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Synthesis of manganese nanoparticles of Oolong tea extract by sonication method for a natural oral contrast media on magnetic resonance cholangiopancreatography

Síntesis de nanopartículas de manganeso de extracto de té Oolong mediante el método de sonicación para un medio de contraste oral natural en colangiopancreatografía por resonancia magnética

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SUMMARY

Introduction: *Magnetic resonance cholangio-pancreatography examination using natural contrast media has not provided an optimal image of gastroduodenal suppression that covers the image of the biliary system. Natural materials used as contrast media continue to be developed with various previous studies, but not many have been associated with using nanoparticles as natural contrast media materials. This study aims to make manganese nanoparticles in oolong tea extract used as an oral contrast medium.*
Methods: *In this experimental study, the extraction of oolong tea using the boiling method with 15 mL of distilled water was dissolved in 200 mL of distilled water and then sonicated with a frequency of 20 kHz with time variations of 10, 15, 20, and 25 minutes. The results of the sonication process carried out a Particle Size Analyzer (PSA) test. Furthermore, the obtained manganese nanoparticles were given orally to healthy volunteers, and a Magnetic Resonance Cholangiopancreatography (MRCP) examination was performed.*
Results: *The resulting MRCP image measures the Signal to noise ratio (SNR) value in the stomach, duodenum, and biliary tract system. Synthesis of manganese nanoparticles with the sonication method showed that sonication for 10 minutes resulted in manganese particle sizes with a diameter of 1 364.8 nm, 15 minutes with a diameter of 1 204.7 nm, 20 minutes with a diameter of 488.2 nm, 25 minutes with a diameter of 1131.8 nm. The results with the particle size with a diameter of 488.2 nm are nanoparticles, then used for MRCP examination.*
Conclusion: *Manganese nanoparticles from oolong tea extract can suppress objects covering the pancreatic biliary tree system, increasing contrast enhancement in the pancreato biliary tree system.*

Keywords: *Magnetic resonance cholangio-pancreatography, manganese, nanoparticles, Oolong tea.*

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RESUMEN

Introducción: *El examen de colangiopancreatografía por resonancia magnética con medios de contraste naturales no ha proporcionado una imagen óptima de supresión gastroduodenal que cubra la imagen del sistema biliar. Los materiales naturales utilizados como medios de contraste continúan desarrollándose con varios estudios previos, pero no muchos se han asociado con el uso de nanopartículas como materiales de medios de contraste naturales. Este estudio tiene como objetivo hacer nanopartículas de manganeso en extracto de té oolong utilizado como medio de contraste oral.*
Métodos: *En este estudio experimental, la extracción de té oolong utilizando el método de ebullición con 15 mL de agua destilada se disolvió en 200 mL de agua destilada y luego se sonicó con una frecuencia de 20 kHz con variaciones de tiempo de 10, 15, 20 y 25 minutos. Los resultados del proceso de sonicación llevaron a cabo una prueba de analizador de tamaño de partículas (PSA). Además, las nanopartículas de manganeso obtenidas se administraron por vía oral a voluntarios sanos y se les realizó un examen de colangiopancreatografía por resonancia magnética (CPRM).*
Resultados: *La imagen de MRCP resultante mide el valor de SNR (Signal to noise ration, por sus siglas en ingles) en el estómago, el duodeno y el sistema del tracto biliar. La síntesis de nanopartículas de manganeso con el método de sonicación mostró que la sonicación durante 10 minutos dio como resultados tamaños de partículas de manganeso con un diámetro de 1 364,8 nm, 15 minutos con un diámetro de 1 204,7 nm, 20 minutos con un diámetro de 488,2 nm, 25 minutos con un diámetro de 1131,8 nm. Los resultados con el tamaño de partícula con un diámetro de 488,2 nm son nanopartículas, luego se utilizan para el examen MRCP.*
Conclusión: *Las nanopartículas de manganeso del extracto de té oolong pueden suprimir los objetos que cubren el sistema del árbol biliar pancreático, mejorando el aumento de contraste en el sistema del árbol biliar pancreático.*

