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Targeting Metabolic Syndrome and Type 2 Diabetes Mellitus with Heavy Metal-Based Nanoparticles: A Comprehensive Review of Therapeutic Applications and Mechanistic Insights

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Abstract

The increasing prevalence of metabolic syndrome and diabetic complications has led to an urgent need for more effective and targeted therapeutic strategies. Nanotechnology, particularly the use of metal-based nanoparticles, has emerged as a promising approach to address the limitations of traditional drug delivery systems. Recent advancements in the design of nanomaterials for targeted therapeutic delivery have shown remarkable promise, offering exciting new possibilities in therapeutic innovation. By engineering nanomaterials to transport biological molecules, researchers can induce specific physiological changes with minimal side effects and optimized dosing, transforming next-generation treatments for various diseases. MNPs are gaining considerable attention for their unique capabilities in drug delivery. Their high surface-area-to-volume ratio allows for versatile surface modifications, while enhancing drug efficacy through targeted delivery. MNPs also improve drug stability, extend circulation time, and ensure efficient distribution to desired sites.

In this context, the current review delves into the complex pathophysiological mechanisms linking obesity, insulin resistance, and T2DM, with a particular focus on the role of adipose tissue inflammation. It further explores how heavy metal-based nanoparticles may offer a multifaceted therapeutic approach, addressing key metabolic disturbances through innovative mechanisms. This review explores the potential of heavy metal-loaded nanoparticles in the management of metabolic syndrome and T2DM-related complications. Specifically, we focus on their ability to improve insulin sensitivity and target key pathological pathways associated with IR, oxidative stress, and inflammation. The mechanisms through which metal-based NPs modulate cellular responses, such as enhancing antioxidant defenses and influencing signaling pathways like AMPK, Nrf2, and NF-κB, are discussed in detail. Furthermore, we examine the role of nanoparticles in the delivery of nucleic acids and other bioactive molecules, which offer novel therapeutic avenues for overcoming the challenges of enzymatic instability and cellular uptake. Although these nanoparticles show great potential, issues related to biocompatibility, toxicity, and regulatory compliance still need to be addressed. Future directions include the development of more efficient nanoparticle formulations, better understanding of their long-term effects, and optimization of clinical protocols to maximize their therapeutic potential in treating metabolic syndrome and diabetic complications.

Keywords: Metal-based nanoparticles, insulin resistance, metabolic syndrome, diabetic complications, nanomedicine, targeted therapy.

1. Background

Over the past century, changes in human behavior and lifestyle have led to an alarming increase in the prevalence of T2DM and obesity globally, highlighting the complex interplay between genetic and environmental factors in the development of T2DM. Early detection and effective management of both obesity and T2DM are essential to reduce the risk of future complications [1]. For many years, there has been a recognized link between obesity and T2DM, primarily because obesity can lead to Insulin resistance (IR). Insulin resistance is a key factor in the development of T2DM and is associated with a number of additional pathophysiologic conditions, including hypertension, hyperlipidemia, atherosclerosis (metabolic syndrome), and polycystic ovarian disease [2]. Nanoparticles can potentially revolutionize the treatment of this condition and potentially decelerate or even reverse its progression. Recently, nanoparticles such as cerium, zinc oxide, magnesium, and selenium NPs products have been used to treat diabetes [3].

Given the growing burden of metabolic syndrome and diabetes and the limitations of current therapeutic strategies, metal-based nanoparticles (MNPs) have emerged as promising tools due to their unique physicochemical properties, including enhanced bioavailability, targeted delivery, and antioxidant capabilities. These nanoparticles offer novel approaches to modulate metabolic pathways, reduce oxidative stress, and improve insulin sensitivity, making them relevant candidates in the context of nanomedicine-based interventions for diabetes management.

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2. Pathophysiological Basis of Metabolic Syndrome

2.1. Obesity-Induced IR: A Key Link to Type 2 Diabetes Mellitus

It is also worth considering the possibility that IR and hyperinsulinemia may not only result from obesity but could also contribute to its development. The relationship among obesity, IR, and type 2 diabetes mellitus (T2DM) complications is highly complex and multifaceted. IR is strongly associated with obesity, particularly central adiposity. Non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines are released by adipose tissue; these substances disrupt insulin signaling and exacerbate IR as illustrated in figure (1) [4,5].

Insulin resistance reduces the body's ability to use insulin effectively, leading to elevated blood glucose levels and increased insulin production (hyperinsulinemia) [6]. T2DM mellitus (T2DM) is largely caused by IR [7]. Hyperglycemia is the result of the body's inability to adequately regulate blood glucose levels when IR and pancreatic beta-cell malfunction coexist. Numerous metabolic conditions, such as dyslipidemia, hypertension, and cardiovascular disease, are associated with IR and T2DM [8,9]. Nephropathy, retinopathy, and neuropathy are among the microvascular consequences of T2DM that are made worse by obesity [10]. Because of variables like dyslipidemia and hypertension, obesity and IR raise the risk of macrovascular complications, such as cardiovascular disease [11,6].

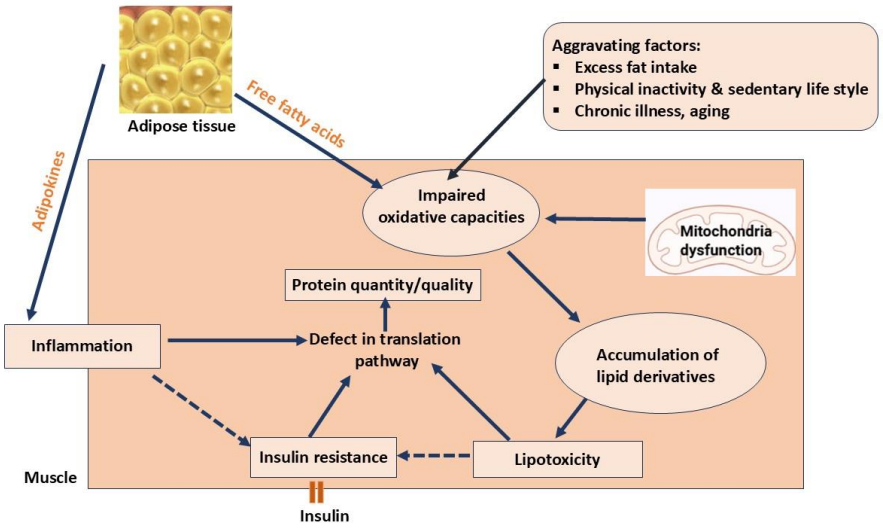

Figure (1): Illustration of the molecular mechanisms underlying obesity-induced insulin resistance (IR) and its interrelationship with disrupted skeletal muscle protein metabolism.

2.2. Mechanisms Underlying Obesity-Induced Insulin Resistance

IR is significantly influenced by obesity through several interrelated mechanisms. Firstly, obesity particularly the accumulation of visceral fat, leads to chronic low-grade inflammation in adipose tissue. This inflammation is characterized by macrophage infiltration and the release of pro-inflammatory cytokines such as TNF-α, which interfere with insulin signaling and contribute to the development of IR [12].

Secondly, adipocyte dysfunction plays a key role; as adipose tissue expands, adipocytes become dysregulated, resulting in elevated circulating levels of free fatty acids (FFAs). These FFAs can impair insulin signaling in muscle and liver tissues, thereby worsening IR [2]. Thirdly, hormonal changes associated with obesity, such as increased expression of 11β-HSD1 in adipose tissue, lead to elevated glucocorticoid levels. These hormonal alterations can further impair insulin sensitivity and enhance hepatic glucose production [5]. Finally, obesity directly disrupts insulin signaling pathways, notably the IRS/PI3K/PKB axis, leading to impaired glucose uptake in skeletal muscle and adipocytes, as well as dysregulated hepatic glucose output as illustrated in figure (2) [13]. In all, IR brought on by obesity is a complicated process that includes hormonal changes, metabolic dysregulation, and inflammation. It ultimately plays a role in the emergence of T2DM and other metabolic diseases [14].

2.3. Role of Adipose Tissue in Insulin Sensitivity and Glucose Metabolism

Adipocytes, or fat cells, are important targets for insulin activity and play a crucial part in maintaining energy balance. The insulin receptor substrate (IRS) proteins and the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway are the main mechanisms by which a series of intracellular signaling events are initiated when insulin binds to its receptor on the adipocyte surface [15]. The stimulation of glucose uptake is one of insulin's most significant actions in adipocytes. Insulin promotes the movement of GLUT4 (glucose transporter type 4) vesicles from intracellular spaces to the plasma membrane, which makes it easier for glucose to enter cells. After that, this glucose is used for energy storage, mostly by lipogenesis, which turns it into triglycerides [16].

