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Review Article

Diabetes Mellitus: Current Understanding, Emerging Targets, And Natural Therapies

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ABSTRACT

Type II diabetes is an incurable condition that affects a substantial number of individuals globally. It covers around 90% of the overall number of diabetes cases. It has already expanded globally and has emerged as a substantial cause to disability and death, especially among younger age cohorts. India has witnessed an epidemiological shift, which indicates that there has been a drop in mortality owing to illnesses that may be spread, as well as disorders associated to pregnancy, delivery, neonates and nutrition. At the same time, there has been a rise in non-communicable illnesses and trauma. Several cross-sectional studies undertaken in various regions of India have showed a rise in the incidence of diabetes, with a surge in prevalence from 16.4 to 20.3 in smaller cities and peri-urban areas. In rural regions, the incidence of diabetes grew from 5.8% to 14.7%, whereas in urban areas it climbed from 7.2% to 16.2%. Drugs like metformin, insulin, and GLP-1 receptor agonists have proven success in the treatment of diabetes. Nevertheless, the quest for novel treatment targets continues. This review explores the involvement of AMPK, FBPase, GK, GPR119, GSK-3, PTP1B and SGLT2 in the evolution of diabetes mellitus. The review additionally looks at the possibility of natural therapies, namely the antidiabetic benefits of herbs like Cinnamomum zeylanicum, Panax Ginseng, and Momordica Charantia and other plants. This review provides a multidimensional picture of diabetes care by combining current research on traditional treatments, new pharmacological targets, and plant-based medicines. It underlines the importance of ongoing research and a multifaceted approach that combines innovative treatments, lifestyle changes, and global health activities to combat the increasing diabetes epidemic.

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INTRODUCTION

Diabetes is related with shortened lifespan, small blood vessel malfunction, higher risk of large blood vessel disorders (for example, cardiac disease, stroke), and lower quality of life. Diabetes occurs from numerous pathogenic reasons. These therapies entail damage to the β-cells of the pancreas, resulting in insulin insufficiency and also creating insulin resistance. Insulin insensitivity or absence leads to difficulties with glucose, lipid and protein metabolism owing to the deleterious impact of insulin on tissue targets.[1] Diabetes has been recognized for more than 2,000 years as a grave and fatal ailment. Aretaeus, an ancient Greek physician from the 1st century A.D., emphasized the lethal characteristics of the disease, which he named "diabetes" after the Greek term for "siphon". Ancient physicians, like Aretaeus, possessed knowledge of the symptoms of diabetes but lacked the ability to effectively treat it. [2] [3] Diabetes has evolved as an epidemic at some period in most developing economies, such as China and India. Diabetes is spreading the quickest in low- and middle-earnings nations, according to the sector fitness organisation. fast socioeconomic changeover, blended with development and industrial development, is the major explanation of the worldwide increase in the epidemic like conditions of diabetes, with other hazard variables consisting of population expansion, awful eating habit, and a sedentary life-style all gambling vital parts.[6]

Current Scenario of Diabetes Mellitus

Pacific Islanders, Asian Indians, and Native Americans are more likely to develop type 2 diabetes than other individuals around the world. The number of persons diagnosed with type 2 diabetes increased significantly around the year 2000. [7] There are seven. Men are more likely than women to get diabetes, accounting for 8.8% of cases. Diabetes affects 463 million people globally, with 374 million suffering from impaired glucose tolerance, a kind of prediabetes. The Western Pacific area contains 163 million diabetics, followed by South East Asia and Europe. North America and the Caribbean have fewer instances than the Middle East and North Africa. The numbers are lowest in South and Central America, as well as Africa. The diabetes pandemic is not restricted to Europe or North America. [8] China, India, and the United States had the most diabetes cases in the year. China and India are expected to have the largest diabetes burden by 2045. Population growth and aging are linked to a rise in diabetes incidence in major countries such as China and India. There is no mention about [9]. Diabetes prevalence is increasing more rapidly in low- and middle-income nations than in high-income ones. According to the Global Burden of Disease study, diabetes is more common in low- and middle-income countries than in high-income ones. [10] The number of persons with diabetes increased between 1990 and 2017. The primary causes of the diabetes burden include metabolic, environmental, and behavioural factors. In developing countries with inadequate healthcare infrastructure, more than half of people have undiagnosed diabetes. Approximately one in every two persons has diabetes that has not been discovered. [11].

