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The Potency of Oral L-Arginine Suplementation Based on Chitosan-Coated Gold Nanoparticles (c-AuNPs) as Preeclampsia Prevention in Pregnant Women

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ABSTRACT

Background: Preeclampsia is the second leading cause of death for pregnant women in Indonesia. The last two decades show that the incidence of preeclampsia tends to increase in Indonesia by 128,273/year or around 5.3%. However, until now the handling of preeclampsia in Indonesia is still not optimal. This disease is difficult to detect and often appears suddenly, so it is necessary to take preventive measures as an important step in reducing morbidity and mortality from this disease. Previous studies have shown that L-Arginine exhibits potential properties in preventing preeclampsia. **Objective:** This literature review aims to determine the potential for oral L-Arginine supplementation based on c-AuNP to prevent preeclampsia in pregnant women. **Methods:** The search for literature uses keywords namely "L-Arginine", "nitric oxide pathway", "preeclampsia", "prevention of preeclampsia", and "c-AuNPs" with search engines such as Google Scholar, Science Direct, ResearchGate, and NCBI. Inclusion and exclusion criteria were used to eliminate unrelated journals so that 38 journals were obtained within the last ten years in this literature. **Discussion:** The main mechanism of L-Arginine which contributes to the reduction in morbidity of preeclampsia is an increase in vascular NO synthesis. Clinical trials have shown that dietary supplementation of L-Arginine 3 g/day for three to four weeks for women with preeclampsia is known to lower blood pressure, improve fetal health and growth, and benefit pregnancy in the long term, and RCTs in preeclamptic women taking low doses (3 g/day) started early and consistently at 20 weeks of gestation have been shown to significantly reduce the risk of preeclampsia. The use of chitosan-coated gold nanoparticles (c-AuNPs) as encapsulation in proteins is known to increase the bioavailability of oral supplementation and improve the clinical condition of patients. **Conclusion:** L-Arginine has great potential as a supplement to prevent preeclampsia by increasing vascular NO synthesis where NO deficiency in pregnant women can cause changes in uteroplacental structure. However, the use of L-Arginine in combination with c-AuNP has not been known until now so that further research regarding the effectiveness of L-Arginine supplementation orally with c-AuNPs and the optimal dosage as a preeclampsia preventive supplement is needed.

Keywords: c-AuNPs, L-Arginine, nitric oxide pathway, preeclampsia, prevention of preeclampsia

ABSTRAK

Latar belakang: Preeklampsia merupakan penyebab kematian ibu hamil terbanyak kedua di Indonesia. Dua dekade terakhir menunjukkan insidensi preeklampsia cenderung meningkat di Indonesia sebesar 128.273/tahun atau sekitar 5,3%. Namun, hingga saat ini penanganan preeklampsia di Indonesia masih belum maksimal. Penyakit ini sulit dideteksi dan sering timbul secara tiba-tiba sehingga upaya pencegahan perlu dilakukan sebagai langkah penting dalam menekan morbiditas dan mortalitas akibat penyakit ini. Penelitian sebelumnya diketahui bahwa L-Arginine menunjukkan sifat-sifat yang potensial dalam mencegah terjadinya preeklampsia. **Tujuan:** *Literature review* ini ditujukan untuk mengetahui potensi suplementasi L-Arginine per oral dengan sistem penghantar c-AuNP sebagai tindakan preventif preeklampsia pada ibu hamil. **Metode:** Pencarian literatur menggunakan kata kunci yaitu "L-Arginine", "nitric oxide pathway", "preeklampsia","pencegahan

