

MYCO-MEDIATED SYNTHESIS AND α -GLUCOSIDASE INHIBITORY ACTIVITY OF SILVER NANOPARTICLES PRODUCED BY XYLARIACEOUS FUNGI

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Abstract. Metal nanomaterials could be applied in various fields and could be synthesized via living organisms such as plants, bacteria and fungi. Here, the ability of *Xylaria* sp.5 to produce silver nanoparticles (AgNPs) and α -glucosidase inhibitory activities by the AgNPs produced by *Xylaria* sp.5 were investigated. The culture broth of *Xylaria* sp.5 was used to synthesize AgNPs by using 0.1 M of silver nitrate (AgNO₃) solutions. The mycogenic crystals were investigated for the morphological characteristics and chemical composition by scanning electron microscope (SEM) equipped with energy dispersive X-ray spectroscopy (EDS), Fourier-transform infrared spectroscopy (FTIR) and X-ray powder diffraction (XRD). The results showed that AgNPs were successfully produced. Moreover, AgNPs were tested for α -glucosidase inhibitory activities. The crude enzyme derived from rat intestine consisted of maltase and sucrase. The percentage of inhibition at 50 mg/ml of maltase and sucrase was 63.21 ± 0.67 and 54.42 ± 0.11 , respectively. This study demonstrated that the supernatant culture broth of *Xylaria* sp.5 can be used to synthesize AgNPs which possess α -glucosidase inhibitory activities. Collectively, this method could be a promising alternative for low cost and non-polluting production of AgNPs which could be potentially utilized for the treatment of type 2 diabetes mellitus.

Keywords: *green synthesis, biosynthesis, metal nanomaterial, antidiabetic activity, Xylaria sp.*

Introduction

Nanobiotechnology is an integrated technology between biotechnology and nanotechnology to engineer the value-added products at nanoscale (Adebayo et al., 2021). This discipline indicates the biological research with different fields of nanotechnology, including the production of nanoparticles by living organisms. Currently, the nanoparticles are synthesized by chemical and physical methods, but these methods have some potential drawbacks. They can generate toxic byproducts that can be harmful to the environment and human health. These methods can also be expensive, complex, and difficult to scale causing nonreproducible quality and performance (Mohd Yusof et al., 2019). Additionally, the use of nanoparticles synthesized by chemical and physical methods may face additional regulatory

challenges due to their potential toxicity and environmental impact (Nguyen and Nguyen, 2019).

To address these shortcomings, biological methods could be a promising alternative because these methods require mild reactions, which makes them environmentally friendly. Nowadays, nanomaterials are widely applied in daily life products that directly contact with the human body such as pharmaceutical products and cosmetics (Sutharappa Kaliyamoorthy, et al., 2022; Santhosh et al., 2022). Therefore, biosynthetic nanoparticles are more acceptable in the field of pharmaceutical and medical applications (Mousavi, et al., 2018). Silver nanoparticles (AgNPs) are one of the metal nanoparticles that play a major role in a wide range of applications such as antibacterial, antiviral, anticancer, antimalarial, antioxidant and anti-Alzheimer activity (Mousavi et al., 2018; Popli et al., 2018; Lee and Jun, 2019). Diabetes mellitus is a metabolic disorder, and it is a term for several conditions, including hyperglycemia, altered lipid, protein, and carbohydrate metabolism (Rodríguez-Correa et al., 2020). Both type 1 and 2 diabetes cause a high blood sugar level but differ in their pathogenesis. Type 1 diabetes or insulin-dependent diabetes is a chronic disease caused by the inability of the pancreas to produce insulin due to destruction of beta cells, while type 2 diabetes or non-insulin dependent diabetes is mainly related to insulin resistance (Shanker et al., 2017). Type 2 diabetes is a major global health issue affecting millions of people worldwide. According to the International Diabetes Federation, in 2021, approximately 537 million people worldwide had diabetes, with 90-95% having type 2 diabetes (International Diabetes Federation, 2021).

