IJPSR (2020), Volume 11, Issue 9 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 December 2019; received in revised form, 24 March 2020; accepted, 26 March 2020; published 01 September 2020

EFFICACY AND MECHANISM OF ACTION OF *MORINGA OLEIFERA* IN DIABETES

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Keywords:

Diabetes mellitus, *Moringa oleifera*, Therapeutic, Efficacy, Mechanism, Receptor

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ABSTRACT: Diabetes mellitus (DM) is a globally spreading metabolic disorder with a high incidence rate. About 425 million cases took place in 2017 and expected to rise up to 693 million by 2045. In diabetes, the patient elevation of blood glucose level occurs due to the deformation of insulin receptor action/secretion or both. Long term increases in blood glucose level causes chronic effects such as dysfunction and damage of various organs such as eyes, nerves, kidney heart and blood vessels. There are many treatment regimens available in market, but do not able to provide complete relief and cause severe side effects. To overcome these types of problems it becomes important to find different therapeutic targets and use it in combination with conventional medicine for the treatment of diabetes. To surmount the side effect of presently available treatments, now researchers relay on herbal plants. In this review, we discussed the diabetes occurrence, epidemiology, types, different target receptors, and available treatments and describe briefly role of different plant constituents in diabetes management and focused on a main plant, *Moringa oleifera*.

INTRODUCTION: Diabetes mellitus (DM) is a metabolic disorder, and its incidence is spreading globally [1]. As per the previous reports, approximately 425 million people were found with diabetes in 2017 and expected to rise up to 693 million by 2045 [2]. DM is characterized by high blood glucose (HBG) level due to deformation in insulin receptor action/or secretion or both. HBG for a long time causes chronic effects like dysfunction and damage of various organs such as eyes, nerves, kidney heart and blood vessels [3]. Such complications are due to disarrangement in body system for storing and mobilizing of metabolic components of carbohydrate, protein, and lipid [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(9).4201-13

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(9).4201-13

Type 1 Diabetes mellitus (Type-1 DM) is related to childhood and well known as insulin-dependent and juvenile-onset diabetes. In this type of diabetes, due to dysfunctioning/impairment in pancreatic cells, these cells are unable to produce insulin sufficiently. Its reason can be a genetic predisposition or faulty beta cell that produces insulin [4]. Type 2 Diabetes mellitus (Type-2 DM), also known as non-insulin dependent and adult-onset diabetes, but nowadays, over weighted people are more likely to develop this type of diabetes. It happens when the pancreas unable to produce enough insulin as it should be or because of insulin resistance [5].

Gestational diabetes developed during pregnancy and diagnosed between the middle or late period of pregnancy due to this growth, and the development of baby can be effected. It resolves after pregnancy. It happens as hormonal change is more likely to develop during pregnancy, which leads to insulin resistance [6].

Different Target in Diabetes: In all diabetic patients, 90-95% is from type 2 diabetes the most prevailing type of diabetes. The cause of type 2 diabetes is complex and multifactorial, and it can be affected by both genetically as well as environmentally. Many therapeutic targets are there for the treatment of type 2 diabetes, but there is a chance to develop resistance by using conventional medicine as a monotherapy. In addition, monotherapy treatment regimens do not provide relief from the complications permanently and also cause many side effects itself, so it becomes important to find different therapeutic targets and use it in combination with conventional medicine for the treatment of diabetes [7-9].

Different targets such as GLP-1, GIP, DPP4 inhibitor, GPR119, GPR40 and GPR120, SGLT2, Diacylglycerolacyltransferase, 11β-hydroxysteroid dehydrogenase-1, Peroxisome proleiferator-activated receptor.

A. GLP-1: GLP 1 is mainly secreted by the small intestine in response to a meal and stimulates insulin secretion, also inhibits glucagon secretion, gastric emptying, and food intake. A small percentage of GLP1 is secreted from the pancreas and follows the ingestion of food. GLP1 amino acid sequence is different according to the origin of a peptide. GLP1, which is derived from the intestine, is of 7-36 amino acids that are present in high amount in plasma as compared to pancreatic origin derived GLP1, which is of 1-36 amino acids. The metabolism and degradation of GLP1 are done rapidly by DPP4. GLP1 receptor is widely present in the pancreas, lungs, kidney, stomach, intestine, heart, pituitary, and in skin [10]. GLP1 analogs are classified as following and displayed below in **Fig. 1**.

1. Exendin-Based Therapies: Exendin contains 39 amino acid, a naturally occurring peptide from the venom of Heloderma lizard. The homology of exendin is 53% similar to human GLP1. Glycine replaces the second amino acid residue of the N-terminal region. *e.g.*, Exenatide and Exenatide LAR. It is resistant to DPP4 inhibition.

2. DPP-IV-Resistant GLP-1 Analogs: Potential sites are modified on the bases of the half-life of GLP1. Lixisenatide a 44 amino acid containing drug based on the structure of exendin, is modified in c-terminus with six lysine residue that prevents it from metabolism by DPP-4.

3. Analogs of Human GLP-1: GLP-1 can be conjugated to substances, for example, unsaturated fats, egg whites, in order to hinder its renal discharge. Unsaturated fat conjugation of GLP-1 encourages its authoritative to serum egg whites and has been utilized to create enduring peptide analogs E. gliraglutide [11].

a. **Advantage:** No risk of hypoglycemia, weight loss is also seen.

b. **Disadvantage:** Injection form, Limited by Gastrointestinal tract tolerance/nausea. In rare cases, May increases pancreatitis and thyroid cancers [12].

