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Role of Gymnemic Acid in Type-2 Diabetes Mellitus – A Review

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ABSTRACT

Diabetes mellitus (DM) can be a group of metabolic diseases characterized by high blood sugar over a prolonged period of time. Those symptoms are similar to increased thirst, hunger and frequency of urination caused by raised blood sugar. Diabetes mellitus is a major cause of morbidity and mortality, and has been associated with early onset of secondary complication. Diabetes causes major Secondary complications like retinopathy, nephropathy and peripheral neuropathy, Cardio myopathy, Diabetic Foot ulcer, Diabetic ketoacidosis (DKA). Gymnema sylvestre is a plant with strong anti-Hyperglycemic effects. Gymnema sylvestre products contain the active component Gymnemic acid (GA), which has been shown to prevent obesity and exert an antidiabetic effect. It also prevents absorption of glucose & decreases the weight of the body. All of them target to a receptor: Insulin Secretageous & Insulin Sensitizers like Biguanides, glinides, sulphonyl ureas and thiazolidinediones. In type 2 diabetes (T2DM) and in obesity-related disorders. GLP-1 agonists, sulphonyl ureas, glinides, and thiazolidinediones target receptors discovered a decade earlier. PPAR, GIP, FFA1, and melatonin are recent targets that are already being investigated for the development of novel diabetic therapeutics.

Keywords: Sylvestre, Hyperglycemia, Anti- Hyperglycemic effect, Metabolism, Gymnemic acids herbal drug, Gymnema.

INTRODUCTION

Diabetes mellitus is derived from the Latin term mellitus, which means sweet, and the Greek word diabetes, which means siphon, which means to pass through. According to historical research, Apollonius of Memphis coined the term "diabetes" around the years 250–300 BC. The term diabetes mellitus was coined when the ancient Greek, Indian, and Egyptian civilizations realized that urine in this condition was sweet. The pancreas' involvement in the etiology of diabetes was identified by Mering and Minkowski in 1889. A metabolic condition, diabetes mellitus (DM) is characterized by abnormally high blood glucose levels. Type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes resulting from endocrinopathies and steroids are among the various types of diabetes mellitus.[1]

Diabetes mellitus is a condition of macromolecule metabolism marked by a decreased body's capacity to respond to hormones and maintain appropriate blood sugar (glucose) levels.[1] malady} may develop into a chronic illness if the duct gland is unable to generate hormones or if the body is unable to utilize the hormones that are produced. Endocrine may be an endocrine produced by the duct gland that functions as a kind of key to allow aldohexose from the food we frequently eat to enter the bloodstream and deliver energy to the body's cells. Every macronutrient that is consumed is countermined into aldohexose in the blood. Endocrinology facilitates aldohexose uptake by cells.[2]

A class of metabolic illnesses characterized by persistently elevated blood sugar levels is called diabetes mellitus (DM), or simply diabetes. The signs of elevated blood sugar include increased thirst, appetite, and frequency of urine. Diabetic problems might arise

if left untreated. An acute consequence of diabetes is nonketotic hyperosmolar coma and diabetic ketoacidosis. Heart disease, stroke, renal failure, ulcers on the feet, and eye impairment are examples of serious long-term hazards.[3]

CLASSIFICATION OF DIABETES MELLITUS

Diabetes is caused by either an inadequate pancreatic synthesis of insulin or an inappropriate cellular response to insulin. Diabetes mellitus falls into three primary categories:

• Insufficient insulin production by the body is the cause of type 1 diabetes. "Juvenile diabetes" or "insulin-dependent diabetes mellitus" (IDDM) were previous names for this condition.
• Insulin resistance is the first stage of type 2 diabetes mellitus, where cells are unable to react to insulin as they should. Lack of insulin may also develop as the condition worsens. The terms "adult-onset diabetes" and "non-insulin-dependent diabetes mellitus" (NIDDM) were formerly used to describe this kind fig 1. Excessive body weight and insufficient exercise are the main causes.
• Gestational diabetes, is the third main form and occurs when pregnant gestational diabetes.

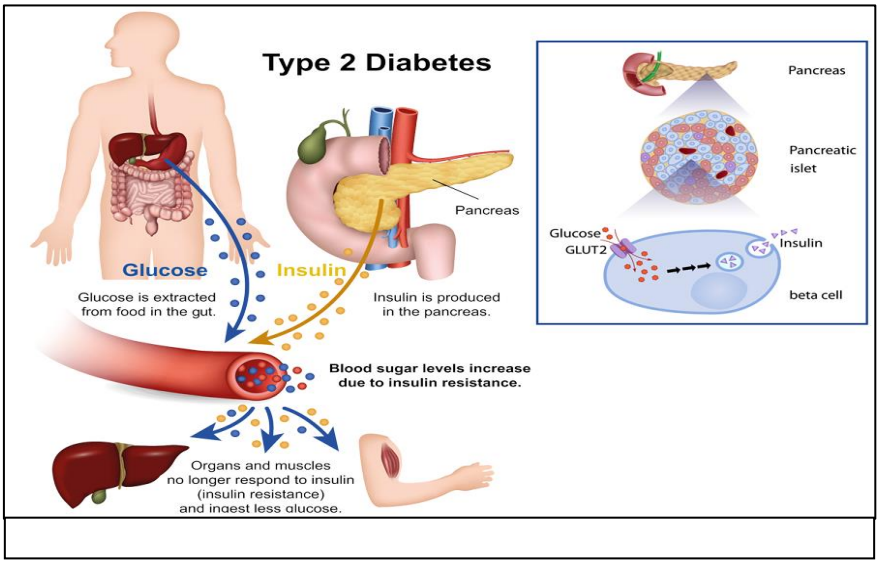

Fig:1

INSULIN DEPENDENT DIABETES (TYPE1 IDDM)

Response diabetes is another name for this kind of diabetes, which was once known as juvenile-onset or ketosis-prone polygenic illness. The patient may also be informed about Graves' disease, Addison's disease, Hashimoto's thyroiditis, and other autoimmune conditions. Type I diabetes, commonly known as insulin-dependent diabetes mellitus (IDDM), primarily affects children and young adults. It can be lethal and typically manifests abruptly.

NON-INSULIN DEPENDENT POLYGENIC DISDORDER MELLITUS (TYPE2 NIDDM)

Type 2 diabetes is another name for diabetes mellitus that is resistant to ketosis. Against the backdrop of insulin resistance, the secretary lacks the progressive hypoglycemic agent (American Polygenic Disorder Association, 2014). This kind of polygenic disease often results in people who are resistant to the effects of hypoglycemic medications. In polygenic conditions, semi-permanent problems in the kidneys, eyes, nerves, and blood vessels—which can take any form—are the main cause of morbidity and death.[2]

GESTATIONAL DIABETES

Gestational diabetes mellitus (GDM) is the physiological status of aldohexose intolerance that shows up or first emerges in pregnant women. The equivalent physiological disorder is termed Diabetes Mellitus(GDM) in pregnancy for girls with undiagnosed, asymptomatic of being pregnant type 2 diabetes and women are defined as having Type 1 diabetes mellitus in pregnancy according to the World Health Organization.

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ALTERNATIVE SPECIFIC SORT (MONOGENIC TYPE)

The most prevalent variation of heritable polygenic diseases are caused by mutations on body twelve in a very interior organ transcription problem known as hepatocyte nuclear problem (HNF)-1a [2].

SIGNS AND SYMPTOMS

Symptoms of uncontrolled diabetes include weight loss, polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased appetite) fig 2.

