2

REVIEW OF LITERATURE

Diabetes mellitus has emerged as a significant public health concern in recent decades. Prolonged diabetes is associated with a range of complications, including coronary heart disease, stroke and macrovascular disorders such as peripheral vascular disease. It also contributes to microvascular complications like retinopathy, peripheral neuropathy and kidney dysfunction. In individuals with type 2 diabetes mellitus (T2DM), heart failure often represents an early manifestation of cardiovascular disease. This metabolic disorder primarily arises from inadequate insulin secretion combined with impaired insulin action. Insulin, an essential anabolic hormone, regulates the metabolism of carbohydrates, lipids and proteins, playing a crucial role in maintaining glucose homeostasis (Antar *et al*., 2023). Obesity, characterized by excessive fat accumulation, negatively impacts overall health. This condition typically results from an imbalance between caloric intake and energy expenditure. Obesity is linked to a heightened risk of numerous diseases and conditions associated with increased mortality, including cardiovascular disease, chronic kidney disease, hypertension, hyperlipidemia, various forms of cancer, type 2 diabetes mellitus, non-alcoholic fatty liver disease, osteoarthritis and depression (Lin and Li, 2021).

Excess body fat, particularly when stored in internal organs and the abdominal region, along with elevated triglyceride levels in the liver and muscles, substantially increases the risk of prediabetes and type 2 diabetes. This risk is largely due to the impact of fat accumulation on insulin resistance and β-cell function. The presence of excessive and unhealthy body fat contributes to metabolic disturbances and conditions such as atherogenic dyslipidemia, non-alcoholic fatty liver disease, insulin resistance, β-cell dysfunction and diabetes-related complications. Generally, an increase in body mass index (BMI), indicative of greater adiposity, correlates with a higher likelihood of developing type 2 diabetes mellitus (Klein *et al*., 2022).

In light of these concerns, comprehensive efforts have been undertaken to collect relevant literature to inform this study. A thorough review of available sources indicates that limited prior research has explored the specific aspects addressed in the present work. In particular, literature on the antidiabetic and antiobesity potential of *Boerhavia diffusa* L. (*B. diffusa*) remains sparse. Therefore, the following sections provide a review of the literature pertinent to the current topic: Therapeutic Effects of Silver Nanoparticle Synthesized Ethanolic Extract of *Boerhavia diffusa* L. on Experimentally Induced Diabetes and Obesity in Rats. The subsequent sections are organized as follows:

2.1 Diabetes Mellitus

2.2 Obesity

2.3 Nanotechnology

2.4 Medicinal Plants

2.5 *Boerhavia diffusa* L.

2.1 Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disorder characterized by persistently elevated blood glucose levels resulting from insulin deficiency or resistance, which leads to abnormal metabolism of carbohydrates, lipids and proteins. The dysfunction of pancreatic β-cells in insulin production is primarily influenced by a combination of genetic predisposition and environmental factors. Diabetes is a widespread global health issue affecting millions of individuals across all age groups. The disease is broadly categorized into two main types: Type 1 Diabetes Mellitus (T1DM), also known as insulin-dependent diabetes mellitus and Type 2 Diabetes Mellitus (T2DM), referred to as non-insulin-dependent diabetes mellitus (Antar *et al*., 2023).

T1DM is an autoimmune condition wherein pancreatic β-cells are destroyed by immune-mediated mechanisms, impairing insulin production; this process is influenced by both genetic susceptibility and environmental triggers. Conversely, T2DM arises from impaired or insufficient insulin secretion and increased insulin resistance in peripheral tissues, progressively leading to hyperglycemia. Over time, diabetes can result in serious complications such as nephropathy, cardiovascular disease and heart failure (Jyotsna *et al*., 2023).

According to the most recent report by the World Health Organization (WHO, 2024), diabetes remains one of the leading global health challenges, responsible for approximately 1.6 million direct deaths in 2021, along with an additional 530,000 deaths attributed to kidney diseases caused by diabetes (Wu *et al*., 2023). Furthermore, elevated blood glucose contributes to nearly 11% of all cardiovascular deaths worldwide, emphasizing the severe impact of diabetes and its complications on public health. The International Diabetes Federation (IDF, 2024); Rooney *et al*., 2025) reported that an estimated 589 million adults (aged 20-79) were living with diabetes globally in 2024, accounting for 11.1% of the global adult population, with projections indicating an alarming rise to over 700 million by 2045 if current trends continue. In alignment with these findings, the GBD 2021 Diabetes Collaborators (2023) (Al-Jawaldeh and Abbass, 2022) further emphasized a substantial global increase in diabetes prevalence from 1990 to 2021, with projections suggesting a dramatic surge in disease burden by 2050. The increasing prevalence of diabetes reflects the combined influence of urbanization, sedentary lifestyles, unhealthy dietary habits and population ageing, highlighting the urgent need for global strategies aimed at prevention, early detection and effective disease management (Perumal *et al*., 2022).

2.1.1 Classification of Diabetes Mellitus

Diabetes mellitus can be broadly classified into four primary categories: Type 1 diabetes, Type 2 diabetes, other specific types of diabetes and gestational diabetes.

2.1.1.1 Type 1 Diabetes Mellitus

Type 1 Diabetes Mellitus (T1DM) is an autoimmune condition in which the pancreas fails to produce or secrete insulin due to immune-mediated destruction of pancreatic β-cells. This type of diabetes often begins in childhood, hence it is sometimes referred to as juvenile-onset diabetes; however, it can also occur in adults. T1DM is considered a serious, life-threatening disease globally. In this condition, T lymphocytes destroy pancreatic β-cells, causing a complete lack of insulin secretion and leading to persistent hyperglycemia (Chinsembu, 2019). Both genetic predisposition and environmental factors contribute to the development of T1DM. Globally, over 9,000 children are diagnosed with T1DM annually. The pathogenesis of T1DM involves the presence of autoantibodies linked to β-cell apoptosis

and dysglycemia, particularly in children with a family history of the disease. Prolonged T1DM can result in severe complications, such as nephropathy, neuropathy, retinopathy, cardiovascular disease, cerebrovascular disease and peripheral arterial disease. For the past two decades, intensive insulin therapy has remained the primary treatment approach to maintain blood glucose levels close to normal. Unfortunately, T1DM currently has no cure and individuals must rely on lifelong insulin therapy (Janez *et al*., 2020).

2.1.1.2 Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes worldwide. This chronic metabolic disorder arises from a combination of pancreatic β-cell dysfunction (resulting in impaired insulin secretion) and tissue insulin resistance, leading to sustained hyperglycemia. If not properly managed, T2DM can damage the heart, blood vessels, kidneys, nerves and eyes over time. Obesity, particularly central or visceral fat accumulation, is a major contributor to insulin resistance in T2DM. Adipose tissue dysfunction promotes inflammatory processes and increases the release of free fatty acids, exacerbating insulin resistance. The development of T2DM is influenced by various environmental and lifestyle factors, including sedentary behaviour, consumption of calorie-dense diets, increasing life expectancy and the global rise in obesity prevalence. Studies have shown that multiple organs including the pancreas, liver, kidneys, intestines and adipose tissue are involved in the pathophysiology of T2DM (Galicia-Garcia *et al*., 2020).

2.1.1.3 Other Types of Diabetes Mellitus

Diabetes mellitus also includes several other forms, categorized under "other specific types" of diabetes. These include Maturity-Onset Diabetes of the Young (MODY), Latent Autoimmune Diabetes in Adults (LADA) and endocrinopathies. These types are often linked to genetic abnormalities that impair insulin secretion. MODY is caused by mutations in autosomal dominant genes, resulting in diminished insulin secretion and persistent hyperglycemia. LADA, on the other hand, is an autoimmune form of diabetes that resembles T1DM because it gradually impairs insulin production. It typically manifests in adulthood and often requires insulin-based therapy for management (Afroj *et al*., 2022).

2.1.1.4 Gestational Diabetes Mellitus

Gestational Diabetes Mellitus (GDM) is a condition characterized by hyperglycemia first detected during pregnancy. GDM is a major global public health concern, as it poses risks to both maternal and neonatal health, increasing the likelihood of morbidity and mortality. Women with GDM are at a higher risk of developing T2DM later in life and are also more likely to experience pregnancy complications such as gestational hypertension and the need for caesarean delivery. Infants born to mothers with GDM face an elevated risk of congenital anomalies, neonatal hypoglycemia and future development of T2DM (Zhang *et al*., 2021).

2.1.2 Mechanism of Diabetes Mellitus

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both. The pathogenesis and progression of diabetes involve multiple interrelated mechanisms, including insulin resistance, β-cell dysfunction, inflammation, oxidative stress and lipotoxicity (Galicia-Garcia *et al*., 2020).

FIGURE 2.1

MECHANISM OF DIABETES MELLITUS

Genetic and Environmental Factors
↓
Insulin Resistance → Peripheral Tissues (Muscle, Adipose, Liver)
↓ Glucose uptake ↓ → ↑ Hepatic glucose production → Hyperglycemia
(Raval *et al*. (2018) Galicia-Garcia *et al.* (2020) Eckel *et al*. (2021)
β-Cell Dysfunction → Glucotoxicity and Lipotoxicity → Oxidative Stress
→ Apoptosis
→ ↓ Insulin Secretion → Hyperglycemia
(Chen *et al*. (2019) Prentki and Nolan. (2021)

Chronic Inflammation → ↑ TNF-α, IL-6, IL-1β → Impaired Insulin Signaling
→ β-Cell Dysfunction and Insulin Resistance
(Donath. (2021) Pirozzi. (2021)
Oxidative Stress → ↑ ROS → Damage to β-cells and peripheral tissues → Worsening Insulin Resistance and Hyperglycemia Zhao *et al*. (2021)
Lipotoxicity → Excess Lipids in Liver, Pancreas, Muscle → ER Stress and Mitochondrial Dysfunction → β-Cell Apoptosis (Prentki and Nolan. (2021)
Gut Microbiota Dysbiosis → Altered SCFAs and Metabolites
→ Systemic Inflammation and Insulin Resistance

(Luo *et al*., 2022)

2.1.2.1 Insulin Resistance

One of the primary mechanisms underlying Type 2 diabetes mellitus (T2DM) is insulin resistance, where peripheral tissues particularly skeletal muscle, liver and adipose tissue fail to respond adequately to insulin. This impairment leads to decreased glucose uptake in muscle and adipose tissue and increased hepatic glucose production, resulting in hyperglycemia (Khalilov and Abdullayeva, 2023). The excessive accumulation of free fatty acids and inflammatory cytokines in obese individuals further exacerbates insulin resistance by interfering with insulin signaling pathways (Eckel *et al*., 2021).

