Science and Technology Indonesia
e-ISSN:2580-4391 *p*-ISSN:2580-4405
Vol. 10, No. 1, January 2025

Research Paper

Uncaria gambir Based Green Synthesis of Inorganic Nanoparticles for Photothermal Induced Thrombolytic and Antibacterial Applications

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Abstract
Application of natural compounds in the field of nanoparticle synthesis have been explored due to their robust application and safety. Additionally, these compounds exhibit activities which can be utilised for their medicinal purposes. One of the most useful compounds is catechin, a polyphenolic compound present in high concentration in *Uncaria gambir*. Herein, we developed inorganic nanoparticles (NPs) based on green synthesis with gambir extract (GE) to produce iron oxide (GE-IONP), gold (GE-AuNP) and silver nanoparticles (GE-AgNP). These nanoparticles were then subjected to observation towards their photothermal activity for the treatment of thrombosis and antibacterial activity. Based on our evaluation, the NPs we obtained were able to exude photothermal effect, indicated by the significant increase of temperature of the solution of around 5-15 °C. Evaluation of thrombolytic potential towards thrombus with an in vitro model showed reduction of thrombus mass of around 40-50%, significantly improves the thrombolytic activity compared to GE alone. Antibacterial activity of laser induced GE-AgNP, GE-AuNP and GE-IONP on *Escherichia coli* and *Staphylococcus aureus* demonstrated similar strength in inhibiting bacterial growth with broad spectrum antibiotics. Samples containing the NPs that were irradiated with laser were more efficient in preventing bacterial growth when compared to the NPs samples that were not subjected to laser, proving the synergistic mechanism of NPs and laser towards antibacterial effect. Based on the results we obtained, gambir based inorganic particles showed promising results as thrombolytic and antibacterial agent.

Keywords
Silver Nanoparticles, Gold Nanoparticles, Iron Oxide Nanoparticles, Thrombolytics, Antibacterial

Received: 7 October 2024, Accepted: 30 December 2024
https://doi.org/10.26554/sti.2025.10.1.303-312

1. INTRODUCTION

Gambir (*Uncaria gambir*) is one of the most widely used medicinal plant in South-East Asia, owing to its high catechin content compared to other known medicinal plants. Munggari et al. (2022) have summarised the application of gambir for various medicinal purposes including antimicrobial, anticancer, antiinflammation, anti-helmintic, antihyperglycemic, anti-hyperuricemia, anti-lipid peroxidase and anti-hyperlipidemic. Catechin, a compound classified as flavonoid, is the most abundant secondary metabolite in gambir and have demonstrated its activity as a strong antioxidant (Munggari et al., 2022). Due to this strong antioxidant activity, gambir is an excellent candidate as bioreducing agent for the synthesis of inorganic nanoparticles, such as iron oxide (IONP), gold (AuNP), and silver (AgNP) nanoparticles.

Green synthesis of nanoparticles has demonstrated excellent consistency and quality for aiding synthesis of nanoparticles while providing additional advantages including environmental safety, nontoxic process and high biocompatibility (Kadhim et al., 2023; Liaqat et al., 2022). Secondary metabolites including flavonoid have shown good reducing capability, which is essential for the synthesis of inorganic nanoparticles, including IONP, AuNP and AgNP. Reducing agents mediates seed growth during the synthesis of these nanoparticles, often categorised as mild to rapid growth (Ying et al., 2022; Yoo et al., 2022). There are only a few reports on the utilisation of gambir for inorganic particles synthesis, and none have been reported so far for the treatment of thrombosis (Arief et al., 2015; Labanni et al., 2022; Syukri et al., 2020).

Several reports have shown the excellent potential of inorganic materials at mediating the process of thrombolysis (Vazquez-Prada et al., 2023). Based on several understanding, it is postulated that inorganic materials assisted with process of photothermal and photodynamic resulting from the conversion of light energy from visible or infrared light (Figure 1A). This light energy is then converted to heat (photother-

mal) or radical induced formation (photodynamic), which is known to expedite the process of fibrin weakening hence causing thrombolysis (Zhang et al., 2019). Synergistic application of photothermal sensitive materials could also be a strategy to enhance the delivery of thrombolytic with minimal side effects that are detrimental towards the utilization of thrombolytic (Refaat et al., 2021; Zhang et al., 2019).

The utilisation of inorganic nanoparticle for antibacterial activity have been widely research and discussed, however the incorporation of photothermal activity to enhance the ability of these nanoparticles still leaves a lot to explore (Liu et al., 2023). Based on current reports, there are two ways, photosensitising materials such as these inorganic nanoparticles can enhance the antibacterial activity (Figure 1B). One of the methods is photothermal, by utilising hyperthermia generated by the photosensitisers, protein degradation occurs and disrupt bacterial membrane, leading to bacteria deaths. The other method is photodynamic, a more complex mechanism which combined the photosensitisers, light and oxygen to generate reactive oxygen species (ROS) to cause oxidative damage to the bacteria (Ma et al., 2019; Xu et al., 2019). With this knowledge, we developed IONP, AuNP, and AgNP by utilising gambir water extract (GWE) as a bioreducing agent for inorganic nanoparticles synthesis for thrombolytic and antibacterial activity.