Symptoms may appear gradually and be modest or nonexistent, but they can also appear quickly (weeks or months) [3]

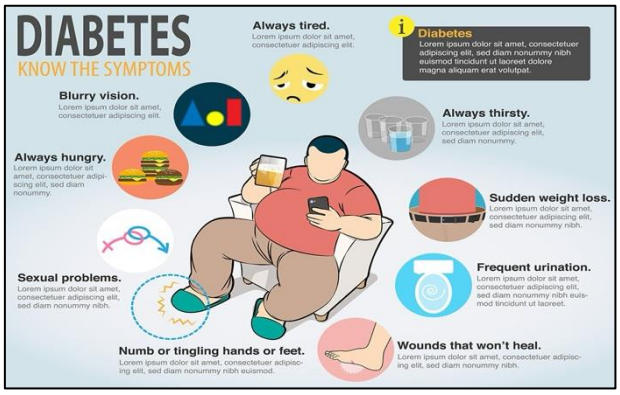

Fig:2

ETIOLOGY

Beta cells, which produce insulin, and alpha cells, which secrete glucagon, are the two primary subtypes of endocrine cells found in the pancreatic islets of Langerhans.

The environment of glucose influences beta and alpha cells to continuously alter the amount of hormones they secrete. Sugar levels become unnecessarily unbalanced when the ratio of insulin to glucagon is out of balance. Hyperglycemia in diabetic mellitus (DM) is caused by either insufficient or inadequate insulin activity.

T1DM is typified by the pancreatic beta cells being destroyed, usually as a result of an autoimmune disease. Because beta cells are completely destroyed as a result, there is either no insulin or very little of it.

The start of type 2 diabetes is more subtle, with a functional insulin deficit brought on by an imbalance between insulin sensitivity and levels. Although it is complex, obesity and age are two common causes of insulin resistance.

Generally, genetic background is critical as a risk factor for both types. Over the years, with research in the human genome, numerous loci carrying a risk for diabetic mellitus have been identified. Human leukocyte antigen (HLA) and major histocompatibility complex (MHC) polymorphisms influence the risk for type 1 diabetes.

The interaction between genetics and lifestyle in type 2 diabetes is more intricate. Compared to T1DM, T2DM appears to have a higher genetic profile, based on abundant data. Most people who suffer from the condition have at least one parent who has type 2 diabetes.

Non-insulin-dependent diabetes that is detected early (often under 25 years of age) is the hallmark of the heterogeneous condition known as MODY. Unlike T1DM, it does not require autoantibodies and has an autosomal dominant transmission. Numerous genes are implicated with this illness, such as glucokinase (GCK) and hepatocyte nuclear factor-1-alpha (HNF1A) mutations, which are found in 52–65 and 15–32 percent of cases of MODY, respectively.

The genetics of this illness are still unknown because some patients have mutations but never have symptoms, and other patients will experience MODY symptoms but have no detectable mutation.

Gestational diabetes is the term used to describe any type of diabetes that develops during pregnancy. HLA antigens, particularly HLA DR2, 3, and 4, may be involved, albeit the exact cause of it is still unknown. Another theory regarding gestational diabetes is the involvement of excessive proinsulin; also, some research indicates that proinsulin may cause beta-cell stress. Conversely, some contend that elevated levels of hormones such estrogen, progesterone, cortisol, prolactin, and human placental lactogen may impact peripheral insulin sensitivity and beta-cell function.

Many of these endocrinopathies, among them acromegaly, Cushing syndrome, glucagonoma, hyperthyroidism, hyperaldosteronism, and somatostatinomas, have been associated with glucose intolerance and diabetes mellitus as a consequence of the glucogenic effects of the endogenous hormones elaborated in excess in these diseases. Disorders such as idiopathic hemochromatosis leading to loss of beta cells because of excessive deposition of iron in the pancreas are associated with diabetes mellitus. [1]

EPIDEMIOLOGY

The past several decades have seen a sharp rise in the prevalence of diabetes mellitus worldwide, and this trend is predicted to continue. Over 90% of those with diabetes mellitus in the United States have type 2 diabetes which affects about 16 million people overall. Every year, about 800,000 Americans receive a diabetes mellitus diagnosis; many more go untreated.[5]

The population with DM is projected to increase from 366 million in 2011 to 552 million by 2030. All countries experience increasing trends of type 2 diabetes and low- and middle-income nations account for 80% of those affected. There were 4.6 million deaths due to DM in 20118. By 2030, type 2 DM will affect 439 million individuals. Worldwide Environmental and lifestyle risk factors account for a significant portion of the variation in type 2 diabetes incidence between geographical regions9. According to predictions, throughout the next 20 years, individuals will be more likely to have diabetes, with type 2 DM becoming more common. The majority of this increase is expected to happen in emerging. [4]

PATHOPHYSIOLOGY

In patients with diabetes, hyperglycemia may occur. It's possible that the pathophysiology of diabetes mellitus is unclear because the condition might frequently have several causes.

Even when hyperglycemia occurs alone, it can harm the pancreatic beta cells and prevent insulin from being released. When hyperglycemia spirals out of control, the result is an affected metabolic state.

Insulin resistance is a result of proinflammatory cytokines and excess fat, which accelerate the breakdown of fat and disrupt glucose transport. When the body doesn't produce enough insulin, it raises glucagon levels by mistake, which makes hyperglycemia worse. Type 2 diabetes includes insulin resistance, but the full effects of the condition do not manifest until the patient's insulin output is inadequate to compensate for their insulin resistance.

Chronic hyperglycemia also makes proteins and lipids nonenzymatically glycated.

HbA1c testing allows quantification of just how much that is the case. Glycosis injures the tiny blood vessels of the kidneys, retina, and peripheral nerves. The process becomes more vigorous with high glucose fig 3. This damage prevents some of the oft-seen complications of diabetes-from blindness and dialysis to amputation-as well as diabetic retinopathy, nephropathy, and neuropathy.

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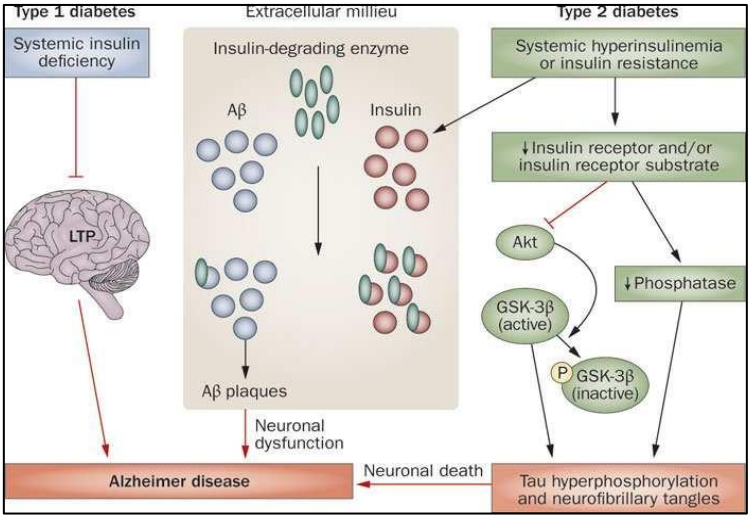

Fig:3

THE ROLE OF PANCREAS IN HOMEOSTASIS

The pancreas was first identified as an organ more than two thousand years ago by Herophilus of Chalcedon, who is frequently called the father of anatomy. In the late 1800s, Claude Bernard's studies on pancreatic juice and digestion clarified certain previously unclear functions of the organ. Subsequently, pancreatic research greatly accelerated. Anyone working in the field of diabetes is familiar with Paul Langerhans' 1869 description of the pancreatic islets of Langerhans.

Initially, the complexity of the pancreas was recognized. The islets of Langerhans' beta and alpha cells could be distinguished using standard histology techniques in 1907, but it wasn't until 1959 that the location of insulin's beta cells was confirmed [8]. The same is true with glucagon, which was discovered to be unique to alpha cells only in 1962 after it was first discovered in 1923.

The anomalies associated with diabetes are further discussed by Jennings and colleagues in relation to changes in critical processes in the formation of the mammalian pancreas. Examples of such phenotypes that are replicated in human model systems or individuals with neonatal diabetes include pancreas agenesis, absence of islet formation, or absence of beta cells in mice caused by mutations in particular transcription factors that contribute to the development of the mammalian pancreas.

