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Original article

Suppressive actions on in vitro AGE formation of zinc complexes depend on different coordination modes, such as $Zn(O_4)$ and $Zn(S_2O_2)$

Yuki Naito [1)], Kana Hayashi [1)], Masaki Kojima [1)], Katsuyuki Tsukamoto [1)], Masayuki Yagi [2)], Yutaka Yoshikawa [3)], Hiroyuki Yasui [1)]

1) Laboratory of Analytical and Bioinorganic Chemistry, Kyoto Pharmaceutical University, Kyoto, Japan
2) Anti-Aging Medical Research Center and Glycative Stress Research Center, Doshisha University, Kyoto, Japan
3) Department of Health, Sports, and Nutrition, Kobe Women's University, Kobe, Japan

Abstract

Diabetes mellitus is closely related to diseases such as macrovascular disorders. The main causes of macrovascular disorders are the products of non-enzymatic glycation reactions, i.e., advanced glycation end products (AGEs). Zinc (Zn) complexes are known to exhibit hypoglycemic activity, with some Zn complexes suppressing AGE formation. In this study, we show that the relationship between the suppressive activities against AGE formation in Zn complexes and hypoglycemic activity depends on the coordination mode. We compare the $Zn(O_4)$-type zinc complexes $[Zn(mal)_2]$ and $[Zn(opd)_2]$ and the $Zn(S_2O_2)$-type Zn complexes $[Zn(tmal)_2]$ and $[Zn(opt)_2]$. The formation of fluorescent AGEs is suppressed by all Zn complexes, while pentosidine formation is suppressed by $[Zn(mal)_2]$ (IC_{50} = 308 ± 88 μM) and $[Zn(opd)_2]$ (IC_{50} = 47 ± 7 μM) but not by $[Zn(tmal)_2]$ or $[Zn(opt)_2]$. From our previous studies, the $Zn(S_2O_2)$-type Zn complexes are predicted to exhibit stronger antiglycation effects than $Zn(O_4)$-type Zn complexes: however, $Zn(S_2O_2)$-type Zn complexes do not always exhibit strongly suppress antiglycation or pentosidine formation. We found that $Zn(O_4)$-type Zn complexes exhibit a stronger antiglycation effect than $Zn(S_2O_2)$-type Zn complexes.

***KEY WORDS*:** glycation, pentosidine, Zn complex, $Zn(O_4)$, coordination mode

Introduction

As of 2021, the global population with diabetes is estimated to be 537 million and is expected to reach 783 million by 2045 [1)]. Currently, approximately 20 million cases of diabetes or pre-diabetics have been identified in Japan [2)]. Diabetes mellitus is classified into types 1 and 2 according to its pathogenesis. Continued hyperglycemia caused by both types of diabetes mellitus induces diabetic complications and significantly reduces the patient's quality of life [2)]. To prevent diabetic complications, diabetes treatment involves lifestyle changes and drug therapy with the goal of controlling blood glucose levels.

In addition to the three major complications—ephropathy, retinopathy, and neuropathy—diabetes also causes vascular complications [3-5)]. Non-enzymatic glycative reactions of proteins in the body, followed by their conversion to advanced glycation end products (AGEs), are important causes of these complications [6)]. In food products glycative reactions have distinctive early and late stages. In the early stages of the reaction, reducing sugars are bound to the terminal amino groups of proteins, and Schiff bases and Amadori rearrangement products are generated. In vivo, it has been suggested that dicarbonyl compounds, which are highly reactive and contain aldehyde groups, are increased after meal-induced hyperglycemia, and that these substances may cause protein modification [7)]. One of the compounds produced during the early stage reaction is HbA1c, which is an indicator of past blood glucose status. In the later reaction, AGEs are generated through various reactions [8)]. It has been suggested that the accumulation of AGEs from the insulin biosynthesis stage in patients with type 2 diabetes reduces

