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Type 2 Diabetes Mellitus and the Structure of Available Medication: A Review

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Abstract

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia due to failure in the secretion, action, or both of insulin. Insulin is a hormone that regulates blood sugar. Increased production and ineffective scavenging of reactive oxygen species may play a critical role in diabetes mellitus. Diabetes mellitus is mainly categorized into 2 types: type 1 and type 2. The latter is the most predominant form of diabetes. The presence of diabetes mellitus confers an increased risk of many devastating complications among which cardiovascular diseases, peripheral vascular diseases complications such as coronary artery disease, stroke, neuropathy, renal failure, retinopathy amputations, and blindness. The incidence of this critical disease can be either delayed or prevented by the organization of dietary nutrition (high in green leafy vegetables) and regular exercise (the main benefits of exercise will be gain even if the person does not lose weight). In addition to these, oral hypoglycaemic agents, such as insulin, biguanides, sulphonylureas, meglitinides, and more recently developed therapeutic classes including amylin agonists (with the first-in-class pramlintide approved in 2005), glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors are useful in the treatment of type 2 diabetes mellitus. Most importantly, the use of medicinal plants against diabetes mellitus is frequent in African countries such as Ethiopia.

Keywords: Type 2 Diabetes Mellitus, Medicinal Plant; Pharmacotherapy, Prevention, Symptoms

1. Introduction

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin that it produces. Insulin is a hormone that regulates blood sugar. Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia due to failure in secretion, action, or both of insulin. **[14]**. Increased production and ineffective scavenging of reactive oxygen species may play a critical role in diabetes mellitus. The disturbance of the antioxidant defense system in diabetes is mainly because of alteration in antioxidant enzymes, impaired glutathione metabolism, and decreased ascorbic acid levels. It is becoming the third “killer” of mankind along with cancer, cardiovascular and cerebrovascular diseases. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves, blood vessels, eyes, and kidneys. Also, diabetes increases the risk of heart disease and stroke **[15]**.

The World Health Organization (WHO) reported that, globally, more than 425 million people are living with diabetes, and more than 30 million Americans have diabetes. The prevalence of DM nearly doubled between 1980 and 2014, rising from 4.7% to 8.5%, and is expected to increase another 50% by 2045. According to the WHO, DM was the direct cause of 1.6 million deaths making it the seventh leading cause of death in 2016 **[33]**. Diabetes mellitus (DM) is reported as a medical condition whereby the human body fails to properly metabolize glucose for use as energy, as a result of insulin resistance (type 2 diabetes) or insulin insufficiency (type 1 diabetes **[26]**.

McCance and Huethe (2007) state that DM is used to describe a condition characterized by chronic hyperglycemia and other disorders of carbohydrate, fat, and protein metabolism. Glucose is extracted from sweet foodstuffs, for example, cakes, or from starchy foods, such as potatoes, pasta, or bread when they are digested and absorbed. Glucose is utilized by the cells to produce energy. The uptake of glucose by the cells is regulated by the hormone insulin, which is produced by the beta cells of the islets of Langerhans in the pancreas. Since a rise in blood glucose stimulates insulin secretion, a lowering of blood glucose caused by the action of insulin inhibits further insulin secretion through the negative feedback system **[30]**.

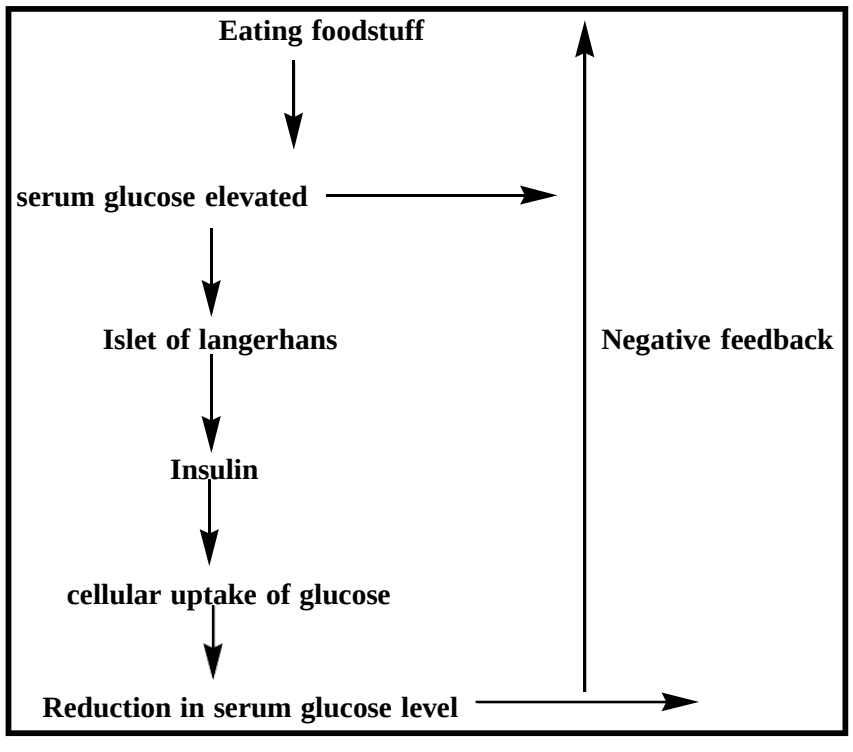

Figure 1: Negative feedback of insulin control **[23]**.

The above **(Figure 1)** shows that low levels of blood sugar stimulate the secretion of glucagon. Increased glucagon causes stored glycogen in the liver to be converted into glucose for release into the bloodstream. As blood sugar levels rise, the glucagon stops, but high blood sugar levels result in the release of insulin. Increased insulin levels cause the intake of glucose into muscle cells and convert excess glucose into glycogen for storage in the liver. When blood sugar levels drop, the cycle starts again. Glucagon is a pancreatic hormone that is involved in hyperglycaemia, stimulating hepatic glucose production by increasing glycogenolysis and gluconeogenesis. Glucagon increases hepatic glucose and ketone production - catabolic features of insulin deficiency **[23]**. The presence of diabetes mellitus confers an increased risk of many devastating complications such as cardiovascular diseases, peripheral vascular diseases complications such as coronary artery disease, stroke, neuropathy, renal failure, retinopathy amputations, and blindness. Also, it is an endocrine dysfunction resulting from insulin deficiency or the incapability of peripheral tissues to respond to insulin **[25]**.

Methodology:

The method we used to conduct the review process is Document Analysis. This document analysis is based on Scott's (1990) principle. This principle has three criteria.