The pathophysiology of diabetes is due to aberrant insulin synthesis by the pancreas after development. Still, a lot of information about how insulin is made in pancreatic islet beta cells is still unknown. However, a growing body of research indicates that deficiencies in insulin synthesis play a role in the etiology of monogenetic types of diabetes as well as type 1 and type 2 diabetes Vasiljevi and colleagues provide a summary of the latest research on the post-transcriptional mechanisms controlling insulin production and how deficiencies in these mechanisms might lead to diabetes.

It is generally acknowledged that beta cell failure is necessary for hyperglycemia to occur, and that beta cells also contribute to the development of type 2 diabetes. It is generally accepted that the essential aberration in type 2 diabetes in the presence of insulin resistance is beta cell malfunction that arises early in the disease process. A different concept has recently been put up, according to which excessive beta cell stimulation in the first place causes insulin hypersecretion, which in turn causes obesity and insulin resistance before finally leading to beta cell exhaustion.[6]

The regulation of insulin release from pancreatic β-cells closely controls blood glucose levels. The ability of β-cells to absorb glucose and the signaling pathways that follow that affect the rate of exocytosis are essential for this homeostatic function.

The messengers derived from the binding of glucagon or the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) to their respective receptors work in concert with the glucose signals to release insulin. The cooperative function of β-cells could potentially work in tandem with the regulation of glucose by glucagon and GIP-releasing cells. A balance between glucose's effects on hypothalamic control of food intake and, consequently, the amount of ingested nutrient load, and its effects on the release of hormones that regulate nutrient intake may also be necessary.

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Metabolic signals mediate the glucose-dependent control of insulin release. Numerous converging discoveries in mouse islet cells have led to the proposed connection between the intake of glucose and the exocytosis of secretory vesicles. In summary, the GLUT2 glucose transporters are expressed by pancreatic β-cells and allow for fast uptake of glucose, irrespective of the amount of sugar present outside the cell. When glucose levels are low (less than 2.5 mmol/l), β-cells phosphorylate less substrate. This is likely due to the poor expression of high-affinity hexokinase isoforms (hexokinase I, hexokinase II, or hexokinase III [HK]) in these cells.

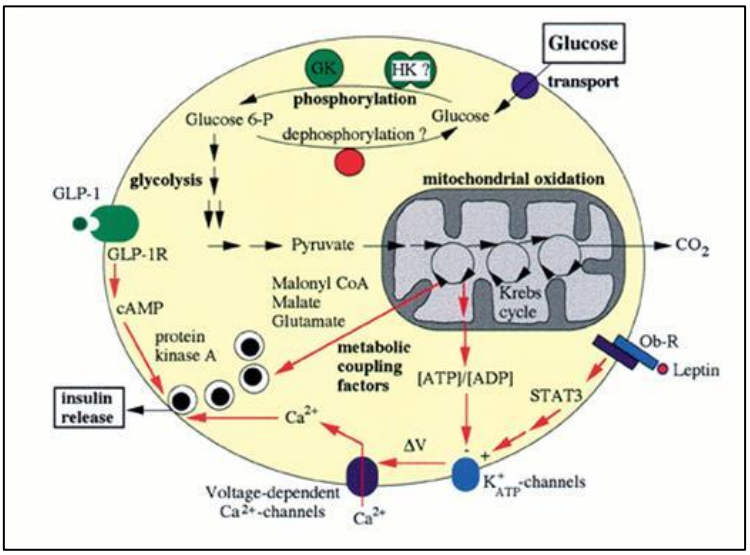

Fig:4

The modern hypothesis claims that glucose metabolism in the β-cells activates the biosynthesis and subsequent secretion of insulin. The glucokinase in the mammalian β-cells acts as a bottleneck for further metabolic flux due to its inhibition of the rate of glucose phosphorylation Fig4 .This rate does indeed depend on the extracellular glucose concentration since the kinetic properties of GK have been shown to be dependent on glucose concentration. It is also unclear if G6P dephosphorylation and other hexokinases can interfere with this bottleneck stage. The uptake of pyruvate by mitochondria and further metabolism with involvement of both carboxylation and decarboxylation facilitates the generation of several exocytosis messengers, such as the ATP/ADP ratio and the release of mitochondrial metabolic intermediates. Activated GLP-1Rs, GIP, and glucagon all amplify the generation of cAMP, thereby strengthening the glucose signaling pathways. [7]

DIAGNOSIS OF DM

A single aberrant blood sugar reading should never be used to diagnose polygenic illness in a symptomless individual.

As the effects on the individual are wide-ranging and prolonged, the practitioner should be certain that the diagnosis of polygenic disease is fully established if one is made.

How polygenic diseases are classified Diabetes mellitus, blood sugar, excretory product sugar, aldohexose tolerance check, urinary organ threshold of renal symptom, extended aldohexose tolerance curve, cortisone stressed aldohexose tolerance check, end venous aldohexose tolerance test, and oral aldohexose tolerance check.[2]

COMPLICATIONS

Retinopathy, neuropathy, nephropathy, cardiovascular problems, ulceration, and other serious diabetic consequences are caused by tissue or vascular damage that develops as the illness worsens. Individuals with type 1diabetes who have had the condition for a long time are at risk for both macrovascular (heart, peripheral vascular, and coronary artery) and microvascular problems. High blood pressure, high cholesterol, and obesity are frequently linked to the development of big artery atherosclerosis in patients with type 2 diabetes. Heart problems and end-stage renal failure claim the lives of the majority of type 2 diabetes patients.

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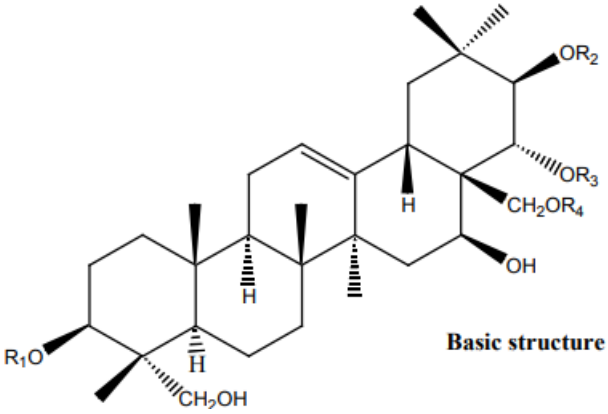
TREATMENT INSULIN AND ORAL HYPOGLYCEMIC DRUGS

Insulin therapy ought to follow nature's lead, as it is exceptionally effective in preventing hypoglycemia in between meals and reducing postprandial hyperglycemia. Insulin injection sites can be intramuscular or intravenous, and both are crucial for the optimal and safe functioning of the drug. There are various insulin formulations available, including those for humans, cattle, and pork.
Adverse effects and problems are common with insulin therapy. When an incorrect amount of insulin is administered when meals and insulin injections are not timed correctly, the most significant side effects are weight gain and hypoglycemia.
Gaining weight due to increased muscle mass and truncal fat is an inevitable side effect of starting insulin therapy for uncontrolled diabetes. Additionally, less energy is lost as a result of glycosuria.[4]

GYMNEMIC ACID



Basic structure of Gymnemic acids

GYMNEMA SYLVESTRE

The plant is indigenous to tropical Africa, Australia, and central and western India. Sanskrit: Meshashringi, Madhunashini; Hindi: Gur-mar, Merasingi; Marathi: Kavali, Kalikardori, Vakundi; Gujrathi: Dhuleti, Mardashingi; Telugu: Podapatri; Tamil: Adigam, Cherukurinja; and Kannada: Sannagerasehambu are few other places to find this name.fig 5.