2. EXPERIMENTAL SECTION

2.1 Materials

Materials for synthesis including hydrochloroauric acid ($HAuCl_4$), silver nitrate ($AgNO_3$), and ferric chloride (Fe_3O_4) were obtained from Sigma-Aldrich. Stabilisers and additional compounds used in synthesis such as ascorbic acid and poly(vinyl) pyrrolidone (PVP K-30) were purchased from Rofa Chemicals Yogyakarta. Solvents in p.a. grade, including ethanol, acetic acid and HCl 37% were obtained from Merck, while catechin standard was purchased from Sigma-Aldrich. Fresh leaves of *Uncaria gambir* were obtained from Banyuasin, South Sumatera.

2.2 Preparation of *Uncaria gambir* Extracts

We prepared three types of *Uncaria gambir* extract with water, ethanol and ethyl acetate as the primary solvents. Water extract was obtained using maceration method following the method we have previously conducted with satisfactory results (Fithri et al., 2024). For the preparation of water extract, fresh leaves were washed with clean water and then boiled for 1.5 hours followed by pressing of the leaves to obtain a concentrated macerate. The solution was then filtered through a fine mesh cloth and collected on a wide opening container. Extract was allowed to solidify and dried for 1-2 days. The resulting dried powder was stored in an airtight container for better preservation until further use.

Ethyl acetate and ethanol extracts were prepared with maceration technique with a ratio of 1:10 between fresh gambir leaves and solvents. The maceration process was conducted for 48 hours with occasional stirring. After 48 hours, the solvent was collected and separated from the leaves and evaporated under mild heat (~60 °C) until a thick extract was obtained.

2.3 Thin Layer Chromatography of Gambir Extracts

Thin layer chromatography was conducted on an activated silica gel GF254 6 × 6.5 cm plate. Catechin as a standard and extracts with a concentration of 1000 ppm were carefully applied on the plate (~10 μL). The plate was then inserted into a chamber that was saturated with chloroform and ethyl acetate (2:1) as the mobile phase. Spots were observed and detected using a 254 and 366 nm UV lamps followed by $FeCl_3$ spray as detection method.

2.4 Synthesis of Gambir Extract Silver Nanoparticles (GE-AgNP)

A stock solution of gambir extract was prepared by dissolving 5 mL of the extract in 5 mL of solvent, resulting in a 50% stock extract solution with a total volume of 10 mL. The green synthesis method was followed for the synthesis of silver nanoparticles. For the reduction of Ag^+ ions, 0.25 mL of extract was added drop wise into 5 mL of 2 mM aqueous solution of $AgNO_3$, stirred at 100 rpm and heated at 80 °C for 12 minutes. The change in colour was observed from dark brown to reddish brown which indicated the formation of silver nanoparticle. The solution was then centrifuged for 15 minutes at 4000 rpm and redispersed in polyvinyl pyrrolidone (PVP K-30) resulting in AgNP formed from 0.5% of gambir extract (GE). Similar protocol was conducted to obtain AgNP from 1, 2, 5 and 10% of GE.

2.5 Synthesis of Gambir Extract Gold Nanoparticle (GE-AUNP)

To obtain AuNP, GE with varying concentration from 0.5; 1; 2; 5; and 10% were inserted drop by drop into 1 mL of $HAuCl_4$ 2 mM solution. After insertion, distilled water was added into the mixture until the final volume of 5 mL. The mixture was kept homogenous by stirring at 100 rpm for 30 minutes, successful synthesis can be observed by the solution colour change from red to purple. To separate unreacted components, the solution was centrifuged at 4000 rpm for 30 minutes and redispersed in PVP.

2.6 Synthesis of Gambir Extract Iron Oxide Nanoparticle (GE-IONP)

A 50% stock solution of gambier extract was prepared and 0.5 mL of the stock solution was taken and diluted to 5 mL for each extract. Around 0.02 g of ferric chloride tetrahydrate ($FeCl_2.4H_2O$) was dissolved in 100 mL of distilled water to prepare 1 mM $FeCl_2.4H_2O$ stock solution. Synthesis of iron oxide nanoparticles was obtained by mixing 5 mL of 1 mM $FeCl_2.4H_2O$ solution and 5 mL of gambir extracts. Solution was subjected to heat by microwave at low-medium radiation. The best results were obtained when the 10 mL mixture was exposed to heat for 35 seconds at 450 watts (medium low).