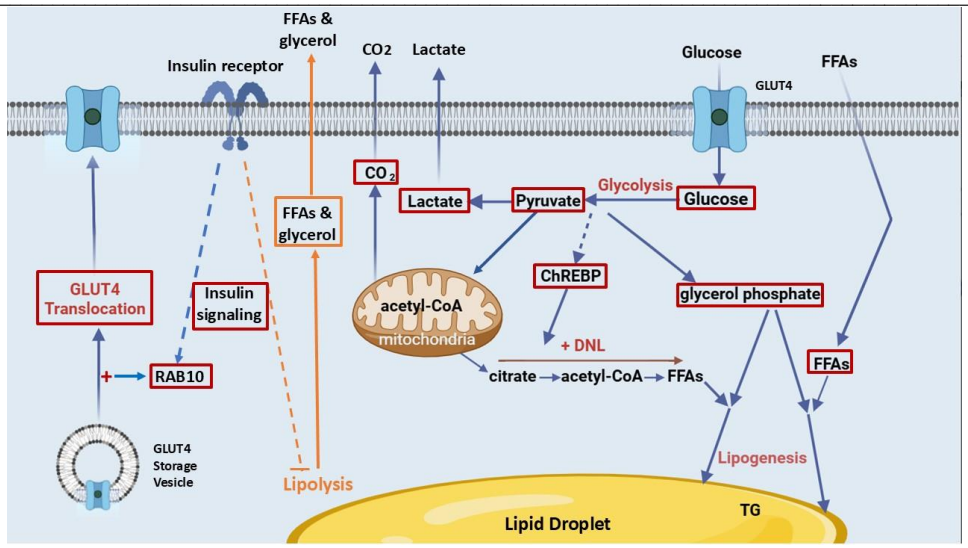

Figure (2): Illustration of insulin-regulated signaling pathways in adipocytes, highlighting the key molecular mechanisms involved in glucose uptake, lipogenesis, and inhibition of lipolysis.

Insulin has anti-lipolytic properties in adipocytes in addition to improving glucose absorption. It lowers the amount of free fatty acids (FFAs) released into the bloodstream by blocking the activity of two important enzymes involved in the breakdown of stored triglycerides: hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL). Since increased FFAs lead to IR in peripheral tissues, this inhibition of lipolysis is essential for preserving insulin sensitivity. Insulin also affects the release of adipokines, increasing insulin-sensitizing proteins like adiponectin and decreasing pro-inflammatory mediators like TNF-α and IL-6. Collectively, these mechanisms enable insulin to regulate insulin sensitivity in adipocytes to control insulin sensitivity, systemic energy balance, and local lipid and glucose metabolism [17].

By simultaneously inhibiting hepatic glucose production, suppressing lipolysis, and enhancing glucose uptake in muscle tissue, insulin functions as the conductor of a finely tuned metabolic orchestra ensuring harmony in glucose homeostasis and preventing the onset of diabetic complications [18]. Through promoting glucose uptake in insulin-sensitive tissues (liver, skeletal muscle, and adipose tissue) and preventing glucose synthesis in the liver, insulin lowers blood glucose levels. Insulin-sensitive tissues lose their ability to respond to insulin, which results in IR. In the insulin target tissues, insulin-mediated glucose absorption is compromised in this situation. Because of the suppression of the insulin signaling pathway, resulting in impaired glucose uptake [19].

2.4. Adipose Tissue Inflammation and Its Impact on Insulin Signaling

Adipose tissue inflammation plays a pivotal role in the development of IR through multiple interconnected mechanisms. One key factor is the overproduction of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which promote serine phosphorylation of IRS, thereby disrupting insulin signaling and reducing glucose uptake in skeletal muscle and adipocytes [20,12].

Additionally, inflammation in adipose tissue is marked by the infiltration of macrophages, particularly the pro-inflammatory M1 subtype, which release inflammatory mediators that further impair insulin sensitivity [21]. An imbalance in adipokines also contributes to this process; while adiponectin, an insulin-sensitizing adipokine, is typically reduced in obesity, pro-inflammatory adipokines are elevated, collectively aggravating IR [22]. Moreover, inflammation can disrupt normal fat storage, leading to ectopic fat deposition in organs such as the liver and muscles, where it interferes with insulin signaling pathways and worsens IR [23]. Overall, adipose tissue inflammation establishes a vicious cycle that not only amplifies IR but also contributes to the pathogenesis of metabolic disorders like T2DM.

3. Obesity-Induced Insulin Resistance: Cellular and Molecular Mechanisms

One of the central mechanisms contributing to the onset and progression of T2DM is IR induced by obesity. This resistance is driven by an intricate interplay of cellular, immunological, and metabolic stressors that culminate in a progressive decline in insulin action and β-cell function. One of the primary causes is the accumulation of lipotoxic substances due to adipose tissue malfunction. As visceral fat expands beyond its physiological capacity, it releases excessive amounts of non-esterified fatty acids (FFAs), glycerol, and pro-inflammatory cytokines, including TNF-α and IL-6. These bioactive molecules interfere with insulin signaling by impairing the phosphorylation of insulin receptor substrates, disrupting downstream pathways essential for glucose uptake and metabolism [24].

When the storage capacity of adipose tissue is exceeded, lipids begin to accumulate ectopically in non-adipose tissues such as the liver and skeletal muscles. This ectopic lipid deposition results in the generation of toxic lipid intermediates, such as ceramides and diacylglycerols, which further inhibit insulin signaling cascades, thereby exacerbating IR [25]. Alongside lipid overflow, obesity provokes a chronic state of low-grade inflammation. Adipose tissue becomes infiltrated by pro-inflammatory M1 macrophages that secrete cytokines such as TNF-α and IL-1β. These cytokines activate stress kinases like JNK and IKKβ, which phosphorylate insulin receptor substrate-1 (IRS-1) on serine residues, a modification that disrupts insulin signaling [26]. Furthermore, there is a dysregulation in adipokine secretion, characterized by reduced levels of

adiponectin an insulin-sensitizing, anti-inflammatory adipokine and elevated levels of resistin, which exacerbates the pro-inflammatory milieu and aggravates IR [27].

3.1. Mitochondrial Dysfunction and Endoplasmic Reticulum Stress Insulin Resistance

Mitochondrial and endoplasmic reticulum (ER) stress also play significant roles in the pathogenesis of IR. Elevated levels of FFAs exceed the capacity of mitochondrial β-oxidation, leading to the production of reactive oxygen species (ROS), which damage key components of the insulin signaling machinery [28]. Simultaneously, nutrient overload disrupts ER function and activates the unfolded protein response, which triggers inflammatory pathways such as JNK and NF-κB, further impairing insulin signaling [8].

3.2. Pancreatic β-Cell Dysfunction and the Progression to Type 2 Diabetes Mellitus

As peripheral IR intensifies, the pancreas initially responds through compensatory hyperinsulinemia to maintain normoglycemia. However, chronic demand for insulin production ultimately leads to β-cell exhaustion and apoptosis [29]. This process is compounded by the direct lipotoxic effects of FFAs and ceramides on pancreatic β-cells, which compromise insulin biosynthesis and secretion [30].

3.3. Neurohormonal and Genetic Influences on Insulin Resistance

Neural and hormonal factors also contribute to obesity-induced IR. Obesity is associated with leptin resistance, which impairs the hormone's ability to regulate appetite and energy expenditure, but also disrupts its role in modulating insulin secretion, thereby promoting hyperinsulinemia [31]. Furthermore, the activation of the sympathetic nervous system, often observed in obesity, enhances lipolysis and increases circulating FFAs, perpetuating the cycle of IR [32]. On a molecular level, genetic and epigenetic factors add to another layer of complexity. Polymorphisms in genes such as NAT1 and NAT2, which are involved in detoxification and inflammation pathways, have been associated with heightened susceptibility to IR and mitochondrial dysfunction, further predisposing individuals to T2DM [33].

