chills, soreness, itching, or swelling in the mouth or throat	alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) all showed increased liver function. lowering fasting blood sugar, raising insulin levels, and enhancing cellular sensitivity	[115]
22.	Afzelia africana	Rats	100, 200 mg/kg	10 days	drowsiness, dizziness, hypotension or a headache	Pancreatic tissue regeneration stimulate inintracellular glucose transport, increase glucose uptake by various cells	[116]
23.	Uvaria chamae roots	Sprague dawley Rats	100, 250, 400 mg/kg	8 days	kidney stones	Extracts improved HDL-C, lipid profiles, and blood glucose levels.Hypoglycaemic effects in dose dependent manner, regeneration of islet of Langerhans, enhance insulin sensitivity	[117]
24.	Camellia sinesis	Rats	60, 120 and 480 mg /ml	7 days	jitteriness, nausea, skin rashes, and liver toxicity	Examining their impact on cellular glucose absorption and fat accumulation, ameliorates insulin secretion, inhibits the DPP-IV enzyme, enhances glucose tolerance, and increases active GLP-1 -amylase inhibition, decreased starch digestion and absorption, and sod inhibition. dependably transporting glucose	[118]
25.	Cinnamonum zeylanic	Wistar albino rats	150, 200 mg/kg	7 days	diarrhea, vomiting, dizziness,	Nrf2, PI3K/Akt and MAPK pathways activate Inhibit α-glucosidase activity,	[119]

	um				drowsiness	chronic malabsorption of carbohydrate, suppression of post meal glucose	
26.	Callistephus chinesis flower (ethylacetate extract)	Rats	2 mg/ml	7 days	GI disturbances	decreasing fasting glucose levels, increasing insulin release by triggering beta cells or sensitizing insulin Inhibit α-glucosidase due to quercitin	[120]
27.	Corchorus olitorius (jute)	Rats	100, 200 mg/kg	120 minutes	swelling of the mouth or lips, and respiratory problems	stimulation of insulin secretion, increasing β-cell proliferation, thus promoting insulin sensitivity Manage postpramdial hyperglycaemia, inhibit α-amylase and α-glucosidse	[121]
28.	Holarrhena antidysentrica	Rats	300 mg/kg	21 days	Nausea · Flatulence · Constipation · Anxiety, nervousness, and sleeplessness, · Vertigo	stimulation of histaminergic receptors and Ca^{++} antagonist mechanisms Inhibit α-amylase, α-glucosidse in dose dependent manner	[122]
29.	Ficus deltoidea	Mouse	125, 250 and 500 mg/kg/d	4 weeks	skin allergies, kidney and liver function	regulating blood sugar, blood pressure and cholesterol levels Inhibit intestinal α-glucosidse and improve insulin mediated glucose uptake into adipocyte	[123]
30.	Olea europaea L (alcoholic extract)	Male Wistar rats	200, 400 mg/kg	10 weeks	dizziness, lightheadedness, stroke, and even kidney failure	decrease post-prandial blood glucose Reduced starch breakdown and absorption in vivo, lowers fasting plasma insulin level and Hb in placebo patients	[124]
31.	(Free and bound phenolic extract) Glycine max L	Rats	200, 500 mg/kg	28 days	nausea, vomiting, and upset stomach	strong nutritional value, a low glycemic index, and the capacity to reduce blood sugar levels inhibition of glucosidase and amylase	[125]
32.	Catharanthus roseus	Mice	500, 1000 and 2000 ppm	20 weeks	nausea, vomiting, hair loss, hearing loss, dizziness, bleeding, nerve	prolonged action in reduction of blood glucose Enhance intestinal glucose uptake, increase glucose-6-phosphate dehydrogenase, facilitate	[126]

					problems, seizures, liver damage	glycaemic control, catalyze the oxidation of malate to oxaloacetate, utilize glucose levels	
33.	Chloroxylon swieteni a (Methanolic and aqueous extract)	Male albino wistar rats	250 mg/kg	45 days	None	Moderate reduction in blood glucose and glycosylated Hb level	[127]
34.	Forsythia suspense (Ethyl acetae fraction of methanol extract)	Male kunning mice	50, 100 and 200 mg/kg	4 weeks	Fever. · Gonorrhea,Heart disease HIV/AIDS, Nausea and vomiting, Pain and swelling	Reduced levels of hepatic lipid, triglycerides, acid phosphatase, alkaline phosphatase, aspartate transaminase, and total cholesterol were also seen. Significant improvements were seen in glucose tolerance.	[128]
35.	Coccinia grandis (ethanolic extract)	Male Wistar rats	5 mg/kg	9 days	Nausea, headache, and drowsiness	a dose-dependent rise in blood insulin level	[129]
36.	Dioscorea polysaccharies	Rats	100 mg/kg	3 weeks	vomiting, upset stomach, and headache	Improve insulin resistance, diminution of phosphorylation of ERK, increase of GLUT-4 transporters	[130]
37.	Astragalus membranaceus	Mouse	200 mg/kg	3 weeks	rash, itching, nasal symptoms, or stomach discomfort	Increase better glycemic control by increasing insulin sensitivity, Akt activation and upregulation of GLUT-4	[131]
38.	Gastrodia elata	Rats	20 mg/kg	8 weeks	skin allergies, hair loss , and other allergic reactions	Reduce insulin resistance through decrease in fats accumulation in adipose tissues, decrease fats oxidation	[132]
39.	Cinnamomum verum and Carria aromaticum	Mice	150 mg/kg	4 weeks	diarrhea, vomiting, dizziness	Increase of hepatic glycogenesis, modulate insulin signaling	[133]
40.	Litchi	Rats	100	5 weeks	itching and rash	Reduction of insulin resistance,	[134

	chinesis		mg/kg		on the skin, swelling of the lips and the throat and diarrhea	anti-oxidative effects	]
41.	Ervatania microphylla	Mice	10 mg/kg	8 weeks	constipation, dry mouth, and insomnia	Facilitate differentiation and regeneration of pancreatic beta cell, decrease fibrosis of islet cell and increase level of insulin	[135]
42.	Anoectochilus roxburghii	Mice	100, 300 mg/kg	25 days	hepatotoxicity, reproductive toxicity, pruritus, rash, urticaria	Attribute beta cell repair or regeneration, beta cell survival	[136]
43.	Gymnema sylvestre	Rats	0.84µg/ml	3 weeks	headache, nausea, lightheadedness, shakiness and dizziness	boosts insulin production, encourages islet cell regeneration, and improves glucose uptake	[137]
44.	Carthamus tinctorius (hydroalcoholic extract)	ICR mice	120 mg/kg	6 weeks	bleeding issues such stomach or intestinal ulcers, hemorrhagic illnesses, or clotting abnormalities	Enhance insulin secretion, suppress α-glucosidase activity	[138]
45.	Momordica charantia	Sprague Dawley rats	100 mg/kg		vaginal bleeding, contractions, and other gastrointestinal symptoms	Increase insulin secretion from beta cells, inhibit glucose reabsorption and peripheral glucose in gut, suppression of gluconeogenic enzyme	[139]
46.	Panax ginseng	Mouse	150 mg/kg	12 weeks	gastrointestinal discomfort, euphoria, sleeplessness, headaches, high or low blood pressure, mastalgia, and vaginal bleeding	Reduction in insulin resistance, improve beta cell functions, protect beta cell apoptosis, antioxidant activity by up regulation of glutathione	[140]
47.	Curcuma longa	Mouse	250 µg/ml	2 weeks	stomach upset, nausea, dizziness, or diarrhea	Lower insulin resistance and inhibit α-glycosidase activity	[141]