preeklampsia", dan "c-AuNPs" dengan mesin pencari berupa *Google Scholar, Science Direct, ResearchGate,* dan NCBI. Kriteria inklusi dan eksklusi digunakan untuk mengeliminasi jurnal yang tidak berkaitan sehingga didapatkan 38 jurnal dalam kurun waktu 10 tahun terakhir pada penulisan ini. **Pembahasan:** Mekanisme utama L-Arginine yang berkontribusi terhadap penurunan morbiditas preeklampsia adalah peningkatan sintesis NO vaskular. Uji klinis menunjukkan suplementasi diet L-Arginine 3 g/hari selama tiga sampai empat minggu untuk wanita dengan preeklampsia diketahui dapat menurunkan tekanan darah, meningkatkan kesehatan dan pertumbuhan janin, dan juga kehamilan yang menguntungkan dalam jangka panjang, serta RCT pada wanita preeklampsia yang menggunakan dosis rendah (3 g/hari) yang dimulai lebih awal dan konsisten pada minggu ke-20 masa kehamilan terbukti signifikan mengurangi risiko preeklampsia. Penggunaan nanopartikel emas berlapis kitosan (c-AuNPs) sebagai enkapsulasi pada suatu protein diketahui dapat meningkatkan bioavailabilitas pemberian suplementasi secara oral serta meningkatkan keadaan klinis pasien. **Simpulan:** L-Arginine memiliki potensi besar sebagai suplementasi preventif preeklampsia dengan meningkatkan sintesis NO vaskular dimana defisiensi NO pada ibu hamil dapat menginduksi perubahan struktur uteroplasenta. Namun penggunaan L-Arginine dikombinasikan dengan c-AuNP belum diketahui sampai saat ini sehingga diperlukan penelitian lebih lanjut terkait efektivitas suplementasi L-Arginine per oral berbasis c-AuNPs serta dosis yang optimal sebagai suplemen preventif preeklampsia.

Kata Kunci: c-AuNPs, L-Arginine, jalur nitrit oksida, preeklampsia, pencegahan preeklampsia

INTRODUCTION

Preeclampsia is one of the most common pregnancy complications and causes many deaths. Preeclampsia is a multisystemic hypertensive disorder in pregnancy that occurs in pregnant women after 2 weeks of gestation which can cause complications in about 6-10% of all pregnancies.[1] WHO estimates that the incidence of preeclampsia in developing countries is seven times higher (2.8% live births) compared to developed countries (0.4% live births).[2] With the most significant morbidity and mortality, preeclampsia occurs in 5% to 7% of all pregnant women and is responsible for more than 70,000 maternal deaths and 500,000 fetal deaths worldwide each year. [3]

Based on the 2015 Inter-Census Population Survey, the Maternal Mortality Rate (MMR) in Indonesia was at 305/100,000 live births, making Indonesia a relatively high maternal mortality rate compared to other ASEAN countries. The three leading causes of maternal death are bleeding (30%), hypertension in pregnancy (25%), and infection (12%). The incidence of preeclampsia in Indonesia is 128.273/year or about 5,3%. The occurrence of preeclampsia in the mother has a long-term impact on the baby being born, such as low birth weight (LBW) due to premature delivery or experiencing stunted fetal growth. Moreover, it contributes to the high rates of perinatal morbidity and mortality. [4] Related to this, Indonesia occupies ten countries with the highest neonatal or infant mortality rate (IMR) globally caused by low birth weight, one of which is most often affected by preeclampsia.[5]

Reducing maternal mortality is one of the global targets in the 2030 Sustainable Development Goals (SDGs) which refers to Universal Good Health and Well Being, which is the first point that the world pushes the target for reducing maternal mortality rates to be below 70 per 100.000 live births.[6] Given the high MMR in Indonesia, which is still far from the SDGs target, a more up-to-date strategy and synergy between the government and health workers are needed to create implementable steps to reduce maternal mortality.

Currently, the handling of preeclampsia in Indonesia is still not optimal because there is no theory that is able to explain the pathogenesis of preeclampsia clearly and the lack of readiness of facilities and infrastructure in the region. It is thought that the primary cause of preeclampsia is inadequate placentation. Failure of trophoblast invasion and remodelling of the uterine arteries results in high uterine circulation resistance, reducing blood flow and placental ischemia. The resulting reperfusion causes an increase in oxidative stress leading to a broad systemic inflammatory response and altered angiogenic signalling factors. Eventually, there will be generalised endothelial dysfunction, which is considered central to all maternal manifestations of preeclampsia.[7] One of the complications that often causes death due to preeclampsia is neurological complications in eclampsia, stroke, and cerebral oedema.[8]

Prevention is one of the crucial steps in reducing morbidity and mortality due to preeclampsia. Prevention includes lifestyle changes, routine antenatal care, nutritional supplementation, and medications such as low-dose aspirin, heparin, antioxidants, calcium supplementation, proton pump inhibitors, or metformin. The only effective prevention is the administration of low-dose aspirin to women at high risk of preeclampsia at <16 weeks of gestation. However, aspirin is not indicated in pregnancies without risk factors for preeclampsia.[9]