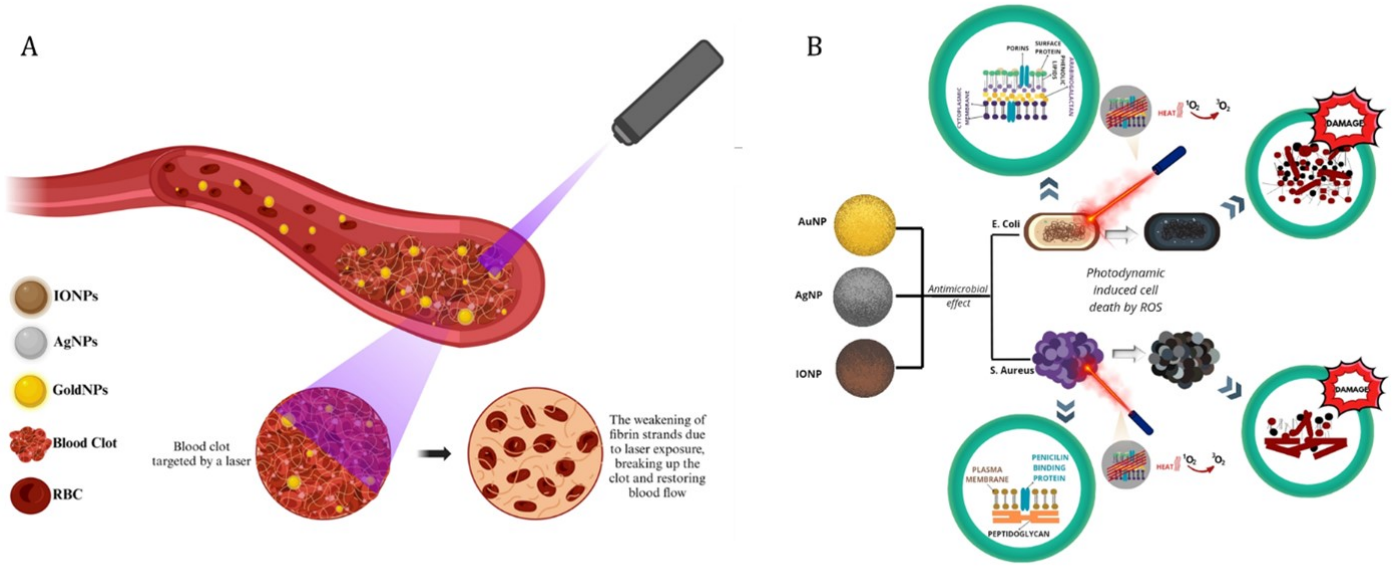

Figure 1. Potential Mechanism of Inorganic Particles in Assisting the Process of Thrombolysis (A) and Antibacterial Properties (B). Images Were Created with Biorender™ and Canva Pro

Solution was centrifuged at 4000 rpm for 30 minutes. Supernatant was discarded and pellet was resuspended in PVP to obtain the final GE-IONP.

Spectrophotometric Wavelength Scan Evaluation To observe the visible wavelength spectra, 1 mL of nanoparticles were scanned on a spectrophotometric UV-Vis (Biobase). Graph was plotted between wavelength in nm (x axis) and absorbance (y axis).

2.7 Particle Size and Zeta Potential

To evaluate size and dispersion of particles samples were analysed using particle size analyser (Malvern). Additionally, zeta potential was also evaluated for observation of particles charge.

2.8 Photothermal Effect

Effectivity of GE-AgNP, GE-AuNP and GE-IONP in producing photothermal effect was explored in the presence of visible laser at 550 nm. Laser with a diameter of 0.5 cm^2 and single intensity of 0.3 mW/cm^2 was directed at the centre of a 2 mL nanoparticle solution of 100 ppm in concentration. Temperature increase was observed every 30 seconds using a thermometer probe for 5 minutes.

2.9 Thrombolytic Assay of Gambir Extract and Nanoparticles

Whole blood from healthy volunteers was collected using sodium citrate vacutainers (Monotes). Prior to creating the blood clot, 2 mL PCR tube (Onemed) was weighed and 40 μL of $CaCl_2.2H_2O$ (Sigma-Aldrich) 1 M was inserted into the tube followed by 760 μL of citrated blood. To allow blood clots to form, the mixtures were incubated at 37 °C for 60 minutes. Stable blood clots were washed with 1 mL of PBS 3-4 times under gentle rotation (50 rpm). Washed blood clots were then immediately used for thrombolysis analysis or stored at 4 °C for a maximum of 4 hours.

2.10 Thrombolytic Assay without Laser

Blood clots were weighed prior to the assay. Blood clot and 500 µL of samples were put into 2 mL PCR tubes (Axygen) for thrombolytic assay. Tubes containing blood clots and samples were incubated at 37 °C for 90 minutes. The remaining blood clots were then reweighed to evaluate the percentage of clot lysis (Equation 1). Nattokinase (Doctor's Best) of 1000 IU was used as positive control and PBS 7.4 as the negative control.

$$\%\text{Clot Lysis} = \frac{\text{clot weight before assay} - \text{clot weight after assay}}{\text{clot weight before assay}} \quad (1)$$

2.11 Thrombolytic Assay Using Laser

Similarly to previous protocol, blood clots prior to assay were weighed, followed by insertion of 500 μL samples into a small vial (d=1.3 cm). Vials containing blood clot and samples were positioned in the middle of the laser, with the laser located 10 cm high from the samples. Laser irradiation at 550 nm, 0.3 mW/cm^2 was carried out for 2 minutes individually. Blood clots were reweighed to calculate the percentage of clot lysis using Equation 1 above.

