KnE Life Sciences
SIRES
Science and Technology Research Symposium (SIRES)
Volume 2022

Conference Paper

In-Silico Investigation of Beta-Cyclodextrin as a Stabilizer for Pineapple Peel Extract Mediated Silver Nanoparticles

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Abstract.
Pineapple peel waste was used in this study as a source of ferulic acid that has antioxidant and antibacterial properties. Pineapple peel extract can be used as a bioreductor in the synthesis of silver nanoparticles (AgNPs). Beta cyclodextrins are often added as stabilizers in the synthesis of AgNPs to increase their stability. This study aimed to investigate through in silico study the efficacy of beta cyclodextrin as a stabilizer in the synthesis of AgNPs. It also investigated whether ferulic acid plays the role of a bioreductor in the stabilization mechanism of the AgNPs. Molecular docking simulation was used to investigate the efficacy of beta cyclodextrin as a stabilizer in AgNPs synthesis using MGLTools 1.5.6 with AutodockTools 4.2. The visualization of each complex was observed using BIOVIA Discovery Studio Visualizer 2020. The results of this study showed that beta cyclodextrin had better affinity by stabilizing six AgNPs atoms, which was indicated by a free binding energy value of -5.15 kJ/mol. The presence of ferulic acid in the extract which was used as a bioreductor in the synthesis of AgNPs also had a better affinity for the six AgNPs atoms which was indicated by free binding energy of -2.51 kJ/mol. It can be concluded that beta cyclodextrins play the role of being a stabilizer in AgNPs synthesis.

Keywords: in silico, beta-cyclodextrin, silver nanoparticles

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Published 27 December 2022

Publishing services provided by Knowledge E

Selection and Peer-review under the responsibility of the SIRES Conference Committee.

1. INTRODUCTION

Pineapple (*Ananas comosus* L.) is a leading agricultural commodity in Indonesia. In the period 2011 - 2015, West Java became one of the suppliers of pineapple production with the third position after Lampung and North Sumatra. West Java contributed 10.39% of the total 73.08% pineapple production in 2016 [1].

80% of the utilization of pineapples is made into canned pineapple or concentrated pineapple syrup, while the remaining 20% is sold in the domestic market [2]. Pineapple can be used by making various products such as jam, syrup, chips, and juice, or simply consumed directly without going through any processing processes.

Pineapple waste (skin, leaves and weevils) increases along with the increase in pineapple production, especially its skin which makes up a portion of 30-42% [2]. Many pineapple skins are processed into syrup and used as animal feed. The fibers in pineapple leaves can be processed into paper and textiles [1]. Pineapple waste can also be used as a source of bromelain, namely from weevils, leaves, and crown of pineapple [2].

Pineapple peel is widely used as a source of pectin [2]; source of cellulose and semicellulose [3,4]. In addition, pineapple peel is also known to contain polyphenolates, flavonoids, vitamins, and other components [5]. Several studies have also concluded that pineapple peel extracts have antimicrobial properties against Staphylococcus aureus [6], Streptococcus mutans [7], Pseudomonas aeruginosa [8], Escherichia coli [9].

Based on research Hendrawan [10], the ethanol extract of 100% pineapple peel has antibacterial activity against Propionibacterium acnes. Apart from that, pineapple peel extract also has antioxidant activity [11-13]. According to research Saraswaty et al. [13] the antioxidant activity of pineapple peel extract comes from the total content of phenol, ferulic acid, vitamin A and vitamin C. From these studies it is also known that the highest total phenol content is in

water extract, which is 0.9 mg/g GAE (Gallic Acid Equivalent). This antioxidant content is thought to be responsible for health benefits.

Nanotechnology is a new paradigm in drug delivery systems. Recently, the manufacture of herbal medicinal preparations based on nanotechnology is quite developed, one of which is the manufacture of curcumin nanoparticles, which in fact can increase antioxidant and antihepatomal activity [14]. The synthesis of metal nanoparticles can be carried out using the bottom-up method using plant extracts as a bioreductor. One of the obstacles in the manufacture of metal nanoparticles, especially silver nanoparticles (AgNPs) is that because of their large surface area, AgNPs tend to agglomerate so they tend to be unstable. Therefore, during the synthesis process, stabilizers are often added, including beta cyclodextrins. Nowadays, there was no research has been conducted in silico to predict the mechanism of beta cyclodextrin as a stabilizer in the synthesis of AgNPs using plant extracts as a bioreductor.

In this study, the interaction between beta cyclodextrins and AgNPs was investigated using pineapple peel extract as a bioreductors. In addition, it will also be investigated how many AgNPs can be stabilized by the presence of beta cyclodextrins as a stabilizer.

2. MATERIALS AND METHODS

2.1. Materials

2.1.1. Molecules Structure

The molecule structure used in this study is silver nanoparticles (AgNP) which form a complex with beta- cyclodextrin and ferulic acid. The molecular structure of the test compound used in this study is shown in Figure 1.

