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Research Article

Nanoparticle Characterization of *Allium sativum*, *Curcuma mangga* and *Acorus calamus* as a Basic of Nanotechnology on Jamu Subur Kandungan Madura

Bayyinatul Muchtaromah[1,*], Didik Wahyudi[1], Mujahidin Ahmad[1], Rahmi Annisa[2]

ABSTRACT

Introduction: The increasing of researcher attraction on the herbal drug after so long ignored due to difficulties in processing has opened a new door for the development of a novel of "jamu Subur Kandungan". However, the constraints that then faced in consuming "jamu Subur Kandungan", an herbal reproductive drug, are the solubility and poor absorption in the intestine. Therefore, this study aims to characterize nanoparticle of the combination of garlic (*Allium sativum*), temu mangga (*Curcuma mangga*) and jeringau (*Acorus calamus*) encapsulated by chitosan. **Material and Methods:** the simplicial of garlic (*Allium sativum*), temu mangga (*Curcuma mangga*) and jeringau (*Acorus calamus*) was purchased from Materia Medica Batu Malang Indonesia. Nanoparticle of combination of garlic, temu mangga and jeringau was produced by ionic gelation method. Nanoparticle characterization was assessed by Scanning electron microscopy (SEM), Spectrophotometer Fourier Transform Infra-Red (FTIR), Particle Size analyzer (PSA) and X-ray diffraction (XRD). **Result:** The ionic gelation method succeeded to make nanoparticle. The produced nanoparticle was around 438-1159 nm. The length of sonication has proven to make the particle size smaller. The particle size distribution of chitosan at the time of 90 min sonication and 150 min was classified as uneven because of the particle size clustered in the range 500-1000 nm and 3000-5000 nm. The hydroxyl (OH) group appeared at wave number 3429-2466 cm^{-1}, while the amide functional group appeared at wave numbers (1648-1652 cm^{-1}. Phosphate groups (P = O) also appeared, which is a TPP residue, at a wavenumber 1384 cm^{-1}. **Conclusion:** Chitosan-garlic nanoparticles (*Allium sativum*), temu mangga (*Curcuma mangga*) and jeringau (*Acorus calamus*) were successfully produced with ionic gelation method.

Key words: Characterization, Garlic, Ionic gelation, Jeringau, Nanoparticle, Temu mangga.

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INTRODUCTION

Infertility is one of the reproductive diseases, which affects several couples in the world. It is a global phenomenon affecting an average of 10% of human reproductive age population. Various factors cause infertility in woman, including intrinsic such as anatomic,[1] genetic,[2] hormonal, and immunological disorder factor or extrinsic like sexually transmitted infection (STI), tuberculosis of the pelvis and obesity.[3,4]

The various chemical drugs have been developed to treat infertility, but many of the people in the world has been dependent on herbal medicine for healthcare[5] since it has a fewer negative effect as compared to the synthetic drug. Indonesia is the world's second-largest country by diversity after Brazil that has considerable biodiversity potential in the world. According to Pan *et al.*[6], about 30,000 to 40,000 types of medicinal plants both on land and in the sea that spread from Aceh to Papua are potential as herbal medicine. It makes Indonesia as one of the countries that use many natural medicines (herbs), as well as in traditional form (herbal medicine) or the modern style (pill, capsule, powder, and others).

The biological activity of medicinal plants from all over the world has been studied based on popular use in the local community. One of the famous traditional herbals in Indonesia is called Jamu. One of Jamu that believed by the local community in Madura, East Java, Indonesia to elicit woman fertility is "Jamu Subur Kandungan". "Jamu Subur Kandungan" contains 15% garlic (*Allium sativum*), 15% rhizome of temu mangga (*Curcuma mangga*), 12% rhizome of jeringau (*Acorus calamus*), and other materials until 100%, which is well known as fertility enhancer.[7] Our studies have shown that spice blend of garlic (*Allium sativum*), temu mangga (*Curcuma mangga*) and jeringau (*Acorus calamus*) has high antioxidant activity and can be used as antifungal and antibacterial.[7,8]

The containing spices in "Jamu Subur Kandungan" are individually considered as remedies for many diseases. Water extract of temu mangga can suppress free radical, inhibits peroxide formation during lipid oxidation,[9] and as antiallergic.[10] Furthermore, jeringau (*Acorus calamus*) with its phytochemical compounds has considered as an anti-inflammatory.[11] In the other hand, garlic (*Allium sativum*) has been reported as antibacterial, antiviral, antifungal and antiprotozoal.[8]

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The increasing of researcher attraction on the herbal drug after so long ignored due to difficulties in processing[12] has opened a new door for the development of the novel of herbal drug. However, the constraints that then faced in consuming herbal drugs are the solubility and poor absorption in the intestine.[13] Furthermore, herbal drugs have shown have good activity in assays in vitro but no reproducible in the experiment *in vivo*.[14] Therefore, several nanotechnology approaches and encapsulation method have attempted to break this barrier.