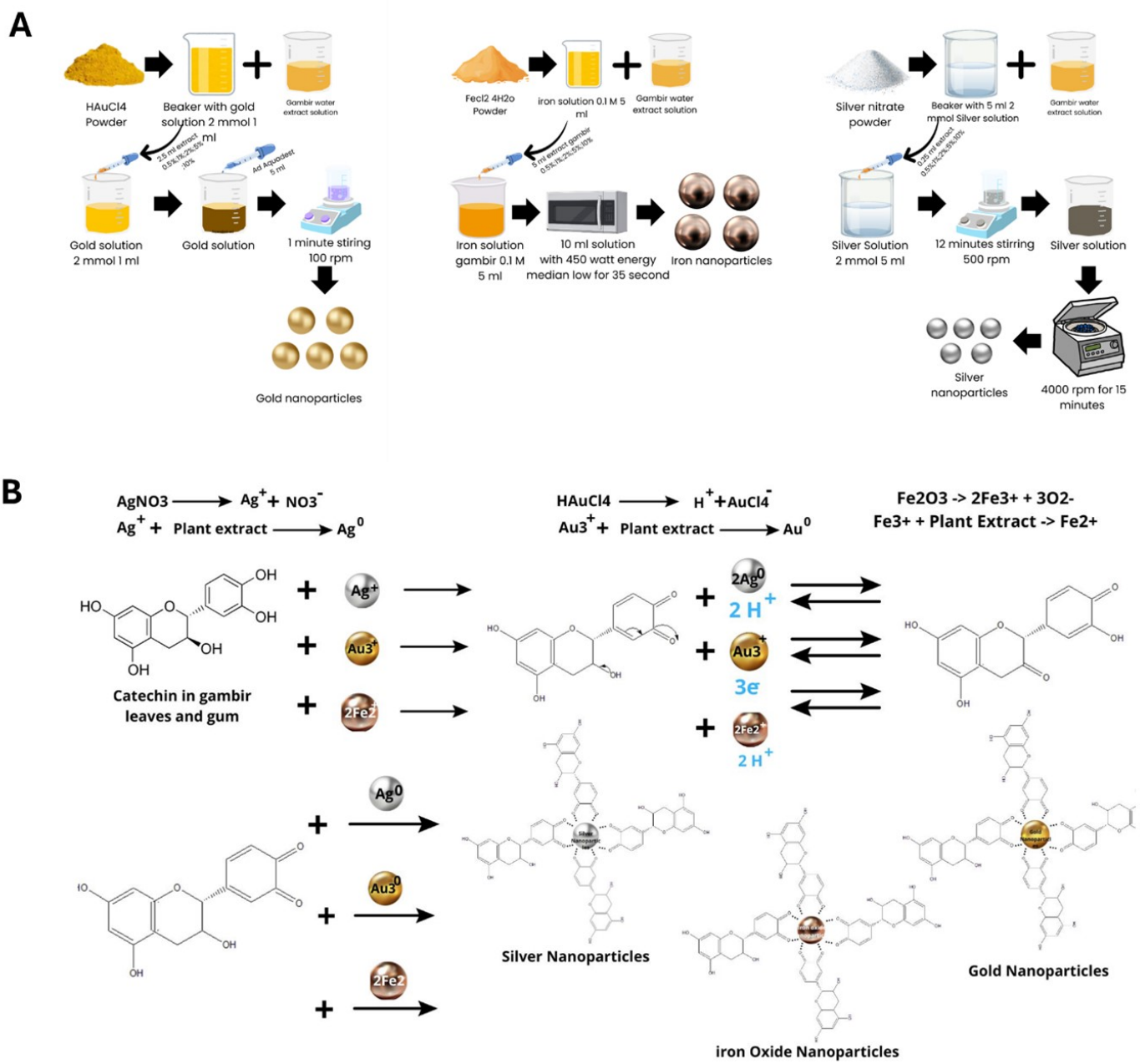

Figure 2. (A) Method of Synthesis of the Inorganic Particles, from L-R: AgNP, AuNP and IONP, (B) Mechanism of Catechin Acting As a Reducing Agent Crucial for the Synthesis Process for AgNP, AuNP and IONP

2.12 Antimicrobial Activity of Natural Photosensitisers

The microorganisms used in this study were *Staphylococcus aureus* and *Escherichia coli*. Before each experiment, the strains were cultivated aerobically in 20 mL of nutrient broth at 37 °C or 24 hours. After 24 hours of incubation, suspension of bacteria (~106 CFU) was transferred to test tubes containing 2 mL of samples. Groups were divided into several groups, including negative control (no treatment group) and positive control using 0.5% of Amoxicillin and Erythromycin. Treated groups with laser, including the laser only, GE-AgNP, GE-AgNP and GE-IONP were irradiated with 550 nm, 0.3 mW/cm^2 for 10 minutes. After exposure, a small sample was taken with an inoculating loop and streaked onto a prepared nutrient agar plate. Samples were then incubated at 37 °C for 24 hours, and colonies were observed. All the experimental procedures were performed under aseptic conditions.