1. Originality of the documents to be used. In this review, all the literature that we used are original articles.

2. Authenticity of the document used. The authenticity of the articles used to prepare this review is ascertained.

3. Credibility of the documents used. All articles used in this review are authored by known researchers. This can be proved by the references cited throughout the paper. All the materials used for writing this article are primarily gathered and sorted out based on their relevance. The materials used are qualitative-based literature. A detailed analysis of the materials by classifying them into subtopics that compare and contrast them was undertaken to elucidate the overall issues of the topic.

2. History Of Type 2 Diabetes

Diabetes mellitus (DM) is a globally epidemic metabolic disorder with a global prevalence of 8.4%, with the highest levels (9.2%) reported in the Middle East region **[27]**. Diabetes mellitus has been known since antiquity, its treatments have been known since the Middle Ages, and the elucidation of its pathogenesis occurred mainly in the 20th century. Non-progressing Type 2 diabetics almost went undiagnosed. Diabetes has been prevalent since approximately 1550 B.C. Egyptian doctors defined it as a disease that causes the patient to lose weight rapidly and urinate frequently. This is considered to be the first definition of diabetes mellitus. The name diabetes was coined by the Greek Physician Aretaeus. He recorded the disease with symptoms such as constant thirst (polydipsia), loss of weight, and excessive urination (polyuria). He named the condition 'diabetes', which means 'a flowing through'. After this period, diabetes name is rarely mentioned. Indeed, it seems to have been a mystery during the Middle Ages **[22]**.

In 1921, Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski but went a step further and managed to show that they could reverse the induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs. This was a step forward in the elucidation of the endocrine role of the pancreas in metabolism and the existence of insulin. These scientists proceeded to isolate insulin from the bovine pancreas at the University of Toronto in Canada, thereby leading to the availability of an effective treatment for diabetes mellitus, with the first clinical patient being treated in 1922 (Piero, 2015).

2.1. Types of Diabetes Mellitus (DM)

The first principally accepted classification of diabetes was revealed by the UN agency in the year 1980 and, it changed within the year

1985. The foremost common and necessary sort of primary or upset diabetes is the focus of our discussion. It should vary from secondary diabetes which incorporates kinds of symptoms related to recognizable causes within which destruction of exocrine gland islets is induced by inflammatory exocrine gland diseases, surgery, tumors, certain medications, iron full (Hemochromatosis), and sure acquired or genetic endocrinopathies. The classification encompasses each clinical stage and aetiological sorts of diabetes and different classes of hyperglycemia **[21]**. There are two types of Diabetes mellitus – Type 1, "Juvenile Diabetes mellitus" (Insulin Dependent Diabetes Mellitus, IDDM), which is hereditary and is treated by giving insulin; and Type 2, "Adult Type" (Non-Insulin Dependent Diabetes Mellitus, NIDDM), which occurs in elderly people and is treated by controlling the diet and giving oral anti-diabetic drugs. The main symptoms of type 1 and type 2 diabetes are increased thirst, increased urinary output, ketonemia, and ketonuria, that is, the presence of ketone bodies in the blood and urine. Diabetes should be suspected when any of these symptoms are present (Kuma et al., 2013).

Type-2 diabetes mellitus (T2DM) is a major public health problem. Around 425 million people globally were diagnosed with T2DM in 2017, and this is predicted to increase to 629 million by 2045. T2DM is also a significant risk factor for cardiovascular diseases, the leading cause of morbidity and mortality in the population worldwide **[41]**. Type 2 diabetes mellitus (T2DM) is ranked among one of the most challenging global epidemics because it affects both human health and economies. The number of people plagued with T2DM worldwide in the past 20 years has more than doubled **[43]**.

T2DM is a chronic disease caused by complex interactions of genetic and environmental factors. The role of both our genetic makeup and the environment is a contributing factor to insulin resistance and β-cell dysfunction. In recent times, there have been arguments saying that changes in the gene makeup cannot be the main cause for the upsurge in the prevalence of T2DM. However, changes in dietary and lifestyle patterns are fundamental to grasping this epidemic **[43]**.

Type 2 diabetes mellitus is an increasingly common disorder of carbohydrate and lipid metabolism. Two important characteristics of this disease are insulin resistance, the failure of peripheral tissues; including liver, muscle, and adipose tissue to respond to physiologic doses of insulin, and the failure of pancreatic cells to properly secrete insulin in response to elevated blood glucose levels. Obesity is a significant risk factor for the development of type 2 diabetes mellitus. An extremely lean and lipoatrophy model has revealed a similar predisposition to developing diabetes. Although it may seem paradoxical that both increased adiposity and severely reduced fat mass cause diabetes, a common pathophysiologic process in fat may be responsible for the predisposition to develop hyperglycemia in both conditions **[2]**.

Noninsulin-dependent diabetes mellitus is characterized by reduced insulin secretion in response to glucose levels and insulin resistance, which leads to the inefficient absorption of glucose into the cell for energy. It is present in 90% of the diagnosed cases of diabetes and affects 18% of the population above 65 years of age, usually occurring in obese individuals. These individuals have normal or even greatly elevated insulin levels. Perhaps, the elevated insulin production results from overeating. It eventually suppresses the synthesis of insulin receptors (a plasma membrane-bound glycoprotein). This hypothesis concludes that diet alone is usually sufficient to control this type of diabetes **[22]**.

2.2. Symptoms of Type 2 Diabetes

Symptoms of diabetes mellitus include polyuria, polydipsia, polyphagia, nocturnal enuresis, paresthesia, peripheral neuropathy, pruritis, vulvovaginitis, recurrent blurred vision, fatigue, weakness and often asymptomatic in type 2 diabetes mellitus **[7]**. Insulin deficiency eventually leads to weight loss despite an increase in appetite. Fatigue, nausea, and vomiting have more chances of developing infections. Often, symptoms come on slowly. Long-term complications from high blood sugar include heart disease, strokes, and diabetic retinopathy which can result in blindness, kidney failure, and poor blood flow in the limbs which may lead to amputations **[20]**.

2.3. Main Causes for the Incidence of Type 2 Diabetes

Many factors play a critical role in the incidence of this medical problem, like diet, obesity, lack of sleep, and nutritional supplements received by the mother during pregnancy. However, the main critical factors that play a role are lifestyle, genetic factors, and other medical problems. On the other, it is caused by a combination of genetic factors related to impaired insulin secretion and insulin resistance and environmental factors such as lack of exercise, stress, as well as aging **[31]**.

2.4. Diet and Exercise Factors

Compared to people without diabetes, people with type 2 diabetes are nearly 2.5 times more likely to have a heart attack, heart failure, and stroke. Several potentially modifiable risk factors are related to diabetes, including insulin resistance, obesity, physical inactivity, and dietary factors. Dietary factors are of paramount importance in managing and preventing type 2 diabetes. Diabetes is one of the most significant global public health issues, which needs urgent solutions for slowing or even reversing this trend by investing in modifiable factors, including diet, physical activity, and weight. The importance of nutrition in managing and preventing type 2 diabetes through weight and metabolic control is evident **[34]**.