4. Clinical Transition from Insulin Resistance to Type 2 Diabetes Mellitus

Clinically, the progression to overt T2DM is marked by the failure of insulin-sensitive tissues to maintain glucose homeostasis. In the liver, impaired insulin signaling fails to suppress gluconeogenesis, leading to excessive hepatic glucose production [34]. In skeletal muscle and adipose tissue, the translocation of GLUT4 transporters to the plasma membrane is diminished, resulting in reduced glucose uptake and peripheral glucose intolerance [35]. Eventually, the chronic burden of hyperglycemia and lipotoxicity leads to progressive β-cell dysfunction and failure, which marks the transition from IR to established T2DM [36].

5. Nanoparticle-Based Interventions in Insulin Resistance and Type 2 Diabetes Mellitus

5.1 Introduction to Nanoparticles and Nanotechnology

Nanoparticles are solid, colloidal particles that typically range from 10 to 1000 nm in diameter. However, according to European and other international standards, they are more narrowly defined as structures with three-dimensional dimensions not exceeding 100 nm. These nanostructures offer distinct advantages over bulk materials, such as an enhanced surface-to-volume ratio and superior magnetic properties. Nanotechnology involves the study, design, and application of materials at the nanoscale. It integrates various scientific disciplines, including physics, chemistry, materials science, biology, and pharmaceutical sciences. Due to their unique size-dependent properties, nanoparticles are increasingly utilized across various industrial applications (Figure 3). Particularly in medicine and pharmacology, their ability to be engineered for specific functionalities makes them a highly promising tool for targeted therapies and drug delivery [37,38].

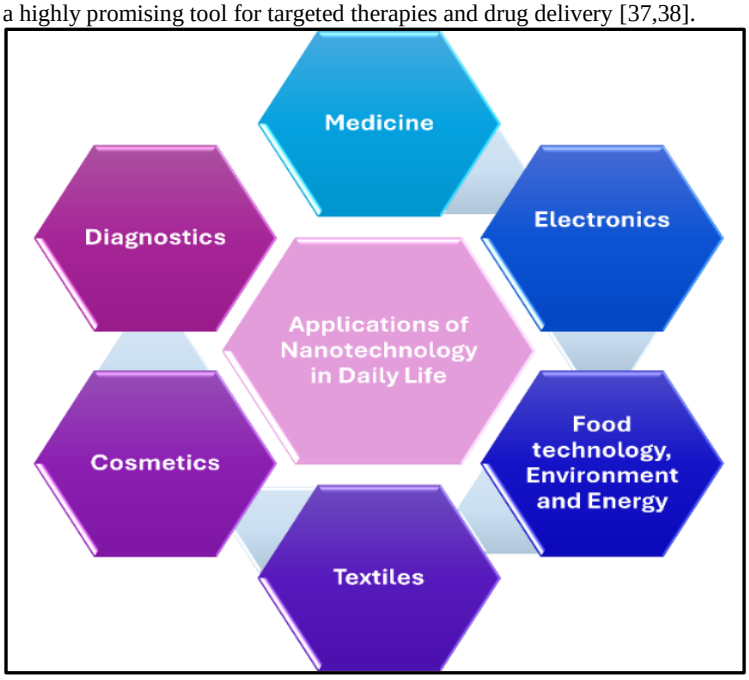

Figure (3): Multifaceted Applications of Nanotechnology in Daily Life: An illustrative overview highlighting key domains including medicine, diagnostics, cosmetics, textiles, electronics, and food technology/environment/energy, where nanotechnology plays a transformative role.

5.2 Synthesis and Functionalization of Nanoparticles

There are several methods for synthesizing nanoparticles from noble metals. A common approach involves the chemical reduction of noble metal precursors, such as silver nitrate or chloroplatinic acid, to form silver or platinum nanoparticles, respectively. This reduction process typically employs a reducing agent that also stabilizes the particles, such as sodium citrate in the case of gold nanoparticles, to prevent aggregation. By adjusting parameters like temperature, precursor and reductant concentrations, and reaction duration, nanoparticles of different sizes and shapes can be produced. Recently, there has been a growing interest in green chemistry approaches that minimize the use of harmful chemicals. These eco-friendly methods often involve reducing agents derived from natural sources, including lactic acid, citrus fruits, and coffee seeds. This approach is cost-effective, simple, safe, non-toxic, and environmentally friendly. As an integral part of sustainable clean technologies, green nanotechnology aims to utilize surplus bioactive materials to produce eco-friendly nanomaterials that are both more valuable and less harmful to the environment [39].

5.3 Classification of Nanoparticles

Nanoparticles can be classified based on their overall shape into 0-Dimensional (0D), 1-Dimensional (1D), 2-Dimensional (2D), and 3-Dimensional (3D) structures. Each dimensional classification reflects distinct geometric properties that influence their behavior and applications in various fields (Figure 4). Nanoparticles are also categorized based on their composition, including polymeric, inorganic, and lipid-based nanoparticles. Polymeric nanoparticles include polymersomes (vesicles formed from amphiphilic block copolymers), polymer micelles (aggregates of surfactant molecules dispersed in a liquid colloid), and dendrimers (highly branched, star-shaped macromolecules). Inorganic nanoparticles consist of iron oxide nanoparticles (commonly used in magnetic applications), silica nanoparticles (noted for their stability and biocompatibility), gold nanoparticles (known for their unique optical properties), and quantum dots (semiconductor nanoparticles that exhibit quantum mechanical behaviors). Lipid-based nanoparticles include liposomes (vesicles composed of lipid bilayers), emulsions (mixtures of two immiscible liquids with one dispersed in the other), and lipid nanoparticles, which are commonly employed in drug delivery systems and biomedical applications [40].

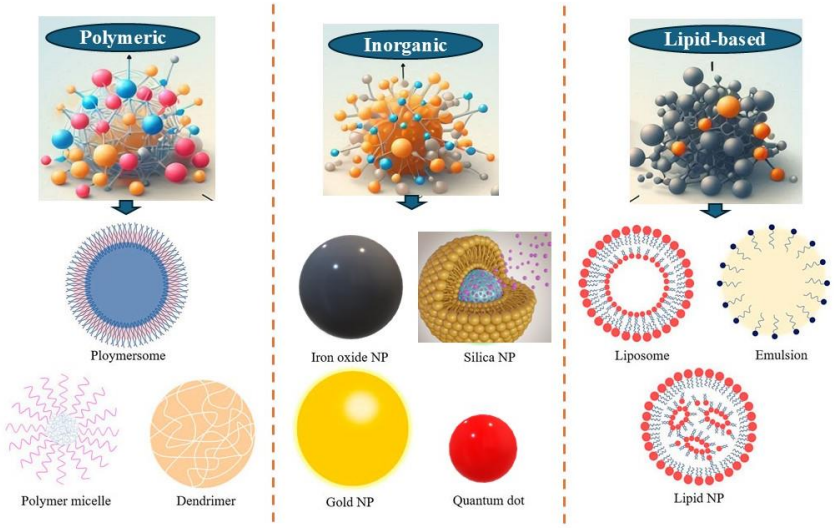

Figure (4): Classification of Nanoparticles Used in Drug Delivery Systems: An overview of polymeric, inorganic, and lipid-based nanoparticles, including examples such as polymersomes, dendrimers, gold nanoparticles, quantum dots, liposomes, and lipid nanoparticles, each exhibiting distinct structural and functional properties tailored for therapeutic applications

5.4 Green Nanotechnology in Biomedical Applications

Green nanotechnology focuses on the biosynthesis of nanomaterials using natural bioactive agents, including plant-based materials, microbes, and various biowastes like agricultural byproducts, eggshells, fruit peels, and vegetable waste. This approach is cost-effective, simple, safe, non-toxic, and environmentally friendly. Green nanotechnology is an integral part of sustainable clean technologies, aiming to utilize surplus bioactive materials to produce eco-friendly nanomaterials that are both more valuable and less harmful to the environment [41]. Drug delivery systems are actively being developed to enhance the delivery and effectiveness of therapeutic agents such as drugs, vaccines, and proteins. Green nanomedicine has emerged from the integration of eco-friendly chemistry with nanotechnology in this field. Studies highlight growing interest in green-synthesized nanomaterials, especially metal nanoparticles, polymers, and biological agents for drug delivery. Current efforts focus on using natural sources like plant extracts and microbes to develop sustainable drug carriers, with an emphasis on low-toxicity, green synthesis methods [42].