In South Asia, people have been under greater risk, and most of patients have type 2 diabetes mellitus (Narayan and Kanaya, 2020). Treatment for type 2 diabetes is to reduce the level of blood sugar after a meal by using the carbohydrate hydrolytic enzymes inhibitors such as acarbose, voglibose and miglitol (Xiong et al., 2020). It has been reported that the metal nanoparticles, such as silver, gold, and zinc oxide possess strong antidiabetic activity by inhibiting enzyme activity involving in glucose metabolism which enables improved glucose homeostasis and insulin sensitivity and could be potentially utilized for therapeutic inhibitors (Guo et al., 2020). α -Glucosidase is a key enzyme associated with the digestion of carbohydrates and is a target for the treatment of type 2 diabetes. Inhibition of α -glucosidase activity causes a reduction in postprandial glucose levels and improved glucose homeostasis. Several natural and synthetic α -glucosidase inhibitors have been developed and are used in the management of diabetes (Dirir et al., 2022).

Numerous studies have documented the biosynthesis of silver nanoparticles (AgNPs) using living organisms, including plants, bacteria, and fungi (Siddiqi et al., 2018). However, there are a few reports on synthesis of AgNPs by the xylariaceous fungi. The genus *Xylaria* is macro-fungi of the family Xylariaceae which are widely distributed in tropical and temperate region and are the potential source of bioactive secondary metabolites for novel medicines, biocatalysts, agrochemicals, and nutraceuticals (Backer and Stadler, et al., 2021). Moreover, the bioorganic compounds, including anthraquinones, xanthenes, terpenoids, polyphenolics and flavonoids have been also produced by fungi. These bioactive compounds are the excellent capping and reducing agents in the process of metal nanoparticles synthesis (Guilger-Casagrande and Lima, 2019; Zahoor et al., 2021).

Although fungi are the center of interest in research of biosynthesis of metal nanoparticles, xylariaceous fungi have been reported in very few. Sumanth et al. (2020) reported the biosynthesis of zinc oxide nanoparticles (ZnO NPs) from *Xylaria acuta*.

The synthesized ZnO NPs showed an excellent antimicrobial and anticancer activity. Choong et al. (2018) studied the green synthesis of AgNPs by endophytic fungi isolated from orchids (*Dendrobium* sp.) and they found that *Xylaria feejeensis* exhibited the ability to synthesize AgNPs which showed highest inhibition against *Escherichia coli*, *Micrococcus luteus* and *Enterobacter aerogenes*. Furthermore, xylaric acid was the bioactive terpenoids produced by *Xylaria primorskensis*. This compound demonstrated a high potential to produce AgNPs and showed bioactivity such as antioxidant, antibacterial, and anticancer activity against human lung cancer cells. Xylaric acid AgNPs not only enhanced anticancer activity but also induced apoptosis of A549 cell line (human lung cancer cell line) (Adnan et al., 2018). The goal of this research was to investigate the ability of *Xylaria* sp.5 for synthesis of AgNPs and evaluate the potential of myco-derived AgNPs in α -glucosidase inhibitory activity.

Materials and methods

Fungal strain and cultivation

Stromata of *Xylaria* sp.5 were collected from Ko Chang Island, Mu Ko Chang National Park, Trat province, Thailand. This sampling was conducted in June 2018 and was sub-cultured at monthly intervals (Sutjaritvorakul and Chutipaijit, 2020). The fungi were identified and authenticated on the basis of macro- and microscopic characteristics according to Koyani et al. (2016). To obtain pure culture, the stromatal surface were washed with sterile distilled water and were isolated from ascospores by single spore isolation technique under light microscopy (Velmurugan et al., 2013). The fungal cultures were cultivated on potato dextrose agar (PDA; 4 g/l potato starch, 20 g/l dextrose and 15 g/l agar). The pure culture was maintained on PDA in room temperature (25°C) (Lopez et al., 2022).

Myco-mediated synthesis of silver nanoparticles

The mycelium disk (5 mm in diameter) of *Xylaria* sp.5 were inoculated into the Erlenmeyer culture flasks containing 100 ml of potato dextrose broth (PDB; 4 g/l potato starch and 20 g/l dextrose) and incubated at 25°C for 7 days (Fig. 1A). After culture period, the culture broth was filtered by using Whatman No.1 filter paper. The filtrate was added to silver nitrate (AgNO₃) solution of 1 mM concentration to formation of AgNPs. The ratio of culture broth to AgNO₃ was 1:1 (v/v) and incubated for 48 h at room temperature (Sutjaritvorakul and Chutipaijit, 2018). In this research, PDB was used as a negative control. The mixture was centrifuged for 15 min at 12000 rpm. The mycogenic precipitates were washed with sterilized distilled water and were dried in hot air oven at 60°C for 10 h. Finally, it was maintained in a desiccator (Li et al., 2021; Mathur et al., 2021).