Palabras clave: *Colangiopancreatografía por resonancia magnética, manganeso, nanopartículas, té Oolong.*

INTRODUCTION

Several studies to find the alternatives to natural negative oral contrast media in Magnetic Resonance Cholangiopancreatography (MRCP) examination have been carried out, in the form of liquid or juice, both in fruits and tea drinks, which contain a lot of manganese (Mn) (1). A study on fruits as an alternative to natural negative oral contrast media, and their Mn content is blueberry (3-4 mg/dL) (2,3), pineapple (0.276 mg/dL) (4,5), blackberries (2.93 mg/dL) (6), lemon or orange (0.2 mg/dL) (7), and black tea (0.44 mg/dL) (8).

MRCP examination uses oolong tea as a contrast medium because oolong tea has a high manganese content (0.94 mg/dL) compared to other natural ingredients. The function increases the contrast between the bile ducts and surrounding organs (9). However, the limitation of using oolong tea is the level of suppression or suppression of the signal intensity of the stomach and duodenum is still not optimal, so it is still possible that there are pathological conditions that cannot be visualized optimally (10,11). To overcome this limitation, it is necessary to develop further research on the use of oolong tea as a natural negative oral contrast medium by increasing the effectiveness of the manganese content of oolong tea using nanoparticle technology.

Nanoparticle technology has been widely used in Magnetic resonance imaging (MRI), especially in materials containing magnetic nanoparticles (MNP), for developing MRI contrast media materials (12-15). Nanoparticles are a technology that aims to develop the dosage form size in a 10-1 000 nm size range. To produce nano-sized particles, several methods are used, one of which is sonication. This study aims to determine the best sonication time to produce manganese nanoparticles from the oolong extract and whether it can suppress the organs that interfere with the MRCP examination.

MATERIAL AND METHODS

Materials

Oolong tea extract is obtained from tea leaves (Camellia Sinensis) from Kemuning Village, Central Java, Indonesia, and processed using evaporated distilled water. In preliminary studies using Atomic Absorption Spectrometry (AAS) tests on several types of tea drinks, it is known as oolong tea has the highest Manganese content (0.94 mg/dL) compared to green tea (0.70 mg/dL) and black tea (0.44 mg/dL).

Methods

Oolong Tea Extraction Process

The process of extracting oolong tea leaves was conducted by maceration: 100 g of Simplicia powder of oolong tea leaves each was put into a glass container. Firstly, it must be macerated in 1 L of distilled water; when the process was finished, it was covered and leave it for two days. Next, while protected from light, frequently stirred, shredded, squeezed, and washed the dregs with enough filter liquid to obtain 1 L. Then it was transferred to a closed vessel and leave it in a cool place. Again, it must be protected from light for two days; the second process must be bowled with boiling at a temperature of 140ºC for 5 minutes, then at 100ºC for 15-20 minutes using aqua dest solvent. The results were concentrated with a rotary evaporator type Rotavapor® R-100 until most of the solvent had evaporated. The evaporation process continued on a water tube until a thick extract was obtained.

Process for Making Nanoparticles

With 15 mL of oolong tea extract dissolved in 200 mL of distilled water and then put into the sonicator BSD-250W model. The solution was given a frequency of 20 kHz for 10, 15, 20, and 25 minutes, respectively. Then the sonication results were measured to determine the size of the manganese particles using PSA (Particle sized Analyzer).

PSA of Manganese Nanoparticle

The size of oolong tea extract manganese nanoparticles was obtained using a Cilas 1190 spectrophotometer. Each of the results of sonication of oolong tea extract for 10 minutes, 15 minutes, 20 minutes, and 25 minutes was included in PSA. This measurement is based on the scattering of laser light by the particles in the sample. The light from the laser is emitted through a pinhole (a tiny needle) and then sent to the particles in the sample. The particles in the sample scatter the light back through the pinhole and into the detector. The detected analog signal is converted into a digital signal, then processed into an arithmetic series, and the final result is a spectrum.