48.	Zingiber officinale	Mouse	250 mg/kg	4 weeks	belly discomfort, diarrhea, or heartburn, as well as a burning sensation in the mouth or throat	Islet cell protection, increase insulin receptor signalling	[142]
49.	Ribes nigrum	Rats	100, 500 mg/kg	7 days	Headache. Diarrhea. Gas and belching	Decrease blood sugar level, enhance glucose tolerance, inhibition of α-glucosidase and α-amylase acivity, delay carbohydrate digestion and absorption in intestine	[143]
50.	Daucus carota linn.	Rats	250, 500 mg/kg	14 days	kidney damage and nerve problems	Reduce diabetic nephropathy, decrease serum LDL, VH levels	[144]
51.	Boswellia serrate	Mouse	10 mg/kg	21 days	stomach pain, nausea, diarrhea, headache, heartburn, and itching	Increase mRNA, protein expression of PPAR-γ, increase lipoprotein lipase Increase glucose uptake in insuin sensitive cells, increase stimulation of insulin pathways mediators	[145]
52.	Myrtus communis	Rats	25, 50µg/ml		feeling nauseous hypotension, and problems with blood flow	Reduced serum levels of glucose, triglycerides, urine volume, and protein due to -glucosidase inhibitory action	[146]
53.	Postulaca oleracea	Male wistar rats	250 mg/kg	4 weeks	Kidney stones	decreases blood sugar and controls how blood lipids and glucose are metabolized	[147]

Herbs used in diabetes management

For many years, researchers have used plants as a significant resource to create new medications for human illnesses. This section [148] contains just a small percentage of the hundreds of plants that have been studied for diabetes. The many phytochemical qualities of the herbs are also covered in the paragraph that follows, which will aid researchers in determining whether to utilize a certain herb to treat a particular medical condition [149].

There are several methods to minimize the bad effects of diabetes and the difficulties that follow, but herbal formulations are preferred since they are less costly and have less side effects [150] [151]. Approximately 60% of individuals use conventional medications manufactured from medicinal plants. Diabetes is a dangerous condition that has a broad range of effects on individuals globally [152]. It has been shown to be a serious health problem in India, especially in urban areas [153]. There is a list of medicinal plants with recognized antidiabetic characteristics and their favorable impact on herbal diabetes therapies [154]. In the past, medicinal plants have mostly been used to discover new solutions for human health conditions [155]. In the past, several plants have been recommended for the treatment of diabetes. Moreover, several researches have noted that

some plants contain anti-diabetic properties [156]. While there is little proof of their therapeutic utility, these claims are often supported by animal models and even in vitro investigations [157]. The emphasis of the present research was on medicinal herbs, whose hypoglycemic effects have been verified by several preclinical and clinical investigations on diabetic patients [158].

1.1 Acacia arabica (Babool)

In the Unani system of medicine, Babool (Acacia Arabica) is regarded as a plant with medicinal properties for various human body systems. The plant's medicinal properties include the bark, root, gum, leaves, pod, and seeds. Acacia Arabica (Babool) has been studied pharmacologically and phytochemically [159]. The creation of contemporary pharmaceuticals from Acacia arabica for the treatment of different ailments may be stressed, as pharmacologists eagerly anticipate the production of novel medications from natural sources. Numerous phytoconstituents, vital components of this plant's therapeutic significance, are present [160]. The purpose of the research was to determine if mice that had been given alloxan to cause diabetes may benefit from aqueous leaf extracts of Acacia nilotica. The findings demonstrate the anti-diabetic effect of aqueous leaf extracts from A. nilotica. Herbal extracts have been reported to be more efficient when administered intraperitoneally than orally [161].

Additionally, phenols, alkaloids, flavonoids, tannins, and saponins were found in the aqueous leaf extracts of A. nilotica by qualitative and quantitative phytochemical screening [162]. Acacia Arabica extract is utilized as an antioxidant, antihyperlipidemic, and hypoglycemic drug to study its effects on streptozotocin-induced diabetic rats [163]. The results of this investigation indicate that Acacia arabica extract possesses hypoglycemic, hypolipidemic, and antioxidant capabilities; as a result, its potential for treating diabetes in people may be explored [164].

1.2 Aegle marmelosa

In Ayurveda, aegle marmelosa leaf extract is used to cure diabetes. It has been suggested that Aegle marmelosa contains anti-diabetic and antioxidant effects. The findings demonstrate that Aegle marmelosa extract significantly lowered alloxan-induced oxidative stress and reduced blood sugar [165]. The prominent medicinal plant Aegle marmelosa, often known as the bael tree, is used to treat diabetes in the Ayurvedic and Siddha systems of medicine as well as in folk remedies [166]. Additionally, the feasibility of using calluses made from A. marmelosa leaf explants for the treatment of diabetes was investigated [167] in comparison to regular plant material. The research found that the in vitro callus culture of A. marmelosa had the same potential for managing diabetes as the original leaf extract [168].

1.3 Datura stramonium

A folk remedy used in Ethiopia, Datura stramonium Linn, has been demonstrated to have antidiabetic action in an in vitro research [169]. The research also aimed to evaluate hydromethanolic seed extract's anti-diabetic effects in mice. According to the research, Datura stramonium Linn hydromethanolic seed extract demonstrated strong antihyperglycemic and free radical scavenging capabilities [170]. Nature has given us a plethora of phytochemicals that may have an antidiabetic effect. Datura stramonium has traditionally been used to treat diabetes mellitus [171]. The researcher's wants to see whether the plant's hydromethanolic seed extract had any kind of antidiabetic properties in *in vivo* experiments [172]. The study revealed that Datura stramonium hydromethanolic seed extract possessed significant antihyperglycemic and antioxidant activity [173].

1.4 Piper longum (Piper longum)

All diabetic medications, including insulin and oral diabetics, have adverse effects. According to the WHO, it is challenging to identify new antidiabetic natural herbal drugs with minor or no side

effects [174]. In light of this, the goal of the present investigation was to determine if the aqueous root extract of Piper longum (PlrAqe) had any antihyperglycemic or hyperlipidemic effects on diabetic rats (STZ) produced by streptozotocin. The results show that in STZ-induced diabetic rats, plant extract may reduce diabetes complications. [175]. As a result, this species might be considered a potential source for identifying new oral antihyperglycemic agents with the introduction of novel and innovative, transformative technologies such as recombinant DNA [176]. According to the pharmacological profile, the plant has antidiabetic, antihyperlipidemic properties, hepatoprotective, neuroprotective, and antioxidant properties. It is cardioprotective, antibacterial, aphrodisiac relieves respiratory disorders and can also be used as a digestive agent [177].

1.5 Coriandrum sativum

The herb coriander, also known as Coriandrum sativum, has long been used to treat diabetes. The aim of this study was to analyze existing studies on the efficacy of coriander in treating diabetes in animal models using a database. The publications were found using PubMed [178]. It was confirmed that there is a high level of interestin diabetes research. It has also been discovered that approximately 6.92 percent of the articles containing the keyword "Coriandrum sativum" are related to diabetes [179]. It is possible to conclude and suggest that coriander may be appropriate for attempting to lower the plasma glucose level of diabetic animals [180]. To show the phytochemical makeup of a petroleum ether extract of C. sativum (CPE) seeds, we employed chromatographic, spectroscopic, and healthy spectrometric analyses in this work [181]. Finally, using the STZ-NAD model, we were able to correctly predict that the properties of bioactive components CPE would impede the development of DM. Further research on C. sativum is necessary since it has the potential to be used as an adjuvant for anti-diabetic treatment [182].

1.6 Zingiber officinale (Zingiber officinale)

One of the antioxidant supplements from the diet that are being evaluated as possibilities for treating diabetes is ginger (Zingiber officinale). The therapeutic benefits increase insulin sensitivity and shield the body from the negative consequences of diabetes [183]. The results show that ginger has hypoglycemic potential and lowers diabetic complications, thus it should be taken into consideration while treating this condition [184]. The antidiabetic activity of Zingiber officinale aqueous extract against Streptozotocin-induced diabetes in Sprague Dawley rats is the subject of a research. The results show that Zingiber officinale aqueous extract possesses hypoglycemic characteristics [185].

