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Potential Combination of Xanthone Compounds from Mangosteen Fruit (*Garcinia mangostana*) with Eugenol Compounds in Basic Leaf (*Ocimum sanctum*) as Alternative Therapy in Preeclampsia

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A B S T R A C T

Preeclampsia is a hyperdynamic condition that is syndromed by hypertension and proteinuria after 20 weeks of pregnancy. Preeclampsia incident is the first cause of 6- 8 % number morbidity/mortality maternity and fetus in the world. Preeclampsia is related to the disability of physiology adaptation that can decrease perfusion of uteroplacental. Xanthone derivatives in mangosteen have been reported to possess a wide range of biological properties, including antioxidant and antihypertensive activities. Eugenol is a primary component of basil oil. It is known for its antioxidant, antiinflammatory, and vasorelaxant actions. These beneficial effects of eugenol make it an excellent therapeutic candidate for the treatment of hypertensive disorders of pregnancy. This study wants to analyze the best available research evidence on the potential combination of xanthone compounds from mangosteen fruit (*Garcinia mangostana*) with eugenol compounds in basil leaf (Ocimum sanctum) as an alternative therapy in preeclampsia. A literature review was conducted in the electronic databases PubMed and Google Scholar using the index terms "xanthone" and "eugenol" and "hypertension" and "preeclampsia." All types of studies were included for this study, such as randomized controlled trials, systematic reviews, literature reviews, and pilot studies published between 2010 and 2021. Articles which not written in English were excluded from the study. This search resulted in 10 papers. Antioxidant properties of mangosteen peel extract compounds derived from xanthone, the most significant component is α-mangosteen and γ-mangosteen. Eugenol is vasorelaxant action by increasing the expression of its target genes, Sarco/endoplasmic reticulum Ca^{2+}-ATPase and adequate potassium-calcium- activated potassium channels channel, thereby relaxing vascular smooth muscle cells and decreasing blood pressure. With this review, we suggest that eugenol, which is a vasorelaxant combined with xanthone which is an antioxidant by obstructing free radical and oxidative stress, can be a potent therapeutic for preeclampsia and intend to motivate researchers (e.g., chemistry, biology, pharmaceutical, and therapeutic areas) to provide evidence of these compounds for the management of preeclampsia.

1. Introduction

Preeclampsia is a pregnancy syndrome that affects multiple organ systems, characterized by hypertension and proteinuria after 20 weeks. Globally, the incidence of preeclampsia ranges from 5-7% in pregnancy. In developing countries like Indonesia, the number is relatively high, namely about 5-10% of pregnancies, and contributes to high maternal and fetal morbidity and mortality.[8] Placental trophoblast cells invade the uterine arteries (spiral arteries in humans) during embryo implantation and induce its remodeling while obliterating the tunica media of the myometrial spiral arteries, which allows the arteries to accommodate

increased blood flow to nourish the developing fetus. This abnormal spiral artery remodeling was seen and described over five decades ago in pregnant women who were hypertensive which, if not treated, may lead to preeclampsia and eclampsia, a severe form of hypertension and convulsions, and may also consequent in coma and death.[8]

Hemodynamic changes can occur in pregnant women with preeclampsia; decreasing placental perfusion will induce transcription factor HIF-1α. HIF-1α correlated with the increase in cytokines TNF-α through NFkB and improvement of antiangiogenic molecules VEGFR-1 or sFlt-1, which suppress angiogenesis and inhibit the vascularization of the placenta. Poor placental perfusion will activate free radicals. The results are decreased blood flow to the kidneys, a 50% reduced glomerular filtration rate, increased sensitivity to vasopressor substances, decreased renin-angiotensin, and decreased prostaglandin E levels.[8] The current treatment for hypertensive pregnancy disorders is to control and manage blood pressure and seizures with antihypertensive and magnesium sulfate. However, the ultimate option is to deliver the fetus and placenta. Recently antioxidants are recommended in potential prevention strategies based on the data showing that endothelial dysfunction indicates preeclampsia where increased oxidative stress exists, especially in the placenta. Many researchers used an antioxidant approach to cure cellular disorders, such as giving a combination of vitamin C, E, aspirin, and fish oil. These antioxidant supplements were able to inhibit the action of free radicals that can improve the placenta's response to overcome hypoxia.[6,8] Mangosteen (*Garcinia mangostana* Lin.) is a tree indigenous to Southeast Asia and Indonesia and grown in Hawaii and Puerto Rico. Additionally, mangosteen is well-recognized for its medicinal benefits because it has xanthone. Nowadays, xanthones and xanthone derivatives are isolated from plants or chemically synthesized. A substantial number of studies demonstrated that xanthones and xanthone derivatives have extensive biological and pharmacological activities such as anti-inflammatory, antihepatotoxic, antitumor, and antimicrobial activities. Its antioxidant is higher than vitamin E and vitamin C, which is better to inhibit the action of free radicals and increased lipid peroxidation (F2-isoprostane dan MDA), TNF-α, and expression NFkC-p50 than vitamin E and vitamin C.[6]

