Review

A comprehensive review on zinc(II) complexes as anti-diabetic agents: The advances, scientific gaps and prospects

Chika Ifeanyi Chukwuma[a],*, Samson S. Mashele[a], Kenneth C. Eze[b], Godfrey R. Matowane[a], Shahidul Md. Islam[c], Susanna L. Bonnet[d], Anwar E.M. Noreljaleel[d], Limpho M. Ramorobi[a]

[a] Department of Health Sciences, Faculty of Health and Environmental Sciences, Central University of Technology, Bloemfontein, South Africa
[b] Faculty of Medicine, Nnamdi Azikiwe University, Awka (Nnewi Campus), Anambra State, Nigeria
[c] Depart of Biochemistry, School of Life Sciences, University of KwaZulu-Natal, Westville, Durban South Africa
[d] Department of Chemistry, Faculty of Natural and Agricultural Sciences, University of the Free State, Bloemfontein, South Africa

ABSTRACT

Zinc has gained notable attention in the development of potent anti-diabetic agents, due to its role in insulin storage and secretion, as well as its reported insulin mimetic properties. Consequently, zinc(II) has been complexed with numerous organic ligands as an adjuvant to develop anti-diabetic agents with improved and/or broader scope of pharmacological properties. This review focuses on the research advances thus far to identify the major scientific gaps and prospects. Peer-reviewed published data on the anti-diabetic effects of zinc(II) complexes were sourced from different scientific search engines, including, but not limited to "PubMed", "Google Scholar", "Scopus" and ScienceDirect to identify potent anti-diabetic zinc(II) complexes. The complexes were subcategorized according to their precursor ligands. A critical analysis of the outcomes from published studies shows promising leads, with Zn(II) complexes having a "tri-facet" mode of exerting pharmacological effects. However, the promising leads have been flawed by some major scientific gaps. While zinc(II) complexes of synthetic ligands with little or no anti-diabetic pharmacological history remain the most studied (about 72 %), their toxicity profile was not reported, which raises safety concerns for clinical relevance. The zinc(II) complexes of plant polyphenols; natural ligands, such as maltol and hinokitiol; and supplements, such as ascorbic acid (a natural antioxidant), L-threonine and L-carnitine, showed promising insulin mimetic and glycemic control properties but remain understudied and lack clinical validation, in spite of their minimal safety concerns and health benefits. A paradigm shift toward probing (including clinical studies) supplements, plant polyphenol and natural ligands as anti-diabetic zinc(II) complex is, therefore, recommended. Also, promising anti-diabetic Zn(II) complexes of synthetic ligands should undergo critical toxicity evaluation to address possible safety concerns.

1. Introduction

Diabetes mellitus is a metabolic disease with different etiological facets. It is characterized by persistent hyperglycemia, which is linked to deranged carbohydrate, fat and protein metabolism due to inadequate insulin secretion (type 1 diabetes) and/or action (type 2 diabetes) [1]. Type 2 diabetes (T2D) is the most prevalent type of diabetes and a major threat to global public health and the socio-economic status of people in most parts of the world [2]. It is linked to several metabolic defects and organ malfunctions or damages, with loss of insulin action and β-cell function being the most prominent defects, which adversely affect blood glucose levels [3,4].

Commercial drugs such as biguanides, sulfonylureas, thiazolidine-dione, α-glucosidase and dipeptidyl-peptidase IV inhibitors and insulin- and incretin-based therapeutic agents are the available drugs for the treatment or management of diabetes [5]. However, dietary adjust-ments and the use of nutraceuticals have become popular therapeutic approaches for diabetes, particularly in functional medicine [6,7]; perhaps, due to the unpleasant side effects associated with most commercial anti-diabetic drugs [8]. Nutraceuticals such as vitamins, lipids,

amino acids, natural polyphenols, carbohydrates, probiotics and mineral elements have been explored, considerably, in recent years. Vitamins and trace minerals, such as zinc, chromium, copper, magnesium, iron, manganese and selenium are known for their diabetes-associated health benefits [9,10]. They function as essential coenzymes and co-factors for optimum glucose, lipid and protein metabolism [9,10]. Thus, their deficiencies have been associated with diabetes and related diseases, while pharmacological studies have given credence to their modulatory effects on glucose and lipid metabolism in diabetes, obesity and related metabolic disorders [9]. Zn(II), particularly, has been reported to show relatively high insulin mimetic properties with less toxicity compared to other mineral elements [11]. Thus, it has been a potential target for the development of therapeutic agents for diabetes. In fact, many clinical studies reviewed by Jayawardena et al. [12] and Chabosseau and Rutter [13] have consistently shown the association between physiological Zn(II) status or Zn(II) treatment and diabetes.

The possible association between Zn(II) and diabetes has long been postulated. This was set in motion by the discovery of Zn(II) as a component of crystallized insulin, which also influences insulin functionality [14,15]. Zn(II) is secreted by the pancreatic β-cells *via* exocytosis during insulin secretion [16]. This is because matured insulin is stored as a crystalline hexamer of Zn(II) in the insulin secretory granules of the β-cells. During insulin secretion in response to elevated blood glucose, Zn(II) is co-secreted with insulin *via* exocytosis into extracellular cellular spaces [16].

Several regulatory proteins such as the Zn(II) importers and Zn(II) transporters largely regulate Zn(II) homeostasis in the cytosol of pancreatic β-cells. Studies on these cellular transporters have revealed the involvement of Zn(II) in insulin secretion, glycemic control and diabetic disorders [13]. Zn(II) transporter 8 (ZnT8) has been identified as the most prominent Zn(II) transporter influencing insulin secretion and functionality. It is encoded by the SLC30A8 gene and transports cytosolic Zn(II) into insulin secretory granules for hexamerization and storage of insulin [13,17]. The genome-wide association studies have identified the SLC30A8 gene as a factor linked to the risk of diabetes, since possession of a variant allele (rs13266634) of this gene may increase the risk of diabetes by 17 % [13,18,19].

Further studies have shown that mice models with deleted ZnT8 gene displayed impaired glucose tolerance and insulin secretion and had lower peripheral insulin concentration [20,21]. In addition, the insulin secretory granules of β-cells with depleted ZnT8 showed less dense insulin cores and abnormal morphology [20–23]. In mice, increased expression of ZnT8 improved glucose tolerance and insulin sensitivity and reduced glucagon secretion by pancreatic α-cells [13]. According to the authors, cellular Zn(II) may potentiate the above-mentioned effects through an autocrine or paracrine cell signaling process [13,24].

Several mechanisms have been put forward to explain the anti-diabetic effects of Zn(II) (Fig. 1). Although Zn(II) has been shown to inhibit intestinal α-glucosidase activity [25], its insulin mimetic action has been reported to be the most prominent anti-diabetic mode of action. Zn(II) stimulates both lipogenesis and glucose transport in adipocytes [26,27]. Using HEK-293 cells, Ilouz et al. [28] demonstrated that the insulin mimetic action of Zn(II) could be mediated through the direct inhibition of endogenous glycogen synthase kinase-3β, which could lead to increased glycogen synthesis. Additionally, Zn(II) stimulates the cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase (PDE) activity [29,30], an enzyme that inactivates cAMP, and thus, downregulates cAMP-mediated lipolytic and glycogenolytic signaling [11]. Moreover, the activity of glycolytic enzymes, phosphofructokinase and pyruvate kinase, has been shown to be increased by Zn(II) treatment, *in vitro* [31].

In human and mouse skeletal muscle cells, Zn(II) modulated insulin signaling, which resulted in enhanced glucose oxidation and glycemic control [32]. Other studies suggest that the modulatory effect of Zn(II) on insulin signaling may be linked to phosphorylation of adenosine monophosphate-activated protein kinase and insulin receptor sub-unit; activation of protein kinase B (Akt) signaling pathway; and increase of glucose transporter type 4 (GLUT-4) expression and translocation, which will, collectively, promote glucose uptake in skeletal muscle cells and adipocytes [26,30,33–37]. In fact, Zn(II)-deficient rats adipocytes showed reduced binding of insulin to insulin receptors [38], while Zn(II) treatment dose-dependently stimulated insulin specific binding to different cell (rat adipocytes and hepatocytes and human lymphocytes) and tissue (human placenta) membranes with well-characterized insulin receptors [39]. Also, Zn(II) may have an indirect effect on Akt activation that is independent of insulin action; perhaps, through induction of H_2O_2 production from epididymal cells, which will lead to the activation of focal adhesion kinase pathway, and ultimately, the phosphoinositide 3-kinase (PI3k)/Akt signaling pathway [34].

Considering the above-mentioned modulatory effects of Zn(II) on glucose and lipid metabolism, it is not surprising why many ligands have been complexed with Zn(II) with the aim of developing potent anti-diabetic agents. It is believed that Zn(II) complexation with ligand improves bioavailability, while affording beneficial effects on glucose metabolism [40,41]. The outcome of these advances supports the anti-diabetic potential of Zn(II) complexes. Unfortunately, the research progress has been flawed with some key scientific gaps, which has not been reported in the previous incomprehensive reviews on anti-diabetic and insulin mimetic Zn(II) complexes [40,42,43]. Therefore, this review comprehensively and critically analysed the anti-diabetic studies on Zn(II) complexes, with the aim of identifying the major scientific gaps and highlighting the potential future prospects in anti-diabetic drug discovery. Additionally, the review attempts to explain the influence of the coordination mode (C_M) between Zn(II) and the ligands, as well as the lipophilic property of the complexes on the bioavailability and anti-diabetic activities of the complexes.

2. Methodology

A literature search was done on different scientific search engines including, but not limited to "PubMed", "Google Scholar", "Scopus" and ScienceDirect. The aim was to identify peer-reviewed published data on the anti-diabetic effects of Zn(II) complexes that were published in English as shown in the study selection process (Fig. 2). The search was done from September 2018 until May 2019. The search terms used included the following: "minerals and diabetes"; "zinc and diabetes"; "zinc and insulin" "metal complexes and diabetes"; "zinc complexes and diabetes"; "insulin mimetic metals"; "insulin mimetic metal complexes"; "insulin mimetic zinc complexes"; "zinc and zinc complexes and lipolysis"; "metal and metal complexes and lipolysis"; "zinc and zinc complexes and glucose uptake"; "metal and metal complexes and glucose uptake". From the results of the search, only anti-diabetic complexes containing Zn(II) as the sole metallic mineral were considered, to be certain that the observed effects of the complexes are solely influenced by Zn(II), and not, other metallic minerals. The identified anti-diabetic Zn(II) complexes, based on the above-set criteria, were sub-categorized according to the class or type of precursor ligands: synthetic ligands, naturally occurring ligands, ligands used as supplements and/or medications and plant-derived polyphenol ligands. The anti-diabetic experimental data along with other basic information about the complexes, such as the Zn(II)-ligand coordination modes (C_M) and lipophilicity (log P), were critically analysed. The chemical names, synonyms, and chemical formula of the complexes' ligands were confirmed on the "pubchem.ncbi.nlm.nih.gov" database (accessed between 15 April to 21 June 2018).

To ascertain the extent to which Zn(II) influenced the properties of its ligands or the efficacy of the synthesized Zn(II) complexes, the anti-diabetic potency ratio (ψ) of the complexes relative to the different controls (precursor ligands, zinc sulfate, zinc chloride, zinc gluconate, zinc acetate and standard anti-diabetic drugs) was computed as follows:
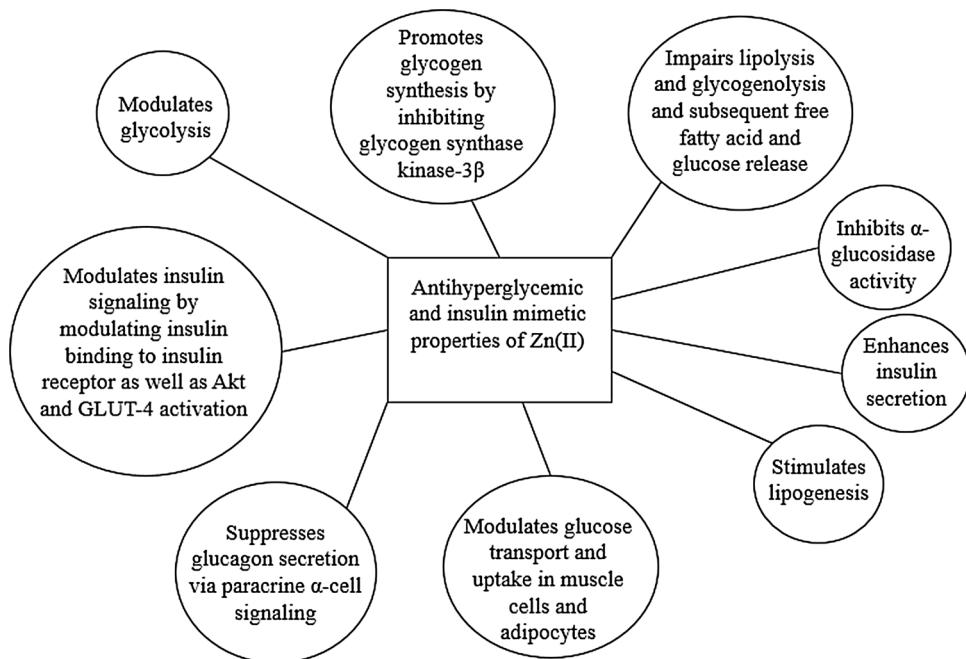
Fig. 1. Anti-diabetic and insulin mimetic properties of Zn(II) and possible modes of action.
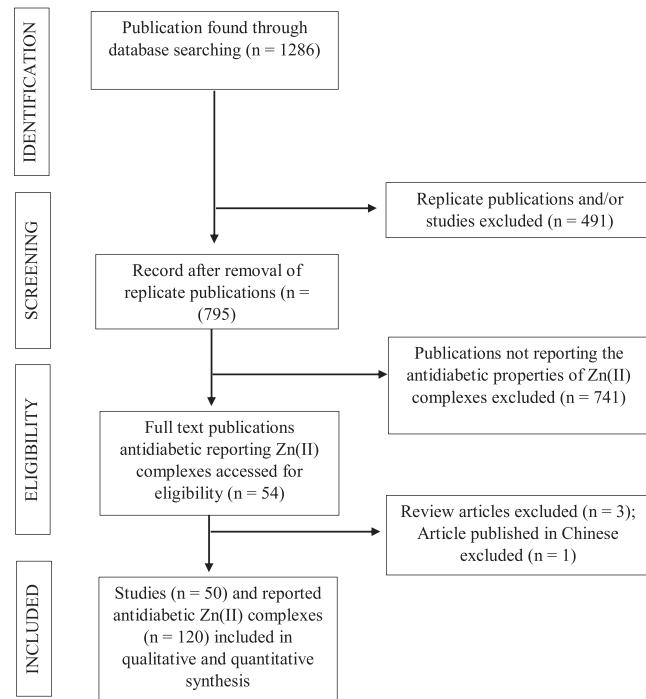

Fig. 2. Flow diagram showing the study selection process.

$$\psi = \frac{Activity\ of\ complex\ (\%)}{Activity\ of\ contol\ (\%)}\ or\ \left(\frac{IC_{50}\ of\ complex}{IC_{50}\ of\ control}\right)^{-1}\ or$$
$$\left(\frac{EC_{50}\ of\ complex}{EC_{50}\ of\ control}\right)^{-1}$$

Where, IC_{50} is the inhibition concentration required to cause 50 % inhibition of lipolysis in adipocytes or the activities of carbohydrate digesting enzymes and EC_{50} is the effective concentration required to cause 50 % glucose uptake in adipocytes.