1.7 Cinamomum zeylanicum

An evergreen tree in the Lauraceae family called cinnamon (Cinnamomum zeylanicum) has been picked for generations in Asian nations. Many different ailments may be treated with cinnamon bark [186]. Numerous essential oils and tannins may be found in cinnamon. It possesses strong anti-ulcerogenic, anti-ulcerogenic, antipyretic, anti-diabetic, and antioxidant effects [187]. Administration of cinnamon essential oil dramatically decreased blood glucose levels in alloxan-induced diabetic mice. This effect may have been caused by the reversal of insulin resistance or by an increase in insulin production by mending injured pancreatic -cells [188]. Additionally, flavonoids are known to serve as insulin secretagogues and heal injured -cells in rats given alloxan [189].

1.8 Datura stramonium

A well-known medicinal plant from the Americas, Datura stramonium Linn (Astenagra in Amharic), belongs to the genus Datura and the family Solanaceae [190]. Following diabetes induction, measurements of the diabetic mice's fasting blood glucose levels were made once a week [191]. The seed extract substantially (p0.0l) decreased fasting BGL at dosages of 100 mg/kg, 200 mg/kg, and 400 mg/kg [192]. The hydromethanolic seed extract of Datura stramonium exhibited significant blood glucose-lowering and antioxidant activities. For the bioassay-guided fractionation, isolation, and characterisation of active substances with glucose-lowering activity, more study is required [193] [194].

1.9 Eugenia jambolana

In Indian traditional medicine, E. jambolana is often used to treat a range of illnesses. The kernel, leaves, and septum of E. jambolana, among other components, show antihyperglycemic effects [195]. It has been shown that the ethyl acetate portion of E. jambolana seed has antihyperglycemic activity [196]. The high solubility of bioactive phytomolecules such gallic acid and polyphenolic compounds may be the cause of the antihyperglycemic activity of E. jambolana's ethyl acetate fraction in both short- and long-duration models [197]. The ethyl acetate fraction of E. jambolana seed has strong anti-diabetic effect in experimental model rats at the genetic level [198].

1.10 Trigonella foenumgraecum L.

All diabetic treatments, including oral hypoglycemics and insulin, have the potential to have negative side effects [199]. In accordance with WHO recommendations, it may be difficult to find novel anti-diabetic medications made from medicinal plants that have minimal or no negative effects [200]. In this regard, the goal of the research was to evaluate the effects of Trigonella foenumgraecum L. root aqueous extract (PlrAqe) on hyperlipidemia and hyperglycemia in streptozotocin-induced diabetic rats (STZ) [201]. The results support the hypothesis that the plant extract may control hyperglycemia and the consequences of diabetes in STZ-induced diabetic rats. This plant may thus be considered as a possible source for the creation of innovative oral hypoglycemic drugs with the introduction of fresh and inventive transformative technologies like recombinant DNA [202].

1.11 Linnaeus Ficus religiosa

The religious ficus, Ficus religiosa The peepal tree, commonly known as Linn, is a member of the Moraceae family. In Ayurvedic medicine, its bark is used to cure diabetes [203]. It has antidiabetic qualities due to the presence of phytosterolin in the root bark and -sitosterol-D-glucoside in the stem bark [204]. All of the animals' blood glucose levels were significantly lowered by the three

treatments. In comparison to 25mg/kg, the impact was more prominent at 50 and 100mg/kg. The FRAE also revealed a considerable rise in body weight, liver and skeletal muscle glycogen content, serum insulin, and rats with STZ-induced diabetes [205] [206]. The medication may be tested for the chemical constituent in charge of the action and utilized as an adjuvant in diabetes treatment [207].

1.12 Gymnema sylvestris (Gymnema sylvestris)

Central and peninsular India are home to the important Asclepiadaceae plant known as Gymnema Sylvestre [208]. The plant's extracts are potent natural diabetes medications. One of the plant's most important antidiabetic components is gymnemic acid, which gives the plant its therapeutic usefulness [209]. It possesses powerful anti-diabetic and anti-obesity characteristics, limits glucose absorption, and lowers body weight, according to several research. Gymnema has the potential to repair pancreatic beta-cells, making it a potential medication for the management of diabetes mellitus and its consequences. Gymnemic acids A and B have been shown to have antiviral properties against the influenza virus [210] [211]. A potential utility in avoiding the development of dental plaque has also been researched, however formal trials to support this usage are missing [212].

1.13 Hagenia abyssinica (Hagenia abyssinica)

Hagenia abyssinica (Bruce) J. F. Gmel is a member of the Rosaceae family's monospecific genus Hagenia [213]. It is also known as kosso and African rosewood. H. abyssinica extract ameliorates metabolic abnormalities associated with diabetes and may reduce the risk of hyperglycemia-related complications [214]. Consequently, it appears that the beneficial effects of H. abyssinica on diabetes are due to the synergistic effects of its bioactive compounds, including phenols, triterpenoids, flavonoids, saponins, and anthraquinones [215].

1.14 Momordica charantia L.

Momordica charantia L., also known as bitter gourd, melon, and karela, is an annual ascending plant in the Cucurbitaceae family. As research has progressed, numerous phytochemicals, such as saponins, polysaccharides, triterpenes, proteins, vitamins, minerals, flavonoids, ascorbic acid, and steroids, have been discovered [216]. In addition, antioxidant, hypoglycemic, antitumor, antibacterial, skin care, anthelmintic, neuroprotective, anti-inflammatory, antiviral, immune-modulatory, wound healing promoting, antimutagenic, antiulcer, liver protection, and antiobesity properties have been established [217]. The concentration of the saponin-rich component of Momordica charantia L. stimulated insulin secretion in MIN6 pancreatic cells [218]. The survival of RIN-m5F pancreatic cells treated with high glucose and MC aqueous extract was substantially greater than that of untreated glucotoxicity cells, according to an experiment [219].

1.15 O. sanctum

This plant is predominantly found in tropical and subtropical regions, including India. It is widely employed in the treatment of diabetes due to its hypoglycemic and antihyperlipidemic properties [220]. Glibenclamide plus O. Sanctum was more efficacious than oral hypoglycemic agents alone at reducing fasting and postprandial blood glucose levels in type 2 diabetes patients [221]. Glibenclamide and O. Sanctum decreased Glycosylated Haemoglobin (HBA1c) levels significantly [222]. The acute antidiabetic effects of O. sanctum ethanolic extracts were investigated in rodents with type 1 and type 2 diabetes induced by chemical means [223]. The effects of extracts on glucose absorption, intestinal disaccharide activity, gastrointestinal motility in rats with type 2 diabetes,

glucose uptake, and insulin action in 3T3- L1 cells were evaluated [224]. The extract (1.25 g/kg bw) significantly enhanced oral glucose tolerance and suppressed blood glucose elevation in both normal rats and rats with type 2 diabetes [225].

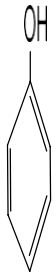
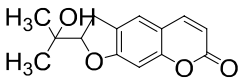
1.16 Piper longum

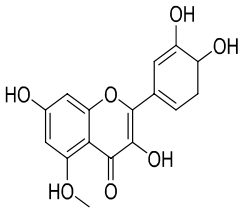
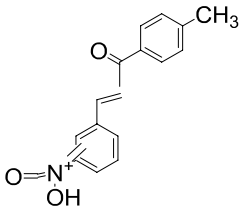
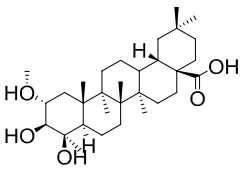
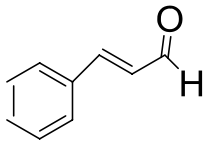
Piper longum has potent hypoglycemic and anti-lipid peroxidative effects in animals with alloxan-induced diabetes [226]. In our research, untreated diabetic rodents had elevated serum levels of urea and creatinine, which are significant indicators of renal impairment [227]. Following PlrAqe treatment, the concentrations of urea and creatinine in diabetic rodents were significantly reduced. PlrAqe appears to safeguard the kidneys of diabetic rodents [228] [229].

