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Zinc (II) Complexes as Anti-Diabetic Agents: A Comprehensive Review of Advances, Scientific Gaps, and Prospects

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Abstract

Zinc has emerged as a promising component in the development of anti-diabetic agents due to its crucial role in insulin storage, secretion, and insulin mimetic properties. This review explores the progress in utilizing zinc (II) complexes, formed with various organic ligands, to develop potent anti-diabetic agents with enhanced pharmacological properties. We systematically examine published research on the anti-diabetic effects of zinc (II) complexes, sourced from reputable databases such as PubMed, Google Scholar, Scopus, and ScienceDirect. Complexes are categorized based on their precursor ligands, and a critical analysis reveals promising leads but also significant scientific gaps. While synthetic ligands dominate the research landscape, their toxicity profiles remain largely unreported, raising concerns about clinical applicability. Conversely, complexes formed with natural ligands like plant polyphenols, maltol, hinokitiol, and supplements such as ascorbic acid, L-threonine, and L-carnitine exhibit promising anti-diabetic properties with minimal safety concerns yet remain underexplored and lack clinical validation. We advocate for a paradigm shift towards investigating these natural ligands and supplements in anti-diabetic zinc (II) complexes, coupled with rigorous toxicity evaluations for synthetic ligands, to address safety concerns and enhance clinical relevance.

Keywords: Zinc (II) complexes, anti-diabetic agents, insulin mimetic, pharmacological properties, scientific gaps, natural ligands, toxicity evaluation, clinical validation..

Introduction:

Diabetes mellitus presents a complex array of metabolic dysregulations, characterized by persistent hyperglycemia stemming from inadequate insulin secretion (type 1 diabetes) or action (type 2 diabetes). Type 2 diabetes (T2D) stands as the predominant form globally, posing significant health and socioeconomic challenges.[1-6] Its pathogenesis involves multifaceted metabolic abnormalities, prominently impaired insulin action and β-cell dysfunction, leading to dysregulated blood glucose levels.[7]

Traditional pharmacotherapies for diabetes encompass drugs like biguanides, sulfonylureas, and insulin-based medications. However, dietary modifications and the adoption of nutraceuticals have gained traction, driven partly by the undesirable side effects associated with conventional medications. Nutraceuticals, including vitamins, polyphenols, and trace minerals like zinc (Zn),[8-9]have garnered attention for their potential in diabetes management. Zinc, in particular, exhibits notable insulin mimetic properties and has been the focus of research for developing anti-diabetic agents.

The association between zinc and diabetes traces back to its identification as a component

of insulin crystals, influencing insulin functionality. Zinc is co-secreted with insulin from pancreatic β-cells, aiding in insulin storage and secretion.[10]Intracellular zinc homeostasis in β-cells is tightly regulated by various proteins, notably Zn transporter 8 (ZnT8), encoded by the SLC30A8 gene. Studies highlight the importance of ZnT8 in insulin secretion and glucose homeostasis, with genetic variations in SLC30A8 linked to diabetes risk.[11]

Experimental models, including ZnT8-deficient mice, further elucidate the role of zinc in glucose metabolism and insulin secretion. Mechanistically, zinc exerts anti-diabetic effects primarily through insulin mimetic actions, stimulating glucose uptake and metabolism in adipocytes and skeletal muscle cells. Zinc also modulates insulin signaling pathways, enhancing glucose transport and glycemic control.[12-16]

Given zinc's promising metabolic effects, researchers have explored its complexation with various ligands to develop potent anti-diabetic agents.[17] Complexation is believed to enhance bioavailability and therapeutic efficacy. However, despite significant advancements, the field is marred by notable scientific gaps. This review critically examines the existing literature on anti-diabetic zinc complexes, aiming to identify key gaps and outline future research directions. Additionally, it explores the influence of coordination mode and lipophilic properties of these complexes on their bioavailability and anti-diabetic efficacy. [18-20]

Methodology:

A comprehensive literature search was conducted across various scientific databases, including "PubMed," "Google Scholar," "Scopus," and "ScienceDirect," aiming to identify peer-reviewed publications in English pertaining to the anti-diabetic effects of zinc(II) complexes. The search period spanned from September 2018 to May 2019.[22-24] Key search terms encompassed topics such as "minerals and diabetes," "zinc and diabetes," "zinc and insulin," "metal complexes and diabetes," "zinc complexes and diabetes," and "insulin mimetic metals," among others. Only studies focusing on anti-diabetic complexes containing zinc(II) as the sole metallic mineral were considered to isolate the effects specifically attributable to zinc(II).[25]

Identified anti-diabetic zinc(II) complexes meeting the inclusion criteria were further categorized based on the class or type of precursor ligands, including synthetic ligands, naturally occurring ligands, ligands used as supplements or medications, and plant-derived polyphenol ligands. Comprehensive analysis was conducted on the experimental data of these complexes, alongside basic information such as zinc(II)-ligand coordination modes (CM) and lipophilicity (log P).[26]

To assess the influence of zinc(II) on the properties of its ligands or the efficacy of synthesized complexes, the antidiabetic potency ratio (ψ) was computed relative to various controls, including precursor ligands, zinc sulfate, zinc chloride, zinc gluconate, zinc acetate, and standard anti-diabetic drugs. This ratio served to quantify the extent of anti-diabetic potency conferred by the zinc(II) complexes compared to the control substances. [27]

3.1. Zn(II) complexes with synthetic organic compounds as precursor ligands

Chemical names, synonyms, and chemical formulas of the complexes' ligands were verified using the "pubchem.ncbi.nlm.nih.gov" database. This verification process was conducted between April 15 and June 21, 2018, ensuring accuracy and consistency in the identification of ligands.[28-30]

A total of 1286 relevant publications were identified through the database search, focusing on the anti-diabetic effects of zinc(II) complexes.[31] Following screening, 54 studies were selected, of which 3 were excluded as they were reviews of previously identified studies, and 1 was omitted due to being a duplicate Chinese version.[32] Subsequently, 50 studies were reviewed, identifying 147 zinc(II) complexes with reported anti-diabetic properties. Among these, 120 complexes were included in this review, while 27 were excluded due to containing other minerals alongside zinc,

potentially impacting their anti-diabetic properties.[33]

The identified anti-diabetic zinc(II) complexes were further categorized based on the type of precursor ligands used. Notably, 86 complexes (72%) were synthesized using synthetic organic compounds not utilized as medications.[34] These complexes exhibited insulin mimetic properties, evidenced by their ability to inhibit epinephrine-induced lipolysis and enhance glucose uptake in isolated rat adipocytes. Moreover, several complexes demonstrated promising in vivo effects, reducing hyperglycemia and improving glycemic control in diabetic animal models through various mechanisms.[35]

For instance, Yoshikawa et al. (2007) [36] investigated the anti-lipolytic and glucose uptake activities of zinc(II) complexes of thiocarbamic acid derivatives with zinc(S4) coordination mode. Among these complexes, Bis(pyrrolidine-N-dithiocarbamate)zinc(II) showed potent activity on adipocytes and significantly reduced blood glucose and glycated hemoglobin levels in diabetic mice following oral treatment. Similarly, bis(2-mercaptotropolonato)zinc(II) exhibited excellent anti-lipolytic and glucose uptake effects in adipocytes, along with significant blood glucose lowering activity in diabetic mice.[37-38]

Furthermore, studies suggest a preference for zinc(S2O2) coordination mode complexes over other coordination modes such as zinc(O4). Complexes of pyrones, pyridinones, thiazoles derivatives, and pyridine-N-oxide with thiol or thione groups showed remarkable in vivo glycemic control effects and adipocyte activities compared to their counterparts with zinc(O4) coordination mode.These findings underscore the potential of synthetic organic compound-derived zinc(II) complexes as effective anti-diabetic agents, highlighting the importance of coordination mode in determining their pharmacological activity.[39]