Development of nanomaterial and drug delivery system using encapsulation technology is able to deliver the herbal drug to the target site at the right time and in the right place.[15] One of the polymeric microspheres that have been widely used in nano-encapsulation technology is chitosan that extracted from crustacean shell waste.[16] Desai & Park[17] and Patel *et al.*[18] proved that crosslinked chitosan microspheres with tripolyphosphate (TPP) could be used as a drug treatment by the spray-drying method. Besides, chitosan is biodegradable, biocompatible, nonimmunogenic, and noncarcinogenic, making it suitable for use in pharmaceutical technology.[19]

No attempts have been tried to develop an antifertility herbal drug-using nanotechnology combined with drug delivery system. Therefore, this study aims to characterize nanoparticle of the combination of garlic (*Allium sativum*), temu mangga (*Curcuma mangga*) and jeringau (*A. calamus*) encapsulated by chitosan.

MATERIAL AND METHODS

Nanoparticle production of the extract of garlic, temu mangga, jeringau

Simplisia macerated using 70% ethanol solvent, soaked for 24 hours then filtered. The maceration process is repeated three times to obtain a clear colored filtrate. The filtrate obtained was concentrated with a rotary evaporator at 50 °C.[20]

Chitosan nanoparticle

Chitosan is made nanoparticle before being used to coat garlic, temu mangga and jeringau nanoparticle extract. 400 mL of 2% chitosan is dissolved in acetic acid and stirred using a magnetic stirrer. Chitosan solution is put in three beakers with the following treatment: First, 100 ml of chitosan coupled with 50 mL TPP, sonicated for 90 min. Second, 100 mL of chitosan plus 50 mL TPP, sonicated for 120 min. Third, 100 ml of chitosan coupled with 50 ml TPP, sonicated for 150 min.

Chitosan coating of nanoparticles of the extract of garlic, temu mangga, jeringau, and their combination

A total of 1 g of garlic, temu mangga and jeringau resulting from sonification are dissolved in 35 ml ethanol and added with 15 mL aquadest. The solution is added with 100 mL of TPP (tripolyphosphate) chitosan (1:2) dissolved in 2% glacial acetic acid. Stirring is performed using a magnetic stirrer for 2 h at a stable speed. The nanoparticle of chitosan, each nanoparticle of the extract of garlic, temu mangga, jeringau, and their combination was separated by centrifugation. The nanoparticle is placed in the freezer at ± -4 °C for two days and continued in the refrigerator with at ± 3°C until it becomes dry solid.

Characterization of the size and morphology of nanoparticles using SEM

The powder of garlic, Temu Mangga, Jeringau, and their combination are placed in stub using two-sided tape. The powder is conditioned to be electrically conductive with a beam of thin-layer platinum from the coater for 30 seconds at a pressure below 2 Pa and a current strength of 30 mA. Photos were taken at 10 kV electron voltages with desired magnification.[21]

Characterization of Functional Groups of Nanoparticles Using Fourier Transform Infrared (FTIR)

A total of 2 mg of powdered nanoparticles sample is mixed with 100 mg KBr. The powder mixture is dried with a vacuum freeze dryer for one day.[22] Furthermore, The powder mixture is subjected to infrared rays at 4000 - 400 cm^{-1} wavelength using 100 scans on Spectrum One Spectrometer (Perkin Elmer, Norwalk, CT, USA).

Characterization of crystallinity degree of nanoparticles using X-Ray Diffraction (XRD)

A total of 200 mg of sample is printed on 2 x 2.5 cm mold made from aluminium. The degree of crystallinity is determined using XRD with a wavelength source of 1.5406 Å.[23]

Characterization of particle size using Particle Size Analyser (PSA)

Particle size test was performed using a digital microscope as well as PSA (Particle Size Analyzer) testing. Samples were taken using a spatula, then dissolved in 3 mL of ethanol and stirred until homogeneous. The solution is then inserted into a tube with a maximum solution height of 15 mm. Then, the sample measured diameter distribution using VASCO Nano Particle Analyzer.

Data analysis

The data were analyzed descriptively, including morphology, size particle, functional groups, and crystallinity degree of the nanoparticle.

RESULTS

Nanoparticle characterization using Particle size analyzer

PSA analysis was conducted to determine the size and distribution of particles in each sample. The particle size of the ionic gelation method in this study ranged from 438-1159 nm (Figure 1). In this study, NaTPP stabilizer is used which aims to stabilize chitosan nanoparticles by inhibiting the formation of aggregates so that it is expected that the average particle size of these chitosan nanoparticles can be sized below the size range of the chitosan solution. In general, the nano size of chitosan particles, temu mangga coated chitosan, garlic coated chitosan and combination of garlic, temu mangga and jeringau coated chitosan has a similar size which ranges from 438-713. In contrast to Jeringau coated chitosan, which has a relatively large size compared to other samples which range from 607-1159 (Figure 1).