Corresponding author: Yuki Naito, PhD
Laboratory of Analytical and Bioinorganic Chemistry,
Division of Analytical and Physical Sciences, Kyoto Pharmaceutical University,
5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan
TEL: +81-75-595-4630 FAX: +81-75-595-4753 e-mail: naito@mb.kyoto-phu.ac.jp
Co-authors; Hiroyuki Yasui
Laboratory of Analytical and Bioinorganic Chemistry,
Division of Analytical and Physical Sciences, Kyoto Pharmaceutical University,
5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan
TEL: +81-75-595-4629 FAX: +81-75-595-4753 e-mail: yasui@mb.kyoto-phu.ac.jp

insulin secretion: thus, suppression of AGE generation has attracted attention for the treatment of diabetes[9]. AGE-induced glycation stress is not limited to diabetes but affects the entire body, contributing to osteoporosis and Alzheimer's disease, for example, and is thought to lead to lifestyle-related diseases and aging[10,11].

Pentosidine (*Fig.1*) is a fluorescent AGE isolated from human brain dura mater collagen in 1989[12] and is produced from the amino termini of ribose, arginine, and lysine. Plasma pentosidine levels are elevated in diabetic patients and in patients with chronic renal failure and are currently used as early clinical markers of nephropathy. Recently, pentosidine has attracted attention as a biological indicator of bone aging, and is therefore expected to be facilitate the diagnosis of osteoporosis[13].

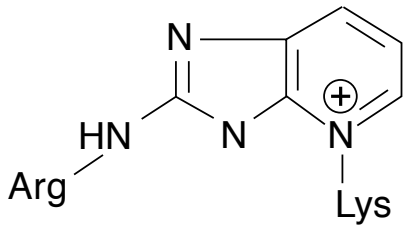
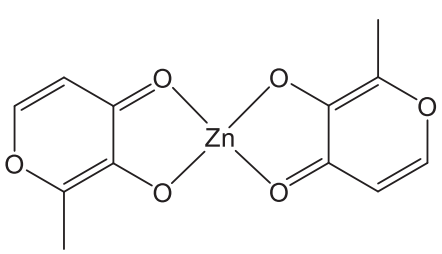
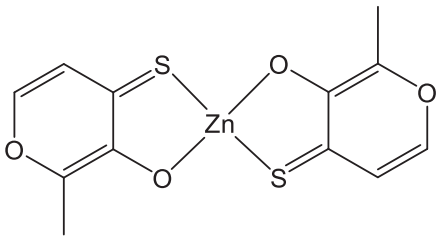


Fig.1. **Structure of pentosidine**

Zn is an essential trace element present in the body at approximately 2 g, and the relationship between Zn and diabetes has long been known[14,15]. In 1980, an experiment using fat cells from rats showed the insulin-like effect of Zn ions[16]. In 1998, water containing Zn chloride ($ZnCl_2$) was fed to ob/ob mice—a model of type 2 diabetes—which reduced fasting blood glucose levels by approximately 25 %[17]. In 2000, it was reported that the bis(maltolato)Zn(II) complex ($[Zn(mal)_2]$)—a Zn complex—exhibited high insulin-like activity[18]. We previously demonstrated the antidiabetic effects of Zn complexes such as $[Zn(mal)_2]$[19,20]. Recently, we reported that enhanced activation of the insulin signaling pathway by a Zn complex induced antidiabetic effects in a mouse model of diabetes[21]. Furthermore, we reported for the first time the antiglycosylation activity of Zn complexes[22]. Further elucidating the effects of Zn complexes on protein glycation may provide important insights for the prevention of diabetic complications. The Zn atom in $Zn(O_4)$-type Zn complex is coordinated by four O atoms, while that in $Zn(S_2O_2)$-type Zn complexes is coordinated by two O atoms and two S atoms, and that in $Zn(N_2O_2)$-type Zn complexes is coordinated by two O atoms and two N atoms[23]. A comparison of the antidiabetic effects of the various coordinated forms is useful for clarifying the properties of Zn complexes. In this study, we investigated the effects of the coordination form of Zn complexes on AGE formation, with a particular focus on the $Zn(O_4)$-type coordination forms, *i.e.*, $[Zn(mal)_2]$ and the bis(2-hydroxypyridine *N*-oxide)Zn complex ($[Zn(opd)_2]$), and $Zn(S_2O_2)$-type coordination forms, i.e., the bis(thiomaltolato)Zn(II) complex ($[Zn(tmal)_2]$) and bis(2-mercaptopyridine *N*-oxide) Zn(II) complex ($[Zn(opt)_2]$) (*Fig.2*). The difference in the suppression of AGE formation due to the coordination mode of the Zn complexes was investigated, and the amount of pentosidine produced by the glycation reaction was quantified via high-performance liquid chromatography (HPLC) with fluorescence detection.