3. Result and discussion

A total of 1286 publications relating to the review scope were found on the database of the search engines based on the search term used (Fig. 2). Fifty-four studies and/or publications matched anti-diabetic studies on Zn(II) complexes. Of these, 3 were excluded as reviews of some of the already identified studies, while 1 was excluded as a Chinese version of another. The remaining 50 studies were selected and reviewed. From these studies, 147 Zn(II) complexes with reported anti-diabetic properties were identified. From these, only 120 were selected and reported in this review, while 27 were excluded as anti-diabetic Zn (II) complexes containing other minerals, such as copper and selenium, which may influence the complexes' anti-diabetic properties. The Zn(II) complexes with potent anti-diabetic effects are discussed below and sub-categorized based on the type of precursor ligands.

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

Eighty-six (72 %) of the reported anti-diabetic Zn(II) complexes were synthesized using synthetic organic compound precursors that are not used as medications (Fig. 3 and Table 1). Most of these complexes demonstrated insulin mimetic properties by inhibiting epinephrine-induced lipolysis and enhancing glucose uptake in isolated rat adipocytes (Table 1). In vivo, some of the potent complexes reduced hyperglycemia and improved glycemic control in diabetic animal models by different mechanisms.

Following previous propositions on the use of thiocarbamate derivatives in the treatment of diseases, including diabetic neuropathy, Yoshikawa et al. (2007) [44] investigated and reported the promising anti-lipolytic (IC_{50} = 5.1–21.3 μM; Ψ = 38$_{ZS}$ – 158.8$_{ZS}$) and glucose uptake (EC_{50} = 6.4–10.3 μM) activities of several Zn(II) complexes of thiocarbamic acid derivatives with Zn(S_4) C_M in isolated rat adipocytes. Bis(pyrrolidine-N-dithiocarbamate)zinc(II), which had the most potent activity on adipocytes, further reduced blood glucose (BG) (≃27 %) and glycated hemoglobin (HbA1c) (≃29 %) levels and hyperinsulinemia (≃59 %,) and improved glucose tolerance (GT) in T2D KK-A^y mice, following a 25 d oral (10–15 mg Zn/kg) treatment [44]. However, some other studies suggest that Zn-ligand complexation with Zn(S_2O_2) C_M
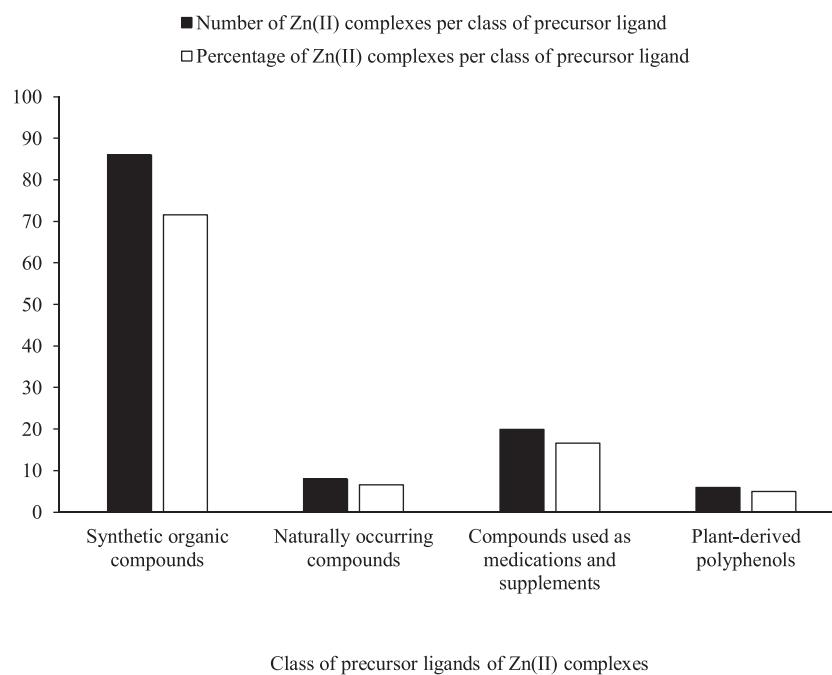
Fig. 3. Number and percentage of reported anti-diabetic Zn(II) complexes according to the class of precursor ligands.

may afford better activities. This is because among some Zn(II) complexes of tropolone derivatives, the bis(2-mercaptotropolonato)zinc(II) and bis(4-isopropyl-2-mercapto-tropolonato)zinc(II) complexes with Zn (S_2O_2) C_M showed better insulin mimetic properties than the others having Zn(S_4) C_M [45]. Particularly, bis(2-mercaptotropolonato)zinc(II) showed excellent anti-lipolytic (IC_50 = 12 μM; Ψ = 36.7_ZS) and glucose uptake (EC_50 = 0.7 μM; Ψ = 251_ZS) effects in adipocytes as well as BG lowering (≃50 %) activity in T2D KK-A^y mice, following a 25 d oral treatment (10 mg Zn/kg) (45) (Table 1).

Several other studies have also supported the preference of Zn(S_2O_2) C_M complexes as potential anti-diabetic agents compared to those with other coordination modes, including Zn(O_4) C_M. Zn(II) complexes of pyrones (including maltol and allixin), pyridinones and thiazoles derivatives with the thiol or thione group [C_M: (S_2O_2)], as well as, Zn(II) complex of pyridine-N-oxide with mercapto group [C_M: Zn(S_2O_2)] showed remarkable *In vivo* glycemic control effect, adipocyte anti-lipolytic (IC_50 = 2–45 μM; Ψ = 33.6_ZS - 292.5_ZS) and glucose uptake (EC_50 = 79 μg/10^6 cells and 6.1 μM; Ψ = 56.1_ZS) activities compared to the glycemic control, anti-lipolytic (IC_50 = 0.166–1.9 mM; Ψ = 0.3_ZS – 3.9_ZS) and glucose uptake (EC_50 = 0.1–1 mM) activities of their non-thiol and non-mercapto counterparts with Zn(O_4) C_M [11,46–56] (Tables 1 and 2)

Chaves et al. (2009) [49] attributed the potent cellular and *In vivo* insulin mimetic activities of Zn(II) complexes with thiol- or mercapto-containing C_M to their hydrophobic or lipophilic properties as indicated by their positive partition coefficients (log P). The partition coefficient of complexes denotes their dispersion ratio between two immiscible solvents (unequal polarity), usually between non-polar and aqueous solvents. The higher the log P value of the complex, the more hydrophobic it is. Hydrophobicity is a desired characteristic of Zn(II) complexes because it increases their permeability through the lipid bilayer membrane of cells to exert pharmacological effects. Chaves et al. (2009) [49] showed that Zn(II) complex of maltol with Zn(O_4) C_M showed lower log P (-0.04) than its corresponding thiol-containing analogue [C_M: Zn(S_2O_2)], bis(thiomaltol)zinc(II) complex (log P = 0.54), which presumably, is responsible for the stronger anti-lipolytic activity of the latter (IC_50 = 3.3 μM; Ψ = 156_ZS) compared to that of the former (IC_50 = 360 μM; Ψ = 1.4_ZS) in isolated rat adipocytes (Tables 1 and 2). The stronger lipophilic property of the Zn(II) complexes with Zn(S_2O_2)

C_M compared to their counterparts with Zn(O_4) C_M has been attributed to the less electronegative and more polarizable nature of the sulfur than the oxygen atom, and thus shows a weaker H-bond interaction with water molecules than the oxygen atom [49].

Several studies have, also demonstrated the linear correlation between the lipophilicity or log P values of Zn(II) complexes and their anti-lipolytic (linear regression, R = 0.935 – 0.992) and glucose uptake activities (R = 0.869 – 0.935) [44,57,58]. Regardless of the C_M [Zn(O_4) or Zn(S_4) or Zn(N_2O_2) or Zn(S_2O_2)], the insulin mimetic activities of the complexes increased with increasing log P values. Moreover, when the insulin mimetic activities of bis(pyrrole-2-carboxylato)zinc(II) [C_M: Zn(N_2O_2)], bis(α-furonic acidato)zinc(II) [C_M: Zn(O_4)], bis(thiophene-2-carboxylato)zinc(II) [C_M: Zn(S_2O_2)] and bis(thiophene- 2-acetato)zinc(II) [(C_M: Zn(S_2O_2)] were compared, the complexes with the Zn(S_2O_2) C_M showed better glucose uptake activities (EC_50 = 0.15 and 0.12 mM; Ψ = 1.7_ZS and 2.1_ZS, respectively) than the complexes with Zn(N_2O_2) (EC_50 = 0.19 mM; Ψ = 1.3_ZS) and Zn(O_4) (EC_50 = 0.23 mM; Ψ = 1.1_ZS) C_M [58] (Tables 1 and 2). Interestingly, their glucose uptake activities (EC_50 = 0.23, 0.19, 0.15 and 0.12 mM; Ψ = 1.1_ZS, 1.3_ZS, 1.7_ZS and 2.1_ZS, respectively) were directly proportional to their log P values (-2.23, -1.76, -1.61 and -1.55), regardless of the C_M [58] (Tables 1 and 2).

To understand the mechanism behind the glycemic control effects of Zn(S_2O_2) C_M complexes, Basuki et al. [48] studied the effect of bis(1-oxy-2-pyridine-thiolato)zinc(II), a Zn(S_2O_2) C_M complex, on insulin signaling. The complex induced Akt/PKB phosphorylation/activation, which was suppressed by Wortmannin (a PI3K inhibitor), suggesting an indirect Akt phosphorylation, mediated by the activation or modulation of PI3K and its upstream cascades. Activated Akt contributes to phosphorylation/activation of GKS3β and concomitant translocation of GLUT-4 to adipocyte membrane [48], suggesting the ability of the complex to promote glycemic control by increasing glucose uptake and glycogen synthesis in adipocytes. Blood and Cellular Zn(II) levels were higher in the complex treated-cells than the ZnCl_2-treated cells, indicating that the complexation increased intracellular Zn(II) uptake [48,52]. This is because Zn(S_2O_2) coordination increases the lipophilicity of the complex (log P = 0.69), thus promoting cellular membrane permeability and Zn(II) uptake to influence better effects on cellular targets [48] (Fig. 4a).

Table 1
Anti-diabetic properties of Zn(II) complexes with synthetic organic compounds as ligands.