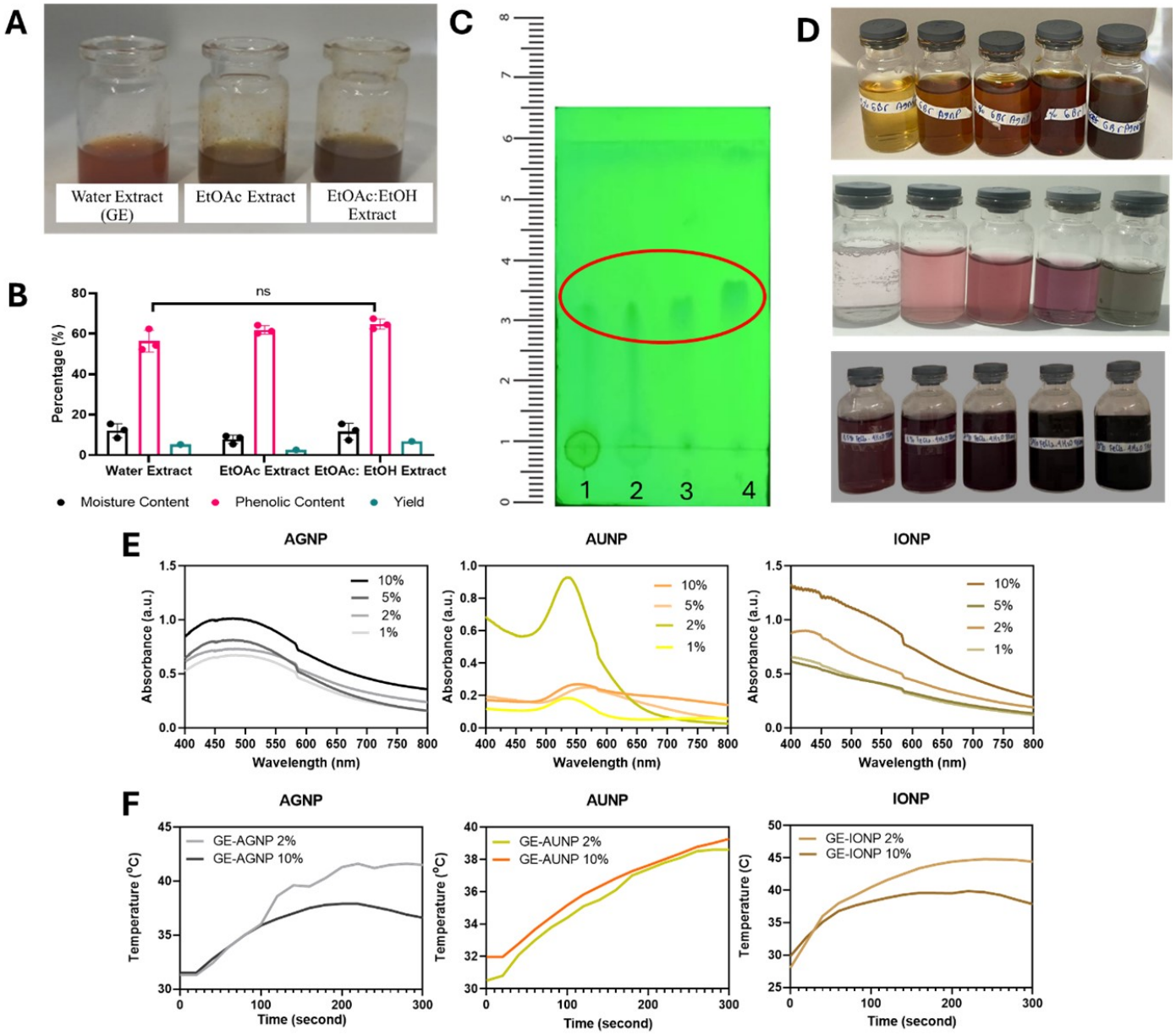

Figure 3. (A) Extracts of Gambir leaves, Obtained by Maceration Technique (B) Characterisation Results of Rxtracts, Including Moisture Content, Phenolic Content and Yield, with No Significant Difference Statistically between Groups (C) Thin Layer Chromatography Analysis of the Catechin Content in the Extract, with 1-4 Labelled As Catechin Standard, Water Extract, Ethyl Acetate Extract and Ethyl Acetate:Ethanol Extract Respectively (D) Synthesised Inorganic Particles from Top to Bottom GE-AgNP, GE-AuNP and GE-IONP with Concentration of GE from 0.5, 1, 2, 5 and 10% (E) Spectrophotometric Wavelength of AgNP, AuNP and IONP which Demonstrated Desirable Results, with Strong Absorbance Present at the Range of 500-550 nm (F) Photothermal Evaluation of the Synthesised Nanoparticles, Demonstrating Temperature Tncrease of 5 to 15 °C

2.13 Statistical Analysis and Illustration

Data included within this report were analysed for statistical significance using one-way ANOVA and Tukey multiple comparison test (Graphpad Prism 8), with * $P < 0.05$ considered significant while ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$ to be very significant. Illustrations were created using Adobe Illustrator, Biorender and Canva Pro.

3. RESULT AND DISCUSSION

Synthesis of inorganic nanoparticles utilising *Uncaria gambir* in this research were conducted based on the reduction ability of natural compounds found in gambir extract (GE) such as phe-