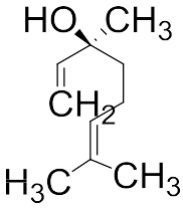
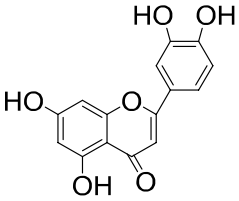
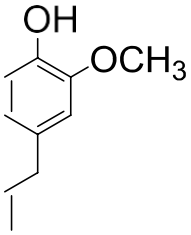
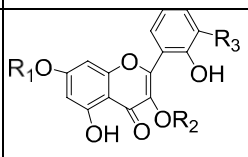
1.17 Zingiber officinale (Zingiber officinale)

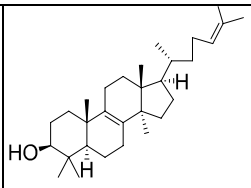
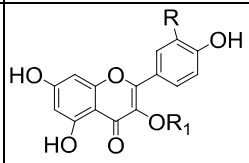
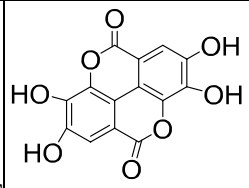
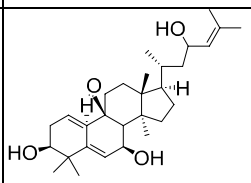
Ginger (Zingiber officinale, Zingiberaceae) is among the most popular species in the world [230]. It has a lengthy history of use as a herbal medicine to treat a variety of maladies, including vertigo, pain, dyspepsia, and cold-induced syndromes, dating back to its Southeast Asian origins and subsequent dissemination to Europe [231]. Recent research indicates that ginger has anti-cancer, anticoagulant, anti-inflammatory, and analgesic properties [232]. Maintaining normal blood glucose levels is dependent on the amount of insulin present in the blood. Ginger increases serum insulin levels, enhances insulin sensitivity, and decreases blood glucose levels during fasting [233]. Table 4 provides a concise summary of the phytochemical properties, origin, bioactive components, structure, and effects of various herbal medications. The phytochemical properties of the herbs are also listed, allowing researchers to determine which herb should be used to treat a particular medical condition.

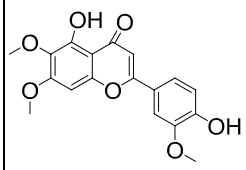
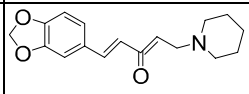
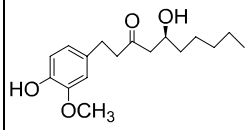
Table 4:- Effects of Herbal Drugs, their phytoconstituents, source, chemical structure and their Pharmacological activity listed below in table

Sr. No	**Name (Herbal Medicine)**	**Synonyms**	**Source (Part Use)**	**Bioactive Components**	**Structures**	**Animal models**	**Effect**	**Reference**
1.	Acacia arabica (AA)	Babool, Unani Tibbi	Bark, Roots, gums, leaves, pods, seeds	Phenols, alkaloids, flavonoids, Tannins, Saponins		Streptozocin induced diabetic rats	Antidiabetic, antihyperlipidaemic, antioxidants	[234] [235]
2.	Aegle marmelosa (AM)	Bael Tree	Fruit pulp, leaf	Alkaloids, carbohydrates, glycosides, flavonoids, tannins, Coumarin, sterol, triterpenes		Alloxan induced diabetic rats	Antioxidants, antibacterial, antifungal, antiproliferative against human tumor cell line K562, analgesic, anti-inflammatory, anti- arthritis, hepatoprotective, cytoprotective, antidiarrhoeal	[236] [237]

3.	Allium cepa (AC)	Bulbous plant	Dried bulb	Quercitin-1, cycloalliin-2, s-methyl- L-cysteine -		Alloxan induced diabetic Rattus norvegicus	Hypoglycemia, hypolipidaemic	[238]
4.	Aloe ver a (AV)	Aloe barbedensis	leaves	Phenolic compound, flavanoids		STZ induced diabetic rats	Hypolipidaemia, improve ce llular integrity, CVD, kidney failure	[239]
5.	Terminalia arjuna (TA)	Arjuna Tree	Stem, Bark	Arjunic acid, Terminic acid, Glycosides, Tannins, Saponins, flavones		Alloxan induced diabetic rats	Antioxidant status in liver and kidneys, Lipid lowering	[240]
6.	Cinnamonum zeylanicum (CZ)	Raspberry	Inner bark	Coumarin		Streptozocin induced diabetics	Antioxidants, lipid-lowering, Blood glucose lowering	[241]

7.	Coriandrum sativum (CS)	Chinese parsley cilantro	Fresh leaves	Phenolic compou nds		Alloxan induced diabetes in experime ntal animals	Antidiabet ic, hepatoprot ective activity, Antiperoxi dative, hypolipida emic	[242]
8.	Datura stramonium (DS)	Jimson weed, Thorn apple	Seed extract	Flavanoids, anthraq uinone glycosid es, saponin s, Terpeno ids, tannins		STZ induced diabetes in mice	Antioxida nt potential, hypoglyce mic effect	[243]
9.	Eugenia jambolana [EJ]	Syzygiu m jambola na, Indian blackber ry, Jamun	Seed extract, Fruit pulp	-		STZ induced diabetic male albino rats	Antihyper glycaemic activity, antioxidan t	[244]
10.	Trigonella foenumgraec um L (TFG)	Fenugre ek plant	Seed powder	Flavano ids, stilbene s glycosid es		High-fat diet-fed and STZ-induced mice with type-2 diabetes	Hypolipid aemic, antidiabeti cs	[245]

11.	Ficus religiosa Linn (FR)	Pippala tree, Ashwatha tree, Sacred fig	Leaves, fruits	s-allyl cysteine sulphoxide, l-chiro- inositol		Experimentally induced type 2 diabetic rats	Antidiabetics, anxiolytics, antioxidants	[246]
12.	Gymnema sylvestris R.Br. (GS)	Periplocaof woods, Gurmar	leaves	Gymnemic acid		STZ induced diabetes in Wistar rats	Antioxidants, hypolipidaemic, weight control, anti-obesity	[247]
13.	Hagenia abyssinica (HA)	African redwood	leaves	Gymnemic acid		STZ induced diabetes in Wistar rats	Antioxidants, anti-hyperlipidemias, antioxidants	[248]
14.	Momordica charantia L (MC)	Bitter gourd, Bitter melon	Fresh fruit juice	momordicin, Charantin, chorine, cryptoxanthin, cucurbitin		Alloxan monohydrate induced type- 1 diabetes in albino rats	Antidiabetic, anticholesterolemic effects	[249]

15.	Ocimum sanctum (OS)	Ocimum tenuiflorum, Holy basil or tulsi	leaves	Cirsilineol, cirsimaritin, isothymosin		STZ induced diabetes in Wistar rats	Antidiabetic, antioxidative	[250]
16.	Piper longum (PL)	Long(black)pepper, Indian long pepper	Roots, aqueous extract	Piperine		STZ induced diabetes in Wistar rats	Antidiabetic, antihyperlipidaemic, CVD, hepatic & renal disorders	[251]
17.	Zingiber officinale (ZO)	Amomum zingiberL	Fresh & dried rhizome	Gingerol		STZ induced type-1 diabetic rats	Lowers glucose & lipids levels, antitumor, antimicrobial	[252]

Current Ongoing Clinical Trials

Ahead the FDA approves a novel drug or medical device for use by the general public [253], it is subjected to extensive testing in clinical trials on patients. Clinical trials are crucial to the development of novel diabetes and other disease treatments [254]. There have been very few clinical trials reported for the treatment of diabetes mellitus [255]. This could be attributed to a lack of complete understanding of the disease's underlying mechanism, which prevent the patients from receiving complete relief [256].