$[Zn(mal)_2]$



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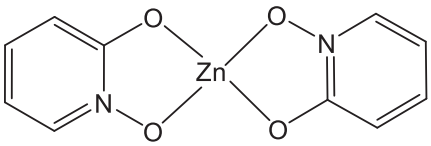
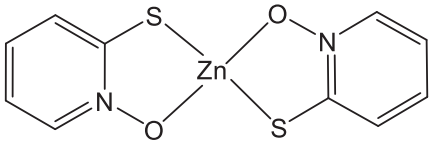


$[Zn(opd)_2]$



$[Zn(opt)_2]$

Fig.2. **Structures of the tested Zn complexes**

Materials and methods

Chemicals

Zn sulfate heptahydrate ($ZnSO_4 \cdot 7H_2O$), di-potassium hydrogen phosphate, sodium borohydride, sodium hydroxide (for volumetric analysis), tris(hydroxymethyl)aminomethane, acetonitrile, and acetic acid were obtained from Nacalai Tesque, Inc. (Kyoto, Japan). Lithium hydroxide monohydrate, toluene, sea sand (for chemicals), chloroform, ethanol, methanol, Zn acetate dihydrate, dimethyl sulfoxide (DMSO), D-(+)-glucose, sulfuric acid, potassium dihydrogen phosphate, formic acid, 6 M hydrochloric acid, 100 w/v % trichloroacetic acid solution, ammonium formate, and carboxymethyl cellulose sodium salt were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). 3-Hydroxy-2-methyl-4-pyrone (maltol), Lawesson's reagent, and aminoguanidine (AG) were obtained from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Silica gel 60 (0.040-0.063 mm) was obtained from Merck Millipore (Germany), and human serum albumin (HSA) was obtained from Sigma–Aldrich (USA). A pentosidine standard was obtained from GL Sciences (Tokyo, Japan).

Preparation of Zn complexes

$[Zn(mal)_2]$, $[Zn(opd)_2]$, and $[Zn(opt)_2]$ were prepared as previously described[24]. The prepared complexes were characterized via elemental analysis and infrared (IR) absorption spectroscopy (Shimadzu FT-IR 8100A on KBr pellets; SHIMADZU Co., Kyoto, Japan).
Anal. Found (%): C, 39.60; H, 4.11. Calcd. (%) for $[Zn(mal)_2] \cdot 2.7H_2O$; C, 39.57; H, 4.26. IR spectra (complex/ligand); υ C = O; 1614 cm^{-1}/1653 cm^{-1}.
Anal. Found (%): C, 41.07; H, 2.85; N, 9.44. Calcd. (%) for $[Zn(opd)_2] \cdot 0.4H_2O$; C, 41.02; H, 3.03; N, 9.57. IR spectra (complex/ligand); υ pyridine ring; 1,626 cm^{-1}/1,638 cm^{-1}, 1,524 cm^{-1}/1,537 cm^{-1}.
Anal. Found (%): C, 26.97; H, 2.46; N, 6.23. Calcd. (%) for $[Zn(opt)_2] \cdot 7.1H_2O$; C, 26.95; H, 5.02; N, 6.29. IR spectra (complex/ligand); υ S-H; absent/2,600 cm^{-1}.

Thiomaltol (tmal)—the ligand of the $[Zn(tmal)_2]$ complex—and $[Zn(tmal)_2]$ were prepared using a previously reported method[25-27]. The resulting yellow precipitate was collected via vacuum filtration, washed several times with water, and dried overnight *in vacuo* (yield: 89.44 %).
Anal. Found (%): C, 41.23; H, 2.76. Calcd. (%) for $[Zn(tmal)_2] \cdot 0.1H_2O$; C, 41.24; H, 2.94. IR spectra (complex/ligand); υ C = S; 1,573 cm^{-1}/1,622 cm^{-1}. ^{13}C-NMR (DMSO-d6). Tmal: 185.98 (C3), 150.59 (C2), 149.01 (C5), 146.85 (C1), 124.82 (C4), 15.30 (C6). $[Zn(tmal)_2]$: 175.52 (C3), 159.34 (C2), 147.18 (C5), 154.00 (C1), 122.54 (C4), 16.64 (C6).