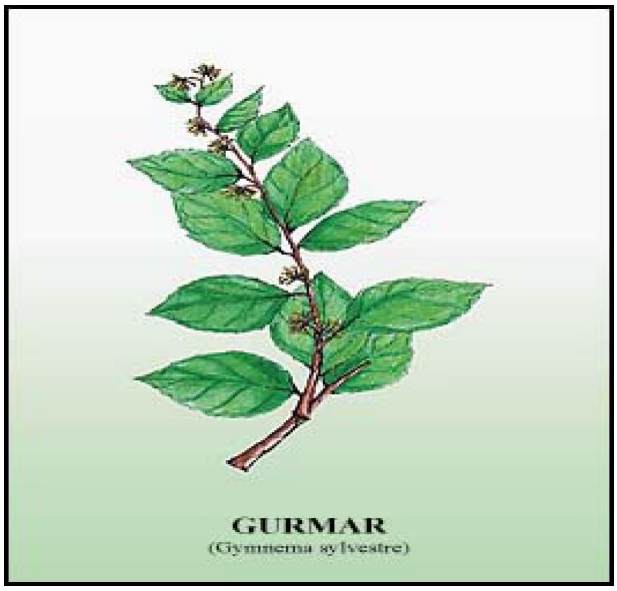


Fig:5

Asclepiadaceae's vulnerable species, G. sylvestre, is a slow-growing, perennial woody climber used in medicine that can be found in central and peninsular India. Strongly antidiabetic, this plant finds application in homeopathic, ayurvedic, and folk medicinal systems. It is also utilized in the management of snakebite, family planning, allergies, inflammations, and asthma. Its antibacterial,

antihypercholesterolemic, hepatoprotective , and sweet-suppressive properties are also present. Moreover, it inhibits Prodenia eridania's ability to feed; it guards against Streptococcus mutans-caused dental cavities; and it's used in skin care products.[8]

Gymnemic acids are found in its leaves and are a blend of anthroquinones, acidic glycosides, and at least 17 distinct saponins. Following their effective extraction and purification from G. sylvestre leaves, gymnemic acids' antidiabetic properties were discovered.[9]

PHYTOCHEMISTRY OF G. SYLVESTRE

Triterpene saponins from the oleanane and dammarene classes are present in G. sylvestre leaves. While dammarene saponins are gymnemasides, oleanane saponins are gymnemic acids and gymnemasaponins. Other components found in plants include anthraquinones, flavones, hentri-acontane, pentatriacontane, α and β-chlorophylls, phytin, resins, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin related glycosides, and stigmasterol. Alkaloids in the plant extract also pass testing.
This plant produces anthroquinones and their derivatives, as well as acidic glycosides, from its leaves.[8]

IN VITRO AND IN VIVO PHARMACOLOGICAL ACTIVITY REPORTS ON GYMNEMA SYLVESTRE

Gymnema sylvestre has been shown to have a wide range of pharmacological potential, including anti-inflammatory, anti-infectious, hypoglycemic, immunosuppressive, anti-cancer, and—most importantly—anti-diabetic effects, in both in vitro and in vivo studies on the plants fig 6 medicinal value.[10]

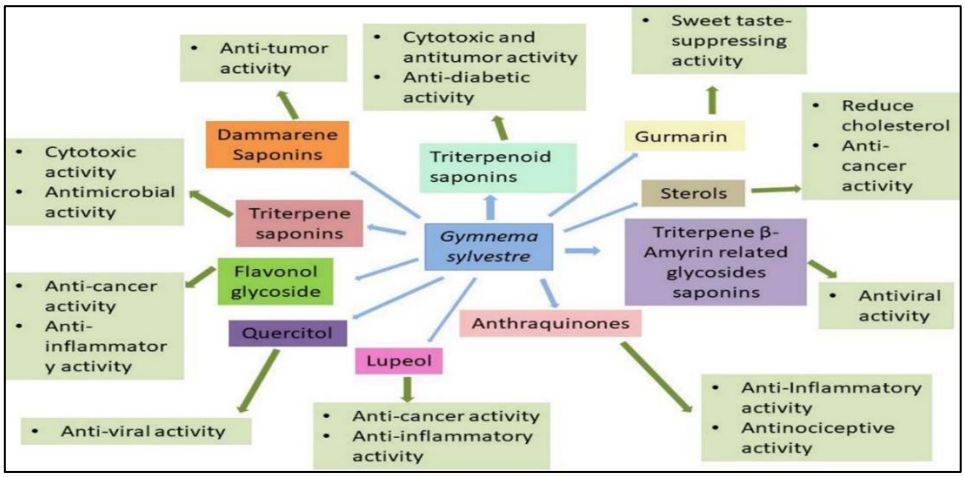


Fig:6

MECHANISM OF ACTION OF GYMNEMA SYLVESTRE

Gymnemic acids from the leaves of G. sylvestre have anti-obesity properties and slow the blood's absorption of glucose from the gut. Gymnemic acid molecules and glucose molecules share a similar structure. These chemicals, known as gymnemic acid, attach to the receptor on the tongue's taste buds, blocking sugar molecules from activating them and inhibiting the absorption of sugar.Likewise, the isolation of gurmarin from G. sylvestre leaves yields a peptide with a similar effect of inhibiting the consumption of meals high in sugar. Potential pathways explaining the hypoglycemic effects of gymnemic acids from G. sylvestre leaves include increased pancreatic secretion of insulin, stimulation of islet cell regeneration, and enhanced glucose consumption through increased activity of the enzyme that catalyzes glucose utilization by an insulin-dependent pathway.

By binding to the intestinal Na+-glucose transporter receptors, gymnemic acid molecules can prevent the absorption of glucose. It has been found that gymnema sylvestre lowers blood glucose levels in both animals and people with type 2 diabetes by increasing insulin secretion. Terpenoids, cumarins, flavonoids, and other secondary plant metabolites including glutamic acid and arginine have also been shown by several researchers to have antidiabetic properties.[9]

G. sylvestre leaves have been used in herbal medicine to treat adult-onset diabetes mellitus (NIDDM), and it has been discovered that they cause hypoglycemia in experimental animals.Patients with diabetes benefit from the stimulation of the pancreas that results in an increase in insulin release when they take gymnema leaf extract. More research is needed to determine the clinical value of these compounds in treating hypercholesterolemia, or high serum cholesterol, even though it has been observed that these

compounds also promote the excretion of cholesterol in the faeces. When Gymnema is taken for its ability to decrease glucose in diabetics, these additional activities would be seen as adverse responses.

It has been discovered that the peptide "Gurmarin," which is present in gymnema leaf extract, interferes with the tongue's taste buds' capacity to detect bitter and sweet tastes. The impact of gymnemic acid is comparable. It is thought that by blocking the perception of sweetness, those who take it may consume fewer sweet meals, which may contribute to its hypoglycemic impact.

MECHANISM OF ACTION OF GYMNEMA SYLVESTRE FOR ANTIDIABETIC ACTIVITY

Gymnema sylvestre's ability to prevent diabetes has been explained by a number of different ways. Gymnemic acids can lower blood sugar levels by preventing the gut from absorbing sugar molecules. Gymnemic acid, a combination of saponins, is one of the components of Gymnema sylvestre. Gymnemic acid blocks the intestinal receptor site for sugar, blocking its absorption and lowering blood sugar levels. Its atomic structure is identical to that of glucose molecules. α-glucosidase inhibitors are present, as indicated by the rapid screening performed by Affinity Ultrafiltration HPLC-MS.