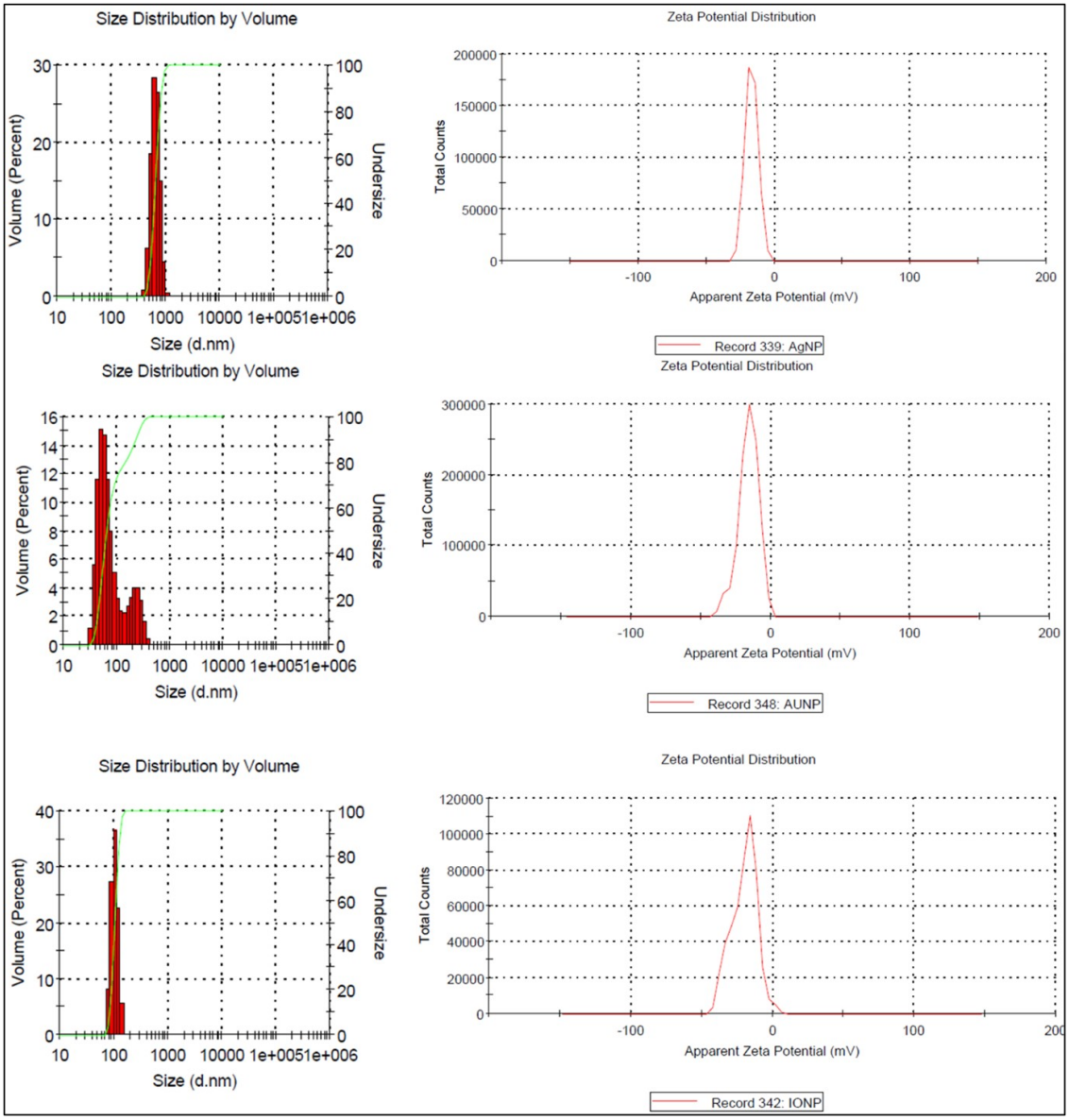

Figure 4. Particle Size Analysis (Left) and Zeta Potential (Right) Evaluation of GE-AgNP, GE-AuNP, and GE-IONP (Top to Bottom Sequentially)

nolic and flavonoids, including catechin. Additionally, these compounds have also demonstrated the ability to catalyse and stabilise the formation of inorganic nanoparticles (Asif et al., 2022; Bharadwaj et al., 2021). The method of synthesis for AgNP, AuNP and IONP as well as the proposed catechin initiated reducing mechanism can be found in Figure 2(A) and (C).

Firstly, we conducted evaluation on which extract to use for this study, as we purposely design this project to obtain the extract with the strongest reducing potential. Based on the phenolic content evaluation (Figure 3B), we observed no significant differences in phenolic content between the extracts. This indicates that the extraction process was able to sufficiently collect the phenolic content including flavonoids and catechin, which will be necessary for this study. Furthermore, we conducted thin layer chromatography test with catechin standard (Figure 3C labelled 1) to prove the presence of catechin in the extract (Figure 3C labelled 2 to 4). Based on this evidence, we move forward with the synthesis of the inorganic nanoparticles using gambir water extract (GE), as water is the safest and most economical solvent. Additionally, it is noted that water extract is the most common solvent of choice for green synthesis to reduce the harm on environment and reduce organic solvent use (Santhosh et al., 2022; Villagrán et al., 2024).

Resulting GE-AgNP and GE-IONP produced brownish colour with GE-AuNP showcasing a typical shade of purple

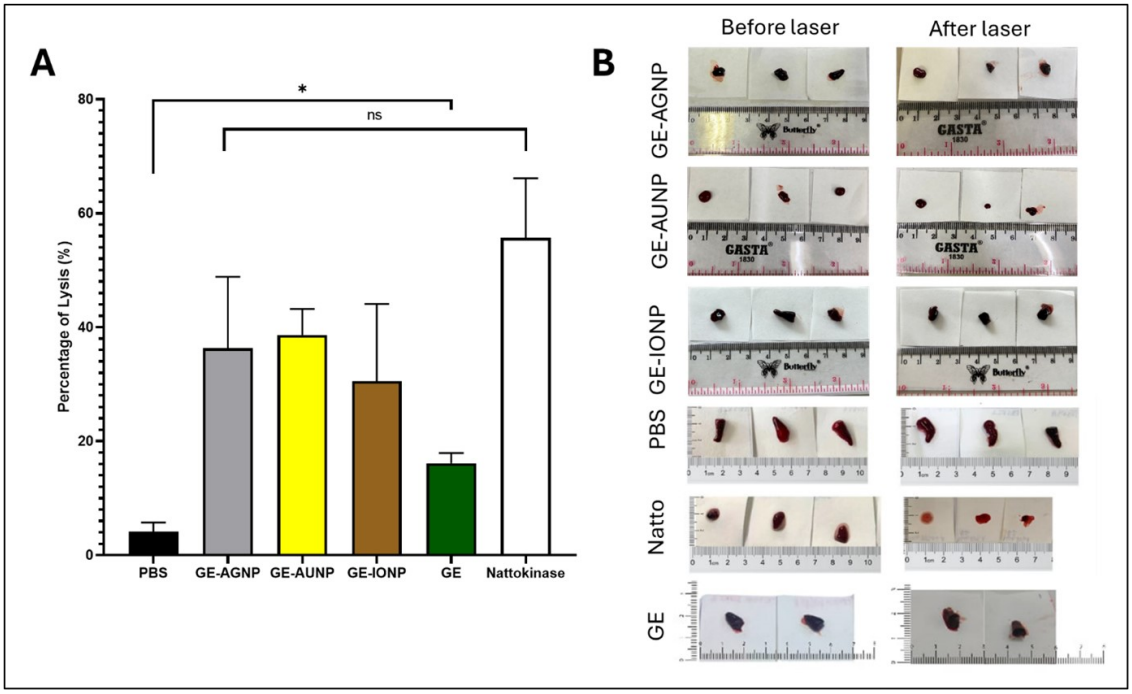

Figure 5. (A) Thrombolytic Analysis of GE-AgNP, GE-AuNP, GE-IONP and GE Compared to PBS and Nattokinase As Positive Control (* P-value < 0.05) (B) Blood Clots Obtained after the Treatment, Indicating a Reduction of Clot Size Due to the Treatment