Types of Diabetes:

Diabetes Mellitus Type 1:

This type of diabetes is defined by insulin insufficiency induced by insulin depletion from the cells of the pancreas of Langerhans. Immunologically-mediated diabetes arises when an immunological attack decreases the number of β-cells, resulting decreased insulin production.[18] According to North American statistics, diabetes mellitus affects people who are otherwise healthy and weigh a normal amount at the time of diagnosis. Insulin sensitivity and responsiveness are generally normal, particularly

in the early phases. Although type 1 diabetes can afflict both adults and children, it was originally linked with children.[19] Brittle diabetes, also known as unstable or labile diabetes, is characterized by substantial and frequent blood sugar changes with no clear cause or biological basis. These variations are frequently accompanied with endocrinopathies and irregular, unexpected hypoglycemia, which is a counter-regulatory reaction to hypoglycemia that can be hazardous. It is estimated that these anomalies affect 1% to 2% of persons with type 1 diabetes. [20] Type 1 diabetes is predominantly hereditary, with many gene variants known to increase diabetes risk. Environmental factors, such as viral infections or dietary choices, can cause the onset of diabetes in genetically predisposed people. According to some study, the relationship among type 1 diabetes and Coxsackie B4 virus is unrelated to lifestyle factors. Hence, type 1 diabetes mellitus is defined by the reduction in the number of pancreatic β-cells that produce insulin, which ultimately leads to the deacrease in the insulin sensitivity. [21]

Diabetes Mellitus Type 2:

Resistance to insulin, which is possibly caused by decreased insulin synthesis, is a distinguishing feature of type 2 diabetes. The insulin receptor in the body's tissues is assumed to play a role in insulin resistance, while the particular processes are unknown. Diabetes mellitus cases with known defects are classified separately, with type 2 diabetes being the most common. In the early stages of type 2 diabetes, the most common problem is decreased insulin sensitivity. At this point, hyperglycemia can be controlled using a variety of procedures and drugs that improve insulin sensitivity or limit glucose synthesis in the liver. Type 2 diabetes is primarily caused by lifestyle decisions and genetics.[22] A high waist-hip ratio is generally a risk factor in type 2 diabetes, even among non-obese persons. Dietary variables also play a key influence in increasing the risk. Excessive use of beverages with sugar has been related to an increased probability of getting type 2 diabetes. The type of fat in the diet is essential, with saturated and trans fats boosting risk, while monounsaturated and polyunsaturated fats assist in reducing it. Additionally, consuming significant quantities of rice appears to boost the risk. Lack of physical activity is considered to contribute to 7% of instances. [23]

Gestational Diabetes Mellitus

Gestational diabetes mellitus, commonly known as hyperglycemia of pregnancy, refers to hyperglycemia that initially appears during pregnancy. While GDM can occur at any point during a woman's pregnancy, it most commonly affects expecting moms between the 2ndand 3rdtrimesters. According to the ADA (American Diabetes Association), gestational diabetes accounts for 7% of all pregnancy problems.[24]

Gestational diabetes may result in the progression of diabetes later in life for women’s who suffer with it during the pregnancy, as are their children. High blood pressure, hypertension, and increased amniotic fluid levels can all worsen the course of GDM, increasing the likelihood of caesarean sections. When the mother's blood contains too much sugar, the growing baby may have an abnormally big size (macrosomy) as well as developmental defects. Even after delivery, newborn respiratory distress and adult obesity can occur. The other symptoms include the old age, fat, and overweight.[25]

