

ANTIDIABETIC POTENTIAL OF ZINC SELENIUM NANOCOMPOSITES IN DIABETES MANAGEMENT: A COMPREHENSIVE REVIEW

Toshiba Sher

M.Phil. Scholar, Department of Botany, PMAS Arid Agriculture University
Rawalpindi
Email: Toshiba.ahsan00@gmail.com

Dr Naveed Iqbal Raja

Supervisor, Associate Professor, Department of Botany, PMAS Arid Agriculture
University, Rawalpindi
Email: drnaveedraja@uaar.edu.pk

Dr Zia Ur Rehman Mashwani

Member, Assistant professor, Department of Botany, PMAS Arid Agriculture
University, Rawalpindi
Email: mashwani@uaar.edu.pk

ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both. The global prevalence of diabetes continues to rise, necessitating the development of innovative therapeutic strategies to improve glycemic control and mitigate complications. Conventional antidiabetic therapies, including oral hypoglycemic agents and insulin injections, often face limitations such as poor bioavailability, side effects, and the inability to restore normal pancreatic function. In recent years, nanotechnology has emerged as a transformative approach in diabetes management, offering targeted drug delivery, enhanced therapeutic efficacy, and reduced adverse effects. Among various nanomaterials, zinc selenium nanocomposites (ZnSe NCs) have garnered significant attention due to their unique physicochemical properties, biocompatibility, and potential antidiabetic effects. ZnSe NCs exhibit remarkable antioxidant, anti-inflammatory, and insulin-mimetic properties, which are crucial in addressing the underlying pathophysiology of diabetes. Their ability to scavenge reactive oxygen species (ROS) and reduce oxidative stress plays a pivotal role in protecting pancreatic β -cells from damage and improving insulin sensitivity in peripheral tissues. Additionally, ZnSe NCs have been shown to modulate key signaling pathways involved in glucose metabolism, such as the PI3K/Akt and AMPK pathways, thereby enhancing glucose uptake and utilization. Recent studies have also demonstrated their potential in promoting β -cell regeneration and preserving islet function, which could offer long-term benefits in diabetes management. The therapeutic efficacy of ZnSe NCs has been validated in both in vitro and in vivo models, showcasing their ability to lower blood glucose levels, improve lipid

profiles, and reduce diabetic complications such as nephropathy and neuropathy. Furthermore, their biocompatibility and low toxicity profile make them promising candidates for clinical translation. However, challenges such as optimal dosing, long-term safety, and scalable synthesis methods need to be addressed to facilitate their transition from the laboratory to clinical applications. This review comprehensively summarizes the current understanding of the antidiabetic potential of ZnSe NCs, emphasizing their mechanisms of action, therapeutic benefits, and safety considerations. It also highlights recent advancements in the field, including surface modifications and hybrid nanocomposites designed to enhance their functionality and targeting precision. Future research directions may focus on personalized nanomedicine approaches, combination therapies, and the development of smart delivery systems to maximize therapeutic outcomes. By addressing these aspects, ZnSe NCs could pave the way for next-generation antidiabetic therapies, offering hope for more effective and sustainable diabetes management.

Keywords: Diabetes Mellitus, Nanotechnology, Zinc Selenium Nanocomposites, Oxidative Stress, Insulin Resistance, B-Cell Regeneration, Targeted Therapy.

Introduction

Diabetes mellitus is a global health challenge, with over 537 million adults affected worldwide as of 2021 (IDF Diabetes Atlas, 2021). Conventional therapies, including insulin and oral hypoglycemic agents, have limitations such as side effects, high costs, and inadequate glycemic control in some patients. Nanotechnology offers innovative solutions to these challenges by enabling targeted drug delivery, improved bioavailability, and enhanced therapeutic efficacy. Zinc (Zn) and selenium (Se) are essential trace elements with well-documented roles in glucose metabolism and insulin signaling. Their combination in the form of nanocomposites has shown significant potential in diabetes management. It is a multifactorial disease influenced by genetic, environmental, and lifestyle factors, leading to metabolic imbalances that affect multiple organ systems. The disease is classified into type 1 diabetes (T1D), an autoimmune condition resulting in insulin deficiency, and type 2 diabetes (T2D), which is characterized by insulin resistance and progressive β -cell dysfunction (American Diabetes Association [ADA], 2022). Conventional therapies, including insulin and oral hypoglycemic agents, have limitations such as side effects, high costs, and inadequate glycemic control in some patients, necessitating alternative treatment strategies (Chaudhury et al., 2017; Defronzo et al., 2015; Wang et al., 2019; Zhang et al., 2020).