Physicochemical characterization of the mycogenic silver nanoparticles

The morphological investigation of mycogenic AgNPs and the elemental composition analysis was carried out by Scanning electron microscopy (SEM) equipped with Energy dispersive X-ray spectroscopy analysis (EDX) (JEOL: JSM7610f, Oxford: X-MAXN) operated at 15.0 kV. SEM analysis was conducted to determine the surface topology of mycogenic AgNPs, and the elemental mapping technique was performed to investigate the distribution of metal species in the nanoparticles. Moreover, the mycogenic AgNPs were determined by X-ray diffraction (XRD, Rigaku, SmartLab). The investigation

operated at 40 kV using Cu–K α radiations in 2θ range from 5° to 80° . Fourier transform infrared spectroscopy (FTIR, PerkinElmer Scientific, Spectrum Two FT-IR Spectrometer) was performed to identify the possible functional groups of biomolecules responsible for capping of AgNPs. The measurements were carried out in the range of $400\text{--}4000\text{ cm}^{-1}$ (Sutjaritvorakul and Chutipaijit, 2018; Ahsan et al., 2020).

α -Glucosidase inhibitory activity from rat intestine

Measurement of α -glucosidase inhibitory activity of biosynthesized AgNPs was measured by the method developed by Dumsud et al. (2021). For this research, α -glucosidase is crude enzyme produced from rat intestine consisting of maltase and sucrase. The enzyme was received from rat intestinal acetone powder (Sigma, St. Louis); then the powder (1 g) was homogenized with 0.9% NaCl (30 ml) and followed by centrifugation (12,000 g) for 30 min. Briefly, 10 μ l of the test sample supplemented with myco-derived AgNPs and 10 μ l of substrate solution (maltose: 10 mM, 20 μ l; sucrose: 100 mM, 20 μ l, respectively) in 0.1 M phosphate buffer (pH 6.9) were mixed, and the reaction mixture was incubated at 37°C for 20 min (maltose) and for 60 min (sucrose). The mixtures were discontinued in boiling water for 10 min to stop reaction, and glucose assay were determined by the glucose assay kit (Proficient lab) and measured at 500 nm. Acarbose was used as the positive control for this experiment. The percentage of inhibition was calculated by using the following equation:

$$\text{The percentage of } \alpha\text{-glucosidase inhibitory activity} = \frac{(A_0 - A_1)}{A_0} \times 100 \quad (\text{Eq.1})$$

where A_0 denotes the absorbance of the control and A_1 denotes the absorbance of the sample.

The percentage of α -glucosidase inhibitory activity was calculated according to *Equation 1*. The results were presented as the mean value of three independent replicates with standard deviations (SD).

Results and discussions

Physicochemical characterization of the mycogenic silver nanoparticles

When fungal cell filtrate was added to AgNO_3 solution, the color changed from light yellow to dark brown (*Fig. 1B, C*). After a reaction period of 48 hours, the resulting mycogenic precipitates were examined for morphological characteristics using Scanning Electron Microscopy (SEM). The SEM images shown in *Figure 2* displayed mostly spherical particles with a smooth surface. The mycogenic nanoparticles were further analyzed and identified using Energy Dispersive X-ray Spectroscopy (EDS) and X-ray diffraction (XRD). The SEM-EDS spectrum showed strong peaks of silver (Ag) at 3 KeV for elemental compositional analysis. The maximum distribution of silver elements was observed through elemental mapping investigation of the nanoparticles (*Fig. 3*). The XRD pattern of the mycogenic synthesis crystals (*Fig. 4*) exhibited diffraction peaks at 2θ values of 38.10° , 44.28° , 64.42° and 77.37° , corresponding to 111, 200, 220 and 331, respectively. The presence of unindexed peaks was due to the mycochemical compounds produced by *Xylaria* sp.5. The XRD pattern confirms that the mycogenic crystals were silver nanoparticles (AgNPs).

