

INTRODUCTION

Diabetes mellitus is classified into three primary types: Type 1 diabetes (T1D), Type 2 diabetes (T2D) and Gestational Diabetes Mellitus (GDM). T1D results from autoimmune destruction of insulin-producing β -cells in the pancreas, leading to absolute insulin deficiency. While typically emerging in childhood or adolescence, it can manifest at any age. Adult-onset cases, sometimes referred to as latent autoimmune diabetes in adults (LADA), are increasingly recognized and managed as T1D based on autoantibody presence and clinical progression (Sreenivasamurthy, 2021). T2D accounts for approximately 85-90 percent of all diabetes cases globally and is characterized by insulin resistance and inadequate compensatory insulin secretion. It is closely linked with obesity, sedentary lifestyles and dietary factors, placing it at the center of the global "diabesity" epidemic (Sun *et al.*, 2022; Garg and Agarwal 2024). On the other hand, GDM is defined as hyperglycemia first detected during pregnancy and affects roughly 6-10 percent of pregnancies. Importantly, women with GDM have a markedly increased risk estimated 7 to 9 fold higher of developing T2D later in life (Diaz-Santana *et al.*, 2022; Saedi *et al.*, 2025). Additionally, GDM may herald long-term metabolic and cardiovascular consequences for both mother and child. This interconnected framework of diabetes types underscores the need for early diagnosis, targeted prevention and continuous monitoring across the lifespan, particularly in high-risk populations (Aidoo, 2025).

The global burden of diabetes mellitus has reached critical levels, with the International Diabetes Federation (IDF) reporting that, as of 2020, approximately 537 million adults are affected by the disease (Huang *et al.*, 2025). Projections indicate that this figure will rise to 783 million by 2045, underscoring the urgent need for global health interventions. In the United States alone, an estimated 34.2 million individuals roughly 10.5 percent of the population are living with diabetes (Ugli *et al.*, 2024). The economic impact is also staggering, with diabetes-related healthcare expenses and productivity losses amounting to \$327 billion annually (Ali, 2024). Notably, the burden is

disproportionately heavier in low and middle-income countries, where limited healthcare resources result in delayed diagnoses and suboptimal treatment, leading to severe complications. The COVID-19 pandemic has further compounded these challenges, as individuals with diabetes face a heightened risk of severe outcomes (Khunti *et al.*, 2022).

A range of factors contribute to the onset of diabetes, encompassing non-modifiable elements such as age, genetic background and ethnicity and modifiable factors like diet, physical activity and body composition (Dawson *et al.*, 2022). Notably, obesity especially the accumulation of visceral adipose tissue plays a central role in driving insulin resistance and the pathogenesis of type 2 diabetes (T2D) (Wondmkun, 2020). Visceral fat is metabolically active and contributes to chronic low-grade inflammation and impaired insulin signaling, thereby promoting the development of T2D (Janochova *et al.*, 2019). Additionally, a sedentary lifestyle exacerbates the risk of diabetes, while regular physical activity has been shown to enhance insulin sensitivity and reduce the likelihood of T2D onset (Carbone *et al.*, 2019). Unhealthy eating patterns, marked by excessive consumption of refined carbohydrates and a lack of dietary fiber, play a significant role in promoting both obesity and insulin resistance. In contrast, diets abundant in whole grains, fruits and vegetables have been shown to exert protective effects against metabolic dysfunction. Additionally, recent studies emphasize the importance of "chrononutrition" which involves aligning meal timing with the body's natural circadian rhythms to improve metabolic outcomes and reduce the risk of diabetes related complications (Reytor-Gonzalez *et al.*, 2025). These developments underscore the need for a holistic approach to diabetes management that incorporates medical, behavioral and psychological strategies (Indrawan *et al.*, 2024).