Aging, obesity, insufficient energy consumption, drinking alcohol, smoking, etc. are independent risk factors of pathogenesis. Obesity (particularly visceral fat obesity) due to a lack of exercise is accompanied by a decrease in muscle mass, induces insulin resistance, and is closely associated with the rapid increase in the number of middle - and high-aged patients. The changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars, and

the decrease in dietary fiber intake, contribute to obesity and cause the deterioration of glucose tolerance. Even mild obesity (Body Mass, Index, BMI 25) causes a 4 - to 5-fold increase in the risk of developing diabetes if accompanied by an increase in visceral fat mass **[38]**. Body Mass Index (BMI) is an anthropometric indicator used to categorize levels of adiposity. Higher BMI levels can be used to assess the risk for the development of T2DM and other chronic health conditions. According to the World Health Organization, BMI is an effective indicator of obesity. low BMI (<20) is an independent risk factor for the development of diabetes **[28]**. In addition to being overweight and obese, risk factors for developing type 2 diabetes include increasing age and lifestyle factors such as physical inactivity, unhealthy diet, etc. People from lower socioeconomic groups are particularly at risk. The more risk factors present, the greater a person's chance of developing type 2 diabetes **[36]**.

2.5. Prevention

The incidence of this critical disease can be either delayed or prevented by the organization of dietary nutrition (high in green leafy vegetables) and regular exercise (the main benefits of exercise will be gain even if the person does not lose weight). Moreover, it has been proven that the combination of these two points diet and exercise are very effective in preventing the incidence of type 2 diabetes mellitus and regulation of blood sugar within those patients even more than the effect of diabetic treatment i.e., metformin. Lifestyle modifications such as weight control, increased physical exercise, and smoking cessation are potentially beneficial in preventing diabetes mellitus and its complications **[8]**. People should be encouraged to adopt preventive interventions for diabetes such as maintaining normal body weight (BMI 18.5–24.9 kg/m2), engaging in regular aerobic physical activity such as brisk walking (at least 30 min per day), limiting consumption of alcohol and consume a diet rich in fruits, vegetables, low-fat dairy products. Several studies of community-based noncommunicable disease prevention projects attempted to prevent the onset of diabetes through lifestyle modification, reduction in obesity, and through pharmacological means **[29]**.

Community-based strategies for the prevention of diabetes are the following: **1**) primary prevention, **2**) secondary prevention, **3**) tertiary prevention. Among the three, the former is related to lifestyle modifications. Primary prevention includes two approaches: the high-risk approach and the population approach. The high-risk strategy primarily aims to bring preventive care to individuals with a family history of diabetes who carry a genetic susceptibility, individuals with impaired glucose tolerance, aging individuals, sedentary individuals, and obese proportion population. Population strategy aims to lower the mean level of risk for the entire population by increasing physical activity, improving diet, and reducing obesity. Primary prevention refers to preventing diabetes from occurring. Secondary prevention refers to preventing complications in those who already have diabetes (e.g., prevention of neuropathy), and tertiary prevention refers to the prevention of worsening complications (e.g., amputation resulting from injury to a neuropathic foot) or death **[11]**.

2.6. Pharmacotherapy

Diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Many pharmacotherapies have been approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes. In addition to insulins, biguanides, sulphonylureas, meglitinides, and, more recently developed therapeutic classes including amylin agonists (with the first-in-class pramlintide approved in 2005), glucagon-like peptide-1(GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors are useful medications. In addition to the development of new pharmacological treatments, many other changes have taken place in the diabetes landscape during the past decade, including evidence from major clinical trials such as the Canagliflozin Cardiovascular Assessment (CANVAS) and Liraglutide Effect and Action in Diabetes. The main objective of these drugs is to correct underlying metabolic disorders, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes **[16]**.

Diet and lifestyle strategies are to reduce weight, improve glycaemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes. Diabetes is best controlled either by diet and exercise (non-pharmacological) or by diet with herbal or oral hypoglycaemic agents or insulin (pharmacological) (Akhtar et al., 2013).

2.7. Importance of Medicinal Plants and Traditional Medicines

Medicinal plants, since time immemorial, have been used in virtually all cultures as a source of medicine. It has been estimated that about 80-85% of the population both in developed and developing countries rely on traditional medicine for their primary healthcare needs and it is assumed that a major part of traditional therapy involves the use of plant extracts or their active principles. Due to the lack of organized healthcare systems in developing countries like Ethiopia, people with chronic diseases like diabetes are among the worst sufferers in their communities. Hence, most of the population still has limited access or no access, especially those in remote areas, to modern medicines. Instead, they use traditional medicines for a range of diabetic complications. Scientific validation of several Indian plant species has proved the efficacy of botanicals in reducing the sugar level, even though many remain to be scientifically investigated. The main disadvantages of the currently available drugs are that they have to be

given life-long and produce side effects. More than 1200 plant species have been used to treat diabetes in folk medicine **[25]**.

Today, many treatments that involve the use of medicinal plants are recommended. Most plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and can often have anti-diabetic effects. The anti-hyperglycemic effects that result from treatment with plants are often due to their ability to improve the performance of pancreatic tissue, which is done by increasing insulin secretions or reducing the intestinal absorption of glucose **[18]**. Herbal medicine which has been traditionally used against diabetes Mellitus is the safest way to manage this disease. Plants with medicinal properties serve as the biggest source of traditional medicines that have been continuously practiced since a long time ago in the form of herbal drugs and are easily available as a source of treatment all over the world. There are several medicinal plants reported that help to reduce high blood glucose levels **[40]**. Several medicinal plants have been used as dietary adjuncts in the treatment of numerous diseases without proper knowledge of their function. Although phytotherapy continues to be used in several countries, few plants have received scientific or medical scrutiny. Plants that are most effective and the most commonly studied concerning diabetes and their complications are: Allium cepa, Allium sativum, Aloe vera, Cajanucajan, Cocciniaindica, aesalpiniabonducella, icusbengalenesis, Gymnemasylvestre, Momordicacharantia, cimumsanctum, Pterocarpus marsupium, Swertiachirayita, Syzigiumcumini, Tinosporacordifolia and Trigonellafoenumgraecum. Among these reserves, scientists evaluated M. charantia, Eugenia jambolana, Mucunapruriens, T. cordifolia, T. foenumgraecum, O. sanctum, P. marsupium, Murrayakoeingii, and Brassica juncea. All plants have shown varying degrees of hypoglycemic and anti-hyperglycemic activity **[37]**.