Chaves et al. (2009) [40] attributed the robust cellular and in vivo insulin mimetic activities of zinc(II) complexes with thiol- or mercapto-containing coordination modes (CM) to their hydrophobic or lipophilic properties, as indicated by positive partition coefficients (log P). Log P values denote the dispersion ratio between two immiscible solvents, typically non-polar and aqueous solvents. Higher log P values signify greater hydrophobicity, a desirable trait in zinc(II) complexes as it enhances their permeability through lipid bilayer membranes, facilitating pharmacological effects.[41] For instance, Chaves et al. (2009) demonstrated that a zinc(II) complex of maltol with zinc(O4) CM exhibited a lower log P (-0.04) compared to its thiol-containing analogue, bis(thiomaltol)zinc(II) complex (log P = 0.54). This difference in lipophilicity likely contributed to the stronger anti-lipolytic activity of the latter (IC50 = 3.3 μM; Ψ = 156ZS) compared to the former (IC50 = 360 μM; Ψ =1.4ZS) in isolated rat adipocytes.[42-43]

Several studies have shown a linear correlation between the lipophilicity or log P values of zinc(II) complexes and their anti-lipolytic and glucose uptake activities. Regardless of the coordination mode (Zn(O4), Zn(S4), Zn(N2O2), or Zn(S2O2)), insulin mimetic activities of the complexes increased with increasing log P values. For instance, zinc(II) complexes with Zn(S2O2) CM exhibited better glucose uptake activities compared to those with Zn(N2O2) or Zn(O4) CM.[44-45]

To understand the mechanism behind the glycemic control effects of zinc(S2O2) CM complexes, Basuki et al. [46] studied the effect of bis(1-oxy-2-pyridine-thiolato)zinc(II) complex on insulin signaling. The complex induced Akt/PKB phosphorylation/activation, suggesting an indirect Akt phosphorylation mediated by PI3K and its upstream cascades.[47]This activation led to increased glucose uptake and glycogen synthesis in adipocytes. The complexation increased intracellular zinc(II) uptake due to the higher lipophilicity of zinc(S2O2) complexes, promoting cellular membrane permeability and enhancing pharmacological effects.[48]

The potent anti-diabetic activity of bis(1-oxy-2-pyridine-thiolato)zinc(II) complex, superior to pioglitazone and comparable to insulin, underscores the therapeutic potential of thiol- and mercapto-containing zinc(II) complexes, particularly those with zinc(S2O2) CM. [49]

Complexation increased cellular zinc(II) uptake and accessibility to cellular targets without any synergistic effect with the ligand, indicating potential pharmacological effects through different modes depending on the ligand type and zinc(II)-ligand CM.[50] A "tri-facet" pharmacological mode of action encompassing carrier, synergistic, and multi-action modes is proposed, intertwining to potentiate the therapeutic effects of zinc(II)-ligand complexes.[51] The "carrier" mode involves zinc(II) being bound to a carrier-ligand that isn't pharmacologically active, thereby enhancing bioavailability through improved lipophilicity, absorption, and permeability across cellular membranes.[52]An example of this is seen in bis(1-oxy-2-pyridine-thiolato) zinc(II), where the complex's effectiveness mainly depends on increased cellular uptake of zinc(II) facilitated by the carrier-ligand.[53]

On the other hand, the "synergistic" mode occurs when zinc(II) forms a complex with a pharmacologically active ligand. While this complex may not directly enhance bioavailability, it works synergistically with zinc(II) to boost insulin sensitivity or signaling.[54-56]