Eugenol may dilate arteries by increasing the expression of its target genes, Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and significant potassium (BK) calcium-activated potassium channels (KCa 1.1 or KCNMA1 gene) channel, thereby relaxing vascular smooth muscle cells and decreasing blood pressure.[3]

Pathomechanism of preeclampsia that happens at the beginning of pregnancy, where oxidative stress increases, it is possible to be cured by antioxidant from mangosteen peel extract so it can prevent or protect membrane cell from free radical that can damage it, combined with eugenol has highly potent vasorelaxant effect in the middle uterine artery, and its effect is partly mediated through activation of the TRPV1 channel, suggesting its potential value as a nutraceutical agent and therapeutic candidate for the treatment of hypertensive disorders of pregnancy. This review was to analyze the best available research evidence on the potential combination of xanthone compounds from mangosteen fruit (Garcinia mangostana) with eugenol compounds in basil leaf (Ocimum sanctum) as an alternative therapy in preeclampsia.[4,8]

2. Methods

The researcher searched for all studies published between 01 January 2010 and 01 August 2021, using Google Scholar and PubMed. The following keywords were applied during the literature search: "Xanthone AND "Pregnancy," "Eugenol" AND "Pregnancy" “Xanthone” AND “Vascular," "Eugenol" AND "Vascular." The researcher added additional studies through a manual search, which is relevant to this review. The inclusion criteria were studies that describe the effect of hypertension. The exclusion

criteria were studies that include other conditions (e.g., comorbid conditions (anxiety, socioeconomic status, nutrition level, and some previous pregnancies), endocrine problems, neurovascular problems, geriatric problems, immunopathological problems, hematological problems, and oncology problems that could play an essential role in the experience of hypertension.

Moreover, because these confounding factors are difficult to account for in this study, the adjusted results were used and discussed in this article when available. In the first step, the researcher assesses the titles and abstracts of the studies to exclude reports based on the criteria. In the second step, the researcher read and evaluated the full-text studies that met the requirements.

3. Results and Discussion

The PubMed and google scholar search results identified 149 potential studies, with 122 remaining studies after removing duplicates. After reviewing the titles and abstracts from 122 studies, 20 studies were identified for possible inclusion in the review. After examining the full text of the 20 studies against the inclusion criteria, nine studies were excluded.

Reasons for exclusion were: studies that include other conditions (exp: Comorbid conditions (anxiety, socioeconomic status, nutrition level, and some previous pregnancies), endocrine problems, neurovascular problems, geriatric problems, immunopathological problems, hematological problems, and oncology problems. See Figure 1 for the process of search results. The 10 selected studies consisted of 9 experimental studies and 2 randomized controlled clinical trials conducted in different countries such as Indonesia [8,11], Brazil [2,5], India [1,4,9], the USA [3,6,10], and Poland [7].

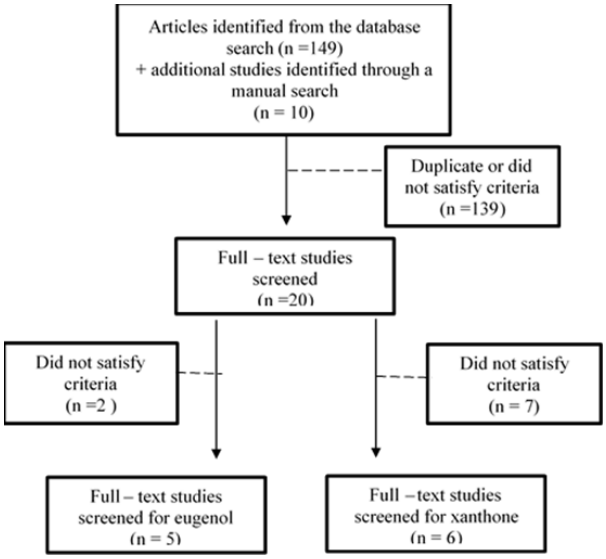

Figure 1. The process of search results

Participants in each study were varied, wherein RCTs the number of participants ranged from 30 to