The length of sonication has proven to make the particle size smaller. In general, the sonication time of 150 min results in smaller particle size compared to 120 min. However, the sonication time above 90 min produces a relatively equal particle size of 120 min, even in some samples resulting in larger particle size (Figure 1). The results of this study proved that the ionic gelation method, combined with the sonication method is still relevant to be used in the synthesis of nanoparticles.

The particle size distribution of chitosan at the time of 90 min sonication and 150 min was classified as uneven because of the particle size clustered in the range 500-1000 nm and 3000-5000 nm, respectively. This is different from the 120 min sonication time where the particle size distribution is mostly clustered in the range 300-1000 nm, and very little is clustered at a size of 2000 nm (Figure 2). However, the average particle size is still in the nano-sized category because it is still below 1000 nm (Figure 1).

Similar cases were detected in the particle size distribution of temu mangga chitosan-coated. Particle size distribution tended to cluster at a

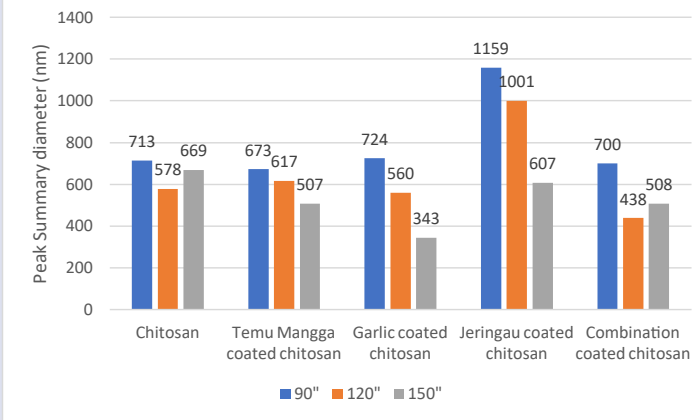

Figure 1: The average nanoparticle size of each sample.

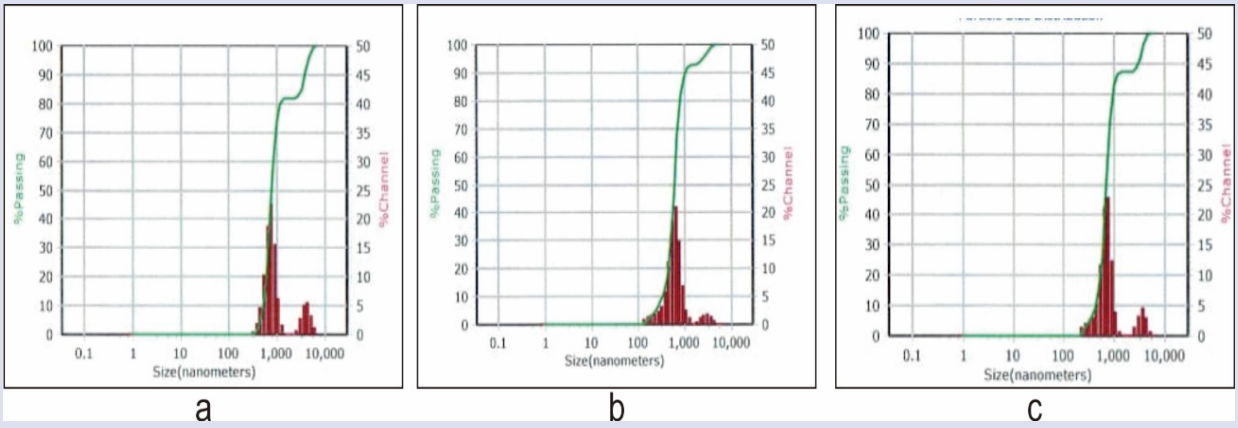

Figure 2: Chitosan particle size distribution using PSA; a. 90 minutes sonication time, b. 120 minutes sonication time and c. 150 minutes sonication time.

size of 500-4000 nm at the time of 90 and 150 min (Figure 3). However, this is different from the 120 min sonication time where the particle size distribution is relatively uniform at 331-2000 nm.

The particle size of Jeringau coated chitosan is relatively large when compared to other samples (Figure 1). The distribution of Jeringau coated chitosan particles also shows a similar trend. Jeringau coated chitosan particle size distribution tends to cluster at the size above 1000 nm (Figure 4).