As this metabolic disorder rapidly progressing among the urban diabetic populations therefore maximum therapeutic alternatives approximately 60 have been approved by the FDA [257]. From 2015 through 2020, 375 clinical studies including about 100 antidiabetic drugs are registered. Ten of these treatments already have commercial authorization from regulatory bodies in other countries and might possibly apply for FDA approval [258]. One-fourth of these drugs are in phase III studies. Additionally clinical trials on 100 drugs are carried on beyond insulin, metformin and other drug combinations like sitagliptins etc [259]. DPP-4 inhiboitors and SGLT-2 inhibitors have gained a special importance in pharmaceutical market which are less expensive alternatives in developing

countries [260]. Since the FDA authorized human insulin (Humulin) in 1982, 59 different antidiabetic medications have been approved [261]. The authorized medications include 23 original pharmacological combinations of two or more antidiabetic medicines and 36 novel molecular entities as monotherapies [262]. A major clinical development is in process for diabetes management which is in phase III trials.

Clinical trial is a very important step to ensure the safety and effective use of a medicine among human beings. It needs the completion and analysis of safe, effective results from phase I through phase III by USFDA regulatory agencies [263]. US Food and Drug Administration's authorize 100 new medicines every year [264].

Some of the completed or ongoing trials on antidiabetic herbs (DPP-4 Inhibitors) are listed below in table no. 05 with their complete profile.

Table 05: Clinical Trial of Herbal Drugs in various Phases for Diabetes mellitus Metabolic Disorder

Sr. No.	Herbal Drug	Sample size	Duration of Study	Purpose	Phase	Status	Design	Study Year	Reference
1.	American ginseng	770	≥ 30 days	Treatment	Phase 2	Completed	R	3 July, 2013	[265]
2.	*Cinnamon zeylenicum*	25	12 weeks	Treatment	Phase 3	completed	PC, R	21 Feb, 2016	[266]
3.	*Trigonella foenum graecum*	154	90 days	Treatment	Phase 1	completed	R	11 oct, 2016	[267]
4.	*Allium sativum L.*	110	5 weeks	Treatment	Phase 4	completed	R	7 July, 2020	[268]
5.	*Bitter melon*	95	10 weeks	Treatment	Phase 2	completed	R	26 jan, 2015	[269]
6.	*Azadirachta indica*	80	12 weeks	Treatment	Phase 1	completed	R, DB, PC	17 Nov, 2020	[270]
7.	*Onion cepa*	28	8 weeks	Treatment	Phase 1	completed	R	3 june, 2016	[271]
8.	Plantago psyllium	30	40 days	Treatment	Phase 2	completed	R	2 may, 2017	[272]
9.	Siberian ginseng	15	5 days	Treatment	Phase 2	completed	R	Sep, 2018	[273]
10.	Tinospora cardifolia	60	15 days	Treatment	Phase 3	completed	R	1 Feb, 2016	[274]
11.	Urtica diocia	46	3 months	Treatment	Phase 1	completed	R, DB, PC	2013	[275]
12.	Nigella sativa	57	3 months	Treatment	Phase 1	completed	PC	23 Feb, 2015	[276]
13.	Coccinia grandis	79	3 months	Treatment	Phase 3	Recruiting	R, DB, PC	Jan, 2021	[277]

14.	Cinnamonum verum & Cassia aromaticum	997	3 months	Treatment	Phase 2	completed	R	Juna, 2020	[278]
15.	Silybum marianum	60	90 days	Treatment	Phase 4	completed	R, DB, PC	6 Feb, 2017	[279]
16.	Carthamus tinctorius	67	2 weeks	Treatment	Phase 3	Recruiting	R, DB, PC	10 Jan, 2022	[280]
17.	Berberis vulgaris	75	8 weeks	Treatment	Phase 3	Recruiting	R	5 July, 2021	[281]
18.	Momordica charantia	23	8 weeks	Treatment	Phase 2	completed	R, DB, PC	15 Oct, 2014	[282]
19.	Ilex paraguariensis	973	16 weeks	Treatment	Phase 2	completed	R	June, 2019	[283]
20.	Boswellia serrata	71	12 weeks	Treatment	Phase 4	completed	R	March, 2014	[284]
21.	Postulaca oleracea	32	12 weeks	Treatment	Phase 3	completed	R, DB, PC	8 Feb, 2016	[285]

Acroniums: CO; Cross-Over, DB; Double-Blind, PC; Placebo-controlled, NR; Non-Randomized, R; Randomized Requirements for a Drug Delivery System.

There are lots of methodologies through which a drug is able to produce its maximum efficacy on target tissue with in an optimum concentration range [286]. Below or above optimum concentration will not be able to produce its therapeutic effect at all. Different drug carriers like soluble polymers, micro particles, synthetic polymers, microcapsules, micelles, lipoproteins and liposomes are used to target the drug loaded system at the site of interest [287]. Multiple mechanisms, including diffusion through the carrier matrix, diffusion through the carrier wall, and a combined diffusion or attrition process, are involved in the drug's release [288]. Currently, medication targeting systems are being developed to decrease medication loss and degradation, prevent adverse side effects, and increase drug bioavailability [289].

Using nanoscale materials as diagnostic instruments or to transport therapeutic medications to specific targeted regions in a controlled manner is the field of nano delivery systems [290], which is still immature but expanding rapidly. By delivering targeted and site-specific medications, nanotechnology has a number of benefits for the treatment of chronic human diseases. Recently, numerous noteworthy applications of nanomedicine have emerged [291][292]. Microparticles are defined as having dimensions measured in micrometers (typically 1 to 1000 m) and possessing distinct structural characteristics, such as low bioavailability, poor water solubility, and lack of blood-brain barrier (BBB) permeability. Recent advances in the understanding of drug pharmacokinetic and pharmacodynamic behavior have led to the creation of novel drug delivery systems, which are new systems that adopt a more logical approach to the design of the ideal drug

delivery system [293] [294].

In controlled release drug delivery systems, the drug is released at a predetermined rate based on the intended therapeutic concentration and the pharmacokinetic properties of the drug. Nanoparticles of polymer transport insulin [295]. These biodegradable polymers containing a polymeric insulin matrix are encapsulated in a membrane containing nanoholes that permit glucose oxidation [296]. From implantable electronic devices to single polymer chains, drug delivery systems must be biocompatible with both body processes and the substance to be delivered. DDS modify the biodistribution and pharmacokinetics of the associated drug: that is, the time-dependent proportion of the administered dose in the various organs of the body [297].

Niosomes have been used as a system to increase the bioavailability of drugs with limited aqueous solubility and to make active drugs available at the site of action for a prolonged period of time [298]. When sodium deoxycholate was used as a surfactant, it was discovered that insulin-loaded niosomes were stable in the presence of proteolytic enzymes of the gastrointestinal tract [299]. In order to make these systems available on a global scale, it is necessary to consider their safety profile, pharmacology, environmental effects during formulation, and prospective effects on health care [300].

Moreover, the developed formulations must be comprehensively optimised in a variety of animal species in order to reduce the occurrences of clinical failure in a variety of human subjects [301]. The development of robust glucose-sensitive nanoparticles as well as integrated glucose-sensing and insulin-delivering nanoformulations [302] could be investigated as an additional therapeutic possibility. These ongoing advancements in nanotechnology offer optimism for the development of an effective anti-diabetic treatment in the near future [303]. In addition to reducing the need for repeated administration to combat noncompliance, novel drug delivery methods contribute to an increase in therapeutic value by reducing toxicity and increasing bioavailability [304].