2.2. Hardware

This research was conducted using hardware in the form of a computer with an Intel (R) Core i3-6100 CPU @ 2.30GHz (4 CPUs) specification, 4096 MB RAM memory, 320GB hard drive, and VGA Intel HD Graphics 520.

2.3. Software

The computer is equipped with software with the Windows 7 operating system equipped with Gaussian 09, Gauss View 5.0.8, MGLTools 1.5.6 equipped with AutoDock 4.2, PatchDock, BIOVIA Discovery Studio Visualizer 2016.

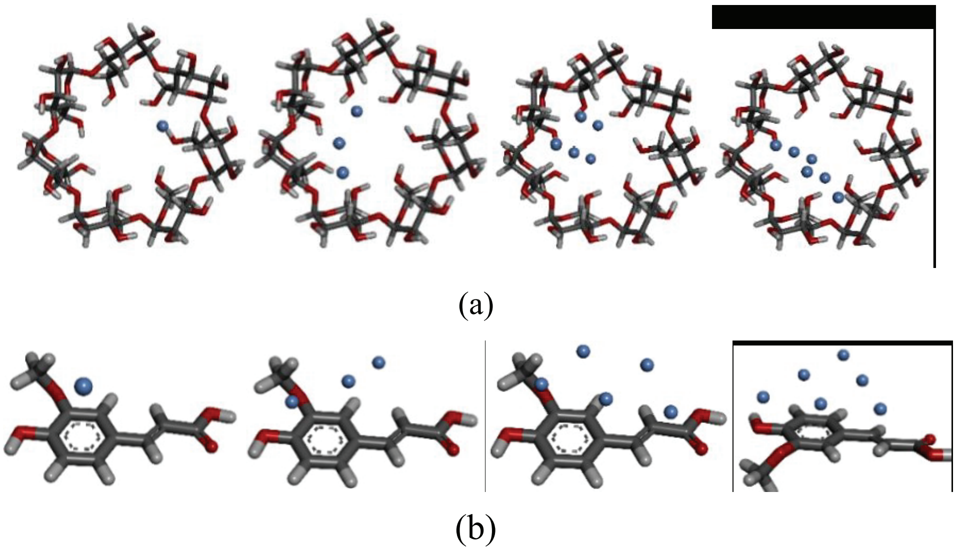


Figure 1: Molecular structure of (a) AgNPs-beta-cyclodextrin and (b) AgNPs-ferulic acid.

2.4. Methods

2.4.1. Silver Nanoparticle Structure Modeling (AgNPs)

The molecular structure of the silver nanoparticle compound (AgNP) was first modeled in three dimensions using GaussView 5.0.8 and Gaussian09 software.

2.4.2. Geometry Optimization of Silver Nanoparticles Compound (AgNP)

Optimization of the molecular structure of silver nanoparticles (AgNP) was carried out using GaussView 5.0.8 and Gaussian09 software using the Density Functional Theory (DFT) B3LYP method based on the 3-21G set.

2.4.3. Beta-Cyclodextrin and Ferulic Acid Preparation

The molecular structure of beta-cyclodextrins and ferulic acid was downloaded in three-dimensional form from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/).

2.4.4. Complex Formation Simulation

The optimized silver nanoparticle compound (AgNP) molecules were then simulated for complex formation of beta-cyclodextrin and ferulic acid compounds. Complex formation simulations were carried out using PatchDock software.

3. RESULTS AND DISCUSSION

In this study, the AutodockTools 4.2 software was used to perform docking so that the best interaction between beta cyclodextrin as stabilizer can be found. In the end, the mechanism of beta-cycodextrin stabilization against silver nanoparticles can be determined. The interaction and stabilization are best characterized by small values of bond free energy. In addition, the interaction between ferulic acid, a content of pineapple peel extract (4), was also tested, whether it also plays a role in stabilizing silver nanoparticles. The results showed that to produce the best stabilization, both ferulic acid (AF) as a bioreductor, as well as beta cyclodextrin, must interact with six silver nanoparticles atoms. These six silver nanoparticles atoms will be stabilized by entering the bowls which are in the beta cyclodextrin structure. This is indicated by the value of the smallest bond-free energy, which is-2.51 kJ / mol and -5.15 kJ / mol.

From the results of this interaction, it is known that beta cyclodextrin (BCD) interacts with silver nanoparticles better than ferulic acid. The results of molecular docking can be seen in **Table 1.**

TABLE 1: Free binding result from molecular docking of BCD and AF with silver nanoparticle.