2.1.2.2 β -Cell Dysfunction

Progressive β-cell dysfunction is central to the development of diabetes. In response to insulin resistance, pancreatic β-cells initially increase insulin secretion; however, chronic metabolic stress eventually leads to β-cell exhaustion and apoptosis. Factors such as glucotoxicity (chronic high glucose levels), lipotoxicity (accumulation of toxic lipid intermediates) and oxidative stress impair β-cell function and survival. The decline in functional β-cell mass results in inadequate insulin secretion and worsening hyperglycemia (Chen *et al*., 2019).

2.1.2.3 Inflammation

Chronic low-grade inflammation plays a pivotal role in the development of both insulin resistance and β-cell dysfunction. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) are elevated in individuals with obesity and T2DM (Donath, 2021). These cytokines impair insulin signaling pathways and contribute to the destruction of pancreatic β-cells (Pirozzi *et al*., 2021).

2.1.2.4 Oxidative Stress

Oxidative stress is another critical factor in diabetes pathogenesis. The overproduction of reactive oxygen species (ROS), driven by hyperglycemia and lipotoxicity, damages cellular components and exacerbates insulin resistance and β-cell dysfunction. Antioxidant defense mechanisms are often compromised in diabetic patients, further amplifying oxidative damage (Zhao *et al*., 2021).

2.1.2.5 Lipotoxicity

Excess lipid accumulation, particularly in non-adipose tissues such as liver, pancreas and muscle, contributes to insulin resistance and β-cell dysfunction phenomenon known as lipotoxicity. Elevated circulating free fatty acids disrupt insulin signaling and promote apoptosis of β-cells through endoplasmic reticulum stress and mitochondrial dysfunction (Prentki and Nolan, 2021).

2.1.2.6 Gut Microbiota Dysbiosis

Emerging evidence highlights the role of gut microbiota in the development of diabetes. Alterations in gut microbial composition, known as dysbiosis, can affect

glucose metabolism, inflammation and insulin sensitivity. Certain bacterial metabolites, such as short-chain fatty acids, influence host metabolic homeostasis and imbalances can contribute to metabolic diseases including diabetes (Luo *et al*., 2022).

2.1.3 Symptoms and Signs of Diabetes Mellitus

Identifying the symptoms of diabetes mellitus can be difficult, as many individuals remain asymptomatic or may not recognize early signs until complications develop. Common symptoms include increased urination (polyuria), persistent thirst (polydipsia) and excessive hunger (polyphagia), all resulting from elevated blood glucose levels (American Diabetes Association (ADA), 2022). Other manifestations often include dehydration, unexplained weight loss, blurred vision and frequent fatigue and mood disturbances such as irritability (Choudhury and Rajeswari, 2021). Additionally, individuals may experience recurrent infections particularly of the skin, oral cavity, urinary tract and genital region due to compromised immune function (Shahabudin *et al*., 2024). Signs such as delayed wound healing, erectile dysfunction and velvety darkened skin patches (*Acanthosis nigricans*), typically observed on the neck and arms, can indicate underlying insulin resistance (Perumal *et al*., 2022). In some cases, episodes of reactive hypoglycemia and neurological symptoms such as drowsiness may occur. If left untreated, chronic and uncontrolled diabetes can cause severe complications, including cardiovascular and neurological damage, increasing the risk of diabetic coma and mortality (Lin and Li, 2021).

2.1.4 Enzymes and Genes Involved in Diabetes Mellitus

The progression of diabetes mellitus involves numerous enzymes and genes that play crucial roles in disease onset and development. These enzymes regulate key processes such as autophosphorylation of insulin receptors and glucose uptake into cells. A central component in this process is glucose transporter type 4 (GLUT4), which facilitates glucose entry into cells in response to insulin signaling. Glucokinase, another vital enzyme, plays a fundamental role in glucose homeostasis. It is responsible for catalyzing the first step of glucose metabolism by converting glucose to glucose-6-phosphate. The activity of glucokinase is modulated by the glucokinase regulatory protein (GKRP), particularly in the liver, while transcriptional factors regulate its activity in pancreatic β-cells

(Alam *et al*., 2021). Mutations in the glucokinase gene are linked to maturity-onset diabetes of the young (MODY), underscoring its significance in maintaining normal glucose metabolism. Moreover, increased dietary carbohydrate intake upregulates glucokinase activity, contributing to enhanced glucose tolerance (Iizuka, 2021).

Another key enzyme, α-amylase, is involved in carbohydrate digestion by breaking down starch into simpler sugars. Specifically, pancreatic α-amylase cleaves the α-1, 4 glycosidic bonds in starch, facilitating its conversion to absorbable glucose. Since the brain relies heavily on glucose for energy, the breakdown of complex starches into glucose is vital for proper neurological function. However, excessive α-amylase activity may contribute to elevated blood glucose levels, increasing the risk of hyperglycemia in individuals with impaired insulin secretion or sensitivity. In addition, the regulation of glycolysis a primary glucose metabolic pathway also influences insulin secretion and the metabolic activity of various cells. By enhancing glycolytic flux through the modulation of key regulatory enzymes, it may be possible to improve glucose utilization and provide novel therapeutic strategies for managing diabetes mellitus (Kaur *et al*., 2021).

2.1.4.1 Diabetic Retinopathy

Diabetic retinopathy is one of the most common microvascular complications of diabetes mellitus. Its pathogenesis involves several key mechanisms, including the production of advanced glycation end products (AGEs), the overproduction of vascular endothelial growth factor (VEGF) and increased oxidative stress due to reactive oxygen species (ROS). Diabetic retinopathy is classified into two stages: non-proliferative and proliferative. Non-proliferative diabetic retinopathy represents the early stage of the disease, often presenting with few or no symptoms. During this phase, the retinal blood vessels weaken and develop small hemorrhages, known as dot hemorrhages, caused by lipid exudate deposition. In addition, microaneurysms form, leading to fluid leakage and macular edema (Takamura *et al*., 2023).

In contrast, proliferative diabetic retinopathy occurs at a more advanced stage. It is characterized by neovascularization, or the abnormal formation of fragile new blood vessels on the retinal surface. These new vessels frequently leak blood into the vitreous humor, resulting in cotton wool spots white patches visible on the retina. Without proper

treatment, proliferative diabetic retinopathy can lead to serious complications, including vision impairment and blindness (Maranta *et al*., 2021).

2.1.4.2 Diabetic Nephropathy

Diabetic nephropathy is now considered as one of the most prevalent causes of renal failure and end stage renal disease worldwide. Approximately one-third of people with diabetes are at risk of developing these microvascular complications. Current treatments primarily aim to slow disease progression, as reversing kidney damage remains challenging. Notably, early-stage diabetic nephropathy is difficult to detect, as hallmark symptoms such as proteinuria and microalbuminuria often appear only in later stages (Thomas and Versypt, 2022).

The pathogenesis of diabetic nephropathy is complex and multifactorial, involving a variety of molecular pathways and mediators. The exact mechanisms remain incompletely understood but include disrupted metabolic homeostasis, hemodynamic abnormalities and altered hormonal regulation. Key contributors to disease progression include reactive oxygen species (ROS), connective tissue growth factor (CTGF), transforming growth factor-β (TGF-β1), protein kinase C(PKC), advanced glycation end products (AGEs), mitogen-activated protein kinases (MAPKs) and the renin angiotensin aldosterone system (RAAS). Current therapeutic strategies aim to control blood pressure and blood glucose, targeting the reduction of albuminuria, which is associated with improved renal outcomes (Samsu, 2021).

2.1.4.3 Diabetic Neuropathy

Diabetic neuropathy is a chronic and common complication of diabetes mellitus, affecting both type 1 and type 2 diabetes patients and it can even manifest in prediabetic individuals. Two prevalent forms of diabetic neuropathy are distal symmetric polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN). Despite advancements in diabetes care, there are currently no FDA-approved treatments that can reverse the underlying nerve damage associated with diabetic neuropathy. Therefore, prevention strategies, early screening and pain management remain central to clinical practice (Sathienluckana *et al*., 2024).

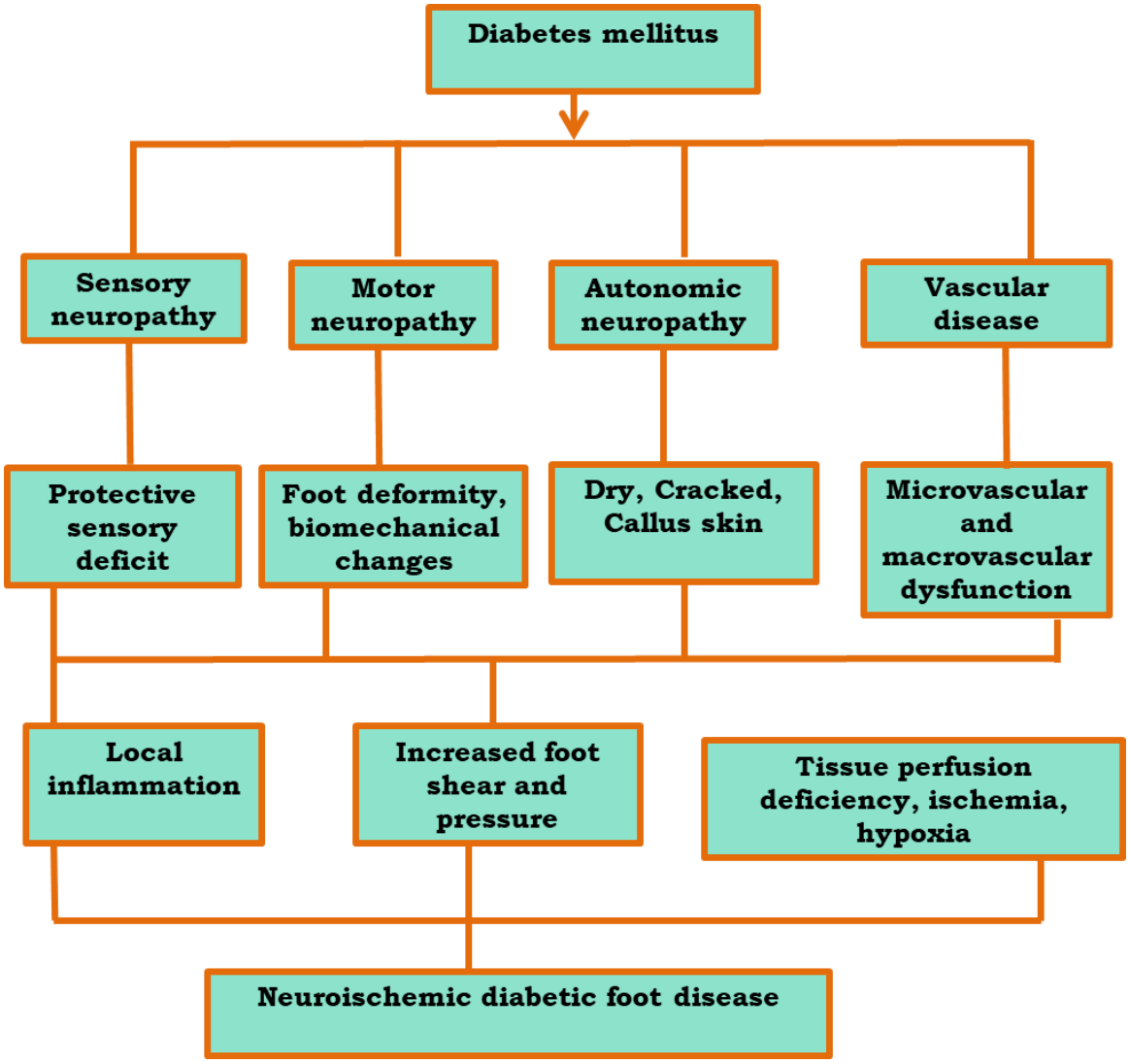
Distal symmetric polyneuropathy typically affects the lower limbs and hands, presenting with symptoms such as tingling, numbness and pain. Diabetes can also contribute to other types of generalized neuropathies, including autonomic neuropathies. These include diabetic cystopathy (bladder dysfunction), cardiac autonomic neuropathy, erectile dysfunction, gastrointestinal dysmotility and focal neuropathies such as radiculopathy and polyradiculopathy (Feldman *et al*., 2019).