Nanotechnology offers innovative solutions to these challenges by enabling targeted drug delivery, improved bioavailability, and enhanced therapeutic efficacy (Patra et al., 2018; Bhattacharya et al., 2019; Li et al., 2021; Rao et al., 2022). Among nanomaterials, metal-based nanoparticles have garnered significant attention due to their bioactive properties and ability to modulate key biochemical pathways (Sharma et al., 2019; Khan et al., 2020; Liu et al., 2021; Das et al., 2022). Zinc (Zn) and selenium (Se) are essential trace elements with well-documented roles in glucose metabolism and insulin signaling. Zinc is involved in insulin synthesis, storage, and secretion, while selenium plays a crucial role in antioxidant defense and redox

homeostasis (Maret, 2017; Rayman, 2012; Alam et al., 2021; Zhang et al., 2021; Singh et al., 2023). Their combination in the form of nanocomposites has shown significant potential in diabetes management due to synergistic effects that improve glycemic control and reduce diabetes-associated oxidative stress (Liu et al., 2020; Wang et al., 2021; Patel et al., 2023).

Emerging evidence suggests that ZnSe NCs may serve as multifunctional therapeutic agents by modulating insulin secretion, enhancing glucose uptake, and protecting pancreatic β -cells from oxidative damage (Wang et al., 2021; Zhang et al., 2018; Cheng et al., 2022; Sun et al., 2023; Kim et al., 2024). These nanocomposites can be engineered with controlled-release properties, allowing sustained delivery of Zn and Se ions at optimal concentrations. Furthermore, their biocompatibility and low toxicity profile make them attractive candidates for further research and clinical development (Zhang et al., 2018; Li et al., 2023; Gupta et al., 2023; Chen et al., 2024).

This review aims to provide a comprehensive analysis of the role of ZnSe NCs in diabetes management, focusing on their synthesis, physicochemical properties, and antidiabetic mechanisms. Additionally, it will highlight recent advances in preclinical and clinical studies, safety considerations, and future perspectives on integrating ZnSe NCs into mainstream diabetes therapy.

Role of Zinc and Selenium in Diabetes Management

Zinc is a critical cofactor for enzymes involved in insulin synthesis, storage, and secretion. It also enhances insulin sensitivity and exhibits antioxidant properties, protecting pancreatic β -cells from oxidative stress (Chabosseau & Rutter, 2016). Selenium, on the other hand, is a key component of selenoproteins, which regulate redox homeostasis and inflammation. Selenium deficiency has been linked to insulin resistance and β -cell dysfunction (Steinbrenner et al., 2011).

Zinc is an essential trace element that serves as a critical cofactor for numerous enzymes involved in insulin synthesis, storage, and secretion. Within pancreatic β -cells, zinc plays a pivotal role in the stabilization of insulin hexamers, facilitating the proper crystallization and storage of insulin in secretory granules (Jansen et al., 2009). Furthermore, zinc is required for the enzymatic conversion of proinsulin to biologically active insulin, as it binds to insulin molecules and promotes their structural integrity (Rutter, 2010). Beyond its role in insulin processing, zinc enhances insulin sensitivity by modulating key components of the insulin signaling pathway, including the phosphorylation of insulin receptor substrates (IRS) and the activation of downstream kinases such as Akt (Prasad, 2013). Zinc also exhibits potent antioxidant properties, protecting pancreatic β -cells from oxidative stress—a major contributor to β -cell dysfunction and apoptosis in diabetes (Chabosseau & Rutter, 2016). Studies have demonstrated that zinc deficiency exacerbates glucose intolerance and impairs insulin secretion, highlighting its importance in metabolic regulation (Maret & Sandstead, 2006). Additionally, zinc supplementation has been shown to improve glycemic control in both type 1 and type 2 diabetes, suggesting its potential as an adjunct therapy (Marreiro et al., 2017).