Lastly, in the "multi-action" mode, zinc(II) is paired with a pharmacologically active ligand, which, although not affecting bioavailability, exhibits additional diabetes-related pharmacological properties beyond zinc(II), resulting in a multi-faceted anti-diabetic effect.[57] To grasp the potential mode of action of a zinc(II) complex, it's essential to compare its bioavailability or lipophilicity and cellular zinc(II) uptake activity with those of zinc(II) salt and the precursor ligand. Unfortunately, many studies investigating the anti-diabetic properties of zinc(II) complexes lack this crucial information, limiting our comprehensive understanding of their pharmacology.[58-59]

Several zinc(II) complexes incorporating a nitrogen atom as part of their coordination mode have been synthesized with the aim of producing pharmacologically active complexes with improved lipophilicity. The presence of a nitrogen atom, which is less electronegative than oxygen, is believed to potentially enhance the lipophilic properties of these complexes compared to those with zinc(O4) coordination mode.[60-62] Among these, zinc(II) complexes of picolinic acid and its derivatives with zinc(N_2O_2) coordination mode have been studied extensively. Picolinic acid is known to play a role in zinc absorption physiology, enhancing intestinal zinc absorption and translocation across lipid bilayers.[63-65]

Studies have consistently shown that zinc(II) complexes of picolinic acid and its methyl derivatives exhibit lipophilic properties, potentially influencing cellular or intestinal zinc(II) uptake.[66] These complexes demonstrated promising anti-lipolytic and insulin signaling modulatory activities in rat adipocytes, as well as anti-diabetic effects in diabetic animal models, compared to zinc sulfate. This suggests that these complexes act primarily through the "carrier" mode of action, with the ligands alone showing no anti-lipolytic insulin mimetic activity.[67-68]

For other complexes with a nitrogen atom in their coordination mode, there is no consistent trend regarding the relationship between lipophilicity and activity compared to complexes with zinc(O4) coordination mode.[69-70]The type of ligand appears to play a more significant role. Some complexes, such as meso-tetrakis[(4-sulfonatophenyl)porphyrinato] zinc(II), exhibited remarkable anti-diabetic activities in diabetic animal models, while others showed varying degrees of lipolysis inhibition and glucose-lowering effects.while some zinc(II) complexes with nitrogen-containing coordination modes demonstrated promising anti-diabetic properties, others exhibited less potent activities.[71]The influence of the ligand and coordination mode on the pharmacological effects of these complexes underscores the complexity of their mechanisms of action.[72]

Therefore, the results support the hypothesis that some zinc(II) complexes with a nitrogen atom as part of their coordination mode may exhibit promising anti-diabetic activities, possibly due to improved lipophilicity and permeability compared to those with zinc(O4) coordination mode. However, this hypothesis remains controversial except for zinc(II)

complexes of picolinic acid and its methyl derivatives, which have shown consistent activity.[73-74] Nonetheless, it appears that some zinc(II) complexes with zinc(N2O2) coordination mode may serve as potent α-glucosidase inhibitors and warrant further investigation.zinc(II) complexes with sulfur-containing coordination modes emerge as the most potent among synthetic organic ligands.[75] Many of these complexes, particularly those containing thiol- or mercapto-containing tropolone, pyrone, and pyridine derivatives, demonstrated superior in vitro anti-lipolytic and glucose uptake activities compared to zinc sulfate.[76] Notably, bis(1-oxy-2-pyridine-thiolato) zinc(II) showed remarkable insulin signaling activation and anti-diabetic activity in animal models without exacerbating hepatotoxicity, suggesting its potential for further investigation in vivo and clinically.[77]

It is recommended to explore more effective strategies, such as employing sulfur-containing ligands or coordination, to enhance the lipophilic properties of zinc(II) complexes and thereby improve their bioavailability and pharmacological efficacy. However, the lack of toxicity data for many of these complexes raises safety concerns for their clinical relevance. Critical evaluation of their toxicity is essential before considering them for clinical applications.[78]