Simultaneously, obesity has emerged as a global epidemic, further amplifying the prevalence of chronic diseases. According to the World Health Organization (WHO), by 2022, nearly 2 billion adults worldwide were classified as overweight, including more than 650 million who were obese (Elhisadi, 2022). Since the mid-1970s, the prevalence of obesity has nearly tripled globally, which has significantly contributed to the rising incidence of type 2 diabetes, cardiovascular diseases and various types of cancer (Tripathi *et al.*, 2019). In the United States, 42.4 percent of adults are obese, resulting in an estimated \$173 billion in annual healthcare costs associated with obesity-related

conditions (Ezendu *et al.*, 2025). This dramatic rise in obesity is driven not only by lifestyle choices but also by socioeconomic factors that influence diet and physical activity levels.

Obesity is commonly measured by body mass index (BMI), which classifies individuals from underweight to obese based on standard thresholds (World Health Organization, (2022); Taieb *et al.*, 2022). Moreover, fat distribution, particularly central obesity, is more strongly associated with metabolic disorders and cardiovascular diseases than other types of fat accumulation (Kang and Neeland 2023). A combination of genetic, environmental and behavioral factors contributes to obesity development. Still, the rapid increase in global rates is largely attributed to the widespread availability of high-calorie, nutrient-poor foods and increasingly sedentary lifestyles (Aremu *et al.*, 2025).

Addressing the growing burden of lifestyle-associated diseases requires a comprehensive public health strategy that emphasizes prevention, early diagnosis and effective therapeutic management (Garg, 2025). A deeper understanding of the complex interactions between genetic predispositions, lifestyle factors and environmental influences is critical for developing targeted interventions to curb the rising prevalence of these interrelated conditions (Fischer, 2024).

Obesity and diabetes remain major interconnected public health challenges worldwide, imposing substantial burdens on individuals and healthcare systems. Excess accumulation of visceral adipose tissue is a critical factor in the onset of Type 2 diabetes (T2D), as it promotes insulin resistance and disrupts normal metabolic processes. Both conditions are influenced by shared environmental, genetic and lifestyle factors and their co-occurrence exacerbates health outcomes, including cardiovascular disease and organ damage. As the prevalence of these conditions continues to rise, there is an urgent need for comprehensive interventions that address their underlying causes and progression (Alhuneafat *et al.*, 2025).

In recent years, increasing attention has been focused on alternative therapeutic approaches, particularly the application of medicinal plants alongside conventional medications for the management of chronic metabolic complications (Nyakudya *et al.*, 2020). Many of these plants are rich sources of bioactive compounds that have demonstrated efficacy in modulating blood glucose levels, enhancing insulin sensitivity and alleviating inflammation associated with obesity

(Unuofin and Lebelo, 2020). Combining traditional medicinal treatments with standard pharmaceutical interventions may offer a multifaceted approach to mitigating the effects of these intertwined diseases (Kalariya *et al.*, 2023). Understanding the mechanisms by which natural compounds interact with metabolic pathways could open new avenues for more effective treatments (Al-Azzawi *et al.*, 2024).

The growing prevalence of obesity and T2D has sparked interest in alternative and complementary therapies to manage these conditions (Mc Benedict *et al.*, 2024). Both obesity and T2D are characterized by insulin resistance, dyslipidemia and chronic inflammation, which increase the risk of cardiovascular disease and other complications (Piche *et al.*, 2020). While standard pharmacological treatments such as metformin and glibenclamide remain effective in managing blood glucose levels and improving insulin sensitivity, they often come with side effects and limited efficacy in addressing obesity (Bodier *et al.*, 2025). As a result, there has been a shift towards exploring natural remedies, particularly medicinal plants, which offer multi-faceted benefits including antioxidant, anti-inflammatory and lipid-lowering effects (Manful *et al.*, 2025). These plant based treatments, when used alongside conventional drugs, have shown promise in enhancing insulin sensitivity, regulating blood sugar levels and improving lipid profiles (Thaiudom *et al.*, 2025). By targeting multiple metabolic pathways, they provide a holistic approach for the management of metabolic disorder, offering potential therapeutic advantages over standard single target drugs (Lillich *et al.*, 2021).