Phytonanotherapy in the Management of Diabetes

The planet is home to a wide variety of native medicinal flora. The World Health Organization (WHO) prioritizes healthcare that is environmentally benign, non-hazardous, and cost-effective, such as the use of medicinal plants to treat a variety of diseases [305]. Unique to phytonanotherapy, the synergistic properties of plant and metal NPs offer clinically bioequivalent effects to many synthetic medications with minimal adverse effects [306]. This could provide an effective alternative treatment for chronic diseases, circumventing the disadvantages of synthetic monotherapy and permitting medicinal plant therapy to coexist with existing synthetic treatments [307]. The pharmaceutical formulation consists of nanoparticles of solid lipids. Particulate systems, such as nanoparticles, are utilized as a physical method for modifying and enhancing the pharmacokinetic and pharmacodynamic properties of diverse drug molecules [308]. It is possible to create nanoparticles through chemical, physical, and biological processes [309]. Although the chemical method of synthesis requires little time to produce a large number of nanoparticles, capping agents are required to stabilize the nanoparticles' size [310].

Phytotherapeutics require a systematic strategy to providing the components in a sustained way in order to maximise patient compliance and minimise repetitive dosing [311]. This can be done by creating innovative drug delivery systems (NDDSs) for herbal components [312]. NDDSs not only lessen the need for repeated administration to overcome noncompliance, but they also

contribute to therapeutic efficacy [313]. Via reducing toxicity and improving bioavailability Nanoparticles (NPs) are loaded with therapeutic substances for delivery to target cells. In addition, metal nanoparticles appear to be less toxic than mineral compounds and serve multiple functions within the body [314].

Metallic nanoparticles: Nanotechnology is creating nanoparticles of copious metal oxides like gold, silver, zinc, magnesium, titanium, etc., with sizes ranging from 1 to 100 nm. Because of their non-invasiveness and site-specificity, the use of metallic nanoparticles is becoming the most appealing and promising phytonanotherapy option [315]. Metallic nanoparticles have significant potential for improving diabetes care because they allow for the oraldelivery of insulin to a specific site, increasing its bioavailability and pharmacological efficacy [316]. A metallic nanoparticle's optical properties are primarily determined by its surface plasmon resonance, where plasma on refers to the collective oscillation of free electrons within the metallic nanoparticle. Physical, chemical, and biological methods are used to produce nanoparticles [317] [318].

Nanoparticles of zinc oxide

Anti-diabetic, antibacterial, anticancer, antifungal, drug delivery, and anti-inflammatory characteristics are among the many biological uses for ZnO NPs. Zinc is necessary for insulin production, secretion, and storage and is crucial for insulin structure [319].

Magnesium (Mg)

Magnesium (Mg) is an essential ion in glucose regulation. Mg is also implicated in several enzymes involved in phosphorylation and glucose metabolism, and it may potentially play a role in insulin production [320].

Cerium oxide nanoparticles

In the periodic table, the lanthanide series contains numerous rare earth elements, including Ce. CeO2 nanoparticles have demonstrated promise as a potential treatment for oxidative diseases, surpassing several existing treatments for brain injury [321].

Copper ions

Copper is a transition metal that participates in numerous biological reactions. Cu NPs possess exceptional antioxidative properties and inhibit alpha-amylase and alpha-glucosidase in animals.

Moreover, Cu NPs substantially reduced diabetics' functional cardiovascular abnormalities. These NPs may increase nitric oxide bioavailability and reduce oxidative stress in the vascular endothelium [322].

Selenium nanoparticles (NPs)

Selenium is a trace element found in nearly all plant life. A selenium deficiency in the body has been linked to numerous diseases, including diabetes. Se NPs' antioxidant properties are also less hazardous than selenium itself [323]. Due to their ability to scavenge various peroxides, protect lipids and cellular macromolecules from oxidative membrane damage, and increase glutathione peroxidase and thioredoxine reductase levels, Se nanoparticles possess antioxidant properties [324].

Silver nanoparticles

In numerous medical, food storage, textile coating, and environmental applications, AgNPs have been utilized as anti-bacterial agents. AgNPs have been utilized as antibacterial agents in a variety of applications spanning from the disinfection of medical devices and household appliances to water treatment [325]. AgNPs exhibited potent antibacterial activity against Escherichia coli.

Synthesis of silver nanoparticles and their applications [326] [327].

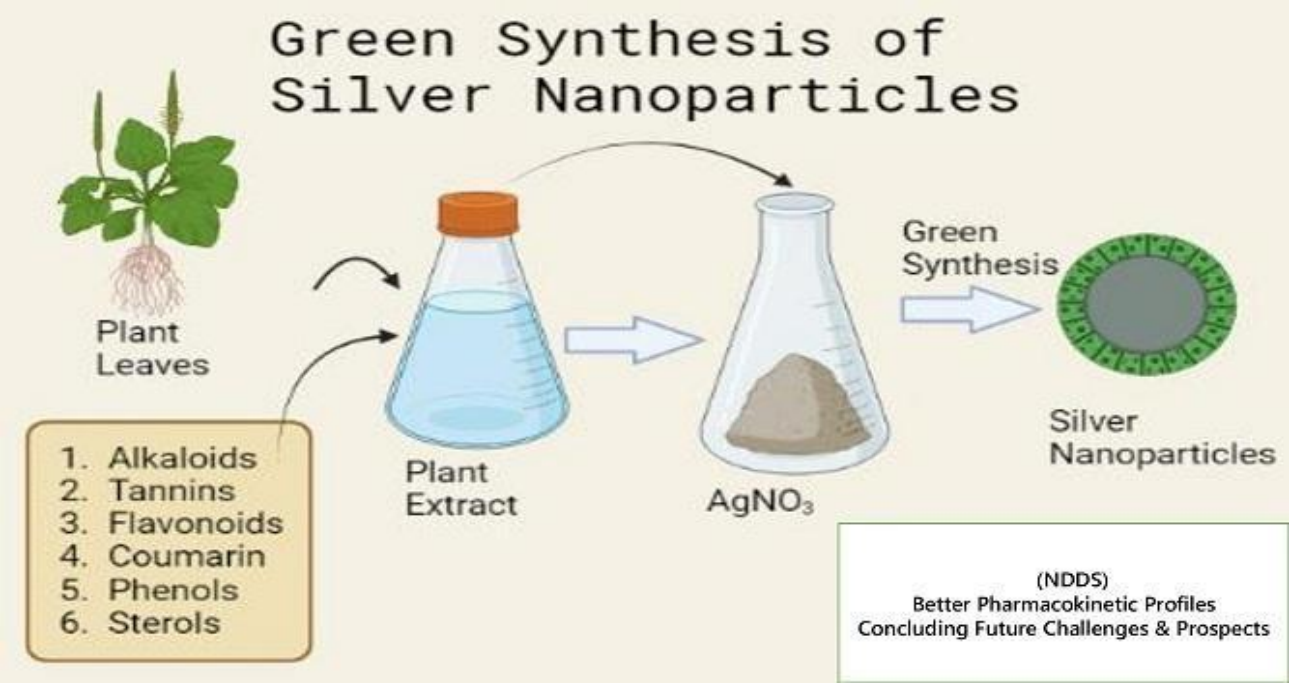


Figure -7: Emergence of Silver Nanoparticles using $AgNO_3$ as reducing Agent.

Silver Nanoparticles of herbal extract utilize various AgNO3 concentrations; the samples' visual appearance changed shortly after incorporation of the plant extract, indicating that a reduction reaction occurred. Initially, the reacting mixture is a faintly yellowish liquid that eventually turns dark reddish brown. As the reaction continued, the solutions changed color, becoming orange, red, and brown. This is a significant indicator of the origin or development of silver nanoparticles. In addition, the formulation was confirmed using UV spectroscopy at 420 nm.

Pharmacokinetic parameters for herbal drugs & their nanoparticles:- In numerous in vitro and in vivo models, the pharmacokinetic and pharmacodynamic properties of anti-diabetic medications were evaluated using innovative drug delivery systems (NDDS) [328]. The NDDS technology, which is simple, fast, cost-effective, and environmentally favorable, improves preclinical output. It provides enhanced in vitro drug release, enhanced drug efficacy, enhanced glucose uptake, enhanced insulin sensitivity, enhanced collagen fiber density, enhanced glucokinase enzyme activity, and enhanced GLUT-4 activity [329].