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
6-methylpicolinic acid	Bis(6-methylpicolinato)zinc(II)	$Zn(N_2O_2)$	0.075	45 d i.p. (4 mg Zn/kg) and oral (30 mg Zn/kg) treatment reduced BG (≈18 and 19 %, respectively) level and hyperinsulinemia (≈63 and 44 %, respectively) and improved GT in T2D GK rats		Fugong et al. [60]
			0.075	Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.31 mM); 14 d i.p. treatment (3 mg Zn/kg) reduced BG (≈53%) and HbA1c (≈7%,) levels and improved GT in T2D KK-A^y mice.	$L(5.1_{ZS})$	Yoshikawa et al. [61]
3-methylpicolinic acid	Bis(3-methylpicolinato)zinc(II)	$Zn(N_2O_2)$	0.07	Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.4 mM).	$L(4_{ZS})$	Yoshikawa et al. [61]
2-mercaptotropolone	Bis(2-mercaptotropolonato)zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis (IC50 = 12 μM) and increased glucose uptake (EC50 = 0.7 μM) in isolated rat adipocytes. 25 d oral treatment (10 mg Zn/kg) reduced BG (≈50%) and HbA1c (≈58%,) levels and hyperinsulinemia (≈40%) and improved GT in T2D KK-A^y mice	$L(36.7_{ZS}, 0.03_{IN}); U(251_{ZS}, 0.01_{IN})$	Murakami et al. [75]
2-mercapto-thiotropolone	Bis(2-mercapto-thiotropolonato)zinc(II)	$Zn(S_4)$		Inhibited lipolysis (IC50 = 145 μM) and increased glucose uptake (EC50 = 19 μM) in isolated rat adipocytes	$L(3_{ZS}, 0.002_{IN}); U(9.3_{ZS}, 0.0005_{IN})$	Murakami et al. [75]
4-isopropyl-2-mercapto-tropolone	Bis(4-isopropyl-2-mercapto-tropolonato)zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis (IC50 = 34 μM) and increased glucose uptake (EC50 = 5 μM) in isolated rat adipocytes	$L(12.9_{ZS}, 0.01_{IN}); U(35.2_{ZS}, 0.002_{IN})$	Murakami et al. [75]
4-isopropyl-2-mercapto-thiotropolone	Bis(4-isopropyl-2-mercapto-thiotropolonato)zinc (II)	$Zn(S_4)$		Inhibited lipolysis (IC50 = 225 μM) and increased glucose uptake (EC50 = 31 μM) in isolated rat adipocytes	$L(2_{ZS}, 0.001_{IN}); U(5.7_{ZS}, 0.0003_{IN})$	Murakami et al. [75]
3-hydroxy-2-methyl-4(H)-pyran-4-thione	Bis(3-hydroxy-2-methyl-4(H)-pyran-4-thiono)zinc (II)	$Zn(S_2O_2)$		Inhibited lipolysis (IC50 = 2 μM) and increased glucose uptake (EC50 = 79 μg/10^6 cells) in isolated rat adipocytes. 28 d oral treatment (2.5 - 10 mg Zn/kg) reduced BG (≈53%) and HbA1c (≈18%,) levels and hyperinsulinemia (≈59%); improved GT (≈45%); and increased islet number (≈80%) and size (≈37%) in T2D ob/ob mice	$L(292.5_{ZS})$	Nishiguchi et al. [54]
Ethylmaltol	Bis(ethylmaltolato)zinc(II)	$Zn(O_4)$	1.24	Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.44 mM).	$L(2.3_{ZS})$	Adachi et al. [11]
3-hydroxy-4-pyrone	Bis(3-hydroxy-4-pyronato)zinc(II)	$Zn(O_4)$	−0.19	Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.57 mM).	$L(1.8_{ZS})$	Adachi et al. [11]
				Inhibited lipolysis in isolated rat adipocytes (IC50 = 166 μM)	$L(3.5_{ZS})$	Nishiguchi et al. [55]
2-ethyl-3-hydroxy-4-pyrone	Bis(2-ethyl-3-hydroxy-4-pyronato)zinc(II)	$Zn(O_4)$	−1.30	Inhibited lipolysis (IC50 = 189 μM) and increased glucose uptake (EC50 = 110 μM) in isolated rat adipocytes	$L(3.1_{ZS})$	Nishiguchi et al. [55]
Thioallixin-N-methyl	Bis(thioallixin-N-methyl)zinc(II)	$Zn(S_2O_2)$		28 d oral treatment (15 mg Zn/kg) reduced BG (≈52 %) and HbA1c (≈69 %) levels and hyperinsulinemia (≈66 %) and improved GT in T2D KK-A^y mice		Adachi et al. [47]
2-hydroxypyridine-N-oxide	Bis(2-hydroxypyridine-N-oxido)zinc(II)	$Zn(O_4)$	−1.22	Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.41 mM).	$L(2_{ZS})$	Yoshikawa et al. [46]
			−0.75	Inhibited lipolysis in isolated rat adipocytes (IC50 = 261 μM).		Fujimoto et al. [53]
2-mercaptopyridine-N-oxide	Bis(2-mercaptopyridine-N-oxidato)zinc(II)	$Zn(S_2O_2)$	0.67	Inhibited lipolysis in isolated rat adipocytes (IC50 = 8.9 μM). increased glucose uptake (EC50 = 2.2 μM) in isolated rat adipocytes		Fujimoto et al. [53] Nishiguchi et al. [55]
1-oxy-2-pyridine-thiol	Bis(1-oxy-2-pyridine-thiolato)zinc(II)	$Zn(S_2O_2)$	0.69	Inhibited lipolysis in isolated rat adipocytes (IC50 = 17 μM). Dose-dependently increased Akt and glycogen synthase kinase 3β (GSK3β) phosphorylation and time dependingly increased GLUT-4 translocation in 3T3-L1 adipocytes.	$L(58.8_{ZS}); AP(1.3_{IN})$ and GK (2.0_{IN}) 50 μM, $G4(1.0_{IN})$	Basuki et al. [48]

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Table 1 (*continued*)

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
			0.48	Inhibited lipolysis (IC$_{50}$ = 12.6 µM) and increased glucose uptake (EC$_{50}$ = 6.1µM) in isolated rat adipocytes. 16 d oral treatment (7.5 mg Zn/kg) reduced BG (≃48%) and HbA1c (≃52%) levels and hyperinsulinemia (≃32%) in T2D KK-A^y mice.	L(33.6$_{ZS}$); U(56.1$_{ZS}$); B (2.5$_{PZ}$, 5.3$_{LI}$); H(2.9$_{PZ}$); P (6.4$_{PZ}$)	Yoshikawa et al. [52]
				28 d oral treatment (0.75–5 mg Zn/kg) reduced BG level (≃32%) and hyperinsulinemia (≃27%) in T2D KK-A^y mice.	B(5.3$_{ZG}$); P(3.7$_{ZG}$)	Moroki et al., 2014 [56]
1-oxy-2-pyridone	Bis(1-oxy-2-pyridonato)zinc(II)	Zn(O$_4$)	−1.22	Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.51 mM). Dose-dependently increased Akt phosphorylation in 3T3-L1 adipocytes.	L(3.9$_{ZS}$)	Basuki et al. [48]
Thiomaltol	Bis(thiomaltolato)zinc(II)	Zn(S$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 3.3 µM).	L(156$_{ZS}$)	Chaves et al. [49]
1,2-dimethyl-3-hydroxypyridone	Bis(1,2-dimethyl-3-hydroxypyridonato)zinc(II)	Zn(O$_4$)	−0.69	Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 1.9 mM).	L(0.3$_{ZS}$)	Chaves et al. [49]
			−0.29	Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.36 mM). Single i.p. treatment (10 mg Zn/kg) reduced BG level (≃84%) after 33 h in STZ-induced T1D rats	L(1.4$_{ZS}$); B(8.4$_{ZS}$)	Moniz et al. [51]
Poly(Υ-glutamic acid)	Poly(Υ-glutamic acid)-zinc(II) complex	Zn(O$_4$)		Inhibited lipolysis (IC$_{50}$ = 0.183 mM) and increased glucose uptake (EC$_{50}$ = 0.143 mM) in isolated rat adipocytes. 30 d oral treatment (10 - 20 mg Zn/kg) reduced BG (≃38%) and HbA1c (≃26%) levels and hyperinsulinemia (≃45%) and improved GT in T2D KK-A^y mice.	L(2.7$_{ZS}$); U(1.4$_{ZS}$); B(2.2$_{ZS}$); H(2.3$_{ZS}$); P(1.7$_{ZS}$)	Karmaker et al. [64]
2-aminomethyl-pyridine	Bis(2-aminomethyl-pyridinato)zinc(II)	Zn(N$_4$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.85 mM). 14 d i.p. treatment (2 mg Zn/kg) reduced BG (≃37%) and HbA1c (≃32%) levels and hyperinsulinemia (≃42%) and improved GT in T2D KK-A^y mice.	L(1.9$_{ZS}$)	Yoshikawa et al. [63]
1,5,9-Triazanonane	1,5,9-triazanonane-zinc(II) complex	Zn(N$_3$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.85 mM).	L(1.9$_{ZS}$)	Yoshikawa et al. [63]
1,5,8,12-Tetraazadodecane	1,5,8,12-tetraazadodecane-zinc(II) complex	Zn(N$_4$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.97 mM).	L(1.6$_{ZS}$)	Yoshikawa et al. [63]
1-benzyl-3-ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrol- 4-ol	Bis(1-benzyl-3-ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrol- 4-olato)zinc(II)	Zn(O$_4$)	0.62	Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.27 mM).	L(2.8$_{ZS}$)	Kawarada et al. [65]
1-(4-fluorophenyl)methyl-3-ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrole-4-ol	Bis[1-(4-fluorophenyl)methyl-3-ethoxycarbonyl-2,5-dihydro- 5-oxo-1H-pyrrole-4-olato)zinc(II)	Zn(O$_4$)	0.66	Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.46 mM).	L(1.6$_{ZS}$)	Kawarada et al. [65]
1-(4-methylphenyl)methyl-3-ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrol-4-ol	Bis[1-(4-methylphenyl)methyl-3-ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrol-4-olato)zinc(II)	Zn(O$_4$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.26 mM).	L(2.9$_{ZS}$)	Kawarada et al. [65]
1-(4-chlorophenyl)methyl-3-ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrol-4-ol	Bis[1-(4-chlorophenyl)methyl-3-ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrol-4-olato)zinc(II)	Zn(O$_4$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.31 mM).	L(2.4$_{ZS}$)	Kawarada et al. [65]
1-{3,5-bis(trifluoromethyl)phenyl}methyl-3-ethoxycarbonyl- 2,5-dihydro-5-oxo-1H-pyrrol-4-olate	Bis[1-{3,5-bis(trifluoromethyl)phenyl}methyl-3-ethoxycarbonyl- 2,5-dihydro-5-oxo-1H-pyrrol-4-olato]zinc(II)	Zn(O$_4$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.82 mM).	L(0.9$_{ZS}$)	Kawarada et al. [65]
3-carboxy-pyrazole	Bis(3-carboxy-pyrazole)zinc(II)dihydrate	Zn(N$_2$O$_2$)		21 d oral treatment (15 mg Zn/kg) reduced BG level (≃33 %) and improved GT in STZ-induced diabetic male Wistar rats.		López-Viseras et al. [69]
N-salicylidene-β-alanine	N-salicylidene-β-alanine-zinc(II) complex	Zn(NO$_2$)		Inhibited yeast (IC$_{50}$ ≃ 2.7 µM) and rat intestinal (IC$_{20}$ ≃ 126 µM) α-glucosidase	yG(0.9$_{ZA}$, 1.5$_{ZG}$); iG(1.1$_{ZA}$; 1.9$_{ZG}$)	Miyazaki et al. [72]
N, N'-bis(salicylidene) ethylenediamine	N, N'-bis(salicylidene) ethylenediamine-zinc(II) complex	Zn(N$_2$O$_2$)		Inhibited yeast (IC$_{50}$ ≃ 3 µM) and rat intestinal (IC$_{20}$ ≃ 188 µM) α-glucosidase.	yG(0.8$_{ZA}$, 1.3$_{ZG}$); iG(0.7$_{ZA}$; 1.3$_{ZG}$)	Miyazaki et al. [72]
N, N'-bis(salicylidene)phenylenediamine	N, N'-bis(salicylidene)phenylenediamine-zinc(II)	Zn(N$_2$O$_2$)		Inhibited yeast α-glucosidase (IC$_{50}$ ≃ 16 µM).	yG(0.2$_{ZA}$, 0.2$_{ZG}$)	Miyazaki et al. [72]

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Table 1 (*continued*)

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
1-[(2-dimethy- laminoethylimino) methyl] naphtholate or DMN	1-[(2-dimethy- laminoethylimino) methyl] naphtholate-zinc(II) complex OR $Zn_2(DMN)_2Cl_2$	$Zn(N_2O_2)$		Inhibited yeast ($IC_{50} \simeq 4\ \mu M$) and rat intestinal ($IC_{20} = 86\ \mu M$) α-glucosidase. Improved maltose ($\simeq 45\%$) and glucose ($\simeq 17\%$) tolerance in ddY mice.	yG(0.6_{ZA}, 1_{ZG}); iG(1.6_{ZA}; 2.8_{ZG}); GT(0.7_{ZA}, 0.6_{LI}); MAT(1.6_{ZA}; 1.3_{LI})	Miyazaki et al. [72]
3-hydroxy-2-methyl-4-pyridone	Bis(3-hydroxy-2-methyl-4-pyridonato)zinc(II)	$Zn(O_4)$	−0.45	Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 0.28$ mM). Single i.p. treatment (10 mg Zn/kg) reduced BG level ($\simeq 27\%$) after 33 h in STZ-induced T1D rats.	L(1.9_{ZS}); B(2.7_{ZS})	Moniz et al. [51]
1-ethyl-3-hydroxy-2-methyl-4-pyridone	Bis(1-ethyl-3-hydroxy-2-methyl-4-pyridonato)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 1.17$ mM).	L(0.4_{ZS})	Moniz et al. [51]
2-ethyl-3-hydroxy-4-pyridone	Bis(2-ethyl-3-hydroxy-4-pyridonato)zinc(II)	Zn(O4)		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 0.52$ mM).	L(1_{ZS})	Moniz et al. [51]
2-ethyl-3-hydroxy-1-methyl-4-pyridone	Bis(2-ethyl-3-hydroxy-1-methyl-4-pyridonato)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 0.55$ mM).	L(1_{ZS})	Moniz et al. [51]
3-hydroxy-1-(2-hydroxyethyl)-2-methyl-4-pyridone	Bis(3-hydroxy-1-(2-hydroxyethyl)-2-methyl-4-pyridonato)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 7.94$ mM).	L(0.1_{ZS})	Moniz et al. [51]
3-hydroxy-1-(2-hydroxyethyl)-2-ethyl-4-pyridone	Bis(3-hydroxy-1-(2-hydroxyethyl)-2-ethyl-4-pyridonato)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 9.95$ mM).	L(0.1_{ZS})	Moniz et al. [51]
Pyrrole-2-carboxylate	Bis(pyrrole-2-carboxylato)zinc(II)	$Zn(N_2O_2)$	−1.76	Inhibited lipolysis ($IC_{50} = 0.28$ mM) and increased glucose uptake ($EC_{50} = 0.19$ mM) in isolated rat adipocytes	L(1_{ZS}); U(1.3_{ZS})	Nishide et al. [58]
α-furonic acid	Bis(α-furonate)zinc(II)	$Zn(O_4)$	−2.23	Inhibited lipolysis ($IC_{50} = 0.31$ mM) and increased glucose uptake ($EC_{50} = 0.23$ mM) in isolated rat adipocytes	L(0.9_{ZS}); U(1.1_{ZS})	Nishide et al. [58]
Thiophene-2-carboxylate	Bis(thiophene-2-carboxylato)zinc(II)	$Zn(S_2O_2)$	−1.61	Inhibited lipolysis ($IC_{50} = 0.27$ mM) and increased glucose uptake ($EC_{50} = 0.15$ mM) in isolated rat adipocytes	L(1_{ZS}); U(1.7_{ZS})	Nishide et al. [58]
4-sulfonatephenyl-porphyrinato	Meso-tetrakis[(4-sulfonatophenyl)porphyrinato] zinc(II)	$Zn(N_4)$		Inhibited lipolysis ($IC_{50} = 0.07$ mM) and increased glucose uptake ($EC_{50} = 0.088$ mM) in isolated rat adipocytes. 28 d oral treatment (10 - 20 mg Zn/kg) reduced BG ($\simeq 55\%$) and HbA1c ($\simeq 20\%$) levels and hyperinsulinemia ($\simeq 70\%$) and improved GT in T2D KK-A^y mice.	L(6.2_{ZS}); U(2_{ZS}); B($1-8_{ZS}$); H (10_{ZS}); P(11.7_{ZS})	Saha et al. [66]
Thiophene-2-acetate	Bis(thiophene- 2-acetato)zinc(II)	$Zn(S_2O_2)$	−1.55	Inhibited lipolysis ($IC_{50} = 0.26$ mM) and increased glucose uptake ($EC_{50} = 0.12$ mM) in isolated rat adipocytes.	L(1.1_{ZS}); U(2.1_{ZS})	Nishide et al. [58]
2-picolinamide or pa-a	2-picolinamide-zin(II) complexes: Zn(pa-a)₃Cl₂ and Zn(pa-a)₃(ClO4)₂	$Zn(N_2O_2)$		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 0.7$ mM). 14 d i.p. treatment (4 mg Zn/kg) with Zn(pa-a)₃Cl₂ reduced BG ($\simeq 41\%$) and HbA1c ($\simeq 23\%$) levels and improved GT in T2D KK-A^y mice.	L(2.3_{ZS})	Ueda et al. [73]
6-methyl-2-picolinemethylamide OR 6mpa-ma	6-methyl-2-picolinemethylamide-zinc(II) complexes: Zn(6mpa-ma)₂Cl₂ and Zn(6mpa-ma)₂SO₄	$Zn(N_2O_2)$		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 0.95$ and 0.97 mM for both complexes, respectively). 14 d i.p. treatment (4 mg Zn/kg) with Zn(6mpa-ma)₂SO₄ reduced BG ($\simeq 44\%$) and HbA1c ($\simeq 27\%$) levels and improved GT in T2D KK-A^y mice.	L(1.7_{ZS}) and L(1.6_{ZS}) for both complexes, respectively	Ueda et al. [73]
				Zn(6mpa-ma)₂SO₄ inhibited α-glucosidase activity on maltose ($IC_{50} = 7.5\ \mu M$) and sucrose ($IC_{50} = 9.6\ \mu M$).	yG(1_{ZC}, 77.9_{AC}) and yG(1_{ZC}, 42.1_{AC}) for both substrates, respectively	Ueda et al. [71]
1,2-dihydro-2-oxo-1-pyrimidinol	Bis(1,2-dihydro-2-oxo-1-pyrimidinolato)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 5.45$ mM).	L(0.1_{ZS})	Yamaguchi et al. [57]
1,2-dihydro-4,6-dimethyl-2-oxo-1-pyrimidinol	Bis(1,2-dihydro-4,6-dimethyl-2-oxo-1-pyrimidinolato)zinc(II)	$Zn(O_4)$	−0.3	Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 4.54$ mM).	L(0.2_{ZS})	Yamaguchi et al. [57]
1,2-dihydro-4-butylamino-2-oxo-1-pyrimidinol	Bis(1,2-dihydro-4-butylamino-2-oxo-1-pyrimidinolato)zinc(II)	$Zn(O_4)$	−0.74	Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 6.06$ mM).	L(0.1_{ZS})	Yamaguchi et al. [57]
1,2-dihydro-4-hexylamino-2-oxo-1-pyrimidinol	Bis(1,2-dihydro-4-hexylamino-2-oxo-1-pyrimidinolato)zin(II)	$Zn(O_4)$	0.55	Inhibited lipolysis in isolated rat adipocytes ($IC_{50} = 2.58$ mM).	L(0.3_{ZS})	Yamaguchi et al. [57]