Medicinal plants have been recognized for their therapeutic potential in controlling chronic metabolic abnormalities due to their bioactive compounds that exert various pharmacological effects (Tran *et al.*, 2020). Many plants contain phytochemicals such as flavonoids, polyphenols and alkaloids, which have been shown to possess antidiabetic and antiobesity properties (Dinda and Dinda, 2022). For instance, these compounds can enhance insulin sensitivity, promote glucose uptake by cells and modulate lipid metabolism, ultimately leading to improved glycemic control and weight management (David, 2025). Research indicates that certain plant extracts can inhibit key enzymes involved in carbohydrate digestion, such as α -amylase and α -glucosidase, thereby reducing postprandial glucose spikes and supporting improved overall metabolic health (Kashtoh and Baek, 2023).

In addition to their direct effects on glucose and lipid metabolism, medicinal plants can also modulate obesity-associated inflammation and oxidative stress (Saad, 2023). Sustained inflammation and oxidative stress are recognized as major contributors to metabolic dysfunction, as they promote insulin resistance and disturb normal physiological homeostasis (Rohm et al., 2022). Many medicinal plants have demonstrated the ability to scavenge free radicals and enhance the body's antioxidant defences, thereby mitigating oxidative stress and improving the inflammatory response. For instance, studies have shown that certain plant extracts can lower levels of pro-inflammatory cytokines while enhancing anti-inflammatory pathways, thereby contributing beneficial effects towards metabolic regulation (Zielinska-Blizniewska *et al.*, 2019).

Furthermore, the integration of medicinal plants into dietary regimens may offer a holistic approach in managing obesity and diabetes. Utilizing these plants as functional foods can complement traditional treatments, promoting weight loss and better glycemic control while minimizing the side effects commonly associated with pharmacological interventions (Rahman *et al.*, 2022). The synergistic effects of combining medicinal plants with standard medications could enhance therapeutic outcomes and improve patient adherence to treatment plans (Chaachouay, 2025). This multifaceted approach underscores the importance of exploring the therapeutic potential of medicinal plants in addressing the growing prevalence of diabetes and obesity globally. The integration of medicinal plants with nanoparticles has emerged as a promising strategy in modern medicine, particularly for managing conditions like diabetes and obesity (Stoleru *et al.*, 2024).

Nanoparticles, such as silver or gold nanoparticles, can be synthesized using bioactive compounds derived from medicinal plants, creating a synergistic effect that enhances their therapeutic potential (Ronavari *et al.*, 2021). This green synthesis approach harnesses the natural antioxidant, anti-inflammatory and antidiabetic properties of medicinal plants, while also improving the bioavailability, stability and targeted delivery offered by nanoparticles (Krishnamoorthy *et al.*, 2023). The combination enhances efficacy in managing metabolic disorders, as nanoparticles enable controlled and sustained release of active plant-derived compounds, optimizing their pharmacokinetics and therapeutic outcomes in the treatment of obesity and diabetes (Karnwal *et al.*, 2024).

Nanotechnology, which involves manipulating materials on a scale smaller than 100 nanometers, has emerged as a groundbreaking field with applications spanning medicine, engineering, biotechnology and more. Its impact is particularly notable in medicine, where nanoparticles offer new possibilities for targeted drug delivery and improved therapeutic outcomes (Malik *et al.*, 2023a). Due to their extremely small size, nanoparticles possess unique physicochemical properties that distinguish them from their larger counterparts, enhancing their efficiency and functionality in biological systems (Joudeh and Linke, 2022). However, alongside these advancements, nanotechnology continues to face significant challenges, including concerns regarding potential toxicity and environmental safety (Babatunde *et al.*, 2019). Conventional methods for nanoparticle synthesis frequently rely on hazardous chemicals, underscoring the growing demand for greener, more sustainable production techniques (Kirubakaran *et al.*, 2025).