Measurement of fluorescent AGEs in HSA-glucose glycative reaction model

The suppressive effect of Zn complexes on AGE formation was evaluated using the HSA-glucose glycative reaction model, as described in previous reports[28,29]. AG—a glycation inhibitor—was used as a positive control. Sample buffer (50 mM phosphate buffer (pH 7.4) and HSA (8 mg/mL)) was prepared. The Zn complexes were dissolved in 100 % DMSO and added to the sample buffer in 1 % DMSO. The samples were then incubated at 60 °C for 40 h and centrifuged at 18,000 × g, 25 °C for 10 min, and the supernatants were collected. The fluorescence intensity of the supernatants was measured to quantify the fluorescent AGEs (excitation wavelength 360 nm/fluorescent wavelength 450 nm) using a 96-well black-bottom plate with a TECAN infinite F200PRO (TECAN, Switzerland). The obtained values were calculated as AGE formation rates using the formula presented below. The fluorescence values were adjusted using a 5 μg/mL quinine sulfate solution.

AGE formation rate (%) = 100 – suppression rate (%)
Suppression rate (%) = $\{1 - (A - B) / (C - D)\} \times 100$
A: Reaction solution (sample buffer + 200 mM glucose + tested sample)
B: Reaction solution without glucose (sample buffer + tested sample)
C: Without sample (sample buffer + 200 mM glucose)
D: Blank (sample buffer)

Measurement of pentosidine in HSA-glucose glycative reaction samples via HPLC-FL method

In accordance with previous reports, the supernatants of the HSA-glucose glycative reaction samples were pretreated[30,31]. The supernatants were reduced in advance with a sodium borohydride solution (200 mM, pH 9.2) to prevent pentosidine formation during hydrolysis for 30 min at 25 °C. Proteins were removed using 20 % and 5 % TCA solutions. After the supernatant was removed, ultrapure water was added, and the precipitate was resolved. Iron-free hydrochloric acid (6 M) was added, and the mixture was heated at 105 °C for 18 h for hydrolysis. After hydrolysis, 1.5 M Tris was added to dilute the hydrochloric acid in the solution, which was then centrifuged using a Centricut Ultra Mini (KURABO, Japan). The hydrolyzed samples were pretreated using a Monospin AG column (GL Sciences, Japan) and the eluates were obtained using a measurement sample. Analytical HPLC was performed using a Shimadzu LC-20AB (Shimadzu Corporation, Kyoto, Japan) with a reverse phase silica gel Inert Sustain AG column (3 μm, 100 mm × 4.6 mm ID; GL Sciences) and an RF-20A (Shimadzu Corporation) fluorescence detector. The measurement conditions for HPLC were as follows: column temperature, 20 °C; eluent, solution A (0.1 % formic acid (v/v) in H_2O) and solution B (100 % acetonitrile); elution conditions, step gradient (0 % B (0–10 min), 50 % B (10–12 min), 0 % B (12–30 min)); flow rate, 1.0 mL/min; detection method; fluorescence, (excitation [Ex] wavelength 325 nm, emission [Em] wavelength 385 nm); injection volume, 20 μL.

Statistical analysis

Data are expressed as the mean ± standard deviation. Multiple comparisons with the AG group for the HSA-glucose glycation model and with $ZnSO_4$ for the quantitative analysis of pentosidine were performed using analysis of variance and Dunnett's post hoc test with the Bell Curve for Excel (Social Survey Research Information Co., Ltd., Japan).