2.7.1. Bitter Melon (Momordica charantia) (Cucurbitaceae)

Momordica charantia (MC) is one of the most common vegetables in the tropical region, particularly in Vietnam, India, China, East Africa, South–North Asia, and Central and South America. It is a member of the Cucurbitaceae family and is known as bitter melon or bitter gourd. Besides using MC as a vegetable, it is supposed to be herbal medicine, used as folk medicine. Some of its bioactivities are anti-inflammatory activity, anti-oxidant activity, anti-viral activity, anti-cancer activity, anti-bacterial activity, and especially anti-diabetic activity **[42]**.

2.7.2. Allium Cepa (Onion) and Allium Sativum(Garlic)

Allium cepaand Allium sativum are members of the lily family, having blood glucose lowering, anti-oxidant, anti-hypertensive, and anti-hyperlipidemic effects. Volatile oils in raw onion and garlic have been reported to lower fasting blood glucose levels in both animal and human trials. The active compounds are believed to be sulfur-containing compounds: allyl propyl disulfide (APDS) in onions and diallyl disulfide (allian) in garlic. These active compounds lower glucose levels by competing with insulin (a disulfide) for insulin-inactivating sites in the liver, resulting in increased levels of plasma insulin **[42]**.

2.7.3 Nigella Sativa (Black Seed)

Seeds of Nigella sativa (black seed) have been used for centuries as a natural remedy for various ailments. Hypoglycemic, antioxidant, hypotensive, hypolipidemic, and antimicrobial effects of N. sativa have been experimentally reported **[1]**. In clinical studies, its therapeutic effect on metabolic syndrome and diabetes has been shown in recent years **[1]**. It is reported that oxidative stress (OS) plays a significant role in the development of diabetic complications because OS leads to declining the efficacy of insulin-producing cells or pancreatic beta cells (PBCs) that sequentially alter the insulin-producing processes in the body. Black seed and its active compounds have potential contrary to diabetic complications because it declines OS that ultimately aids in conserving the insulin-producing cells (PBCs) cubicle. When diabetic patients used up to 2g of seeds for 3 months each day, which resulted in deductions in glucose levels and improved the function of insulin-producing cells (PBCs), it was suggested that N. sativa seeds are helpful to treat type 2 diabetes **[1]**.

2.7.4 Mangifera Indica (Mango)

Mango leaves have been reported to be very useful for managing diabetes. The tender leaves of the mango tree contain tannins called anthocyanidins that may help in treating diabetes. The aqueous extract produces a reduction of blood glucose levels in normoglycemic and glucose-induced hyperglycemia, however, does have not any effect on streptozotocin-induced diabetic mice under the same conditions when compared with that of an oral dose of chlorpropamide. The study indicates that the aqueous extract of the leaves of M. indica possesses hypoglycemic activity **[3]**.

2.7.5 Syzygium Cumini (Black Berry)

The presence of alkaloids, amino acids, steroids, and triterpenoids in ethyl acetate and methanol extracts of S. cumin seed extract was revealed in the initial phytochemical screening. S. cumini seed has been known to possess various medicinal properties apart from anti-diabetic activity such as anti-inflammatory and analgesic activities. Mycaminose, isolated from S. cumin seeds extract, possesses anti-diabetic properties whose mechanism of action is much more similar to that of Glibenclamide – a drug that stimulates insulin secretion from pancreatic beta cells. It was also found that ethyl acetate and methanol extract of S. cumin seed possess an antidiabetic effect in STZ-induced diabetic rats **[39]**.

3. Isolated Compound Used In The Management Of Type 2 Diabetes Mellitus

3.1. Plant Constituents

Throughout history, different remedies and drugs have been used to treat T2DM, including insulin. Some of them have been included in

the therapeutic arsenal of medicine, and others are used as complementary therapy in patients with hyperglycemia. Several of these compounds have been obtained from plants or microbes. Classic examples are galegine, phenolic compounds and pycnogenol derived from plants, and acarbose, miglitol, and voglibose from microbes **[9]**. The first medicinal plant described with a clear antidiabetic effect was Galega officinalis. (Fabaceae), which has been prescribed since the Middle Ages to treat diabetes mellitus. From this plant, also called goat's rue, French lilac, or Italian fitch, a guanidine derivative, galegine, was isolated. This compound, whose chemical structure is quite similar to the antidiabetic drug metformin, **(Figure 2)** is responsible for the lowering of blood glucose produced by the plant extract **[35]**.