60 and the distribution of male and female participants in 2 RCTs are similar not only for male but also female participants.[6,11] The type of animals in each experimental study varied, they used Wistar rats.[1,2,5,7,8,9,10], Sprague-Dawley rats[3], and used goats4. Five experimental studies and one xanthone have a potential antihypertensive activity.[5,6,7,9,11] One experimental study resulted that mangosteen has a potential antihypertensive activity in pregnant women.[8] Two experimental studies and One RCT resulted from eugenol as a possible antihypertensive activity.[1,2,3,10] One experimental study resulted from eugenol having vasorelaxation in the uterine.[4]

Table 1. Summary of studies

Article	Ref.	Design Study	Sample	Main Results
Eugenol improves the damage of tissue and oxidative stress in adult female rats after ovarian torsion/detorsion	Barghi et al	Experimental	48 female Wistar rats	Eugenol, an antioxidant and anti-inflammatory agent, could be used experimentally to diminish the I/R damage in the ovary through the attenuation of detrimental histological events, decreasing the serum level of MDA and testosterone and increasing the level of SOD and GPX enzymes.
Reproductive Toxicity of Eugenol in Wistar Rats	Silva et al	Experimental	Nine pregnant Wistar rats	At all tested doses of eugenol, the groups treated during the pre-implantation presented alterations in the maternal organs, increased pre-and post-implantation loss, and stillbirth records. The groups treated during organogenesis also showed alterations in the maternal organs and reduced placental indexes, added to the skeletal alterations, in all treatment doses. There were no significant fetal visceral changes
Eugenol dilate rat cerebral arteries by inhibiting smooth muscle cell voltage-dependent calcium channels	Neves et al	Experimental	12 Sprague-Dawley rats (~250 g) were euthanized by intraperitoneal injection of sodium pentobarbital solution (150 mg/kg)	Arteries at low pressure (10 mmHg) were constricted with a bath solution containing 60 mM K+. This procedure constricted arterial diameter to 123.2 ± 14.6 µm, from a passive diameter of 138.6 ± 12.8 µm, or by 23.4 ± 2.2%. Increasing concentrations of eugenol dilated K+-constricted cerebral arteries with an IC50 of 323.3 ± 14.0 µM. These data suggest that eugenol dilates cerebral arteries via a mechanism that involves voltage-dependent Ca2+ channel inhibition.
Eugenol induces potent vasorelaxation in uterine arteries two from pregnant goats – A promising natural therapeutic three agent for hypertensive disorders of pregnancy.	Parija et al	Experimental	Six pregnant goats and six nonpregnant goats	When incubated with eugenol, MUA rings of nonpregnant uteri significantly relaxed the arterial rings precontracted with PE (Rmax = 36.83±0.66%, pIC50 = 6.93±0.09).
Vasodilator and Antioxidant Effect of Xanthones Isolated from Brazilian Medicinal Plants	Do at al	Experimental	Mice	The presence of a hydroxy group in position 1 seemed to decrease the vasodilator effect. In contrast, a hydroxy in position four and an increased number of hydroxy groups improved the vasorelaxation potential of xanthones.