Moreover, it increases the levels of TNF, IL-4, IL-6, IL-10, GK, IRA, GLUT-2, SH, SOD, VEGF, and TGF while decreasing the levels of IL-1b, -glucosidase, PKLR, MDA, MAPK, ROS, and renal fibrosis. Compared to other dosage formulations, it improves therapeutic efficacy, solubility, stability, and bioavailability [330]. Additionally, it reduces body weight and glucose levels. Phytonanotherapy reduces hyperglycemia-induced apoptosis, oxidative stress, DNA damage, and impaired glucose uptake in L6 skeletal muscle cells more effectively and with a lower dose than other treatments [331] [332]. The many herbal drugs In Table 6, which summarizes nanoparticle formulations, various NDDS and in vitro results are briefly discussed together with phytoconstituents of the plant.

Table No.- 06 Pharmacokinetic Parameters of Novel Herbal Drug Nanoparticles Formulation

Sr. No.	**Plants Used**	**Phytoconstituents**	**NDDS**	**Outcome**	**References**
1.	Ocimum basilicum, Ocimum Pharmacokinetic parameters for herbal drugs & their nanoparticles sanctum	Alpha-pinene, beta- myrcene, 4-Hexen- 1- ol acetate	AgNPs	Extract AgNPs shows 79- 89% inhibition for in vitro α-glycosidase whereas 49-66% inhibition ofExtract	[333]
2.	Aloe vera	Aloin	Aloe loaded chitosan NP	Aloe loaded NP shows maximum in vitro drug release during cancer treatment to improve effectiveness and reduce adverse effects.	[334]
3.	Taxus brevifolia	Taxanes	Liposomes	Inclusion into liposomes led to decreased tissue toxicity & increased efficacy of drug	[335]
4.	Leonotis leonurus	Labdane	Nanostructured lipidCarrier	↑insulin sensitivity ↑Glucose uptake	[336]
5.	Dendrocalamu s hamilton	Cellulose, lignin	Nanobiocomposite (cellulose nanocrystals and AgNPs)	↓TNFα ↓IL6 ↑PDGF ↑FGF ↑VEGF ↑ TGFβ ↑Fiber density of	[337]

				collagen	
6.	Pouteria sapota	Allene carotenoid	Synthesized green Ag nanoparticle	↓blood glucose ↑serum insulin ↓ alpha amylase ↑glucose uptake	[338]
7.	Stevia rebaudiana	Steviol glycoside	Chitosan nanoparticles	↓FBS ↓HbA1c ↑SOD ↑ CAT ↑GSH	[339]
8.	Syzygium cumini	Delphinidin, cyaniding	PLGA nano-encapsulated	↑consumption of glucose ↑glucokinase ↑GLUT4 ↓ plasma glucose, ↓NF-κB ↓ iNOS	[340]
9.	Syzygium cumini	Delphinidin, cyaniding	Green synthesized Ag nanoparticle	↓cell size ↓lipid peroxidation	[341]
10.	Eysenhardtia	Dihydroxychalcone	Green synthesized	↓blood glucose ↓insulin	[342]
11.	Polystachya	Linarin	Ag nanoparticle	secretion ↓TC	[343]
12.	Musa paradisiaca	Myrcene	Green synthesized Ag nanoparticle	↓blood glucose ↓HbA1c ↑insulin ↑glycogen	[344]
13.	Cassia fistula	Oxalic acid, oxyanthroquinone	Green synthesized Au nanoparticle	↓Blood glucose ↓HbA1c ↓ LDL-C ↑ HDL-C	[345]
14.	Gymnema sylvestre	Gymnemic acid	Green synthesized Au nanoparticle	↓ TNFα ↓IL6 ↓CRP ↓HbA1c ↓ LDL-C ↑HDL-C	[346]
15.	Sambucus nigra	Anthocyanin, cyanin	Green synthesized Au nanoparticle	↓ blood glucose ↓MDA ↓ COX2	[347]
16.	Marsilea quadrifolia	Trans-Farnesol	Green synthesized Au nanoparticle	↑ glucose utilization	[348]
17.	Chamaecostus cuspidatus	α-tocopherol	Green synthesized Au nanoparticle	↓Blood glucose ↑body weight ↓super oxide anion ↓lipid peroxidation	[349]
18.	Stevia rebaudiana	stevioside	TiO2 nanomaterial	↓blood sugars ↑insulin ↓HbA1c ↓TC ↓TAG	[350]

19.	Moringa oleifera	Gallic acid	Green synthesized ZnO nanoparticle	↓ α-amylase ↓α-glucosidase	[351]
20.	Tamarindus indica	Tartaric acid	Green synthesized ZnO nanoparticle	↓ α-amylase ↓α-glucosidase.	[352]
21.	Hibiscus subdariffa	Allo-hydroxy citric acid lactone	Green synthesized ZnO nanoparticle	↓TNF-α ↓IL-1b ↓IL- 6 ↑ IL-4 ↑ IL-10	[353]
22.	Copaifera sp.	Copaiba oil	Nano encapsulated	↑SH ↑Gpx ↑SOD ↑Nfr2 ↓RV hypertrophy	[354]
23.	Bambusa bambos	Cellulose, lignin	Nanobiocomposite (cellulose nanocrystals and AgNPs)	↓TNFα ↓IL6 ↑PDGF ↑FGF ↑VEGF ↑ TGFβ ↑Fiber density of collagen	[355]
24.	Argyreia nervosa	Aryl esters, scopoletin	Green synthesized Ag nanoparticle	↓α-amylase ↓ α-glucosidase	[356]
25.	Cinnamomum litseifolium	Cinnamaldehyde, cinnamic acid	Nanoemulsion	↓ α-amylase ↓α- glucosidase	[357]
26.	Costus speciosus	costunolide	PLGA nano-encapsulated	glucose in the blood, insulin (I&II), and GLUT4 GLUT2	[358]
27.	Ficus religiosa	lanosterol	Solid lipid nanoparticle	↓ blood glucose ↑insulin level	[359]
28.	Momordica charantia	charantin	Nanoemulsion	↑SOD, ↑GPx, ↓MDA	[360]
29.	Zingiber officinale	gingerols	Green synthesized AgNPs	↓ blood sugar	[361]
30.	Silybum marianum	silibinin	Synthesized green ZnO nanoparticle	↓FBS, TC, TAG ↑insulin, HDL-C	[362]
31.	The Nasturtium officinale	myristicin	Green nanoparticles of ZnO synthesized	↓FBS, TC, TAG, insulin, HDL-C, and TAG	[363]
32.	Punica granatum	Oleanolic acid	Green synthesized Au nanoparticle	↓MAPK/NF-κB/STAT3 ↓ RAGENOX-4/p47phox ↓ROS ↑Nrf2 ↓renal fibrosis	[364]

33.	Morus alba	prenylflavin	Synthesized green Ag nanoparticle	↓deterioration in retinal cell layer ↓ Aluminum and carbohydrates	[365]
34.	Smilax glabra	smiglabrone	Green synthesized Au nanoparticle	↓TNFα and IL-β ↓leptin ↑adiponectin ↓body mass index and blood glucose levels	[366]
35.	Curcuma longa	curcumin	Curcumin-self-nanophospholipid dispersions	enhance therapeutic effectiveness, solubility, stability, and bioavailability	[367]
36.	Vaccinium macrocarpon	Resveratrol	lipid nanocarriers	enhanced bioavailability, targeted targeting, advanced therapeutic effectiveness, and improved patient compliance	[368]
37.	Matricaria chamomilla	Naringenin	Self-nanoemulsified naringenin	enhance medication absorption, release, and oral bioavailability	[369]
38.	Scutellaria baicalensis	Baicallin	Baicalin- entrapped nanoliposome	increased biodistribution and oral bioavailability	[370]
39.	Reseda luteola	Luteolin	Solid lipid nanoparticles containing luteolin	Enhance solubility, biological half- life and bioavailability	[371]
40.	Mangifera indica	Mangiferin	Self-assembled phospholipidic nanomicelles containing mangiferin Solid lipid nanoparticles containing luteolin	improve the biopharmaceutical attributes	[372]
	Rheum		Emodin-loaded	improve oral	