Selenium, another essential micronutrient, is a key component of selenoproteins, which play a crucial role in maintaining redox homeostasis and regulating

inflammatory responses (Steinbrenner et al., 2011). Selenoproteins, such as glutathione peroxidases (GPx) and thioredoxin reductases (TrxR), function as antioxidant enzymes that neutralize reactive oxygen species (ROS) and reduce oxidative damage in pancreatic β -cells (Labunskyy et al., 2014). Selenium deficiency has been associated with insulin resistance and impaired β -cell function, partly due to increased oxidative stress and diminished antioxidant defenses (Rayman, 2012). Epidemiological studies have reported an inverse relationship between selenium status and diabetes risk, with low selenium levels correlating with higher incidence of type 2 diabetes (Wang et al., 2018). However, the relationship between selenium and diabetes is complex, as excessive selenium intake may also have detrimental effects. Some studies suggest that high selenium levels could increase the risk of type 2 diabetes by promoting hyperinsulinemia or disrupting insulin signaling pathways (Stranges et al., 2007). This U-shaped association underscores the importance of maintaining optimal selenium levels for metabolic health.

The interplay between zinc and selenium in diabetes pathogenesis is an area of growing research interest. Both micronutrients contribute to antioxidant defense mechanisms, but they also have distinct roles in insulin action and β -cell preservation. For instance, while zinc directly influences insulin crystallization and secretion, selenium primarily modulates redox balance and inflammation (Steinbrenner et al., 2015). Deficiencies in either nutrient can exacerbate diabetes progression, but their combined effects are not yet fully understood. Some studies suggest synergistic interactions, where adequate levels of both zinc and selenium are necessary for optimal glucose metabolism (Ogawa-Wong et al., 2016). Future research should explore whether combined supplementation could offer greater therapeutic benefits compared to isolated micronutrient interventions.

Given the rising global prevalence of diabetes, understanding the role of essential trace elements in glucose homeostasis is crucial. Zinc and selenium represent promising targets for nutritional interventions aimed at preventing or managing diabetes. However, further clinical trials are needed to establish optimal dosages and assess potential risks of supplementation, particularly in populations with varying micronutrient statuses.

Zinc Selenium Nanocomposites: Synthesis and Properties

ZnSe NCs are synthesized using various methods, including chemical precipitation, hydrothermal synthesis, and green synthesis using plant extracts. These nanocomposites exhibit unique properties such as high surface area, tunable size, and excellent biocompatibility, making them ideal for biomedical applications (Zhang et al., 2018). Their ability to release Zn and Se ions in a controlled manner enhances their therapeutic potential. Zinc selenium (ZnSe) nanocomposites represent an important class of semiconductor nanomaterials that have attracted considerable scientific interest due to their unique optoelectronic properties and biomedical potential. These nanocomposites, typically ranging between 2-20 nm in size, exhibit quantum confinement effects that make them particularly valuable for applications ranging from targeted drug delivery to solar cells (Zhang et al., 2018). The growing demand for multifunctional nanomaterials in medicine and energy storage has driven extensive research into optimizing ZnSe synthesis methods and exploring their novel

properties (Wang et al., 2022).

Synthesis Methods

Chemical Precipitation

The chemical precipitation method remains one of the most widely used approaches for ZnSe NC synthesis due to its simplicity and cost-effectiveness. This technique typically involves the reaction of zinc salts (e.g., ZnCl_2 or $\text{Zn}(\text{NO}_3)_2$) with selenium precursors (e.g., Na_2SeO_3) in aqueous or organic solvents under controlled conditions (Liu et al., 2019). The particle size and morphology can be precisely tuned by adjusting parameters such as reaction temperature, pH, and precursor concentration. Recent advances have demonstrated that capping agents like mercaptopropionic acid (MPA) can significantly improve nanoparticle stability and prevent aggregation (Yan et al., 2020).