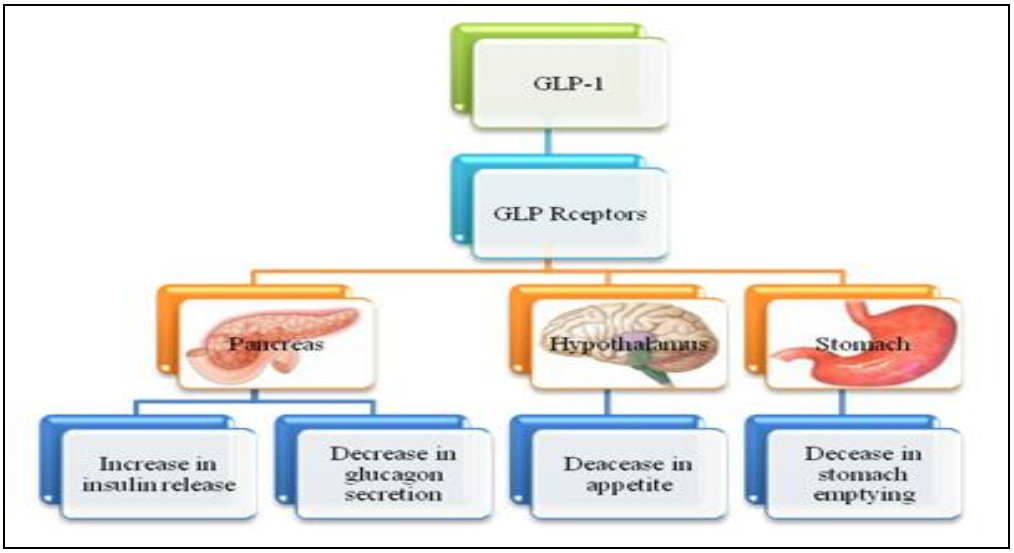

FIG. 1: SITE AND ACTION OF GLP1

B. DPP4 Inhibitor: DPP4 inhibitors are the class of oral hypoglycemic agents. They act by inhibiting the DPP4 enzyme. DPP4 is present all over the surface of most types of cells that deactivates an assortment of other bioactive peptides includes GLP1 and GIP [13].

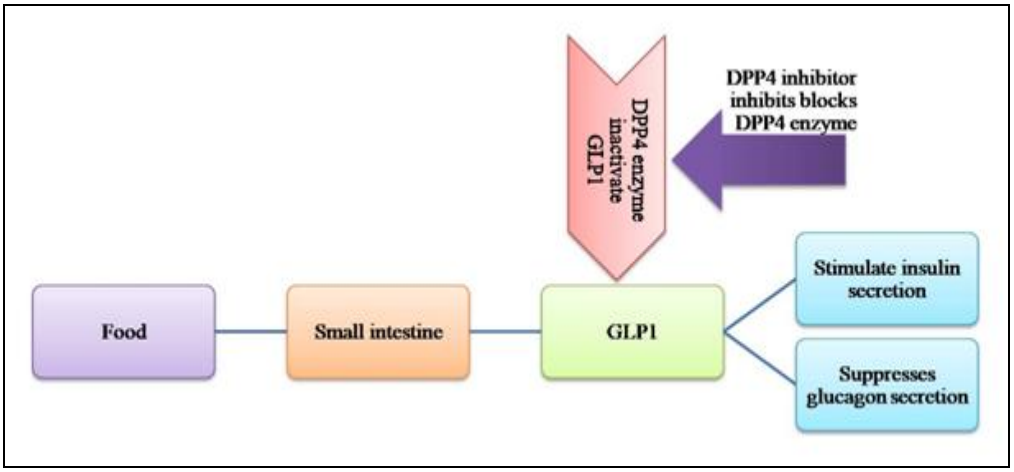

FIG. 2: MECHANISM OF ACTION OF DPP4 INHIBITOR

DPP4 inhibitor which are available in markets are sitagliptin, linagliptin, saxagliptin, alogliptin and they comes in combination with metformin also [14]. Advantage includes almost no risk of hypoglycemia, well-tolerated and Weight neutral and disadvantage includes modest efficacy, rarely it can increases pancreatitis and some chances of interference with the immune system [12].

C. GPR119: GPR119 is a G protein-coupled receptor. It is mainly present in the pancreases and GI tract. Its activation causes a reduction in meal intake. GPR119 has shown the function of regulating incretin as well as secretion of insulin hormone. Hence new drug acting on this receptor can be suggested for the treatment of diabetes [15]. GPR119 agonists act on the GPR119 receptor to increase cAMP level in beta cells of the pancreas thus increases glucose-stimulated insulin secretion in the same manner as GLP1 and GIP do [16]. GPR119 agonists regulate the release of insulin from beta cells and metabolic function in skeletal and cardiac muscle [12].