Some Other Specific Types of Diabetes Mellitus

Latent Autoimmune Diabetes of Adults

This type of diabetes i.e., Latent Autoimmune Diabetes of Adults is an autoimmune illness characterized by adult-onset, hyperglycemia-associated autoantibodies, and no requirement for insulin treatment following diagnosis. Some adults may have a slow-developing Type 1 diabetes with

autoantibodies. Some persons with type 2 diabetes become insulin-dependent, indicating a slowly advancing version of type 1 diabetes (LADA). [26]

Maturity Onset Diabetes of the Young

This is an autosomal hereditary condition characterised by early presentation, non-autoimmune or insulin resistance-related features, and enduring endogenous insulin formation. It is caused by heterozygous mutations in transcriptional regulators of pancreatic β-cell differentiation and maturation.[27]

Monogenic Diabetes

This diabetes occurs due to a single mutation in a dominant autosomal gene. Various examples of this type of diabetes include illnesses like diabetes in newborns and diabetes with maturity-onset of the young. About one percent to five percent of the cases of diabetes are linked to this type of diabetes. MODY is a genetic disorder and typically appears before age 25. [28]

Double Diabetes

Double diabetes is defined by the increased levels of glucose in children and early adolescents, including indications from both types of diabetes.[29]

Diabetes Insipidus

Diabetes insipidus occurs when the body excretes considerable amounts of dilute urine due to vasopressin shortage,excessive water consumption or AVP resistance. [30]

Neonatal Diabetes Mellitus

This form of diabetes arises generally in the initial six-month period of the life. The condition may emerge via any one gene deficiency. The deficiency affects the synthesis of insulin. [31]

Pathophysiology of Diabetes Mellitus

Hyperglycemia and both physiological and behavioral reactions are directly related. The brain detects hyperglycemia and uses nerve impulses to communicate with the pancreas and other organs to lessen its effects.

Type 1 diabetes mellitus

IDDM is defined by an autoimmune destruction of pancreatic β-cells, resulting to a decrease in insulin production and accompanying metabolic problems. Patients with IDDM demonstrate aberrant pancreatic α-cell activity, leading to higher glucagon synthesis and an absence of insulin secretion. Normally, hyperglycemia reduces glucagon synthesis; however, in IDDM, hyperglycemia lacks to lower glucagon output.[32] Elevated glucose levels worsen metabolic problems stemming from insulin insufficiency. One of the most noticeable symptoms of metabolic disturbance is the rapid development of diabetic ketoacidosis in absence of insulin therapy. Although insulin insufficiency is the primary problem in IDDM, administering insulin provides additional challenges. Multiple metabolic mechanisms lead to diminished tissue response to insulin. Insulin shortage induces uncontrolled lipolysis, resulting in excessive amounts of free lipids in the plasma, that in return inhibits glucose absorption in peripheral organs and skeletal muscle.[33] This reduced glucose utilization, combined with a shortage of insulin, changes the expression of genes necessary for response to insulin in the targeted tissues, including the enzymes in the liver and the GLUT-4 transporters for glucose in adipose tissue. The primary metabolic disturbances caused by insulin insufficiency in IDDM include the change in the metabolism process of molecules such as glucose proteins and lipids.

Effects on the glucose metabolism:

Uncontrolled IDDM leads to increased hepatic glucose production. Initially, liver glycogen stores are mobilized, followed by glucose synthesis through hepatic gluconeogenesis. Insulin deficiency also lowers glucose uptake in organs other than the liver. Insulin enhances glucose absorption, notably in adipose tissue and skeletal muscle, by boosting the translocation of glucose transporter proteins to the plasma membranes of

these organs. Reduced glucose absorption by peripheral tissues results in a lower rate of glucose metabolism. Additionally, insulin modulates hepatic glucokinase activity, and a slower rate of glucose phosphorylation in hepatocytes leads to more glucose entering the bloodstream. Insulin also impacts other enzymes involved in the anabolic metabolism of glucose. Plasma glucose levels increase due to heightened hepatic glucose synthesis and reduced metabolism in peripheral organs. When the kidneys' capacity to reabsorb glucose is surpassed, glucosuria ensues. Glucose works as an osmotic diuretic, resulting to increased water and electrolyte loss when renal glucose excretion rises. The consequent water loss and decreased blood volume induce the thirst mechanism (polydipsia). The negative caloric balance generated by glucosuria and tissue catabolism leads to increased appetite and food intake, known as polyphagia.[34]