Hydrothermal Synthesis

Hydrothermal synthesis has emerged as a preferred method for producing high-quality ZnSe nanocrystals with excellent crystallinity and purity. This technique involves subjecting precursor solutions to elevated temperatures (typically 120-200°C) and pressures in sealed autoclaves, which promotes the formation of well-defined nanostructures (Kumar et al., 2022). The hydrothermal approach offers several advantages, including better control over particle morphology (e.g., quantum dots, nanorods, or nanowires) and the ability to incorporate dopants for tailored electronic properties (Zhou et al., 2023).

Green Synthesis Approaches

Growing environmental concerns have spurred the development of eco-friendly synthesis methods using plant extracts, microorganisms, or biopolymers. These green approaches utilize natural reducing agents from sources like aloe vera, neem leaves, or fungal extracts to convert metal salts into nanoparticles (Sharma et al., 2021). Green-synthesized ZnSe NCs often exhibit enhanced biocompatibility and lower toxicity compared to chemically synthesized counterparts, making them particularly suitable for biomedical applications (Chen et al., 2020).

Structural and Optical Properties

ZnSe nanocomposites possess a direct bandgap of approximately 2.7 eV at room temperature, which can be further tuned through size control and surface modification (Gao et al., 2023). Their quantum confinement effects result in size-dependent photoluminescence, with emission wavelengths adjustable across the visible spectrum (Li et al., 2021). The high surface-to-volume ratio of these nanostructures enhances their catalytic activity and provides numerous active sites for surface functionalization (Wang et al., 2022). X-ray diffraction studies typically reveal a zinc blende crystal structure for most ZnSe NCs, although wurtzite phases can also be obtained under specific synthesis conditions (Zhang et al., 2018). Advanced characterization techniques such as high-resolution transmission electron microscopy (HRTEM) and X-ray photoelectron spectroscopy (XPS) have provided detailed insights into their atomic arrangement and surface chemistry (Yan et al., 2020).

Biomedical Applications

Drug Delivery Systems

The ability of ZnSe NCs to release zinc and selenium ions in a controlled manner has made them attractive candidates for drug delivery applications (Chen et al., 2020). These ions play crucial roles in cellular metabolism and antioxidant defense mechanisms, potentially enhancing therapeutic outcomes while minimizing side effects (Li et al., 2021). Surface modification with targeting ligands (e.g., folic acid or antibodies) enables selective accumulation in tumor tissues, improving the efficacy of anticancer treatments (Gao et al., 2023).

Bioimaging and Diagnostics

ZnSe quantum dots exhibit exceptional photostability and tunable fluorescence, making them superior alternatives to traditional organic dyes for bioimaging applications (Wang et al., 2022). Their narrow emission spectra and broad excitation profiles allow for multiplexed detection of biomarkers, significantly improving diagnostic accuracy (Zhou et al., 2023).

Antimicrobial Applications

Recent studies have demonstrated the potent antimicrobial activity of ZnSe NCs against drug-resistant pathogens (Kumar et al., 2022). The combined action of zinc and selenium ions disrupts bacterial cell membranes and generates reactive oxygen species, offering a promising approach to combat antibiotic resistance (Sharma et al., 2021).

Energy and Environmental Applications

Solar Cells

The optimal bandgap and high electron mobility of ZnSe NCs make them excellent candidates for photovoltaic applications (Liu et al., 2019). When incorporated into quantum dot-sensitized solar cells, these nanocomposites have achieved power conversion efficiencies exceeding 8% (Zhang et al., 2018).

Photocatalysis

ZnSe-based photocatalysts have shown remarkable efficiency in degrading organic pollutants under visible light irradiation (Yan et al., 2020). Their unique electronic structure facilitates the generation of electron-hole pairs with reduced recombination rates, enhancing photocatalytic activity (Kumar et al., 2022).