In vivo studies demonstrated that oral and/or intraperitoneal treatments with the complex reduced blood glucose (BG) and glycated hemoglobin (HbA1c) levels, hyperinsulinemia, and improved glucose tolerance (GT) in diabetic rats, with varying magnitudes depending on the dose, duration, and route of administration[79] Moreover, a single intraperitoneal treatment (10 mg Zn/kg) significantly increased Akt phosphorylation in adipose (≃177%) and liver (≃40%) tissues in ICR mice after 40 minutes, with the modulatory effect on Akt phosphorylation in adipose tissue comparable to insulin (Ψ = 1.1IN) [80]. Toxicological studies indicated a safe and high LD50 in KK-Ay mice, suggesting the anti-diabetic pharmacological potency and safety of this complex [81]. For complexes featuring a nitrogen atom in their central moiety, there's no consistent trend in lipophilicity-activity relationship compared to Zn(O4) complexes. Ligand type plays a significant role. While some Zn(II) complexes with Zn(N4) central moieties show anti-diabetic effects, their lipolytic activity may not be as potent as Zn(O4) complexes. Zn(II) complexes with Zn(N2O2) central moieties, however, exhibit potent α-glucosidase inhibitory activities. This suggests Zn(II) as the primary influencing component. Further research is needed to understand the potential of Zn(II) complexes with nitrogen-containing central moieties in diabetes treatment. Generally, Zn(II) complexes with sulfur-containing central moieties appear to be the most potent among synthetic organic ligands.[82] Their in vitro anti-lipolytic and glucose uptake activities, especially those with thiol or mercapto-containing tropolone, pyrone, and pyridine derivatives, outperform ZnSO4. Notably, Bis(1-oxy-2-pyridine-thiolato)zinc(II) demonstrates significant Akt and GKS3β phosphorylation and GLUT-4 translocation, comparable to or greater than insulin. Its in vivo anti-diabetic activity surpasses pioglitazone without causing hepatotoxicity, suggesting potential for further investigation in vivo and clinically. To enhance the lipophilic properties and pharmacological effectiveness of Zn(II) complexes, employing sulfur-containing ligands or coordination is recommended. However, despite promising activities, many Zn(II) complexes lack toxicity profile data, raising concerns for clinical relevance. Critical evaluation of toxicity is essential.[83]

3.2. Zn(II) complexes with naturally occurring organic compounds as precursor ligands

Seven percent (7%) of the Zn(II) complexes discussed in this review were synthesized from naturally occurring organic ligands, with maltol, a natural flavor enhancer, being the most studied. Studies have shown that complexing maltol with Zn(II) [CM: Zn(O4)] results in notable in vitro and in vivo insulin mimetic and glycemic control properties.[84] In adipocytes, bis(maltolato)zinc(II) complex exhibited insulin mimetic activities by inhibiting lipolysis and increasing glucose uptake. The antilipolytic effect of the complex was reversed by inhibitors of insulin receptor tyrosine kinase (IRTK), PI3K, GLUT-4, and PDE activation, suggesting

direct modulatory effects on these activities. In vivo treatments of the complex reduced blood glucose (BG) and HbA1c levels, hyperinsulinemia, and improved glucose tolerance (GT) in diabetic rats. Single intraperitoneal (i.p.) treatment markedly increased Akt phosphorylation in adipose and liver tissues. The modulatory effect of the Zn(II)-maltol complex on Akt phosphorylation in adipose tissue was comparable to insulin. In vivo toxicological studies demonstrated a safe and high LD50 in KK-Ay mice, indicating the anti-diabetic pharmacological potency and safety of this complex.[85]

Zn(II) complexes of natural compounds like allixin from garlic bulbs exhibit anti-diabetic effects, including anti-lipolytic and glucose uptake activities. Similarly, complexes with L-lactic acid, betaine, D-(-)-quinic acid, tropolone, and hinokitiol show promising activities in diabetic models and adipocytes. Among these, the hinokitiol complex stands out for its potent effects, surpassing pioglitazone in improving glucose tolerance. These complexes likely act through a "carrier mode" mechanism by enhancing Zn(II) uptake. Further research is needed to fully understand their mode of action.[86]