seen on most AuNP (Figure 3D). Spectral analysis using spectrophotometric visible in the range of 400 to 800 nm showed all inorganic particles have a strong absorbance in the 500-550 nm range, which is necessary to photosensitise the laser that is utilised in this study of 550 nm (Figure 3E). We evaluated the photothermal efficiency by measuring the change in temperature with laser irradiation of 0.3 mW/cm^2. All nanoparticles showed excellent performance in increasing temperature and maintaining the heating capacity without any significant reduction in temperature during the irradiation time of 5 minutes. This is in accordance with various reports regarding AgNP, AuNP, and IONP that have shown excellent properties as a photothermal sensitive materials (Wang et al., 2020, 2022).

Size characteristics also shown we were able to produce nanoparticles within the range of nanometer sized, with size of GE-AgNP, GE-AuNP and GE-IONP of 544 nm, 167 nm, and 168.3 nm respectively (Figure 4). GE-AgNP were larger, as we purposely design the particle to exert strong absorption at more than 500 nm. Most of the reports, showed smaller sized AgNP strongest absorption were at lower wavelengths of around 400-450 nm, which is not ideal for our approach of using laser of 550 nm (Arief et al., 2015; Asif et al., 2022). It is noted that the utilisation of this particle would be on the main systemic circulation, and on the surface of the blood clot or bacterial cells. Based on this purpose, maintaining size of below 100 nm particles is not a necessity, due to activity of the nanoparticles not intended to permeate through cell membranes, Zeta potential of the resulting nanoparticles were around -15.7 to -19.8 mV which indicate all the particles generated and tested were relatively stable with the PVP coating.

Evaluation of the photothermal induced thrombolysis demonstrated promising results as can be seen in Figure 5. When compared to nattokinase (a thrombolytic utilised to maintain blood circulation) despite nattokinase showing higher average lysis, GE-AgNP, GE-AuNP, and GE-IONP showed no statistically different results, with GE-AgNP showcasing the best results out of the three inorganic particles. GE without any particles also showed lysis of up to around 18%, indicating gambir water extract with laser has thrombolytic potential. When compared to the PBS with laser group (black bar), significant difference in percentage of lysis was obtained. The mechanism of how inorganic particles could act as thrombolytic agent, is based on two main reasons. The first is the photothermal effect, which is the conversion of light energy, into heat. This substantial increase of temperature or hyperthermia, caused fibrin matrix degradation, weakening the strength of the clot. Secondly, the heat generated prevent further proteolytic activation of the fibrinogen to occur, which sufficiently suppresses the generation of fibrin which leads to thrombolysis (Fithri et al., 2023). This result was able to conclusively demonstrate the ability of gambir extract inorganic nanoparticles as a thrombolytic agent.

We further evaluated the potential of these inorganic particles by observing the effect of GE-AgNP, GE-AuNP and GE-IONP on two different strains of bacteria. *Escherichia coli* (EC) and *Staphylococcus aureus* (SA) were selected due to their