Considering that preeclampsia is a disease that is difficult to detect and often occurs suddenly, prevention efforts need to be made by utilizing L-Arginine, an amino acid precursor of Nitrogen Monoxide (NO), which shows potential vascular relaxant properties in preventing preeclampsia in pregnant women through oral supplementation.[7] Oral L-Arginine supplementation can be administered through a chitosan-coated gold nanoparticle delivery system (c-AuNPs). C-AuNPs are a potential matrix to be used as a drug carrier for oral protein delivery.[10] Nanoparticles offer a possible solution to increase the bioavailability of L-Arginine in the body, have greater stability during in vivo storage, and provide easy scaling without an aseptic process for oral administration.[11]

Referring to the problem of high maternal and fetal mortality due to preeclampsia and the opportunities that can be utilized in the health sector, this literature review was made to determine the potential for oral L-Arginine supplementation based on c-AuNPs as a preventive measure for preeclampsia in pregnant women. This literature review can contribute to developing knowledge in the medical field.

METHOD

Search keywords had been determined, such as "L-Arginine", "nitric oxide pathway", "preeclampsia", "preeclampsia prevention", and "c-AuNPs". The literature search was conducted using search engines in several databases such as Google Scholar, Science Direct, ResearchGate, and NCBI. The inclusion criteria in this literature search were evidence-based medicine research journals at levels 1, 2 and 3 and experimental research both in vitro, in vivo, and clinical research with publication provisions within the last ten years. The exclusion criteria used were journals in languages other than Indonesian and English.

Evaluation of inclusion and exclusion criteria was carried out by assessing the title and abstract as a first step so that 52 journals were obtained, and then the full text was reviewed whether there was a

correlation of keywords with each other in the journal to support writing a description or analysis in this literature review so that 14 journals were excluded. From the literature search results using inclusion and exclusion criteria, this study used 38 journals.

DISCUSSION

Pathogenesis of Preeclampsia

Preeclampsia can be characterized by persistently elevated blood pressure (systolic BP 140 mmHg and/or 90 mmHg diastolic, based on at least two measurements taken at 4-hour intervals) with proteinuria or systemic involvement.[12] Preeclampsia is a disease caused by a multifactor genetic, immunogenic, environmental, or a complex combination of different factors.[13] The pathogenesis of preeclampsia is not fully understood. However, the placenta has an essential role in the etiology of preeclampsia. [14] Pathological examination of the placenta in pregnancies with advanced preeclampsia reveals placental infarction and sclerotic narrowing of the arterioles.[15] The mechanism of preeclampsia involves two stages. The first stage is incomplete remodelling of the spiral arteries in the uterus leading to ischemia of the placenta. Moreover, the second stage is the release of antiangiogenic factors from the ischemic placenta into the maternal circulation, which causes endothelial damage.[16]

During implantation, the placental trophoblast invades the uterus and induces remodelling of the spiral arteries by obliterating the tunica media from the myometrial spiral arteries.[12] This allows the arteries to accommodate increased blood flow regardless of maternal vasomotor changes to maintain fetal development. This remodelling requires the trophoblast to adopt an endothelial phenotype and various adhesion molecules.[13] However, if remodelling is impaired, it can result in oxygen deprivation, leading to a state of relative ischemia and increased oxidative stress during intermittent perfusion states.[12] The defining clinical manifestation of preeclampsia occurs in the second stage. Chronic placental hypoperfusion triggers abnormal production and release of various bioactive factors into the maternal circulation. Excessive release of angiogenic proteins such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble Endoglin (sEng) which capture circulating substances play a role in reducing proangiogenic substances such as vascular endothelial growth factor (VEGF), placental growth factor (PlGF) , and transforming growth factor (TGFβ). These circulating substances target endothelial cells causing widespread endotheliosis, endothelial dysfunction, multisystem vasospasm, reduced plasma volume, oxidative stress, and hyperinflationary states.[12], [17]