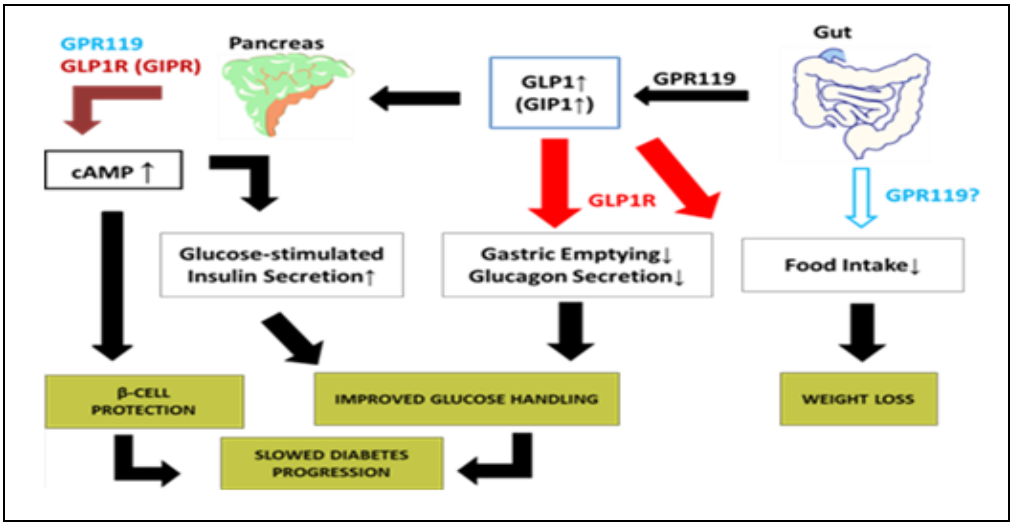

FIG. 3: SITE AND ACTION OF GPR119

D. GPR40 and GPR120: GPR40 a class of G-protein coupled receptor mostly present in beta cells of pancreas [17]. GPR40 is a receptor for medium-chain and long-chain free fatty acids. Free fatty acids are not just only a nutrient but also shows function as cell signaling mediator and implicated in much metabolic disorder which includes diabetes also [18]. Long term exposure of the

beta cell to fatty acid can increase the release of basal insulin, but it inhibits glucose-induced insulin secretion [19]. It acts by increasing intracellular calcium concentration that leads to glucose-induced insulin secretion and also the secretion of GLP-1, GIP, and CCK [20, 21].

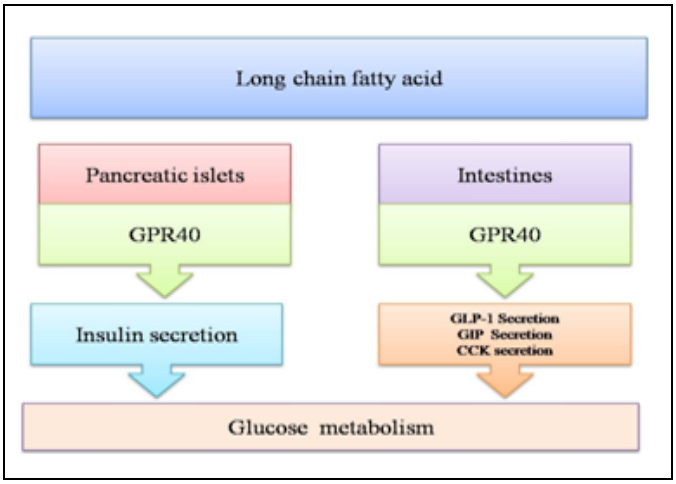

FIG. 4: MECHANISM OF ACTION OF GPR 40

GPR120 is a G-protein coupled receptor that responds to long-chain fatty acids mainly by omega-3 fatty acid [22, 23] present in small intestine, pancreas, adipocytes, and macrophages also. It induces various cellular functions by several secondary pathways thus increase hormone release like cholecystokinin and GLP1 in the response of intestinal fatty acid [24, 25]. GPR120 has a role in improving bone density and metabolism. Disadvantage – GPR40 can cause lipotoxicity [12].

E. SGLT2: Sodium-glucose co-transporter 2 (SGLT2) is a transport protein present in proximal tubules of the kidney that facilitate reabsorption of glucose back into the kidney. SGLT2 inhibitors are also known as gliflozin drugs. It is recommended that people who have poor blood glucose control and a high HbA1c level. SGLT2 inhibitors act by blocking the reabsorption of glucose in the kidney that results in glucose excretion, which lowers the blood glucose level. SGLT2 is responsible for the 90% reabsorption of glucose in the kidney. SGLT2 also allows uptake of glucose in the muscle cells, increases insulin sensitivity, decreases gluconeo-genesis also it improves the first phase of insulin release from beta-cell [26, 27].

SGLT2 drugs that are available in the market are canagliflozin, dapagliflozin, and empagliflozin [28]. SGLT-2 drugs cause weight loss, low risk of hypoglycemia, and reduction in blood pressure. The disadvantage includes vulvovaginal candidiasis, mycotic infections, reduce intravascular volume, orthostatic hypotension, hyperkalemia, renal insufficiency and increase LDL cholesterol [29]. The mechanism of action of SGLT2 is given in **Fig. 5**.