2.1.4.4 Diabetic Foot Ulcer

Globally, diabetes is becoming increasingly prevalent, driven by factors such as aging populations, sedentary lifestyles, unhealthy diets, population growth and obesity. One of the most severe complications faced by individuals with diabetes is the diabetic foot ulcer (DFU). Studies report that approximately 25 percent of diabetic patients will develop a foot ulcer during their lifetime. DFUs arise due to a combination of factors, including diabetic peripheral neuropathy, peripheral arterial disease and various patient specific characteristics such as age, smoking, foot deformities, poor glycemic control, ulcer size, hypertension and lipid abnormalities. In many cases, untreated or poorly managed DFUs significantly increase the risk of lower limb amputation in diabetic patients (Lee *et al*., 2020).

FIGURE 2.2

PATHOGENESIS OF DIABETIC FOOT ULCER



(Lee *et al.*, 2020)

2.1.5 Management of Diabetes Mellitus

Diabetes mellitus is a complex, non-communicable hormonal disorder that is increasing rapidly across the globe. It significantly elevates the risk of developing metabolic complications, resulting in the accumulation of excess glucose and lipids in the bloodstream and heightened oxidative stress. If left unmanaged, diabetes can lead to serious complications, including damage to the kidneys, eyes, vascular system and nervous system (Antar *et al.*, 2023).

Effective management of diabetes mellitus requires an integrated approach, combining lifestyle modifications, modern therapeutic interventions and nutritional strategies. Lifestyle changes are particularly vital in both the prevention and management of diabetes. Individuals are advised to reduce sedentary behaviour, engage in regular physical activity and adopt a balanced and nutritious diet. Physical activity plays an essential role in lowering blood glucose levels and improving overall metabolic health (Lee *et al*., 2020).

Nutritional interventions should emphasize the consumption of vegetables, low-fat dairy products, lean proteins, whole grains and fruits, while limiting sugar and fat intake. Additionally, lifestyle measures such as smoking cessation and moderation of alcohol consumption are crucial in reducing the risk of diabetes and improving its management (Aloke *et al*., 2022).

In recent decades, the range of therapeutic options available for managing diabetes mellitus has expanded significantly. However, conventional pharmacological therapies can sometimes be associated with adverse effects, such as hypoglycemic coma, liver damage and kidney injury. As a result, there has been increasing interest in medicinal plant-based therapies as alternative or complementary treatment options. The World Health Organization (WHO) recognizes the potential of medicinal plants in the treatment of diabetes, particularly in resource limited settings, where access to modern medications may be constrained (Perumal *et al*., 2022b).

Numerous studies have demonstrated that phytocompounds derived from medicinal plants possess significant antidiabetic properties. These compounds can effectively lower blood glucose levels through a variety of mechanisms, including enhancing insulin secretion, improving insulin sensitivity and reducing oxidative stress. The antidiabetic activity of these phytochemicals is largely attributed to their unique chemical structures and biological properties. Moreover, plant-based therapeutics is generally cost-effective, accessible and well tolerated, making them an attractive option for long-term diabetes management (Clement *et al*., 2022).

2.1.6 Therapeutics of Diabetes Mellitus

The primary therapeutic strategies for managing diabetes mellitus aim to target the underlying mechanisms of the disease, including insulin resistance, insufficient insulin secretion and the progression of diabetes-related complications. The available pharmacological treatments encompass insulin therapy, non-insulin hypoglycemic agents and emerging modalities such as gene therapy. Among the non-insulin hypoglycemic agents, key categories include insulin sensitizers, glucose regulators, insulin analogues, insulin secretagogues and α-glucosidase inhibitors. Insulin secretagogues act by binding to the sulfonylurea receptor on ATP-sensitive potassium channels present in pancreatic β-cells, thereby stimulating insulin secretion. This class of drugs includes sulfonylureas and meglitinides. Sulfonylureas are further categorized into three generations:

- First-generation sulfonylureas include chlorpropamide, tolbutamide, acetohexamide and tolazamide.
- Second-generation sulfonylureas include gliclazide, glyburide and glipizide.
- Third-generation sulfonylureas include glimepiride (Tomlinson *et al*., 2022).

The mechanism of action is consistent across all three generations, although second and third-generation agents are associated with a potential for weight loss (Padhi *et al*., 2020). Another critical target in diabetes management is the inhibition of carbohydrate metabolism enzymes such as α-amylase and α-glucosidase. Alpha-glucosidase inhibitors work by reducing the absorption of carbohydrates in the gastrointestinal tract, leaving them partially undigested. This slows the release of glucose into the bloodstream, thereby mitigating postprandial hyperglycemia (Blahova *et al*., 2021).

Insulin sensitizers, also known as Peroxisome Proliferator Activated Receptor (PPAR) agonists, modulate carbohydrate and lipid metabolism. They enhance insulin sensitivity at the cellular level, promote glucose uptake in skeletal muscles and suppress hepatic glucose production by inhibiting gluconeogenesis. This class of drugs helps maintain glucose homeostasis and offers significant therapeutic benefits for patients with Type 2 Diabetes Mellitus (Perumal *et al*., 2022b).

Gene therapy is an emerging frontier in the treatment of diabetes mellitus. It focuses on addressing the root causes of the disease with the potential to reverse its progression. Gene therapy approaches are classified into immune gene therapy, regulatory gene therapy and replacement gene therapy. Therapeutic agents used in these approaches include DNA, mRNA, siRNA and antisense oligonucleotides, which are designed to modulate gene expression and restore normal insulin function (Ruchien *et al*., 2023).

2.2 Obesity

Obesity has emerged as a major public health concern worldwide, having reached alarming prevalence across both developed and developing countries. It is characterized by an excessive accumulation of adipose tissue that can adversely affect overall health and well-being. The condition primarily results from an imbalance between caloric intake and energy expenditure and is influenced by a combination of genetic predisposition, unhealthy dietary patterns and sedentary lifestyle choices (Lin and Li, 2021).

Multiple studies indicate that sedentary behavior, overeating, genetic variations and epigenetic mechanisms significantly contribute to the pathogenesis of obesity. Among various assessment tools, Body Mass Index (BMI) remains the most widely used parameter to categorize individuals as underweight, normal weight, overweight or obese, offering a simple yet effective classification (Mohajan and Mohajan, 2024).

Chronic or long-term obesity substantially increases the risk of developing a spectrum of comorbidities, including asthma, several forms of cancer, Type 2 diabetes mellitus, hyperlipidemia and cardiovascular diseases. Thus, addressing obesity through preventive strategies, early interventions and public health education is imperative to curb its associated health burdens (Safaei *et al*., 2021).

2.2.1 Etiology

Obesity arises primarily from an imbalance between energy intake and energy expenditure. When the body consistently consumes more calories than it utilizes, the surplus energy is stored as fat within adipocytes. Over time, these adipocytes undergo hypertrophy (increase in size) and hyperplasia (increase in number), which are recognized as hallmark pathological changes in obesity (Horwitz and Birk, 2023).

The clinical complications associated with obesity stem not only from the sheer mechanical burden of excess fat mass but also from the metabolic effects triggered by enlarged adipocytes. These hypertrophied adipocytes secrete elevated levels of free fatty acids, pro-inflammatory cytokines, adipokines and bioactive peptides, which collectively contribute to systemic inflammation, insulin resistance and increased risk of obesity-related diseases (Álvarez-Castro *et al*., 2022).

2.2.2 Assessment of Obesity

Obesity is commonly defined as an excessive accumulation of body fat, which predisposes individuals to a variety of health complications. One of the most widely used, simple and cost-effective methods to assess overweight and obesity is the Body Mass Index (BMI). BMI provides a standardized measure that allows for comparison of weight status across different populations. There is a well established correlation between BMI, body fat percentage and the risk of morbidity and mortality. However, it is important to recognize that BMI interpretation can be influenced by factors such as age, gender and ethnicity (Mallik *et al*., 2023).

BMI is calculated as:

BMI = weight (kg) / height² (m^2)

Obesity is classified based on body mass index (BMI, kg/m^2) as follows: individuals with a BMI below 18.5 are considered underweight with no associated disease risk; those with a BMI of 18.5–24.9 are in the normal range with no disease risk, a BMI of 25.0–29.9 indicates overweight with increased disease risk; Obesity Class 1 (BMI 30.0– 34.9) carries a high risk; Obesity Class 2 (BMI 35.0–39.9) carries a very high risk; and Extreme Obesity Class 3 (BMI $\geq$ 40.0) is associated with an extremely high risk for type 2 diabetes, hypertension and cardiovascular disease (Yao *et al*., 2025).