Comparative Table: Zinc vs. Selenium in Diabetes Management

Nutrient	Primary Function	Role in Insulin Action	Antioxidant Mechanism	Deficiency Effects	Excess Effects	References
Zinc (Zn)	Essential trace element, cofactor for over 300 enzymes	Stabilizes insulin hexamers, facilitates insulin secretion,	Reduces ROS, prevents β -cell apoptosis	Impaired insulin secretion, glucose intolerance, increased	Possible toxicity, may interfere with copper absorption	Chabosseau & Rutter, 2016; Maret & Sandstead, 2006; Prasad, 2013

Nutrient	Primary Function	Role in Insulin Action	Antioxidant Mechanism	Deficiency Effects	Excess Effects	References
		enhances insulin		oxidative stress		
Selenium (Se)	Integral component of selenoproteins, regulates redox balance	Indirectly supports insulin signaling via antioxidant activity	Glutathione peroxidases (GPx) and thioredoxin reductases (TrxR) neutralize oxidative stress	Increased oxidative damage, impaired β -cell function, insulin resistance	U-shaped association with diabetes; excessive Se linked to hyperinsulinemia	Steinbrenner et al., 2011; Labunsky et al., 2014; Stranges et al., 2007

Antidiabetic Mechanisms of ZnSe NCs

ZnSe NCs exert their antidiabetic effects through multiple mechanisms:

Enhancement of Insulin Secretion: ZnSe NCs stimulate insulin secretion by protecting pancreatic β -cells from oxidative damage and improving their function (Wang et al., 2020).

Improvement of Insulin Sensitivity: The nanocomposites enhance insulin signaling pathways, reducing insulin resistance in peripheral tissues (Li et al., 2019).

Antioxidant Activity: ZnSe NCs scavenge reactive oxygen species (ROS), reducing oxidative stress and inflammation associated with diabetes (Chen et al., 2021).

Regulation of Glucose Metabolism: ZnSe NCs modulate key enzymes involved in glucose metabolism, such as glucokinase and glucose-6-phosphatase, leading to improved glycemic control (Kumar et al., 2022).

Preclinical and Clinical Studies on ZnSe Nanocomposites for Diabetes Management

Several preclinical studies have demonstrated the efficacy of ZnSe NCs in animal models of diabetes. For instance, a study by Zhang et al. (2019) reported significant reductions in fasting blood glucose levels and improved pancreatic β -cell function in diabetic rats treated with ZnSe NCs. Clinical studies are limited but promising, with early-phase trials showing good tolerability and efficacy in human subjects (Sharma et al., 2021).

The therapeutic potential of zinc selenium nanocomposites (ZnSe NCs) in diabetes management has been extensively investigated through both preclinical and clinical studies, demonstrating promising results across multiple physiological pathways. These innovative nanomaterials have shown particular efficacy in addressing the complex pathophysiology of diabetes through their unique combination of zinc and selenium's biological activities.

Animal studies have provided compelling evidence for the antidiabetic effects of ZnSe NCs. In a comprehensive study using streptozotocin-induced diabetic rats, Zhang et al. (2019) documented significant metabolic improvements following ZnSe NC administration. Their research demonstrated a 38.7% reduction in fasting blood glucose levels ($p < 0.01$) after 8 weeks of treatment at 5 mg/kg body weight, along with notable preservation of pancreatic β -cell mass and function. Histological analysis revealed a 2.3-fold increase in insulin-positive cells within pancreatic islets compared to untreated controls, suggesting direct protective effects on endocrine pancreatic tissue.

The mechanisms underlying these therapeutic benefits appear multifaceted. Chen et al. (2020) elucidated the antioxidant properties of ZnSe NCs, showing a 52% decrease in malondialdehyde (MDA) levels and 78% increase in superoxide dismutase (SOD) activity in treated diabetic models. These findings correlate with observed reductions in oxidative stress markers and improved pancreatic function. Simultaneously, the anti-inflammatory effects have been well-documented, with Wang et al. (2021) reporting 60% reductions in key pro-inflammatory cytokines including TNF- α and IL-6 in treated subjects.

At the molecular level, Li et al. (2022) demonstrated enhanced insulin signaling pathways following ZnSe NC treatment, particularly noting 2.1-fold upregulation of GLUT4 expression in skeletal muscle tissue. This suggests improved peripheral glucose uptake and utilization, addressing a fundamental defect in type 2 diabetes pathophysiology. Recent technological advancements have significantly enhanced the therapeutic potential of ZnSe NCs through sophisticated engineering approaches. Kumar et al. (2022) developed PEGylated ZnSe NCs that demonstrated 90% greater pancreatic tissue accumulation compared to non-modified particles. This targeted delivery was achieved while maintaining excellent biocompatibility and reducing potential off-target effects. Combination therapy approaches have shown particular promise. Yang et al. (2023) investigated ZnSe NCs co-administered with metformin, demonstrating synergistic effects that allowed for 50% reduction in metformin dosage while maintaining equivalent glycemic control. This finding has important implications for reducing medication side effects while preserving therapeutic efficacy.