Table 1 (*continued*)

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
1,2-dihydro-4-(methoxycarbonylmethyl)-amino-2-oxo-1-pyrimidinol	Bis[1,2-dihydro-4-(methoxycarbonylmethyl)-amino-2-oxo-1-pyrimidinolato]zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 1.49 and 1.05 mM for S and R stereoisomers).	L(0.5_{ZS}) and L(0.5_{ZS}) for both stereoisomers, respectively	Yamaguchi et al., 2006 [57]
Dimethyldithiocarbamic acid	Bis(dimethyldithiocarbamate)zinc(II)	$Zn(S_4)$	1.59	Inhibited lipolysis (IC_{50} = 10.4 μM) and increased glucose uptake (EC_{50} = 10.3 μM) in isolated rat adipocytes.	L(77.9_{ZS})	Yoshikawa et al. [44]
Diethyldithiocarbamic acid	Bis(diethyldithiocarbamate)zinc(II)	$Zn(S_4)$	1.69	Inhibited lipolysis (IC_{50} = 10.3 μM) and increased glucose uptake (EC_{50} = 8.5 μM) in isolated rat adipocytes.	L(78.6_{ZS})	Yoshikawa et al. [44]
N-ethyl-N-phenyldithiocarbamic acid	Bis(N-ethyl-N-phenyldithiocarbamate)zinc(II)	$Zn(S_4)$	1.48	Inhibited lipolysis (IC_{50} = 21.3 μM) and increased glucose uptake (EC_{50} = 9.9 μM) in isolated rat adipocytes.	L(38_{ZS})	Yoshikawa et al. [44]
Pyrrolidine-N-dithiocarbamic acid	Bis(pyrrolidine-N-dithiocarbamate)zinc(II)	$Zn(S_4)$	1.76	Inhibited lipolysis (IC_{50} = 5.1 μM) and increased glucose uptake (EC_{50} = 6.4 μM) in isolated rat adipocytes. 4 d i.p. treatment (1 mg Zn/kg) reduced BG level (≃61%). 25 d oral (10 – 15 mg Zn/kg) treatment reduced BG (≃27%) and HbA1c (≃29%) levels and hyperinsulinemia (≃59%,), and improved GT in T2D KK-A^y mice.	L(158.8_{ZS})	Yoshikawa et al. [44]
Diacetyl-bis(N4-methylthiosemicarbonate)	Diacetyl-bis(N4-methylthiosemicarbazonate)-zinc(II)	$Zn(N_2S_2)$	1.18	14 d oral treatment (10 mg Zn/kg) reduced BG level (≃24 %) and improved GT in T2D KK-A^y mice.	BG(2.9_{ZS})	Kadowaki et al. [67]
3,4-heptanedione-bis(N4-methylthiosemicarbazonate)	3,4-heptanedione-bis(N4-methylthiosemicarbazonate)-zinc(II) complex	$Zn(N_2S_2)$		Single i.p. treatments (1 and 3 mg Zn/kg) reduced BG level (≃59 and 51 %, respectively) after 6 h in T2D KK-A^y mice. 14 d oral treatment (10 mg Zn/kg) reduced BG level (≃40%) and improved GT in T2D KK-A^y mice.	BG(4.7_{ZS}) for oral treatment	Kadowaki et al. [67]
N,N′-trimethylene-bis-glycine	N,N′-trimethylene-bis-glycine-zinc(II) complex	$Zn(N_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 3.18 mM).	L(0.3_{ZS})	Yoshikawa et al. [68]
N,N′-ethylene-bis-β-alanine	N,N′-ethylene-bis-β-alanine-zinc(II) complex	$Zn(N_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.82 mM).	L(1_{ZS})	Yoshikawa et al. [68]
N,N′-trimethylene-bis-L-valine	N,N′- trimethylene-bis-L-valine-zinc(II) complex	$Zn(N_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.92 mM).	L(0.9_{ZS})	Yoshikawa et al. [68]
5-Nitrosalicylic acid	Bis(5-nitrosalicylate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.75 mM). 24 d oral treatment (15 mg Zn/kg) reduced BG (≃14%) and HbA1c (≃12%) levels and hyperinsulinemia (≃31%) and improved GT (≃14%) in T2D GK rats.	L(1.6_{ZS})	Yoshikawa et al. [70]
5-bromosalicylic acid	Bis(5-bromosalicylate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.91 mM).	L(1.3_{ZS})	Yoshikawa et al. [70]
5-chlorosalicylic acid	Bis(5-chlorosalicylate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.88 mM).	L(1.4_{ZS})	Yoshikawa et al. [70]
5-fluorosalicylic acid	Bis(5-fluorosalicylate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.99 mM).	L(1.2_{ZS})	Yoshikawa et al. [70]
5-iodosalicylic acid	Bis(5-iodosalicylate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.84 mM).	L(1.5_{ZS})	Yoshikawa et al. [70]
5-methylsalicylic acid	Bis(5-methylsalicylate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.99 mM).	L(1.2_{ZS})	Yoshikawa et al., 2011a [70]
1-(4′-methoxyphenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione	Bis[1-(4′-methoxyphenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.017 mM).		Katoh et al. [50]
1-(4′-methylphenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione	Bis[1-(4′-methylphenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.25 mM).		Katoh et al. [50]
1-(4′-bromophenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione	Bis[1-(4′-bromophenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.016 mM).		Katoh et al. [50]
1-(4′-nitrophenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione	Bis[1-(4′-nitrophenyl)-3-hydroxy-2-methyl-4(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.027 mM).		Katoh et al. [50]
4-(4′-methoxyphenyl)-3-hydroxythiazole-2(3 H)-thione	Bis[4-(4′-methoxyphenyl)-3-hydroxythiazole-2(3 H)-thione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.037 mM).		Katoh et al. [50]

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Table 1 (*continued*)

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
4-(4′-methylphenyl)-3-hydroxythiazole-2(3 H)-thione	Bis[4-(4′-methylphenyl)-3-hydroxythiazole-2(3 H)-thione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.03 mM).		Katoh et al., 2009 [50]
4-phenyl-3-hydroxythiazole-2(3 H)-thione	Bis[4-phenyl-3-hydroxythiazole-2(3 H)-thione]zinc (II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.036 mM).		Katoh et al. [50]
4-(3′-fluorophenyl)-3-hydroxythiazole-2(3 H)-thione	Bis[4-(3′-flourophenyl)-3-hydroxythiazole-2(3 H)-thione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.018 mM).		Katoh et al., 2009 [50]
4-(4′-fluorophenyl)-3-hydroxythiazole-2(3 H)-thione	Bis[4-(4′-flourophenyl)-3-hydroxythiazole-2(3 H)-thione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.021 mM).		Katoh et al. [50]
4-(4′-chorophenyl)-3-hydroxythiazole-2(3 H)-thione	Bis[4-(4′-chlorophenyl)-3-hydroxythiazole-2(3 H)-thione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.036 mM).		Katoh et al. [50]
4-methyl-3-hydroxythiazole-2(3 H)-thione	Bis[4-methyl-3-hydroxythiazole-2(3 H)-thione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.014 mM).		Katoh et al., 2009 [50]
1-methyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-methyl-3-hydroxy-2(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.018 mM).		Katoh et al. [50]
1-propyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-propyl-3-hydroxy-2(1 H)-pyridinethione]zinc (II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.018 mM).		Katoh et al. [50]
1-dodecyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-dodecyl-3-hydroxy-2(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.045 mM).		Katoh et al. [50]
1-(2′-phenylethyl)-3-hydroxy-2(1 H)-pyridinethione	Bis[1-(2′-phenylethyl)-3-hydroxy-2(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.036 mM).		Katoh et al. [50]
1-ethyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-ethyl-3-hydroxy-2(1 H)-pyridinethione]zinc (II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.018 mM).		Katoh et al. [50]
1-butyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-butyl-3-hydroxy-2(1 H)-pyridinethione]zinc (II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.021 mM).		Katoh et al. [50]
1-phenylmethyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-phenylmethyl-3-hydroxy-2(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.022 mM).		Katoh et al. [50]
1-(3′-phenylpropyl)-3-hydroxy-2(1 H)-pyridinethione	Bis[1-(3′-phenylpropyl)-3-hydroxy-2(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.024 mM).		Katoh et al. [50]
1-(1′-phenylethyl)-2-methyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-(1′-phenylethyl)-2-methyl-3-hydroxy-2(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.034 and 0.021 mM for R and S stereoisomers).		Katoh et al. [50]
1-(1′-phenylpropyl)-2-methyl-3-hydroxy-2(1 H)-pyridinethione	Bis[1-(1′-phenylpropyl)-2-methyl-3-hydroxy-2(1 H)-pyridinethione]zinc(II)	$Zn(S_2O_2)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 0.021 and 0.019 mM for R and S stereoisomers).		Katoh et al. [50]

DEFINITIONS: "ψ" is the anti-diabetic potency ratio of the complexes compared to the precursor ligand of complexes (LL), Zn(II) sulfate (ZS), Zn(II) acetate (ZA), Zn(II) chloride (ZC), Zn(II) gluconate (ZG), insulin (IN), acarbose (AC) and pioglitazone (PZ) in the following modes of action: Akt/PKB phosphorylation in adipocyte (AP); inhibition of lipolysis(L) and intestinal (iG) and yeast (yG) α-glucosidases; increase of glucose uptake (U); reduction of blood glucose (B) and HbA1c (H) levels and hyperinsulinemia (P); GSK3β phosphorylation (GK); GLUT-4 translocation (G4) and improvement of glucose (GT) and maltose (MAT) tolerance; C_M, coordination mode; IC_{50}, inhibition concentration required to cause 50 % inhibition; EC_{50}, effective concentration required to cause 50 % glucose uptake; Log P, partition coefficients. ABBREVIATIONS: Akt, protein kinase B; BG, blood glucose; GT, glucose tolerance; HbA1c, glycated hemoglobin; i.p., intraperitoneal injection; STZ, streptozotocin; T1D, type 1 diabetes; T2D, type 2 diabetes.

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Table 2
Anti-diabetic properties of Zn(II) complexes with naturally occurring organic compounds as ligands.