Impact on lipid metabolism:

Insulin promotes the storage of dietary energy as glycogen in hepatocytes and skeletal muscles after meals. It also stimulates hepatocytes to produce and accumulate lipids in adipose tissues. Triglycerides are quickly mobilized in uncontrolled insulin-dependent diabetic mellitus (IDDM), resulting in increased plasma free fatty acid levels. To generate energy, numerous tissues, with the exception of the brain, receive and utilize free fatty acids. In the absence of insulin, malonyl-CoA levels fall, whereas fatty acyl-CoA transport into mitochondria increases. Acetyl-CoA is generated during mitochondrial fatty acid oxidation and can then be oxidized further in the TCA cycle. In hepatocytes, acetyl-CoA is primarily transformed into ketone bodies rather than oxidized in the TCA cycle. The brain, heart, and skeletal muscles need ketone bodies for energy. In IDDM, high levels of free fatty acids and ketone bodies limit glucose intake, leading in hyperglycemia. Ketoacidosis happens when the body generates greater ketone bodies compared to it can process. [35]

Effects on proteins:

Insulin modulates the expression of numerous genes, either favorably or adversely, altering total metabolism. It has a strong effect on protein metabolism, boosting the rate of protein synthesis while lowering protein degradation. Consequently, an insulin shortage leads to accelerated protein catabolism. The enhanced rate of proteolysis results in higher plasma amino acid concentrations. [36]

Type 2 Diabetes Mellitus

Tests like OGTT classifies the essential aspects of NIDDM s) into four separate groups that are given below:

1. Individuals having diabetes along with over fasting hyperglycemia.
2. Individuals with altered glucose tolerance demonstrate hyperglycemia while having the greatest amounts of plasma insulin, demonstrating insulin resistance. As poor glucose tolerance advances to diabetes mellitus, insulin levels diminish, suggesting that persons with NIDDM have decreased insulin production.
3. Individuals with normal glucose tolerance.
4. Individuals with chemical diabetes (also known as low glucose tolerance).
5. Individuals with diabetes and modest fasting hyperglycemia.

Insulin resistance and depletion are prominent among typical NIDDM patients. While insulin resistance is a major cause of NIDDM, some studies argue that insulin shortage is the primary reason, as even modest insulin resistance alone is insufficient to produce NIDDM. Most patients with the typical type of NIDDM display both problems. Recent data suggests that a member of the nuclear hormone receptor superfamily of proteins has a function in the etiology of type 2 diabetes. Thiazolidinediones are a relatively new

family of medicines designed to boost the body's insulin sensitivity. These chemicals bind to and affect the activity of the peroxisome proliferator-activated receptor gamma (PPARγ).[37]

Targets for the Diabetes Mellitus

α-Glucosidase Inhibitors:

These drugs help to lower the post-meal rise in blood glucose levels by reducing carbohydrate absorption. While they slightly reduce hemoglobin A1c (HbA1c) levels, they do not diminish fasting plasma glucose levels. The most frequent medications in this class include carbohydrate, voglibose, and miglitol. α-glucosidases, enzymes associated with the intestinal wall, break down starch into oligosaccharides and disaccharides, releasing glucose in the colon. This hydrolysis is necessary for the absorption of carbohydrates in the form of monosaccharides. By blocking α -glucosidases, medications such as acarbose, voglibose, miglitol, and emiglitate reduce carbohydrate digestion and absorption, thereby lowering the post-meal surge in blood glucose levels.[51]

Sodium Glucose Transporter Inhibitors (SGLT-2 Inhibitors):