41.	officinale	Emodin	nanoemulsion	bioavailability	[373]
42.	Rosemarinus offficinalis	Rosmarinic acid	Rosmarinic acid-chitosan nanoparticles	high heat stability, in vitro release, and effective antioxidant action	[374]
43.	European barberry	Berberine	Berberine-assembled solid lipid nanoparticles	improve berberine's oral bioavailability, stability, and anti-diabetic activity over the free medication	[375]
44.	Centella asiatica	Asiatic acid	Nanostructured lipid carriers containing PEGylated asiatic Acid	increased small intestine penetration and transport capacity	[376]
45.	Glycyrrhiza glabra	Glycyrrhizin	Chitosan-gum arabic nanoparticles assembled with glycyrrhizin	increased bioavailability and long-term release	[377]
46.	Prunus mahaleb	α-Eleostearic Acid	enriched with -Eleostearic acid nanoemulsion	Improved formulation for the treatment of diabetes and toxicosis.	[378]
47.	Scutellaria barbata	Scutellarin	Scutellarin-loaded amphiphilic	increased bioavailability and long-term release	[379]
48.	Silybum marianum	Silymarin	Silymarin-loaded Soluplus-TPGS nanomicelles	Improvements have been made to water solubility, biological stability, P-gp inhibition, gastrointestinal absorption, and cellular uptake.	[380]
49	Camelia sinesis	Catechins	Chitosan nanoparticles with catechin grafting	Better antioxidant capacity than native catechins	[381]
				ameliorate hyperglycemia-induced apoptosis,	

50.	Rasp berries	Pelargonidin	Pelargonidin-PLGA nanoparticles	oxidative stress, DNA damage, and glucose consumption impairment more effectively and at a lower dosage than natural pelargonidin	[382]
51.	Nigella sativa	Thymoquinone	Thymoquinone-loaded gum rosin nanocapsules	cure hyperglycemia, dyslipidemia, and haemoglobin glycosylation more effectively at a considerably lower dose	[383]
52.	Bamboo Tree	Ferulic acid	Nanoparticles of ferulic acid-chitosan	Excellent therapeutic efficacy in lowering blood glucose levels and	[384]
53.	Terminalia arjuna	Arjunic acid	Au NPs	Economically possible may be used in controlling human and agricultural pathogens.	[385]
54.	Curcuma longa	curcumin	sodiumalginate-gum arabic nanoparticles	Good therapeutic potential for the prevention and treatment of solid malignancies, including hepatic, breast, cervical, and cutaneous cancers.	[386]

Conclusions and Prospectives

DPP-4 inhibitors are superior GLP-1 receptor-based therapies; they reduce gastric emptying and food intake, increase glucose-dependent insulin secretion, and suppress glucagon post-meal release. They increase endogenous GLP-1 concentrations without increasing the risk of hypoglycemia,

which stimulates insulin release and inhibits glucagon secretion [388]. They have a range of 0.5 to 1.0% HbA1c effectiveness potential, and their safety profile is very good. DPP-4 inhibitors are generally safe, successful in T2DM patients, and we anticipate that these will be able to assist patients in achieving their glycemic objectives in a supportive therapy environment [389] [390].

The therapeutic molecule made from herbal plants is effective in treating diabetes and other vascular problems. For its therapeutic purpose, these phytochemicals are more biocompatible than other synthetic compounds [391]. However, they have super biopharmaceutical and pharmacokinetic characteristics, which limit their therapeutic relevance. To solve this issue and increase treatment efficacy and patient compliance, a number of pharmacological initiatives have been considered. Nanotechnology has been identified as the most effective method to address this issue [392].

With the breadth of numerous applications, nanoscience and nanotechnology have advanced quickly in recent years. Metallic nanoparticles have a number of advantages in clinical practise, including superior biocompatibility and stability, low operating and capital costs, and minimal environmental impact [393]. The development of metallic nanoparticles with antioxidant properties appears to be an especially promising therapeutic option because it may allow for highly targeted or localised therapy [394]. Site-directed sustained delivery with enhanced curative potential, patient compliance, and the absence of undesirable toxic side effects and hypersensitivity reactions are crucial characteristics of herbal drugs [395]. The unique advantages of nano antioxidants for clinical application from the fact are that they can be made larger than the cutoff size for kidney filtration (10 nm), extending the circulation period in comparison to small molecules [396] [397]. There is a need to demonstrate increased bioavailability, target specificity, and the utilisation of various aspects of nanotechnology. Not only synthesised herbal-mediated metal nanoparticles biodegradable, biocompatible, and non-toxic properties, but they also have a greater capacity to penetrate biological cell membranes and act more rapidly, resulting in increased bioavailability as an alternative herbal treatment for diabetes [398] [399].

Summary

In summary, nanoparticle formulations of plant-derived herbal medicinal compounds offer improved pharmacological and biopharmaceutical profiles, which remove all related barriers to provide the greatest therapeutic outcome [400]. This study focuses on the preclinically and clinically successful herbal anti-diabetic nanoscale formulations that use mechanisms, such as DPP-4 inhibition, to manage diabetes and its associated problems. In order to entirely eradicate this ailment, researchers are advised to continue their study on this subject.

ABBREVIATIONS

DPP-4: Dipeptidyl peptidase-4

TGF: Transforming Growth Factor

CeO: Celenium Oxide
NDDS: Novel Drug Delivery System
ZnO: Zinc Oxide
AgNP: Nanoparticles
ROS: Reactive oxygen species
FBS:Fasting blood sugar
HDL:High density lipoprotein
SOD:Superoxide Dismutase
GP: Glycoproteins
MDA:MassDrug Administeration
GLUT:Glucose Transporter
PDGF:Platelet DerivedGrowth Factor
FGF:Fibroblast Growth Factor
VEGF:VascularEndothelialGrowth Factor
LDL:Low Density Lipoprotein
TC:Total Cholesterol
TAG:Tri Acyl Glycerol
DDS:Drug Delivery System
BBB:Blood Brain Barrier
THC:Tetra Hydro Cannabinol
CBD:Cannabidiol
EGCG:EpiGalloCatechin-3-gallate
PBT2:Polybutylene Terephthalate
SD-809: Tablet for Chorea disease
FDA:Food & Drug Administeration
STZ: Streptozocin
WHO: World Health Organization
CPE: Petroleum Extract of Ether
Inos: Inducible nitricoxide synthase
NrF-2: Nuclear factor erythroid 2–related factor 2
FBS: Fasting Blood Sugar
CAT: Anti-immunotoxin cell
TGF: Transforming growth factor
NDDS: Novel Drug Delivery System
COX-2: Carboxylase enzyme
STAT: Instantly
PLGA:Poly lactic co-glycollic acid
DNA:Deoxy ribonucleic acid
TNF-α:Tumour Necrosis Factor
IL:Inter Leukin
MAPK:Mitogen activated Protein Kinase
NF: Nuclear Factor kappa B
HOMA-IR: NMR: Homeostatic Model Assessment of insulin resistance
PPAR-γ: Peroxisome proliferator activated receptor
URT1: Upper respiratory track -1
TNFR2: Tumor necrosis factor receptor
TG:Tri Glyceride
TC:Total Cholesterol
LL:Lipoprotein-lipase
CVD:Cardio Vascular Disease
HBA1c: Haemoglobin A1c
DM:Diabetes mellitus
MDA:Mass Drug administeration
CAT:Computerized Axial Tomography
CPE:Continuing Pharmacy Education
NAD:Nicotinamide Adenine Dinucleotide
GLP:Glucagon Like Peptidase
PABA:Para Amino Benzoic Acid
DHF:Design History File
T2DM:Type-2 Diabetes mellitus
LPO:Lipid peroxidation

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