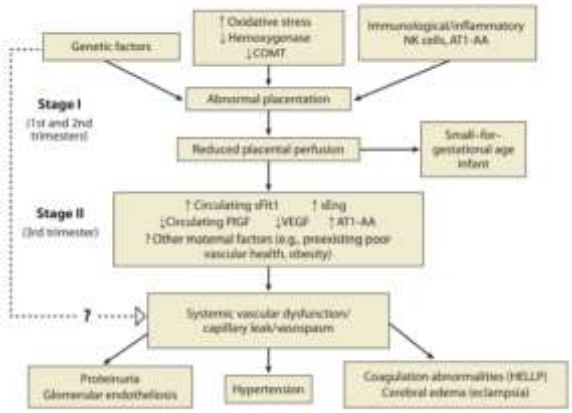

Figure 1. The Pathogenesis of Preeclampsia.[17]

The nitric oxide system/Nitro oxide synthase (NOS) system also plays a role in preeclampsia. NO is a potent vasodilator that induces relaxation in vascular smooth muscle cells via the cyclic adenosine

monophosphate pathway. Decreased levels of NO and increased levels of arginase (which degrades precursor molecules in the NOS pathway) have been reported in preeclampsia. NO deficiency has been shown to correlate with metabolic disorders seen in preeclampsia, such as hypertension, proteinuria, and platelet dysfunction. NO deficiency has been reported to induce uteroplacental changes such as a reduction in uterine artery diameter, spiral artery length, and uteroplacental blood flow.[18]

Preeclampsia is characterized by decreased bioavailability of NO, which explains peripheral vasoconstriction, endothelial dysfunction, and the systemic clinical manifestations of preeclampsia. Previous studies revealed that the mean NO concentration in preeclamptic women was 43.1 +/- 12.7 microM, which was significantly lower than normal pregnant women at the same gestational age (249.7 +/- 51.3 microM). In cases of preeclampsia with low NO production (low NO2/NO3 levels), several alterations in the L-Arginine-NO pathway have been described in (Figure 2).[19]

1. Deficiency in L-Arginine substrate or its transport.
2. Deficiency of cofactors required for normal activity of eNOS, such as ionic calcium and BH4.
3. Accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of eNOS.
4. There is a polymorphic change in eNOS which results in lower enzymatic activity.

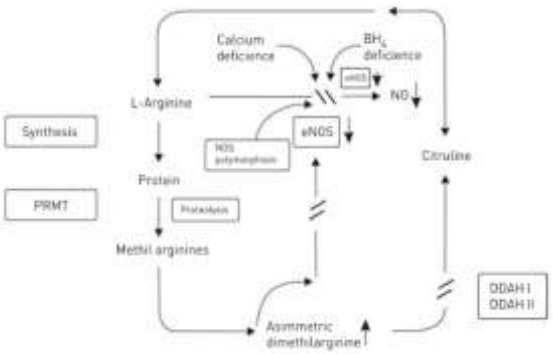

Figure 2. Changes in Factors Affecting NO Production in the Vascular Endothelium During Pregnancy.[19]

The Potency of L-Arginine in Prevention of Preeclampsia

L-Arginine is an amino acid precursor of NO and is involved in the endogenous nitro vasodilator system. NO is synthesized from L-Arginine using the enzyme group of NO Synthase (NOSs, EC1.14.13.39) to be called the L-Arginine-nitric oxide pathway (Figure 1). The vascular endothelium synthesizes NO. The reaction of NO with ferrous in heme prosthetic groups from soluble guanylate cyclase can increase the concentration of cyclical GMP in vascular smooth muscle, causing vascular relaxation (vasodilation).[20]

Changes in NO activity, including peroxynitrite production and the availability of other free radicals, have a pathophysiological role in the progression of hypertension in pregnancy. In animal models, inhibition of NO production induces findings similar to those reported in human preeclampsia, including hypertension, proteinuria, and fetal growth restriction.[21] Increased NO can increase the availability of endogenous L-Arginine and further increase tissue blood perfusion, thereby increasing oxygen and nutrient delivery. Pregnant women with preeclampsia are also known to have altered amino acid metabolic profiles, significantly a decrease in the NO precursor, L-Arginine.[22] This suggests

that L-Arginine supplementation has the potential to reduce the risk of developing gestational hypertension.

