ISSN No:-2456-2165

# Effect of Kenikir (*Cosmos Caudatus*) on Malondialdehyde (MDA) and Blood Pressure When Hypertension in Pregnancy : A Systematic Review

Diyas Windarena[1*]
[1]Poltekkes Kemenkes Semarang,
Master of Applied Science in Midwifery,
Tirto Agung Rd., Semarang, Jawa Tengah 50268, Indonesia

Donny Kristanto Mulyantoro[2]
[2]Balai Litbang Kesehatan Magelang
Borobudur Rd., Magelang,
Jawa Tengah 56553, Indonesia

Diyah Fatmasari[3]
[3]Poltekkes Kemenkes Semarang, Master of Applied Science in Midwifery,
Tirto Agung Rd., Semarang, Jawa Tengah 50268, Indonesia

**Abstract:- Hypertension in pregnancy is one of the causes of morbidity and mortality for pregnant women and babies. In a hypertensive state during pregnancy, there is oxidative stress which can be identified by checking the levels of malondialdehyde (MDA). Oxidative stress increases the complications of hypertension in pregnancy. Oxidative stress is characterized by a decrease in endogenous antioxidants, so to increase antioxidant levels in the body it is necessary to consume exogenous antioxidants, for example quercetin. The main flavonoids component of Kenikir (Cosmos Caudatus) is quercetin. The purpose of this systematic review is to analyze the effect of Kenikir (Cosmos Caudatus) or quercetin as the main flavonoid component of Kenikir on malondialdehyde (MDA) levels and blood pressure in hypertension in pregnancy through the results of previous research. The method used is PRISMA. Literature search using the database PubMed, cochrane, ScienceDirect, google scholar and DOAJ with the same keywords and published in 2015 - 2020. The literature search was conducted in May-June 2020. The results obtained 25 studies that met the inclusion criteria. The results showed that the extract of Kenikir (Cosmos Caudatus) contained quercetin 2.186 g / 100g. From the article review, it was found that Kenikir or quercetin as a flavonoid component of Kenikir can reduce levels of malondialdehyde (MDA) between 4.85-170 nmol / ml and reduce blood pressure between 3 - 38.3 mmHg. There are 3 articles that show insignificant results in lowering blood pressure. So it can be concluded that Kenikir's active compound, quercetin, can reduce levels of malondialdehyde (MDA) and has the potential to lower blood pressure when Hypertension in pregnancy.**

**Keywords : Cosmos Caudatus, Blood pressure, malondialdehyde.**

## I. INTRODUCTION

Globally, data for the years 2002 - 2009 show that about 2.4 million mothers died due to complications during antenatal, intranatal, and postpartum periods. About 14% of deaths are related to hypertension in pregnancy and 12.9% of them occur in developing countries.[1] The results of the Inter-Census Population Survey (SUPAS), the maternal mortality rate (MMR) in Indonesia in 2015 decreased from 2012, from 359 per 100,000 live births to 305 per 100,000 live births. Even though it has decreased, this number has not succeeded in achieving the 2015 MDGs (Millennium Development Goals) target of 102 per 100,000 live births. The SUPAS results show that the maternal mortality rate is three times higher than the MDGs target.[2] Meanwhile, the SDGs (Sustainable Development Goals) target MMR of 70 per 100,000 KH in 2030.[3] During 2012 - 2013, the second most common cause of maternal mortality in Indonesia is hypertension in pregnancy.[4] Based on the 2013 research from Riskesdas results, the prevalence of hypertension in pregnant women was 6.18%.[5]

Hypertension in pregnancy is a disease that can increase the incidence of morbidity and mortality for mother and fetus.[6] Hypertension in pregnancy is a condition in which a pregnant woman has systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg at two examinations within 4 - 6 hours, and occurs in pregnant women who were previously normotension.[7] Hypertension in pregnancy is divided into four categories, namely chronic hypertension, gestational hypertension, superimposed preclapsia, and preeclampsia - eclampsia.[8]

Hypertension in pregnancy is triggered by various factors. The percentage of hypertension in primigravida mothers is 6 - 17% while multigravida is 2 - 4%.[9] With a history of hypertension, and 2.37 times in overweighed mothers. Meanwhile, pregnant women who have six signs, namely overweight, chronic hypertension, low education level, age <20 years or> 35 years, and primigravidas will be

at risk of 22.8 times experiencing Hypertension in pregnancy.[6][10][5]

A 2012 – 2016 studies in China shows that each subtype of Hypertension in pregnancy in a single pregnancy affects the risk of different infant mortality. Pregnant women with chronic hypertension are at risk of experiencing newborn death 2.32 times, superimposed preclapsia 6.66 times, preeclampsia - eclampsia 4.15 times and gestational hypertension 1.21 times. While pregnancy gemelli does not have a significant effect on fetal mortality.[11] Pregnant women with hypertension are three times more likely to have low birth weight babies, and four times give birth to babies with low APGAR scores in the first five minutes of the birth process.[12]

The management of hypertension in pregnancy can be divided into pharmacology and non pharmacology. Pharmacological management categorizes hypertension into three types, namely mild hypertension, moderate hypertension, and severe hypertension. Management of mild hypertension does not require antihypertensive drugs because it causes hypotension and fetal distress.[9] Controlling the risk of hypertension can be done with dietary modification.[5] One of the antihypertensive drugs that are allowed for handling hypertension in pregnancy is methyldopa.[7] However, methyldopa has side effects that can cause hypotension in newborns and hepactotoxicity in pregnant women.[9][13]

Because of the side effects caused by administering antihypertensive drugs, so we need a new therapeutic approach to non-conventional more effective and safer. This approach can also be used as a solution in the management of mild hypertension to prevent more serious complications. Several flavonoids studied in various models of vascular disorders exhibit antioxidant, vasodilator, anti-inflammatory, antiaterogenic, and antithrombotic properties. Quercetin, a flavonoids derivative, has beneficial effects on cardiovascular diseases such as hypertension and atherosclerosis.[14] Exposure to quercetin during pregnancy results in an increase in the defense system of fetal liver enzymatic antioxidants. Thus, in addition to having a positive effect on the mother, it can also prevent anomalies in the fetus.[15] The high content of antioxidants in the body can improve heart conditions and reduce levels of malondialdehyde (MDA) which is the end result of free radicals.[14]

MDA is a reactive aldehydes that is produced from the reaction of hydroxyl radicals/ free radicals and epithelial membrane phospholipids.[16] Increased (MDA) is a picture of oxidative stress.[17] Oxidative stress causes endothelium damage and affects vasodilator production, thereby triggering an increase in blood pressure.[18] Hypertension in pregnancy is a state of oxidative stress that is greatly increased due to decreased antioxidants.[14] Zolfaghari's research which tested the effect of Unripe Grape Extract (UGE) produced a positive effect, namely a decrease in MDA levels and an increase in Super Oxide Dismutase (SOD) and Nitric Oxide (NO). However, it also increases the Mean Arterial Pressure (MAP) so that it is suspected that Unripe Grape Extract (UGE) has a cardiotonic effect.[19] Fresh grapes contain quercetin 3.11 mg / 100g.[20]

One plant that has a high content of quercetin is Kenikir (Cosmos Caudatus). To get a higher quercetin content, extraction can be done. Kenikir leaf extract produces Kenikir extract (Cosmos Caudatus) with high quercetin levels of 2.186g / 100 g. Kenikir leaves (Cosmos caudatus) which are extracted are obtained from traditional markets in the city of Semarang. Kenikir extract is made and tested for its quercetin content in the Food Science Laboratory of UNIKA Soegiyaprana Semarang. Antioxidant activity with the DPPH test shows that Kenikir extract has IC50 (Inhibitory Concentration) 21.31 µg / mL. The antioxidant activity of Kenikir (Cosmos Caudatus) is better than α-tocopherol and BHA and other plants that are considered to have high antioxidants.[21]

Quercetin exhibits positive properties against free radicals as it can increase antioxidants in the body. Therefore, quercetin has the potential to be an antihypertensive, where in hypertension in pregnancy there is an imbalance of oxidant and antioxidant levels in the body. Apart from being an antioxidant, quercetin also has a role as a vasodilator which has a positive effect on vasoconstriction of blood vessels in hypertension.[14] Antioxidant activity with the DPPH test shows that Kenikir extract has an IC50 (Inhibitory Concentration) of 21.31 µg / mL. Kenikir (Cosmos caudatus) antioxidant activity is better than α-tocopherol and BHA and other plants that are considered to have high antioxidants.[21]

Research on the influence of Kenikir (Cosmos Caudatus) on hypertension has been done. A study conducted by Loh SP invitro found that Ulam Raja / Kenikir had the effect of being able to manage hyperglycemia and hypertension.[22] Meanwhile, Amalia's research showed that Cosmos / Kenikir water extract was able to prevent an increase in heart rate and stroke volume due to adrenaline induction and had a diuretic effect. So it has the potential as an antihypertensive.[23]

The content of quercetin and the high antioxidant activity of Kenikir leaves allows this plant to be an adjuvant theapy in treatment with methyldopa to increase the effectiveness of the drug. Quercetin has hepatoprotective properties so that it can be combined with methyldopa which has a hepatotoxicity effect. What needs to be considered is that plants are a complex mixture of chemical components.[14]

Pay more attention to the use of antihypertensive drugs in pregnancy, given the special condition of pregnant women due to the presence of placental and fetal units.[14] Research on the use of Kenikir (Cosmos Caudatus) for hypertension therapy is still slightly. The reports obtained are still in vivo and in vitro studies. So, we need literature that examines the benefits of Kenikir (Cosmos Caudatus) on hypertension in pregnancy for further development. Therefore it is necessary to search for scientific evidence

from the literature which aims to identify the effect of Cosmos Caudatus on malondialdehyde (MDA) and blood pressure in hypertension in pregnancy.