Through these sustainable approaches, green nanotechnology helps increase drug bioavailability, boost therapeutic effectiveness, and reduce environmental harm. In cancer therapy, photodynamic therapy (PDT) stands out as a promising strategy that uses light, photosensitizers, and oxygen to selectively destroy cancer cells while minimizing damage to healthy tissue. Although PDT faces limitations, such as shallow light penetration and inconsistent effectiveness across different tumor types, advancements in green nanotechnology are opening new possibilities for enhancing its performance and improving

treatment results [43]. Nanotechnology in the medical field is characterized by its applications in wound healing, antibacterial resistance therapies, minimizing harm to healthy cells, and enhancing diagnostic techniques through nanomedicine [44]. Furthermore, Nanomedicine involves drug and gene delivery, protein detection, diabetes treatment, tissue engineering, probing of DNA structure, tumor disinfection, and cancer therapy [45,46].

5.5 Applications of Nanotechnology in Medicine: Nanomedicine

Nanomedicine leverages nanotechnology for medical purposes, using nanoparticles for diagnosing, monitoring, preventing, and treating illnesses. By tailoring nanomaterials in terms of size, shape, and composition, they can be designed to target specific biological sites, offering a promising future for clinical advancements. These materials interact with biological systems at the nanoscale, where disease-related processes, such as abnormal proteins or infections, occur. The effectiveness of nanomaterials depends on their design, as understanding molecular processes allows for precise targeting of the disease site [47]. Moreover, the surface interactions between nanoparticles and biological components, like proteins and cell membranes, play a crucial role in their behaviour within the body. The unique properties of nanoparticles such as their high surface-to-volume ratio enhance their reactivity, allowing them to bind efficiently with biomolecules when exposed to biological fluids like blood or lung fluids. Nanotechnology is revolutionizing biomedicine by enabling the creation of diagnostic tools, drug delivery systems, and imaging agents, making it possible to detect diseases more accurately and deliver treatments more effectively [48,46,49].

5.6 Heavy Metal Nanoparticles: Emerging Tools in Biomedical Applications

The biomedical relevance of metal-based nanoparticles, such as gold, silver, and iron oxide, is rapidly expanding. These nanoparticles are used in a variety of applications, including therapy, imaging, and diagnostics. For example, gold nanoparticles exhibit unique optical properties and can be used for targeted drug delivery and imaging applications. Silver nanoparticles are known for their antimicrobial properties and are utilized in wound healing and infection prevention. Iron oxide nanoparticles are widely used in magnetic applications, particularly in magnetic resonance imaging [3], management of obesity associated secondary hypogonadism syndrome [50] and cancer therapy [51]. The themed issue on nanoparticles in medicine offers a comprehensive exploration of the roles of metal-based nanoparticles, covering their applications in multimodal imaging, in vitro detection, in vivo diagnostics, chemotherapy, gene therapy, immunotherapy, phototherapy, and their translation into clinical practice [47].

5.7. Pathophysiology and Mechanisms of Action: How Heavy Metals Loaded Nanoparticles Influence Insulin Sensitivity and Glucose Homeostasis

Metabolic syndrome and T2DM are characterized by IR, dysregulated glucose metabolism, and chronic inflammation, which ultimately contribute to hyperglycemia, altered lipid metabolism, and increased cardiovascular risk. The complex pathophysiology of these conditions involves various molecular and cellular pathways, including insulin signaling disruption, oxidative stress, inflammation, and dysregulated lipid metabolism [52]. Recent advances in nanotechnology, particularly heavy metal-loaded nanoparticles (HMNPs), have shown promising therapeutic potential in improving insulin sensitivity and managing T2DM-related complications. These nanoparticles, composed of metals like gold, silver, copper, and iron, exhibit unique properties that allow them to interact with biological systems more efficiently than traditional drugs [53,54,55]. Heavy metals loaded nanoparticles have emerged as innovative modulators of key metabolic processes lipolysis, glycolysis, gluconeogenesis, glycogenesis, and protein catabolism offering potential therapeutic value in managing metabolic syndrome and diabetes. These nanoparticles often incorporating trace metals like zinc, chromium, vanadium, and others enhance cellular uptake and bioavailability, allowing them to influence enzyme activity and signaling pathways with greater precision. In lipolysis, certain metal ions can stimulate or regulate hormone-sensitive lipase, promoting controlled fat breakdown. In glycolysis, metals such as zinc and chromium improve insulin sensitivity and glucose uptake, enhancing the efficiency of glucose metabolism. Gluconeogenesis is modulated by nanoparticles that suppress excessive glucose production in the liver, particularly through inhibition of key enzymes like PEPCK and glucose-6-phosphatase. In glycogenesis, these metal-based carriers can activate glycogen synthase via improved insulin signaling, promoting glucose storage and reducing hyperglycemia. Lastly, in protein catabolism, nanoparticles may help attenuate muscle breakdown by stabilizing energy metabolism and reducing the stress-related hormonal signals that trigger amino acid mobilization [56]. Altogether, heavy metal loaded nanoparticles offer a promising approach to fine-tune these metabolic pathways, potentially preventing or reversing the progression of diabetes and related metabolic disorders (Figure 5).

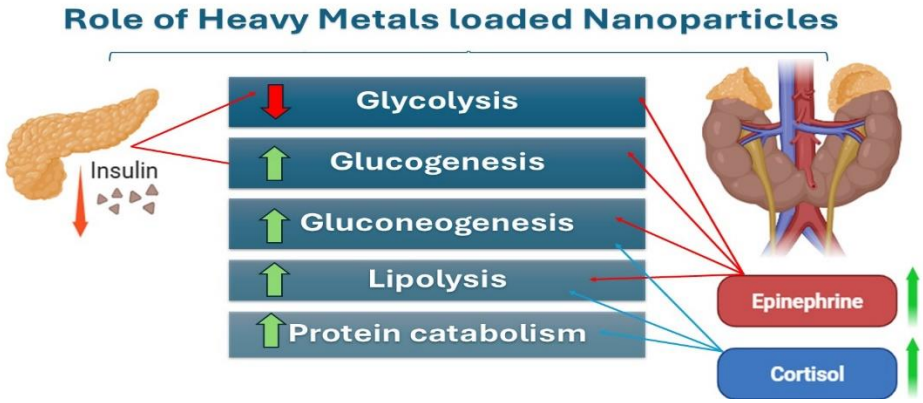

Figure (5): Role of Heavy metals Loaded Nanoparticles: Heavy Metals: A Promising Approach to Combat Metabolic Syndrome and Diabetes Progression

Figure 6 showed that heavy metal loaded nanoparticles composites were revealed to exhibit antidiabetic via multiple mechanisms [57], which include suppression of glucose absorption, restoration of the functional mass of beta cells, enhancement of insulin expression, attenuation of insulin resistance, restoration of glucose hemostasis as well as utilization, and regulation of lipid and carbohydrate metabolism [58,59,60]. These nanostructures orchestrate a concerted activation of pivotal signaling cascades, including the PI3K/Akt and AMPK pathways, culminating in the upregulation of GLUT transporters and a pronounced improvement in cellular glucose uptake and insulin sensitivity. Concurrently, they exert a suppressive effect on hepatic gluconeogenesis by downregulating enzymatic drivers such as glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) [61;62].

Moreover, these nanoparticles influence transcriptional governance through modulation of factors like FoxO and PGC-1α, while also attenuating systemic inflammation by dampening pro-inflammatory cytokines such as TNF-α and interleukins. By enhancing the phosphorylation state of insulin receptor substrate-1 (IRS-1), these nanoscale agents potentiate downstream insulin signaling, highlighting their potential as integrative metabolic modulators [61]. Collectively, this intricate molecular choreography underscores the therapeutic promise of heavy metal-loaded nanomaterials in the comprehensive management of diabetes. Below, we elaborate on the detailed mechanisms through which some HMNPs influence insulin sensitivity [62,63].