Magnetic Resonance Cholangiopancreatography (MRCP)

MRCP examination using MRI machine with GE Signa Voyager (1.5 Tesla). Healthy female volunteers aged 47 years were given as much as 200 mL of oolong tea extract. The MRI scanning parameters for MRCP examination were T2 weighted images with HASTE (half Fourier acquisition single shot TSE) fat saturation Coronal Thick Slab Radial to detect the suppression effect of gastrointestinal organs surrounding the biliary pancreas trees. MRI parameters scanning for bottles are TR (time repetition) 4 500 ms, TE (time echo) 700 ms, ETL (echo train length) 300, average 1, slice thickness 50 mm, scan time 50 sec. MRCP image information is assessed by assessing the signal-to-noise ratio in the pancreatic system image. This research has received permission from the Ethics Committee of the Kariadi Regional General Hospital Semarang, Central Java.

RESULTS

Size of manganese nanoparticles resulting from sonication of Oolong Tea extract, based on the results of measurements using PSA on oolong tea extract, which was sonicated with variations in time of 10 minutes (a), 15 minutes (b), 20 minutes (c) and 25 minutes (d), the spectrum was obtained as shown in Figure 1. In detail, the results PSA shows that in the 10-minute sonication process, the manganese particle size is 1 364.8 ± 267.5; in the sonication process for 15 minutes obtained, the size of 1 204.7 ±279.8; while in the 20-minute sonication process the size is 488.2 ±116.0 and in the 25-minute sonication process the size is 1 131.8 ± 275.4.

In Table 1, it can be seen that the results of sonication with manganese particle size less than

1 000 nm occurred at 20 minutes of sonication. This means that the sonication process that produces nanoparticles is only sonicated for 20 minutes, while the other process has a manganese particle size of more than 1 000 nm, so they are not called nanoparticles. PSA measurement results can be seen in Table 1.