Insulin-dependent enzymes such as hexokinase, glycogen synthetase, glyceraldehydes 3-phosphate dehydrogenase, and glucose 6-phosphate dehydrogenase are said to be activated more by it, while insulin-independent enzymes like glycogen phosphorylase, gluconeogenic enzymes, glucose 6-phosphatase, fructose 1,6-diphosphatase, and sorbitol dehydrogenase are reported to be inhibited. This also increases the activity of phosphorylase.[10]

An insulin-resistant state that results from insulin's failure to bind to its insulin receptor is one of the causes underlying adult-onset diabetes mellitus. Though more research is needed to validate its validity and determine whether the effect is therapeutically useful, gymnema may be able to overcome this barrier. If this benefit is validated, gymnema may assist increase insulin uptake by cells in diabetes mellitus with adult onset (NIDDM) and juvenile onset (IDDM) fig 7. Since insulin is not secreted from the pancreas in the case of IDDM, it is injected using a syringe.[8]

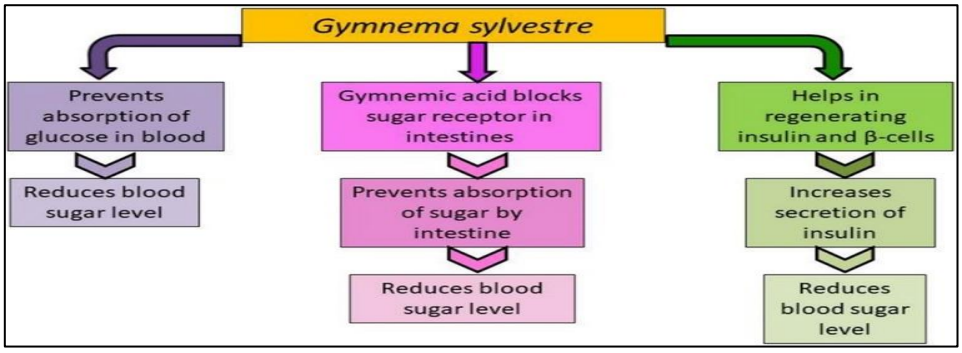


Fig:7

ROLE OF GYMNEMA SYLVESTRE IN AYURVEDA SUPPORTED BY EXPERIMENTAL AND CLINICAL STUDIES

Plants and products generated from them have been an important part of the healthcare system in ancient human communities. In order to satisfy the need for new chemical entities in the healthcare sector, plant sources are researched and utilized. The evolution of Ayurveda and plant-based remedies for health issues from common place life experiences is part of India's cultural history. More than 80% of people in developing countries get their primary medical care from traditional practitioners, according to World Health Organization (WHO) projections.

The cornerstone and foundation of almost all traditional medical systems are medicinal herbs. The Indian Materia Medica contains about 2000 natural remedies, almost all of which are derived from diverse old systems and traditional practices. Numerous authors have detailed G. sylvestre's numerous pharmacological characteristics [11].

TOXICOLOGICAL REPORTS ON GYMNEMA SYLVESTRE

In a toxicology investigation, albino mice given Gymnema sylvestre treatment had an LD50 level of 3990 mg/kg, and the safety ratios for mice with normal and diabetic conditions were reported to be 11.08 and 16.03, respectively. There were no negative autonomic, neurologic, or behavioural consequences found in this investigation. A further study that used mice given the plant

extract intraperitoneally found that the ethanol and water extract of Gymnema sylvestre had an LD50 of 375 mg/kg. A patient receiving Gymnema sylvestre treatment for diabetes mellitus was one example of a drug-induced liver damage (DILI).
Both diabetic and non-diabetic patients have been reported to experience hypoglycemia due to this plant, and in the case of the diabetic animal model, one study found that the hypoglycemic effect persisted long after Gymnema sylvestre administration was discontinued.

However, in a trial where Gymnema sylvestre was given to male and female Wistar rats for 52 weeks, no harmful effects were noted.[10]

ISOLATION AND CHARACTERIZATION OF GYMNEMIC ACID FROM GYMNEMA SYLVESTRE IN CONTROL OF DIABETES

PROCESSING OF PLANT MATERIAL

About 3 kg of thoroughly cleaned leaves from each ecotype were placed in a covered jar for later use after being powdered, dried under shade, and run through 40 sieves.

Using petroleum ether, chloroform, and methanol, the dried power material was continuously heated through Soxhlet extraction.

EXTRACTION OF GYMNEMIC ACID BY HOOPERS'S METHOD

Step1: Petroleum ether extraction

One kilogram of dried leaf powder was placed inside a sanitized soxhlet extraction apparatus. After adding seven liters of petroleum ether (60–800C), the mixture was extracted for 24–36 hours, or until all of the constituents were dissolved in the petroleum. In a distillation unit, petroleum extract is gathered and turned into alcohol. After that, 250 grams of petroleum ether extracts were obtained as net weight.A petroleum ether extraction method was employed to defat dry leaf powder.

Step2: Extraction with 90% methanol

Then, 90% methanol is used to extract the plant material. After adding 90% methanol, the extraction was run for 24 to 36 hours to get a complete methanol-soluble extract. Following the distillation of the methanol-soluble extract, 175 grams of the thick paste were obtained.

Step3: Isolation of pure gymnemic acid from methanol extract

After 45 minutes to an hour of continuous stirring, a 175g thick paste of methanol soluble extract was dissolved in 1% aqueous KOH solution. To separate the particles that haven't dissolved, the solution is filtered using filter paper. Gymnemic acid precipitation occurred as diluted HCl was gradually added while being stirred continuously. Drying was done after the precipitate was filtered out using a suction device. The pure gymnemic acid was obtained.

VARIOUS COLOR TESTS TO CONFIRM THE GYMNEMIC ACID

Gymnemic acid gave positive test for phenolics, steroids and glycoside.

Phenolic test: In a sterile test tube, two milliliters of methanol were dissolved using a pinch of gymnemic acid. Next, a small amount of 1% alcoholic ferric chloride was introduced.

Steroid test: A solution of 2 ml CHCl3 and 1 ml acetic anhydride was mixed with a pinch of gymnemic acid. From the tube walls, a few drops of conc. H2So4 were introduced.

Glycoside test: In a dry test tube, a pinch of gymnemic acid was taken and dissolved in two milliliters of methanol. From the test tube's sidewalls, 1 ml of alpha naptholalcoholic solution was introduced.[12]

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USE OF GYMNEMA SYLVESTRE AS DIETARY SUPPLEMENT

Gymnema sylvestre extract is used as a dietary supplement in Europe. The European Food Safety Agency acknowledges that this plant has the ability to keep organisms' sugar levels normal. According to their conditions of use, the extract must contain 400–800 mg of gymnema, or 100–200 mg of gymnemic acid.

The use of Gymnema-based food supplements in conjunction with (or as a replacement for) approved antidiabetic medications may be risky when done without medical supervision due to unknowns regarding the composition of various Gymnema preparations, possible herb-drug interactions, and worries about glucose-lowering or hypoglycemic effects.[10]

DRUG BINDING TO THE RECEPTORS IN MOLECULAR LEVEL

1: PPAR (Peroxisome proliferator-activated receptors: The subcellular organelles called peroxisomes are present in both human and animal cells. They are involved in metabolic processes such as the metabolism of lipids, cholesterol, and free fatty acids .which helps the body become more insulin-sensitive. PPARs, also known as peroxisome proliferator-activated receptors, are transcription factors that control gene expression. They are classified into three types: PPARα, PPAR-γ, and PPARβ/δ. Thiazolidinediones, or PPAR-γ agonists increase the body's overall insulin sensitivity by activating the receptor. Following activation, they lower blood levels of free fatty acids and alter adipokinese, which is made possible by decreasing the liver's production of glucose, enhancing the uptake of glucose by skeletal muscle and adipose tissues, and raising the pancreatic release of insulin. [13]

Transrepression is a common technique used by various types of immune cells, such as B cells, T cells, macrophages, and dendritic cells. It is based on protein-protein interactions. In brief, PPARs and the p65 subunit of NF-κB interact with each other to suppress NF-κB activity, which is the most commonly observed transrepression mechanism. Other mechanisms include PPAR-mediated regulation of IκB, PPAR-mediated tethering to activator protein 1 (AP-1), nuclear factor of activated T cells (NFAT), and signal transducers and activators of transcription (STATs) fig 8. Additionally, when PPARs are activated by ligands, they stabilize corepressor complexes on the promoter of inflammatory genes, resulting in their down regulation. [15]