The particle size of the combined sample was relatively the smallest compared to the other samples (Figure 5). Even so, the particle size distribution is also more uniform. The 120 min sonication time is proven to produce smaller and more uniform particle sizes, below 1000 nm.

Characterization of chitosan nanoparticles using FTIR

The nanoparticles from chitosan showed a peak at 3406, 1649, 1556, 1541, 1348, 1091 and 842 characteristics of O-H stretch, N-H, C-NH_3, CH Residual, -C-OH and C-H, respectively (Figure 6). Combination of garlic, temu mangga and jeringau coated chitosan after sonification at 90, 120 and 150 minutes in this study showed a peak at relatively the same with chitosan. This result showed that the chitosan successfully coated the combination of garlic, temu mangga and jeringau in the difference sonication time. However, the intensity of the characteristic of coated chitosan was shown at 90 min sonication time.

Characterization of nanoparticles using SEM

Ionic gelation method was proven to be able to generate garlic extract into nanoparticle (Figure 6). Length of sonification 150 min was proven to generate the smallest nanoparticle compared to 90 min and 120 min. This result was along with PSA analysis that nanoparticle of garlic extract was in the range of 343-724 nm (Figure 7).

Ionic gelation method was also proven to generate jeringau chitosan-coated to be a nanoparticle. However, nanoparticle jeringau chitosan-coated seems greater than the nanoparticle of garlic (Figures 8 and 9). This may occur due to the existence of the chitosan inside.

The combination of garlic, temu mangga and jeringau for consistency chitosan-coated showed the greater size compared to garlic but smaller than jeringau chitosan-coated. The characterization of the combination of jeringau, garlic, and temu mangga was important to know the size of a particle of the composition of "Jamu Subur Kandungan". This result also indicated that the ionic gelation method was succeeded in producing nanoparticle and applicable on an industrial scale.

Characterization of nanoparticles using XRD

X-Ray Diffraction (XRD) was performed to determine molecular structures of the crystal. Length of sonification did not affect the molecular structure of chitosan (Figure 10A). Length of sonification of 90 min (Figure 10A blue diffractogram) has the same graphical view with 120 min (Figure 10A green diffractogram) and 150 min (Figure

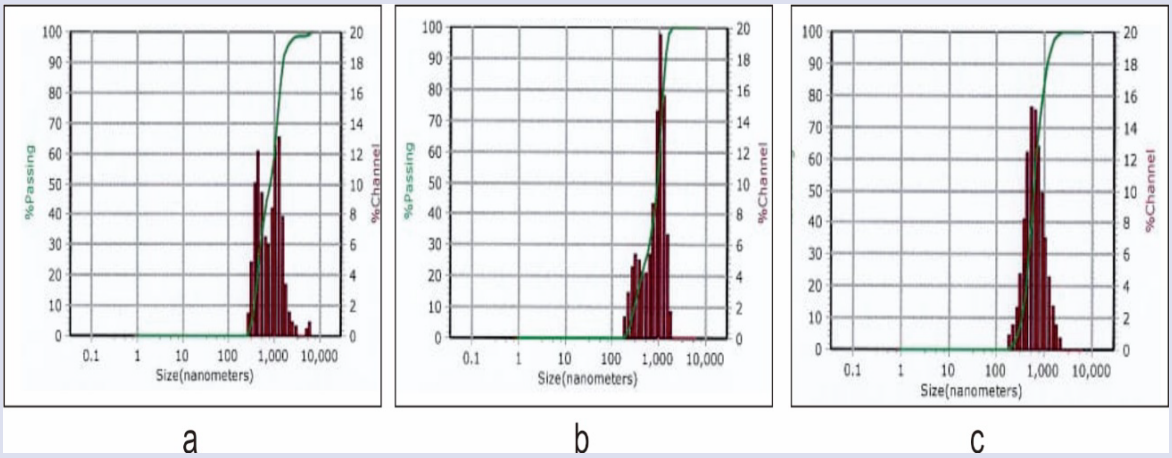

Figure 3: Particle size distribution of temu mangga coated chitosan using PSA; a. 90 min, b. 120 min, and c. 150 min sonication time.