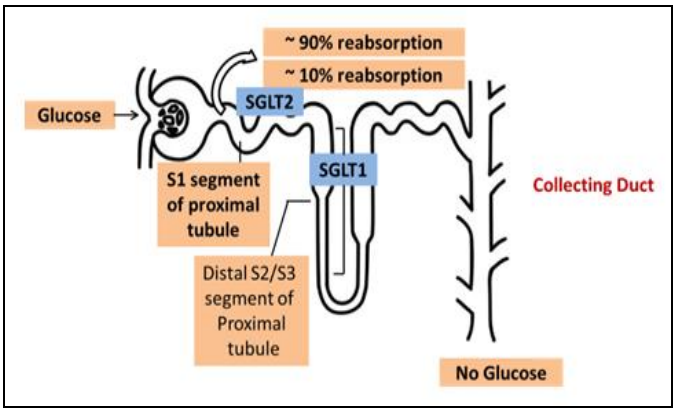

FIG. 5: MECHANISM OF ACTION OF SGLT-2

F. Diacylglycerol Acyltransferase (DGAT-1): DGAT-1 is a key enzyme that plays a significant role in the last step of triglyceride biosynthesis. DGAT-1 is used as a therapeutic target for diseases, such as obesity and diabetes, as excessive deposition of triglyceride is the cause of these diseases. The human liver is a significant organ for triglyceride synthesis, and DGAT1 is richly present in that [30]. Other parts where DGAT1 is expressed are the small intestine, adipose tissue and mammary gland [31]. The mechanism of action of DGAT-1 is given in **Fig. 6**.

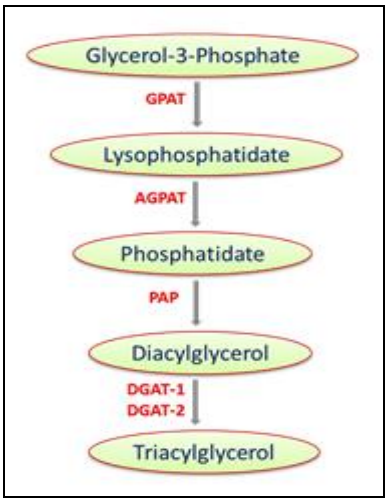

FIG. 6: MECHANISM OF ACTION OF DGAT-1

Abbreviations- GPAT: Glycerol-3-phosphate; acyltransferase; AGPAT: 1-acylglycerol-3-phosphate acyltransferase; PAP: lipin: phosphatidate phosphatase; DGAT: Diacylglycerol acyltransferase)

G. 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1): Glucocorticoids such as cortisol is important mediators in the regulation of cardiovascular and metabolic functions. Through activation of glucocorticoid or mineralocorticoid receptors, glucocorticoids impact vascular, adipose, liver, and kidney functions [32, 33]. Diabetes is related to abnormal regulation of glucocorticoid metabolism; glucocorticoids antagonize the function of insulin and also inhibit secretion of insulin from beta-cell of pancreas [34]. 11β-HSD1 catalyses the intracellular conversion of cortisone to cortisol. Inhibition of 11β-HSD1 has therapeutic benefits in type 2 diabetes [35]. Disadvantage - mineralocorticoid induced side effects [12].

H. Peroxisome proliferator-activated receptor (PPAR): PPARs are the group of nuclear receptor protein that plays a role in transcription factor which regulates the expression of gene. PPARs comprises of three types PPARα, PPARγ, and PPARβ/δ. PPARα regulates energy homeostasis by reducing triglyceride level. PPAR-γ regulates glucose metabolism by insulin sensitization, whereas PPAR-β/δ regulates fatty acid metabolism [36, 37]. Fatty acid and eicosanoid derivatives are the natural PPAR ligands. On the other hand, fibrates and thiazolidinediones are synthetic ligands used for glucose and lipid metabolism control [38]. Disadvantage - congestive heart failure, fluid retention, and edema [12].

Treatment Available for the Diabetes: The major goal in the treatment of diabetes mellitus is to control blood glucose level to prevent compli-cations which are associated with this [39].

Diabetes is a diagnosis by various following test:

1. **Random Blood Sugar Test:** A blood sample is taken after food if blood sugar level showing the value of 200mg/dl or high it will be considered as diabetic.
2. **Fasting Blood Glucose Test:** A blood sample is taken before morning food intake, and the sugar level should be below 126 mg/dl otherwise, it will consider as diabetic. Between 100 mg/dl to 125 mg/dl is called prediabetic.
3. **Oral Glucose Tolerance Test:** Test is done after overnight fasting and then taking sugary liquid containing 75 gm of glucose. The blood sugar level is tested after two hrs. The blood sugar level should be below 141 mg/dl.
4. **Glycated Hemoglobin Test (HbA1C):** It shows the history of blood sugar levels for the past three months. The blood sugar level should be below 5.7; the value between 5.7 to 6.4 is considered prediabetic.
5. **Zinc Transporter 8 Auto Antibody:** This test is used to determine type1 diabetic patients [40, 41].

To maintain good metabolic control in diabetes mellitus, change in lifestyle, and pharmacological treatment, both are required [42].

Lifestyle Changes: Dietary modification and physical exercise are considered as two basic factors of energy balance as well as in the treatment of diabetes. Appropriate rest is required for maintaining energy levels so to be fit. It is advised to sleep for 7 h daily at night, which reduces many cardiovascular and metabolic risks [43-46].

1. Diet: At the point when healthful mediation is mulled over, the co-morbidities that can coincide in a diabetic patient additionally must be considered. The suggestions on dietary viewpoints can add to accomplish the ideal blood glucose, pulse, lipid profile, and weight total caloric intake depend upon various factors like overweight or obesity [42]. Most diabetic patients are overweighed, which is directly related to insulin resistance and insulin secretion, which worsens the condition of diabetes. In this case, the main objective is to reduce weight by reducing caloric intake. Reduction in weight will improve insulin sensitivity hence parameters of glycemic control, and if the patient is not overweighed diet for them should be isocaloric, so caloric intake management should be according to individual patient requirements [44-46].