Ferulic Acid and AgNP Complex	BCD and AgNP Complex
1. Ferulic Acid + AG1: +0,59 kJ/mol	1. BCD + AG1: +0,08 kJ/mol
2. Ferulic Acid + AG3: -1,46 kJ/mol	2. BCD + AG3: -2,93 kJ/mol
3. Ferulic Acid + AG5: -2,22 kJ/mol	3. BCD + AG5: -4,64 kJ/mol
4. Ferulic Acid + AG6: -2,51 kJ/mol	4. BCD + AG6: -5,15 kJ/mol

The interaction between AF and AgNPs as well as BCD and AgNPs can be seen in **Figures 2 and 3** and the number of interactions between BCD and AgNPs can be seen in **Table 2.**

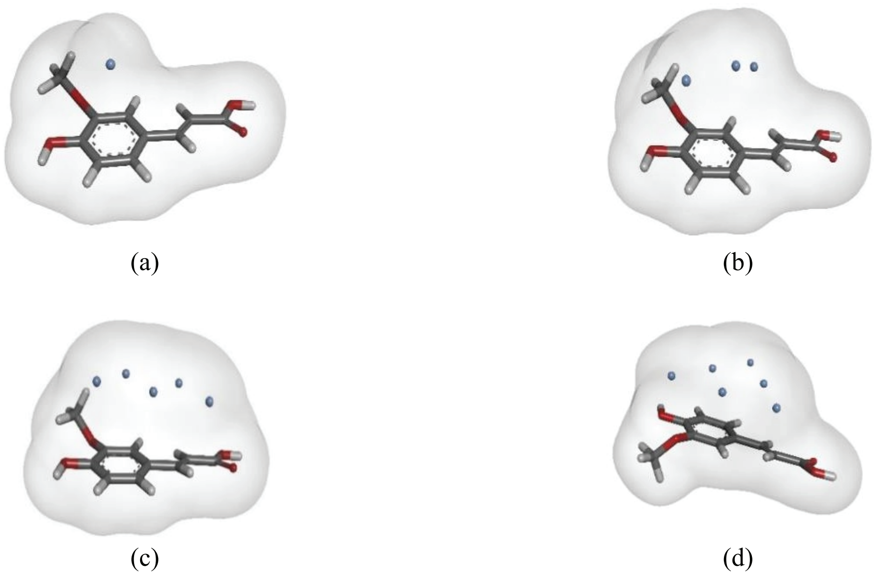
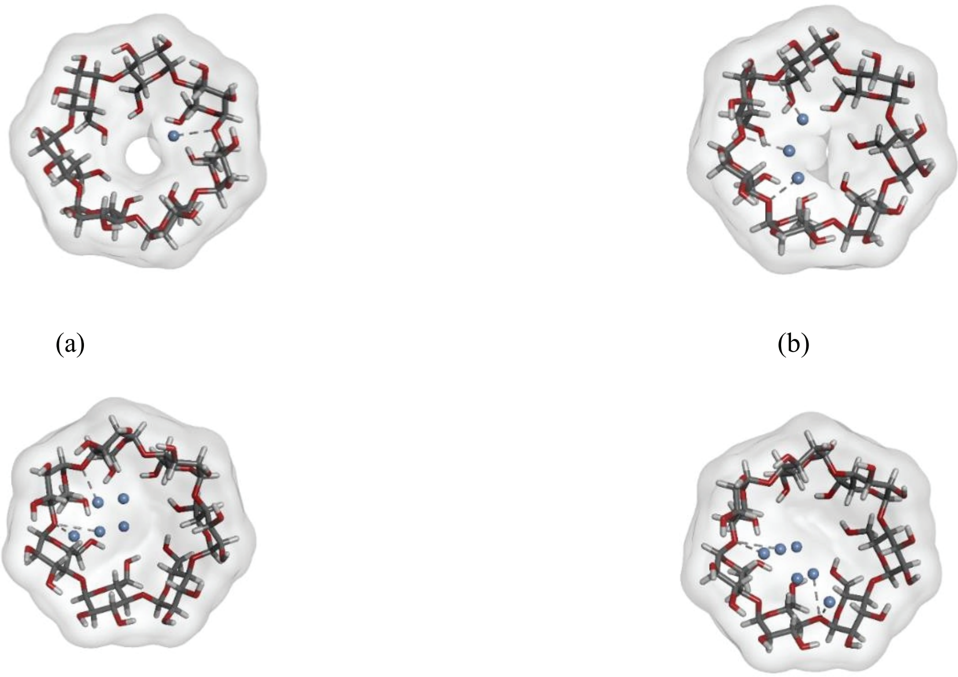


Figure 2: Interaction between Ferulic Acid (AF) and AgNPs; (a) AF + AG1; (b) AF + AG3; (c) AF. +AG5; (d) AF + AG6.

TABLE 2: Number of interactions between BCD and AgNPs.