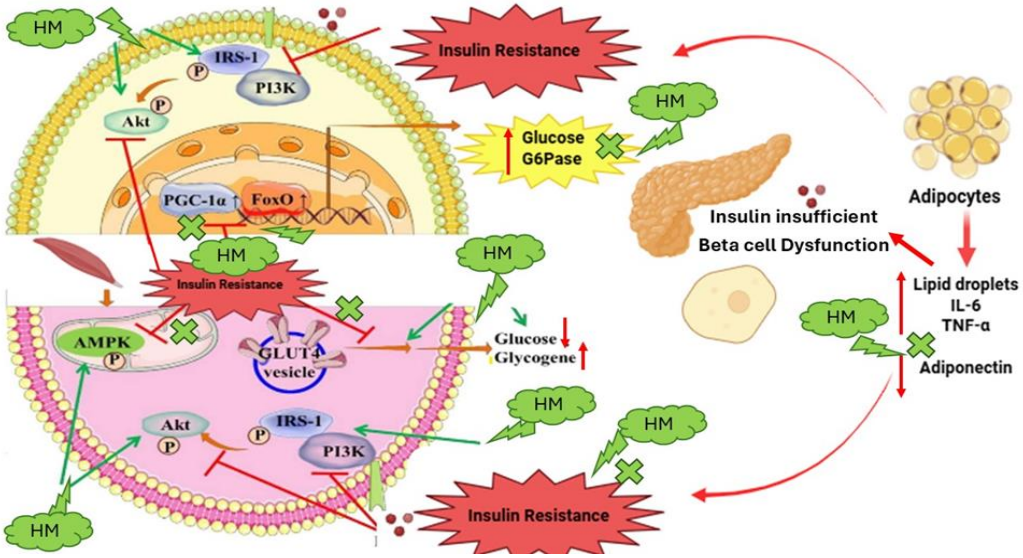

Figure (6): Multifaceted Therapeutic Potential of Heavy Metal-Loaded Nanoparticles in Diabetes Management

Heavy Metal-Loaded Nanoparticles modulate a diverse array of molecular targets implicated in glucose homeostasis and insulin signaling, offering promising therapeutic avenues for diabetes management. Key molecular players influenced include Akt: protein kinase A, AMPK: 5′ AMP-activated protein kinase, FoxO: forkhead box protein O, G6Pase: glucose 6-phosphatase, GLUT: glucose transporter, HM: Heavy Metal-Loaded Nanoparticles, IL: interleukin, IRS-1: insulin receptor substrate-1, PEPCK: phosphoenolpyruvate carboxykinase, PGC-1α: peroxisome proliferator-activated receptor-γ coactivator-1α, PI3K: phosphoinositide 3-kinase, TNF-α: tumour necrosis factor-α.

5.7.1. Modulation of Oxidative Stress

Oxidative stress plays a central role in the development of IR and the progression of metabolic syndrome. In individuals with IR, an overproduction of ROS in tissues such as adipose, muscle, and liver contributes to damage of cellular structures, including lipids, proteins, and DNA. ROS impair insulin signaling pathways and promote inflammation, further exacerbating IR [64].

Heavy metal-loaded nanoparticles, such as those composed of gold, silver, and copper, possess strong antioxidant properties. These nanoparticles can scavenge ROS and neutralize free radicals through their high surface area and reactivity. By reducing oxidative stress, HMNPs help restore normal insulin receptor function and enhance the sensitivity of insulin signaling pathways [51]. Specifically, the nanoparticles can increase the activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase, which are critical for maintaining cellular redox balance and protecting insulin receptor function from oxidative damage [9,65].

5.7.2. Enhancement of Insulin Receptor Signaling

A key mechanism by which HMNPs improve insulin sensitivity is through the modulation of insulin receptor signaling [66]. IR is marked by the impaired activation of the insulin receptor and downstream signaling molecules, such as the IRS, phosphoinositide 3-kinase (PI3K), and protein kinase B (Akt). These signaling pathways are essential for mediating insulin's actions on glucose uptake, lipid metabolism, and protein synthesis [67].

HMNPs can improve insulin receptor signaling by promoting the phosphorylation of IRS proteins and enhancing the PI3K/Akt pathway, which facilitates glucose uptake into cells. In particular, HMNPs have been shown to activate the PI3K/Akt signaling cascade, leading to increased GLUT4 translocation to the cell membrane and enhanced glucose uptake, especially in muscle and adipose tissues. Moreover, HMNPs can modulate the expression of key genes involved in insulin signaling, further amplifying their effects on glucose metabolism and insulin sensitivity [68,69]

5.7.3. Anti-Inflammatory Effects

Chronic low-grade inflammation is a hallmark of IR and metabolic syndrome. Elevated levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and C-reactive protein (CRP), interfere with insulin signaling and promote the development of IR. These cytokines activate several inflammatory pathways, including nuclear factor-kappa B (NF-κB), which further disrupt insulin receptor function and contribute to metabolic dysfunction [70].

Heavy metal-loaded nanoparticles exert potent anti-inflammatory effects by modulating the NF-κB signaling pathway and reducing the secretion of pro-inflammatory cytokines. For example, gold nanoparticles have been shown to reduce the expression of TNF-α and IL-6 in macrophages, while silver nanoparticles can inhibit NF-κB activation in adipocytes. By suppressing inflammation, HMNPs help restore insulin sensitivity and prevent the progression of metabolic syndrome and T2DM [71,72].

5.7.4. Regulation of Lipid Metabolism and Adipogenesis

Dysregulated lipid metabolism, including increased lipogenesis, decreased lipolysis, and the accumulation of visceral fat, is closely associated with IR. Excessive fat deposition in tissues, particularly in the liver and muscle, impairs insulin signaling and promotes the development of T2DM [73].

Heavy metal-loaded nanoparticles can influence lipid metabolism by modulating key metabolic pathways involved in adipogenesis and lipogenesis [74]. Some studies suggest that nanoparticles, mostly those made of metals like copper and zinc, can regulate the expression of genes such as PPAR-γ (peroxisome proliferator-activated receptor gamma) and C/EBPα (CCAAT-enhancer-binding protein alpha), which are involved in fat cell differentiation and lipid storage. By regulating these pathways, HMNPs can reduce fat accumulation and promote the breakdown of stored lipids, thus improving insulin sensitivity [75,76].

Additionally, certain nanoparticles, like those loaded with gold or copper, have been shown to influence mitochondrial function, which plays a critical role in energy metabolism and the regulation of insulin sensitivity. Nanoparticles may enhance mitochondrial biogenesis and function, improve cellular energy production and reduce lipid accumulation in insulin-sensitive tissues [77].

5.7.5. Modulation of Gut Microbiota

Emerging evidence suggests that gut microbiota play a critical role in the development of IR and metabolic syndrome [78]. Dysbiosis, or an imbalance in gut bacteria, has been linked to inflammation, impaired glucose metabolism, and IR. Heavy metal-loaded nanoparticles have the potential to influence gut microbiota composition and restore microbial balance [79].

Research has shown that nanoparticles can interact with gut microbes, modulating the gut microbiome to improve metabolic health. By influencing microbiota, HMNPs can reduce gut-derived inflammation and improve insulin sensitivity. Some studies suggest that nanoparticles, particularly those with silver and copper, can selectively target harmful bacteria in the gut, thus promoting the growth of beneficial microbes that help regulate glucose metabolism and insulin sensitivity [80].

5.7.6. Activation of AMPK Pathway

AMP-activated protein kinase (AMPK) is a key regulator of cellular energy balance and insulin sensitivity. Activation of AMPK enhances glucose uptake, fatty acid oxidation, and mitochondrial function while inhibiting lipogenesis. IR is often associated with impaired AMPK activation [81].

Heavy metal-loaded nanoparticles can activate the AMPK pathway, enhancing glucose and lipid metabolism. Some nanoparticles, such as those made from gold or copper, have been shown to activate AMPK directly, leading to improved insulin sensitivity and better metabolic control. By stimulating AMPK, HMNPs help restore cellular energy homeostasis and improve insulin receptor function [82].

Heavy metal-loaded nanoparticles represent a novel and promising approach for enhancing insulin sensitivity and managing metabolic syndrome and T2DM-related complications. By modulating oxidative stress, improving insulin receptor signaling, reducing inflammation, regulating lipid metabolism, influencing gut microbiota, and activating key metabolic pathways like AMPK, HMNPs offer a multifaceted mechanism of action that targets the root causes of IR [83]. While the preclinical data are promising, further clinical studies are needed to fully understand the therapeutic potential, safety, and long-term effects of HMNPs in the treatment of metabolic disorders and T2DM [84].

5.8. Heavy Metals in Nanoparticles Studies: Effects on Glucose Metabolism and Insulin Signaling

Numerous studies have demonstrated the role of metals in glucose metabolism and their link to T2DM. Vanadium, chromium, magnesium, and zinc have all been implicated in blood sugar regulation and T2DM treatment [85]. Table (1) demonstrates the essential signaling pathways in glucose homeostasis, lipid metabolism and diabetes. Several studies, as outlined below, highlight the therapeutic promise of heavy metal-based nanoparticles (HMNPs) in the management of diabetes and metabolic syndrome.