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
3-hydroxy-2-methyl-4-pyrone (Maltol)	Bis(maltolato)zinc(II)	$Zn(O_4)$	0.6	Inhibited lipolysis (IC50 = 0.54 mM) and increased glucose uptake (EC50 = 1 mM) in isolated rat adipocytes; 14 d i.p. treatment (4.5 mg Zn/kg) reduced BG (≃52%) and HbA1c (≃19%) levels and improved GT in T2D KK-A^y mice	$L(1.9_{ZS})$	Adachi et al. [11]
			−1.46	30 d i.p. (4 mg Zn/kg) and oral (30 mg Zn/kg) treatments reduced BG (≃18 and 19 %, respectively) and HbA1c (≃13 % for oral treatment) levels and hyperinsulinemia (≃49 and 76%, respectively) and improved GT in T2D GK rats		Fugong et al. [60]
				Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.59 mM).	$L(1.4_{ZS})$	Yoshikawa et al. [46]
				14 d i.p. (3 mg Zn/kg) treatment reduced BG and HbA1c levels and improved GT in T2D KK-A^y mice		Kojima et al. [62]
				Single i.p. treatment (10 mg Zn/kg) increased Akt phosphorylation in ICR mice adipose (≃177 %) and liver (≃40 %) tissues after 40 min.	$AP(14.8_{ZS}, 3.5_{ZA}, 1.1_{IN}); LP(0.4_{IN})$	Naito et al. [74]
				Showed insulin mimetic effects by modulation of the activities of adipocyte IRTK, PI3-K, GLUT-4 and PDE.		Yoshikawa et al. [30]
			−1.94	Inhibited lipolysis (IC50 = 166 µM) and increased glucose uptake (EC50 = 233 µM) in isolated rat adipocytes.	$L(3.5_{ZS})$	Nishiguchi et al., 2018 [55]
				Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.38 mM).	$L(1.4_{ZS})$	Chaves et al. [49]
				Single i.p. treatment (10 mg Zn/kg) reduced BG level (≃46 %) after 33 h in STZ-induced diabetic rats	$B(4.6_{ZS})$	Moniz et al. [51]
				Inhibited lipolysis in isolated rat adipocytes (103 % at 0.125 mM). 14 d i.p. treatment (4.5 mg Zn/kg) reduced BG level (≃21 %) and hyperinsulinemia (≃39 %) and improved GT in T2D KK-A^y mice.	$L(1_{IN})$	Yoshikawa et al. [77]
3-hydroxy-5-methoxy-6- methyl-2-pentyl-4-pyrone (allixin)	Bis(allixinato)zinc(II)	$Zn(O_4)$	1.65	Inhibited lipolysis (IC50 = 0.37 mM) and increased glucose uptake (EC50 = 0.6 mM) in isolated rat adipocytes; 14 d i.p. treatment (4.5 mg Zn/kg) reduced BG (≃68%) and HbA1c (≃46%) levels and hyperinsulinemia (≃79%) and improved GT in T2D KK-A^y mice	$L(2.7_{ZS})$	Adachi et al. [11]
				28 d oral treatment (15 mg Zn/kg) reduced BG (≃49 %) and HbA1c (≃19 %) levels in T2D KK-A^y mice		Adachi et al. [47]
Pyridine-2 carboxylic acid (Picolinic acid)	Bis(picolinato)zinc(II)	$Zn(N_2O_2)$	−1.95	14 d i.p. (3 mg Zn/kg) treatment reduced BG and HbA1c levels and improved GT in T2D KK-A^y mice	$L(2.5_{ZS})$	Kojima et al. [62]
				Showed insulin mimetic effects by modulation of the activities of adipocyte IRTK, PI3-K, GLUT-4 and PDE.		Yoshikawa et al. [61]; Yoshikawa et al. [30]
L-lactic acid	Bis(L-lactate)zinc(II)	$Zn(O_4)$	0.018	Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.81 mM); 13 d i.p. treatment (3 mg Zn/kg) reduced BG level (≃30%) in T2D KK-A^y mice	$L(1_{ZS})$	Kojima et al. [79]
Betaine	Zn(betainato)3(ClO4)2	$Zn(O_n)$		Inhibited lipolysis in isolated rat adipocytes (IC50 = 1.06 mM).	$L(1.3_{ZS})$	Kojima et al. [79]
D-(-)-quinic acid	Bis(quinate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC50 = 0.98 mM); 13 d i.p. treatment (3 mg Zn/kg) reduced BG (≃47%) and HbA1c (≃30%) levels in T2D KK-A^y mice	$L(0.8_{ZS})$	Kojima et al. [79]
2-hydroxy-2,4,6-cycloheptatrien-1-one (tropolone)	Bis(tropolonato)zinc(II)	$Zn(O_4)$		Inhibited lipolysis (IC50 = 113 µM) and increased glucose uptake (EC50 = 72 µM) in isolated rat adipocytes; 25 d oral treatment (10mg Zn/kg) reduced HbA1c level (≃22%) and hyperinsulinemia (≃70%) and improved GT in T2D KK-A^y mice	$L(3.9_{ZS}, 0.003_{IN}); U(2.4_{ZS}, 0.0001_{IN})$	Murakami et al. [75]
Hinokitiol	Bis(hinokitiolato)zinc(II)	$Zn(O_4)$		Inhibited lipolysis (IC50 = 101 µM) and increased glucose uptake (EC50 = 62 µM) in isolated rat adipocytes	$L(4.4_{ZS}, 0.003_{IN}); U(2.8_{ZS}, 0.0002_{IN})$	Murakami et al. [75]
				20 µM increased glucose-induced Akt phosphorylation in islet cells (≃359 %). 120 d oral treatment (10–30 mg Zn/kg) reduced HbA1c level (≃12%) and hyperinsulinemia (≃38%) and improved IR (49%) and GT (≃48%) in T2D KK-A^y mice	$IP(13.3_{ZS}, 0.8_{IN}); H(0.3_{PZ}); P(0.5_{PZ}); IR(0.6_{PZ}); GT(2.5_{PZ})$	Naito et al. [80]

DEFINITIONS: "ψ" is the anti-diabetic potency ratio of the complexes compared to Zn(II) sulfate (ZS), Zn(II) acetate (ZA), insulin (IN), and pioglitazone (PZ) in the following modes of action: Inhibition of lipolysis(L); increase of glucose uptake (U); modulation of Akt phosphorylation in islet cells (IP) and adipose (AP) and liver (LP) tissues; reduction of blood glucose (B) and HbA1c (H) levels and hyperinsulinemia (P); and improvement of insulin resistance (IR) and glucose tolerance (GT); IC50, inhibition concentration required to cause 50 % inhibition; EC50, effective concentration required to cause 50 % glucose uptake; Log P, partition coefficients. ABBREVIATIONS: Akt, protein kinase B; BG, blood glucose; GLUT-4, glucose transporter type 4; GT, glucose tolerance; HbA1c, glycated hemoglobin; i.p., intraperitoneal injection; IR, insulin resistance; IRTK, insulin receptor tyrosine kinase; PDE, phosphodiesterase; PI3-K, phosphoinositide 3-kinase; STZ, streptozotocin; T2D, type 2 diabetes.

(a)

(b)
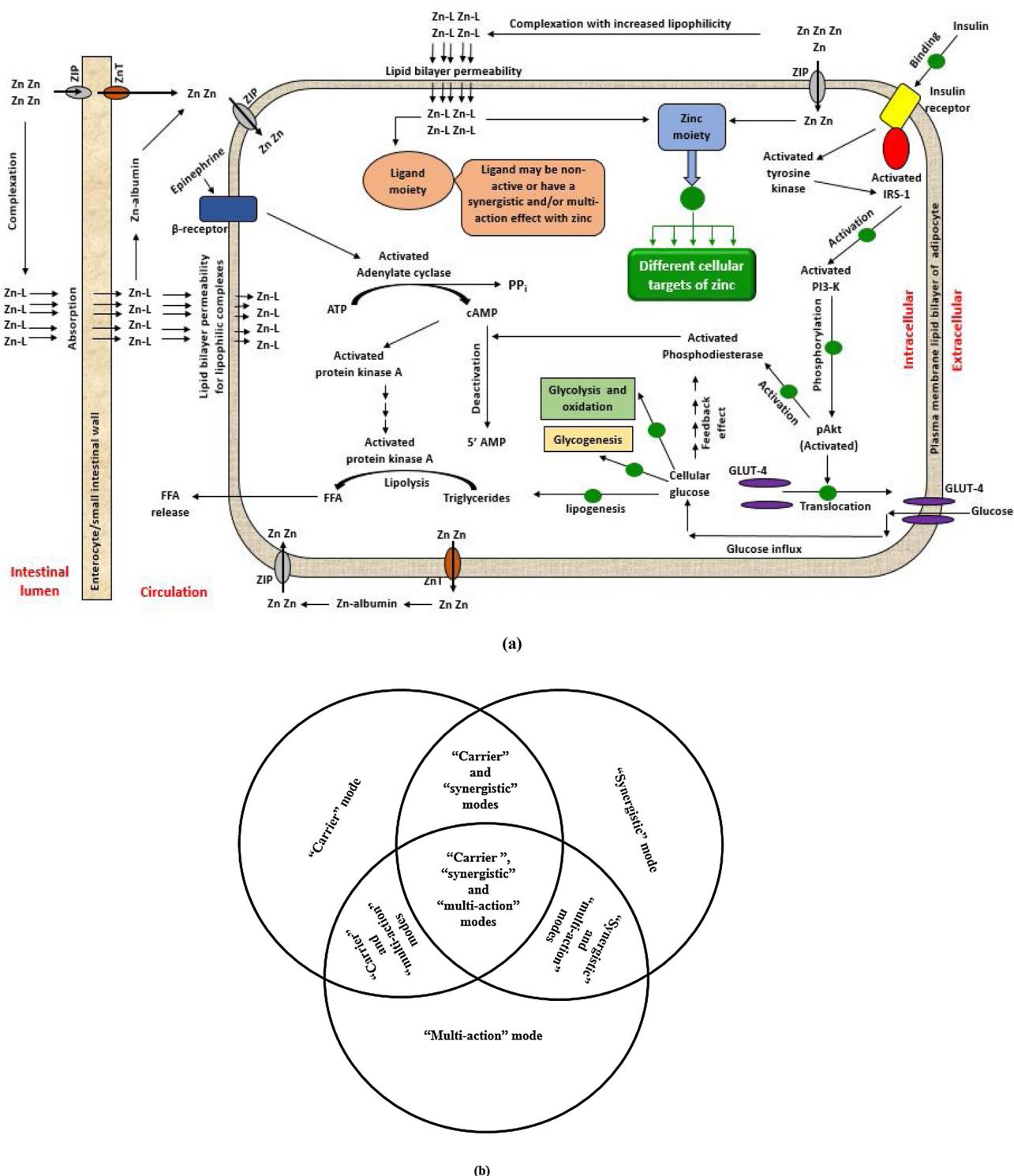
Fig. 4. Diagram showing **(a)** the possible mechanisms underlying the bioavailability and bioactivity of Zn(II) complexes and **(b)** the tri-facet modes through which Zn (II) complexes exert pharmacological effects. 5′ AMP, 5′ adenosine monophosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; FFA, free fatty acids; GLUT-4, glucose transporter type 4; IRS-1, insulin receptor substrate 1; pAkt, phosphorylated Akt or protein kinase B; PI3-K, phosphoinositide 3-kinase; ZIP, zinc importer; Zn, zinc; Zn-L, Zn(II)-ligand complex; ZnT, zinc transporter.

Better cellular accessibility of Zn(II), caused by complexation, further explains why the anti-lipolytic ($\Psi = 33.6_{ZS}$) and glucose uptake ($\Psi = 56.1_{ZS}$) effect of the complex in adipocytes was markedly more potent than ZnSO$_4$ [52]. Additionally, the *In vivo* anti-diabetic activity of the complex was more potent than pioglitazone [B(2.5$_{PZ}$); H(2.9$_{PZ}$); P(6.4$_{PZ}$)] [52], while it induced Akt [AP(1.3$_{IN}$)] and GKS3β [GK(2.0$_{IN}$)] phosphorylation and GLUT-4 translocation [G4(1.0$_{IN}$)] more than or

similarly as insulin (Table 1) [48], which suggests the potent anti-diabetic therapeutic application of bis(1-oxy-2-pyridine-thiolato)zinc(II) and other thiol- and mercapto-containing Zn(II) complexes, particularly those with Zn(S$_2$O$_2$) C$_M$.

In spite of the potent activity of bis(1-oxy-2-pyridine-thiolato)zinc (II) complex, the ligand alone did not show any adipocyte glucose uptake, anti-lipolytic or Akt phosphorylation activity [48,52], suggesting

that complexation increased cellular uptake of Zn(II) and its accessibility to cellular targets, without any Zn(II)-ligand synergistic effect. This scenario suggest that Zn(II)-ligand complexation may potentiate pharmacological effects through different modes, depending on the type of ligand and its effect on zinc, as well as the Zn(II)-ligand C_M. We propose a "tri-facet" pharmacological mode of action, namely (1) "carrier", (2) "synergistic" and (3) "multi-action" modes, which can be interwoven (Fig. 4b).

The "carrier" mode is when Zn(II) is complexed with a non-pharmacologically active carrier-ligand that increases bioavailability due to better lipophilicity, absorption and cellular membrane permeability. This is the mode of action observed for bis(1-oxy-2-pyridine-thiolato) zinc(II), where the activity of the complex was only influenced by the increased cellular uptake of Zn(II). The "synergistic" mode is when Zn(II) is complexed with a pharmacologically active ligand that does not necessarily increase bioavailability, but acts synergistically with Zn(II) to increase insulin sensitivity and/or signaling. The "multi-action" mode is when Zn(II) is complexed with a pharmacologically active ligand that does not necessarily increase bioavailability, but can exert other diabetes-related pharmacological properties different from Zn(II) to cause a multi-mode anti-diabetic effect.

To have an indication of the possible mode of action of a Zn(II) complex, it is, therefore imperative to comparatively understand its bioavailability or lipophilicity and cellular Zn(II) uptake activity, relative to Zn(II) salt and the precursor ligand, which can help inform the pharmacology of the complex. Unfortunately many studies on the anti-diabetic properties of Zn(II) complexes lack this information.

Several Zn(II) complexes with a nitrogen atom as part of their C_M have been, also, synthesized, hoping to find pharmacologically active complexes with improved lipophilicity. Presumably, the less electronegative property of a nitrogen atom compared to an oxygen atom may influence or improve the lipophilic property of these complexes relative to the complexes with $Zn(O_4)$ C_M. Zinc(II) complexes of picolinic acid and derivatives with $Zn(N_2O_2)$ C_M were among the previously studied Zn(II) complexes, because picolinic acid is a bidentate chelating agent, known to play a physiological role in zinc absorption [59]. Studies have shown that it increases intestinal zinc absorption in rats, zinc uptake in isolate duodenal sac and zinc translocation across lipid bilayers [59]. Consistent data showed that Zn(II) complexes of picolinic acid and its methyl derivatives exhibited lipophilic properties (log P = 0.018 – 0.075), which may influence cellular or intestinal Zn(II) uptake, evident by the higher blood zinc level of KK-A^y rats fed with bis(6-methylpicolinato)zinc(II) compared to those fed with $ZnCl_2$ [60]. Accordingly, the complexes showed promising anti-lipolytic (IC_{50} = 0.31 – 0.64 mM; Ψ = 2.5$_{ZS}$ – 5.1$_{ZS}$) and insulin signaling modulatory activities in rat adipocytes, as well as, anti-diabetic activities in T2D KK-A^y mice compared to $ZnSO_4$ [60–62] (Tables 1 and 2). These reports suggests Zn(II) complexes of picolinic acid and its methyl derivatives exert pharmacological effects through the "carrier" mode of action. Moreover, the ligands (picolinic acid and its methyl derivatives) alone did not show anti-lipolytic insulin mimetic activity in isolated adipocytes [61].