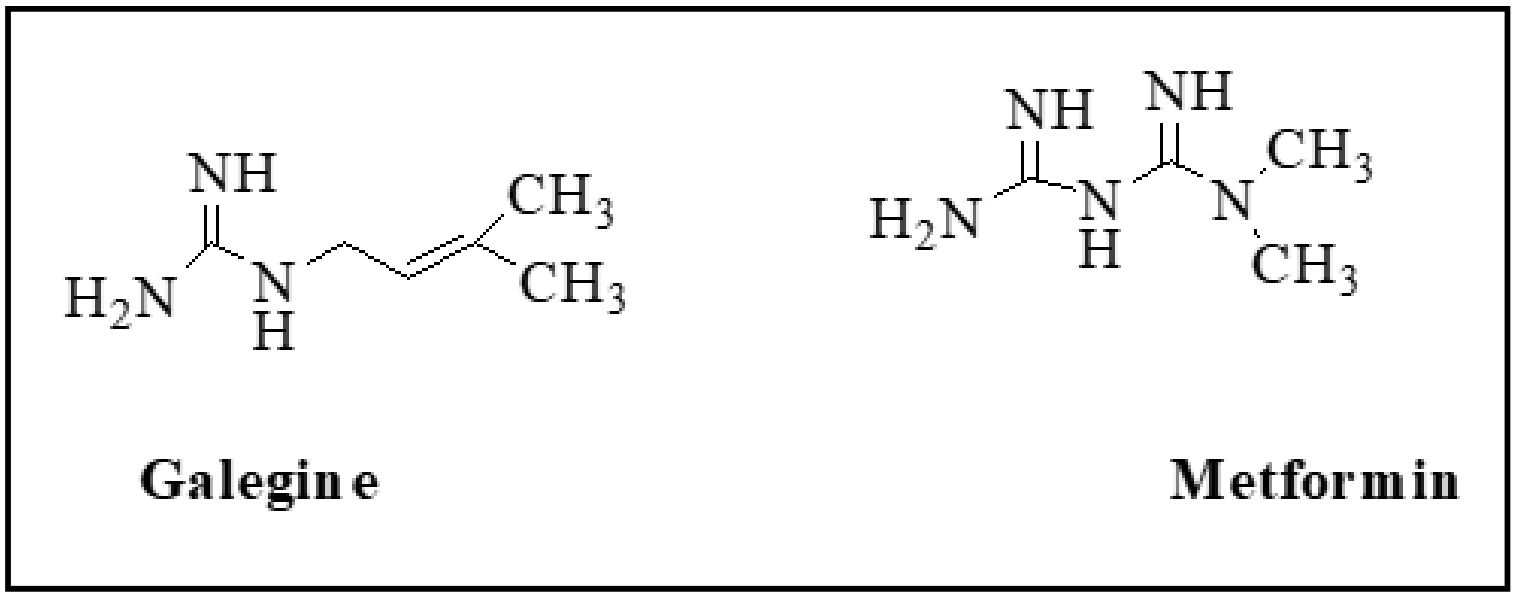

Figure 2: Structure of Galegine and Metfomin

From the current literature, it is evident that M. charantia is the most widely used and popular anti-diabetic plant. Medicinally, the plant, its fruit and its powder extract possess a long history of use in the treatment of numerous diseases including diabetes. Generally, the public has used different parts of M. charantia including the leaves, the stem and mainly the green fruits or seeds to treat diabetes. **Figure 3** shows the chemical structures of momorcharin and momordicin which is believed to possess insulin-like chemical structures and properties **[6]**.

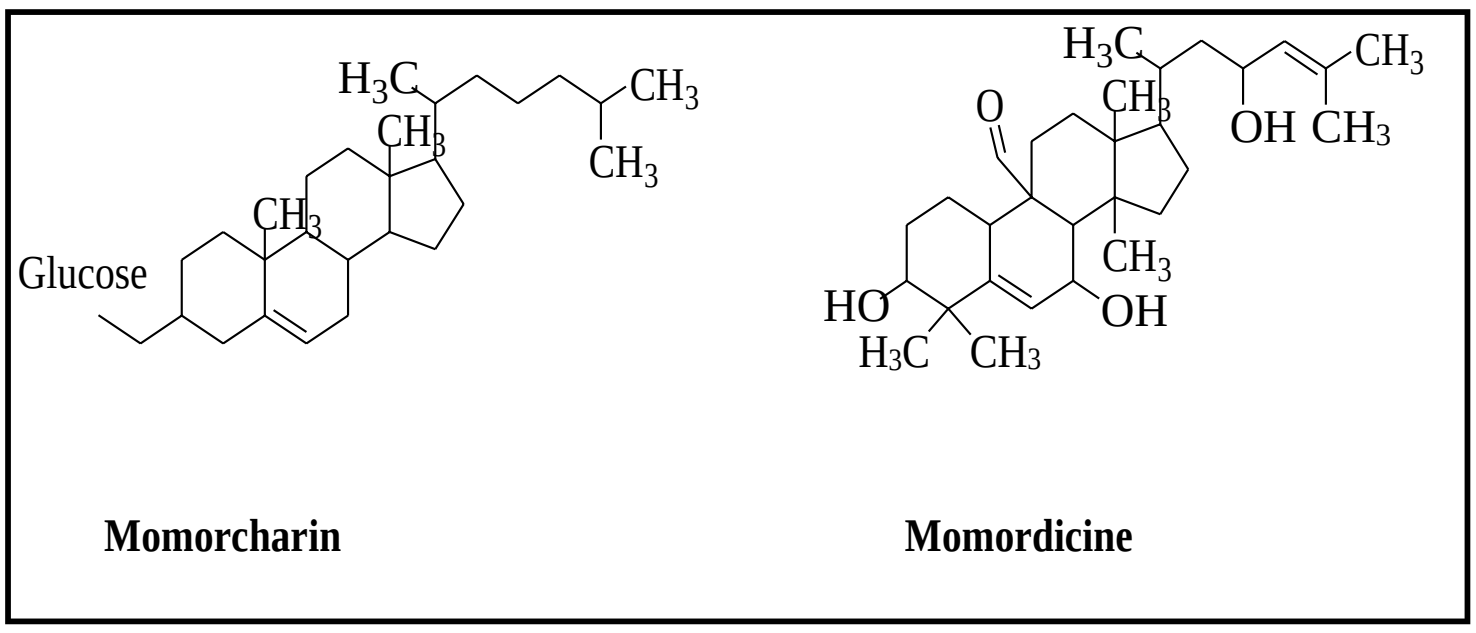

Figure 3: Structure of Momorcharin and Momordicine

3.1.1. Alkaloids

Different alkaloids have been isolated from several medicinal plants and investigated for their possible antidiabetic activity in different animal models. Alkaloids exert a wide range of antidiabetic activities through different mechanisms. Berberine, an important class of alkaloids reported with its mechanism of hypoglycemic or hyperglycemic activity.

In diabetic animal models, flavonoids typically lead to reduced aldose reductase, regeneration of pancreatic β-cells, and increased insulin release. According to their biological properties, polyphenols may be useful nutraceuticals and supplementary treatments and are involved in the regulation of carbohydrate and lipid metabolism, amelioration of hyperglycemia, dyslipidemia, insulin resistance (IR), alleviating oxidative stress, and inflammatory signaling pathways. Naringin, a major flavanone glycoside obtained from grapefruit, was found to reduce blood glucose and IR index, glycosylated hemoglobin, and inflammatory cytokines and increase the levels of serum insulin and glutathione in the antioxidant defense system in diabetic rat models **[45]**.

3.1.2. Berberine

A natural plant alkaloid isolated from the Chinese herb, Coptis chinensis (Huanglian) is commonly used for diarrhea, and a potential glucose-lowering effect has been noted. In vitro and in vivo studies subsequently showed that Berberine has potentially beneficial effects in the treatment of diabetes and obesity. Berberine can reduce body weight and cause a significant improvement in glucose tolerance in db/db mice and high-fat-fed Wistar rats. Berberine **(Figure 4)** may increase glucose-stimulated insulin secretion and proliferation in Min6 beta cells and inhibit -glucosidase activities and reduce glucose absorption in Caco-2 cell, increased insulin, and decrease levels of HbA1c, TC, and TG attenuated axonopathy **[24]**.