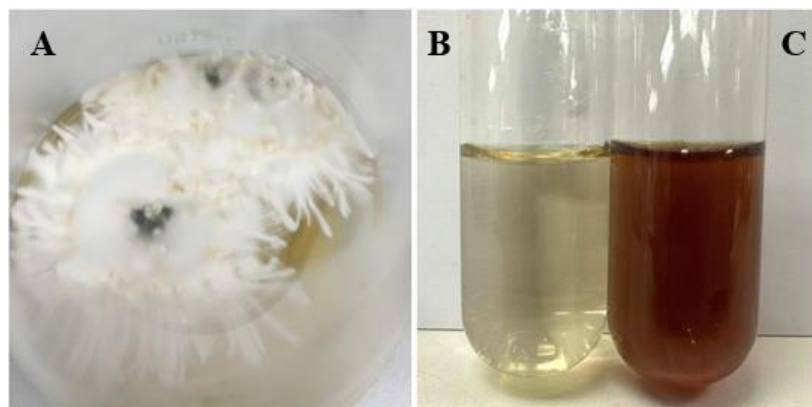


Figure 1. Cultural morphology on PDB (A); The fungal cell filtrate (B); The reaction mixture (C)

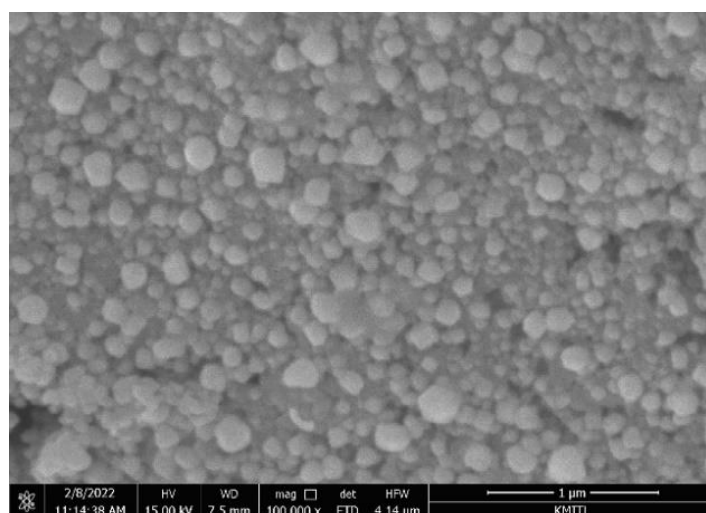


Figure 2. Scanning electron micrograph of mycogenic crystals synthesized by *Xylaria sp.5* corresponds to 1 μ m scale bar

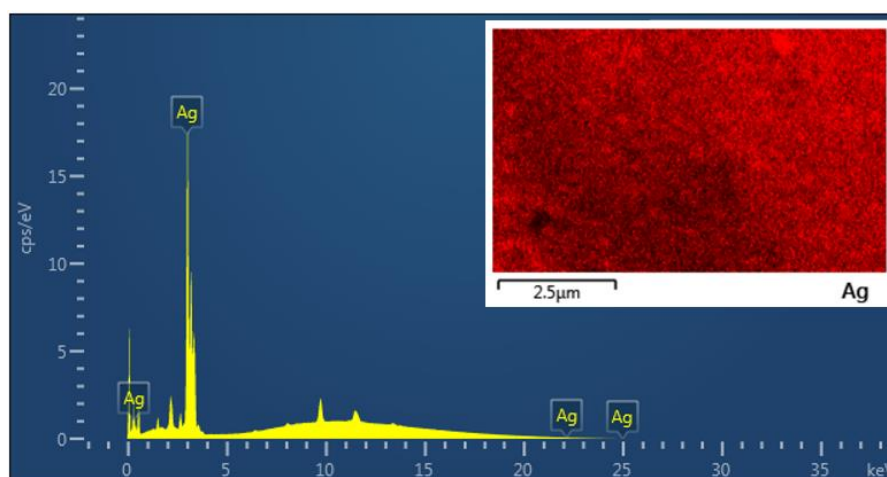


Figure 3. Spectrum analyzed by SEM-EDS and elemental mapping analysis of mycogenic crystals synthesized by *Xylaria sp.5*