BCD Complexes with AgNPs	Number and Distance of Interactions
BCD + AG1: +0,08 kJ/mol	1 interaction: 2.80519 A
BCD + AG3: -2,93 kJ/mol	3 interactions: 3,14764 A; 3,32327 A; 2,64525 A
BCD + AG5: -4,64 kJ/mol	3 interactions: 3,16193 A; 2,77937 A; 2,64372 A
BCD + AG6: -5,15 kJ/mol	4 interactions: 2,63331 A; 3,11966 A; 2,61216 A; 3,08794 A

DOI 10.18502/kls.v7i5.12534



(a) (b)

(c) (d)

Figure 3: Interactions between beta-cyclodextrin compounds (BCD) and AgNPs; (a) BCD + AG1; (b) BCD + AG3; (c) BCD + AG5; (d) BCD + AG6.

The molecular structure model of complex compounds with the best conformation is selected based on the energy of complex formation that has been integrated in the PatchDock software. The energy of the complex formation describes the conformation of the molecular structure of the complex compound being modeled that has approached the actual state. From the data obtained in Figures 1 to 3 and Tables 1 and 2, betacyclodextrins can stabilize AgNPs compared to ferulic acid which is contained in pineapple peel extract. From these results, betacyclodextrins can stabilize 6 AgNPs, where the interaction between BCD and 6 AgNPs provides the smallest bond-free energy value compared to interactions between BCD and the number of other AgNPs. The smallest bond-free energy value indicates the most stable bond and the most stable conformation. In addition, the interactions between BCD and 6 AgNPs have the most interactions compared to interactions with BCD and the number of other AgNPs, which are 4 interactions. When viewed from the image of the interaction between BCD and various amounts of AgNPs in Figure 3, the stabilization mechanism of AgNPs with BCD is in accordance with the NCD (native cyclodextrin) mechanism described to stabilize CuNPs, as described in study Suarez-Cerda et al. [15], where silver nanoparticles were stabilized by how to fill the center of the beta-clodextrin cavity with a maximum amount of 6 AgNPs. An image of the NCD stabilization mechanism against CuNPs can be seen in Figure 4.

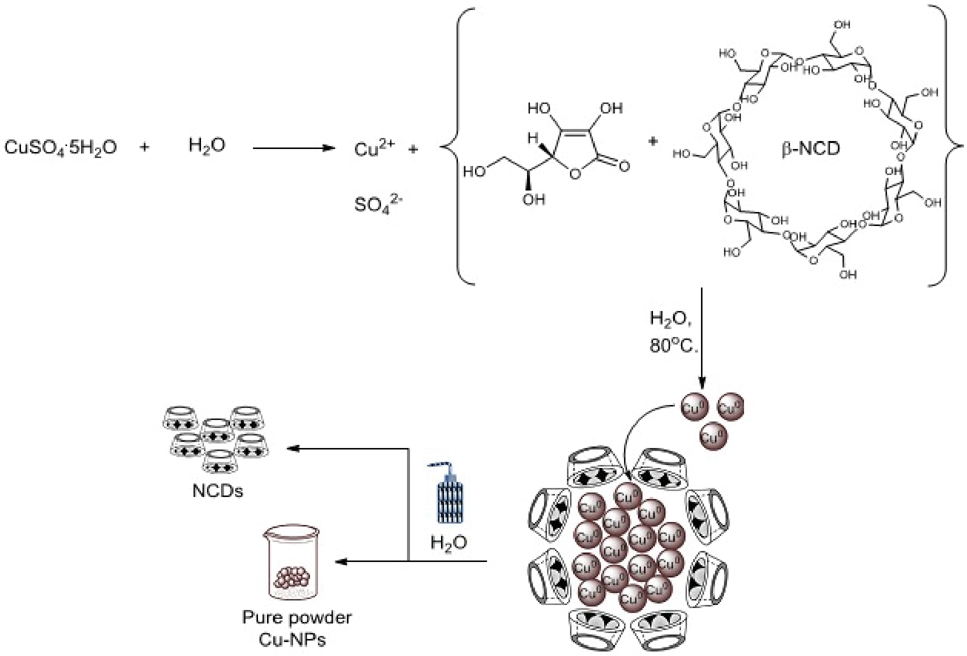


Figure 4: The mechanism of the CuNPs stabilization reaction by NCD.

From Figure 4 the stabilization mechanism of AgNPs by BCD is like that of CuNPs by NCD.

4. CONCLUSION

It can be concluded that BCD can stabilize AgNPs by interacting with 6 AgNPs, where AgNPs will fill the cavity of BCD and produce 4 interactions. Ferulic acid as a component of pineapple peel extract does not play a role in stabilizing AgNPs. However, it only acts as a bioreductor in the synthesis process of AgNPs. This can be developed as a basis for the synthesis of AgNPs by using other fruit peel (waste) extracts, so that it can increase the potential of natural sources extract in the pharmaceutical active ingredients' development for external uses.

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