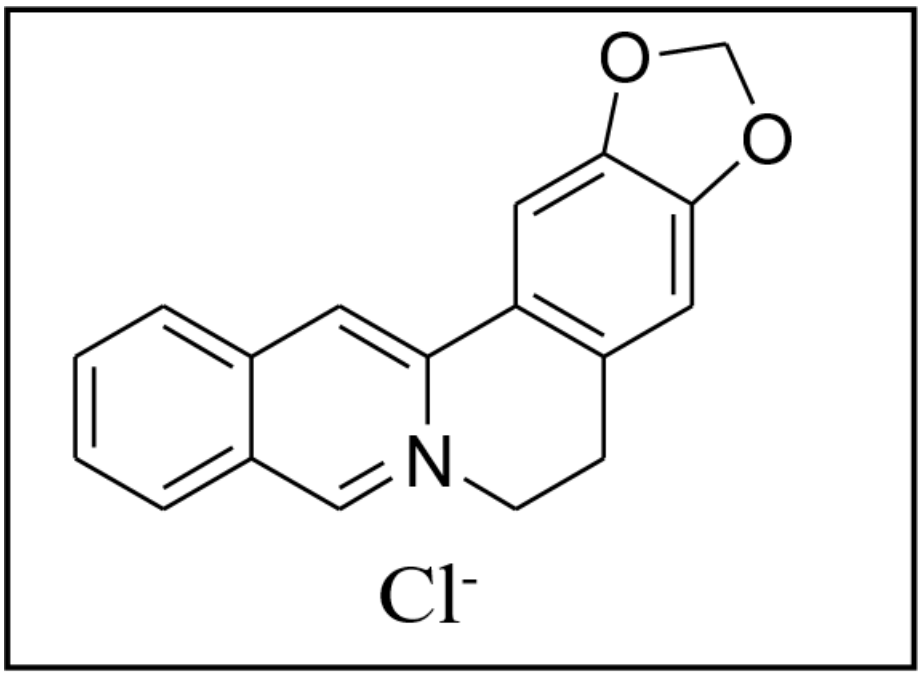

Figure 4: Structure of Berberine

3.1.3. Flavonoids

Flavonoids **(Figure 5)** represent a beneficial group of naturally occurring compounds with hypoglycemic potentials. These are widely distributed in plant kingdoms and exhibit characteristics of pharmacological properties. Flavonoids can be widely classified into different categories like Anthocyanins, catechins, flavanols, flavones, flavanones, etc. Flavonoids have been reported for anti-inflammatory, antidiabetic, anticancer, neuroprotective, and cardio-protective activities. Flavonoids were reported to enhance insulin secretion, promote pancreatic β-cells proliferation and glucose uptake, and reduce insulin resistance, inflammation, and oxidative stress. Some flavonoids have hypoglycemic properties. They may improve altered glucose and oxidative metabolisms of diabetic states. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes mellitus (T2DM) **[12]**. Quercetin was isolated as an active principle from a methanol extract of Chamaecostuscuspidatus(Costaceae) rhizome. It may contribute to the reduction in blood glucose levels and also lipid profile. It has been investigated that quercetin in doses of 10 and 50 mg/kg promotes normalization of the level of glycemia and blood coagulation, increases liver glycogen content, and reduces high blood serum concentrations of cholesterol and low-density lipoproteins, as seen in diabetes **[4]**.

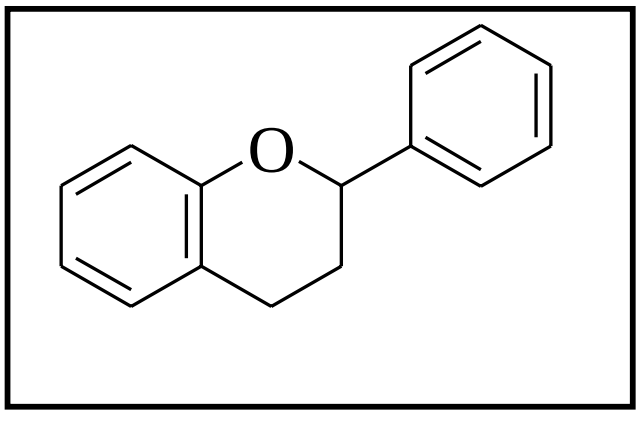

Figure 5: Structure of Flavonoid

3.1.4. Coumarin

The parent molecule of its derivative is the simplest compound of large class of naturally occurring phenolic substances. It was first isolated from tonka beans and is found naturally from human dietary fruits and vegetables such as cassia, lavender, cinnamon, melilot, green tea, peppermint, celery, bilberry, honey, carrots, and other foodstuffs. Coumarin **(Figure 6)** is known to have antioxidant potential like vitamin E (a-tocopherol) and has a lipid-lowering effect. Coumarin is also a potent chemo-preventative agent that reduces nephrotoxicity and inhibits mammary tumor formation in rats **[32]**.

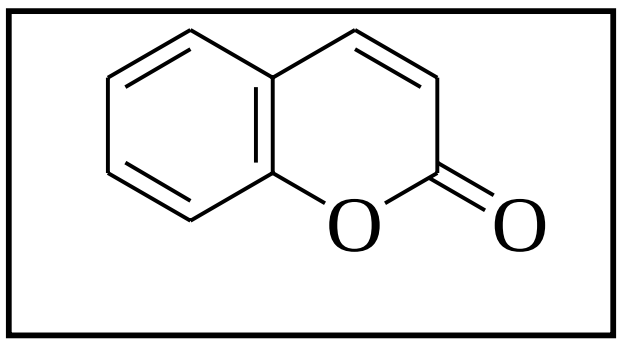

Figure 6: Structure of Coumarin

3.2. Drugs Used in the Management of Diabetes 2 Mellitus

The first pharmacological treatment of T2DM came from insulin isolated from an animal pancreas in the 1920s. In recent years, many orally administered agents and injectable drugs have been developed to treat patients with T2DM. They can be used individually and in combination. These medications are aimed at enhancing blood glucose levels and reducing body weight and the risk of cardiovascular damage. However, the efficacy of drugs for weight loss varies and can range from mild weight loss (less than 3.2% of the initial weight) to strong weight loss (greater than 5% of the initial weight).

3.2.1 Biguanides

Biguanides **(Figure 7)** are among the most commonly recommended oral antihyperglycaemic pharmaceutical agents. Glucophage, Glucophage XR (metformin) is the only biguanide approved in the U.S. Its mechanism of action is through reducing glucose production by the liver, reducing the absorption of glucose, and enhancing the uptake of glucose into skeletal muscle. An advantage of this class of drugs is that it works best when fasting blood glucose levels are above 300, and when sulfonylureas cannot stimulate the release of insulin from beta cells at high levels of glucose. The source of metformin is galegine, a natural product produced by the plant Galega officinalis. The impact of metformin is associated with decreased hepatic glucose production, increased insulin sensitivity in peripheral tissues, and reduced insulin levels during fasting **[8]**.