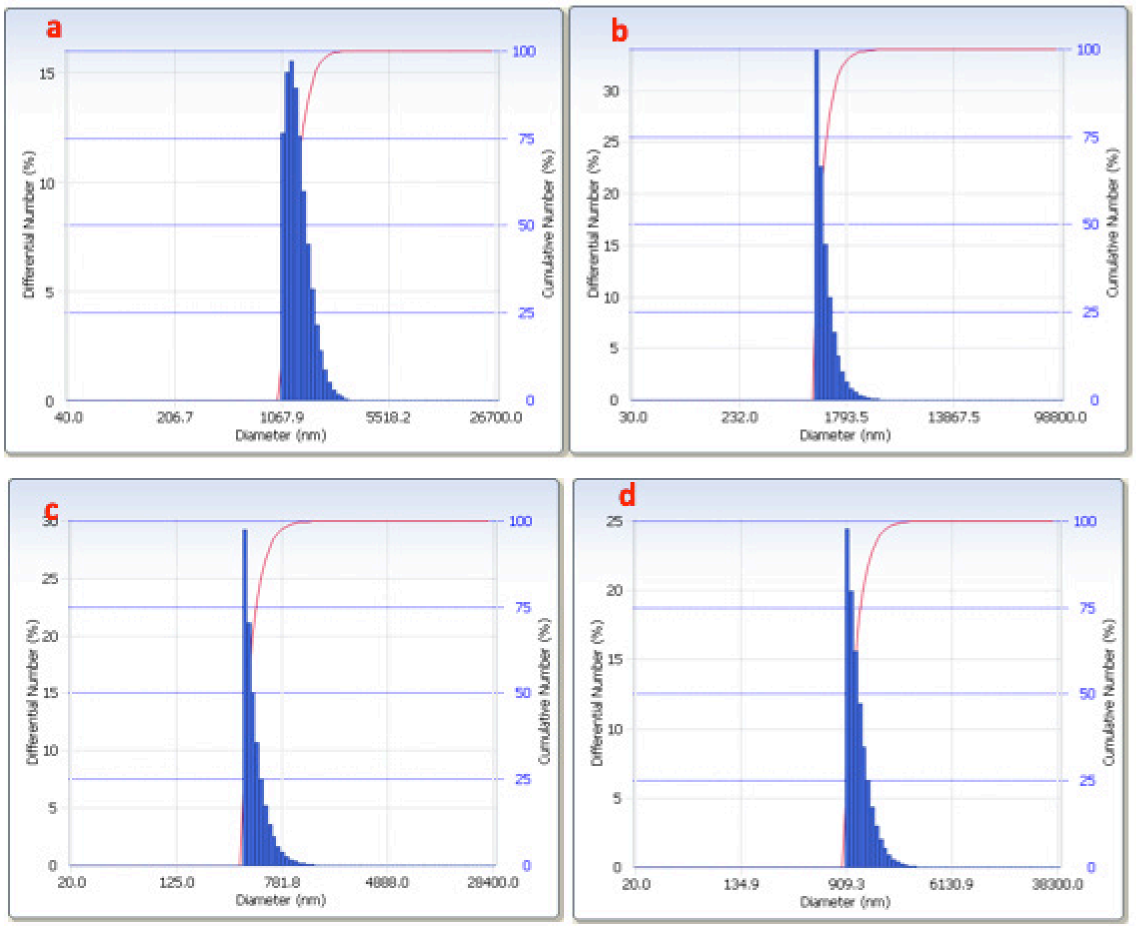

Figure 1. Particle Size Analyzer (PSA). a. 10 minutes, b. 15 minutes, c. 20 minutes, d. 25 minutes

Table 1

Diameter NP MN extract oolong tea

Sonication Time (minutes)	Diameter (nm)	Std. Dev
10	1 364.8	267.5
15	1 204.7	279.8
20	488.2	116.0
25	1 131.8	275.4

The oolong nanoparticle material obtained by sonication for 20 minutes was then given to healthy volunteers by drinking 200 mL orally. The results of MRCP scanning before and after oral administration of oolong nano particle tea contrast media can be seen in Figure 2. Where both before giving contrast (pre-contrast) and after giving contrast (post-contras), ROI (Region of interest) was made in the same organs, namely the stomach (a), duodenum (b), gall bladder (c), and common bile duct (d). Therefore, the ROI results will display their respective SNR values, as shown in Table 2.

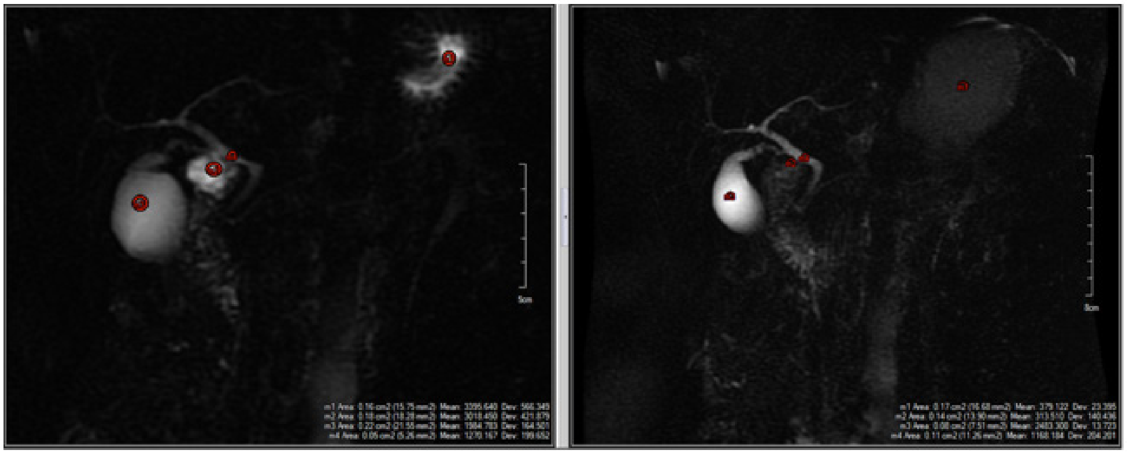

Figure 2. MRCP images of organ stomach (a) and duodenum (b) in pre and post-contrast are suppressed. Organ Gall Bladder (GB) (c) and Cammon Bile Duct (CBD) (d) in pre and post-contrast are hyperintensities.