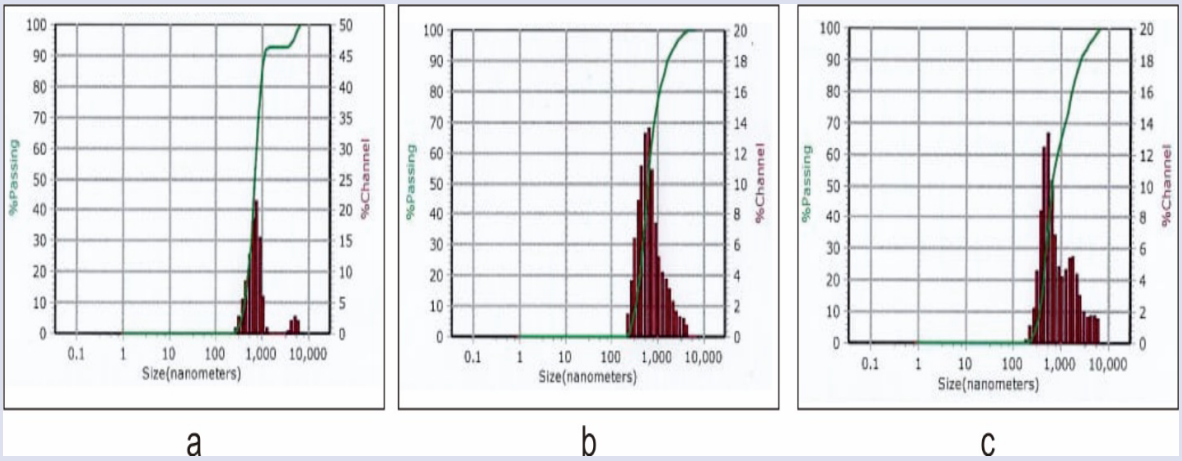

Figure 4: Particle size distribution of Jeringau coated chitosan using PSA at 90 min (a), 120 min (b), and 150 min (c) sonication time.

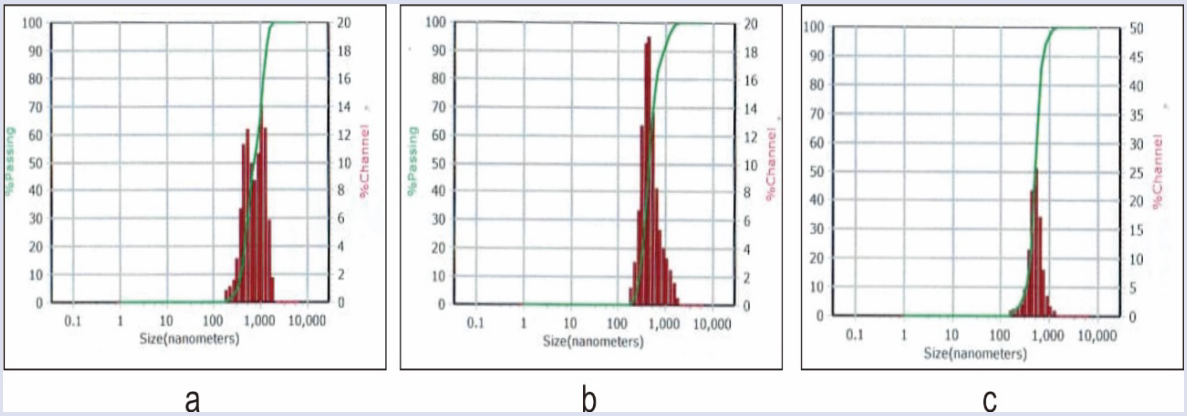

Figure 5: The particle size distribution of the combined sample coated chitosan using PSA at 90 min (a), 120 min (b), and 150 min (c) sonication time.

10A grey diffractogram). Less significant peaks with very low intensity were found in this diffractogram of chitosan nanoparticles showing a dense network structure of interpenetrating polymer chains cross-linked to each other by TPP counter ions. Thus, this diffractogram with lesser peaks showed the formation of chitosan nanoparticles having a strong interaction between chitosan and TPP counter ions.

The same diffractogram also showed by nanoparticle of the combination of garlic, temu mangga and jeringau for consistency (Figure 10B). This condition may arise due to the encapsulation of chitosan to herbalism material. Length of sonification also did not affect the molecular structure of the material (Figure 10B).