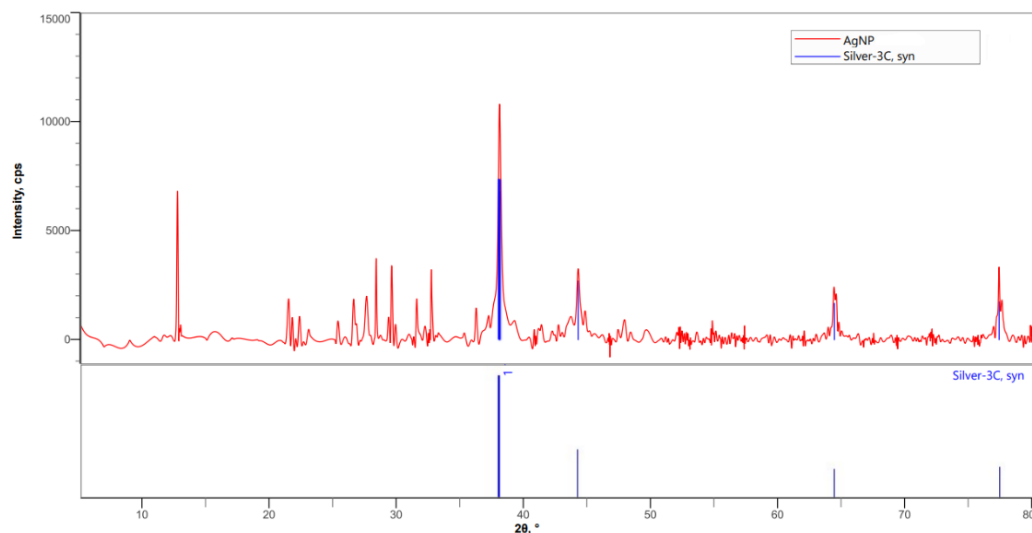


Figure 4. XRD pattern of mycogenic crystals synthesized by *Xylaria sp.5*

Moreover, Fourier transform infrared (FTIR) spectroscopy was performed to investigate the possible functional groups of fungal culture broth and the FTIR spectrum were exhibited in *Figure 5*. The spectrum showed the presence of hydroxy group (-O-H stretch) in the fungal broth is certain from the intense vibration at approximately 3276.07 cm^{-1} (Afolabi et al., 2017). The bands observed at 2932.27 cm^{-1} represents C-H stretch or/and free amino acids (NH_2) (Kędzierska-Matysek et al., 2018; Khalir et al., 2020). Another strong peak was observed at 1567.39 cm^{-1} indicating the stretching vibration of C=O and C=C (Alshuiael and Al-Ghouti, 2020). The peak of 1390.28 cm^{-1} , 1065.65 cm^{-1} and 539.76 cm^{-1} due to -OH bending, C-O stretching and C-H stretching vibrations (Kartick et al., 2013; Khalir et al., 2020).

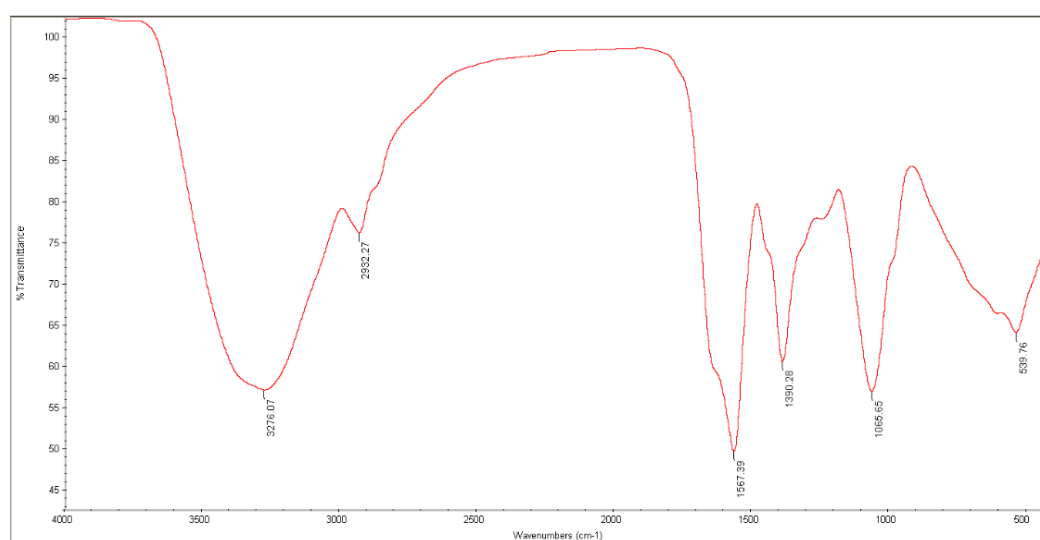


Figure 5. FTIR spectrum of *Xylaria sp.5* cell filtrate

According to the results of the SEM-EDX, FTIR and XRD analysis, the results strongly confirmed that the fungal cell filtrate might act as the reducing agent for the