5.8.1. Zinc Oxide Nanoparticles:

Umrani et al. investigated the antidiabetic activity of zinc oxide nanoparticles in streptozotocin-induced Type 1 and Type 2 diabetic rats. Zinc oxide nanoparticles (1, 3, and 10 mg/kg) administered orally and dramatically reduced blood glucose (29%), non-esterified fatty acids (40%), and triglycerides (48%), while increasing serum insulin by 70% and improving glucose tolerance. The systemic absorption of nanoparticles increased zinc levels in the pancreas, liver, and adipose tissue. RIN-5F rat insulinoma cells showed increased superoxide dismutase activity and insulin production. The nanoparticles were safe up to a dosage of 300 mg/kg [86]. Alkaladi et al. also assessed the antidiabetic effects of zinc oxide and silver

nanoparticles, showing significant decreases in blood glucose, increased serum insulin, and improved glucokinase activity in diabetic rats [87].

Table (1) Impact of Heavy Metals and Metalloids on Critical Signaling Pathways in Glucose Homeostasis, Lipid metabolism and Diabetes

Heavy Metal/Metalloid	Major signaling pathways associated with Glucose Homeostasis and Diabetes	Major signaling pathways associated with Lipid metabolism, adipogenesis, and atherosclerosis
Arsenic	• PI3K/AKT • PPARγ • p38 MAPK • NF-κB/PTEN • Pentose Phosphate Pathway • Pentose/Glucuronate Interconversion • Pro-inflammatory cytokines	• PI3K/AKT • GM-CSF •VEGF • TNFα • IL-1& IL-8 • MCP-1/ VCAM-1/ ICAM-1 • NF-κB and ERK1/2 MAPK
Cadmium	• PPARγ • C/EBPα • NF-κB/PTEN • Gluconeogenesis • Glycogenolysis • Pro-inflammatory cytokines	• iNOS • VEGF • MAPK /p38/ERK • JNK
Chromium	• PI3K/AKT • AMPK • JNK MAPK • P-Tyr Phosphatase Inhibition	• NF-κB • ROS •
Iron	• HIF-1α • AMPK • Pro-inflammatory cytokines	----------
Mercury	• PI3K/AKT	• NF-κB • iNOS • p38/MAPK • TNFα • IFN-γ
Nickel	• Gluconeogenesis • Glycogenolysis	• TNFα /IL-6 • VCAM-1/ MCP-1/ CD68 • AKT, ERK, and NF-κB • VEGF
Vanadium	• P-Tyr Phosphatase Inhibition	• PI3K/AKT • ROS • iNOS/Ca^{2+}-ATPase/Kchannels

5.8.2. Silver Nanoparticles:

Silver nanoparticles (AgNPs) have shown modulatory effects on inflammatory and metabolic alterations induced by non-alcoholic fatty liver disease (NAFLD). AgNPs (100, 150, and 200 μg/kg/day for 4 weeks) administered in a rat model of NAFLD improved insulin levels, hyperglycemia, and dyslipidemia. Inflammatory markers such as monocyte chemoattractant protein-1, C-reactive protein, and TNF-α were significantly reduced [88].

5.8.3. Gold Nanoparticles:

Pure gold nanoparticles (AuNPs) were found to have anti-inflammatory effects on retroperitoneal adipose tissue in a mouse model. AuNPs, administered intraperitoneally in high-fat diet-fed mice, reduced glucose intolerance, dyslipidemia, and fat mass. The results suggest that AuNPs improve metabolic function by regulating inflammation and adiposity [89].

5.9. Heavy Metals Loaded-Nanoparticles: Strategies to Overcome Metabolic Syndrome, Diabetes and Their Complications

Recent advancements highlight the promising potential of HMNPs as therapeutic agents against a spectrum of diabetes-induced vascular complications including nephropathy, retinopathy, cardiomyopathy, neuropathy, lung injury, hepatic dysfunction, adipose tissue impairment, and other micro- and macrovascular pathologies [90]. These nanoparticles exert their effects through a variety of intricate molecular mechanisms. At the core of these complications lies chronic hyperglycemia, which exacerbates oxidative stress by stimulating excessive ROS production while concurrently weakening the endogenous antioxidant defense systems. This redox imbalance initiates a cascade of deleterious events, including persistent inflammation, fibrotic tissue remodeling, impaired autophagy, and programmed cell death.

These pathological responses are primarily triggered by the activation of several key signaling pathways. Among the most significant are the mitogen-activated protein kinase (MAPK) pathway, protein kinase C (PKC), nuclear factor kappa B

(NF-κB), and transforming growth factor-beta 1 (TGF-β1). These pathways, along with members of the Smad protein family (Smad2/3/4), play crucial roles in promoting fibrotic processes. Their activation leads to the upregulation of α-smooth muscle actin (α-SMA) and the accumulation of collagen, which are well-known hallmarks of tissue damage in diabetic conditions.

Conversely, HMNPs act as therapeutic agents that help counteract these harmful processes. They contribute to improved glycemic control, effectively scavenge reactive oxygen species, and disrupt pathological signaling pathways associated with inflammation, fibrosis, and apoptosis. These combined effects highlight the synergistic potential of HMNPs in managing complications related to diabetes, as illustrated in Figure 7.

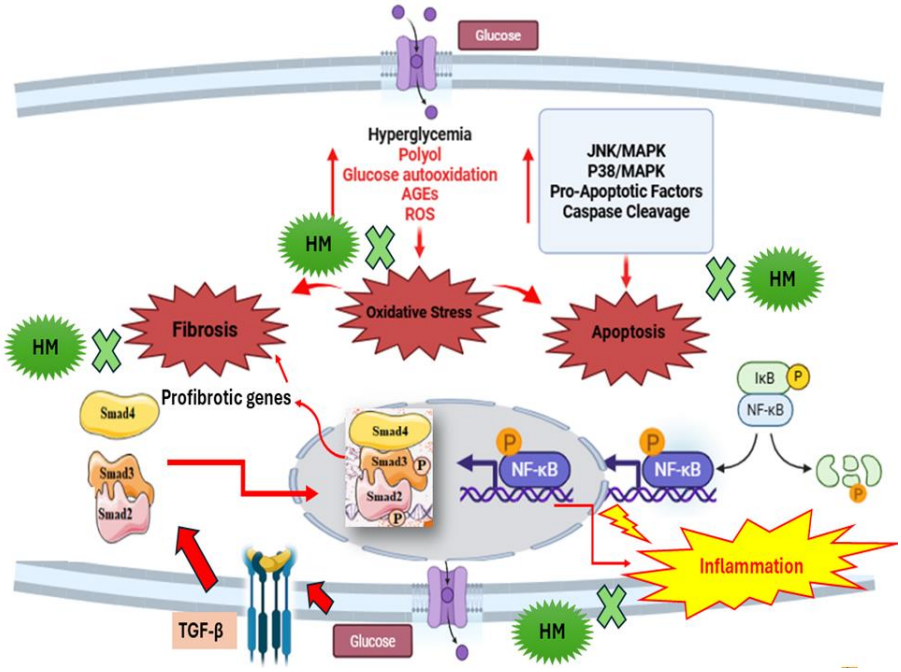

Figure (7): Heavy Metal-Loaded Nanoparticles as a Promising Therapeutic Strategy: Interrupting the Cascades of Diabetes pathogenesis and Consequences. AGEs: advanced glycation end products, HM: Heavy Metal-Loaded Nanoparticles, IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor α, JNK: c-Jun N-terminal kinases, MAPK: mitogen-activated protein kinase, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, ROS: reactive oxygen species, Smad: mothers against decapentaplegic homolog, TGF-β1: transforming growth factor β1.

5.10. Nanoparticles as Drug Carriers: Strategies to Overcome Obesity-Induced Insulin Resistance

The aim of encapsulating medications in nanoparticles is to extend their release into systemic circulation, reducing toxicity and enhancing absorption by target tissues. Obesity, especially induced by high-fat diets (HFD), is a major risk factor for IR and T2DM [91].

5.10.1. Ginger-derived Nanoparticles:

Kumar et al. found that ginger-derived nanoparticles (GDNP) in mice on a high-fat diet (HFD) reduced IR by reestablishing Foxa2-mediated signaling balance in gut epithelium. GDNPs enhanced Foxa2 expression, protecting it from Akt-1-mediated phosphorylation and improving insulin sensitivity [92].