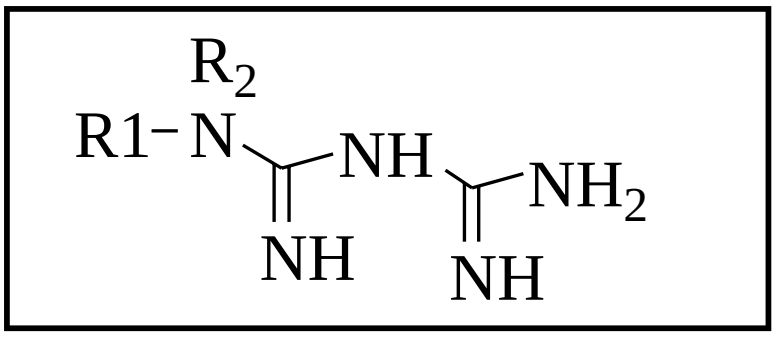

Figure 7: Structure of Biguanides

3.2.2. Metformin

The drug metformin is usually the first line of attack. Structurally it is a biguanide and as such it has connection with guanidine **a** and galegine **b**. **(Figure 8)**, which can both be extracted from the plant goat's rue.

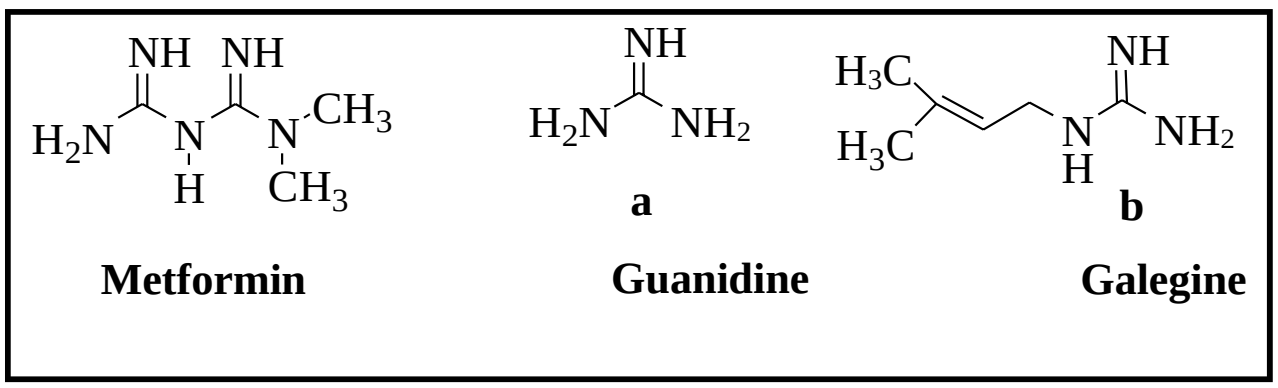

Figure 8: Structure of metformin

Metformin remains the initial treatment of choice (barring contraindications). Though, guidelines suggest if patients are highly motivated and their A1C is less than 7.5%, a 3- to 6-months trial of lifestyle modifications can be used before pharmacotherapy is initiated. The guidelines continue to recommend adding, rather than changing to, additional agents when metformin no longer provides adequate glycemic control or when A1C remains elevated after about a 3-month trial. Specifically, the actions of metformin result in decreased hepatic glucose production decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization **[5]**.

3.2.3. Sulfonylureas

These were **(Figure 9)** the first and most widely used oral hypoglycemic medications for the treatment of type 2 diabetes. They are insulin secreta-gouges, triggering insulin release by direct action on the KATP channel of the pancreatic beta cells. These drugs are classified into first-generation, second-generation, and possibly third-generation agents. The first comprises tolbutamide, tolazamide, chlorpropamide, and acetohexamide; the second consists of glyburide (also known as glibenclamide), glipizide, and gliclazide; and the third generation involves glimepiride. These generations have the same mechanism of action; however, the second and third generations greatly support the loss of weight. Sulfonylureas may also have extra-pancreatic effects, one of which is to increase tissue sensitivity to insulin, but the clinical importance of these effects is minimal. Hypoglycemia and weight gain are some side effects of these agents. Sulfonylureas lower blood glucose levels by stimulating insulin release from the beta cells of the pancreas. The biochemical mechanism of action involves blocking the ATP-sensitive potassium channels. The latter leads to membrane depolarization and to an increase in calcium influx that in turn triggers the release of insulin from the beta islets. It also has more complex effects on insulin blood levels by reducing insulin hepatic clearance **[10]**.

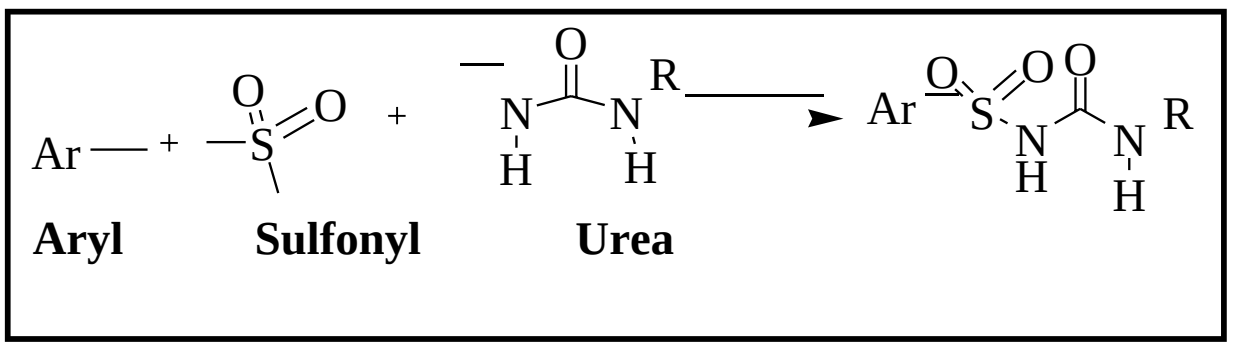

Figure 9: Structure of Sulfourea

3.2.4. Meglitinides

The meglitinides and the sulfonylureas are two classes of oral antidiabetic medications utilized in the management of type 2 diabetes that work by stimulating the release of insulin from pancreatic β-cells. While the meglitinide **(Figure 10)** and sulfonylurea agents differ in chemical structure and act on different receptors, both medication classes act by regulating potassium channels in pancreatic β-cells, thereby increasing insulin secretion. The available meglitinides, as an adjunct therapy to diet and exercise, improve glycemic control in adults with type 2 diabetes mellitus **[10]**.