Daily consumption of mangosteen-based drink improves in vivo antioxidant and anti-inflammatory biomarkers in healthy adults: a randomized, double-blind, placebo-controlled clinical trial.	Xie at al	A randomized, double-blind, placebo-controlled clinical trial	30 men and 30 women	The trial duration was 30 days. ORAC is an antioxidant A biomarker that was measured in both groups. It was found that after the 30-day trial, the group given the mangosteen has 15% more antioxidant capacity in the bloodstream than a group of placebo. The C-reactive protein level decreased 46% in the mangosteen group between the preintervention and postintervention. There were no side effects on hepatic and kidney functions.
Antiarrhythmic, hypotensive, and α1-adrenolytic properties of new 2-methoxyphenylpiperazine derivatives of xanthone	Santos et al	Experimental	The control and study groups consisted of five to eight animals each	Xanthone derivatives with a 2-methoxyphenylpiperazine moiety possess antiarrhythmic, hypotensive, and α1-adrenolytic activity. The data suggest that the antiarrhythmic and hypotensive effects of studied compounds are related to their α1-adrenolytic properties
Mangosteen Peel Ekstracts Decreased NfκB, Salt-1, Tnf-α, Blood Pressure and Proteinurine in Mouse Model of Preeclampsia	Ratna et al	Experimental	Five groups, each group consisting of four mice, groups were negative control group, MMP group, and 3 MSE groups with various dosages (200 mg/kg, 400 mg/kg, and 800 mg/kg)	The result was that the average HIF-1α, NFκB, sFlt-1, MDA, TNF-α, blood pressure, and proteinuria MMP group was higher than MPE. The development of the analysis proved that dosage 800 mg/kg is the most effective to decrease all of the variables, but it was not significant for proteinuria
Antihypertensive activity, toxicity and molecular docking study of newly synthesized xanthone derivatives (xanthonoxypropanolamine)	Goshen et al	Experimental	Albino Wistar rats of either sex	synthesized compounds to rats at doses of 25, 50, and 100mg/kg have more significant antihypertensive activity with almost equal or less toxicity profile in comparison to standard drug Propranolol and Atenolol
Eugenol dilates mesenteric arteries and reduces systemic blood pressure by activating endothelia l cell TRPV4 channels	Neves et al	Experimental	40 male Wistar rats (250 g)	Short interfering RNA (siRNA)-mediated TRPV4 knockdown abolished eugenol-induced ICat activation. An intravenous injection of eugenol caused an immediate, transient reduction in both MAP and HR, which was followed by prolonged, sustained hypotension in anesthetized rats.
Garcinia Mangostana Linn Extract Reduces Systolic Blood Pressure And Inflammation Process In Patient's With Hypertensio n: Comparison With Standard Blood Pressure Medication	Fadlan et al	A randomized, double-blind, placebo-controlled clinical trial	Mildly hypertensive adults, which were measured based on JNC VII, age 50–70 years. The patients were divided into four groups (A, B, C, and D). Group A has received 2520 mg/day GMLE with ACE-i/ ARB, Group B has received 2520 mg/day GMLE with CCB, Group C has received ACE-i with placebo, and Group D has received CCB with placebo	Group A, which received GMLE with ACE-i/ARB, is the best group to reduce systolic blood pressure. In Group A, diastolic blood pressure was also lower, although this change did not differ from another group.The reducing effect in group A was better than other group, p = 0.028, Interestingly, In Group A, we found that there was a significance decreasing in HsCRP compared with B, C,and D (−101 ± 10,3 pg/ml, -96 ± 6,4 pg/ml, -28 ± 12,2 pg/ml, -25 ± 3,7 pg/ml, respectively, p = 0,01). The reducing effect of TNF-a.plasma IL-6 and IL-1 concentration was significantly lower in group A compared with other group (p = 0,01, p = 0,002, p = 0,005, respectively).