2.2.3 Regulators of Body Weight

Body weight is regulated through a complex interplay of hormones, adipokines and neural signals and metabolic pathways. Among these, adiponectin and leptin are two key adipokines secreted by adipose tissue that play crucial roles in maintaining energy balance and metabolic health (Shan *et al*., 2023).

2.2.3.1 Adiponectin

Adiponectin is a protein hormone (adipokine) predominantly secreted by adipose tissue. Its production is stimulated by peroxisome proliferator-activated receptor gamma (PPAR-γ), while it is inhibited by tumor necrosis factor-alpha (TNF-α) and catecholamines. Adiponectin exerts its physiological effects primarily through two functional receptors: AdipoR1 and AdipoR2. This adipokine plays a critical role in energy metabolism in both animals and humans. It enhances glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase (AMPK) in adipose tissues. Additionally, adiponectin regulates lipid metabolism by inhibiting lipolysis, thereby contributing to improved metabolic homeostasis (Yanai and Yoshida, 2019).

Studies have shown that individuals with insulin resistance, such as those with Type 2 Diabetes Mellitus (T2DM), exhibit significantly lower plasma adiponectin levels. Furthermore, the adiponectin gene is located on chromosome 3q27, a region also associated with susceptibility loci for components of metabolic syndrome, emphasizing the hormone's role in obesity related metabolic disorders. Given that adiponectin deficiency is a hallmark of obesity, it is considered a promising therapeutic target for improving insulin sensitivity and metabolic health (Alotaibi *et al*., 2022).

2.2.3.2 Leptin

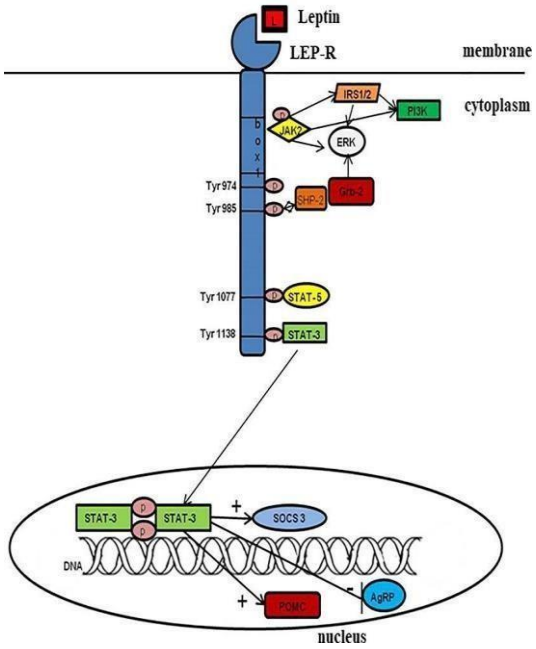
Leptin, another adipokine secreted by adipose tissue, is closely linked to the body's fat stores its secretion is generally proportional to the triglyceride content of fat cells. Leptin is a critical regulator of energy homeostasis, primarily acting through the central nervous system to control food intake, energy expenditure and energy storage. The biological effects of leptin are mediated via its interaction with the leptin receptor (LEPR). Upon binding to LEPR, leptin activates the Janus kinase 2 (JAK2) signaling pathway, leading to phosphorylation of tyrosine residues on the receptor (notably Y1138, Y985 and Y1077). This cascade regulates energy balance through leptin LEPR signaling (Bodur *et al*., 2025).

A key downstream molecule, phosphorylated STAT3 (pSTAT3), influences the expression of genes such as SOCS3, which functions as a feedback inhibitor. When SOCS3 binds to JAK2 and facilitates phosphorylation of Y985, it inhibits JAK2 activity and

attenuates LEPR signaling. This negative feedback loop, when dysregulated, can contribute to leptin resistance, a common feature observed in obesity where high circulating leptin levels fail to produce their expected physiological effects (Le Duc *et al.*, 2021).

FIGURE 2.3

MECHANISM OF LEPTIN



(Kallash and Frishman, 2025)

2.2.3.3 Visfatin

Visfatin is an adipokine that is predominantly expressed in visceral adipose tissue and is known to exert multiple proinflammatory effects while also playing a role in glucose regulation. Findings from meta-analyses of observational studies have reported that individuals with obesity and Type 2 Diabetes Mellitus (T2DM) exhibit elevated circulating plasma visfatin levels. During adipogenesis, visfatin expression increases substantially, promoting both adipocyte differentiation and proliferation. The elevated plasma levels of visfatin observed in individuals with insulin resistance and T2DM are thought to be closely associated with hyperglycemic conditions commonly seen in these metabolic disorders. Despite emerging evidence linking visfatin to metabolic dysregulation, its precise biological role and mechanism of action in obesity and T2DM

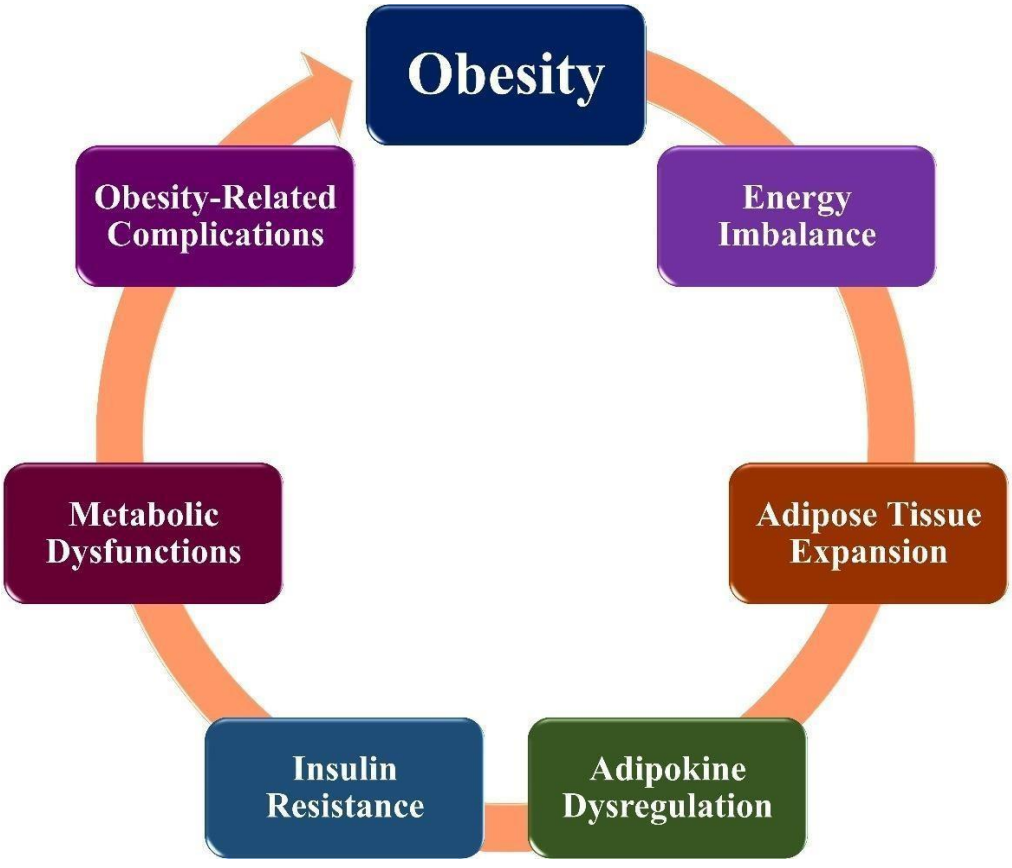
remain to be fully elucidated. Ongoing and future research is essential to deepen our understanding of visfatin's contribution to the pathophysiology of obesity-related metabolic complications (El-Masry *et al*., 2024).

2.2.4 Mechanism of Obesity

Obesity is a complex, multifactorial condition that results from interplay of genetic, behavioural and environmental factors. It is not merely an excess accumulation of body fat but involves significant alterations in energy metabolism, hormonal regulation and immune responses and organ function. Understanding the underlying mechanisms of obesity is crucial for developing effective prevention and treatment strategies (Ghosh *et al*., 2023).

FIGURE 2.4

MECHANISM OF OBESITY



(Blüher, 2019)

Obesity arises primarily due to a chronic imbalance between energy intake and expenditure, wherein caloric consumption exceeds energy utilization, leading to excess fat accumulation in adipose tissue. Modern sedentary lifestyles, increased consumption of high-calorie diets and genetic predispositions contribute significantly to this energy imbalance (Blüher, 2019).

As adipose tissue expands, both in size (hypertrophy) and number (hyperplasia) of adipocytes, it undergoes structural and functional changes (Kim *et al.*, 2020). Enlarged adipocytes secrete altered levels of adipokines such as leptin, adiponectin, resistin and visfatin, disrupting normal metabolic signaling (El-Masry *et al*., 2024).

The expanding adipose tissue also triggers a state of chronic low-grade inflammation by recruiting immune cells, particularly macrophages, into the adipose depots (Shariq and McKenzie, 2020). These immune cells release proinflammatory cytokines, including TNF-α and IL-6, further exacerbating insulin resistance and promoting systemic inflammation.

Insulin resistance, a hallmark of obesity, results from impaired insulin signaling in muscle, liver and adipose tissue (Golacki *et al*., 2022). Elevated levels of free fatty acids, released from enlarged adipocytes, impair insulin receptor signaling and contribute to lipid accumulation in non-adipose tissues such as the liver and muscle (Berge and Geloen, 2020).

Moreover, gut microbiota alterations in obese individuals affect energy homeostasis and metabolism by influencing nutrient absorption and promoting endotoxemia, which contributes to systemic inflammation (Ruze *et al*., 2023). Additionally, neuroendocrine dysregulation involving hypothalamic circuits that control appetite and satiety is often impaired in obesity (Pilitsi *et al*., 2019).

Ultimately, these interconnected mechanisms energy imbalance, adipose tissue dysfunction, inflammation, insulin resistance and neuroendocrine disruption create a vicious cycle that sustains obesity and predisposes individuals to metabolic disorders (Varra *et al*., 2024).

2.2.5 Complications of Obesity

Obesity, characterized by excessive fat accumulation, particularly in the abdominal region, is a critical determinant of insulin resistance and metabolic syndrome. Extensive research has established that obesity and its associated complications substantially reduce life expectancy and serve as strong predictors of premature mortality. Moreover, obesity contributes to a multitude of severe health outcomes, including dyslipidemia, endothelial dysfunction, asthma, hyperandrogenism, hypertension, chronic inflammation, hyperinsulinemia, polycystic ovarian syndrome (PCOS), enhanced blood clotting tendencies and several gastrointestinal and neurological disorders (Calcaterra *et al*., 2020).