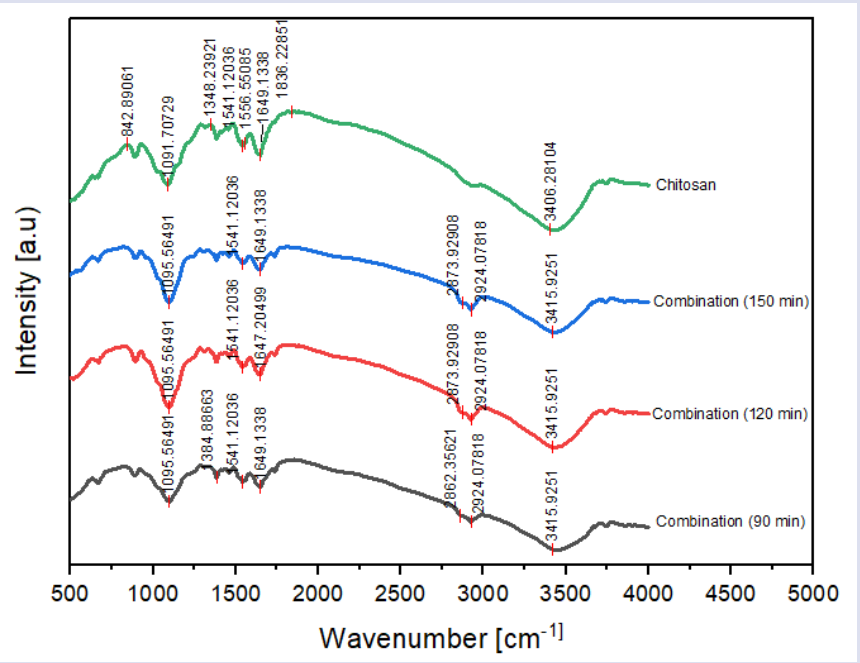

Figure 6: Transmitan Graphic of FTIR spectra of chitosan and combination of garlic, jeringau and temu mangga at difference of sonication time.

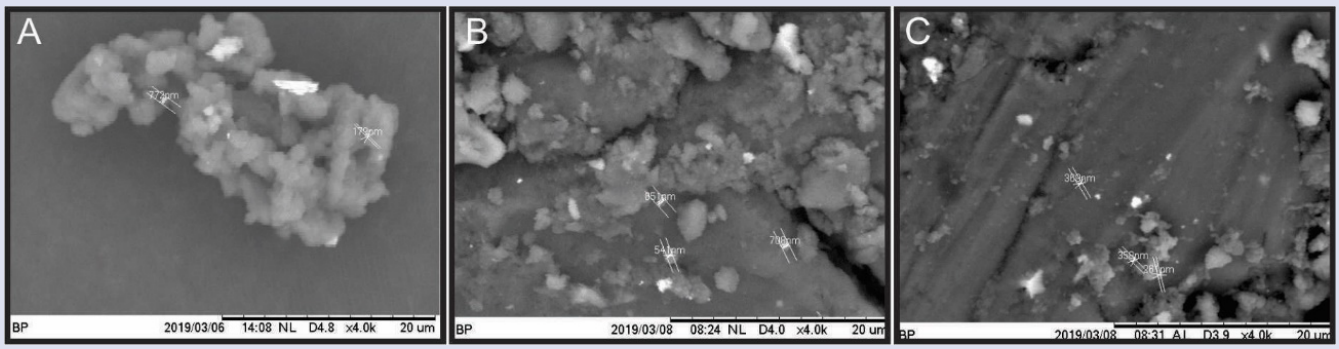

Figure 7: The Morphology of garlic nanoparticle with SEM sonicated at 90 min (A), 120 min (B), and 150 min (C).

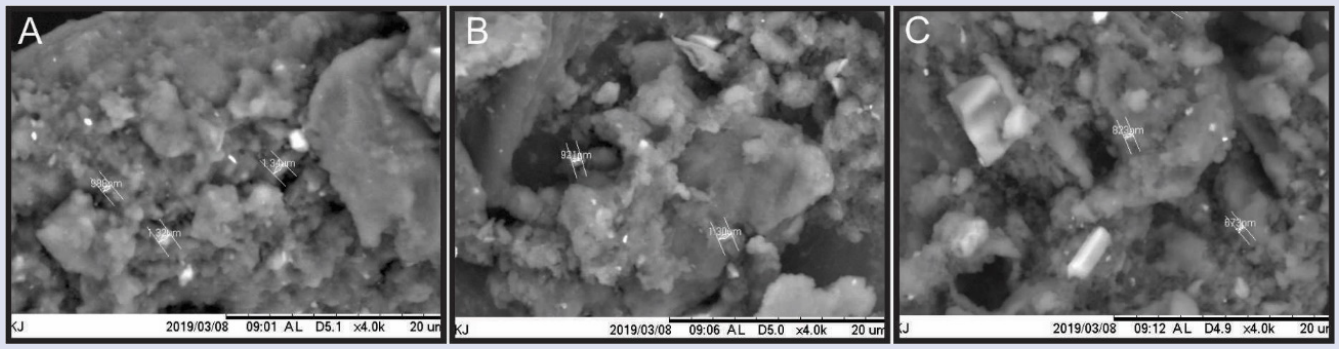

Figure 8: The Morphology of Jeringau nanoparticle with SEM sonicated at 90 min (A), 120 min (B), and 150 min (C).