SGLTs are membrane proteins that aid in transporting ions, osmolytes, amino acids, vitamins, and glucose across the intestinal epithelium and the brush border membrane of proximal renal tubules. SGLT2, a high-capacity, low-affinity transporter, is largely expressed in the kidneys. Responsible for reabsorbing roughly 90% of the filtered glucose, SGLT2 has been a focus in diabetes treatment. SGLT2 inhibitors cause glucosuria by limiting the reabsorption of filtered glucose, potentially contributing in improved glycaemic management in people with type 2 DM. Additionally, there may be a weight loss effect due to calorie decrease related with glucosuria and SGLT2 suppression. Dapagliflozin, a highly selective SGLT2 inhibitor, was developed for treating type 2 diabetes. By inhibiting SGLT2 and thereby reducing glucose reabsorption in the kidney's proximal tubule, dapagliflozin leads to lower fasting and postprandial plasma glucose levels, as well as a drop in glycatedhemoglobin. Its pharmacokinetics and pharmacodynamics allow for once-daily dosage.[53]

Dipeptidyl Peptidase 4 Inhibitors (DPP-4):

GLP-1, or glucagon-like peptide-1, is a crucial hormone in metabolism. After meals, GLP-1, together with glucose-dependent insulinotropic peptide (GIP), slows stomach emptying, increases insulin secretion, and lowers glucagon secretion. However, GLP-1 is rapidly destroyed by the enzyme dipeptidyl peptidase-4 (DPP-4), making it less effective as a therapeutic target. DPP-4 is present in a soluble form and is largely positioned on the surface of diverse cell types in major organs of the body. GLP-1 has a short half-life (less than 2 minutes), which limits its therapeutic usage. DPP-4 inactivates incretins like GLP-1 by cleaving off their two terminal amino acids, lowering their efficacy. Therefore, blocking DPP-4 with medicines can increase the half-life of GLP-1, thusrefiningthe anti-diabetic effects. Studies have revealed that inhibitors of DPP4 can increase the half-life of GLP-1 in both humans and animal models by two to three times. This inhibition has been demonstrated to boost insulin production and GLP-1 levels in vivo, underlining the therapeutic potential of DPP-4 inhibitors in diabetes treatment.[56]

11β-Hydroxysteroid Dehydrogenase:

This enzyme, reliant on nicotinamide adenine dinucleotide phosphate (NADP/NADPH), plays a critical function in metabolism. It is highly expressed in important metabolic tissues such the liver, adipose tissue, and central nervous system. Another isoform, 11β-HSD2, is mostly found in the liver and is dependent on nicotinamide adenine dinucleotide (NAD+). In tissues where 11β-HSD1 is present, it converts cortisone to the active hormone cortisol. Cortisol, a stress hormone

generated by the adrenal glands, stimulates glucocorticoid receptors and other variables implicated in diabetes. Elevated cortisol levels in the blood contribute to impaired glucose metabolism, elevated blood glucose levels, and increased blood fat levels due to accelerated fat metabolism, all of which promote insulin resistance. Increased obesity and blood glucose levels are common characteristics of diabetes. Elevated cortisol levels are connected with central obesity, and a particular mutation in the gene producing 11β-HSD has been linked to juvenile obesity and insulin resistance. Carbenoxolone, a drug used to treat peptic ulcers, is suspected to block 11β-HSD. [55]

G-Protein coupled receptor (GPCR 119)

GPR119 is a Class I G-protein coupled receptor present in muscles, liver, and pancreatic β-cells. Activation of GPR119, like incretin hormones, may improve insulin production and have a favorable effect on insulin secretion when agonists bind to it. GPR119 improves glucose homeostasis in two ways:

1. Through direct release of insulin via glucose activated pathway in β-cells and indirectly through the release of GLP-1
2. The second method is release of the GIP in enteroendocrine cells. [52]

GIP (Glucose-dependent insulinotropic polypeptide):