For the other complexes with a nitrogen atom as part of their C_M, there appears to be no consistent trend of lipophilicity-activity relationship when compared to the complexes with $Zn(O_4)$ C_M; rather the type of ligand seems to play a more influential role. Bis(2-aminomethyl-pyridinato)zinc(II), among other Zn(II) complexes with $Zn(N_4)$ C_M exhibited appreciable BG-, HbA1c- and hyperinsulinemia-lowering, as well as, GT-improving abilities in T2D KK-A^y mice [63]. However, its anti-lipolytic activity (IC_{50} = 0.85 mM) was not as potent as those of the Zn(II) complexes of 1-substituted ethoxycarbonyl-2,5-dihydro-5-oxo-1H-pyrrol- 4-ol derivatives (IC_{50} = 0.26 - 0.46 mM) and poly(Υ-glutamic acid) (IC_{50} = 0.183 mM) with $Zn(O_4)$ C_M [64,65] (Table 1). On the other hand, Saha et al. (2007) [66], reported remarkable cellular anti-lipolytic (IC_{50} = 0.07 mM) and glucose uptake (IC_{50} = 0.088 mM) activities, as well as, In vivo anti-diabetic activities (BG, ≃55 %; HbA1c, ≃20 %; hyperinsulinemia, ≃70 %) of meso-Tetrakis[(4-sulfonatophenyl)porphyrinato] zinc(II) [C_M: $Zn(N_4)$] in T2D KK-A^y mice following a 28 d oral administration of 10–20 mg Zn/kg (Table 1).

Furthermore, while 14 d oral treatment (10 mg Zn/kg) of Zn(II) complexes of diacetyl-bis(N4-methylthiosemicarbazonate) and 3,4-heptanedione-bis(N4-methylthiosemicarbazonate) with $Zn(N_2S_2)$ C_M showed promising BG-lowering (≃24 and 40 %; Ψ = 2.9$_{ZS}$ and 4.7$_{ZS}$, respectively) and GT-improving effects in T2D KK-A^y mice [67], Zn(II) complexes of N,N'-trimethylene-bis-glycine, N,N'-ethylene-bis-β-alanine, N,N'-trimethylene-bis-L-valine and 3-carboxy-pyrazole with Zn (N_2O_2) C_M exhibited somewhat low to moderate lipolysis inhibitions in rat adipocytes (Ψ = 0.3$_{ZS}$ - 1$_{ZS}$, respectively) [68] and In vivo glucose-lowering effect [69]. In fact, their anti-lipolytic activities were lower than those of salicylic acid derivatives with $Zn(O_4)$ C_M (Ψ = 1.2$_{ZS}$ – 1.6$_{ZS}$) [70] (Table 1).

However, the Zn(II) complexes of salicylidene derivatives, 1-[(2-dimethy-laminoethylimino) methyl]naphtholate, 2-picolinamide and 6-methyl-2-picolinemethylamide, with $Zn(N_2O_2)$ C_M consistently showed remarkable α-glucosidase inhibitory activities (Ψ was up to 77.9$_{AC}$) [71,72] and anti-diabetic effects in T2D KK-A^y mice [73] (Table1). Interestingly, while the α-glucosidase inhibitory activities of these complexes were fairly comparable to that of Zinc(II) salts ($ZnCl_2$, zinc gluconate and zinc acetate), the ligands alone did not show α-glucosidase inhibitory activities (Table 1) [71,72], which suggests that Zn(II), rather than the ligands, is the predominant influencing moiety of the complexes. Thus, supporting the α-glucosidase inhibitory glycemic control mechanism of action of Zn(II) (Fig. 1).

These results suggest that although some Zn(II) complexes with a nitrogen atom as part of their C_M may have shown promising anti-diabetic activities, the presumed improved lipophilicity, permeability and activity over those with $Zn(O_4)$ C_M, perhaps, due to the lesser electronegative nature of a nitrogen atom relative to an oxygen atom remain controversial, except for the Zn(II) complexes of picolinic acids its methyl derivatives. Nevertheless, it appears that some Zn(II) complexes with $Zn(N_2O_2)$ C_M may be potent α-glucosidase inhibitors for further studies.

In general, the complexes with sulfur-containing C_M appear as the most potent of the Zn(II) complexes of synthetic organic ligands. The in vitro anti-lipolytic and glucose uptake activities of most them, particularly the thiol-or mecapto-containing tropolone, pyrone and pyridine derivatives appreciably outperformed $ZnSO_4$ [Ψ = L(2$_{ZS}$ – 292.5$_{ZS}$) and U(5.7$_{ZS}$ – 251$_{ZS}$)] [48,49,54,74,75]. Bis(1-oxy-2-pyridine-thiolato)zinc (II) was noteworthy, because it induced Akt [AP(1.3$_{IN}$] and GKS3β [GK (2.0$_{IN}$)] phosphorylation and GLUT-4 translocation [G4(1.0$_{IN}$)] more than or similarly as insulin [48]. Also, its In vivo anti-diabetic activity outperformed that of pioglitazone [B(2.5$_{PZ}$); H(2.9$_{PZ}$); P(6.4$_{PZ}$)], without aggravating hepatotoxicity [52], which warrants further In vivo and clinical studies. It is, therefore recommended that more effective approaches, including using sulfur-containing ligands or coordination, be employed to increase the lipophilic properties of Zn(II) complexes and, consequently, their bioavailability and pharmacological properties. However, in spite of the promising activities of several Zn(II) complexes of synthetic organic ligands reported in this review, many of them lack data on their toxicity profile, which raises safety concerns for clinical relevance. Additionally, many of the synthetic organic ligands or their derivatives have been labeled as toxic on the "pubchem.ncbi.nlm.nih.gov" database (accessed between 15 April to 21 June 2018). Critical toxicity evaluation is, therefore, imperative.

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

Eight (7%) of the Zn(II) complexes reported in this review were synthesized from naturally occurring organic ligands (Fig. 3 and Table 2). Maltol, a natural flavor enhancer is the most studied natural ligand. Although it has been shown that maltol ameliorated oxidative damage in diabetic neuropathy [76], several studies have demonstrated

that complexing it with Zn(II) [C_M: $Zn(O_4)$] conferred notable *in vitro* and *In vivo* insulin mimetic and glycemic control properties on this natural ligand [11,30,46,49,51,55,60,62,74,77] (Table 2). In adipocytes, bis(maltolato)zinc(II) complex showed insulin mimetic activities by inhibiting lipolysis (IC_{50} = 0.125 - 0.54 mM) [11,46,49,55,75] and increasing glucose uptake (EC_{50} = 0.233–1.0 mM) [11,55]. The anti-lipolytic effect of bis(maltolato)zinc(II) was dose dependently reversed by inhibitors of insulin receptor tyrosine kinase (IRTK), PI3K, GLUT-4 and PDE activation, suggesting that the complex may have direct modulatory effect on IRTK, PI3-K, GLUT-4 and PDE activities (30) (Table 2). *In vivo*, oral and/or i.p. treatments of the complex reduced BG and HbA1c levels and hyperinsulinemia and improved GT in diabetic rats by varying magnitudes depending on the dose, duration and route of administration [11,51,60,62,77]. Additionally, single i.p. treatment (10 mg Zn/kg) markedly increased Akt phosphorylation in ICR mice adipose (≃177 %) and liver (≃40 %) tissues after 40 min of treatment [74]. The modulatory effect of Zn(II)-maltol complex on Akt phosphorylation in adipose tissue was comparable to insulin ($\Psi = 1.1_{IN}$) [74], while *In vivo* toxicological studies shows it has a safe and high LD_{50} in KK-A^y mice [62], which suggests the anti-diabetic pharmacological potency and safety of this complex.

Despite the influence of bis(maltolato)zinc(II) and some other complexes on insulin signaling, the exact interaction between zinc(II) complexes and intracellular molecules, including those involved in insulin signaling remains elusive. A previous study has shown that Zn(II) complex of maltol interacts with ATP - a high concentration low molecular weight cytosolic constituent involved in phosphorylative activation of signaling molecule s- forming a fairly stable ternary complex [78]. While authors proposed that this interaction may influence phosphorylation/dephosphorylation steps in cascades of glucose metabolism, there seem to be no direct correlation between the ternary complex formation and activity of the complex. Perhaps, other factors like membrane transport properties of complex may influence the modulatory effect of complex on insulin signaling. On the other hand, it is quite difficult to say which of the "tri-facet" modes is the mode of action for bis(maltolato)zinc(II), since in most of the studies, the insulin mimetic properties of bis(maltolato)zinc(II) was not compared with the precursor ligand. However, bis(maltolato)zinc(II) increased cellular and tissue Zn(II) uptake more than Zn(II) salts [30,74], which potentiated better insulin mimetic properties compared to Zn(II) salts ($ZnCl_2$, $ZnSO_4$ and zinc acetate), thus suggesting a "carrier" mode of action, [30,46,74].

Furthermore, Zn(II) complex of allixin [C_M: $Zn(O_4)$], a phytoallexin found in garlic bulbs, was reported to show anti-lipolytic (IC_{50} = 0.37 mM; $\Psi = 2.7_{ZS}$) and glucose uptake (EC_{50} = 0.6 mM) activities in adipocytes as well as appreciable BG-lowering ability following a 14 d i.p. (4.5 mg Zn/kg) (≃68 %) and 28 d oral (15 mg Zn/kg) (≃49 %) treatments [11,47] (Table 2). The insulin mimetic activities of bis(allixinato)zinc(II) on adipocytes were more potent than those of bis(maltolato)zinc(II) [IC_{50} = 0.54 mM; EC_{50} = 1 mM; $\Psi = L(1.9_{ZS})$] [11] and bis(picolinato)zinc(II) complex with $Zn(N_2O_2)$ C_M [IC_{50} = 0.64 mM; $\Psi = L(2.5_{ZS})$] [61] complexes, which could be attributed to the more lipophilic property of bis(allixinato)zinc(II) (log P = 1.65) compared to bis(maltolato)zinc(II) (log P = 0.6) and bis(picolinato)zinc(II) (log P = 0.018) complexes [11,61] (Table 2). Nevertheless, bis(picolinato)zinc(II) was, also, shown to improve glycaemic control in T2D KK-A^y mice [62] and modulate IRTK, PI3-K, GLUT-4 and PDE activities in adipocytes [30] (Table 2), which suggests the potential therapeutic applications of Zn(II) complexes with natural ligand. Like bis(maltolato)zinc(II), the cellular and tissue Zn(II) uptake profile and lipophilic nature (log P = +ve) of bis(allixinato)zinc(II) and bis(picolinato)zinc(II) relative to Zn(II) salts [11,30,47] suggest a "carrier" mode of action of the complexes.

Zn(II) complexes of ʟ-lactic acid, betaine, ᴅ-(-)-quinic acid, tropolone and hinokitiol with $Zn(O_4)$ C_M include the other Zn(II) complexes of naturally occurring organic ligands with reported anti-diabetic

activities in T2D KK-A^y mice, as well as glucose uptake (EC_{50} = 0.062 – 0.072 mM; $\Psi = 2.4_{ZS}$ - 2.8_{ZS}) and anti-lipolytic (IC_{50} = 0.101–1.06 mM; $\Psi = 0.8_{ZS} – 4.4_{ZS}$) activities in rat adipocytes [75,79,80] (Table 2). Zn(II) complex of hinokitiol appeared to be the most potent [$L(4.4_{ZS})$; $U(2.8_{ZS})$], which modulated glucose-induced Akt phosphorylation (≃ 359 %) in islet cells [$IP(13.3_{ZS})$] and exerted more glucose tolerance in T2D KK-A^y mice than Pioglitazone anti-diabetic drug [$GT(2.5_{PZ})$] [75,80] (Table 2). Unfortunately, the data on zinc tissue levels and insulin mimetic activities of bis(hinokitiolato)zinc(II) complex were not compared to those of Zn(II) salt and the precursor ligands of the complex. Thus, it is difficult to propose which of the "tri-facet" mode is the mode of action of the complex.

A close look at the anti-diabetic Zn(II) complexes with naturally occurring organic ligands showed that although they are predominantly complexes with the $Zn(O_4)$ C_M, some of them, such as the complexes of maltol and hinokitiol exhibited promising pharmacological properties by enhancing Akt phosphorylation in adipose tissue ($\Psi = 14.8_{ZS}$, 3.5_{ZA} and 1.1_{IN}) and islet cells ($\Psi = 13.3_{ZS}$ and 0.8_{IN}), respectively [74,80], while bis(hinokitiolato)zinc(II) showed potential use in modulating glucose tolerance relative to pioglitazone ($\Psi = 2.5_{PZ}$) [80]. Thus, both complexes may be further investigated as therapeutic agents with, perhaps, minimal toxicity concerns relative to the complexes of synthetic organic ligands. To the best of our knowledge and based on the available data of reviewed studies, most of the complexes appear to exert their effect through the "carrier mode" mechanism by enhancing cellular or tissue Zn(II) uptake, without exerting a synergistic effect. However, the mode of action of other complexes cannot be suggested due insufficient data from studies that were not properly controlled. Moving forward, it was rationale to probe other ligands that can innately afford pharmacological effects, thus improving therapeutic action of Zn(II) through a "synergistic" or "multi-action" mode or both (Fig. 4b) as discussed below.

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

To develop anti-diabetic agents with improved efficacy and broader modes of action, some anti-diabetic drugs such as tolbutamide, chlorpropamide, metformin, pioglitazone hydrochloride and glibenclamide have been complexed with Zn(II). Consistent data showed that the blood glucose-lowering effects (≃22 - 55 %; $\Psi = 1_{LI} - 1.3_{LI}$) of these complexes in both normoglycemic [81] and diabetic [82–84] rats were fairly comparable or slightly higher than those of their precursor anti-diabetic drug ligands (Table 3). Although Zn(II) complexes of tolbutamide and chlorpropamide acutely lowered plasma glucose more than the precursor anti-diabetic drugs ($\Psi = 1.3_{LI}$) [81], these drugs are classified as "first generation" sulfonylureas, which are no longer frequently prescribed, due to associated more severe detrimental side effects compared to the "second generation" counterparts. However, the Zn(II) complex of glibenclamide, a "second generation" sulfonylurea, acutely exerted more hypoglycemic effect than the glibenclamide ($\Psi = 1.2_{LI}$ after 8 h) in alloxan-induced diabetic rats showing impaired insulin secretion due to severe pancreatic β-cell damage. While it is not certain from available data whether these diabetic drugs increases Zn(II) permeability, it is known that sulfonylureas increases depolarization-induced calcium influx in pancreatic β-cell to stimulate insulin secretion [82], thus complementing the antihyperglycemic effect of Zn(II). This suggests that Zn(II) complex of glibenclamide exerts anti-diabetic effect through a "multi-action" mode of action (Fig. 4b), which includes insulin mimetic activity, as well as modulation of insulin signaling and secretion.