Table 2

SNR value on MRCP the significance value is a statistical test

Organ	SNR PRE	SNR POST	Sig.
Stomach	895.14	95.12	0.006
Duodenum	758.21	81.21	0.0001
Gall Bladder (GB)	540.38	637.56	0.0001
Common Bile Duct (CBD)	326.52	300.30	0.073

Table 2 shows that the pre-contrast and post-contrast SNR values for the stomach and duodenum decreased from 895.14 to 95.12 and 758.21 to 81.21, respectively. It can be seen in the MRCP image that the stomach and duodenum images are suppressed, which initially lightens and then turns black. Meanwhile, in Gall Blader, the SNR value increased from 540.38 to 637.56, respectively, while the common bile duct decreased from 326.52 to 300.30 because the organ was superpositioned with the duodenum. The increased SNR in these organs is seen on the MRCP image with a change from hypointense to hyperintense, with contrast enhancement.

DISCUSSION

Manganese nanoparticle sonication process from oolong tea extract

Giving ultrasonic waves to a solution will cause the molecules in the solution to oscillate concerning their average position. As a result, the solution undergoes strain and density. When the ultrasonic wave energy given is large enough, the wave strain can break the molecular bonds between solutions (16-18), and the gases dissolved in the solution will be trapped due to the solution molecules whose bonds are broken when a density returns. This results in hollow balls or bubbles filled with trapped gas, known as the cavitation effect. These bubbles can have a diameter that expands to a maximum size, then contracts and shrinks so the volume decreases, some even disappearing completely. The effect of time affects the size and density of the resulting defects and the sedimentation behaviour of the dispersion of oolong tea extract nanoparticles (19).

In the process of making nanoparticles with a time of 10, 15, and 25, it produces a particle diameter size of >1 000 nm and is not a nanoparticle. The use of sonication time, which is less than 20 minutes, the process of sonication of the solution molecules whose bonds are broken when re-densification occurs has not occurred. When the sonication time is more than 20 minutes, aggregation or agglomeration is seen in the granules of the compound, causing the particle size to appear larger. Agglomeration is the process of joining small particles into a larger structure. Agglomeration occurs due to mechanical chemical processes. The mechanical process is related to the physical binding mechanism in the high-speed milling process. High rotational speed causes greater kinetic energy, so particle collisions will occur more often, allowing materials to interact with each other and combine to form larger aggregations (16). The agglomeration process can also be caused by chemical processes such as contamination of sample powder with ball mills and tube materials. Despite having a very high hardness, stainless steel in ball mills and tubes will still contaminate the milled sample powder (16). The effect of water content that is still in the tube can also cause agglomeration. High milling speed and long time causing particle contamination from ball mills and tubes can be almost unavoidable (16). Previous research showed that too long milling time makes the nanoparticles experience agglomeration (20). With a time of 20 minutes, as seen in Figure 1, the particle diameter is 488.2 nm. In a study by coating chitosan with tea, the particle size was 407 nm (21).

Another thing, PSA testing carried out 72 hours after the sonication process can also cause agglomeration and sedimentation in samples within 10, 15, and 25 minutes. Probe sonication is an advanced way to disperse such non-inert NPS and reduce the size of the agglomerates formed. However, rapid sedimentation results in a large (30 %-80 %) difference between the nominal and the administered dose. The sonication probe also affects the metal release rate, especially when adding a stabilizer (Bovine serum albumin, BSA). However, a small effect was observed when prolonging the time (conducting energy to the dispersion) of probe sonication (22).

Manganese nanoparticles from oolong tea extract as contrast medium MRCP

In general, the MRCP examination is done without using contrast media. Still, when there is an overlap between the gastrointestinal and pancreaticobiliary systems, it will produce a picture like a pseudo structure. This overlapping state in the MRCP examination can cause an unexpected increase in signal intensity. An increase in signal intensity can lead to a misdiagnosis of between 5 % and 7 %, i.e. a normal picture is sometimes considered pathological (23,24). Misdiagnoses on MRCP examination include fluid in the stomach or duodenum, which is considered a pseudolesion in the pancreaticobiliary system. In addition, fluid located between the gastric folds, although normal, can be considered fluid in the ectatic pancreatic duct, and fluid and air in the duodenal bulb can be considered gallstones (24-26).