## II. PURPOSE

The purpose of this systematic review was to analyze the effect of Kenikir (Cosmos Caudatus) or quercetin as the major flavonoid component Kenikir against malondialdehyde (MDA) and blood pressure in hypertension in pregnancy through the results of previous studies.

## III. METHODS

The design in this article is a systematic review. The search strategy uses PICOS (population/problem, intervention, comparation, outcome, and study design). The articles reviewed are research articles on hypertension, hypertension in pregnancy and problems related to elevated levels of malondialdehyde (MDA). The intervention in the research study reviewed was the administration of Cosmos caudatus or flavonoids or quercetin compared to the control group. The study design reviewed was experimental study, randomized control and trial, and cross sectional study.

Inclusion criteria is Research articles published in 2015 - 2020, use English and Indonesian language, full text, on in vivo studies of experimental animals used rodentia. Five scientific databases are used to obtain articles with relevant themes, namely pubmed, cochrane, sciencedirect, google scholar, and DOAJ.

The search was carried out between May - June 2020 using keywords and Boolean operators to expand the search. Keywords are adjusted to the Medical Subject Heading (MeSH), namely Cosmos caudatus, Flavonoids, Quercetin, Hypertension, High Blood Pressure, Antihypertensive, Hypertension induced pregnancy, Malondialdehyde and Thiobarbituric Acid Reactive Substances. To concatenate keywords, Boolean operators "AND" and "OR" are applied in the search.

## IV. RESULTS

An initial search through pubmed, cochrane, sciencedirect, google scholar and DOAJ obtained 949 research articles. Initial screening of titles to exclude irrelevant studies instead of using English and Indonesian language resulted in 187 abstracts. Furthermore, a quick screening through the abstract found 133 articles that fit the research theme. The articles that fit the inclusion criteria were found 36 articles that could be continued for analysis. And finally, there are 25 complete articles including full text that can be analyzed through a systematic review.

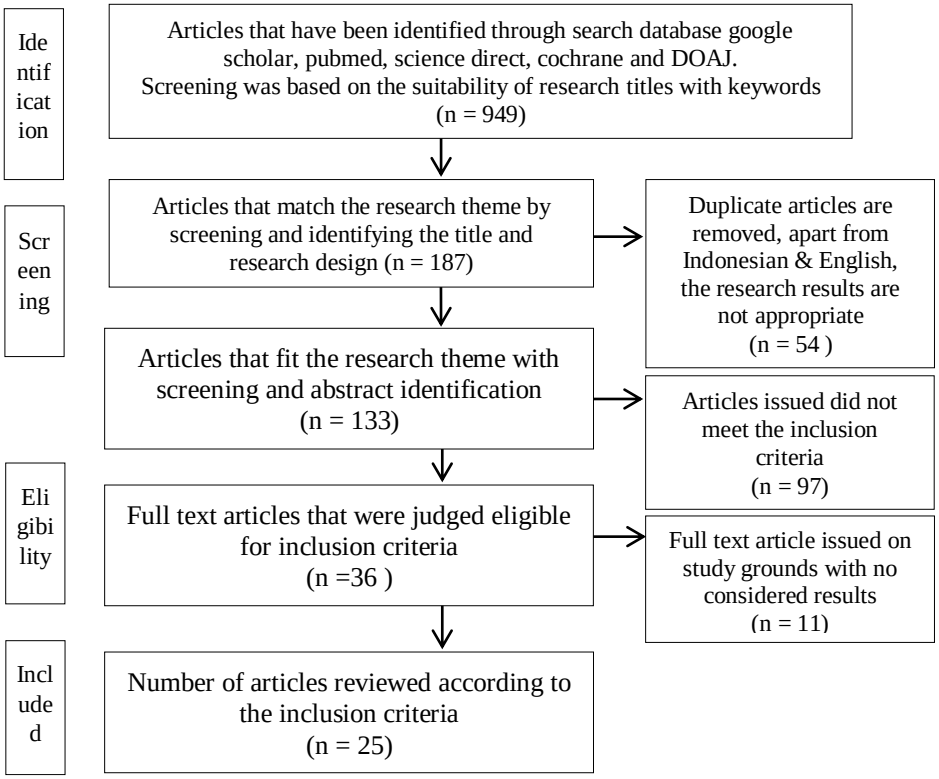


Figure 1 Flowchart / Schematic of Literature Search Flow

| Name of main author, year published, journal, country of publication | Study design, length of study | Population | Intervention and comparison | Research result |
|---|---|---|---|---|
| **Abdullah, Azman 2015** *Journal of applied pharmaceutical science* **Malaysia**[24] | *True experimental* Duration of treatment 21 days | 30 Male mice (Mus musculus) weighing 25-30 g | Group 1 : *Cosmos caudatus* 100 UR<br>Group 2 : *Cosmos caudatus* 500 UR<br>Group 3 : *Cosmos caudatus* 1000 UR<br>Group 4 : Negative control<br>Group 5 : positive control (0,5% butylated hydroxyanisole (BHA) | Cosmos caudatus oral supplementation with quercetin in various doses affected a significant increase in CAT, SOD, and GST. MDA levels decreased significantly ($p < 0.01$) in the group of mice receiving Cosmos caudatus 100 UR and 500 UR therapy compared to the control group. |
| **Novianto, Agil 2016** *Jurnal kesmadaska* **Indonesia**[25] | *True experimental* Duration of treatment 9 days | Male rats (Rattus norvegicus) Wistar strain weighing 150-200 g | Group 1 : given distilled water as a control<br>Group 2 : CMC 1%<br>Group 3 : *Kurkuminoid* 100 mg/kgBW in CMC 1%<br>Group 4 : ethyl acetate leaves of Kenikir 281,25 mg/kgBW<br>Group 5 : ethyl acetate leaves of Kenikir 562,5 mg/kgBW<br>Group 6 : ethyl acetate leaves of Kenikir 1.125 mg/kgBW. | Kenikir ethyl acetate fraction at a dose of 1125 mg / kgBW was able to significantly inhibit the occurrence of lipid / MDA peroxidation ($p < 0.05$) and provide optimal hepatoprotective effect and an indication of decreased lipid peroxide. The decrease in MDA at a dose of 1125 mg / kgBW compared to the positive control was 12.27 µM / g with ($p < 0.05$) |
| **Suhardinata, Fredian 2015** *Journal of nutrition College* **Indonesia**[26] | *True exprimental* dengan *post test only randomized control group design.* Duration of treatment 26 days | 21 male Wistar rats (Rattus norvegicus) | Group 1 : ($K^+$) induction of *streptozotacin* 65 mg/kg and *nicotinamide* 230 mg/kg<br>Group 2 : (P1) induction of *streptozotacin* 65 mg/kg and *nicotinamide* 230 mg/kg + Kenikir leaf extract 700mg/200gBW/day<br>Group 3 : (P2) induction of *streptozotacin* 65 mg/kg and *nicotinamide* 230 mg/kg + Kenikir leaf extract 1400 mg/200gBW/day | Cosmos caudatus doses of 700 mg and 1400 mg were able to reduce plasma MDA levels ($p < 0.05$). The mean MDA level in the control group was 7.7 ± 0.61 nmol / ml, the group with Kenikir 700 mg / kgBW extract was 6.1 ± 0.58 nmol / ml and with 1400 mg / kgBW kenikir it was 2.8 ± 0 , 50 nmol / ml. There were differences in the mean MDA levels between groups ($p < 0.05$)<br>The difference between the mean K + vs P2 was 4.85 nmol / ml |
| **Kocahan, Sayad 2017** *Iranian journal of kidney diseases* **Kanada**[27] | *True experimental* dengan rancangan *post test only control group design.* Duration of treatment 10 weeks | 36 pregnant female Wistar rats (Rattus norvegicus) | Group 1 : control<br>Group 2 :*quercetin* 10 mg/kgBW<br>Group 3 :siklofosfamid 27 mg/kgBW<br>Group 4 :doxorubicin 1,8 mg/kgBW<br>Group 5 : siklofosfamid 27 mg/kgBW and quercetin 10 mg/kgBW<br>Group 6 : doxorubicin 1,8 mg/kgBW and quercetin 10 mg/kgBW | Quercetin treatment significantly ($p < 0.05$) suppressed the increase in malondialdehyde (MDA) in K5 versus K2 and K6 compared to K4. |
| **Celik, Naime 2017** *Nutrition* **Turki**[28] | *True experimental* Duration of treatment 30 days | 32 male Sprague - Dawley rats (Rattus norvegicus) weighing 200 - 300 g | Group 1 : control<br>Group 2 : QUER *(Quercetin)* 50 mg/kgBW<br>Group 3 : HCY (*homocysteine*) 1 mg/kgBW<br>Group 4 : QUER *(Quercetin)* 50 mg/kgBW + HCY (*homocysteine*) 1 mg/kgBW | The MDA level of the HCY group increased significantly (599.70 ± 19.26 nmol / L) compared to the control group (458.26 ± 28.93 nmol / ml) ($p < 0.01$). MDA decreased significantly in the QUER group (377.38 ± 33.20 nmol / ml) and the QUER + HCY group (486.40 ± 23.34 nmol / ml) when compared to the |