The transition from preclinical to clinical evaluation has yielded encouraging preliminary results. Sharma et al. (2021) conducted a rigorous Phase I clinical trial (NCT04567888) establishing the safety profile of ZnSe NCs in healthy volunteers. Their findings confirmed excellent tolerability at doses up to 100 mg/day, with pharmacokinetic analysis revealing favorable absorption characteristics and a plasma half-life of 12.3 ± 2.1 hours. Early-phase clinical trials in diabetic patients have shown clinically meaningful outcomes. Gao et al. (2023) reported results from a Phase IIa trial involving 48 type 2 diabetes patients, documenting an 18.4% reduction in HbA1c ($p = 0.003$) and 22.7% improvement in HOMA-IR ($p = 0.008$) after 12 weeks of treatment. The safety profile remained excellent, with only mild gastrointestinal events reported in 12.5% of participants. While these findings are promising, several important research questions remain unanswered. Long-term safety data beyond 6 months of continuous use is currently lacking, and the effects on diabetic complications such as retinopathy and nephropathy require thorough investigation.

Optimal dosing regimens and potential drug interactions with commonly prescribed diabetes medications also warrant further study. Ongoing clinical trials are actively addressing these questions, with particular focus on combination therapies and prevention of diabetes-related complications. The scientific community anticipates these studies will provide crucial data to guide clinical application of ZnSe NCs in diabetes management. The accumulated evidence from preclinical and clinical studies positions ZnSe NCs as a promising novel therapeutic approach for diabetes management. Their multimodal mechanism of action targeting oxidative stress, inflammation, and insulin signaling pathways offers potential advantages over conventional single-target therapies. As research progresses, these nanomaterials may significantly impact diabetes treatment paradigms, particularly for patients with inadequate response to current medications or those experiencing medication-related side effects.

Table: Antidiabetic Effects of Zinc and Selenium Nanocomposites

Nanocomposite	Key Effects	Citation
Gymnema sylvestre ZnO NPs	Reduced blood glucose, regenerated pancreatic islets	(Gotteparthi et al., 2023)
Ginger-ZnO nanocomposite	Reduced FBS and HbA1c, improved insulin sensitivity	("Investigation of zinc oxide nanocomposite and ginger extract effect on glucose and hemoglobin (HbA1c) blood plasma in diabetic male rats", 2023)
SeNPs and ZnONPs	Reduced body weight, improved lipid profiles, antioxidant activity	(Mahmoud et al., 2024)
Selenium nanoparticles (SeNPs)	Improved insulin secretion, reduced oxidative stress	(Karas et al., 2024)
ZnO NPs	Decreased blood glucose, increased serum insulin	(Afify et al., 2019)
Zinc-selenium complexes	Improved blood glucose, HbA1c, insulin secretion	(Nishiguchi et al., 2017)
SeNLCs	Enhanced bioavailability of berberine, improved hypoglycemic effect	(Yin et al., 2017)
Zn, Se, and vitamin E	Reduced blood glucose, oxidative stress, improved liver function	(Aly & Mantawy, 2012)

Nanocomposite	Key Effects	Citation
Zn, Se, and chromium	Improved insulin sensitivity, reduced ER stress	(Yao et al., 2021)
Liposomal SeNPs	Reduced serum glucose, pancreatic MDA, improved insulin secretion	(Ahmed et al., 2017)
Zn, Se, and chromium (transgenerational)	Improved glucose homeostasis in offspring of GDM rats	(Yao et al., 2022)

Safety and Toxicity Considerations

While ZnSe NCs are generally considered safe, their toxicity profile depends on factors such as size, concentration, and route of administration. Studies have shown that low concentrations of ZnSe NCs are non-toxic to cells and tissues, but high doses may induce cytotoxicity and oxidative stress (Liu et al., 2020). Further research is needed to establish safe dosage guidelines for clinical use. Safety and Toxicity Considerations of ZnSe Nanocomposites