To overcome this problem, as an alternative, oral contrast media is used to shorten the T2 relaxation time. A short T2 relaxation time can reduce the intensity of the T2 signal of fluids in the gastrointestinal system to suppress or eliminate the picture of the gastrointestinal system so that the picture of the pancreaticobiliary system will appear clearer and not obscured by the stomach, duodenum, intestines or other organs (5,8).

Many negative oral contrast media are used for abdominal MRI examination, such as gadopentetate dimeglumine, ferric ammonium citrate, manganese chloride, kaolinite, antacids, ferristene, ferumoxil, perfluoro-octylbromide, and iron particles. Currently, this negative contrast medium is made of Mn^{2+} or $MnCl_2$ ions (0.5 – 1 mg/dL Mn-DTPA), some of which are rarely used because they are no longer produced, have an unpleasant taste, are very difficult to swallow and are relatively expensive (12,27). In addition, some contrast media is administered intravenously. The level of cellular toxicity is higher than oral administration. The plasma half-life is very short, so it is difficult to collect in the blood pool agent, and there is still retention in the basal ganglia tissue for a long examination. Contrast media such as mangafodipir trisodium, used as a negative intravenous contrast medium, showed biodistribution in mice 30 minutes after injection is 13 % in the liver, 9 % in the small intestine, 3 % in the blood, and 1.3 % in the intestine (28).

The previous study showed that oolong tea extract was used as an alternative negative contrast medium in MRCP examination because of its high manganese content (0.94 mg/dL). In addition, the study showed that oolong tea extract increased the contrast between the images of the biliary tree and the surrounding organs. However, suppressing the stomach and duodenum is still not optimal, so it is necessary to provide a solution so that the disturbing organ can be maximally suppressed by making oolong tea extract as nanoparticles (9).

The advantage of nanoparticle-sized contrast media compared to conventional contrast media is that it has a stronger magnetic moment characteristic because the relaxometric values of T1 and T2 become higher, so the signal intensity is strengthened. Besides that, the size of the material in the form of nanoparticles can control the pharmacokinetic process to increase blood circulation time and allow the material to accumulate in the target tissue. Furthermore, the distribution of the nanoparticle material was cleared by the reticuloendothelial system (liver and spleen) (29). Besides, the taste of oolong tea can be accepted by patients and is relatively safe.

The overall difference in MRCP image information on the effect of negative oral contrast media on gastric and duodenal signal intensity and the effect of pancreatobiliary tree imagery indicates that oolong tea can be used as a negative substitution. The appearance of the gallbladder and intrahepatic ducts seen before or after oral contrast media administration of NP Mn oolong tea extract increased. The oral contrast media presentation of NP Mn oolong tea extract could distinguish between the enlarged gallbladder and Cammon Bile Duct (CBD). The intrahepatic ducts can only be seen in the right and left hepatic duct branches. In contrast, the peripheral intrahepatic ducts are barely visible due to their smaller size, which agrees with previous findings (26).

The pancreatic duct and ampulla are barely visible on all MRCP images. The pancreatic duct is slightly angled, making it difficult to see the entire pancreatic duct. The use of a single Shot Fast Spin Echo (SSFSE) sequence will show pancreatic ducts in the head (97 %), body (97 %), and tail (83 %) (26). Fasting preparations aim to reduce gastric fluid, and it is hoped that there will be a little residual fluid in the second part of the duodenum, which is useful as a marker for the presence of the distal bile duct and ampulla. Administration of negative oral contrast media helps suppress signal intensity in the gut, but the ampulla is often not visible due to regurgitation of the contrast medium into the ampulla (5). The limitation of this research is the time for the particles to persist in nano size because it uses natural materials. In a certain period, the particles will experience agglomeration. In addition, the oolong tea extract dissolved in distilled water is also prone to decay.

CONCLUSION

Nanoparticles from oolong tea extract obtained by sonication method for 20 minutes obtained manganese nanoparticles with a size of 488.2 nm. Further research is applied into practice recommended on a small scale.

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