2. Exercise: Exercise and physical activity can play a significant role in the treatment of diabetes. Exercise increases insulin sensitivity, which improves sugar control that gives benefits in blood pressure, lipid profile, maintenance or weight loss, other cardiovascular benefits, improvement of depression, psychological well-being, and better quality of life [43, 47].

Exercise also decreases HbA1C level and improvement in other metabolic parameters. Both resistance and aerobic exercise have shown benefits in the treatment of diabetes. Unstructured physical activity such as walking more climbing stairs are advised to patients of diabetes [42].

Pharmacological Treatment: Type 1 diabetes is treated with insulin as the pancreas is unable to produce insulin; insulin is taken in the form of injection.

Type of injectable insulin

1. **Rapid-acting:** It shows its effect within few minutes, which last upto 4 h.
2. **Regular or short-acting:** It shows its effect within 1 to 2 h, which last upto 6 h.
3. **Intermediate-acting:** It shows its effect within 1 to 2 h and last upto 8 h.
4. **Long-acting:** It shows its effect within 1 to 2 h and last beyond 24 h.
5. **Ultra long-acting:** It shows its effect within 1 to 2 h and last upto 24 h.

Depending upon the individual patient requires different types of insulin is recommended for the patient. One patient can be advised for different types of insulin to meet the requirement of insulin [48].

Many oral hypoglycemic drugs are recommended for the treatment of type 2 diabetes. They are of seven different classes, such as biguanides, sulfonylureas, an alpha-glucosidase inhibitor, thiazolidinediones, a DPP4 inhibitor, GLP1 agonist, SGLT2 inhibitors. All of them have advantages and disadvantages. The oral combination increases patient compliances. The selection of appropriate drugs is based on the patient clinical condition and economic condition. Metformin is a first-line treatment for diabetes type 2. It is useful in decreasing weight and insulin resistance. Sulfonylureas are given when a patient is less than 40 years. Thiazolidinediones have a significant role in maintaining blood sugar levels and also improve the function of the beta cell. DPP4 inhibitor and GLP1 agonist are important for lowering HbA1C level. Most of them are used in combination with metformin. Clinical advantage of pharmacological treatment increases when went with non-pharmacological medications [42, 49].

Role of Different Plants and their Chemical Constituents with their Structures: In the present available treatment of diabetes is done with insulin and other oral hypoglycemic drugs such as sulfonylurea, biguanides, DDP4 inhibitors, and others. Oral hypoglycemic drugs have so many adverse effects, so it is a challenge to manage diabetes without side effects. Thus people relay on herbal substituent [50]; many traditional drugs are used for the prophylaxis and therapeutic effect of many diseases including diabetes also. Most of them are used as a dietary supplement [51].

TABLE 1: SOME COMMON HERBAL DRUGS FOR THE TREATMENT IN DM DESCRIBED BELOW

S. no.	Plant name	Family	Common name	Part of plant used	Extract/Suspension /Powder/juice	Dose	Pharmacological model
1	*Acacia arabica*	Leguminosae	Babul	Bark	Chloroformic extract	200 gm/kg	Streptozotocin (STZ) induced diabetic rat [52]
2	*Adhatoda zeylanica*	Acanthaceae	Malabar nut or adusa	Leaves	Aqueous and methanolic extract	100 gm/kg	Alloxan induced diabetic rats [53, 54]
3	*Aegle marmelos*	Rutacae	Bengal quince, bel or bilva	Fruit	Aqueous extract	250 mg/kg	STZ induced diabetic rat [55]
4	*Acosmium panamense*	Fabaceae	Benth	Bark	Aqueous and butanolic extract	220 mg/kg	STZ induced diabetic rat [54]
5	*Allium cepa*	Liliaceae	Onion	Bulb	Aqueous extract	300 mg/kg	Alloxan induced diabetic rat [56]
6	*Allium sativum*	Liliaceae	Garlic	Bulb	Ethanolic extract	0.5 gm/kg	STZ induced diabetic rat [57]
7	*Aloe barbadensis*	Liliaceae	Aloe	Leaves	Ethanolic extract	300 mg/kg	STZ induced diabetic rat [58]
8	*Artemicia species*	Compositae	Artemisia	Whole plant	Methanolic extract	250 mg/kg	STZ induced diabetic rat [59]
9	*Azadirachtain*	Meliaceae	Neem	Root	Ethanolic extract	800	Alloxan induced