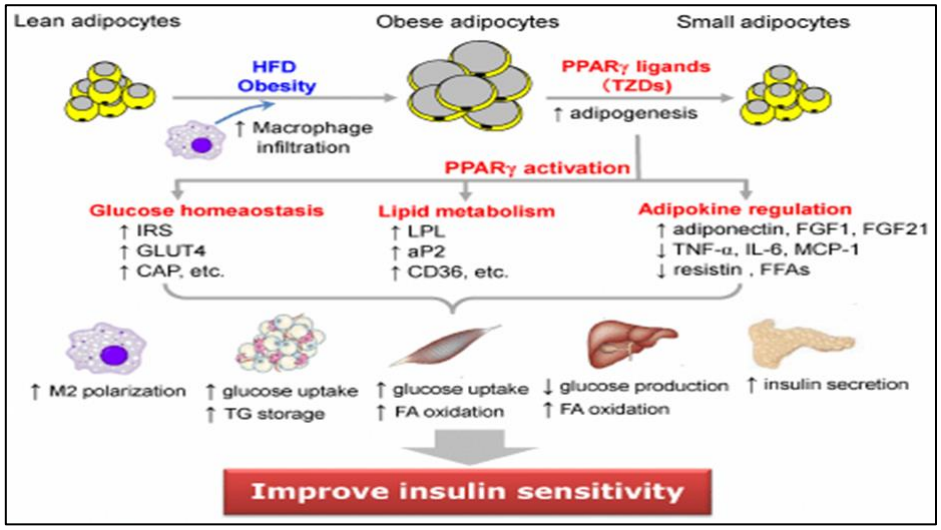

Fig:8

2: GLUTAMINE FRUCTOSE-6-PHOSPHATE AMIDO TRANSFERACE:

As previously mentioned, the majority of glucose that enters the cell is metabolized by glycolysis, with a very tiny portion going through the hexosamine pathway. Hexosamine biosynthesis is well known for its role in insulin resistance and in triggering the synthesis of growth factors. Because it is involved in the catalysis of the initial and rate-limiting steps in the synthesis of hexosamine, the enzyme glutamine fructose-6-phosphate aminotransferase (GFAT) is essential to the hexosamine biosynthesis pathway fig 9. As a result, it is regarded as a crucial treatment target for T2DM.[14]

The measurement of GFAT activity was done as previously mentioned [18]. Using Histopaque-1077 (Sigma-Aldrich, USA), lymphocytes were separated from whole blood in a brief manner. Using an extraction buffer (60 mM KH2PO4, pH 7.0, 1 mM EDTA, and 1 mM dithiothreitol) at 4 °C, cells were lysed. The assay mixture included 2 mg/mL protein extract together with 15

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mM D-fructose-6-phosphate and 15 mM Lglutamine in extraction buffer. The mixture was heated to 100 °C for two minutes to stop the reaction after it had been incubated for one hour at 37 °C. The final product, D-glucosamine-6-phosphate, was calculated using fluorimetry readouts and derivatization by orthophthalaldehyde following cooling and centrifugation.[16]

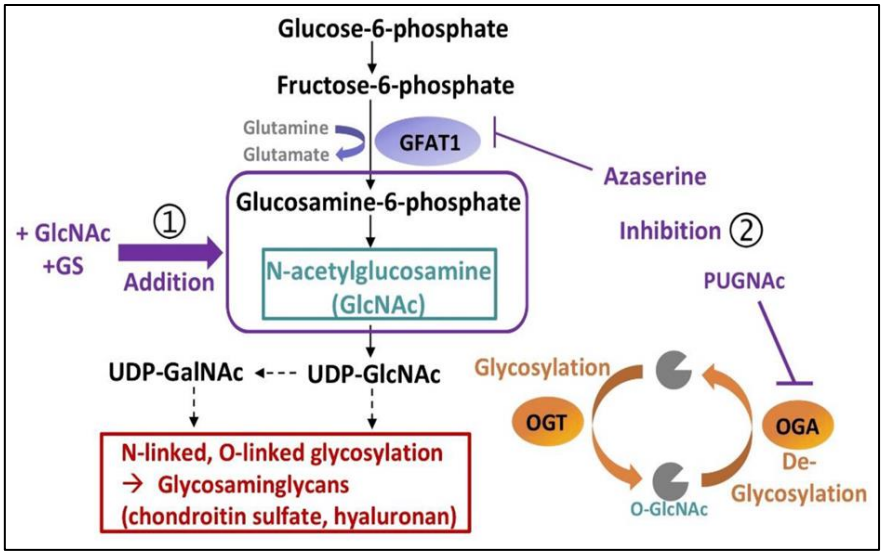

Fig:9

3. GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP)

GLP-1 and GIP are part of the incretin family. While GIP is released by K cells in the duodenum and jejunum, GLP-1 is released by L cells in the colon and distal ileum. The incretin hormone is released with food in the gastrointestinal tract. It also enhances the manufacture of insulin, enhances digestion, and glucose-dependent lipid and carbohydrates breakdown as it activates pancreatic β cell receptors. However, the actual mechanisms through which GLP-1 and GIP regulate blood glucose differ subtly (Figure 1). GLP-1 enhances insulin secretion in the presence of high blood glucose concentrations, lowers glucagon secretion, decreases appetite, slows gastric emptying through stimulation of vagal afferents, activates hindbrain PKA and MAPK, and inhibits the phosphorylation of hindbrain 5'-AMPK. Acid production is suppressed by a gastric peptide called GIP. In [15]

While posing low risk of hypoglycemia, GLP-1RAs work by boosting the glucose-dependent insulin synthesis of the pancreatic β-cells. They have a positive impact on body weight because they slow down stomach emptying and centrally suppress appetite. Unimolecular GLP-1R/GIPR dual agonists, also known as "twincretins," can provide greater efficacy with ongoing efforts to develop additional antidiabetic medications, especially for obese individuals with type 2 diabetes. The benefits of GIP activation in conjunction with GLP-1RAs have been shown by recent studies using GLP-1R/GIPR dual agonists, most notably the SURPASS clinical trials. [18]

4: G-PROTEIN COUPLED RECEPTOR (GPCR 119) :

- **Group A**

Group A Known as the "rhodopsin-like family," 719 GPCR family members are divided into several families, including aminergic, peptide, protein, lipid, melatonin, nucleotide, steroid, alicarboxylic acid, sensory, and orphan.17 They have a conventional transmembrane domain (TMD) that creates a ligand binding pocket along with a total of eight additional helices with a palmitoylated cysteine at the C-terminal fig10.This receptor class is most often therapeutically targeted because of all of their physiological functions. By manually selecting the Drugs FDA original New Drug Application (NDA) and Biologic License Application (BLA) database from data downloaded from August 2017 to June 2020 and cross-referenced with Drugbank20 IUPHAR, and other sources, we verified the drugs approved concerning this class.