To mitigate these concerns, recent innovations have increasingly focused on "green synthesis" approaches, which harness biological processes such as using plant extracts, microbes or biomolecules to create nanoparticles in an environmentally friendly and sustainable manner (Edo *et al.*, 2025). This paradigm shift has enabled the production of nanoparticles that not only reduce ecological and health risks but also enhance drug delivery efficiency, particularly in the management of chronic diseases such as diabetes and obesity (Halagali *et al.*, 2025). Within pharmaceutical nanotechnology, systems like polymeric nanosystems, dendrimers and metallic nanoparticles have been widely explored for their therapeutic potential (Anjum *et al.*, 2021).

Silver nanoparticles (AgNPs), synthesized primarily from silver precursors and typically ranging from 1 to 100 nanometers, have gained considerable attention due to their wide range of biomedical applications (Almatroudi, 2020). Their nanoscale size provides a high surface-area-to-volume ratio, enhancing their biological activity, particularly their potent antimicrobial effects against bacteria, fungi, viruses and protozoa (Rajak *et al.*, 2020). These advancements underscore the growing importance of nanotechnology in modern medicine, with AgNPs playing a crucial role in revolutionizing drug discovery and disease management, particularly in the treatment of infections, chronic diseases and as novel carriers for targeted drug delivery (Jangid *et al.*, 2024). Researchers have been focusing on the potential medical

applications of AgNPs, particularly concerning diabetes and obesity. AgNPs not only exhibit strong antimicrobial effects but have also shown promise in improving insulin sensitivity, which is crucial for managing diabetes. Studies indicate that silver-based nanoparticles can increase calcium ion concentration in cells and activate key phosphorylation pathways that aid in insulin sensitivity (Javed *et al.*, 2021).

These methods use plant extracts, algae, fungi and other microorganisms, which are safer and more environmentally friendly compared to traditional chemical synthesis techniques (Jeevanandam *et al.*, 2022). The antioxidant properties of biologically synthesized silver nanoparticles (AgNPs) are particularly beneficial in managing diabetes, as they help reduce oxidative stress contributing factor to insulin resistance. In addition to their antioxidant capabilities, AgNPs enhance insulin signaling by increasing the expression of Insulin Receptor Substrate 1 (IRS1) and Glucose Transporter Type 2 (GLUT2), both of which are essential for glucose metabolism (EI-Daly *et al.*, 2021). Furthermore, the small size of these nanoparticles enables them to penetrate blood vessels more easily, delivering their effects efficiently without causing significant harm to other organs, making them an ideal candidate for diabetes treatment (Souto *et al.*, 2019).

In recent years, silver nanoparticles (AgNPs) have attracted interest in obesity management due to their potential to modulate metabolic pathways and alleviate inflammation, a key factor connecting obesity and insulin resistance (Paul *et al.*, 2024). Studies have demonstrated that AgNPs may increase energy expenditure by elevating metabolic activity and stimulating the browning of white adipose tissue, which enhances fat degradation and energy consumption (Madbouly *et al.*, 2025). This makes AgNPs a promising tool in managing obesity, especially as obesity is often associated with chronic inflammation and metabolic dysfunction. Moreover, the ability of AgNPs to inhibit enzymes such as α -amylase and α -glucosidase has been shown to slow down carbohydrate digestion and absorption, leading to better control of blood glucose levels post-meal (Umar *et al.*, 2025). Collectively, these studies underscore the growing interest in AgNPs as a dual therapeutic agent for both diabetes and obesity, offering a new frontier in the development of nanodrugs aimed at addressing these interconnected global health challenges (Cheriyian, 2024).