	dica					mg/kg	diabetic rat [60]
10	*Caesalpiniabonducella*	Leguminosae	Fever nut	Seed	Aqueous extract	65 mg/kg	STZ induced diabetic rat [61]
11	*Coccina indica*	Curcurbitaceae	Little gourd	Leaves	Aqueous extract	200 mg/kg	Alloxan induced diabetic [62]
12	*Cyamopsis tetragonoloba*	Fabaceae	Guar	Beans	Methanolic extract	400 mg/kg	STZ induced diabetic rat [63]
13	*Eugenia jambolana*	Myrtaceae	Indian gooseberry	Seed	Ethanolic extract	250 mg/kg	STZ induced diabetic rat [64]
14	*Gymnema sylvestre*	Apocynaceae	Gurmar	Leaves	Methanolic extract	30 mg/kg	STZ induced diabetic rat [65]
15	*Mangifera indica*	Anacardiaceae	Mango	Leaves	Aqueous extract	200 mg/kg	Alloxan induced diabetic rat [66]
16	*Momordica charantia*	Cucurbitaceae	Bitter gourd	Fruit	Fruit juice	10 ml/kg	STZ induced diabetic rat [67]
17	*Ocimum sanctum*	Lamiaceae	Holy basil	Leaves	Methanolic extract	2.5 mg/kg	Alloxan induced diabetic rat [68]
18	*Tinospora cordifolia*	Menispermaceae	Giloy	Root	Aqueous extract	50 mg/kg	Alloxan induced diabetic rat [69]
19	*Withania somnifera*	Solanaceae	Ashwagandha	Root	Methanolic extract	300 mg/kg	STZ induced diabetic rat [70]
20	*Zingiber officinale*	Zingiberaceae	Ginger	Root	Aqueous extract	500 mg/kg	STZ induced diabetic rat [71]

***Moringa oleifera*:** *Moringa oleifera* is also known as horseradish tree, drumstick, benzolive tree, moonga, kelor tree, never die tree, mothers best friend, mlonge, mulangay and so many others, belonging to the family Moringaceae [72]. Due to its numerous application also known as the miracle tree as most of its parts can be used for pharmacological activities. It is widely found around the world as it can withstand in both condition mild frost as well as in severe dry condition [73, 74]. It can also tolerate a wide range of rainfall with a minimum 200 mm to a maximum 3000 mm. Moringa mostly found in the western part and in Himalayan tracts of India, Pakistan, other parts of Asia, Arabia, Africa, now found in Cambodia, Phillippines, Caribbean islands all parts of America, including central, north and south part of it [75]. Moringa is well used in malnutrition especially in nursing mothers and infants, prescribed for mothers as galactagogues so-called mother's best friend.

Moringa is known to contain almost 7 times more vitamin c as compared to oranges, 9 times more protein than yogurt, 10 times more vitamin A than carrot, 15 times more potassium than bananas, 17 times more calcium than milk, 25 times more iron than spinach. It is easily available with affordable price that also makes it suitable for malnutrition remedy. Moringa nutritive properties are present in the whole plant so most of the part of moringa can be eaten like leaves, bark, seeds, pods, flower, pods, and roots [73, 76, 77]. Apart from medicinal and nutraceuticals use, Moringa is also used for its water purification and biodiesel production. Moringa purifies water by its water-soluble proteins, which act as coagulants. Moringa seed oil is commonly known as Ben oil that is used for biodiesel production, as it contains a high value of monounsaturated fatty acids in the form of oleic acid [78].

Taxonomy: The taxonomical classification of *Moringa oleifera* is given below in **Fig. 7**.

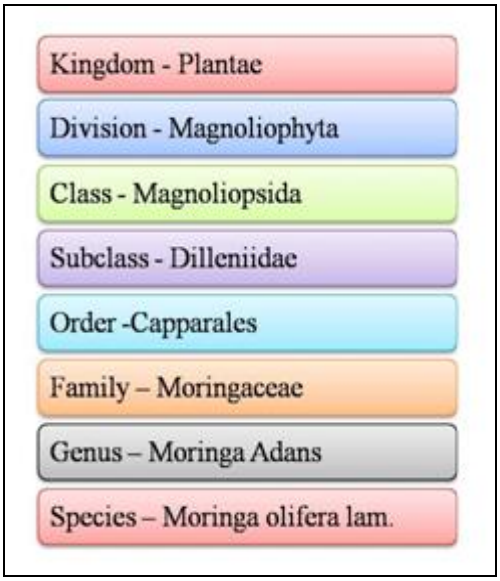

FIG. 7: TOXONOMICAL CLASSIFICATION OF *MORINGA OLEIFERA*

Chemical Constituents: Every part of Moringa is full of nutrients and phytochemical chemicals. Leaves of Moringa contain a high amount of minerals like potassium, calcium, magnesium, zinc, copper, and iron. Vitamins like vitamin A, B, C, D, and E are also present [79, 80]. In phytochemicals, moringa contains tannins, terpenoids, sterols, flavonoids, anthraquinones, saponins, alkaloids, phenolic compounds and reducing sugar [79, 81]. Different parts contain different types of phytochemicals and nutrients, which are shown below in **Table 2**.