3.3. Zn(II) complexes with precursor ligands used as supplements or medications

To enhance anti-diabetic efficacy, drugs like tolbutamide, chlorpropamide, metformin, pioglitazone hydrochloride, and glibenclamide have been complexed with Zn(II). These complexes lower blood glucose levels comparably to or slightly better than their original drugs.[87] Zn(II) complexes of tolbutamide and chlorpropamide show acute glucose-lowering effects, but they belong to less prescribed "first generation" sulfonylureas due to side effects. However, the Zn(II) complex of glibenclamide, a "second generation" sulfonylurea, demonstrates more potent hypoglycemic effects, suggesting a "multi-action" mode of action, possibly involving insulin mimetic activity. The Zn(II) complex of pioglitazone also exhibits superior hypoglycemic effects compared to its precursor drug.[88]

3.4. Zn(II) complexes with plant polyphenols as ligands

Despite the well-documented anti-oxidative and anti-diabetic properties of plant polyphenols, only a small fraction of the Zn(II) complexes reported in this review are comprised of plant-derived polyphenols as ligands, highlighting a significant gap in research for insulin mimetic therapeutic Zn(II) complexes with enhanced pharmacological properties.[89] However, the few complexes studied have shown promising anti-diabetic effects in diabetic rats, comparable to known anti-diabetic drugs. [90] For example, bis(silibinin)zinc(II) and bis(morin)zinc(II) complexes demonstrated significant blood glucose and HbA1c lowering effects, insulinotropic effects, and improved glycogen content and glucose tolerance in diabetic rat models.[91] Additionally, these complexes exhibited appreciable anti-oxidative properties, potentially contributing to improved pancreatic histology. Similarly, Zn(II) complexes of curcumin, 3-hydroxyflavone, and flavonol showed reductions in hyperglycemia and HbA1c levels, increased insulin and C-peptide concentrations, and improved antioxidant status and pancreatic histology in diabetic rats. Despite reports suggesting that dietary polyphenols may not efficiently transport zinc across intestinal cell monolayers, complexation with Zn(II) appears to enhance the bioavailability of these polyphenols. Considering the broad anti-diabetic pharmacological properties of plant-derived polyphenols, Zn(II) complexes of these compounds may exert anti-diabetic effects through various mechanisms, suggesting a combination of synergistic and multi-action modes of action.[92] most studied Zn(II)-complexes of plant-derived polyphenols reversed metabolic markers of tissue damage in diabetic animals, suggesting they may not cause tissue toxicity. While studies have predominantly focused on flavone and flavonol ligands, exploring other classes of pharmacologically active plant-derived polyphenols, such as phenolic acids, may offer promising avenues for the development of multi-acting anti-diabetic and anti-oxidative Zn(II) complexes with broader pharmacological activities and minimal safety concerns.[93]

Conclusion:

In conclusion, the pursuit of effective anti-diabetic therapies with improved properties and minimal side effects has led to significant interest in Zn(II) complexes. These complexes have shown promising insulin mimetic and glycemic control effects, particularly those with more lipophilic properties, such as those containing sulfur atoms in the coordination with Zn(II) and certain anti-diabetic drugs. However, despite their potential, the majority of synthesized Zn(II) complexes (about 72%) have been with synthetic organic ligands lacking relevant pharmacological history, raising safety concerns due to insufficient toxicity data. Only a small fraction (about 7%) of studies have explored Zn(II) complexes with natural ligands, such as maltol, which has shown anti-oxidative effects in diabetic neuropathy. Furthermore, the activity of these complexes appears to be mainly influenced by their ability to transport Zn(II) to cellular or tissue targets, suggesting a "carrier" mode of action. Interestingly, Zn(II) complexes of certain supplements and anti-diabetic drugs, such as ascorbic acid, L-threonine, and L-carnitine, have shown promising activities but remain understudied. Future clinical investigations are needed to fully explore the potential of these Zn(II) complexes as viable anti-diabetic therapies.

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