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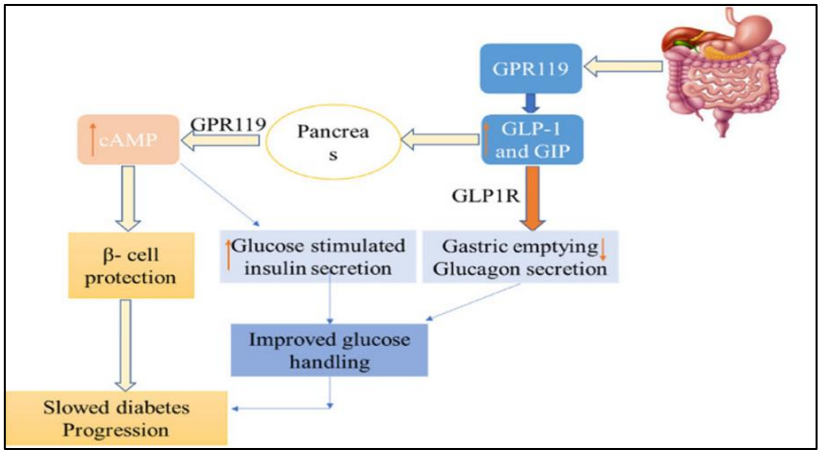

Fig:10

- **Group B**

Within this family of GPCRs, there are two subfamilies: secretin (B1) and adhesion (B2), which have 15 and 33 members, respectively.4, 21 A wide range of substances, such as glucagon, pituitary adenylate cyclase-activating peptide (PACAP), growth hormone-releasing hormone (GHRH), calcitonin gene-related peptide (CGRP), parathyroid peptide hormone (PTH), corticotropin-releasing factor (CRF), and glucagon-like peptides (GLPs), are bound by members of the secretin subfamily, which is linked to large extracellular domains (ECDs). The adhesion subfamily includes nine subgroups, such as immunoglobulin, cadherin, and epidermal growth factor domains, each of which has a unique N-terminal motif. Their effects on migration and cell adhesion set them apart from other GPCRs.22, 23 Apart from its extended N-terminal domain two more unique features of the GPCR are the signaling-related proteolysis site and the GPCR autoproteolysis-inducing domain.

5: SODIUM-GLUCOSE COTRANSPORTER PROTEIN-2 (SGLT-2)

The electrochemical potential of sodium ions is used by SGLTs, which are essential membrane proteins that belong to the mammalian solute carrier family SLC5, to drive the movement of anions, glucose, vitamins, and short-chain fatty acids across concentration gradients. Out of SLC5's six isoforms, SGLT-2 is crucial for the kidney fig 11. The S1 and S2 segments of the renal proximal tubule mostly express SGLT-2, a cotransport protein with a low affinity and high transport capacity that reabsorbs 90% of the glucose from the glomerular filtrate back into the blood. Overexpression of SGLT-2 in type 2 diabetic patients enhances the kidneys' absorption of glucose and elevates blood glucose levels. Thus, by blocking SGLT-2, people may be able to lower their blood sugar levels. [15].

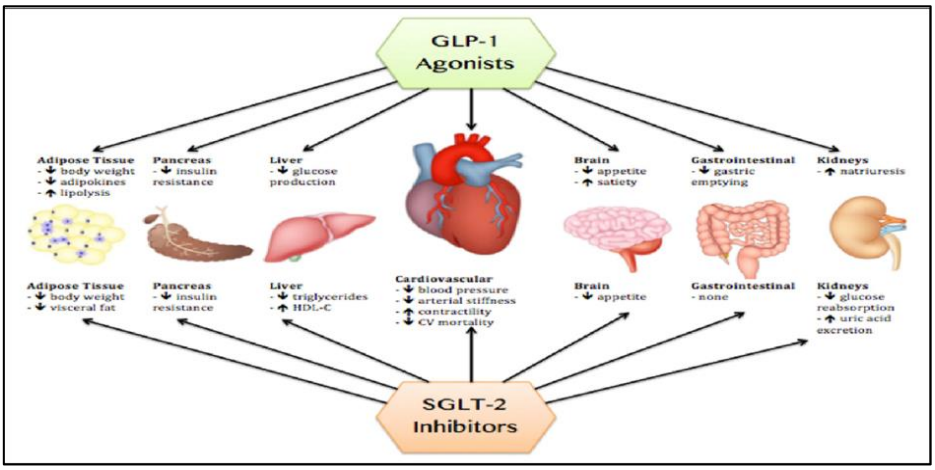

Fig :11

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The SGLT2 inhibitors can reduce this threshold to 40–120 mg/dL. A rare "nondisease," familial renal glucosuria (FRG), on the other hand, is characterized by the absence of functional SGLT2 proteins. They have glucosuria in the presence of normoglycemia. Those who have FRG rarely experience hypotension or hypoglycemia. [7].

6: FFA2/FFA3

According to their chain length, free fatty acids (FFAs) can be classified as signaling agents. They are classified as short-chain fatty acids (SCFAs), long-chain fatty acids (LCFAs), and medium-chain fatty acids (MCFAs). FFAs with these chains of varying length activate transmembrane receptors FFA1, FFA2, and FFA3 fig 12. For instance, it is well known that LCFAs trigger FFA1, which is highly expressed on pancreatic β-cells. It has been demonstrated that the increase in insulin secretion by glucose is strongly impacted by the activation of these receptors. Numerous ligands for FFA1 have been found and investigated because it is evident that this receptor plays a role in the glucose-stimulated production of insulin. SCFAs stimulate FFA2 and FFA3 receptors similarly to FFA1 receptors, although their role.

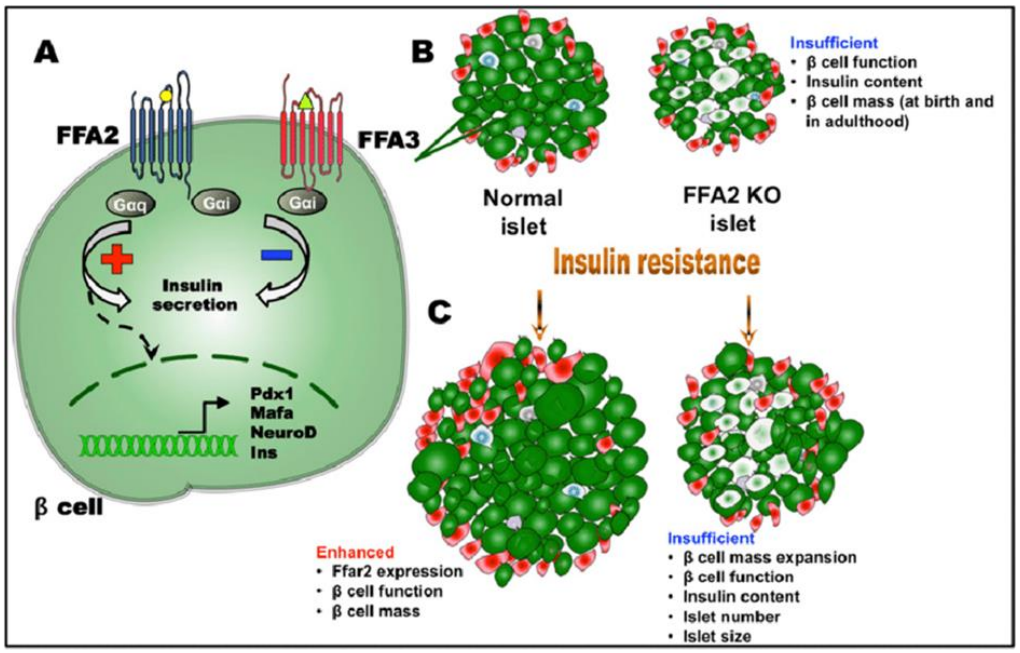

Fig: 12

Several saturated (like palmitic acid, C16:0), mono-unsaturated (like oleic acid, C18:1), and polyunsaturated long-chain FFAs (like linoleic acid, C18:2) activate FFA1, a Gq/11-coupled GPCR that is mostly expressed in pancreatic beta cells. It is linked to a rise in GSIS, or glucose-stimulated insulin secretion. Enteroendocrine cells also express FFA1, which controls the release of incretin hormones like cholecystokinin (CCK) fig 13, which has been demonstrated to control pancreatic secretion, inhibit gastric motility, and reduce energy intake, and glucagon like peptide-1 (GLP-1), an insulinotropic, anorectic peptide that decreases gastric emptying and motility. Although its function in maintaining glucose homeostasis is unclear, FFA1 is also present in the central nervous system (CNS). Alpha cells that produce glucagon have been found to express FFA1.[21].