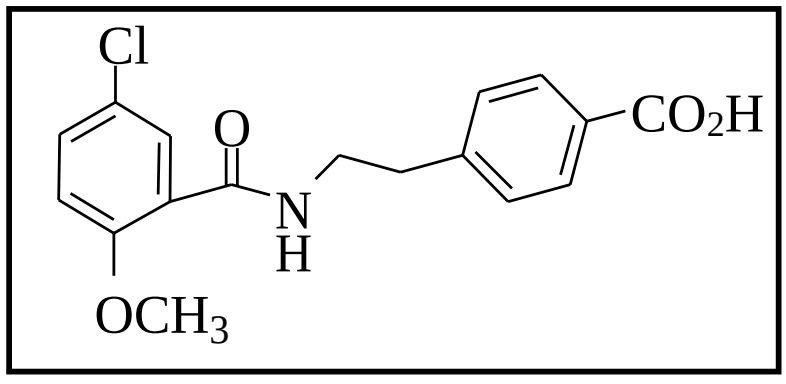

Figure 10: Structure of Meglitinide

Nateglinide (Starlix) and Repaglinide (Prandin) **(Figure 11)** are the two Metaglinides approved in the U.S. They both stimulate the secretion of insulin from the pancreatic beta cells similar to sulfonylureas. These two agents are rapid-acting and have a short half-life of 1 to 1.5 hours. They are mainly metabolized by CYP 2C9 and CYP3A4. When used alone they reduce postprandial glucose levels and HbA1C levels. They should be dosed half an hour prior to each meal and one of the advantages is that they can be used in renal insufficiency. Another advantage is their use as an alternative in hypoglycemic patients with low-dose sulfonylureas. They are both available as single-entity agents, and repaglinide is also available as a fixed-dose combination product with metformin **[13]**.

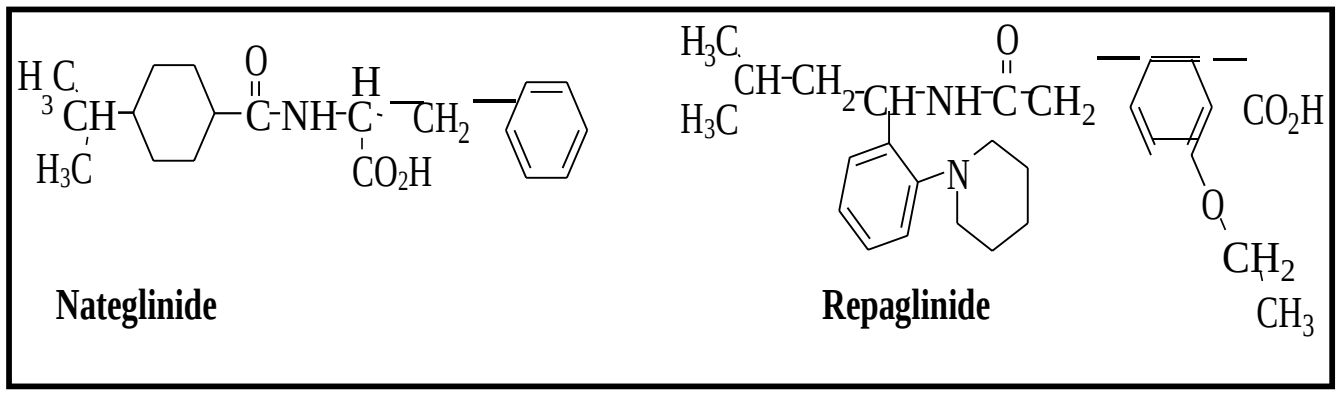

Figure 11: Structure of Nateglinide and Repaglinide

3.3. Recently Introduced Drugs

Drugs recently introduced for the treatment of diabetes are glimepiride, repaglinide and troglitazone. In addition, two new anti-obesity agents (orlistat and sibutramine) have been introduced, which may be relevant to the treatment of Type II diabetes. The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra-pancreatic effects may also play a role in the activity of sulfonylureas. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin **[44]**.

Many studies have shown that the anti-obesity agents sibutramine and orlistat **(Figure 13)**, the only two approved anti-obesity drugs in Taiwan can be used to achieve weight loss in obese, type 2 diabetic patients. Modest weight reduction can improve metabolic control. However, no studies have shown whether sibutramine or orlistat is more suitable for obese, type 2 diabetic patients. The study analyzed the effects of the two anti-obesity drugs on weight loss, glycemic control, lipid parameters, insulin sensitivity, caloric intake, and adverse effects. The main effect of sibutramine on the regulation of food intake appears to be closely related to the enhancement of satiety rather than a direct effect of hunger suppression **[17]**.

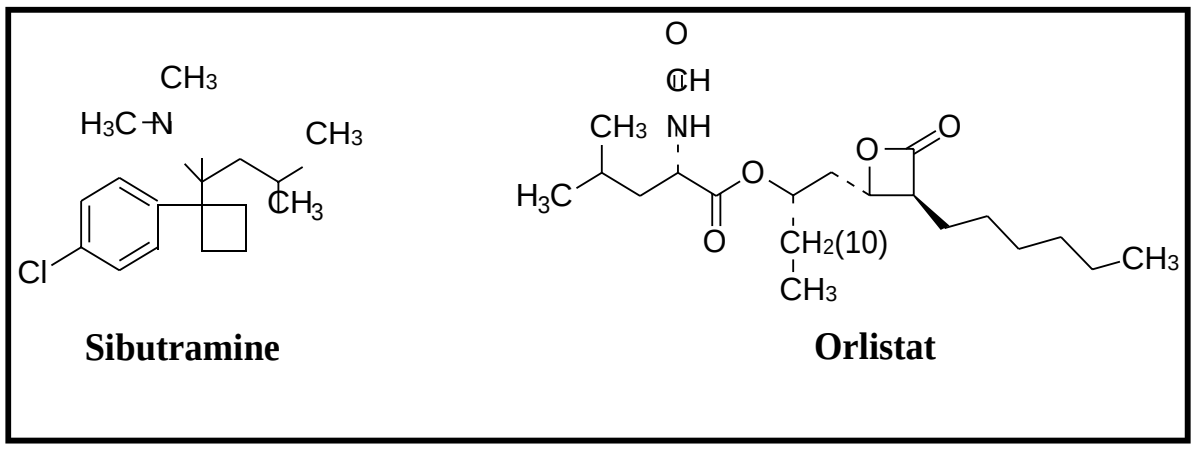

Figure 13: Structure of Sibutramine and Orlistat

4. Conclusion

T2DM is a chronic disease caused by the complex interactions of genetic and environmental factors (dietary and lifestyle factors). The roles of both our genetic makeup and the environment are contributing factors to insulin resistance and β-cell dysfunction. Diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Today, many treatments that involve the use of medicinal plants are recommended. Most plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and can often have anti-diabetic effects. In addition to this, many pharmaco-therapies have been approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes like insulins, biguanides, sulphonylureas, and meglitinides. Diabetes is best controlled either by diet and exercise (non-pharmacological) or by diet with herbal or oral hypoglycaemic agents or insulin (pharmacological).

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