| | | | | |
|---|---|---|---|---|
| | | | | HCY group (p <0.05). |
| **Lin, Xiaojing 2017** *Chemico biological interactions* **Taiwan**[29] | *True experimental* Duration of treatment 100 minutes | Male Sprague Dawley rat (Rattus norvegicus) | Group 1 : NC (*Normothermic controls)*<br>Group 2 : V + HS (*vehicle + heat stroke)*<br>Group 3 : Q + HS (*Quercetin* 30 mg/kg intraperitoneal + *heat stroke)* | The administration of quercetin significantly normalized oxidative stress with a marked decrease in MDA (P <0.05). |
| **Xia, Shu-Fang 2015** *Physiology & behavior* **China**[30] | *True experimental* Duration of treatment 13 weeks | 40 Rats (Rattus norvegicus) male Kunming chiene (KM) 5 weeks old | Group 1 : control<br>Group 2 : CQ1 (0,005% *quercetin*)<br>Group 3 : HFD (high fat diet)<br>Group 4 : HFDQ1 (high fat diet + 0,005% *quercetin*)<br>Group 5 : HFDQ2 (high fat diet + 0,01% *quecetin*) | Quercetin significantly reduced oxidative stress biomarkers (ROS and MDA) compared with the HFD group (p <0.05) |
| **Elbaset, Mohamed 2015** *Sciecedirect* **Mesir**[31] | *True experimental* Duration of treatment 10 days | 40 Rats (Rattus norvegicus) male albino Wistar strain weighing 300 - 350 grams | Group 1 : control<br>Group 2 : ischemic injury model<br>Group 3 : ischemic injury model + (NAC) *N-acetylcysteine* 300 mg<br>Group 4 : ischemic injury model + *quercetin* 20 mg/kgBW | The MDA level in the ischemia injury model group was around 240.10 ± 24.51%, while in the ischemia + quercetin injury group it was around 71.72 ± 3.17% while in the ischemia + NAC injury group the MDA level was around 79.70 ± 9.82 %) (p <0.05) |
| **Roslan, Josef 2017** *Biomed pharmacother* **Malaysia**[32] | *True experimental* Duration of treatment 28 days | Diabetic male rat (Rattus norvegicus) aged 12 weeks | Group 1 : Normal NC + sodium carboxymethyl cellulose (Na-CMC)<br>Group 2 : NC + 10Q (10 mg/kg *quercetin*)<br>Group 3 : NC + 25Q (25 mg/kg *quercetin*)<br>Group 4 : NC + 50Q(50 mg/kg *quercetin*)<br>Group 5 : DC (nikotinamid) + Na-CMC<br>Group 6 : DC + 10Q<br>Group 7 : DC + 25Q<br>Group 8 : DC + 50Q<br>Group 9 : DC + G STZ (600 mg/kg *glibeclamide*) | TBARS / MDA measurements in the diabetes group were significantly reduced (p <0.05) after being given quercetin treatment |
| **Oueslati, Nourhene 2016** *Biomedicine & Pharmacotherapy* **Turnisia**[33] | *True experimental* Treatment duration 21 days | 48 Female rats (Rattus norvegicus) weighing 180 - 220 g are pregnant | Group 1 : Virgin (V)<br>Group 2 : V + GSSE (*grape seed and skin extract) 4g/kg*<br>Group 3 : V + Alloxan 150 mg/kgBW<br>Group 4 : V + Alloxan 150 mg/kgBW + GSSE 4 g/kg<br>Group 5 : pregnant (P)<br>Group 6 : P + GSSE 4 g/kg<br>Group 7 : P + Alloxan 150 mg/kgBW<br>Group 8 : P + Alloxan 150 mg/kgBW + GSSE 4 g/kg | GSSE contains 0.64% quercetin in seeds and 0.47% in the skin.<br>Malondialdehyde (MDA) levels in group 8 decreased significantly compared to the control group, namely K5 (p <0.05) |
| **Gholampour, Firouzeh 2019** *Gen physiol biophys* **Iran**[34] | *True experimental*<br>Treatment duration 14 days | 35 male Wistar rats (Rattus norvegicus) weighing 250 - 300 g | Group 1 : Control<br>Group 2 : DMSO (*dimethyl sulfoxide* 1%)<br>Group 3 : *Quercetin* 50 mg/kg/day + DMSO (*dimethyl sulfoxide* 1%)<br>Group 4 : Fe (*ferrous sulfate 30 mg/kg/day)* | quercetin (K5) reduced MDA levels in liver (p <0.05) and kidney (p <0.001) tissue compared with the Fe (K4) group<br>MDA levels in liver tissue at K4 were 1.75 ± 0.76 mol / g tissue, while K5 was 1.02 ± 0.12 mol / g. Meanwhile, levels of MDA in kidney |

| | | | | |
|---|---|---|---|---|
| | | | Group 5 : Fe + *quercetin* | tissue at K4 1.56 ± 0.16 mol / g while K5 0.71 ± 0.07 mol / g. |
| **Duranti, Guglielmo 2018** *Nutrition research* **Italia**[35] | *Controlled, randomized, crossover, intervention trial* Duration of treatment 14 days | 14 men | Group 1 : quercetin 1000 mg/day<br>Group 2 : Plasebo | There was a significant difference in MDA levels between the placebo and quercetin groups (1.18 ± 0.06 µM / g vs 1.01 ± 0.05 µM / g, P <0.05). |
| **Li, Qinghua 2020** *Biomedicine & pharmacotherapy* **Cina**[36] | *True experimental* with a research design *post test only control group design.* Duration of treatment 19 days | 48 pregnant rats (Rattus norvegicus) Sprague Dawley strain | Group 1 : Normal pregnant mice<br>Group 2 : Normal pregnant mice + *quercetin*<br>Group 3 : pregnant mouse + LPS(induksi preeklampsia)<br>Group 4 : pregnant mouse + LPS + *quercetin* | Quercetin significantly lowered systolic blood pressure in hypertensive mice in pregnancy (from 124.4 ± 1.8 mmHg to 105.2 ± 1.8 mmHg, p <0.01) Quercetin significantly decreased MDA levels in a hypertensive model animal. in pregnancy. |
| **Yang, Shuangyan 2019** *Biomedicine & pharmacotherapy* **Cina**[37] | *True experimental* with a research design *post test only control group design.* Duration of treatment 19 days | 49 Pregnant female sprague dawley rat (Rattus norvegicus) | Group 1 : Normal pregnant mice<br>Group 2 : pregnant mouse + L-NAME<br>Group 3 : pregnant mouse + L-NAME + Aspirin 1,5 mg/kgBW<br>Group 4 : pregnant mouse + L-NAME + *quercetin* 2 mg/kgBW<br>Group 5 : pregnant mouse + L-NAME + Aspirin 1,5 mg/kgBW + *quercetin* 2 mg/kgBW | Giving quercetin and aspirin to animal models of hypertension in pregnancy had a positive effect, namely a significant (p <0.05) reduction in systolic blood pressure and MDA levels compared to the group that was given quercetin alone or aspirin alone. |
| **Moshawih, Said 2017** *Porto Biomedical journal* **Malaysia**[38] | *True experimental* In vitro | Cell culture A-10 (Vascular smooth muscle cells / VSMC from the medial layer of the rat aorta) | *Fraksi Aqueous* (Aq.F) *Cosmos caudatus*<br>Cell culture A-10 was given Aq.F with extract concentrations of 10%, 25% and 50%<br>*Crude Cosmos caudatus*(CEE)<br>Cell culture A-10 was treated with CEE with extract concentrations of 10%, 25% and 50%<br>Butanol *cosmos caudatus* (Bu.F)<br>Cell culture A-10 was treated with CEE with extract concentrations of 10%, 25% and 50%. | The Butanol Cosmos caudatus fraction has the potential to suppress atherosclerosis |
| **Souza, Maria D** *European journal of vascular & endovascular surgery* **2018 Brasil**[39] | *True experimental* Duration of treatment 10 weeks | 422 Male hamster weighing 85 - 120 g Induction of hypertension | Group 1 : *Micronized purified flavonoid fraction* (MPFF) 10 mg/kg/day<br>Group 2 : Active flavonoids from MPFF 10 mg / kg / day<br>Group 3 : Diosmin 10 mg/kg/day<br>Group 4 : vehicle drug<br>Group 5 : Plasebo | *Micronized purified flavonoid fraction (MPFF) significantly prevents inflammation and its ability to maintain venous tone.* |
| **Choi, Seok 2016** *Kidney research and clinical pravtice* **Korea**[40] | *True experimental* Duration of treatment 10 weeks | 85 Rats (*Rattus norvegicus)* male sprague dawley weight 160 – 180 g. 2K1C mouse | Group 1 : 2K1C + *quercetin* (n = 42)<br>Group 2 : control (n = 43) | *Quercetin significantly (p <0.05) affected the blood vessel relaxation response of hypertension-model rats but did not affect the control group.* |