On the other hand, Zn(II) complex of pioglitazone, a thiazolidinedione showed more hypogycemic effect than the precursor anti-diabetic drug [83]. Thiazolidinediones are insulin sensitizers, known to modulate the transcription of the genes involved in the regulation of glucose and lipid metabolism in peripheral tissues such as muscle, adipose

Table 3
Anti-diabetic properties of Zn(II) complexes with ligands used as medication and/or supplement.

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
L-threonine	Bis(L-threoninato)zinc(II) OR Zn(L-Thr)$_2$	Zn(N$_2$O$_2$)		14 d i.p. treatment (3 mg Zn/kg) reduced BG and HbA1c levels and improved GT in T2D KK-A^y mice		Kojima et al. [62]
				Showed insulin mimetic effects by modulation of the activities of adipocyte IRTK, PI3-K, GLUT-4 and PDE.		Yoshikawa et al. [30]
				Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.54 and 0.48 mM for Zn(L-Thr)$_2$ and Zn(D-Thr)$_2$, respectively). 14 d i.p. treatment (3 mg Zn/kg) of Zn(L-Thr)$_2$ reduced BG level (≈52%), and improved GT in T2D KK-A^y mice.	L(1.5$_{ZS}$) and L(1.7$_{ZS}$) for L and D isomers, respectively; B(2.9$_{ZC}$)	Yoshikawa et al. [68]
N-acetyl-L-cysteine	N-acetyl-L-cysteine-zinc(II) complex	Zn(SO)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.7 mM); 28 d i.p. treatment (3 - 5 mg Zn/kg) reduced BG (≈59%) and HbA1c (≈40%,) levels and hyperinsulinemia (≈64%) and improved GT (≈44%) in T2D KK-A^y mice.	L(1$_{ZS}$); B(1.5$_{ZC}$); H(0.9$_{ZC}$); P(1$_{ZC}$); GT(1.6$_{ZC}$)	Adachi et al. [85]
Ascorbic acid	Bis(ascorbate)zinc(II)	Zn(O$_4$)		Dose-dependently modulates adipogenesis and expression of GLUT 4, GPDH, C/EBPα and PPAR-γ in 3T3-L1 adipocytes		Ghosh et al. [92]
				Inhibited lipolysis in isolated rat adipocytes (Relative IC$_{50}$ to Zinc gluconate = 0.69).	L(1.5$_{ZG}$)	Matsumoto et al. [90]
Tolbutamide	K[Zn(tolbutamide)$_3$]	Zn(N$_3$O$_3$)		I.p. treatment (10 mg/mL/100 g bw) reduced PG level (47 %) in normoglycemic rats after 3h.	B(1.3$_{LI}$)	Hatzidimitriou et al. [81]
Chlorpropamide	K[Zn(Chlorpropamide)$_3$]	Zn(N$_3$O$_3$)		I.p. treatment (10 mg/mL/100 g bw) reduced PG level (37 %) in normoglycemic rats after 3h.	B(1.3$_{LI}$)	Hatzidimitriou et al. [81]
Metformin-3-hydroxyflavone	Metformin-3-hydroxyflavone-zinc(II) complex			30 d oral treatment (10 mg/kg) reduced FBG (≈55 %) and HbA1c (≈28 %) levels; increased insulin (≈88 %) and C-peptide (≈64 %) concentrations; and improved GT (≈44 %) and insulin resistance (≈46 %) and sensitivity (≈21 %) in HFD-STZ diabetic Wistar rats.	B(1$_{LI}$, 1$_{MT}$); H(0.8$_{LI}$, 0.9$_{MT}$); GT(1.1$_{LI}$, 1$_{MT}$); IN(1.1$_{LI}$, 1.9$_{MT}$); CP (1.2$_{LI}$, 1.9$_{MT}$)	Koothappan et al. [84]
Vitamin U	Zn(Vit U)$_2$Cl$_2$ complex			Inhibited lipolysis in isolated rat adipocytes (Relative IC$_{50}$ to Zinc gluconate = 0.78).	L(1.3$_{ZG}$)	Matsumoto et al. [90]
L-carnitine	Zn(L-carnitine)$_2$Cl$_2$ complex	Zn(O$_4$)		Inhibited lipolysis in isolated rat adipocytes (Relative IC$_{50}$ to Zinc gluconate = 0.72).	L(1.4$_{ZG}$)	Matsumoto et al. [90]
				Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.8 mM). 16 d oral treatment (20 mg Zn/kg) reduced BG (≈32%) level, and improved GT in T2D KK-A^y mice	L(1$_{ZS}$); B(3.6$_{LI}$)	Yoshikawa et al. [89]
Pioglitazone hydrochloride	[Bis(Pioglitazone)zinc(II)]2Cl$^-$ complex	Zn(O$_4$)		Single oral treatments (10 mg/kg bw) reduced BG level (27 %) in alloxan-induced diabetic Wistar rats after 8 h.		Prakash and Iqbal, [83]
Glibenclamide	Bis(Glibenclamide)zinc(II) complex	Zn(N$_2$O$_2$)		Single oral treatments reduced BG (22 %,) level in alloxan-induced diabetic Wistar rats after 8 h.	B(1.2$_{LI}$)	Rasheed et al. [82]
L- and D-asparagine	Zn(L-Asn)$_2$ and Zn(D-Asn)$_2$	Zn(N$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.65 mM).	L(1.3$_{ZS}$)	Yoshikawa et al. [68]
L- and D-proline	Zn(L-Pro)$_2$ and Zn(D-Pro)$_2$	Zn(N$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.89 mM).	L(0.9$_{ZS}$)	Yoshikawa et al. [68]
L- and D-valine	Zn(L-Val)$_2$ and Zn(D-Val)$_2$	Zn(N$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.77 and 0.87 mM for L- and D-isomer complexes, respectively).	L(1.1$_{ZS}$) and L(0.9$_{ZS}$) for L and D isomers, respectively	Yoshikawa et al., 2001b [68]
Glycine	Zn(Gly)$_2$	Zn(N$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.63 mM).	L(1.3$_{ZS}$)	Yoshikawa et al. [68]
L-alanine	Zn(L-Ala)$_2$	Zn(N$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.55 mM).	L(1.5$_{ZS}$)	Yoshikawa et al. [68]
L-aspartic acid	Zn(L-Asp)$_2$	Zn(N$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 1.25 mM).	L(0.7$_{ZS}$)	Yoshikawa et al. [68]
L-glutamine	Zn(L-Gln)$_2$	Zn(N$_2$O$_2$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.84 mM).	L(1$_{ZS}$)	Yoshikawa et al., 2001b [68]
Aspirin	Bis(aspirinato)zinc(II)	Zn(O$_4$)	1.07 (90)	Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 0.86 mM). 14 d i.p. treatment (1.5 - 3 mg Zn/kg) reduced BG level (≈43%) in T2D KK-A^y mice. 24 d oral treatment (15 mg Zn/kg) reduced BG (≈54%) and HbA1c (≈29%) levels and hyperinsulinemia (≈67%) and improved GT (≈36%) in T2D GK rats.	L(1.4$_{ZS}$); For oral treatment: B(3$_{LI}$); H(3.6$_{LI}$); P(1.8$_{LI}$); GT(2.6$_{LI}$)	Yoshikawa et al. [70]
Salicylic acid	Bis(salicylate)zinc(II)	Zn(O$_4$)		Inhibited lipolysis in isolated rat adipocytes (IC$_{50}$ = 1.0mM). 24 d oral treatment (15 mg Zn/kg) reduced BG (≈18%) and HbA1c (≈10%) levels and hyperinsulinemia (≈15%) and improved GT (≈13%) in T2D GK rats.	L(1.2$_{ZS}$)	Yoshikawa et al. [70]

Table 3 (*continued*)

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
5-aminosalicylic acid	Bis(5-aminosalicylate)zinc(II)	$Zn(O_4)$		Inhibited lipolysis in isolated rat adipocytes (IC_{50} = 1.12 mM).	$L(1.1_{ZS})$	Yoshikawa et al. [70]

DEFINITIONS: "ψ" is the anti-diabetic potency ratio of the complexes compared to the precursor ligand of complexes (LI), Zn(II) chloride (ZC), Zn(II) gluconate (ZG), insulin (IN) and metformin (MT) in the following modes of action: Inhibition of lipolysis(LI); increase of insulin (IN) and C-peptide (CP) concentrations; reduction of blood glucose (B) and HbA1c (H) levels and hyperinsulinemia (P); and improvement of glucose tolerance (GT); C_M, coordination mode; IC_{50}, inhibition concentration required to causing 50 % inhibition; Log P, partition coefficients. ABBREVIATIONS: BG, blood glucose; C/EBP-α, CCAAT/enhancer binding protein alpha; GLUT-4, glucose transporter type 4; GPDH, glycerol-3-phosphate dehydrogenase; GT, glucose tolerance; HbA1c, glycated hemoglobin; HFD, high-fat-diet; i.p., intraperitoneal injection; IRTK, insulin receptor tyrosine kinase; PDE, phosphodiesterase; PI3-K, phosphoinositide 3-kinase; PPAR-ϒ, peroxisome proliferator-activated receptor gamma; STZ, streptozotocin; T2D, type 2 diabetes.

tissue and liver. This suggest that the Zn(II) and pioglitazone moiety of the complex may work synergistically to modulate insulin sensitivity and signaling, thus affording a more potent hypoglycemic effect compared to the precursor anti-diabetic drug. Additionally, complexation resulted in smaller molecular size complex compared to the precursor anti-diabetic drug [83]. This property allowed better intestinal absorption, which may also contribute to the better efficacy of the complex. It may, therefore be proposed that Zn(II)-pioglitazone complex exerts anti-diabetic effect by a combination of the "synergistic" and "carrier" modes of action (Fig. 4b).

N-acetyl-ʟ-cysteine (medication for drug overdose), aspirin (medication for pain, fever and inflammation), salicylic acid (medication for acne and dermatitis) and 5-aminosalicylic acid (medication for inflammatory bowel diseases) are the non-anti-diabetic drugs investigated for possible anti-diabetic effects when complexed with Zn(II) (Table 3) [70,85]. Among the Zn(II) complexes of salicyclic acid and derivatives with $Zn(O_4)$ coord. mode, bis(aspirinato)zinc(II) showed the most potent cellular anti-lipolytic activity (IC_{50} = 0.86 mM; Ψ = 1.4_{ZS}) and *In vivo* anti-diabetic activity [BG(≃54 %; Ψ = 3_{LI}); H(≃29 %; Ψ = 3.6_{LI}); P(≃67 %; Ψ = 1.8_{LI}); GT(≃36 %; Ψ = 2.6_{LI})] in T2D GK rats [70]. Although zinc uptake was not measured and compared between animals groups, the fairly good lipophilicity (log P = 1.07) of the Zinc-aspirin complex [70,86] suggests that it exerts its anti-lipolytic and antihyperglycemic effects through a "carrier" mode of action, since aspirin is not a known anti-diabetic agent.

The amino acids were the most studied supplements (8 out of 11 or ≃73 % of studied supplements) regarding the anti-diabetic potentials of their Zn(II) complex forms. It has been reported that amino acids are good zinc chelators that improve intestinal zinc absorption by transporting zinc across enterocytes into circulation [87]. This suggests why anti-lipolytic activity was shown by Zn(II) complexes of different amino acids in adipocytes [30,62,68], with the Zn(II) complex of threonine being the most potent (IC_{50} = 0.54 mM; Ψ = 1.5_{ZS}). Zinc uptake was significantly ($p < 0.01$) increased by Zn(II)-threonine complex relative to Zn(II) salts, which influenced its insulin signaling-related modulatory effects on IRTK, PI3-K, GLUT-4 and PDE activities in adipocytes [30] and anti-diabetic effects [B(2.9_{zc})] in T2D KK-A^y mice after a 14-d i.p. treatment (3 mg Zn/kg bw) [62,68]. Interestingly, toxicological studies in mice [62] and rats [88] showed an oral LD_{50} of 2710 mg/kg bw in female rats. These results suggest that ʟ-threonine-Zn(II) complex may be further studied as a safe anti-diabetic zinc complex supplement with a potent "carrier" mode of action and minimal toxicity.

Furthermore, some other studies reported the anti-lipolytic activity of ʟ-carnitine-Zn(II) complex in adipocytes [89,90]. Interestingly, carnitine has been reported to promote lipolysis and fatty acid oxidation in adipocytes [91], which suggests a strong influence of Zn(II) on carnitine to confer an anti-lipolytic insulin mimetic activity (IC_{50} = 0.8 mM mM; Ψ = 1_{ZS}), as well as BG-lowering (≃32 %; Ψ = 3.6_{LI}) and GT-improving effects in T2D KK-A^y mice [89] (Table 3). Innately, carnitine showed no noticeable glycemic control effects in the T2D KK-A^y mice [89], suggesting that ʟ-carnitine-Zn(II) complex may exert glycemic control effect through the "carrier" mode of action. Specifically, authors proposed that ʟ-carnitine-Zn(II) is incorporated into the body through the carnitine transporters, thus allowing Zn(II) to reach cellular targets [89]. Moreover, the complex did not cause hepatotoxicity in Wistar rats [90], suggesting its safety as a possible anti-diabetic supplement.