Results

Suppression of fluorescent AGE formation by Zn complexes in HSA-glucose glycation model

The IC_{50} values were calculated from the percentage suppression of AGE formation by the test substance and AG (***Fig. 3, Table 1***). All the Zn compounds, including $ZnSO_4$ and the Zn complexes, suppressed AGE formation significantly more than AG. The Zn complexes exhibited a concentration-dependent suppressive effect. In particular, $[Zn(opd)_2]$—a $Zn(O_4)$-type complex with a pyridine moiety—exhibited an approximately 10 times stronger antiglycation effect than AG. When the ligands were compared with AG, opd and tmal exhibited significantly suppressed effects; however, opt—the ligand of $[Zn(opt)_2]$—did not have a suppressive effect within the concentration range examined. The IC_{50} values of $[Zn(opd)_2]$ were lower than those of the corresponding ligands, indicating that complexation enhanced the antiglycation effect. The IC_{50} values of mal and opd were approximately twice those of the respective complexes.

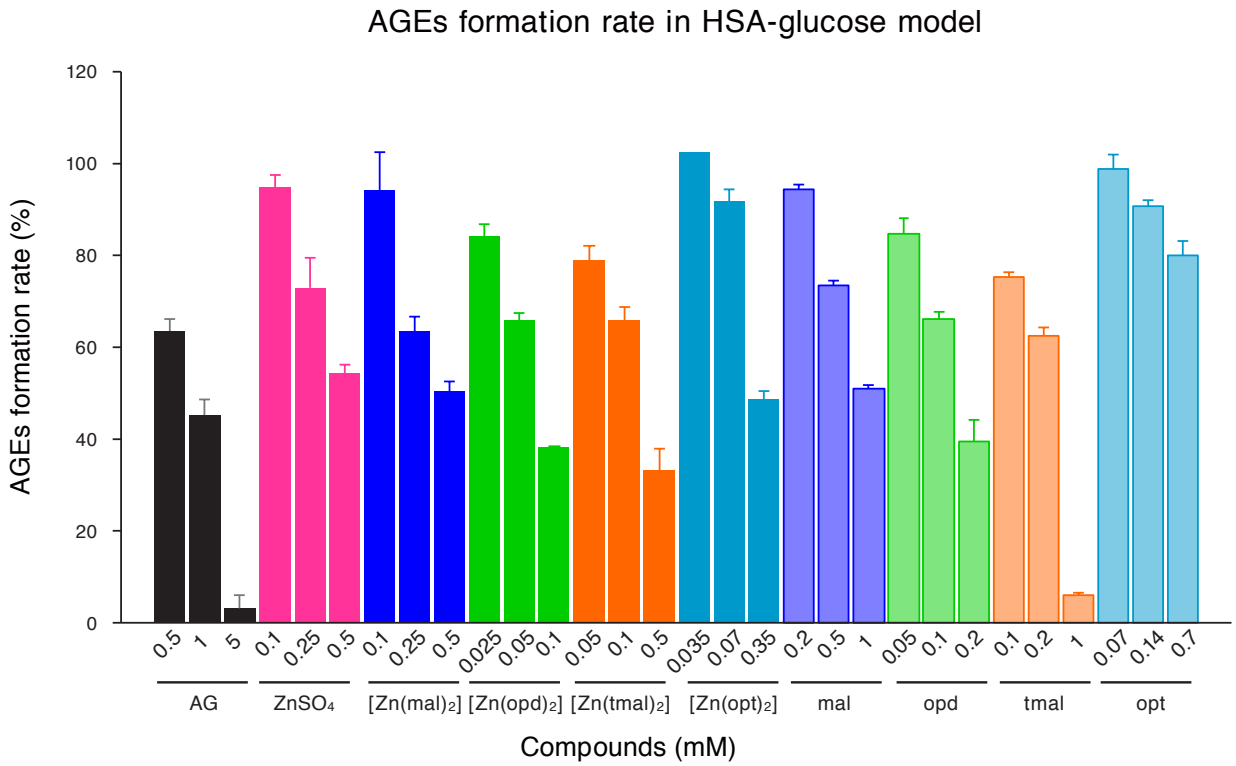


Fig. 3. **AGE formation rates of the tested compounds in the HSA-glucose model**

Table 1. IC_{50} values of the AGE formation rate and pentosidine formation rate in glycative reaction samples

Compounds	IC_{50} (μM) in HSA-Glucose model	IC_{50} (μM) of pentosidine formation
AG	839 ± 79	n. d.
$ZnSO_4$	609 ± 93 **	642 ± 209
$[Zn(mal)_2]$	539 ± 106 **	308 ± 88 ††
$[Zn(opd)_2]$	74 ± 2 **	47 ± 7 ††
$[Zn(tmal)_2]$	223 ± 56 **	n. d.
$[Zn(opt)_2]$	351 ± 39 **	n. d.
mal	1,093 ± 27	472 ± 177
opd	144 ± 6 **	84 ± 9 ††
tmal	254 ± 11 **	287 ± 164 ††
opt	n. d.	n. d.