| | | | | |
|---|---|---|---|---|
| | | (clip attachment of the left renal artery for induction of hypertension) | | |
| **Lin, Xuemei 2020** *Life sciences* **Cina**[41] | *True experimental* Treatment duration 6 weeks | 24 rats(*Rattus norvegicus) The wistar Kyoto (WKY)* dan *spontaneously hypertensive rats (SHRs)* | Group 1 : SKRs<br>Group 2 : SHRs + *quercetin* 10 mg/kgBW<br>Group 3 : WKY<br>Group 4 : WKY + *quercetin* 10 mg/kgBW | Quercetin administration significantly affected the decrease in systolic blood pressure in the WKY + quercetin group compared to the WKY group ($p < 0.01$).<br>It also significantly affected the decrease in diastolic blood pressure in the WKY + quercetin group compared to the WKY group ($p < 0.05$). |
| **Porcu, Elena P 2018** *International journal of pharmaceutics* **Ceko**[42] | *True experimental* Treatment duration 72 hours | 20 Rats (*Rattus norvegicus)* with Hypertensive male | Group 1 : D12L (25 mg quercetin + 300 mg PVP10) is given a dose of 65 mg / kg intravenously<br>Group 2 : PVP10 60 mg/kg (*polyvinylpyrrolidone*) | There was a decrease in blood pressure between the D12L group compared to the control group. Diastolic blood pressure tends to decrease more than systolic. Significantly decreased systolic blood pressure at 5 hours compared to the control group ($P < 0.01$) |
| **Calabro, Veria 2018** *Archives of biochemictry and biophysics* **Argentina**[43] | *True experimental* Treatment duration 4 days | 32 Mouse (*Rattus norvegicus) Sprague dawley* | Group 1 : control group<br>Group 2 : 4 g/kgBB *quercetin*<br>Group 3 : 360 mg/L L-NAME<br>Group 4 : 360 mg/L L-NAME + 4 g/kgBW *quercetin* | *Quercetin significantly prevented the L-NAME-induced increase in blood pressure ($p < 0.01$)* |
| **Pereira, Sherliane 2018** *Atherosclerosis* **Brasil**[44] | *True experimental* Duration of treatment 5 weeks | Rats (Rattus norvegicus) male Wistar strain 180-200 g. 2K1C mouse (clip attachment of the left renal artery for induction of hypertension) | Group 1 : Control<br>Group 2 : Control + *quercetin* 10 mg/kg/day<br>Group 3 : 2K1C<br>Group 4 : 2K1C + *quercetin* 10 mg/kg/day | The maximum systolic blood pressure was 204 mmHg in hypertensive rats when compared to K1 ($p < 0.05$). There was a decrease in systolic blood pressure at K4 compared to control but not significant ($p > 0.05$) |
| **Brull, Verena 2015** *British journal of nutrition* **Jerman**[45] | *A randomised double blinded placebo-controlled cross over trial* Treatment duration 6 weeks | 70 people, aged 25 - 65 years | Group 1 : plasebo (matinol 170 mg/day)<br>Group 2 : *quercetin* 162 mg/day | *Quercetin significantly lowered systolic blood pressure at 24 hours monitoring, which was 3.6 (SD 8.2) mmHg ($p = 0.022$).* |
| **Prado, Maria 2015** *Basic & clinical pharmacology & toxicology* **Meksiko**[46] | *Open label, randomized, controlled trial* Duration of treatment 6 months | 79 patients aged 20 - 55 years with grade I and grade II hypertension without diabetes and kidney disease | Group 1 : Cpr (Captopril 50 mg/day) = 14 people<br>Group 2 : Cpr (Captopril 50 mg/day + DF (*Dietary flavonoids* 425,8 mg/day) = 19 people<br>Group 3 : Tms (Termisartan 40 mg/day) = 25 people<br>Group 4 : Tms (Termisartan) + DF (*Dietary flavonoids* 425,8 mg/day) = 21 people | The difference in mean systolic blood pressure after 6 months of treatment between AHT (antihypertensive treatment) and AHT combination DF (Dietary flavonoid) groups showed a reduction of -31.9 ± 8.2 (AHT) versus -38.3 ± 11 (AHT + DF ), $p = 0.004$. |
| **Burak,** | *Double blinded,* | 67 male and | Group 1 : *Alpha linolenic acid* | There were no significant changes in |

ISSN No:-2456-2165

| | | | | |
|---|---|---|---|---|
| **Constanze 2018** *The end to end journal* **Jerman**[47] | *placebo controlled crossover trial* Duration of treatment 8 weeks | female respondents aged 19-35 years | *(ALA)* 3,3 g/day + 190 mg/day quercetin Group 2 : *Alpha linolenic acid (ALA)* 3,3 g/day + Plasebo | systolic blood pressure in the ALA + quercetin group compared to the ALA + placebo group. (p = 0.129). Significant decrease in diastolic blood pressure (-3.0 ± 6.3 mmHg; P≤0.001) and MAP (-2.5 ± 6.2 mmHg; P = 0.001) |
| **Bondonno, Nicola P 2016** *The American journal of clinical nutrition* **Australia**[48] | *A randomized, controlled, crossover study* Duration of study 3 months Measurements were made after 90 minutes of treatment | 15 people who do not have diabetes and are not taking cholesterol and blood pressure-lowering drugs | Group 1 : 0,2 mg *quercetin-3-0-glucoside* Group 2 : 50 mg *quercetin-3-0-glucoside* Group 3 :100 mg *quercetin-3-0-glucoside* Group 4 : 200 mg *quercetin-3-0-glucoside* Group 5 : 400 mg *quercetin-3-0-glucoside* | There was no significant change in blood pressure or endothelial relaxation with increased NO from the brachial artery after quercetin consumption from 50 to 400 mg. |

Table 1:- Summary of Article Search Results

➢ *Article Search*

There were 25 research articles that met the inclusion criteria. There are 20 articles are experimental studies and 5 studies are randomized control and trial. Of the 25 studies reviewed, from the science direct database as many as 14 articles, published 7 articles, Google Scolar 3 study and DOAJ 1 study.

➢ *Study Characteristics*

Of the 25 articles, 19 were in vivo studies, 1 study was in vitro and 5 were randomized control and trial. The studies reviewed came from various countries, including 3 studies from Malaysia, 3 studies from Indonesia, 3 studies from Brazil, 3 studies from China and 1 studied each from Mexico, Australia, Canada, Turkey, Korea, Germany, Czech, Taiwan, Egypt, Italy, Argentina, Turnisia and Iran.

➢ *Respondent Characteristics*

In a randomized control and trial study, the respondents were aged 19 - 65 years with hypertension or at risk of hypertension. The largest number of respondents in the study was 79 respondents. Gender characters in respondents are almost the same between men and women. Whereas in the in vivo study, the type of experimental animal used was rodentia, namely one mouse (*mus muscullus*), 1 hamster study (*cricetinae*) and 17 studies using rats (*rattus norvegicus*). The weight of rats (*rattus norvegicus*) studied was between 180 g - 300 g. The number of samples in the study was between 20 - 85 samples which were divided into several treatment groups.