Several studies have suggested that L-Arginine supplementation can reduce blood pressure and the risk of preeclampsia.[23] The potential mechanism of action of L-Arginine that contributes to lowering hypertensive morbidity is well known (Table 1) and the most important is an increase in vascular NO synthesis.[24] L-Arginine supplementation Arginine is also known to significantly reduce triglyceride, LDL, and cholesterol levels while considerably increasing HDL levels in hypertensive induced pregnant rats.[25]

Table 1. The Potential Mechanisms of Action of L-Arginine in Hypertension.[24]

The Potential Mechanisms of Action of L-Arginine in Hypertension.
1. Improve endothelial vasomotor function
2. Increased vascular NO synthesis
3. Reduces the activity of endothelin-1 and angiotensin II
4. Favorable change of the ratio of ADMA:L-Arginine
5. Renal hemodynamic modulation
6. Reduces oxidative stress
7. Increased insulin sensitivity

Consumption of L-Arginine is estimated to be 2–3 g/day in the middle to lower economic class people, far below the average female intake of 4.3 g/day. Pregnancy with L-Arginine deficiency and being in an area where the infection is endemic, such as malaria, increases hypouricemia.[24] In addition, the challenge in L-Arginine supplementation is arginase, which catalyses the metabolism of L-Arginine to urea and is highly active in the adult gut. Only 60% of oral L-Arginine evades intestinal metabolism and 15% of circulating L-Arginine is metabolized in the liver.[26] Therefore, a potential solution to lower the risk of preeclampsia is in the presence of challenges in proper L-Arginine supplementation techniques, particularly the requirement to cross metabolic inhibition and transmembrane intracellular delivery.

Oral L-Arginine Supplementation Strategy in Preeclampsia

L-Arginine supplementation has been widely used in susceptible populations, such as pregnant women, premature infants, and individuals with cystic fibrosis, even in individuals with obesity, insulin resistance, and diabetes.[27] Its administration is related to the benefits of L-Arginine, namely increasing vasodilation in several clinical studies in humans regarding hypercholesterolemia and atherosclerosis.[21]

Oral co-administration of L-citrulline and L-Arginine is known to bypass this barrier and increase the bioavailability of L-Arginine supplementation. Recent studies support the effectiveness of oral L-citrulline in increasing L-Arginine bioavailability and NO-dependent signalling.[26] It is known that oral L-Arginine supplementation can reduce BP by 5,39/2,66 mmHg, which is an effect comparable to the pattern change. diet and exercise, while L-citrulline, was probably in the range of 4,1/2,08 to 7,54/3,77 mmHg.[28]

Dietary supplementation of L-Arginine 3 g/day with the use of three to four weeks for women with preeclampsia is known to cause lower blood pressure and improve fetal health and growth, as well as give benefit in pregnancy for long term effect.[29] In contrast, a RCT study in preeclamptic women using high-dose moderate and short-term starting after pregnancy (12 g/day for five days) has shown no significant benefit, so short-term supplementation, especially late in pregnancy, is insufficient to improve

maternal hemodynamics.[30] Low-dose interventions (3 g/day) throughout pregnancy (20th week of gestation) was shown to reduce the risk of preeclampsia significantly.[23] Adverse effects associated with L-Arginine supplementation are known to be associated with common gastrointestinal effects, including nausea, dyspepsia, and diarrhoea, as well as palpitations, headache, and numbness. Some cases have also been reported.[27] Based on research conducted by Gui et.al in 2014 it was found that L-Arginine is protective against preeclampsia because it has no significant side effects and no teratogenic effects have been reported in the third trimester of pregnancy.[9]

The Role of Gold Nanoparticles (AuNP) As Oral L-Arginine Delivery System

Decreased bioavailability in oral formulations occurs due to unfavourable physicochemical properties such as large molecular size, susceptibility to enzymatic degradation, decreased protein stability due to low gastric pH, intestinal membrane barriers that affect absorption, short plasma half-life, immunogenicity, and tendency to undergo aggregation, adsorption, and denaturation.[29] Nanotechnology offers a potential solution to increase the bioavailability of L-Arginine in the body using nanoparticles. Nanoparticles have advantages such as greater stability during storage, in vivo stability after administration and ease of scaling without aseptic processing for oral administration. active to achieve site-specific drug action at optimal therapeutic dose levels and regimens.[30]