GIP is one among the incretin hormones, found in the β-cells, adipose tissue & the brain where it plays a significant part in the type-2 diabetes mellitus and other metabolic conditions by enhancing the insulin response which is induced by the post-prandial rise in glycemia. [54]

Anti Diabetic Activity Reported In Various Plants

1. **Cinnamomum zeylanicum's (Cinnamon):**

Mukul Tailang, Bhaskar K. Gupta, and Amrish Sharma investigated the antidiabetic efficacy of an alcoholic extract of Cinnamomum zeylanicum (cinnamon) leaves using an alloxan-induced diabetic rat model. The study found that cinnamon leaf extract dramatically reduced blood glucose levels in diabetic mice, indicating that it has prospective therapeutic implications for diabetes management. The study design includes the administration of various dosages of the extract to diabetic rats, with the findings indicating a dose-dependent drop in blood glucose. Although the specific mechanisms of action have not been well investigated, bioactive chemicals found in cinnamon, such as cinnamaldehyde and flavonoids, are thought to increase insulin sensitivity and glucose absorption. The study emphasizes on Cinnamomum zeylanicum's potential as a natural antidiabetic medication, but it also urges for more research to better understand the processes involved and examine long-term effects. The research study concluded that the cinnamon can be used as a good approach to treat diabetes mellitus as it involve phytochemical studies and clinical trials to confirm its effectiveness in people.[42]

2. **Panax Ginseng (Ginseng):**

Anoja S. Attele and colleagues conducted a study that focuses on the potentials of Panax Ginseng berry extract, namely ginsenoside, as a natural therapy for Type 2 diabetes. This study looks at the antidiabetic characteristics of Panax Ginseng berry extract in diabetic mice fed a high-fat diet and induced with streptozotocin, which simulates Type 2 diabetes. The study found that ginseng berry extract dramatically reduces blood glucose levels and increases insulin sensitivity in diabetic rats. The phytochemical research indicated that ginsenoside Re as the primary active component responsible for these anti diabetic benefits as it was discovered to increase insulin secretion and glucose absorption, making it a potential molecule for treating hyperglycemia.[43]

3. **Momordica Charantia (Bitter Melon):**

Mona F. Mahmoud and her colleagues found that Momordica Charantia fruit juice had powerful antidiabetic characteristics, proposing that it could be used as a natural diabetes treatment method. This study investigates the anti-diabetic benefits of the plant fruit juice in STZ induced diabetic rats, which are routinely employed to imitate diabetes by destroying insulin-producing pancreatic beta cells. The study looks at the fruit juice's capacity to reduce blood glucose levels and improve diabetes conditions in rats. Momordica Charantia fruit juice was found to drastically lower blood glucose levels and increase glucose tolerance in diabetic mice. The juice's antidiabetic properties are thought to be related to active components such as charantin, polypeptide-p, and different flavonoids, which aid in insulin production and glucose metabolism. The study also concluded that the plant needs further research for the better understanding and determination of the action and the usefulness of the plant in treating the human diabetes.[44]

4. **Trigonella foenum-graecum (fenugreek):**

The researchers, under the leadership of Liaquat Ali and associates, sought to identify the elements that contribute to the reduction of blood glucose levels whether ingested with or without glucose. The complete seed powder, methanol extract, and the residual post-methanol extraction exhibited notable hypoglycemic effects when provided concurrently with glucose. The water extract of the methanol-extractive-free residue exhibited notable hypoglycemic efficacy across several prandial conditions. This research investigates the hypoglycemic effects of fenugreek seed powder and its extracts on normal and diabetic rats, including models of non-insulin-dependent diabetes mellitus (NIDDM). The study shown that the Soluble Dietary Fibre (SDF) component, primarily composed of galactomannan, did not influence fasting blood glucose levels in either normoglycemic or diabetic rats. However, when supplied simultaneously with glucose, it significantly reduced blood glucose levels in NIDDM model rats ($p < 0.05$). The data demonstrate that SDF, specifically galactomannan, plays a role in the hypoglycemic effects of fenugreek seeds. The study reveals that additional molecules may contribute to its anti-diabetic properties, prompting further examination of its therapeutic potential.[45]