➢ *Study Results*

At in vitro study, it was found that Kenikir (Cosmos caudatus) has the potential to suppress atheroclerosis. Atheroclerosis is a group of cardiovascular diseases characterized by chronic inflammation of the walls of the arteries leading to fatty deposition and plaque formation. The effect is the constriction of blood vessels and results in high blood pressure.[38] Hypertension in pregnancy is a state of oxidative stress which is greatly increased due to decreased antioxidants.[14] Increased malondialdehyde (MDA) is a reflection of oxidative stress.[17] The active compound content of Kenikir (Cosmos caudatus) was able to significantly reduce (p <0.05) MDA levels. The administration of 700 mg / kgBB of Cosmos caudatus extract reduced MDA levels to 6.1 nmol / ml, while at a dose of 1400 mg / kg, MDA levels were 2.8 nmol / ml while the control group was 7.7 nmol / ml.[26] In addition, giving 1125 mg / kgBW of Kenikir extract can inhibit the occurrence of lipid peroxides, which are free radicals. The end product of this lipid peroxide is MDA.[49] Cosmos caudatus oral supplement significantly increased endogen antioxidants, that are CAT, SOD and GST. MDA levels decreased significantly (p <0.01) in the experimental group receiving Cosmos caudatus therapy at doses of 100 and 500 for 21 days of treatment compared to the control group.[24]

The active substance in Kenikir (Cosmos caudatus) which has antihypertensive potential is flavonoids. The results showed that administration of flavonoids 10 mg / kgBW significantly prevented inflammation and maintained venous tone.[39] Antihypertensives combined with flavonoids are proven to be able to lower blood pressure better. Administration of flavonoids 425.8 mg / day combined with antihypertensives showed a difference in mean systolic blood pressure after 6 months of treatment. In the group with antihypertensive therapy alone, the reduction in systolic blood pressure was 31.9 mmHg, while in the group given antihypertensives and flavonoids the reduction in systolic blood pressure was 38.3.[46]

The flavonoid derivative which is the main component of Cosmos caudatus is quercetin. The administration of quercetin 10 mg / kgBW / day in experimental animals for 5 weeks was able to reduce systolic blood pressure.[44] Quercetin administration significantly (p <0.05) affected the relaxation of blood vessels in the hypertension model animal but did not affect the normal group. This is because quercetin is a vasodilator that is able to dilate blood vessels so that blood pressure decreases.[40] Research conducted on male and female respondents who received 162 mg / day of quercetin therapy for 6 weeks, significantly (p = 0.022) was

able to reduce sytolic blood pressure by 3.6 mmHg.[45] Quercetin at certain doses also significantly reduced diastolic blood pressure.[47][42] In addition to lowering blood pressure, giving quercetin 360 mg in animal models was significantly ($p < 0.01$) able to prevent hypertension-induced increase in blood pressure.[43] Giving quercetin at certain doses can significantly reduce levels of MDA which is the end result of lipid peroxide.[28][29][30][31][35][32][34] High malondialdehyde is a state of oxidative stress.[29]

Quercetin also has positive benefits on animal models of hypertension in pregnancy. Quercetin administration for 19 days significantly ($p < 0.01$) was able to reduce systolic blood pressure (from 124.4 mmHg to 105.2 mmHg) and significantly ($p < 0.05$) decreased levels of malondialdehyde compared to the control group.[36] While the administration of quercetin combined with aspirin in an animal model of hypertension during pregnancy for 19 days was able to reduce systolic blood pressure better than that given aspirin or quercetin alone. The combination of antihypertensive and quercetin in animal models of hypertension in pregnancy gave a better effect in reducing MDA levels compared to the group given quercetin or antihypertensive alone.[37]

However, in Burak's (2018) study, it was found that there was no significant reduction in systolic blood pressure given quercetin 190 mg / kg BW for 8 weeks.[47] Similar results were also obtained from Pireira's (2018) study by giving quercetin 10 mg / kgBB for 5 weeks, there was a decrease in systolic blood pressure but not significantly.[44] Research conducted by Bondonno (2016) shows that there is no significant change in blood pressure after consuming 50 mg of quercetin.[48]

## V. DISCUSSION

Kenikir (Cosmos caudatus) is a plant of the Asteraceae family, which is a tropical plant. This plant is easy to cultivate and process, and can be reached by all levels of society, especially in Indonesia.[50] Quercetin was identified as the main component of the flavonoid component of Kenikir leaves (Cosmos caudatus).[51] The manufacture of Kenikir leaf extract (Cosmos caudatus) resulted in Kenikir (Cosmos caudatus) extract with a high quercetin content of 2.186g / 100 g.

Literature review on the effect of Kenikir (Cosmos caudatus) extract on blood pressure and levels of MDA on hypertension in pregnancy is still limited. Research conducted by Loh SP in 2011 in invitro found that Cosmos caudatus has the effect of being able to manage hyperglycemia and hypertension.[22] Meanwhile, research conducted by Amalia in 2012 showed that the Cosmos / Kenikir water extract was able to prevent an increase in heart rate and stroke volume due to adrenaline induction and had a diuretic effect so that it had the potential to be an antihypertensive.[23] In vitro research by Moshawih (2017) found that Kenikir (Cosmos caudatus) has the potential to suppress atherosclerosis. Atherosclerosis is a group of cardiovascular diseases characterized by chronic inflammation of the walls of the arteries leading to deposition of fat and plaque formation. The effect is the constriction of blood vessels and results in high blood pressure. Kenikir can suppress atherosclerosis and prevent hypertension because of its high active substance content, one of which is antioxidants.[38]

The antioxidants contained in Kenikir (Cosmos caudatus) which have antihypertensive potential are flavonoids. Administration of flavonoids in animal models of hypertension can significantly prevent inflammation and the ability to maintain venous tone. Vascular tone is associated with vasoconstriction of blood vessels. Meanwhile, vasoconstriction is associated with an increase in blood pressure.[39] Besides being able to prevent hypertension, the combination of flavonoid antihypertensive drugs has shown additional benefits in reducing blood pressure. The study was conducted on 79 patients aged 20 - 55 years with grade I and grade II hypertension who were given antihypertensive drugs and flavonoids 425.8 mg / day for 6 months showed a reduction in blood pressure 38.3 mmHg whereas in the group with antihypertensive therapy alone, pressure reduction the blood was 31.9 mmHg.[46]

One of the risk factors that can increase the incidence hypertension in pregnancy is being overweight. Mothers with overweight have a 2.37 times risk of experiencing hypertension in pregnancy because being overweight is associated with damage to endothelial cells.[10] In addition to allowing it to be used as an antihypertensive, Kenikir can also improve risk factors that can lead to hypertension in pregnancy. Ethanolic Extract from Cosmos Caudatus Kunth Leaf (EECCL) exhibits anti-obesity by inhibiting intestinal lipid absorption and modulation of adipocyte markers. The results of the study in the group of mice that were given the High Fat Diet (HFD) and EECCL doses of 175 and 350 mg / kgBW found that the fecal fat levels of rats were significantly increased compared to the normal group.[52]

MDA levels are significantly increased in hypertension in pregnancy.[53][54][55][56][57][16][17] A condition that is more severe than hypertension during pregnancy is preeclampsia. Mothers with preeclampsia have higher levels of MDA than mothers with hypertension.[17][58][59] Compared with the severity of hypertension in pregnancy, levels of MDA were found to be higher in women with eclampsia when compared with women with hypertension in pregnancy and women with normotension. This suggests that MDA levels can predict the level of saturation of hypertension in pregnancy.[60]

MDA is a marker of oxidative stress.[26] Consumption of Kenikir (Cosmos caudatus) extract at certain doses significantly reduces MDA levels.[26]·[61]·[24] The administration of Kenikir extract at a dose of 1125 mg / kgBW significantly ($p < 0.05$) decreased MDA levels by 12.27 µm / g.[61] The 700 and 1400 mg Cosmos cudatus simplicia intervention was able to significantly reduce plasma MDA. The average MDA level in the control group was 7.7 nm / ml, while in the intervention 1400 mg of Cosmos caudatus extract MDA levels were 2.8 nm / ml.[26]

Kenikir leaves contain potential nonenzymatic antioxidants, the flavonoid group, namely quercetin.[26] Intervention of various doses of quercetin can significantly reduce malondialdehyde levels in oxidative stress.[27][28][29][30][31][35][32][34] The mechanism of quercetin in reducing malondialdehyde levels is through increasing antioxidants. Quercetin will inhibit the formation of free radicals by neutralizing the increase in Reactive Oxygen Species (ROS) and providing cell membrane protection so that lipid peroxide can be prevented. Oxidative stress is the result of an imbalance of antioxidants and free radicals.[27]

Hypertension in pregnancy correlates with increased proinflammatory cytokines and endothelial dysfunction.[37] The proinflammatory factor produced by the placenta due to placental ischemia is IL6.[36]Studies in experimental animal models of hypertension also show that giving Cosmos caudatus extract at a dose of 200 mg / kgBW can significantly reduce IL6 levels. A diet containing quercetin and sustained will accumulate in the blood and significantly increase the concentration of quercetin in the plasma.[62]

The flavonoid content in fresh Kenikir is 52.2 mg / 100g, while the quercetin content is 51.3 mg / 100g.[63] So that it can be seen, the main flavonoid component of Kenikir is quercetin. In a study using experimental animal models of hypertension, it was found that giving certain doses of quercetin resulted in a significant reduction in cytolic blood pressure compared to the control group.[44]·[41] The beneficial effects of quercetin contribute to improving blood vessel remodeling that induces hypertension.[44]