TABLE 2: PARTS OF *MORINGA OLEIFERA* CONTAINING DIFFERENT AMOUNT OF PHYTOCHEMICAL CONSTITUENTS AND NUTRIENTS

Parts	Phytochemicals constituents
Leaves	Glycoside niazirin, niazirinin and three mustard oil glycosides, 4-[4'-O-acetyl- α -L-rhamnosyloxy) benzyl] isothiocyanate, niaziminin A and Balpha and gamma-tocopherol 14-15flavanoid such as apigenin-8-C-glucoside, quercetin 3-*O*-*β*-D-glucopy-ranoside, kaempferol-7-*O*-α-L-rhamnoside, and 5, 7, 2′, 5′-tetrahydroxyflavone, phenolic like chlorogenic acid [80, 82]
Mature flowers	Carotenoids, low saturated fatty acid (SFAs) content and high MUFA and PUFA, glucosinolates, 4-O-(a-L-rhamnopyranosyloxy)-benzylglucosinolate (glucomoringin) [83, 84]
Whole gum exudates	D-galactose, L-arabinose, L-rhamnose, D-glucuronic acid, D-xylose, D-xylose and leucoanthocyanin 12-13 [83]
Stem	4-hydroxylmellein, octacosonoic acid, vanillin, β - sitosterone and β – sitosterol [85]
Bark	4-(α-L-rhamnopyranosyloxy)-benzylglucosinolate 10 [83]
Whole pods	Isothiocyanate, thiocarbamates,O-(1heptenyloxy) propyl undecanoate, nitrites, O-ethyl-4-(alpha-L-rhamnosyloxy) benzyl carbamate, β-sitosterol, methyl- p-hydroxybenzoate [85]
Mature seed	Methyl esterhexadecanoic acid, L-(+)-ascorbic acid 2, 6dihexa-decanoate, Methyl ester-9-octadecenoic acid, Oleic acid, 9-octadecenamide [86]
Seed oil	MUFA, Saturated Fats, high oleic acid (omega-9), behenic acid [87]

Pharmacological Activities of *Moringa oleifera*:

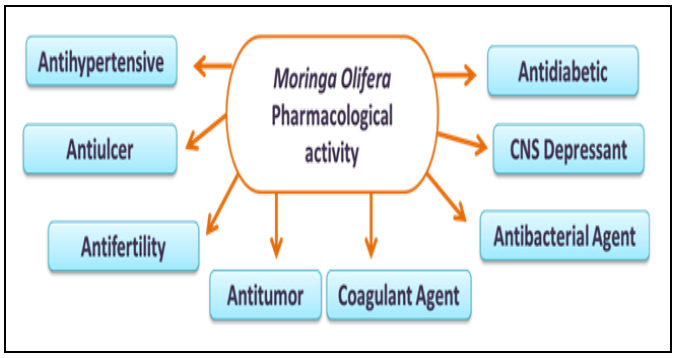

FIG. 8: PHARMACOLOGICAL ACTIVITIES OF *MORINGA OLEIFERA*

Moringa oleifera due to its high nutritive and phytochemical value has many pharmacological activities such as:

1. Antihypertensive: Aekthammarat *et al*., reported that antihypertensive activity of *Moringa oleifera* (aqueous extract) has effectively treat hypertension in Nω-nitro-L-arginine methyl ester (L-NAME) induced hypertension on dosing with 30 mg/kg and 60 mg/kg in dose depending manner by antioxidant effect and promote endothelium dependent vasorelaxation [88].

2. Antitumor: Khalil *et al*., study has reported that ethanolic extract of *Moringa oleifera* has shown antitumor activity on Ehrlich's solid tumor implanted in Swiss male albino mice on different dosing such as 125 mg/kg, 250 mg/kg, and 500 mg/kg. 125 mg/kg and 250 mg/kg shows the degradation of genomic DNA in Ehrlich's solid tumor-mice. Along with 500mg/kg shows delay in growth of the tumor by internucleosomal DNA fragmentation [89].

3. Antiulcer: Ijioma *et al*., study reported that ethanolic extract in aspirin-induced ulcer in rat at dosing with 800 mg/kg exhibit antiulcer activity by increasing mucus globules on surface epithelium [90].

4. Hepatoprotective: Toppo *et al*., study has evaluated that ethanolic leaves extract significantly decrease raised biochemical liver markers such as AST, ALT, ALP, LPO level and increase SOD level on dosing with 500 mg/kg in cadmium-induced toxicity in wistar albino rat by free radical scavenging and antioxidant property [91].

5. Anti-inflammatory: Alimuddin *et al*., a study has shown that ethanolic leaves extract with 400 mg/kg in carrageenan-induced inflammatory in male Wistar albino rats reported for anti-inflammatory action by inhibition of histamine and serotonin mediated effect and also by inhibiting prostaglandin synthesis [92].

6. Antibacterial Activity: Priya *et al*., a study has reported for aqueous extract of fresh stem bark (3.0-4.2 mg/ml), seed (0.5-1.25 mg/ml), and dry pods husk (4.0-5.6 mg/ml) has shown inhibitory activity against many microorganisms in different agar plates of suitable media [93].

7. Antifungal: Patel *et al*., a study has reported that ethanolic and aqueous leaves extract (300 µl) was effective against fungus like *Candida tropicalis* and *Saccharomyces cerevisiae* activity was determined by agar well diffusion method [94].

8. Antifertility: Aggarwal *et al*., a study has reported that ethanolic leaves extract at a dose of 500 mg/kg has shown antifertility activity in female Wistar rats by antiprogestogenic and antiestrogenic effect [95].

9. CNS Depressant: Yunusa *et al*., a study has reported that ethanolic leaves extract at a dose of 400 mg/kg has antidepressant activity by increasing neurotransmitters level in the brain. The activity was determined by the Tail suspension method and Forced swim test [96].

Specific Role in the Treatment of *Moringa oleifera* in DM: Several studies have reported the hypoglycemic activity of *Moringa oleifera.* Khan *et al*., the study reported that Aqueous leaf extract of *Moringa oleifera* with dosing with 100 mg/kg to STZ induced diabetic rat has shown antidiabetic activity by inhibiting the action of α-glucosidase and α-amylase, which improve antioxidant activity, rate of glucose uptake and glucose tolerance [97]. In another study of Une *et al*., a study has shown that ethanolic pod extract in alloxan-induced diabetic rat with 200mg/kg results in hypoglycemic effect by increasing insulin action through potentiating insulin secretion from the pancreas or by its secretion from bound form [98].