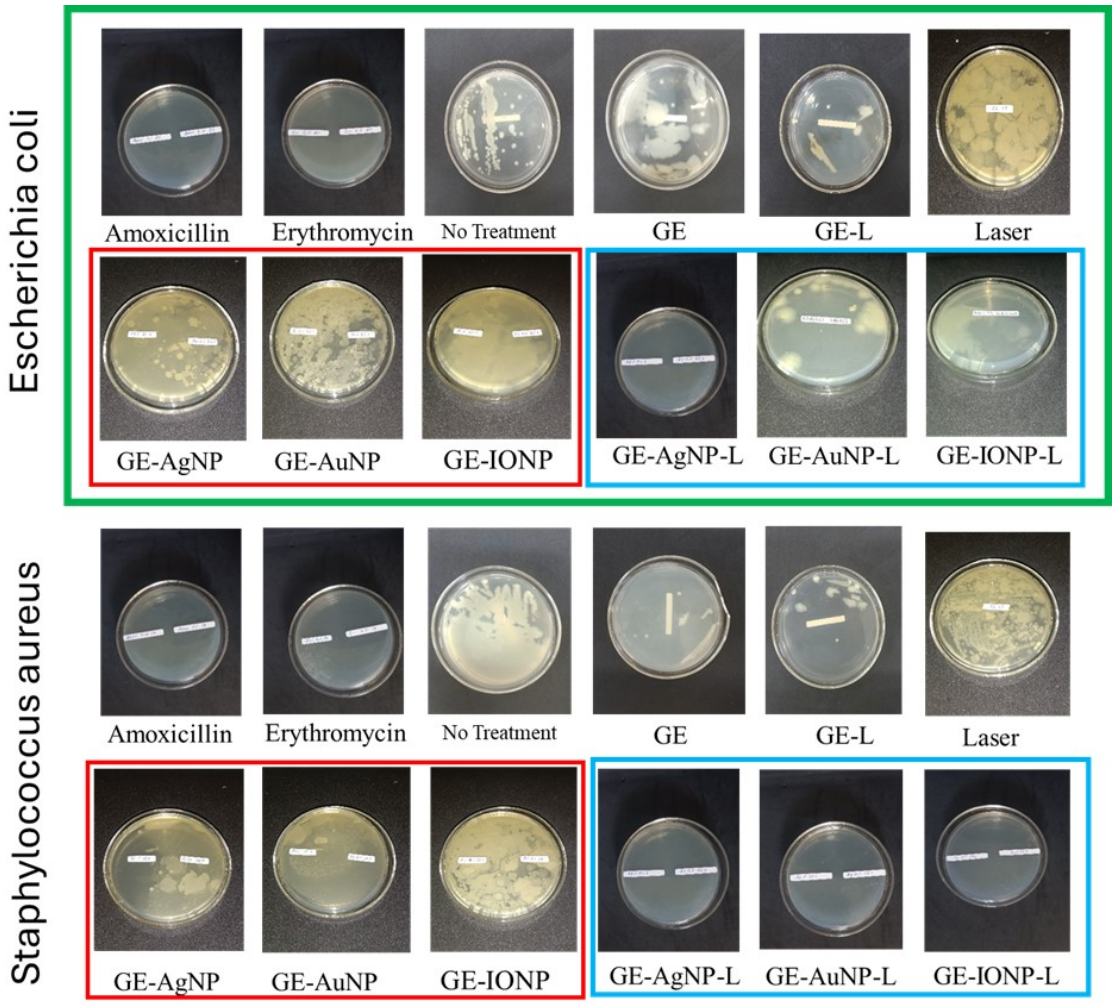

Figure 6. Antibacterial Evaluation of The Nanoparticles on Two Strains of Bacteria, *Escherichia coli* (Pictures within the Green Box) and *Staphylococcus aureus* Visually, Significant Reduction of Bacterial Growth Was Observed with the NP Treated with Laser (Blue Box) Compared to the Groups That Were Not Irradiated with Laser (Red Box)

pathogenic concerns for humans and difference in genus, allowing this research to encompass both the Gram-positive and Gram-negative bacteria. Both EC and SA are becoming more resistant, and due to their highly infectious nature, this is becoming a major concern clinically worldwide (Doua et al., 2023; Tong et al., 2015).

To evaluate the antibacterial activity of the nanoparticles in vitro, the standard plate counting method were used to determine the bacterial viability. For standard plate counting assay, the resultant bacterial solution was sequentially streak onto the agar plates, followed by incubation at 37 °C for 18 hours. The results of colonies growth in both EC and SA after exposure to laser with photosensitisers (Figure 6 blue box) were significantly less than the no treatment group and no laser exposure (Figure 6 red box). In both EC and SA, we also observed GE with laser (GE-L) without any presence of inorganic particles showed strong inhibition, which could be explained by the ability of phytochemical compounds in GE possessing mild photosensitising capability (Kubrak et al., 2022; Wang et al., 2023). Treatment with just laser (without the presence of GE or inorganic particles) or the groups that were incubated with the inorganic particles without laser did not demonstrate any significant antibacterial effect. This proved the initial hypothesis that by combining these particles with laser, the antibacterial effect was synergistic and stronger, allowing more effective antibacterial effect to take place.

In the present study, inorganic particles could exhibit antimicrobial activity through photothermal therapy (PTT), a promising antibacterial therapeutic option to overcome potential drawbacks including resistance of antibacterial treatment. PTT is a minimally invasive antimicrobial approach that has been proposed as adjunctive therapy for the treatment of local infections that are resistant to antibiotics (Polat and Kang, 2021). PTT can activate photosensitisers in the presence of

light causing conversion of light energy to thermal energy leading in protein degradation and bacterial cell death (Hasanin et al., 2021). Compared with other conventional antimicrobials, PTT has several strengths including multitarget process. Furthermore, the mechanism of which PTT causes cell death is more mechanical than biological, which can be a solution to microbial resistance.

4. CONCLUSIONS

Based on the obtained results, we were able to demonstrate the ability of gambir extract as a natural source for green synthesis of inorganic nanoparticles, including silver, gold and iron oxide nanoparticles. The obtained inorganic nanoparticles with a size of 100-500 nm exerted strong absorption within desired wavelength of 500-550 nm, producing strong photothermal activity to sufficiently increase temperature. Furthermore, we have successfully demonstrated the ability of the inorganic nanoparticles to effectively cause thrombolysis, with results demonstrating activity that is statistically indifferent to nattokinase. Antibacterial activity observed on *Escherichia coli* and *Staphylococcus aureus* promising results, with minimal bacterial growth with the laser irradiation treatment. Despite obtaining these information, further analysis with more comprehensive particle characterisation including TEM along with evaluation of thrombolysis and antimicrobial effect in an animal model would be necessary to strengthen the findings obtained in this research.

5. ACKNOWLEDGMENT

Authors would like to express gratitude towards Drug Delivery and Pharmaceutical Technology Group of Universitas Sriwijaya for the collaborative effort in obtaining these data despite the limitations of facilities. Additionally, we would like to thank Research Centre of Inorganic Materials for the instrumental support for the completion of this research. We also extend our gratitude towards Nabila Aprilian, Sri Agustin and Nahla Monaflesia for assisting us in providing several illustrations for this article.

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