AuNP as one of the L-Arginine delivery systems, offers several benefits in achieving target cell therapy as well as as an antiviral. Drug-conjugated AuNPs create quite interesting potential because they are able to bind to a variety of organic and biological molecules, have lower toxicity, and have a stronger absorption spectrum than other nanoparticles.[31] Several studies have revealed that the use of gold nanoparticles as encapsulation in a protein can improve the patient's clinical condition. Insulin-conjugated AuNPs (INS) for oral delivery to treat type 1 diabetes mellitus (DM) was found to improve body weight, lipid profile, urea, creatinine, and liver parameters at high doses. The observed values were close to insulin per intraperitoneal followed by moderate doses.[32] Another study by Zhu et al in 2018 in treating colitis using citrate and polyvinylpyrrolidone (PVP) and tannic acid (TA) as anti-inflammatory is known to improve colonic clinical and histopathological improvement.[33]

Modifying nanoparticles by incorporating target molecules on their surface can be a more efficient way to increase the absorption of nanoparticles. Optimum contact between the carrier and the surface of the biological target is essential in enhancing drug absorption.[30] Nanoparticles must also be able to make strong interactions with the epithelial surface. Extensive efforts have been devoted to achieving the so-called active targeting of nanoparticles to deliver drugs to precise targets based on molecular recognition processes such as ligand-receptor or antigen-antibody interactions.[34] Targeting with small ligands is more likely to be successful because it is easier to handle and manufacture. Moreover, it has the advantage when active ligand targeting is combined with long-circulating nanoparticles to maximize the chances of success in the active targeting of nanoparticles.[35] Ligands conjugated to the engineered nanoparticle surface can influence the mode of cellular internalization.[30] Ligands play an important role in determining nanoparticle size, shape, and distance between particles

and the nature of the link between the ligand and the surface of the nanoparticle and the link between the nanoparticle and its environment.[36]

One of the natural ligands that can be used in the use of nanoparticles is chitosan. Chitosan is a natural macromolecule that is biodegradable and non-toxic. Chitosan consists of glucosamine and N-acetyl-glucosamine.[10] Chitosan has been used to form particulate systems such as lysosomes and nanoparticles, where drug candidates are packaged in polymer membranes.[37] The positively charged surface of chitosan tends to bind to the negatively charged cell membrane. Chitosan will bind to occluding, redistribute F-actin, disrupt plasma membranes, and reduce trans epithelial cell electrical resistance so that it can increase transcellular and paracellular diffusion of the drug.[38] The mucosal adhesive properties of chitosan can increase the diffusion or absorption of drugs by prolonging the time in the stomach.[39] Chitosan was also selected as a ligand for nanoparticles because of its low toxicity, biodegradability, responsiveness to pH and mucosal adhesion, and the chitosan-coated system has been used as an effective oral system for many protein-peptide drugs, non-viral genes, DNA and vaccines. nucleic acids.[40] A study by Alalaiwe et al. reported the oral bioavailability of c-AuNPs by comparing AUCinf after intravenous and oral administration of 0.8 m/kg and 8 m/kg body weight, respectively was found that chitosan can increase permease or absorption so that increase the bioavailability of administration orally.[38] Besides, coating chitosan as a ligand on gold nanoparticles resulted in oral bioavailability of 2.46%, approximately 25-fold higher than that achieved by coating with polyethylene glycol (PEG).[41]

CONCLUSION

L-Arginine, an amino acid precursor of NO, has great potential as a preventive supplementation of preeclampsia by increasing vascular NO synthesis where NO deficiency in pregnant women can induce changes in uteroplacental structure. In condition the treatment is started earlier and continued consistently. Dietary supplementation of L-Arginine at a low dose of 3 g/day for three to four weeks is necessary early in pregnancy (20th week) to reduce the risk of developing preeclampsia. In preventing this, L-Arginine has several advantages, namely lowering blood pressure, improving fetal health and growth, and pregnancy that is beneficial for the long term. Supporting this, L-Arginine has no significant side effects, and no teratogenic effects have been reported. In addition, the use of c-AuNPs as encapsulation in a protein is known to increase the bioavailability of oral supplementation and improve the patient's clinical condition.

RECOMMENDATIONS

Further research on the effectiveness of oral L-Arginine supplementation based on c-AuNPs and the optimal dosage as a preventive supplement for preeclampsia is urgently needed. The synergy of researchers, health workers, and the government is also very much needed to prevent the occurrence of preeclampsia in pregnant women so that it can reduce perinatal morbidity and mortality in Indonesia.

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