2.2.5.1. Cancer

One of the significant complications associated with obesity is an increased risk of cancer. Cancer is characterized by uncontrolled cellular proliferation and invasion into surrounding tissues and individuals with obesity exhibit a markedly higher likelihood of developing malignancies in the breast, uterus, colon, kidney, gallbladder, pancreas and esophagus. In women, excessive estrogen synthesis by adipose tissue heightens cancer risk, particularly postmenopausal breast and endometrial cancers. Obesity also predisposes both men and women to gastrointestinal cancers. For example, obese individuals are more susceptible to esophageal cancer due to chronic reflux esophagitis and localized inflammation. Similarly, colon cancer incidence is elevated among obese individuals, largely due to persistent insulin resistance and the mitogenic effects of insulin-like growth factor (IGF) (Prendergast *et al*., 2022).

2.2.5.2. Musculoskeletal System

Obesity also significantly affects the musculoskeletal system by promoting ectopic fat deposition within skeletal muscles. In addition to excessive subcutaneous and visceral fat accumulation, obese individuals experience lipid infiltration in non-adipose tissues. The elevated circulation of free fatty acids (FFAs) leads to increased fatty acid uptake and storage as extramyocellular lipids in adipocytes between muscle fibers and as intramyocellular lipids (IMCL) within muscle cells. These IMCL deposits primarily consist of triacylglycerols and cholesterol esters, along with metabolic intermediates such as long chain acyl-CoAs, diacylglycerol and ceramides. Studies on muscle tissues from obese individuals consistently

reveal elevated triacylglycerol content and a greater abundance of lipid droplets, indicating impaired lipid metabolism and contributing to muscle dysfunction (Calcaterra *et al*., 2020).

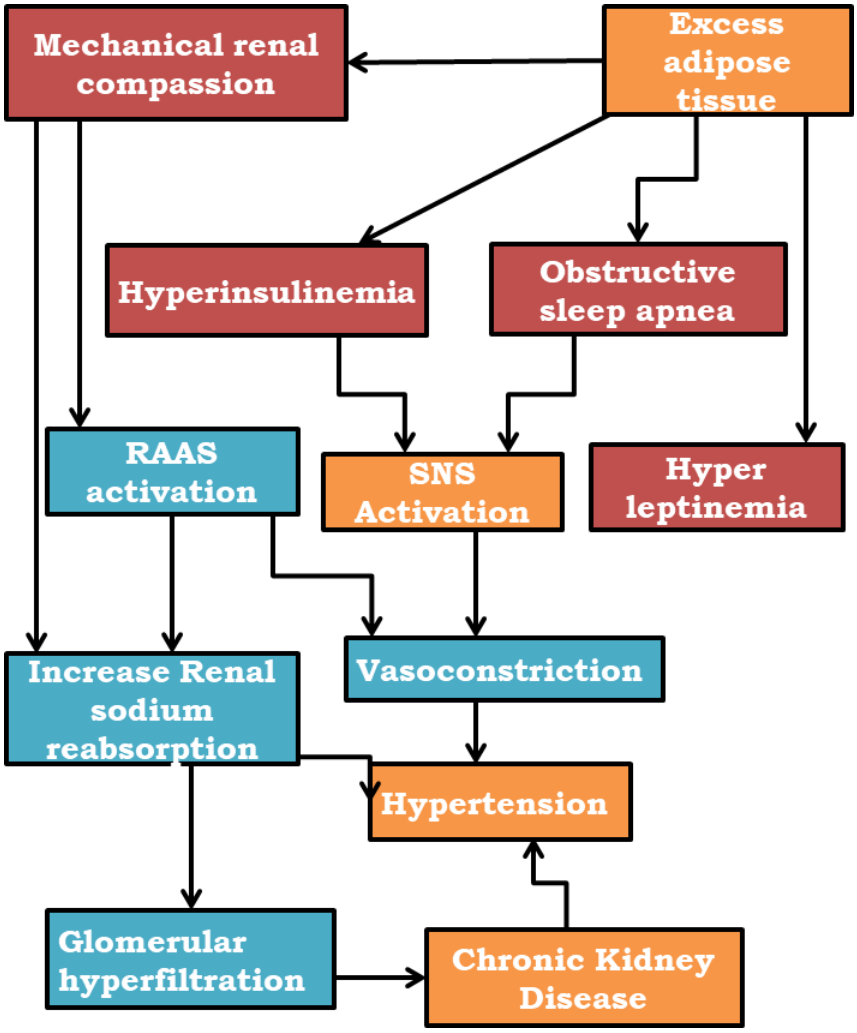
2.2.5.3. Hypertension and Metabolic Complications

Among the most prevalent and serious consequences of obesity are hypertension and metabolic disturbances such as Type 2 Diabetes Mellitus (T2DM). Obesity induced hypertension substantially increases cardiovascular risk and is often associated with left ventricular hypertrophy (LVH), particularly in obese women, indicating subclinical heart disease. Abdominal obesity, in particular, is strongly correlated with acute myocardial infarction risk. Mechanistically, obesity promotes hypertension through multiple interrelated pathways, including enhanced renal sodium retention, expanded vascular volume, overactivation of the renin angiotensin aldosterone system (RAAS) and the sympathetic nervous system and elevated angiotensinogen secretion from adipose tissue (Shariq and McKenzie, 2020).

Alongside hypertension, obesity plays a pivotal role in the onset of T2DM, characterized by impaired insulin secretion and resistance, resulting in chronic hyperglycemia. In such conditions, pancreatic β-cells produce insufficient insulin while peripheral insulin resistance limits glucose uptake by muscle cells, promotes lipolysis and increases hepatic glucose output. Most individuals with T2DM are overweight and the abnormal fat distribution commonly seen in obesity exacerbates insulin resistance. Furthermore, excessive release of free fatty acids from adipose tissue disrupts glucose metabolism and impairs β-cell function, thereby aggravating hyperglycemia and increasing the risk of long-term metabolic complications (Chandrasekaran and Weiskirchen, 2024).

FIGURE 2.5

PATHOGENESIS OF OBESITY RELATED HYPERTENSION



(Shariq and McKenzie, 2020)

2.2.6. Management of Obesity

Obesity is a significant global health issue that is linked to cardiovascular diseases, osteoarthritis, hyperinsulinemia, hyperlipidemia, cancer, asthma and non-alcoholic fatty liver. The main objective in the treatment of obesity is to reduce obesity-related complications and reduce the likelihood of developing future health problems. Fundamental to weight loss is lifestyle modification, which aims to reduce the risk

of weight-related complications. Additionally, dietary changes and physical activity play crucial roles in reducing excess fat accumulation in the body. In cases where lifestyle modifications, dietary and physical therapy are unsuccessful in achieving weight loss and improving obesity, pharmacotherapy based treatments may be necessary (Kim *et al*., 2020)

2.2.7 Antiobesity Drugs

The regulation of energy balance, appetite and feeding behaviors involves a highly complex interaction between various hormones, neuropeptides and signaling pathways in both the central nervous system (CNS) and peripheral tissues. The hypothalamus plays a pivotal role in co-ordinating these regulatory mechanisms and is a major center for the control of energy homeostasis. The development and progression of obesity are strongly influenced by disruptions in these neural and hormonal circuits. Effective antiobesity pharmacotherapy aims to target these pathways to restore a healthy energy balance and to counteract factors promoting excessive fat accumulation. Current antiobesity medications work through various mechanisms, including enhancing satiety, suppressing appetite and increasing energy expenditure or lipid metabolism. One class of antiobesity drugs functions by inhibiting pancreatic and gastric lipase enzymes, thereby reducing fat absorption in the gastrointestinal tract. This leads to a decreased caloric intake from dietary fats. Another class of drugs acts centrally by modulating neurotransmitter pathways, serving as serotonin, dopamine and norepinephrine reuptake inhibitors, which enhance satiety signals and suppress appetite (Pilitsi *et al*., 2019).

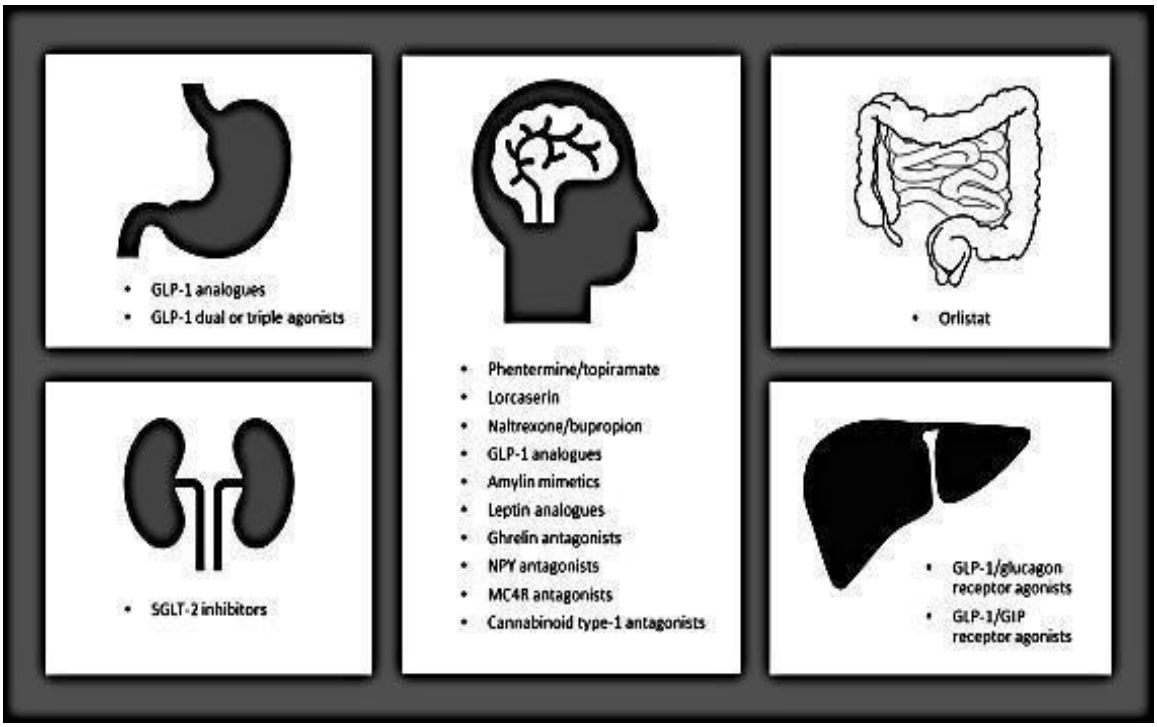
Continued research is focused on developing novel therapeutic agents that can more selectively and safely target the underlying mechanisms of obesity, to achieve sustained weight loss and reduce the associated metabolic complications (Muller *et al*., 2022).