Vitamin C (ascorbic acid) and vitamin U (S-methyl-ʟ-methionine) were the other supplements that were probed for the possible insulin mimetic effects of their Zn(II) complexes. Bis(ascorbate)zinc(II) complex, in particular, exhibited promising insulin mimetic activities by inhibiting lipolysis (Relative IC_{50} to Zinc gluconate = 0.69; Ψ = 1.5_{ZG}) [90]. It also showed insulin mimetic effects modulating adipogenesis/adipocyte differentiation through the modulation of the expression of key proteins (C/EBPα and PPARϒ) influencing adipogenesis and formation of insulin-responsive differentiated adipocytes [92] (Table 3). Its modulatory effect on GLUT-4 expression, further suggests it may also

promote adipocyte glucose uptake, while cytotoxicity studies showed the complex does not exhibit antiproliferative effects in adipocytes [92]. Although diabetes may promote vitamin C deficiency, there has been no direct link between vitamin C and insulin signaling or cellular glucose uptake. Additionally, clinical studies have consistently shown that vitamin C does not increase zinc absorption [93,94], thus it remains elusive whether Zn(II)-vitamin C complex exerts insulin mimetic effects through the "carrier" or "synergistic" or "multi-action" mode of action. Nevertheless, *in vitro* studies suggest that ascorbate share with glucose same tissue-transport carrier [95], which might explain how bis(ascorbate)zinc(II) complex is incorporated into cells or tissue to exert its effects.

In general, while most of the supplements studied as anti-diabetic complexes of Zn(II) may act more as carriers of Zn(II) to cellular targets ("carrier" mode of action), Zn(II) complexes of pharmacological agents, like anti-diabetic drugs appear to exert anti-diabetic effects through a "synergistic" and/or "multi-action" mode of action, thus may be studied further as an Zn(II)-adjuvant complexes to improve the efficacy of commercially available anti-diabetic drugs. Nevertheless, Zn(II) complexes of ascorbic acid, L-threonine and L-carnitine may be potential anti-diabetic supplements with minimal side effects relative to anti-diabetic drugs, following appropriate further studies. In particular, Vitamin C is a known physiological antioxidant that boosts the body's defense against oxidative stress and associated diseases [96,97]. Considering that oxidative stress is a major culprit in the several complications linked to diabetes [98], vitamin C may be a promising ligand for the development of dual-acting therapeutic Zn(II) complex with both anti-oxidative and insulin mimetic activities.

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

The anti-oxidative and anti-diabetic potentials of plant polyphenols have been consistently documented [99,100], making them promising plant-derived ligands for multi-acting anti-diabetic and anti-oxidative Zn(II) complexes. Surprisingly, of the 120 anti-diabetic Zn(II) complexes reported in this review, only 6 (5%) are Zn(II) complexes with plant-derived polyphenols as ligands (Fig. 3), which depict a notable scientific gap in the quest for insulin mimetic therapeutic Zn(II) complexes with enhanced pharmacological properties and minimal side effects. Interestingly, all the Zn(II) complexes with plant-derived polyphenols showed promising anti-diabetic effects in diabetic rats that were, in some cases comparable to known anti-diabetic drugs [41,101–105], despite having Zn(O$_4$) C$_M$ (Table 4).

In high-fat-diet (HFD) and streptozotocin (STZ)-induced T2D Wistar rats, a 30 d oral treatment (5 mg/kg bw) of bis(silibinin)zinc(II) complex lead to BG- ($\simeq$56 %; $\Psi = 1_{MT}$) and HbA1c- ($\simeq$43 %; $\Psi = 1_{MT}$) lowering and insulinotropic ($\simeq$122 %; $\Psi = 0.8_{MT}$) effects that were comparable to that of metformin [105]. Moreover, an equivalent treatment of bis(morin)zinc(II) complex in similar T2D rat model reduced BG ($\simeq$61 %) and HbA1c ($\simeq$44 %) levels; increased insulin concentration ($\simeq$30 %) and muscle ($\simeq$109 %) and liver ($\simeq$51 %) glycogen contents; and improved glucose and insulin tolerance [103] (Table 4). Interestingly, the *In vivo* anti-diabetic activity of bis(silibinin)zinc(II) and bis(morin)zinc(II) complexes were accompanied by appreciable anti-oxidative properties [103,105], which may contribute to the improved pancreatic histology of the diabetic rats treated with the bis(silibinin)zinc(II) complex [105] (Table 3). In STZ-induced diabetic Wistar rats, oral treatment of Zn(II) complexes of curcumin (150 mg/kg bw for 45 d), 3-hydroxyflavone (5 mg/kg bw for 30 d) and flavonol lead to reduced hyperglycemia ($\simeq$24, 52 and 58 %, respectively) and HbA1c level ($\simeq$36, 46 and 35 %, respectively), increased insulin ($\simeq$108, 122 and 122 %, respectively) and C-peptide concentrations and improved GT, antioxidant status and pancreatic histology [41,101,102]. Although the 3-hydroxyflavone-zinc(II) and flavonol-zinc(II) complexes showed better activities than the curcumin-zinc(II) complex, complexation of Zn(II) with curcumin notably enhanced its anti-diabetic effects [$\Psi = $ B

(1.7$_{LI}$), B(1.4$_{LI}$) and B(3.3$_{LI}$)] (41), but still needs validation by comparing to standard anti-diabetic drugs.

Although studies have reported that bioactive dietary polyphenols are not good transporters of zinc across intestinal Caco-2 cell monolayers [106], the study on curcumin-zinc(II) complex suggested that complexation with Zn(II) can improve the bioavailability of dietary polyphenols [41]. Combined with the broad anti-diabetic pharmacological properties of plant-derived polyphenols [99,100], the anti-diabetic effects of Zn(II) complexes of plant-derived polyphenol may encompass several anti-diabetic mechanisms, including modulations of insulin signaling, insulin secretion, β-cell function, lipid and glucose metabolism, antiglycation, and antioxidant effects to ameliorate hyperglycemia and diabetic complications, which suggest a combination of the "synergistic" and "multi-action" modes of action (Fig. 4a). Moreover, most of the studied Zn(II)-complexes of plant-derived polyphenols reversed metabolic markers of tissue damage in diabetic animals, suggesting they may not cause tissue toxicity.

At a glance, the studies reporting the anti-diabetic activities of Zn(II) complexes with plant polyphenols as ligands clearly show that the studied complexes are predominantly those of flavone and flavonol ligands, which have shown promising potential therapeutic application. Nevertheless, it recommended that other classes of pharmacologically active plant-derived polyphenols be explored in this area of research. The phenolic acids, which have been reported as promising anti-diabetic and oxidative agents with broad underlying mechanisms [99,100], may be other plant-derived promising targets for the development of multi-acting anti-diabetic and anti-oxidative Zn(II) complexes with broader pharmacological activities and, perhaps, minimal safety concerns.

4. Conclusion

The search for anti-diabetic therapeutic agents with improved pharmacological properties and minimal side effects remains a global concern. Zn(II) mineral has drawn notable attention in this quest, because of its involvement in physiological insulin storage and release. Genomic and clinical studies have revealed several links between diabetes and cellular Zn(II) transport and concentration, while other studies consistently showed the insulin mimetic and glycemic control potentials of Zn(II) and its chloride and sulfate salts. Consequently, Zn(II) has been complexed with numerous synthetic and natural organic ligands, including commercial anti-diabetic drugs, with the aim of developing potent insulin mimetic and glycemic control agents. The outcome of these advances suggested that Zn(II) complexes are potent anti-diabetic agents and Zn(II) can improve the efficacy of its ligands. The type of ligand, lipophilicity and the type of Zn(II)-ligand coordination appear to be the major factors influencing the efficacy of the Zn(II) complexes with the more lipophilic complexes, particularly those containing sulfur atom in the Zn(II)-ligand coordination and some antidiabetic drugs showing the most potent activities.

In spite of the above-mentioned, it is unfortunate that majority (about 72 %) of the Zn(II) complexes that have been synthesized and studied for possible anti-diabetic activities are with synthetic organic ligands that have little or no diabetes-related pharmacological history (Fig. 3). Additionally, the lack of data on the toxicity profile of these complexes presents safety concerns. Of the few (about 7%) natural ligands studied, only maltol has been linked to an anti-oxidative effect in diabetic neuropathy [76]. The activity of most of the complexes of the synthetic and naturally occurring ligands is majorly influenced by the Zn(II) transport ability of the complex to cellular or tissue target to exert pharmacological effect through a "carrier" mode of action. The promising anti-diabetic activities of Zn(II) complexes of ascorbic acid, L-threonine and L-carnitine supplements, as well as some anti-diabetic drugs remain understudied, despite these ligands have health benefits and are non-toxic at recommended doses. Thus, the Zn(II) complexes of these ligands require further clinical investigations as useful

Table 4
Anti-diabetic properties of Zn(II) complexes with plant-derived polyphenols as ligands.

Ligand	Complex	C_M	log P	Anti-diabetic activity and mode(s) of action	ψ	Reference
Curcumin	Curcumin–zinc(II) complex	$Zn(O_2)$		45 d oral treatment (150 mg/kg bw) reduced plasma glucose (≃24 %) and HbA1c (≃36 %) levels and increased plasma insulin levels (≃108 %) in STZ-induced diabetic SD rats	$B(2.7_{ZS}, 1.7_{LI})$; $H(2.3_{ZS}, 1.4_{LI})$; $IN(2.5_{ZS}, 3.3_{LI})$	Al-Ali et al. [41]
Diosmin	Bis(diosmin)zinc(II) complex	$Zn(O_4)$		30 d oral treatment (20 mg/kg bw) reduced BG (≃56 %) and HbA1c (≃43 %) levels and liver glycogen phosphorylase activity (≃16 %); increased insulin (≃27 %) and C-peptide (≃55 %) concentrations, glycogen synthase activity (≃52 %) and muscle (≃84 %) and liver (≃69 %) glycogen contents; and improved GT and IR (≃44 %) in HFD and STZ-induced T2D Wistar rats	$B(1_{MT})$; $H(0.9_{MT})$; $IN(0.8_{MT})$; $CP(0.8_{MT})$; $LG(1_{MT})$; $MG(0.8_{MT})$; $IR(1_{MT})$; $GS(0.9_{MT})$; $GP(0.8_{MT})$	Gopalakrishnan et al. [104]
Morin	Bis(morin)zinc(II) complex	$Zn(O_4)$		30 d oral treatment (5 mg/kg bw) reduced BG (≃61 %) and HbA1c (≃44 %) levels; increased insulin concentration (≃30 %) and muscle (≃109 %) and liver (≃51 %) glycogen contents; and improved GT, IT and antioxidant status in HFD and STZ-induced T2D Wistar rats		Sendrayaperumal et al. [103]
Silibinin	Bis(silibinin)zinc(II) complex	$Zn(O_4)$		30 d oral treatment (5 mg/kg bw) reduced BG (≃56 %) and HbA1c (≃43 %) levels; increased insulin concentration (≃122 %); and improved pancreas histology and antioxidant status in HFD and STZ-induced T2D Wistar rats	$B(1_{MT})$; $H(1_{MT})$; $IN(0.8_{MT})$	Umamaheswari and Subramanian [105]
3-hydroxyflavone	3-Hydroxyflavone–zinc(II) complex	$Zn(O_2)$		30 d oral treatment (5 mg/kg bw) reduced BG (≃52 %) and HbA1c (≃46 %) levels; increased insulin (≃122 %) and C-peptide (≃46 %) concentrations; and improved GT in STZ-induced diabetic Wistar rats	$B(0.9_{GZ})$; $H(1.1_{GZ})$; $IN(0.7_{GZ})$; $CP(0.6_{GZ})$	Vijayaraghavan et al. [101]
Flavonol	Flavonol-zinc(II) complex			30 d oral treatment (5 mg/kg bw) reduced BG (≃58 %) and HbA1c (≃35 %) levels; increased insulin (≃122 %) concentration; and improved GT, antioxidant status and pancreatic histology in STZ-induced diabetic Wistar rats	$B(1_{GZ})$; $H(0.9_{GZ})$; $IN(0.9_{GZ})$	Vijayaraghavan et al. [102]

DEFINITIONS: "ψ" is the anti-diabetic potency ratio of the complexes compared to the precursor ligand of complexes (LI), Zn(II) sulfate (ZS), metformin (MT) and gliclazide (GZ) in the following modes of action: Increase of insulin (IN) and C-peptide (CP) concentrations, liver (LG) and muscle (MG) glycogen contents and glycogen synthase activity (GS); reduction of blood glucose (B) and HbA1c (H) levels and glycogen phosphorylase activity (GP); and improvement of insulin resistance (IR); C_M, coordination mode; Log P, partition coefficients. ABBREVIATIONS: BG, blood glucose; GT, glucose tolerance; HbA1c, glycated hemoglobin; HFD, high-fat-diet; IR, insulin resistance; IT, insulin tolerance; STZ, streptozotocin; T2D, type 2 diabetes.

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nutraceuticals for diabetes management. Plant-derived polyphenols with reported anti-oxidative and anti-diabetic pharmacological credence, as well as minimal safety concerns remain the least studied Zn (II) complex ligands (only about 5%) (Fig. 3), which questions the path to the ongoing quest for therapeutic Zn(II) complexes with improved anti-diabetic effects and minimal safety concerns.

The above scenario buttresses the unfortunate paradigm shift from the use of the relatively safe traditional herbal and natural medicines towards modern synthetic medicines, which have been linked to several unpleasant side effects. Hence, there are call-outs to the nutritional science community, pharmaceutical and nutraceutical companies, drug discovery institutes, the government, food, nutrition and drug regulatory bodies and other stakeholders to pioneer and pilot the redirection of this shift towards nutritional and natural medicine. More natural supplements like vitamins and plant polyphenols, particularly the flavones, flavonols and phenolic acids should be probed for the development of Zn(II) complexes with improved and broader scope of pharmacological activities, as well as minimal safety concerns. Potent Zn(II) complexes of polyphenol, natural ligands and supplements, such as those of maltol, hinokitiol, ascorbic acid, L-carnitine, L-threonine, curcumin, diosmin and silibinin may be further studied as anti-diabetic nutraceuticals with possible lesser side effects than synthetic western anti-diabetic drugs. Following adequate studies, Zn(II) may be recommended as an adjuvant for commercial anti-diabetic drugs to improve their efficacy. Additionally, sulfur atom may be introduced into the Zn(II)-ligand coordination of studied complexes, which may improve their lipophilicity, bioavailability and pharmacological properties.

On the other hand, toxicity evaluation should be critically done on the promising Zn(II) complexes of synthetic organic ligands like bis(1-oxy-2-pyridine-thiolato)zinc(II) to address possible safety concerns on their potential use as anti-diabetic agents. From the outcome of this review, more investigations, including clinical trials and toxicity evaluation, need to be conducted in this area of research in the following years to elucidated and ascertain the health benefits of various Zn(II) complexes in diabetes management.

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Declaration of Competing Interest

There is no conflict of interest associated with this article.

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