Hypertension is related to endothelial cell dysfunction, this is very important because endothelial cells produce vasodilator factors that can relax blood vessels. Endothelial cells have an important role in the development and treatment of hypertension, so a new strategy is needed, namely targeting endothelial function in treating hypertension. Quercetin has the ability to scavenge free radicals so that it can improve endothelial function.[41] Endothelial cells have the property to produce nitric oxide (NO) which functions as a vasodilator.[64] Taking quercetin in doses ranging from 50, 100 and 200 mg can increase arterial NO. NO is a vasodilator that can improve the vasoconstriction of blood vessels. [48] Oral consumption of Cosmos caudatus can increase CAT and SOD which are endogenous antioxidants.[24]

One of the drugs used for hypertension in pregnancy is methyldopa. However, treatment with methyldopa did not affect the decrease oxidative stress which is MDA levels. It was reported that between patients who were given methyldopa and not given methyldopa, their levels of MDA did not differ significantly.[53] The administration of quercetin intervention in experimental animal models of hypertension in pregnancy can significantly reduce the accumulation of Malondialdehyde (MDA) levels.[36][27] Quercetin can maximize its effects when combined with antihypertensive because in addition to lowering blood pressure, it can also reduce levels of MDA.[27]

Hypertension in pregnancy is associated with a state of oxidative stress. The use of quercetin as a hypertension therapy can lower blood pressure and improve oxidative stress. Quercetin has the effect of increasing vascular reactivity. Quercetin significantly ($p < 0.05$ influenced the vascular relaxation response in animal models of hypertension.[40] Apart from having an antihypertensive effect, giving quercetin also significantly ($p < 0.01$) prevented hypertension-induced blood pressure increases in animal models.[43] In the treatment of hypertension in pregnancy, the combination of quercetin also has a positive effect. Studies conducted on experimental animals model of hypertension in pregnancy that were given quercetin and aspirin therapy showed a significant ($p < 0.05$) reduction in systolic blood pressure was better than the group that only received quercetin or aspirin therapy. Meanwhile, quercetin intervention combined with aspirin in an animal model of hypertension in pregnancy also showed a significant reduction in MDA levels compared to the aspirin-only group.[27] The quercetin treatment together with aspirin had a higher efficiency in reducing IL6 and TNF-α levels compared with aspirin alone. In monitoring fetal well-being, the group given aspirin and quercetin had a higher body weight than the group given aspirin alone.[37]

Research on the effects of quercetin on hypertension in pregnancy is very limited respectively. Researchers only get studies that use experimental animals as models of disease. However, all the research results show significant results because hypertension in pregnancy is associated with decreased antioxidants and increased oxidative stress. Research on animal models of hypertension in pregnancy found that quercetin significantly ($p < 0.01$) decreased systolic blood pressure from 124.4 mmHg to 105.2 mmHg. Quercetin is associated with several pathways that link placental dysfunction. Quercetin supplementation preserves abnormal uteroplacental angiogenic status in a model of hypertension in pregnancy.[36]

Besides being able to lower blood pressure in hypertension in pregnancy, giving quercetin can improve the effects of the drugs. Quercetin prevents the reduction of placental weight as well as fetal weight due to hypertension in pregnancy. Besides being able to lower blood pressure and increase antioxidant levels in the body, giving quercetin also has no side effects on fetal growth in the womb. There were no reported significant differences in fetal weight and placenta between normal and hypertensive groups in pregnancies treated with quercetin.[36]

However, from the results of the reviewed journals there are still several studies that show that giving quercetin at certain doses does not have a significant effect on systolic blood pressure.[47][42][48] This is probably related to the low bioavailability of quercetin that is consumed orally, so it requires modification of quercetin so that it is easily absorbed by the body. In addition, it can also be related to the low dose given so that there is no balance between antioxidants and oxidants in the body.[42]

## VI. CONCLUSION

Giving Kenikir (Cosmos caudatus) with the main content of quercetin can reduce levels of Malondialdehyde (MDA) and has the potential to reduce blood pressure in hypertension during pregnancy.

## REFERENCES

[1]. L. Say *et al.*, "Global causes of maternal death: A WHO systematic analysis," *Lancet Glob. Heal.*, vol. 2, no. 6, pp. 323–333, 2014, doi: 10.1016/S2214-109X(14)70227-X.

[2]. Kemenkes RI, *Profil Kesehatan Indonesia 2018*[Indonesia Health Profile 2018]. Jakarta: Kementerian Kesehatan Reproduksi Indonesia, 2019.

[3]. M. B. Hoelman, B. T. P. Parhusip, S. Eko, S. Bahagijo, and H. Santono, Sustainable Development Goals-SDGs Panduan Untuk Pemerintah Daerah (Kota dan Kabupaten) dan Pemangku Kepentingan Daerah [Sustainable Development Goals-SDGs Guidelines for Local Governments (Cities and Regencies) and Regional Stakeholders] *Sustain. Dev.*, pp. 1–92, 2016.

[4]. Pusdatin, *Situasi Kesehatan Ibu* [Maternal Health Situation]. Jakarta: Pusat Data dan Informasi, 2014.

[5]. N. K. Sari, M. Hakimi, and T. B. Rahayujati, Determinan Gangguan Hipertensi Kehamilan di Indonesia [Determinants of Pregnancy Hypertension Disorders in Indonesia]*Ber. Kedokt. Masy.*, vol. 32, no. 9, pp. 295–302, 2016, doi: 10.22146/bkm.12414.

[6]. A. Sirait, Prevalensi Hipertensi Pada Kehamilan Di Indonesia Dan Berbagai Faktor Yang Berhubungan (Riset Kesehatan Dasar 2007) [Prevalence of Hypertension in Pregnancy in Indonesia and Various Related Factors (Basic Health Research 2007)]*Bul. Penelit. Sist. Kesehat.*, vol. 15, no. 2 Apr, pp. 103–109, 2013, doi: 10.22435/bpsk.v15i2.

[7]. Kemenkes RI, *Pelayanan Kesehatan Ibu di Fasilitas Kesehatan Dasar dan Rujukan. Pedoman Bagi Tenaga Kesehatan*[Maternal Health Services in Primary and Referral Health Facilities. Guidelines for Health Workers]. 2013.

[8]. American College of Obstetricians and Task Force on Hypertension in Pregnancy, "Hypertension in pregnancy," *Obstet. Gynecol.*, vol. 122, no. 5, pp. 1122–1131, 2013, doi: 10.1097/01.AOG.0000437382.03963.88.

[9]. N. Luh, G. Lisniawati, L. P. F. L, and K. W. Astuti, Kajian Penggunaan Obat Antihipertensi pada Pasien Hipertensi Gestasional Rawat Inap di RSUP Sanglah Denpasar Periode Januari 2009 - Desember 2011[Study on the Use of Antihypertensive Drugs in Gestational Hypertension Patients Hospitalized at Sanglah General Hospital, Denpasar, January 2009 - December 2011] *Repos. Unud*, vol. 2011

[10]. B. Setyawati, N. Fuada, S. Salimar, and B. C. Rosha, Faktor Risiko Hipertensi Pada Wanita Hamil Di Indonesia (Analisis Data Riskesdas 2013) [Risk Factors for Hypertension in Pregnant Women in Indonesia (Data Analysis of Riskesdas 2013)] *J. Kesehat. Reproduksi*, vol. 6, no. 2, 2016, doi: 10.22435/kespro.v6i2.4748.77-86.

[11]. T. Xiong *et al.*, "Hypertensive disorders in pregnancy and stillbirth rates: A facility-based study in China," *Bull. World Health Organ.*, vol. 96, no. 8, pp. 531–539, 2018, doi: 10.2471/BLT.18.208447.

[12]. M. Muti, M. Tshimanga, G. T. Notion, D. Bangure, and P. Chonzi, "Prevalence of pregnancy induced hypertension and pregnancy outcomes among women seeking maternity services in Harare, Zimbabwe," *BMC Cardiovasc. Disord.*, vol. 15, no. 1, pp. 1–8, 2015, doi: 10.1186/s12872-015-0110-5.

[13]. R. Slim, C. Ben Salem, H. Hmouda, and K. Bouraoui, "Hepatotoxicity of alpha-methyldopa in pregnancy," *J. Clin. Pharm. Ther.*, vol. 35, no. 3, pp. 361–363, 2010, doi: 10.1111/j.1365-2710.2009.01078.x.

[14]. M. Ożarowski *et al.*, "Pharmacological effect of quercetin in hypertension and its potential application in pregnancy-induced hypertension: Review of in vitro, in vivo, and clinical studies," *Evidence-based Complement. Altern. Med.*, vol. 2018, p. 19, 2018, doi: 10.1155/2018/7421489.

[15]. W. Liu, M. Zhang, J. Feng, A. Fan, Y. Zhou, and Y. Xu, "The influence of quercetin on maternal immunity, oxidative stress, and inflammation in mice with exposure of fine particulate matter during gestation," *Int. J. Environ. Res. Public Health*, vol. 14, no. 6, 2017, doi: 10.3390/ijerph14060592.