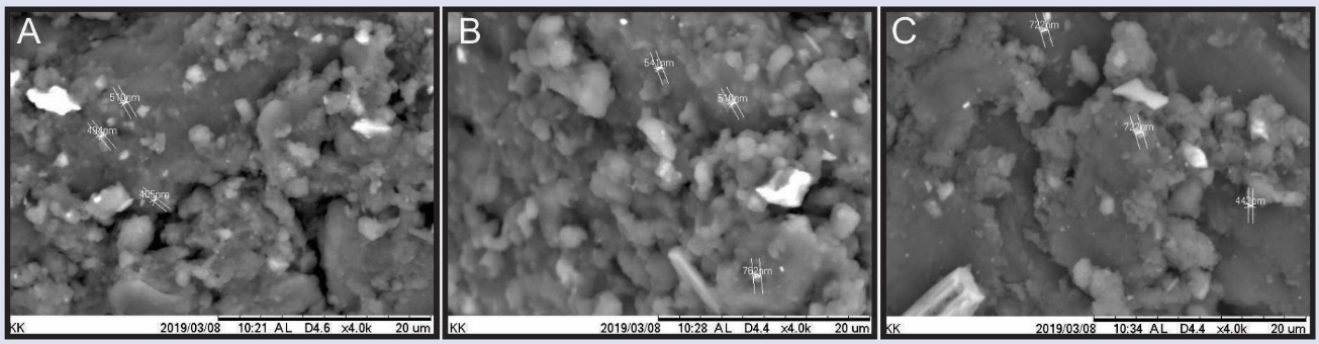

Figure 9: The morphology of the combination of garlic, temu mangga, and jeringau nanoparticle with SEM sonicated at 90 min (A), 120 min (B), and 150 min (C).

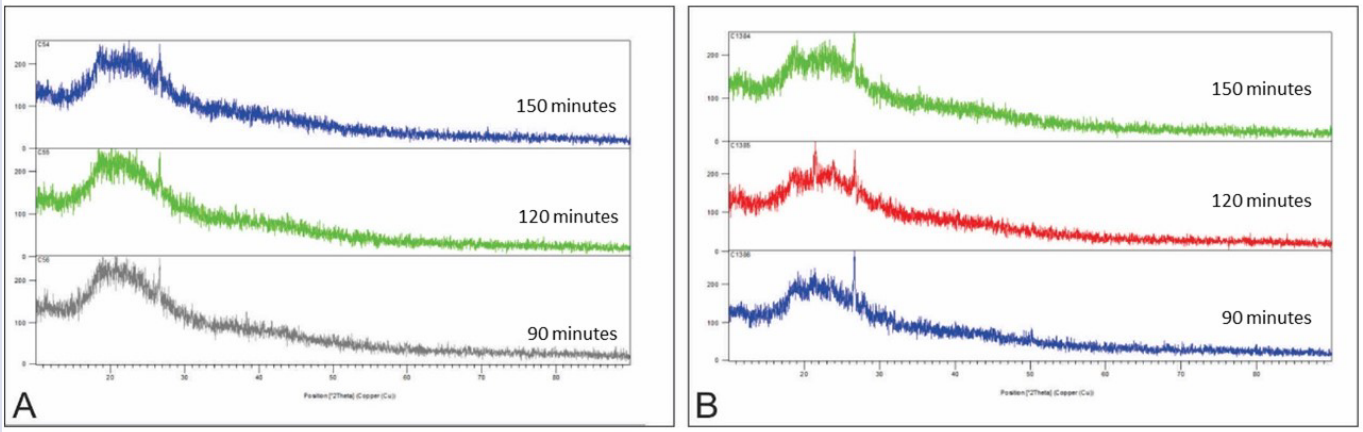

Figure 10: The nanoparticle characterization using XRD. A) Chitosan nanoparticle B) Nanoparticle of garlic, temu mangga and jeringau combination.

DISCUSSION

Nanoparticle production by ionic gelation was may the best-studied chitosan-based nanocomposites,[24] using the sol-gel transition of chitosan in the presence of TPP as a poly-anionic crosslinking agent. This method was widely used as an oral drug delivery system[25] since it has non-toxic reagent and needs low energy for production. Many researchers have produced many protocols for the chitosan nanoparticle preparation. However, the influence of different material and processing factor generated difference result. Therefore, the evaluation of produced nanoparticle by ionic gelation in the different sample was still needed to control the size of the particle obtained.[24]

Ionic gelation method combined with sonication successfully produced nanoparticle of the combination of garlic, jeringau and temu mangga contained in Herbal "Subur Kandungan" in this study. This method also successfully produced nanoparticle in *Tridax procumbens* leaf extract[26] and *Indigofera intricate* plant extract.[27] This method was worthy of being used because of requiring less equipment, no use of organic solvent and simple.[28]

Several factors cause the distribution of uneven particles, including the use of beaker glass sizes that are less precise. Wulandari[5] stated that the difference in the size of a beaker glass as a container for the sonication process causes the differences in particle distribution. The difference in the distribution of sonic waves that lie in a place that has irregular geometry will cause the energy reflected in the emulsion solution molecules to vary so that there are broken solutions faster and some are slower and eventually produce smaller but not homogeneous particle sizes.