5. **Abrus Precatorius Seed (Rosary Pea):**

The study utilized rabbits that were induced with diabetes using alloxan to test the antidiabetic benefits of a 50 mg/kg chloroform-methanol extracts of Abrus precatorius seeds. This extract displayed antidiabetic effect similar to chlorpropamide when taken at varied intervals In contrast, a different investigation on rats employing a 250 mg/kg dosage of an ethanol-water extract from the apical portions of Abrus precatorius showed only a 30% drop in blood sugar levels. The chloroform-methanol extract was more successful in decreasing alloxan-induced hyperglycemia, while marginally less strong than chlorpropamide. Researchers analyzed the effectiveness based on both the length of activity and the decrease in blood glucose levels. Several plant-based remedies have been found and exploited in diabetes care. [46]

6. **Agrimonia Pilosa's :**

Tianyu Jin, Li Chi, and Chongyang Ma examined Agrimonia pilosa's phytochemical and pharmacological qualities, as well as its potential for treating Type 2 diabetes. The plant contains flavonoids and isocoumarins, including agriflavone, kaempferol-3-O-((S)-3-hydroxy-3-methylglutaryl(1 ⟶ 6))-β-d-glucoside, and flavonoid glycosides including kaempferol 7-O-β-D-glucoside and apigenin 7-O-β-D-glucuronide. The study concludes that substances like apigenin 7-O-β-D-glucuronide and ellagic acid inhibit protein tyrosine phosphatase 1B, a major regulator of insulin sensitivity, with large

IC50 values. However, their efficacy may be limited due to their high anionic charge, implying that derivatives of these compounds could improve bioavailability and effectiveness. In addition, Agrimonia pilosa powder has been demonstrated to lower postprandial hyperglycemia, which is important for diabetes management. The chapter explores the inhibition of α-glucosidase by flavonoids, including luteolin, quercetin, vitexin, and isovitexin, with quercetin showing the highest action. The isocoumarin agrimonolide also improves insulin sensitivity and glucose absorption in insulin-resistant cells, with hypoglycemic effects similar to metformin. The study concludes that Agrimonia pilosa can serve as a natural treatment for type 2 diabetes. It also highlights the need for additional research into its therapeutic advantages and processes of the plant.[47]

7. **Rhizophora Mucronata(Asiatic Mangrove):**

Anjan Adhikari, Moumita Ray, Anup Kumar Das, and Tapas Kumar Sur investigated the anti-diabetic and antioxidant activities of Rhizophora mucronata leaves, a mangrove species from India's Sundarbans. The study aimed to determine the efficacy of the leaf extract of the Rhizophora Mucronata, the study used both in vitro and in vivo models. The in vitro investigation revealed considerable antioxidant activity, with the leaf extract having high free radical scavenging capability while in vivo trial of the extract on the diabetic rats effectively reduced blood glucose levels and increased the insulin sensitivity. The study showed that Rhizophora mucronata leaves have significant antidiabetic and antioxidant properties, making them a prospective candidate for the development of medicinal medicines to treat diabetes and oxidative stress-related illnesses.[48]

8. Tecoma (Trumpet Bush):

The antidiabetic effects of Tecoma stans are explained by two alkaloids, tecomine and tecostanine. Youssef Hammouda and M. Samir Amer's work demonstrated that these alkaloids drastically lowered the blood glucose levels in diabetic models. Additionally, subchronic and acute treatment of tecomine has been proven to lower plasma cholesterol and triglyceride levels without changing fasting glucose levels. Tecoma stans aqueous leaf extract improves glucose absorption in both insulin-sensitive and insulin-resistant murine and human adipocytes without eliciting substantial pro-adipogenic or anti-adipogenic side effects. Moreover, an ethanolic extract of Tecoma stans stem (200 mg/kg) exhibited a statistically significant reduction in blood glucose levels, approaching the efficacy of current treatments. This antidiabetic action is considered to result from the stimulation of insulin secretion by pancreatic β-cells. The presence of phytochemicals, including flavonoids, saponins, and alkaloids in the ethanolic extract, is suggested to contribute to the plant's antidiabetic effect. These findings indicate Tecoma stans as a potential natural therapy for diabetes.[49]