Onyagbodorn *et al*., the study reported that ethanolic leaves extract at 100 mg/kg along with seed powder at 100 mg/kg in alloxan-induced diabetic Wistar rat has hypoglycemic action as it increases glucose uptake in muscles, decreases serum HbA1C level and fasting blood sugar thus improves insulin resistance [99]. Patel *et al*., the study reported that methanolic extract of *Moringa oleifera* flower and fruit at 200 mg/kg dose in STZ induced diabetic Wistar female rat shows hypoglycemic action by oxidative properties [100].

Chemical Constituent of *Moringa oleifera* Responsible for Anti-diabetic Action: *Moringa oleifera* contains a great amount of flavonoids, triterpenoids, sterols, phenolic, alkaloidal constituents responsible for antidiabetic property [101]. Quercetin and kaempferol are present in predominant in flavanols. Chlorogenic acid and quinic acid is major phenolic acid [102].

Quercetin: Quercetin is found in large concentrations and potent antioxidants with multiple therapeutic activities. It is reported that quercetin can protect β cells of the pancreas from STZ induced diabetes and apoptosis in rat [103]. The structure of quercetin is given **Fig. 9**.

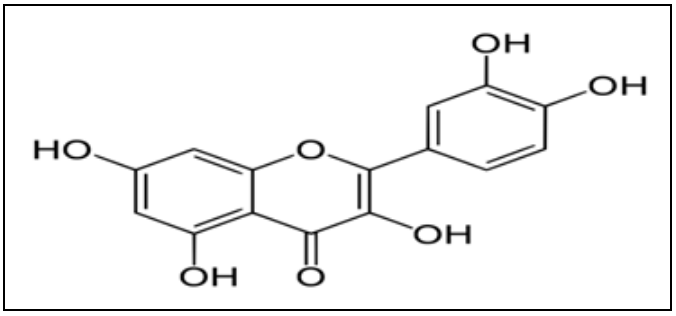

FIG. 9: STRUCTURE OF QUERCETIN

Chlorogenic Acid: It significantly effect glucose metabolism. In oral glucose tolerance test experiment performed on both rats and humans has shown reduced glycemic response in the rat as well as in humans. It inhibits glucose-6-phosphate translocase in diabetes-induced rats thus reduces hepatic glycogenolysis and gluconeogenesis [104]. Structure of chlorogenic acid is given in **Fig. 10**.

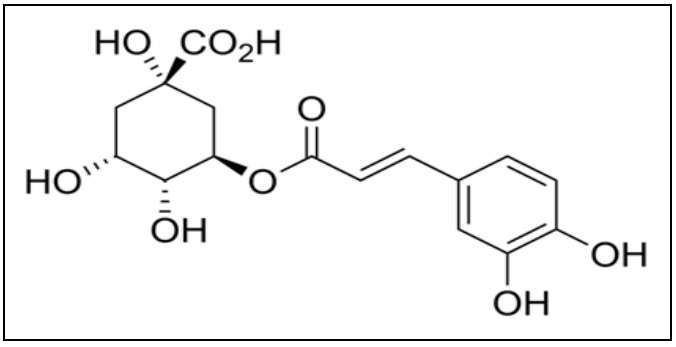

FIG. 10: STRUCTURE OF CHLOROGENIC ACID

Moringinine: Alkaloidal moringinine was initially obtained from the root bark of *Moringa oleifera*,

later it was also found in leaves. Several studies reported this substance lower hyperglycemic effect.

On dosing with 386 mg/kg in drinking water for 17 weeks to diabetes-induced rat has shown a reduction in weight gain, decreases fasting glucose level, plasma triglycerideimprove glucose tolerance [105].

Niaziminin: 2 Nitrile glycosides, aniazirinin and niazirin, 3 mustard oil glycosides, niaziminin A, niaziminin B and isothiocyanate are identified in leaves of *Moringa oleifera*. This compound is also responsible for hypotension action at dosing with 1mg and 3 mg/kg [106].

Different Clinical Trials Related to *Moringa oleifera*: Various clinical trials are going on with *Moringa oleifera* which are given below in **Table 3**.

TABLE 3: CLINICAL TRIALS OF *MORINGA OLEIFERA*

Phase	Drug candidate	Protocol id	Current status
Not applicable	*Moringa oleifera*	NCT03189407	Completed
Phase 1	*Moringa oleifera*	NCT02308683	Completed

The given data is collected from clinicaltrails.gov.in

CONCLUSION: *Moringa oleifera* isan important herbal medicinal plant which is reported for various pharmacological treatments. In this review, the various different targets in Diabetes and mechanism of action of various phytoconstituents present in *Moringa oleifera* in the treatment of diabetes have discussed. This review will promote the growth in research related to medicinal plant *Moringa oleifera*.

ACKNOWLEDGEMENT: The authors wish to thank to Dr. Vikram Sharma, Principal, HIMT college of Pharmacy, Greater Noida for providing support for this study.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

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How to cite this article:
Sneha, Kaurav M and Kumar S: Efficacy and mechanism of action of *Moringa oleifera* in diabetes. Int J Pharm Sci & Res 2020; 11(9): 4201-13. doi: 10.13040/IJPSR.0975-8232.11(9).4201-13.