FTIR analysis was carried out to determine the functional groups that exist in garlic, temu mangga and jeringau coated chitosan. The functional groups contained in chitosan include hydroxyl (OH) and amide groups ($-NH_2$). The hydroxyl functional group on chitosan appears at wavenumbers from 3450 to 3200 cm^{-1}.[29] In this study, the hydroxyl (OH) group appeared at wave number 3429-2466 cm^{-1}, while the amide functional group appeared at wave numbers (1648-1652 cm^{-1} (table 1). Phosphate groups (P = O) also appeared, which is a TPP residue, at a wavenumber 1384 cm^{-1}.

Changes in wave number occur with the length of the sonication time of 90 minutes, 120 minutes and 150 minutes. This change in wavenumber indicates a return interaction between each functional group. Besides being caused by the length of sonication, wavenumber change is most likely caused by the addition of TPP as an emulsion material.[5]

The difference in duration of sonication (120 and 150 minutes) also rises to a new wave number, at wavelengths of 3854 and 3750 cm^{-1} (Figure 6). The emergence of new wave numbers which are included in OH functional groups may be due to interactions with TPP. However, in general, the sonication duration does not affect the wavenumber of chitosan.

CONCLUSION

Chitosan nanoparticles of garlic (*Allium sativum*), temu mangga (Curcuma mangga) and jeringau (*Acorus calamus*) was successfully produced with ionic gelation method. The relationship between the formation of chitosan nanoparticles by this method is based on the electrostatic interaction between the amine group in chitosan with the

negative charge group from the NaTPP polyanion. This finding was a breakthrough in herbalism and can be developed as an alternative drug to treat infertility.

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CONFLICTS OF INTEREST

We declare that we have no conflicts of interest.

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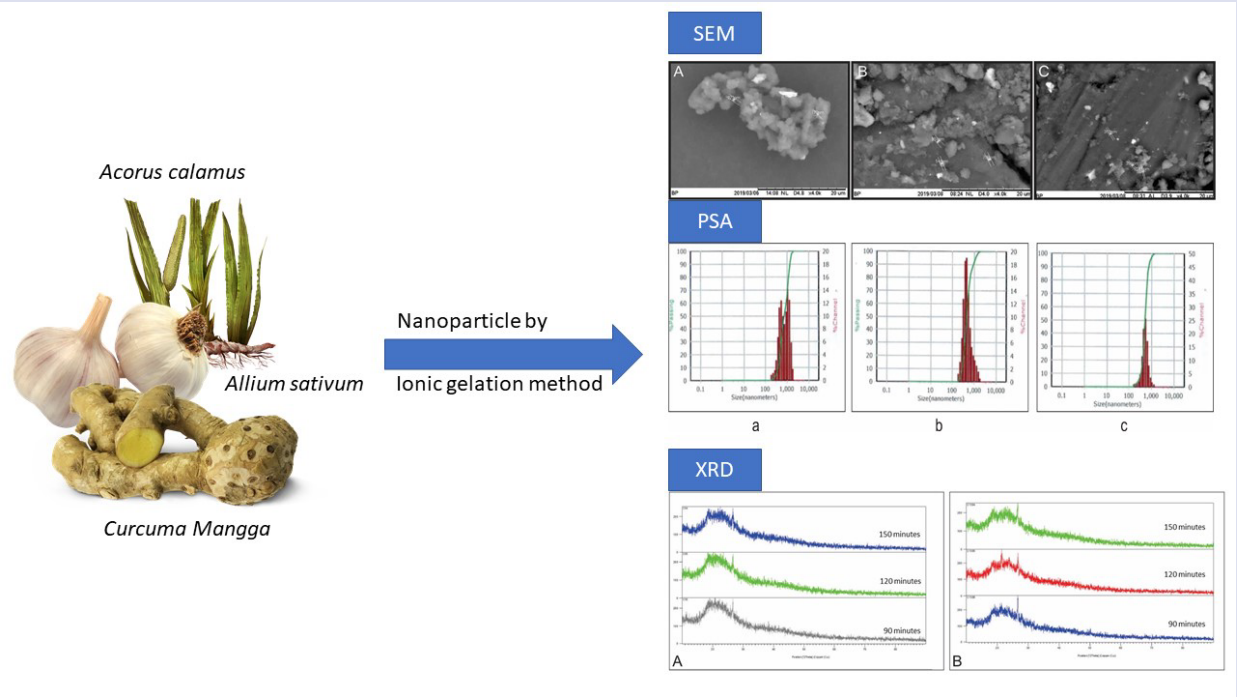
GRAPHICAL ABSTRACT



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