7: GLUCOCORTICOID RECEPTOR

There are several known GR gene polymorphisms and mutations that have been connected to changes in metabolic indices, body composition, and GC sensitivity. ER22/23EK, BclI, N363S, Tth111, GR-9β, and 22 C/A are the most extensively studied polymorphisms of the NR3C1 gene. Two related polymorphisms are denoted by the notation ER22/23EK (rs6189 and rs6190) in codons 22 and 23 of exon 2. These fully linked single nucleotide polymorphisms (SNPs) are associated with GC resistance, even though bearers of the ER22/23EK polymorphism exhibit lower fasting insulin and total cholesterol levels. Furthermore, it has been discovered that the ER22/23EK polymorphism is only associated with a decrease in women's first-phase glucose-stimulated insulin secretion and disposition index. These measurements pertain to the function of the β-cell. Carriers of the ER22/23K polymorphism in men.[8]

The hypothalamic-pituitary-adrenal (HPA) axis controls the production of glucocorticoids by the adrenal cortex. To work in various target organs, they attach to two intracellular receptors: the mineralcorticoid receptor and the glucocorticoid receptor.[9]

Proteins called 11β-hydroxysteroid dehydrogenase (11β-HSD) have an impact on how glucocorticoids behave biologically in target tissues. Cortisone, the inactive metabolites cortisol, is produced by these enzymes. Primarily expressed in the liver and adipose tissue, 11β-HSD type 1 (11β-HSD1) increases the local glucocorticoid action by changing cortisone into cortisol expressed in the kidney, which breaks down cortisol into inactive cortisone to lessen the effects of glucocorticoids.[22]

GLUCOCORTICOID RECEPTOR POLYMORPHISMS IN TYPE 2 DIABETES MELLITUS

Different mutations and polymorphisms in the gene coding the GR have been associated with changes in body composition, metabolic indices, and increased GC sensitivity [23]. The most investigated NR3C1 gene polymorphisms include ER22/23EK, BclI, N363S, Tth111, GR-9β, and 22 C/A. The ER22/23EK (rs6189 and rs6190) polymorphisms are associated with codons 22 and 23 of exon 2. ER22/23EK polymorphism carriers have reduced fasting insulin and total cholesterol, whereas these SNPs are totally explained by GC resistance [139]. ER22/23EK polymorphism was associated with decreased first-phase glucose-stimulated insulin secretion and disposition index in women that are two crucial markers of β-cell function [140]. Carriers of Men. [23]

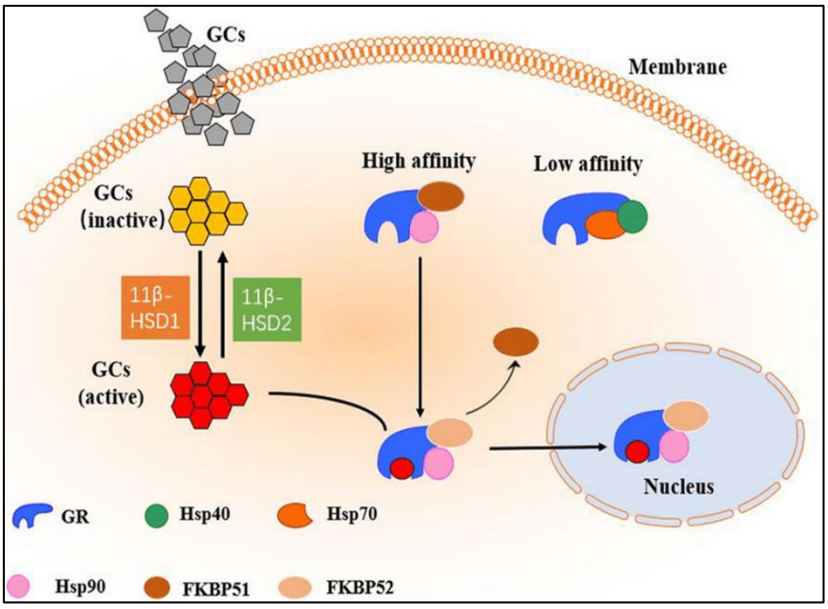

Fig:13

8: MELATONIN

At night, the pineal gland releases the neuroendocrine hormone melatonin. Insulin secretion from the pancreas and glucose regulation have been linked to melatonin. It is therefore a possible goal for the management of diabetes mellitus. It works pharmacologically by interacting with the melatonin receptors MT1 and MT2, which are present on the extracellular membrane of many body cells. Melatonin's MT1 receptor is a key target for regulating blood glucose levels in the body, as evidenced by recent studies showing that melatonin MT1 receptor knockout animals have increased insulin resistance and glucose tolerance. A study also showed that treating diabetics with low circulating melatonin levels fig 14 with melatonin can raise their blood sugar levels.

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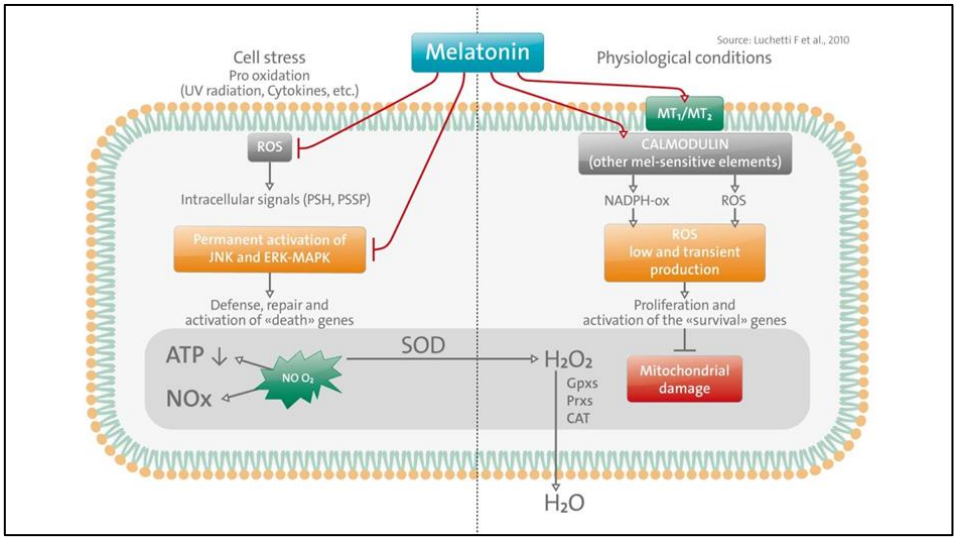

Fig: 14

Healthy circadian rhythms depend on melatonin. Genes MTRN1A and MTRN1B, respectively, encode the melatonin receptors MT1 and MT2. Melatonin's binding to MT1 and MT2 causes the subunits α and β/γ to separate, which in turn triggers downstream signaling pathways such phospholipase A2 (PLA2), adenylyl cyclase (AC), and phospholipase C (PLC) 38. Melatonin signaling, which is important in the development of type 2 diabetes, has been shown to be disrupted by IR 39–42. The pathophysiology of T2DM and obesity involves impaired sleep and circadian rhythms, indicating that metabolic diseases are becoming more common in those with erratic lifestyles, such as night time light, working night shifts, and inconsistent meal timing. Hence, melatonin's chronobiotic and cytoprotective qualities combined.[23]

CONCLUSION:

A promising natural substance obtained from Gymnema sylvestre, gymnemic acid, shows promise in managing diabetes in a variety of ways. It provides a possible path to improved blood sugar control by decreasing the absorption of sugar, increasing the release of insulin, possibly repairing pancreatic cells, and boosting insulin sensitivity. Gymnemic acid exhibits potential as a natural supplement to traditional diabetic therapies, while research is still underway. Before adding gymnemic acid to your regimen, it's important to speak with a healthcare provider because each person's needs and any drug interactions should be carefully taken into account. Gymnemic acid may become a useful tool in the toolbox of diabetes control techniques when more research is done to fully understand its potential.

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