Oral pharmacotherapy for obesity primarily targets the inhibition of pancreatic and gastric lipase, thereby reducing the breakdown and absorption of dietary fats in the intestines. This mechanism effectively lowers caloric intake from fats and has received approval from both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for clinical use. Phentermine, a sympathomimetic amine, functions by stimulating the release of noradrenaline, which enhances satiety signals and suppresses appetite. When used in combination with topiramate, an anticonvulsant, the

weight loss effect is amplified. Though the precise mechanism by which topiramate contributes to appetite suppression remains incompletely understood, clinical evidence supports its efficacy in promoting weight reduction when combined with phentermine (Christaki *et al*., 2025).

FIGURE 2.6

MECHANISM OF ACTION OF ANTIOBESITY DRUG CLASSES



(Muller *et al*., 2022)

Another widely studied agent, lorcaserin, has demonstrated substantial efficacy in reducing body weight, with clinical trials reporting an average weight loss of approximately 6.6 to 8.6 kg over 12 months. Lorcaserin acts as an appetite suppressant by selectively activating 5-HT2C receptors in the hypothalamus, a region of the brain that regulates hunger and satiety. Lorcaserin, a selective serotonin 2C receptor agonist, was indicated for individuals with a body mass index (BMI) $\geq$ 30 kg/m² or those with a BMI $\geq$ 27 kg/m² accompanied by obesity-related comorbidities such as hypertension, type 2 diabetes mellitus or dyslipidemia. However, following safety evaluations, the U.S. Food and Drug Administration (FDA) requested the withdrawal of lorcaserin from the

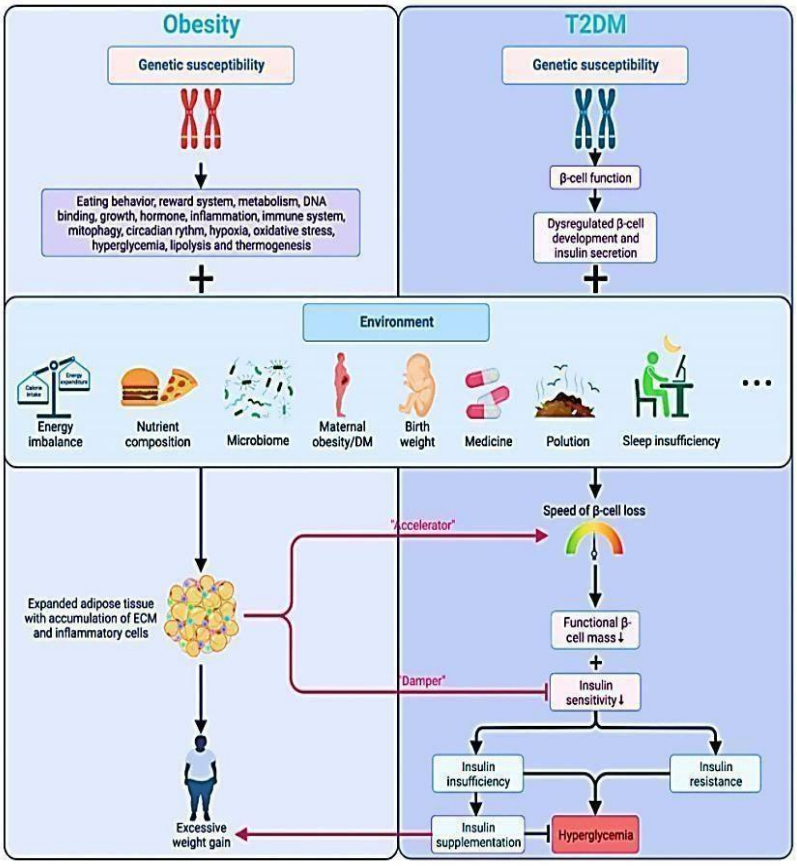
market due to concerns regarding an increased risk of cancer, concluding that the potential risks outweighed the therapeutic benefits (FDA, 2020) (Ho *et al.*, 2023).

2.2.8 Pathophysiological Connection between Obesity and Type 2 Diabetes Mellitus

Obesity, characterized by excessive weight gain and progressive fat accumulation, plays a central role in promoting metabolic disturbances that are strongly linked to the development of Type 2 Diabetes Mellitus (T2DM). In T2DM, hyperglycemia arises due to impaired insulin sensitivity, largely resulting from a reduction in functional β-cell mass and subsequent insulin resistance. The onset and progression of T2DM are profoundly influenced by obesity, which acts through multiple pathways. These include genetic predisposition, epigenetic modifications, environmental factors that negatively impact insulin signaling pathways and progressive β-cell dysfunction. Additionally, imbalances in the microbiome-gut-brain axis contribute further to metabolic dysregulation. Conversely, in some individuals with an inherent predisposition to insulin resistance, T2DM itself can precede obesity. In such cases, chronic hyperinsulinemia and elevated hepatic glucose production create a metabolic environment that fosters weight gain, thereby establishing a vicious cycle between T2DM and obesity (Ruze *et al*., 2023).

FIGURE 2.7

LINK BETWEEN OBESITY AND TYPE 2 DIABETES MELLITUS



(Ruze *et al*., 2023)

2.3 Nanotechnology

Nanoscience is an emerging interdisciplinary field that focuses on exploring innovative materials at the nanoscale, integrating expertise from applied health, molecular chemistry, pharmaceutical sciences, molecular science, optics and engineering. This collaborative approach aims to address challenges in medical and health sciences by developing more effective healthcare systems, advanced nanomedicine tools and novel treatment methods. Nanotechnology is entering a transformative phase, playing a critical role in revolutionizing health sciences and establishing itself as an essential therapeutic resource (Sahu *et al*., 2021).

Nanoparticles, typically ranging from 1 to 100 nanometers in size, have shown great promise as controlled drug delivery agents. By improving the half-life of drugs and

enhancing the solubility of hydrophobic compounds, nanoparticles facilitate controlled or sustained drug release, thereby increasing drug efficacy. Furthermore, nanoparticles can reduce drug toxicity and optimize drug biodistribution within the body. Among these, liposomes represent the first nanoparticle-based drug delivery system and have been effectively used to transport drugs and proteins (Dang and Guan, 2020).

Beyond drug delivery, nanoparticles have promising diagnostic applications, such as serving as contrast agents in medical imaging or detecting specific biomolecules in biological samples. In regenerative medicine, nanomaterials are utilized as scaffolds for tissue engineering and as vehicles for growth factors and signaling molecules that promote tissue repair and regeneration. Although nanomedicine is still in its early stages, it holds substantial potential to significantly enhance the diagnosis and treatment of various medical conditions (Yusuf *et al*., 2023).

2.3.1. Silver Nanoparticles (AgNPs)

Various types of nanoparticles, including zinc (Zn), silver (Ag), iron (Fe) and gold (Au), have been extensively utilized in drug delivery systems. Among these, silver nanoparticles (AgNPs) have garnered significant attention due to their potential to enhance glucose consumption and metabolism by improving hepatic glycogenesis via the insulin signaling pathway. AgNPs have demonstrated lower toxicity and high efficacy in both acute and chronic diabetes mellitus models. Treatment with AgNPs notably improves kidney and liver function profiles. However, the therapeutic efficacy of AgNPs can vary depending on their size and concentration, with larger nanoparticles exhibiting diminished antidiabetic effectiveness. Interestingly, a combination of AgNPs with plant-derived compounds produces significantly greater therapeutic effects than either pure AgNPs or plant extracts alone (Ullah *et al*., 2021a).

Animal studies have shown that AgNPs exert antidiabetic effects by enhancing the activation of the hepatic glucose transporter-2 (GLUT-2) gene, increasing serum insulin levels and elevating liver glucokinase (GK) activity. The enhanced biocatalytic activity of AgNPs contributes to their effective antidiabetic and antimicrobial properties in animal models. Additionally, AgNPs inhibit the activities of α-amylase and α-glucosidase key enzymes involved in carbohydrate metabolism thereby playing a role

in diabetes management. Compared to diabetic control groups, treatment with AgNPs significantly lowers fasting blood sugar (FBS) levels. Remarkably, AgNPs exhibit antidiabetic activity comparable to the pharmaceutical drug acarbose, acting through an alpha-glucosidase inhibitor mechanism (Torabian *et al*., 2022).

Previous research has also highlighted the benefits of plant-associated AgNPs in managing hyperglycemia and other diabetic complications. Although the exact mechanisms underlying their therapeutic actions remain to be fully elucidated, numerous studies demonstrate that plant-derived AgNPs are particularly effective in controlling diabetes and promoting wound healing. These biosynthesized AgNPs often outperform other synthesis methods such as chemical, physical and microorganism-mediated production (Bhattacharjee *et al.,* 2025).

2.3.2 Green Synthesis of Silver Nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) can be synthesized via various methods, broadly categorized into chemical and biological (green) approaches. Traditional chemical synthesis methods employ reducing agents such as sodium borohydride, sodium citrate, citric acid, Tollens' reagent and polyethylene glycol block copolymers. Although effective, these chemical routes are often hindered by significant drawbacks including high costs, toxicity, scalability issues and environmental hazards, which limit their sustainable application (Rai and Avila-Quezada, 2024).

In contrast, green synthesis has emerged as a promising alternative that mitigates many of these limitations. This eco-friendly method utilizes biological entities such as bacteria, fungi, yeast and particularly plant extracts to reduce silver ions and facilitate nanoparticle formation. Besides acting as reducing agents, these biological materials also serve as capping and stabilizing agents, enabling better control over nanoparticle size and preventing agglomeration one of the common challenges in nanoparticle synthesis (Restrepo and Villa, 2021) The green synthesis process is not only cost-effective and scalable but also environmentally sustainable, making it highly suitable for large-scale production.

The natural reducing agents involved in green synthesis are biodegradable and non-toxic and this method offers enhanced precision in controlling nanoparticle

morphology. Consequently, adopting green synthesis promotes safer and more efficient silver nanoparticle production methods, with wide ranging applications across biomedicine, catalysis and environmental remediation (Alharbi *et al*., 2022).