Boerhavia diffusa L. (*B. diffusa*) is a prominent medicinal plant extensively found in various parts of India, South America and Africa (Pandey, 2025). Belonging to the genus *Boerhavia*, the plant is named after Hermann Boerhaave, a renowned Dutch physician of the 18th century, known for his contributions to modern medical science (Thijsse and Wesseling, 2021). The plant's species name refers to its distinctive branching structure, which is characteristic of its growth. This plant is a rich source of bioactive compounds, containing an array of 15 amino acids, along with essential fatty acids such as behenic acid and arachidic acid, along with vitamins and calcium (Salsinha *et al.*, 2022). Notably, the roots of *B. diffusa* contain high concentrations of flavonoids, xanthenes, steroids and other bioactive compounds that contribute to its diverse medicinal applications (Kaur, 2019). While all parts of the plant, including the stem, leaves and roots, have medicinal uses, the origins are particularly significant for their pharmacological properties (Elshafie *et al.*, 2023).

In traditional Ayurvedic medicine, *B. diffusa* is known as a "rasayana," herb reputed for its rejuvenating properties that promote vitality, cognitive enhancement and exhibit potential anti-aging and anticancer effects (Yadav *et al.*, 2025). Modern research has supported its role as an immunomodulatory agent, helping to strengthen the immune system and protect against various diseases (Strzelec *et al.*, 2023). The plant has been traditionally employed to treat several conditions, such as kidney disorders, skin ailments and eye problems. Its anti-inflammatory properties have been particularly noted for managing arthritis and gout, with recent studies confirming significant anti-inflammatory activity in extracts derived from the leaves and flowers of the plant (Banik *et al.*, 2020).

The pharmacological benefits of *B. diffusa* are not limited to its anti-inflammatory effects. It also demonstrates significant antioxidant and diuretic properties, which contribute to kidney health by promoting increased urine output and reducing inflammation within the renal system (Kashyap *et al.*, 2024). Moreover, *B. diffusa* has been found to support wound healing and exhibits antimicrobial activity against various pathogens, aiding in infection prevention and immune system support (Sudheer and Praveen, 2020). Recent studies have also identified its promising anticancer effects, particularly against breast and leukemia cancer cells (Gunaseelan *et al.*, 2022). Despite its extensive traditional usage, the plant continues to attract scientific interest, with ongoing studies aimed at confirming its therapeutic potential and broadening its application in modern medicine.

The global rise in diabetes and obesity has created an urgent need for a innovative therapeutic strategies that can effectively address both conditions. One promising approach involves the use of ethanolic extract of *B. diffusa* synthesized AgNPs (EBdAgNPs), which have demonstrated potential pharmacological benefits. This study aims to systematically investigate the metabolic effects of EBdAgNPs through a clinical approach that encompasses both *in vivo* and *in vitro* methodologies, alongside an examination of gene expression related to diabetes and obesity. By exploring the cellular mechanisms of these nanoparticles and their influence on insulin sensitivity and glucose metabolism, the research seeks to provide insights into their role as a dual therapeutic agent. Ultimately, this investigation aims to bridge traditional herbal medicine with modern therapeutic practices, potentially leading to innovative treatment strategies that utilize the unique properties of silver nanoparticles from *B. diffusa* to enhance metabolic health. The objectives of the present study are designed to systematically explore the therapeutic efficacy of EBdAgNPs through a four-phase research approach.

- **To synthesize and characterize of silver nanoparticles from ethanolic extract of *Boerhavia diffusa* L. (EBdAgNPs)**
- **To investigate the *in vitro* antioxidant and antidiabetic activities of silver nanoparticles synthesized from ethanolic extract of *Boerhavia diffusa* L. (EBdAgNPs)**
- **To examine the *in vivo* antidiabetic and antiobesity effects of silver nanoparticles synthesized from ethanolic extract of *Boerhavia diffusa* L. (EBdAgNPs) in rats**
- **To quantify the relative expression of PPAR- α , PPAR- γ and RBP4 genes using the RT-qPCR method**