The values are expressed as mean ± standard deviation.
** Significance at $p < 0.01$ vs. AG
†† Significance at $p < 0.01$ vs. $ZnSO_4$

Quantitative analysis of pentosidine using HPLC-FL method

The measurements of each sample are presented in ***Fig. 4*** and ***Table 1***. Both $Zn(O_4)$ complexes suppressed pentosidine formation in a concentration-dependent manner. In contrast, the $Zn(S_2O_2)$ complexes $[Zn(tmal)_2]$ and $[Zn(opt)_2]$ did not suppress pentosidine formation at the tested concentrations. With the exception of opt, the ligands of the tested Zn complexes suppressed pentosidine formation.

Discussion

AGEs, which are produced by an accelerated glycative reaction throughout the body under hyperglycemic conditions, have attracted attention in various studies on the treatment studies of diabetes and Alzheimer's disease, because their accumulation is associated with diverse pathological conditions. They are thought to be involved in diabetic complications and aging in general[29]. Therefore, it is expected that further elucidation of the relationship between AGEs and pathological conditions will enable the application of AGEs in the treatment of diabetes and other diseases. Various substances with antiglycation effects, such as flavonoids and L-carnitine, have been evaluated[32-35].

To better understand the antiglycation effects of Zn complexes, we examined Zn complexes with different coordination forms: $Zn(O_4)$ complexes and $Zn(S_2O_2)$ complexes. The evaluation of the suppressive effect of the Zn complexes on AGE formation confirmed that the Zn complexes have an antiglycation effect. The IC_{50} values of mal and opd were approximately twice those of their respective complexes: therefore, the ligand may also influence the antiglycation effect. For a more detailed evaluation of AGEs, a quantitative analysis of pentosidine was performed using HPLC-FL. Pentosidine is a fluorescent AGE. The pentosidine concentration in the blood has been studied as a biomarker of diseases such as diabetes and renal failure[36]. In the HPLC-FL evaluation, the sample solution was glycated HSA-glucose glycative reaction, and pentosidine was extracted. The experimental results indicated that the pentosidine peak appeared at approximately 9.6 min, and the calibration curve exhibited good linearity (data not shown). Concentration-dependent suppression of pentosidine formation was observed with all $Zn(O_4)$-type complexes and ligands: however, the $Zn(S_2O_2)$-type complexes did not suppress pentosidine formation. In other words, the $Zn(O_4)$-type Zn complexes exhibited stronger antiglycation effects. In our previous studies on the antidiabetic effects of Zn complexes, $Zn(S_2O_2)$-type Zn complexes exhibited far stronger insulin-like and blood lowering effects than $Zn(O_4)$-type Zn complexes, maintaining their complex structure according to the hard and soft acid-base rule[37]. The antiglycation effect of Zn complexes is attributed to the suppression of the glycative reaction by the binding of Zn complexes to HSA. $Zn(S_2O_2)$-type Zn complexes have higher stability constants than $Zn(O_4)$-type Zn complexes and are therefore less likely to undergo ligand-exchange reactions