The green synthesis of silver nanoparticles typically follows a bottom-up approach involving three key phases: reduction of silver ions, nucleation and cluster formation and nanoparticle growth. These stages are influenced by factors such as the nature of the reducing agent, silver nitrate ($AgNO_3$) concentration and the pH of the reaction medium. Phytochemicals present in plants play a pivotal role in this process, functioning both as reducing and stabilizing agents. Particularly, the hydroxyl (–OH) groups in phytochemicals bind to Ag^{3+} ions, promoting their reduction to metallic silver (Ag^0) and enabling the successive phases of nanoparticle formation (Ma *et al*., 2022).

Research indicates that green-synthesized silver nanoparticles exhibit enhanced therapeutic properties compared to those produced by conventional chemical methods. This superior efficacy is attributed to the bioactive phytochemicals that remain attached to the surface of the nanoparticles, imparting synergistic biological activities. The combined effects of the nanoparticles and the natural phytochemicals make green-synthesized AgNPs a highly promising approach for biomedical applications (Rahman *et al*., 2022).

2.4. Medicinal Plants

For over a millennium, various plants have been recognized for their therapeutic properties and to this day, many modern medicines have origins rooted in plant-based compounds. Medicinal plants are distributed worldwide, with over 70,000 recorded species from small lichens to towering trees demonstrating potential in treating a wide variety of medical conditions. The use of natural remedies for the prevention and treatment of numerous human illnesses has a long and rich history. This ongoing reliance has profoundly influenced contemporary medical and healthcare practices. Herbal medicine is considered a cornerstone of both ancient and modern healthcare systems. In many developing countries, approximately 75–80 percent of the population depends on natural products for primary healthcare, due to their cultural acceptability and relatively low incidence of adverse effects (Prasath kumar *et al*., 2021).

The therapeutic use of medicinal plants leverages a diverse range of phytochemicals to address numerous health ailments. Compared to synthetic drugs, phytochemicals are generally regarded as safer and more effective, with fewer side effects. Specifically, in the management and control of diabetes, the use of herbal remedies offers benefits such as greater accessibility, reduced costs and diminished adverse reactions. These natural treatments exert their antidiabetic effects through multiple mechanisms: reducing insulin resistance, enhancing insulin secretion, protecting pancreatic beta cells and ultimately lowering circulating blood glucose levels. Several plants with demonstrated antidiabetic properties are currently under investigation for development into modern commercial drugs (Latif and Nawaz, 2025).

The high cost of conventional medications in developing countries drives the widespread use of traditional herbal remedies for diabetes management. Medicinal plants are believed to exert their antidiabetic effects through various pathways, including stimulating insulin production from pancreatic β-cells, improving insulin receptor sensitivity, decreasing insulin resistance and enhancing glucose tolerance. Additionally, they promote better glucose metabolism, increase β-cell mass and function and elevate plasma insulin levels. These actions collectively contribute to the reduction of blood glucose, providing a promising basis for the development of novel antidiabetic drugs that are more potent and have fewer side effects compared to existing therapies (Ansari *et al*., 2022a).

Extracts from various plants such as green tea, garlic, black seed, fenugreek and conjugated linoleic acid have demonstrated significant antiobesity effects, particularly through their direct impact on adipose tissue. A key group of bioactive compounds contributing to these effects is polyphenols a diverse class of plant-derived secondary metabolites known as phytochemicals. These polyphenolic compounds are abundant in fruits, vegetables, grains, legumes and numerous medicinal herbs. Examples include grape seed proanthocyanidin extract, xanthohumol, genistein, daidzein, cyanidin, apigenin, luteolin, kaempferol, myricetin, quercetin and epigallocatechin gallate, all of which have been extensively studied for their obesity combating properties (Idm'hand *et al*., 2020).

TABLE 2.1

MEDICINAL PLANTS USED FOR DIABETES AND OBESITY

Plant Species	Part Used	Preparation	Used For
Atriplex halimus L.	Leaf	Powder, decoction	Diabetes
Allium ampeloprasum L.	Bulb	Raw	Diabetes
Allium cepa L.	Bulb	Raw and juice	Diabetes
Allium sativum L.	Bulb	Raw, powder	Diabetes, Obesity
Pistacia atlantica Desf.	Fruit	Decoction	Diabetes
Pistacia lentiscus L.	Leaf, Gum	Infusion and decoction	Diabetes
Ammi visnaga L.	Inflorescence	Decoction	Diabetes
Apium graveolens L.	Seed	Infusion	Diabetes
Carum carvi L.	Seed	Decoction	Diabetes
Coriandrum sativum L.	Seed	Infusion	Diabetes
Cuminum cyminum L.	Seed	Powder	Diabetes
Daucus carota L.	Root	Juice	Diabetes
Eryngium ilicifolium Lam.	Stem and leaf	Decoction	Diabetes
Pastinaca sativa L.	Root	Raw	Diabetes
Pimpinella anisum L.	Seed	Powder	Diabetes
Trigonella foenum graecum	Seed	Powder, decoction	Diabetes, Obesity
Momordica charantia	Fruit	Juice, decoction	Diabetes
Gymnema sylvestre	Leaf	Powder, infusion	Diabetes, Obesity
Ocimum sanctum	Leaf	Decoction, infusion	Diabetes
Tinospora cordifolia	Stem	Decoction	Diabetes
Garcinia cambogia	Fruit rind	Extract, powder	Obesity
Camellia sinensis	Leaf	Tea infusion	Obesity
Nigella sativa	Seed	Oil, powder	Obesity
Zingiber officinale	Rhizome	Decoction, powder	Obesity
Capsicum annuum	Fruit	Powder, extract	Obesity
Phaseolus vulgaris	Seed	Extract, decoction	Obesity
Citrus aurantium	Fruit peel	Extract	Obesity
Curcuma longa	Rhizome	Powder, extract	Obesity
Lepidium meyenii	Root	Powder	Obesity
Silybum marianum	Seed	Extract	Obesity
Orthosiphon stamineus	Leaf	Decoction, infusion	Obesity

(Idm'hand *et al*., 2020)

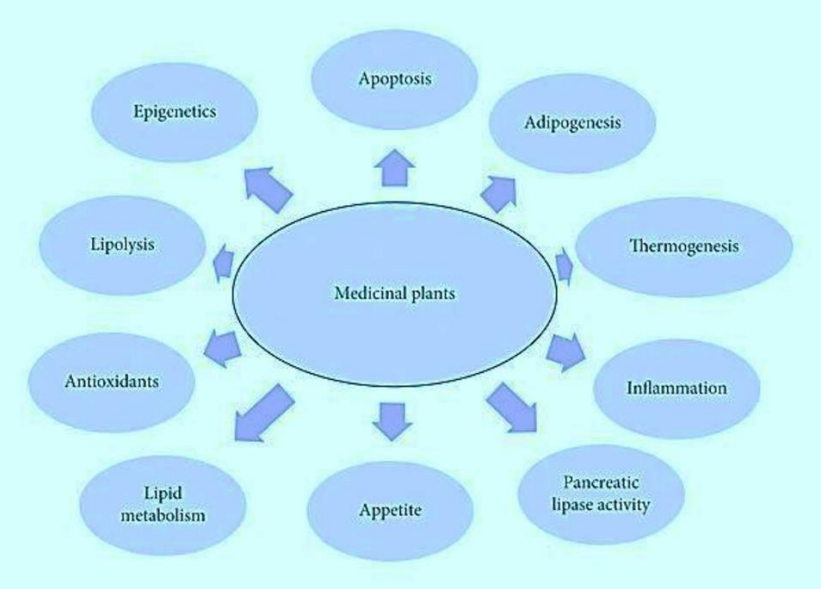
In addition to polyphenols, carotenoids such as esculetin and fucoxanthin, as well as phytoalexins like resveratrol, have been investigated for their beneficial roles in lipid metabolism. Other bioactive food components including phytosterols, polyunsaturated fatty acids and organosulfur compounds also contribute to antiobesity effects. These natural compounds assist in weight management through multiple

mechanisms such as appetite suppression, inhibition of pancreatic lipase activity, enhancement of thermogenesis and lipid metabolism, promotion of satiety and modulation of epigenetic pathways (Saad *et al*., 2021).

Figure 2.8 illustrates the multifaceted role of medicinal plants in influencing various biological processes linked to obesity and metabolic health. Medicinal plants can modulate apoptosis (programmed cell death) and adipogenesis (formation of new fat cells), helping regulate fat storage. They can stimulate thermogenesis, the process of heat production that burns calories and reduce inflammation, which is often associated with obesity-related disorders. By inhibiting pancreatic lipase activity, these plants can reduce dietary fat absorption, while also controlling appetite to limit calorie intake. They improve lipid metabolism, promote lipolysis (breakdown of fats) and act as antioxidants to neutralize free radicals and reduce oxidative stress. Additionally, medicinal plants may influence epigenetics, altering gene expression to favor healthier metabolic outcomes. Together, these mechanisms highlight their potential as natural interventions for managing obesity and related metabolic diseases (Vrânceanu *et al*., 2023).

FIGURE 2.8

MULTIFACETED MECHANISTIC INSIGHTS INTO THE ANTIOBESITY POTENTIAL OF MEDICINAL PLANTS



(Saad *et al*., 2021)

2.5. *Boerhavia diffusa* L.

Boerhavia diffusa L. a member of the Nyctaginaceae family, is a widely recognized flowering plant known by the traditional name "Punarnava," attributed to its notable regenerative properties. This plant is extensively distributed across tropical and subtropical regions, including India, Sri Lanka, Egypt, Sudan, Ghana, South Africa, Nigeria, China, Australia, the Philippines and Iran. Historical and contemporary medicinal literature has documented various therapeutic properties of *Boerhavia diffusa* L. extracts derived from its leaves and roots. These include hypoglycemic, spasmolytic, antimicrobial, immunomodulatory, hepatoprotective, anti-inflammatory, antioxidant and anticancer activities (Kaur, 2019). Phytochemical analysis reveals that *Boerhavia diffusa* L. is rich in diverse bioactive compounds such as isoflavonoids (e.g., 2′-O-methyl abronisoflavone), rotenoids (boeravinones A-J), steroids (boerhavisterol, β-ecdysone), alkaloids (punarnavine), tannins, flavonoids (borhaavone, quercetin, kaempferol), phenolic glycosides, flavonoid glycosides and lignan glycosides (liriodendrin, syringaresinol mono-β-D-glucoside). These constituents collectively contribute to the plant's multifaceted pharmacological effects.