5.10.2. Chitosan Nanomicelles:

Chitosan nanomicelles, conjugated with adipose tissue macrophages (ATMs) and adipocyte targeting ligands, were used to deliver short hairpin RNA (shRNA) targeting pro-inflammatory cytokines TNFα and MCP-1. In obese-diabetic mice, this led to increased adiponectin and reduced inflammatory cytokines, improving insulin sensitivity and glucose tolerance [93].

5.10.3. Adiponectin-Based Nanomedicine:

Banerjee et al. developed a plasmid adiponectin (pADN)-based nanomedicine using chitosan-oleic acid conjugates. This nanomedicine increased insulin sensitivity in obese-diabetic rats by enhancing adiponectin secretion, demonstrating potential for T2DM treatment [94].

5.10.4. Hyaluronic Acid Nanoparticles:

Self-assembled hyaluronic acid nanoparticles (HA-NPs) were investigated for their effects on adipose tissue inflammation and IR in obese mice. HA-NPs reduced pro-inflammatory cytokine production and NLRP3 inflammasome activity in adipose tissue, leading to improved insulin sensitivity and normalized blood glucose levels [95].

5.10.5. Luteolin-loaded Zinc Oxide Nanoparticles:

Luteolin-loaded zinc oxide nanoparticles (Lut/ZnO NPs) improved non-alcoholic fatty liver disease linked to IR in diabetic rats by regulating the PI3K/AKT/FoxO1 pathway. This therapy also decreased lipid accumulation, triglycerides, and cholesterol levels while improving liver function and oxidative stress markers [96].

5.11. Therapeutics Based on Nanoparticles in Clinical Trials

The application of nanoparticles in medicine is progressing, with numerous nanoparticle-based therapies currently advancing through clinical trials. Among these, drug-encapsulated liposomes and polymer-drug conjugates especially PEGylated compounds are the most extensively studied. Table (2,3) demonstrates selected FDA-Approved Nanoparticle-Based Therapeutics: An overview of liposomal and polymeric nanoplatforms.

Table (2): Selected FDA-Approved Nanoparticle-Based Therapeutics in Clinical use: An overview of liposomal and polymeric nanoplatforms

Composition	Trade name	Company	Indication
Liposomal platforms			
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections
Liposomal amphotericin B	AmBisome	Gilead Sciences	Fungal and protozoal infections
Liposomal cytarabine	DepoCyt	SkyePharma	Malignant lymphomatous meningitis
Polymeric platforms			
PEG–adenosine deaminase	Adagen	Enzon	Severe combined immunodeficiency
PEG–GCSF	Neulasta	Amgen	Neutropenia associated with cancer Chemotherapy
PEG–HGF	Somavert	Nektar, Pfizer	Acromegaly

Table (3): Therapeutics Based on Nanoparticles in Clinical Trials From Bench to Bedside: Nanoparticle-Driven Therapeutics in Clinical Trials

Composition	Trade name	Company	Indication
Liposomal platforms			
Liposomal annamycin	L-Annamycin	Callisto	Acute lymphocytic leukemia, Acute myeloid leukemia
Liposomal cisplatin	SLIT Cisplatin	Transave	Progressive osteogenic sarcoma metastatic to the lung
Liposomal doxorubicin	Sarcodoxome	GP-Pharm	Soft tissue sarcoma
Polymeric platforms			
PEG–arginine deaminase	Hepacid	Phoenix	Hepatocellular carcinoma
PEG–camptothecin	Prothecan	Enzon	Various cancers
PEG–naloxol	NKTR-118	Nektar	Opioid-induced constipation

5.11.1. Liposome-Based Therapies:

PEGylation is commonly employed to prevent the rapid clearance of liposomes from circulation by phagocytic cells of the reticuloendothelial system (RES). This modification increases the circulation time and improves therapeutic efficacy. Liposome-based systems have been successfully tested in clinical trials for delivering vincristine in non-Hodgkin's lymphoma treatment, enhancing tumor accumulation and reducing side effects [97].

5.11.2. PEGylated Nanoparticles in Clinical Trials:

PEGylation remains a cornerstone in the development of long-circulating nanoparticle-based therapies. Noteworthy, PEGylated products undergoing clinical evaluation include NKTR-118 (PEG-naloxol) for opioid-induced constipation (phase I), Hepacid (PEG-arginine deaminase) for hepatocellular carcinoma (phase II), and Puricase (PEG-uricase) for hyperuricemia (phase III) [98,39].

5.11.3. Other Nanoparticle Platforms:

Emerging nanoparticle platforms, including nano emulsions, dendrimers, and inorganic nanoparticles, have shown significant promise in enhancing drug delivery, improving precision medicine, and overcoming the limitations of traditional therapies [99,39].

5.12. Nanoparticles in Type 2 Diabetes Mellitus Therapy: Improving Drug Delivery and Cellular Uptake

Nanoparticles have rapidly emerged as a transformative tool in the field of medical applications, particularly in the realm of drug delivery. These nanoscale materials, which typically range from 1 to 100 nanometers in size, exhibit unique physicochemical properties that distinguish them from conventional drugs and delivery systems. Their small size, large surface area, and the ability to modify their surface characteristics allow for enhanced interaction with biological systems, opening new avenues for the treatment of various diseases, including cancer, T2DM, and neurological disorders [100,9].

One of the primary advantages of nanoparticles in drug delivery is their selective targeting capabilities. By modifying the surface properties of nanoparticles, such as attaching targeting ligands (e.g., antibodies, peptides, or small molecules) that recognize and bind specific receptors on the surface of diseased cells, nanoparticles can be directed to the target site with precision. This targeting mechanism minimizes the impact on healthy tissues, reducing systemic side effects and improving

the therapeutic index of drugs [101]. This ability to precisely deliver drugs to specific cells or tissues is particularly important in the treatment of cancer, where conventional chemotherapy often affects both tumor and healthy cells, leading to toxic side effects [102].

Additionally, improved cellular uptake is a crucial feature of nanoparticles. Due to their small size, NPs can easily cross biological barriers, such as cell membranes, which is a major challenge for many therapeutic agents, especially macromolecules like proteins, peptides, and nucleic acids. Nanoparticles can be engineered to interact with cell membranes more effectively, facilitating endocytosis or direct penetration into cells. This enhanced uptake is particularly beneficial for the delivery of poorly permeable drugs or biologics that would otherwise struggle to reach their target cells [103,104].

Another significant benefit of nanoparticles in drug delivery is their enhanced stability. Many drugs, especially those that are sensitive to environmental conditions such as pH, temperature, or enzymatic degradation, can be protected by encapsulating them in nanoparticles. This encapsulation shields the drugs from premature degradation in the bloodstream, thereby preserving their therapeutic activity. Furthermore, nanoparticles can be designed to release their payload in a controlled manner, ensuring that the drug is delivered over an extended period, reducing the need for frequent dosing [105,106].

Moreover, extended drug circulation time is a characteristic that nanoparticles impart to therapeutic agents. Traditional drug delivery methods often suffer from rapid clearance from the bloodstream, limiting the drug's efficacy and requiring frequent administration. Nanoparticles, however, can be engineered with surface modifications, such as polyethylene glycol (PEG), that provide a "stealth" effect, preventing recognition by the immune system and prolonging the circulation time of the nanoparticles in the bloodstream. This prolonged circulation enhances the likelihood that the drug will reach the target site at therapeutic concentrations, further improving its effectiveness [101].

Overall, the unique properties of nanoparticles selective targeting, improved cellular uptake, enhanced stability, and extended circulation time represent significant advancements over traditional therapeutic methods. These properties not only increase therapeutic efficacy by minimizing off-target effects but also enable the delivery of a wider range of drugs, including those that are typically difficult to administer or have limited bioavailability [107]. As research progresses, nanoparticles are likely to become even more integral to modern medicine, offering novel solutions for the treatment of a variety of diseases, with the potential for personalized medicine approaches tailored to the individual patient's needs.

5.13. Application of Nanoparticles in Insulin Delivery

Insulin therapy is essential for treating both type 1 and T2DM. However, only 20% of subcutaneously injected insulin reaches its target, with oral insulin bioavailability being much lower [108,109]. Nanocarrier-based insulin delivery systems are designed to protect insulin from degradation in the digestive system, improve absorption, and enhance bioavailability [110].