Treatment of severe hypertension requires pharmacological intervention using methyldopa, labetalol, and nifedipine; however, current clinical management is limited, and more innovative medical therapies are needed. Labetalol may be associated with fetal growth restriction, and nifedipine may inhibit labor. Hydralazine, other antihypertensive drugs, has been tested in a few controlled trials and may cause neonatal thrombocytopenia. Beta-receptor blockers may reduce uteroplacental blood flow and risk growth restriction when started in the first and second trimesters. It also may cause neonatal hypoglycemia at a higher dose. Hydrochlorothiazide may cause volume contraction and electrolyte disorders. However, it may be helpful when combined with methyldopa to mitigate compensatory fluid retention. During pregnancy, the challenge is deciding when to use antihypertensive medications and what level of BP to target. Despite advancements in therapeutic discoveries, it is crucial to consider the safety of novel agents as therapeutics in pregnant women and the fetus. Small molecules, despite their role in clinical management, possess varying success rates. Sildenafil, a phosphodiesterase inhibitor, for instance, was initially thought to be an excellent uterine vasodilator.[4]

Many studies have shown that xanthones and xanthone derivatives have broad biological and pharmacological activities such as anti-inflammatory, antihepatotoxic, antitumor, and antimicrobial activities. Some studies also state that xanthones have the benefit of being an antihypertensive drug. This is obtained from several studies, Capettini et al. demonstrate that α1- adrenoceptor blocking properties of 2- methoxyphenylpiperazine derivatives of xanthone tested in the present work could contribute to their antiarrhythmic and hypotensive activities, α1- adrenoceptor antagonists inhibit the increase in blood pressure elicited by adrenaline, diminish the hypertensive effect of methoxamine (specific α1- adrenoceptor agonist) and only partially inhibit or have no influence on the rise of blood pressure prompted by noradrenaline.[5] Xanthones' action as an antihypertensive drug is not only by block α1- adrenoceptor but also by blocking calcium channel and β-receptors.[7] From this theory, researchers tried to relate these effects to hypertension in pregnancy, especially in preeclampsia. Because in preeclampsia, hypoxia-inducible factor-1α (HIF-1(alpha)) is a transcription factor transiently expressed as a protein-related with ischemia placenta—the role of HIF prolyl hydroxylases as targets for the beneficial effects of metal chelators. The development of the conceptus in the uterus has the potential to improve transcription factors, NFκB. This process occurs during trophoblast elongation, which is temporally associated with conceptus synthesis and release of IL1B concomitant with pregnancy-specific endometrial up-regulation of IL- 1 receptor. In preeclampsia, shallow trophoblast invasion decreases uteroplacental blood flow, triggering systemic inflammation through the NFkB and MAPK pathways. The increase of sFlt-1 in pregnancy indicated angiogenesis placenta disruption. The lowering of sFlt1 after being intervened showed that mangosteen rind extract can improve the function of the blood artery. Related to the decrease of NFκB from the placenta occurred because of the recovery of the placenta and the decrease of perfusion so that it can grow well. Otherwise, the effect of xanthone protection in reducing oxidative stress exists in α-mangosteen, which prevents injury after perfusion, inducts protein oxidation (protein carbonyl content), lipid peroxidation (malondialdehyde and 4-hydroxynonenal content), and decreasing in glutathione. α-mangosteen can be the scavenger of peroxynitrite anion (ONOO-), singlet oxygen (O2), and superoxide anion (O2-).[8]

It should be noted that the use of a drug must see the value of its toxicity. Xie et al. suggested that Immunity biomarkers IgA, IgG, IgM, C3, and C4 were not affected in either group. In addition, the effects on hepatic function (Aspartate Aminotransferase and Alanine Aminotransferase) and kidney function (creatinine) were not affected after the 30- day consumption.[6]

Eugenol has numerous pharmacological effects,

including inhibiting voltage-gated sodium channels and activating transient receptor potential channel 1 (TRPV1). Electrophysiological studies show that eugenol activates Ca2+-permeable ion channels. One hallmark of hypertension is an increase in voltage-dependent Ca2+ influx through voltage-dependent Ca2+ channels.[1,2] Neves et al., in their experimental study, eugenol relaxed norepinephrine-and histamine-constricted rabbit ear arteries and K+- constricted rabbit aorta. Eugenol relaxed rat aorta precontracted with phenylephrine and high K+, and K+-depolarized rat mesentery bed contracted with bolus injections of $CaCl_2$.[3] However, eugenol is a nonselective TRPV1 agonist, as it also activates other TRP channels, such as TRPA1 and TRPM8, and TRPV4. Parija et al. said that eugenol is a more potent and stronger inducer of vasorelaxation as shown by the more significant inhibitory effect of capsazepine and Ruthenium Red on eugenol-induced vasorelaxation in pregnant middle uterine arterial compared to that in nonpregnant animals. Increased sensitivity of TRPV1 to eugenol during pregnancy could be due to increased sensitivity of TRPV1 and/or activation of other TRP channels, such as TRPV4, TRPA1, and TRPM8.[4]

4. Conclusion

This study showed that eugenol is a potent and strong inducer of vasorelaxation as shown in pregnant middle uterine arterial compared to that in nonpregnant animals and xanthone can decrease the expression of protein HIF-1α, NFκB, sFlt-1, MDA, TNF-α, blood pressure, protein in the urine, and significant to improve blood pressure. A combination of xanthone and eugenol can be therapeutically helpful as vasorelaxant and antioxidant compounds. begs a further investigation of the underlying mechanism.

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