Experimental studies in streptozotocin-induced diabetic animal models have demonstrated *Boerhavia diffusa* L. ability to significantly reduce blood glucose levels and oxidative stress markers, while exhibiting potent free radical scavenging activity. Ethanolic extracts of the plant have been shown to restore carbohydrate metabolizing enzymes to near normal levels and reverse the depletion of liver glycogen in diabetic rats. Mechanistically, these therapeutic effects are mediated by the inhibition of glucose absorption in the jejunum and enhancement of glucose uptake in skeletal muscle tissues (Das *et al*., 2023).

Table 2.2 outlines the major phytochemicals found in different parts of *Boerhavia diffusa* L. and links them to their reported pharmacological activities. Roots are rich in rotenoids, alkaloids and glycosides with diverse effects such as anticancer, hepatoprotective and anti-inflammatory actions, while leaves, stems, flowers and seeds each possess distinct compounds (e.g., flavonoids, phenolics, fatty acids) contributing to antioxidant, antimicrobial, antidiabetic or reproductive health effects.

The aqueous leaf extract of *Boerhavia diffusa* L. has been shown to modulate blood glucose levels and hepatic enzyme activities in diabetic-induced rat models. Specifically, this extract increases hexokinase activity while decreasing the activities of glucose-6-phosphate and fructose-1,6-bisphosphate enzymes, which are key regulators in glucose metabolism. Moreover, chloroform extracts of *Boerhavia diffusa* L. leaves have demonstrated dose-dependent reductions in blood glucose levels in streptozotocin-induced non-insulin dependent diabetic rats. This hypoglycemic effect may arise from the regeneration of pancreatic β-cells or mechanisms acting beyond pancreatic function (Lawal *et al*., 2022).

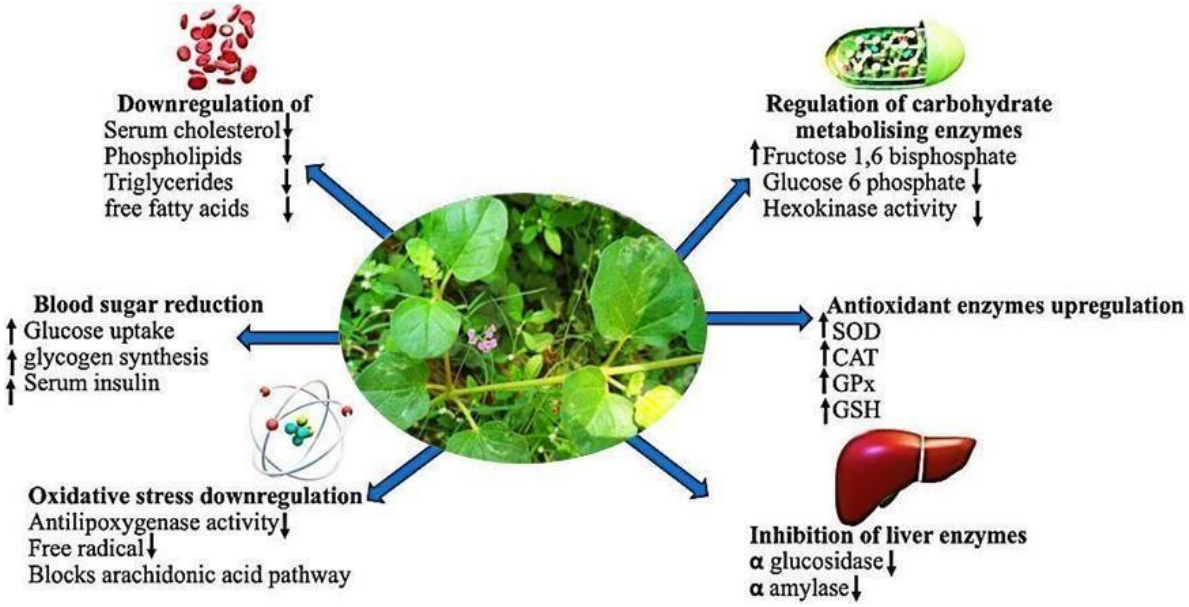
TABLE 2.2

PHYTOCHEMICAL CONSTITUENTS AND PHARMACOLOGICAL ACTIVITIES OF DIFFERENT PARTS OF *Boerhavia diffusa* L.

Plant Part	Major Phytoconstituents	Reported Pharmacological Activities	References
Root	Rotenoids (boeravinones A– J), punarnavine, phenolic glycosides (punarnavoside), lignans (liriodendrin), sterols (β- ecdysone), fatty acids, phenolics	Anticancer/anti-angiogenic, hepatoprotective, antioxidant, diuretic, anti-inflammatory, antistress, Anticonvulsant	Mishra *et al*., (2014); Saraswati *et al*., (2013); Das *et al*., (2023); Kaviya *et al*., (2022)
Leaf	Flavonoids (quercetin, kaempferol, eupalitin derivatives) phenolics, saponins, tannins, proteins, polysaccharides	Antioxidant, antidiabetic, immunomodulatory, hepatoprotective, anti- inflammatory	Mishra *et al*., (2014); Das *et al*., (2023); Kaviya *et al*., (2022)
Stem	Flavonoids, terpenoids, phenolics, alkaloids, sterols	Antioxidant, antimicrobial, hepatoprotective, immunomodulatory	Mishra *et al*., (2014); Das *et al*., (2023); Kaviya *et al*., (2022)
Flower	Phenolics, flavonoids (traces), volatile compounds, vitamins/ minerals	Antioxidant, nutritive value (limited targeted pharmacological studies)	Das *et al*., (2023); Kaviya *et al*., (2022)
Seed	Fatty acids, glycosides, phytosterols, alkaloids, saponins	Antifertility (reported in some animal models), antimicrobial, antioxidant	Mishra *et al*., (2014); Das *et al*., (2023); Kaviya *et al*., (2022)

FIGURE 2.9

MECHANISM OF THE ANTIDIABETIC PROPERTY OF *Boerhavia diffusa* L.



(Prasad and Mishra, 2024)

Enzymes such as α-amylase and α-glucosidase are critically involved in carbohydrate digestion and postprandial glucose regulation, making them therapeutic targets in diabetes management. *Boerhavia diffusa* L. has been found to inhibit both α-amylase and α-glucosidase activities, suggesting its potential to reduce carbohydrate breakdown and glucose absorption (Sinan *et al*., 2021). These findings collectively highlight the significant potential of *Boerhavia diffusa* L. in the phytotherapeutic management of diabetes mellitus and its associated complications (Vasundhara and Devi, 2018).

In addition to its antidiabetic properties, *Boerhavia diffusa* L. exhibits antiobesity effects. In obesity induced rat models, the plant reduces food intake and inhibits the accumulation of carbohydrates and fatty acids in the liver by promoting their conversion into hepatic glycogen rather than fat storage. This metabolic shift is linked to the modulation of both metabolic and serotonin pathways. Supplementation with *Boerhavia diffusa* L. leads to a significant decrease in fat-pad weights in various depots, including perirenal, uterine, spleen, kidney and heart fat pads. Furthermore, it effectively lowers serum cholesterol, triglycerides and low-density lipoprotein (LDL) levels in

hypercholesterolemic animal models. This lipid-lowering effect is partly attributed to the presence of beta-sitosterol, a phytoconstituent structurally similar to cholesterol that competes with cholesterol absorption, thereby reducing LDL cholesterol without adverse effects. Additionally, *Boerhavia diffusa* L. exhibits hepatoprotective properties by significantly reducing serum levels of liver marker enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are elevated during hepatic necrosis or membrane damage. This protective effect further supports its therapeutic value in liver-related complications often associated with diabetes and obesity (Kapoor *et al.,* 2021).

TABLE 2.3

***Boerhavia diffusa* L. PLANT PARTS AND NANOPARTICLE SYNTHESIS**

Plant part	Nanoparticle	Key finding	Reference
Leaf	Silver nanoparticles (AgNPs)	Leaf extract mediated AgNPs exhibited potent antibacterial and wound healing activity.	(Patil *et al*., 2023)
Leaf	Selenium nanoparticles (SeNPs)	Leaf extract- synthesized SeNPs showed strong antioxidant and antiinflammatory activity.	(Sushma *et al*., 2021)
Leaf	Zinc oxide nanoparticles (ZnO NPs)	Leaf-mediated ZnO NPs demonstrated significant anticariogenic and antiinflammatory activity.	(Jayadharani *et al*., 2021)
Root (glycoside rich portion)	Silver nanoparticles (AgNPs) with GRP loaded	Root derived GRP loaded AgNPs enhanced wound healing efficacy when formulated as a nanogel.	(Patil *et al*., 2023)

Table 2.3 complements this by showing how specific plant parts mainly leaves and roots have been used for green synthesis of various nanoparticles, including silver, selenium and zinc oxide. These nanoparticles inherit both the bioactive properties of the

plant extracts and the unique physicochemical attributes of the nanomaterials, resulting in enhanced antimicrobial, antioxidant and wound healing and anti-inflammatory activities (Patil *et al*., 2023).

The literature reviewed underscores the growing global health burden posed by diabetes mellitus and obesity two interrelated metabolic disorders that contribute significantly to morbidity and mortality worldwide. Although a range of pharmacological agents is available for managing these conditions, their long-term use is often limited by adverse effects, reduced efficacy and economic constraints. This has intensified the demand for alternative therapeutic strategies that are safer, more cost-effective and environmentally sustainable (Sushma *et al*., 2021). In recent years, the convergence of nanotechnology and phytotherapy has emerged as a promising frontier in biomedical research, offering enhanced drug delivery, improved bioavailability and targeted therapeutic action. Within this context, *Boerhavia diffusa* L. (Punarnava), a traditional medicinal herb with well documented antioxidant, anti-inflammatory, antidiabetic and antiobesity properties, presents significant therapeutic potential (Jayadharani *et al*., 2021). However, scientific exploration of its efficacy when formulated as green synthesized silver nanoparticles remains limited. Hence, the present study focuses on evaluating the antidiabetic and antiobesity efficacy of silver nanoparticles synthesized using the ethanolic extract of *Boerhavia diffusa* (EBdAgNPs) in experimentally induced rat models. This investigation aims to bridge the gap between traditional herbal medicine and modern nanoscience, providing a novel, eco friendly and biocompatible approach for the management of metabolic disorders such as diabetes and obesity (Patil *et al*., 2023).