[16]. R. R. Dianti, R. Rusdi, and D. Evriyani, "Kadar Malondialdehid Dan Aktivitas Enzim Superoksida Dismutase Pada Hipertensi Dan Normotensi," *Bioma*, vol. 12, no. 1, p. 50, 2017, doi: 10.21009/bioma12(1).6.

[17]. D. Draganovic, N. Lucic, and D. Jojic, "Oxidative Stress Marker and Pregnancy Induced Hypertension," *Med. Arch. (Sarajevo, Bosnia Herzegovina)*, vol. 70, no. 6, pp. 437–440, 2016, doi: 10.5455/medarh.2016.70.437-440.

[18]. B. LaMarca, "Endothelial dysfunction. An important mediator in the pathophysiology of hypertension during pre-eclampsia," *Minerva Ginecol.*, vol. 64, no. 4, pp. 309–320, 2012, [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3796355/.

[19]. B. Zolfaghari, M. Kazemi, and M. Nematbakhsh, "The effects of unripe grape extract on systemic blood pressure and serum levels of superoxide dismutase, malondialdehyde and nitric oxide in rat.," *Adv. Biomed. Res.*, vol. 4, no. August, p. 109, 2015, doi: 10.4103/2277-9175.157822.

[20]. D. Haytowitz, X. Wu, and S. Bhagwat, "USDA database for the flavonoid content of selected foods, release 3.3," *USDA Agric. Res. Serv.*, pp. 1–115, 2018, [Online]. Available: http://www.ars.usda.gov/nutrientdata/flav.

[21]. R. A. Mustafa, A. A. Hamid, S. Mohamed, and F. A. Bakar, "Total phenolic compounds, flavonoids, and radical scavenging activity of 21 selected tropical plants," *J. Food Sci.*, vol. 75, no. 1, 2010, doi: 10.1111/j.1750-3841.2009.01401.x.

[22]. S. P. Loh and O. Hadira, "In vitro inhibitory potential of selected Malaysian plants against key enzymes involved in hyperglycemia and hypertension," *Malays. J. Nutr.*, vol. 17, no. 1, pp. 77–86, 2011, [Online]. Available: https://nutriweb.org.my/mjn/publication/17-1/g.pdf.

[23]. L. Amalia, K. Anggadiredja, I. F. Sukrasno, and R. Inggriani, "Antihypertensive Poency of Wild Cosmos (Cosmos caudatus kunth, asteraceae) Leaf Extract," *Journal of Pharmacology and Toxicology*, vol. 7, no. 8. pp. 359–368, 2012, doi: 10.3923/jpt.2012.359.368.

[24]. A. Abdullah *et al.*, "The effects of Cosmos caudatus (Ulam Raja) on detoxifying enzymes in extrahepatic organs in mice," *J. Appl. Pharm. Sci.*, vol. 5, no. 1, pp. 082–088, 2015, doi: 10.7324/JAPS.2015.50115.

[25]. A. Novianto and Hartono, Uji Aktivitas Hepatoprotektif Fraksi Etil Asetat Kenikir (Cosmos Caudatus) terhadap Tikus yang Diinduksi Paracetamol [Hepatoprotector Activity Test of Kenikir Ethyl Acetate Fraction (Cosmos Caudatus) on Paracetamol-Induced Rats] *Indones. J. Med. Sci.*, vol. 3, no. 1, pp. 35–41, 2016, [Online]. Available: http://ejournal.ijmsbm.org/index.php/ijms/article/view/64.

[26]. F. Suhardinata and E. A. Murbawani, Pengaruh Bubuk Daun Kenikir (Cosmos caudatus) Terhadap Kadar Malondialdehyde Plasma Tikus Wistar Diabetes Diinduksi Streptozotocin [Effects of Kenikir Leaf Powder (Cosmos caudatus) on Maldialdehyde Plasma Levels in Streptozotocin-Induced Diabetic Wistar Rats] *J. Nutr. Coll.*, vol. 4, no. 2, pp. 570–577, 2015, http://eprints.undip.ac.id/47109/.

[27]. S. Kocahan, Z. Dogan, E. Erdemli, and E. Taskin, "Protective effect of quercetin against oxidative stress-induced toxicity associated with doxorubicin and cyclophosphamide in rat kidney and liver tissue," *Iran. J. Kidney Dis.*, vol. 11, no. 2, pp. 124–131, 2017, [Online]. Available: http://hdl.handle.net/11446/2329.

[28]. N. Çelik, A. Vurmaz, and A. Kahraman, "Protective effect of quercetin on homocysteine-induced oxidative stress," *Nutrition*, vol. 33, pp. 291–296, 2017, doi: 10.1016/j.nut.2016.07.014.

[29]. X. Lin *et al.*, "Quercetin protects against heat stroke-induced myocardial injury in male rats: Antioxidative and antiinflammatory mechanisms," *Chem. Biol. Interact.*, vol. 265, pp. 47–54, 2017, doi: 10.1016/j.cbi.2017.01.006.

[30]. S. F. Xia *et al.*, "Differential effects of quercetin on hippocampus-dependent learning and memory in mice fed with different diets related with oxidative stress," *Physiol. Behav.*, vol. 138, pp. 325–331, 2015, doi: 10.1016/j.physbeh.2014.09.008.

[31]. M. Abd-Elbaset, E.-S. A. Arafa, G. A. El Sherbiny, M. S. Abdel-Bakky, and A. N. A. M. Elgendy, "Quercetin modulates iNOS, eNOS and NOSTRIN expressions and attenuates oxidative stress in warm hepatic ischemia-reperfusion injury in rats," *Beni-Suef Univ. J. Basic Appl. Sci.*, vol. 4, no. 3, pp. 246–255, 2015, doi: 10.1016/j.bjbas.2015.07.001.

[32]. J. Roslan, N. Giribabu, K. Karim, and N. Salleh, "Quercetin ameliorates oxidative stress, inflammation and apoptosis in the heart of streptozotocin-nicotinamide-induced adult male diabetic rats," *Biomed. Pharmacother.*, vol. 86, pp. 570–582, 2017, doi: 10.1016/j.biopha.2016.12.044.

[33]. N. Oueslati, K. Charradi, T. Bedhiafi, F. Limam, and E. Aouani, "Protective effect of grape seed and skin extract against diabetes-induced oxidative stress and renal dysfunction in virgin and pregnant rat," *Biomed. Pharmacother.*, vol. 83, pp. 584–592, 2016, doi: 10.1016/j.biopha.2016.07.024.

[34]. F. Gholampour and N. Saki, "Hepatic and Renal Protective Effects of Quercetin in Ferrous Sulfate Induced Toxicity," *Gen. Physiol. Biophys.*, vol. 38, pp. 27–38, 2019, doi: 10.4149/gpb.

[35]. G. Duranti *et al.*, "Chronic consumption of quercetin reduces erythrocytes oxidative damage: Evaluation at resting and after eccentric exercise in humans," *Nutr. Res.*, vol. 50, pp. 73–81, 2018, doi: 10.1016/j.nutres.2017.12.002.

[36]. Q. Li, L. Yin, Y. Si, C. Zhang, Y. Meng, and W. Yang, "The bioflavonoid quercetin improves pathophysiology in a rat model of preeclampsia," *Biomed. Pharmacother.*, vol. 127, no. March, p. 110122, 2020, doi: 10.1016/j.biopha.2020.110122.

[37]. S. Yang, L. Song, X. Shi, N. Zhao, and Y. Ma, "Ameliorative effects of pre-eclampsia by quercetin supplement to aspirin in a rat model induced by L-NAME," *Biomed. Pharmacother.*, vol. 116, no. April, p. 108969, 2019, doi: 10.1016/j.biopha.2019.108969.

[38]. S. Moshawih, M. S. Cheema, Z. O. Ibraheem, N. D. Tailan, and M. N. Hakim, "Cosmos caudatus extract/fractions reduce smooth muscle cells migration and invasion in vitro: A potential benefit of suppressing atherosclerosis," *Porto Biomed. J.*, vol. 2, no. 6, pp. 293–300, 2017, doi: 10.1016/j.pbj.2017.03.008.

[39]. M. das Graças C de Souza, F. Z. Cyrino, J. J. de Carvalho, V. Blanc-Guillemaud, and E. Bouskela, "Protective Effects of Micronized Purified Flavonoid Fraction (MPFF) on a Novel Experimental Model of Chronic Venous Hypertension," *Eur. J. Vasc. Endovasc. Surg.*, vol. 55, no. 5, pp. 694–702, 2018, doi: 10.1016/j.ejvs.2018.02.009.

[40]. S. Choi *et al.*, "Direct vascular actions of quercetin in aorta from renal hypertensive rats," *Kidney Res. Clin. Pract.*, vol. 35, no. 1, pp. 15–21, 2016, doi: 10.1016/j.krcp.2015.12.003.