production of AgNPs. The presence of different of functional groups and biomolecules suggests the synthesized silver nanoparticles were capped by the bioconstituents. The functional groups of many compounds might act as the reducing agent. It could be observed FTIR peak corresponding to amino acid and protein. Both were found in fungal broth, and these were involved in the process of metal ion reduction (Guilger-Casagrande et al., 2019). In addition, many fungi produced nitrate reductase, and this extracellular enzyme played an important role in AgNPs mycosynthesis (Ottoni et al., 2017). Wang et al. (2021) succeeded in producing AgNPs from supernatant of *Aspergillus sydowii*. The shapes of obtained AgNPs were spherical or close to spherical. However, they indicated that there were many other factors affecting production such as temperature, substrate (AgNO_3) concentration and pH.

α -Glucosidase inhibitory activity

The percentage of α -glucosidase inhibitory activity for the AgNPs synthesized by *Xylaria* sp.5 was presented in Table 1. The crude enzyme used in this research consisted of maltase and sucrase, which were derived from rat intestine. Mycogenic AgNPs were found to inhibit the activity of α -glucosidase, with the percentage of inhibition at 50 mg/ml of maltase and sucrase at 63.21 ± 0.67 and 54.42 ± 0.11 , respectively. Although AgNPs exhibited a less pronounced inhibition of α -glucosidase compared to the standard antidiabetic drug acarbose, α -glucosidase inhibition is a crucial process in diabetes treatment. The AgNPs may help reduce the levels of enzymes responsible for catalyzing the hydrolysis of complex carbohydrates and increase the utilization rate of glucose (Govindappa et al., 2018). Previous research reported that the biosynthesis of AgNPs using aqueous extract of *Cladosporium* sp. showed 99.49% inhibition of α -amylase and 9.47% inhibition of α -glucosidase (Popli et al., 2018). Das et al. (2019) studied the green synthesis of AgNPs by *Avicennia officinalis* and found 98% inhibition of α -amylase with IC50 values of 0.28 mg/ml at 0.5 mg/ml and 90% inhibition of α -glucosidase with IC50 values of 0.15 mg/ml at 0.5 mg/ml. The reduction of carbohydrate hydrolyzing enzymes activity may be caused by the interaction between AgNPs and amino acids of the enzyme (Jini et al., 2022). Furthermore, AgNPs have been found to have antidiabetic activity both in vivo and in vitro in many reports (Mikhailova, 2020; Bhardwaj et al., 2020). Khalaf et al. (2023) reported the green synthetic silver nanorods (AgNRs) produced by berberine and they found that AgNRs were effective in reducing glucose level in diabetic rats. In addition, Hyun et al. (2008) reported the absence of any toxicity in rats that treated with AgNPs for 28 days.

Table 1. *α -Glucosidase inhibitory activity of mycogenic AgNPs produced by Xylaria sp.5*

Sample	Percentage of inhibition at 50 mg/ml	
	Maltase	Sucrase
Acarbose	90.14 ± 0.02	90.42 ± 0.12
AgNPs	63.21 ± 0.67	54.42 ± 0.11

Values are expressed as mean \pm SD, ($n = 3$)

Conclusions

The present research investigated the ability of *Xylaria* sp.5 in the synthesis of AgNPs. These metal nanoparticles were successfully synthesized using fungal cell

filtrate, enabling the process eco-friendly, low cost and not requiring toxic chemical agents. The characterization and identification of the produced AgNPs was carried out through SEM-EDX, XRD and FTIR analyses. The results confirmed that the mycogenic crystals were AgNPs with a mostly spherical shape. Additionally, the mycogenic AgNPs showed potential α -glucosidase inhibitory activity, although their activity was lower than that of the control (acarbose). Further studies are required to enhance their α -glucosidase inhibitory activity; however, this metal nanomaterial could be useful for controlling type 2 diabetes.

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