9. **Acacia modesta (Amritsar Gum):**

Sunil Jawla, Y. Kumar, and M.S.Y. Khan examine the antibacterial and antihyperglycemic effects of Acacia modesta leaves. The study investigates the plant's potential in treating microbial infections and regulating excessive blood glucose levels. The research demonstrates that Acacia modesta leaf extracts showed substantial antibacterial activity against several bacterial and fungal strains, showing its potential as a herbal antimicrobial agent. In terms of antihyperglycemic activities, the study reveals that the leaf extracts effectively decrease blood sugar levels in diabetic mice. This hypoglycemic impact is attributable to the presence of bioactive chemicals that promote insulin sensitivity and glucose absorption. The

results suggest the potentially beneficial effects of Acacia modesta leaves in healing infections and managing diabetes, underlining the need for further investigation of its medicinal characteristics.

10 Teucrium polium (Felty Germander):

The study conducted by Ali Akbar Asghari and colleagues analyzes the anti-diabetic effects and bioactive components of Teucrium polium (T. polium). The research indicates that T. polium exhibits considerable anti-diabetic effects through many mechanisms, including boosting insulin production, lowering oxidative damage, repairing pancreatic β-cells, and increasing glucose absorption in muscle tissues by activating GLUT-4 translocation. Additionally, T. polium inhibits α-amylase activity, which contributes to enhanced glycemic control and reduction of insulin resistance. The data imply that T. polium is acceptable at low doses and could act as an effective addition to other anti-diabetic drugs, perhaps lowering adverse effects and boosting efficacy. The plant also shows promise as a dietary supplement for controlling prediabetes. However, the study stresses the need for more investigation into the long-term effects of T. polium on microvascular problems associated with diabetes, such as retinopathy, cardiomyopathy, nephropathy, and endothelial dysfunction. Future studies should focus on identifying biomarkers associated to these problems and exploring the biologic targets and bioactive components of T. polium. The report highlights the plant's extensive pharmacological properties, including antioxidant, anti-inflammatory, hypolipidemic, and liver protective activities, and advocates for further detailed clinical and molecular research to fully grasp its medicinal potential.[50]

CONCLUSION

The worldwide incidence of diabetes has reached frightening proportions, with an estimated 537 million adults affected in 2021 and forecasts of 783 million by 2045. This astonishing growth in the rate of diabetes underlines the critical need for creative treatment techniques to combat this chronic and devastating ailment.While current medications, such as metformin, insulin, and GLP-1 receptor agonists, have proven helpful in controlling diabetes, the search for innovative therapeutic targets continues. Researchers are researching a range of potential compounds that target important pathways involved in glucose and lipid metabolism, insulin sensitivity, and pancreatic function. Emerging targets such AMPK, FBPase, GK, GPR119, GSK-3, PTP1B, and SGLT2 hold the potential to enhance glycemic control, reduce diabetic complications, and improve the overall quality of life for those living with diabetes. By targeting numerous pathways concurrently, combination medicines may offer even greater therapeutic benefits and help lessen the global burden of this disease. As we seek to address the increased prevalence of diabetes, it is vital that we continue to engage in research, education, and public health programs. By working together, healthcare professionals, politicians, and individuals may drive progress in the prevention, early detection, and successful management of diabetes. Through a multidimensional approach that combines cutting-edge medicines, lifestyle modifications, and a commitment to global health justice, we may move towards a future when diabetes no longer poses a substantial danger to human well-being. The moment to act is now, as the health and prosperity of nations globally depend on our collaborative efforts to tackle this grave crisis

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