[41]. X. Lin, T. Han, Y. Fan, S. Wu, F. Wang, and C. Wang, "Quercetin Improves Vascular Endothelial Fungtion Through Promotion of Autophagy in Hypertensive Rats," *Life Sci.*, p. 118106, 2020, doi: 10.1016/j.lfs.2020.118106.

[42]. E. P. Porcu *et al.*, "Aqueous injection of quercetin: An approach for confirmation of its direct in vivo cardiovascular effects," *Int. J. Pharm.*, vol. 541, no. 1–2, pp. 224–233, 2018, doi: 10.1016/j.ijpharm.2018.02.036.

[43]. V. Calabró, M. C. Litterio, C. G. Fraga, M. Galleano, and B. Piotrkowski, "Effects of quercetin on heart nitric oxide metabolism in L-NAME treated rats," *Arch. Biochem. Biophys.*, vol. 647, pp. 47–53, 2018, doi: 10.1016/j.abb.2018.03.041.

[44]. S. C. Pereira *et al.*, "Quercetin decreases the activity of matrix metalloproteinase-2 and ameliorates vascular remodeling in renovascular hypertension," *Atherosclerosis*, vol. 270, pp. 146–153, 2018, doi: 10.1016/j.atherosclerosis.2018.01.031.

[45]. V. Brüll *et al.*, "Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: A randomised double-blinded placebo-controlled cross-over trial," *Br. J. Nutr.*, vol. 114, no. 8, pp. 1263–1277, 2015, doi: 10.1017/S0007114515002950.

[46]. M. M. de Jesús Romero-Prado, J. A. Curiel-Beltrán, M. V. Miramontes-Espino, E. G. Cardona-Muñoz, A. Rios-Arellano, and L. B. Balam-Salazar, "Dietary Flavonoids Added to Pharmacological Antihypertensive Therapy are Effective in Improving Blood Pressure," *Basic Clin. Pharmacol. Toxicol.*, vol. 117, no. 1, pp. 57–64, 2015, doi: 10.1111/bcpt.12360.

[47]. C. Burak *et al.*, "Effect of alpha-linolenic acid in combination with the flavonol quercetin on markers of cardiovascular disease risk in healthy, non-obese adults: A randomized, double-blinded placebo-controlled crossover trial," *Nutrition*, vol. 58, pp. 47–56, 2019, doi: 10.1016/j.nut.2018.06.012.

[48]. N. P. Bondonno *et al.*, "Acute effects of quercetin-3-O-glucoside on endothelial function and blood pressure: A randomized dose-response study," *Am. J. Clin. Nutr.*, vol. 104, no. 1, pp. 97–103, 2016, doi: 10.3945/ajcn.116.131268.

[49]. A. Novianto, A. Nurrochmad, I. P. Sari, and P. Astuti, "Hepatoprotective effect of combination of curcuma domestica val and Phyllanthus niruri linn against paracetamol-induced liver damage in wistar rats," *Int. J. Pharm. Clin. Res.*, vol. 7, no. 6, pp. 450–457, 2015

[50]. A. Prahartini, N. Sahid, and E. Murbawani, Pengaruh Bubuk Daun Kenikir (Cosmos Caudatus) Terhadap Kadar Glukosa Darah Tikus Diabetes Diinduksi Streptozotocin[Effect of Kenikir Leaf Powder (Cosmos Caudatus) on Blood Glucose Levels of Streptozotocin-Induced Diabetic Rats] *J. Nutr. Coll.*, vol. 5, no. 2, pp. 51–57, 2016, doi: 10.14710/jnc.v5i2.16359.

[51]. S. H. Cheng, H. E. Khoo, A. Ismail, A. Abdul-Hamid, and M. Y. Barakatun-Nisak, "Influence of extraction solvents on Cosmos caudatus leaf antioxidant properties," *Iran. J. Sci. Technol. Trans. A Sci.*, vol. 40, no. 1, pp. 51–58, 2016, doi: 10.1007/s40995-016-0007-x.

[52]. H. A. Rahman *et al.*, "Anti-obesity effect of ethanolic extract from Cosmos caudatus Kunth leaf in lean rats fed a high fat diet," *BMC Complement. Altern. Med.*, vol. 17, no. 1, pp. 1–17, 2017, doi: 10.1186/s12906-017-1640-4.

[53]. M. Toljic *et al.*, "Increased oxidative stress and cytokinesis-block micronucleus cytome assay parameters in pregnant women with gestational diabetes mellitus and gestational arterial hypertension," *Reprod. Toxicol.*, vol. 71, pp. 55–62, 2017, doi: 10.1016/j.reprotox.2017.04.002.

[54]. S. Subandrate, M. E. P. A. Faisal, N. W. Anggraini, and S. Sinulingga, "Malondialdehyde levels are higher and glutathione levels are lower in preeclampsia than in normal pregnancies," *Universa Med.*, vol. 36, no. 3, p. 179, Nov. 2017, doi: 10.18051/UnivMed.2017.v36.179-186.

[55]. V. Dsouza *et al.*, "Increased oxidative stress from early pregnancy in women who develop preeclampsia," *Clin. Exp. Hypertens.*, vol. 38, no. 2, pp. 225–232, 2016, doi: 10.3109/10641963.2015.1081226.

[56]. M. K. Verma, A. Jaiswal, P. Sharma, P. Kumar, and A. N. Singh, "Oxidative stress and biomarker of TNF-α, MDA and FRAP in hypertension," *J. Med. Life*, vol. 12, no. 3, pp. 253–259, 2019, doi: 10.25122/jml-2019-0031.

[57]. S. A. Khan, R. Choudhary, A. Singh, and S. H. Bodakhe, "Hypertension potentiates cataractogenesis in rat eye through modulation of oxidative stress and electrolyte homeostasis," *J. Curr. Ophthalmol.*, vol. 28, no. 3, pp. 123–130, 2016, doi: 10.1016/j.joco.2016.05.001.

[58]. A. R. Prijanti *et al.*, "Analysis of oxidative stress markers malondialdehyde, glutathione, nitric oxide, and prorenin level in preeclampsia placental tissues," *Asian J. Pharm. Clin. Res.*, vol. 11, no. 1, pp. 158–161, 2018, doi: 10.22159/ajpcr.2018.v11i1.18330.

[59]. M. Bakacak *et al.*, "Changes in copper, Zinc, and malondialdehyde levels and superoxide dismutase activities in pre-eclamptic pregnancies," *Med. Sci. Monit.*, vol. 21, pp. 2414–2420, 2015, doi: 10.12659/MSM.895002.

[60]. S. Saxena *et al.*, "Role of dyslipidaemia and lipid peroxidation in pregnancy induced hypertension," *J. Clin. Sci. Res.*, vol. 4, no. 3, p. 205, 2015, doi: 10.15380/2277-5706.jcsr.14.059.

[61]. A. Novianto and Hartono, Studi Aktivitas Hepatoprotektif Fraksi Etil Asetat Kenikir (Cosmos caudatus) pada Tikus yang Diinduksi Parasetamol Kajian Stress Oksidatif (Lipid Peroksidase) [Study of Hepatoprotective Activity of Ethyl Acetate Fraction of Kenikir (Cosmos caudatus) in Paracetamol-Induced Rats in the Study of Oxidative Stress (Lipid Peroxidase)] *J. KesMaDaSka*, vol. 7, no. 1, pp. 35–41, 2016, [Online]. Available: http://jurnal.ukh.ac.id/index.php/JK/article/view/122.

[62]. I. G. Agung *et al.*, Pengaruh Ekstrak Etanol Daun Kenikir ( Cosmos caudatus ) terhadap Kadar Glutathion Dan Interleukin 6 Serum Tikus Wistar Jantan yang Diberi Pakan Tinggi Kolesterol Effect of Ethanol Extract of Kenikir Leaf ( Cosmos caudatus ) on Glutathione and Interleukin [Effect of Ethanol Extract of Kenikir Leaf (Cosmos caudatus) on Glutathione and Interleukin Levels 6 Serum of Wistar Male Mice Served with High Cholesterol Effect of Ethanol Extract of Kenikir Leaf (Cosmos caudatus) on Glutathione and Interleukin]vol. 11, pp. 77–85, 2020

[63]. N. Andarwulan, R. Batari, D. A. Sandrasari, B. Bolling, and H. Wijaya, "Flavonoid content and antioxidant activity of vegetables from Indonesia," *Food Chem.*, vol. 121, no. 4, pp. 1231–1235, 2010, doi: 10.1016/j.foodchem.2010.01.033.

[64]. A. Munandar, N. Murcahyani, and H. Busman, Pengaruh Kebisingan Terhadap Kualitas Spermatozoa Mencit (Mus musculus L)[ Effect of Noise on Quality of Mouse Spermatozoa (Mus musculus L)] *Pros. Semin. Nas. sains Teknol. V*, vol. 5, no. 4–43, pp. 307–315, 2013, doi: 10.1017/CBO9781107415324.004.