5.13.1. Oral Insulin Nanocarriers:

Several studies have focused on the development of insulin-loaded nanoparticles to protect insulin from the acidic environment of the stomach and improve intestinal absorption. For example, Collado-González et al. developed nanocomposites made of alginate, dextran sulfate, and chitosan for oral insulin delivery. This formulation showed successful insulin release under physiologically simulated conditions [111].

5.13.2. Gold-Graphene Oxide Nanocomposites:

Golkar et al. synthesized insulin-loaded gold-graphene oxide-sodium alginate (AuGOSA) nanocomposites. This formulation prevented insulin breakdown in synthetic gastric fluids and demonstrated controlled release, reducing blood glucose levels in in-vivo experiments [112].

In conclusion, metal-based nanoparticles represent a promising tool for overcoming the challenges associated with nucleic acid delivery. Continued research into their design, functionalization, and biocompatibility will be crucial for translating these technologies into effective clinical therapies.

5.14. Nanoparticles in the Delivery of Other Hypoglycemic Agents

In addition to insulin, several other hypoglycemic agents are used in the treatment of T2DM, including sulfonylureas, biguanides, and thiazolidinediones. However, the limited solubility of these drugs can hinder their therapeutic efficacy. Nanoparticles offer a unique solution to improve the solubility and bioavailability of these drugs.

For individuals whose diet and exercise do not provide adequate glucose control, five main groups of hypoglycemic medications are available: sulfonylureas, biguanides, meglitinides, thiazolidinediones, and alpha-glucosidase inhibitors [113]. The limited solubility of hypoglycemic medicines in water significantly alters their absorption and therapeutic effectiveness [114]. Numerous studies have documented a unique delivery strategy that improves bioavailability and overcomes drug delivery challenges, thereby enhancing therapeutic efficacy with lower therapeutic doses and better patient compliance.

5.14.1. Sulfonylureas: These are a family of antidiabetic medications that work by increasing insulin release from pancreatic beta cells [115]. One of the most commonly used sulfonylureas is gliclazide, which needs to be taken twice daily [116]. Gliclazide entrapment in a biodegradable and biocompatible carrier may provide prolonged release of the medication into the bloodstream. To overcome the low solubility and bioavailability of gliclazide (GCZ), Patel et al. developed a self-nanoemulsifying drug delivery system (SNEDDS). When compared to plain medication (15.99%), optimized L-SNEDDS showed quicker drug release (97.84%) within 30 minutes of in vitro dissolution. Through extrusion-spheronization, the optimized L-SNEDDS was transformed into solid (S)-SNEDDS as pellets and a self-nanoemulsifying powder (SNEP). After 30 minutes, the in vitro dissolution of SNEP (S3) and pellets was 90.54% and 73.76%, respectively. In vivo experiments revealed a twofold increase in bioavailability with SNEDDS, along with a notable drop in blood glucose levels, indicating that lipid-based systems could be a potential substitute for conventional T2DM treatments [117].

In addition, Averineni et al. developed gliclazide-containing chitosan nanoparticles to provide a sustained release profile appropriate for oral administration with improved effectiveness, potentially resolving the issues with traditional dosage forms.

Gliclazide was released from chitosan nanoparticles in vitro for over 24 hours. After three months under expedited stability conditions, gliclazide-loaded nanoparticle formulations remained stable. Improved pharmacokinetic profiles and sustained action may lower adverse effects and reduce dosage frequency [118].

5.14.2. Metformin: Metformin is a hydrophilic drug with low absorption properties and high solubility. It functions by reducing the liver's synthesis of glucose and increasing peripheral tissues' sensitivity to insulin [119]. To improve its intestinal permeability and gastrointestinal absorption, metformin was encapsulated in alginate nanocapsules (MLANs) using an emulsion cross-linking technique. In vitro drug release experiments and in vivo effectiveness testing showed that MLANs were more efficient and responsive. Overall, MLANs' effectiveness (46.8 mg/kg) was approximately three times more than that of pure metformin (150 mg/kg) [120].

Furthermore, metformin-loaded pectin (PCM) nanoparticles were formulated for long-term effects in the treatment of T2DM mellitus. In vitro extended-release properties were favorable, with the PCMNP-4 displaying 68 ± 4.2% drug entrapment efficiency. Additionally, the nanoparticles exhibited reasonable stability when exposed to increased bovine serum albumin, suggesting they could remain stable in the bloodstream. The findings demonstrated that PCMNPs are safe for oral administration as they are hemocompatible. When compared to metformin, glucose absorption was 1.5 times greater in red blood cells and the L6 skeletal muscle cell line [121]. It was also found that metformin hydrochloride (MH)-loaded niosomes, especially those with a positive charge, could efficiently maintain drug release. The hypoglycemic effect was more prolonged and intense in the pharmacokinetic data of the MH-loaded niosomal preparation compared to the free MH solution. When MH was administered in niosomal form instead of a free drug solution, the area under the blood glucose levels–time curve (AAC), maximal hypoglycemic response, and time of maximum reaction (Tmax) were all considerably larger. Therefore, MH-loaded niosomes hold promise for longer-release preparations with improved hypoglycemic effectiveness [119].

6. Conclusion:

Nanoparticles, particularly those made from heavy metals, emerge as highly promising tools in the therapeutic management of metabolic syndrome and T2DM-related complications. The unique properties of nanoparticles, including their small size, high surface area, and ability to modulate cellular and molecular interactions, offer substantial advantages over conventional treatments. HMNPs, such as gold, silver, and copper-based nanoparticles, have demonstrated significant potential in improving the bioavailability, stability, and therapeutic efficacy of antidiabetic drugs while simultaneously offering novel mechanisms to target the underlying pathophysiological processes of metabolic syndrome and T2DM.

These nanoparticles exhibit potential usefulness in several critical areas: reducing oxidative stress, alleviating inflammation, enhancing insulin sensitivity, improving glucose metabolism, and mitigating complications associated with T2DM, such as cardiovascular damage, neuropathy, and nephropathy. The multifunctional capabilities of these nanoparticles are being explored to enhance drug delivery systems, creating sustained-release formulations, and ensuring targeted action. Moreover, their ability to interact with biological systems at the cellular and molecular levels offers potential therapeutic benefits in addressing IR, beta-cell dysfunction, and chronic inflammation hallmarks of metabolic syndrome and T2DM.

However, while the preliminary findings are promising, several challenges must be addressed before HMNPs can be fully integrated into clinical practice. Issues such as toxicity, long-term safety, biocompatibility, and the large-scale production of these nanoparticles need thorough investigation. Standardization of nanoparticle synthesis, dosage optimization, and the exploration of effective delivery mechanisms are critical to ensuring the clinical success of these therapeutic agents.

7. Future Directions

Future research on HMNPs for the treatment of metabolic syndrome and T2DM-related complications should focus on several key areas. First, extensive toxicity and safety evaluations are crucial to ensure the long-term biocompatibility of these nanoparticles in diabetic patients. Additionally, further investigation into the molecular mechanisms of action is necessary to understand how these nanoparticles modulate oxidative stress, inflammation, and insulin signaling, as well as the potential for targeted delivery to improve therapeutic outcomes. The optimization of nanoparticle formulations, especially those with sustained-release properties, will help enhance drug solubility, bioavailability, and reduce dosing frequency.

Moreover, exploring combination therapies that deliver both antidiabetic drugs and agents with complementary effects may address the complex nature of T2DM. Clinical trials and large-scale studies are vital to validate the safety, efficacy, and appropriate dosing of these nanoparticles in diverse patient populations. Finally, overcoming regulatory and manufacturing challenges through collaborative efforts will be essential for standardizing the production of these therapies and ensuring their consistent quality for clinical application. These future directions will facilitate the development of HMNPs as safe, effective, and scalable treatments for metabolic syndrome and T2DM-related complications.

8. Methodology of Literature Selection

This review was compiled through a comprehensive literature search conducted using databases including PubMed, Scopus, and Web of Science. Keywords such as heavy metal nanoparticles, diabetes, metabolic syndrome, nanomedicine, and metal-based nanotherapeutics' were used to identify relevant publications. The inclusion criteria focused on original research articles and reviews published in English from 2010 to 2024 that addressed the biological activity, therapeutic potential, and mechanistic insights of metal-based nanoparticles in diabetes and metabolic syndrome. Studies that did not focus on the therapeutic or mechanistic relevance of metal-based nanoparticles, or that lacked adequate scientific validation, were excluded. The selected articles were critically evaluated to provide an integrated understanding of the current knowledge and research gaps in this emerging field.

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