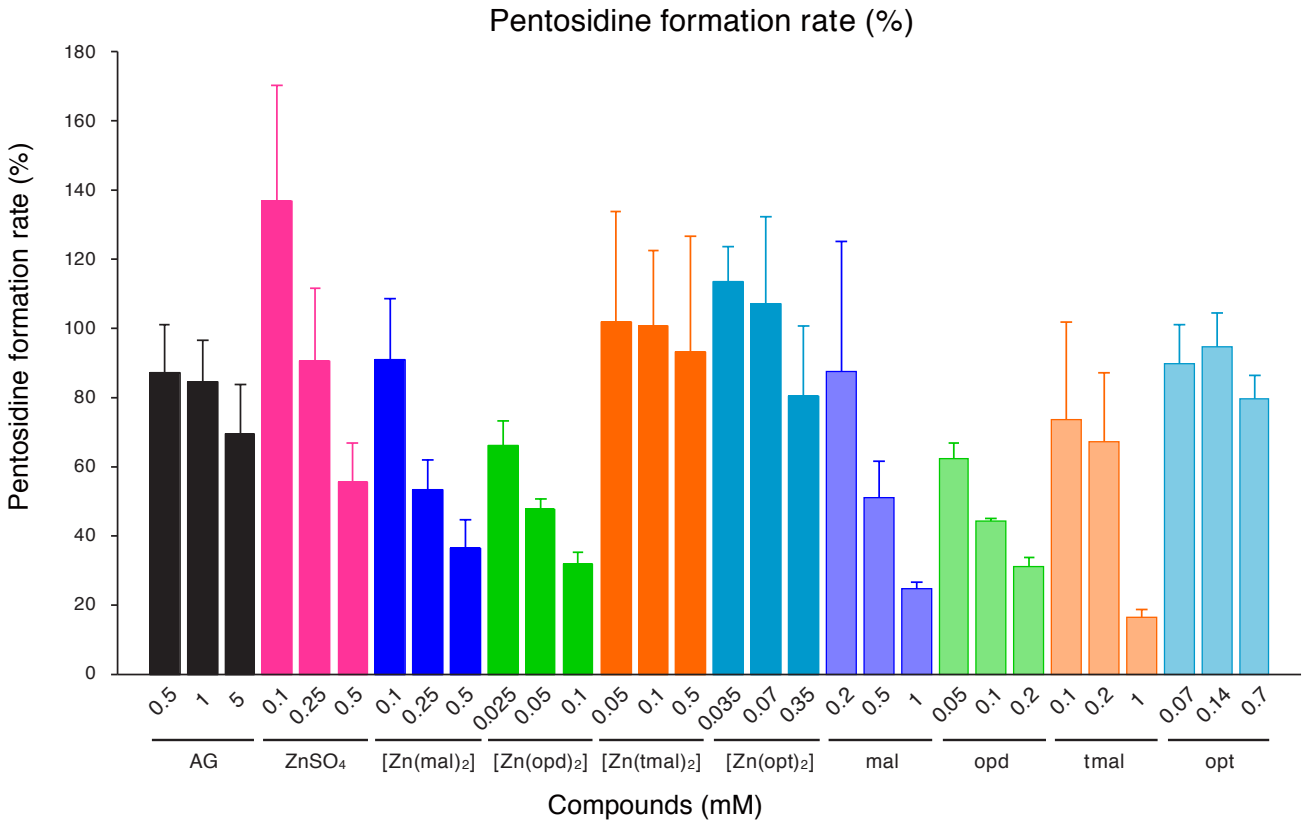


Fig. 4. **Pentosidine formation rates of the tested compounds**

(*e.g.*, with amino acid residues in HSA molecules). Thus, $Zn(S_2O_2)$-type Zn complexes were less likely to bind to HSA molecules, and no suppression of pentosidine production was observed. The Zn ions in $[Zn(mal)_2]$ and $[Zn(opd)_2]$ may bind to the lysine residues of HSA via ligand-exchange reactions and thus suppress the formation of pentosidine.

To date, the long-term effects of the antiglycation action of Zn complexes and their effects on proteins *in vivo* have not been investigated: however, if the relationship between AGEs and Zn complexes can be established, in addition to the antidiabetic effects reported thus far, long-term administration of Zn complexes may prevent diabetic complications and suppress the progression of other diseases. In the future, it will be necessary to consider the distinction between the glycation in food; Maillard reaction and the glycation in the body; glycation stress. Our future task is to create an in vitro experimental system that mimics the glycation reaction in living organisms, evaluate the inhibitory effect of Zn complexes on AGE formation, and elucidate the mechanism of its action.

Conflict of Interest statement

The authors declare no conflicts of interest.

Acknowledgments

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