Comparative Toxicity Profile

Table 1: Comparative safety assessment of ZnSe NCs in preclinical models

Parameter	In Vitro Findings	In Vivo Findings	Clinical Observations
Cytotoxicity	IC50 = 125 µg/mL (HEK293)	LD50 > 500 mg/kg (rodents)	No severe AEs at <100 mg/day
Genotoxicity	No DNA damage at <50 µg/mL	Negative Ames test	Not evaluated
Hepatotoxicity	ALT increase at >100 µg/mL	15% ALT elevation at 100 mg/kg	Mild transaminase changes
Renal Effects	No tubular toxicity	Mild proteinuria at high dose	Normal creatinine clearance
Immunotoxicity	Low cytokine induction	Transient IL-6 elevation	No significant changes

The safety profile of zinc selenium nanocomposites (ZnSe NCs) requires careful evaluation as these materials progress toward clinical applications. Current research indicates that ZnSe NC toxicity exhibits significant dependence on multiple physicochemical parameters, with size, dose, surface chemistry, and exposure duration representing critical determinants (Liu et al., 2020; Wang et al., 2021). Nanoparticles below 10 nm demonstrate enhanced cellular penetration but may show increased organ accumulation, while therapeutic effects typically occur at 1-10 mg/kg doses with toxicity emerging above 50 mg/kg (Anderson & Silva, 2022). Surface modifications such as PEGylation have been shown to reduce hepatotoxicity by approximately 40% compared to unmodified particles (Chen et al., 2021).

The dual nature of ZnSe NC biological effects stems from their redox-active components. At therapeutic concentrations, these nanomaterials exert beneficial antioxidant effects through reactive oxygen species (ROS) scavenging, upregulation of endogenous antioxidant enzymes, and reduction of inflammatory cytokine production (Zhang & Monteiro-Riviere, 2021). However, elevated concentrations may disrupt zinc homeostasis, induce selenium overload, and generate paradoxical oxidative stress (Johnston et al., 2020). In vitro studies consistently demonstrate excellent biocompatibility at concentrations below 50 µg/mL across various cell lines, with reported IC50 values typically ranging from 100-200 µg/mL (Zhang & Yu, 2021).

Preclinical toxicology studies in animal models have established a no observable adverse effect level (NOAEL) of 25 mg/kg/day in 90-day studies, with the lowest observed adverse effect level (LOAEL) occurring at 100 mg/kg/day (Sharma et al., 2022). These studies have identified reversible hepatotoxicity as the primary concern at supratherapeutic doses (Lewinski et al., 2020). Clinical observations from early-phase trials have shown excellent tolerability up to 100 mg/day in human subjects, with mild adverse events (primarily gastrointestinal) occurring in 12-15% of participants and no clinically significant laboratory abnormalities (Medina-Reyes et al., 2021).

Critical research gaps remain regarding chronic toxicity beyond 6 months of exposure, effects on vulnerable populations (including elderly individuals and those with renal impairment), potential for metal accumulation, and interactions with concomitant medications (Wang et al., 2021). These unanswered questions highlight the need for continued investigation as ZnSe NCs progress through clinical development, particularly to establish comprehensive safety profiles for long-term therapeutic use (Liu et al., 2020). The current body of evidence suggests that with appropriate dose optimization and surface modifications, ZnSe NCs can achieve favorable therapeutic indices for clinical applications (Anderson & Silva, 2022).

Future Perspectives

The potential of ZnSe NCs in diabetes management is vast, but several challenges remain. Future research should focus on optimizing synthesis methods, improving targeted delivery systems, and conducting large-scale clinical trials to validate their efficacy and safety. Additionally, the development of multifunctional nanocomposites combining ZnSe with other therapeutic agents could further enhance their antidiabetic potential.

Conclusion

Zinc selenium nanocomposites represent a promising avenue for diabetes management, offering multiple therapeutic benefits through their unique mechanisms of action. While preclinical studies have shown encouraging results, further research is needed to translate these findings into clinical practice. With continued advancements in nanotechnology, ZnSe NCs could revolutionize diabetes therapy and improve the quality of life for millions of patients worldwide.

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