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Clitoria Ternatea as a Potential Herb in Polycistic Ovary Syndrome

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Abstract: *Clitoriaternatea (CT) is an herbal plant that has the potential as a therapeutic agent to manage polycystic ovarian syndrome (PCOS). CT has antioxidant and anti-inflammatory properties that can help reduce inflammation, oxidative stress, and metabolic dysfunctions associated with PCOS. In this study, we conducted a systematic review of relevant research articles on the bioactivity potential of CT as a herbal drug candidate for PCOS. We searched research articles in Indonesian and English published over the last five years (2019-2023) through three databases: PubMed, ScienceDirect, and Google Scholar. We use established inclusion and exclusion criteria to select suitable articles. Out of 24 research articles included in our systematic review, we found that CT has potential as an antidiabetic, antiglucose, anticholesterol, anti-obesity, anti-inflammatory, hepatoprotective, and antidepressant agent. Based on our systematic review, CT shows potential as a therapeutic agent for managing PCOS symptoms. The antioxidant and anti-inflammatory properties of CT can help reduce inflammation, oxidative stress, and metabolic dysfunctions associated with PCOS. However, further research is needed to validate these findings and evaluate the effectiveness of CT in clinical settings.*

Keywords: *bioactivity; clitoriaternatea; herbal drug; polycystic ovary syndrome*

1. INTRODUCTION

PCOS (Polycystic Ovary Syndrome) is a hormonal sickness that impacts ladies of reproductive age. It is characterized by irregular menstrual cycles, high levels of androgens (male hormones), and the development of small cysts on the ovaries (Aflatounian et al., 2020). PCOS can lead to various health problems, including infertility, insulin resistance, obesity, chronic inflammation, and metabolic disorders. These conditions can increase the risk of cardiovascular disease, heart disease, stroke, and liver damage (Vanky&Løvvik, 2020). The use of certain medications for PCOS treatment can also have side effects on liver health. Therefore, finding effective solutions to manage PCOS and its associated complications is crucial (Garad&Teede, 2020).

Inflammation and oxidative strain a substantial function within side the improvement and development of PCOS. Chronic low-grade irritation can disrupt the improvement of ovarian follicles and intervene with ovulation. It can also contribute to insulin resistance, which further exacerbates the hormonal imbalance in PCOS. Oxidative stress, which takes place whilst there's an imbalance among the manufacturing of free radicals and the body's antioxidant defenses, can damage ovarian cells, and impair follicle development. It can also contribute to the formation of ovarian cysts and increase the risk of complications associated with PCOS (Armanini et al., 2022; Başer et al., 2022). Recent research has also explored the role of gut microbiota in PCOS. Disruption of the gut microbiota balance, known as dysbiosis, can affect hormonal regulation and contribute to inflammation and metabolic dysfunction (Zhang et al., 2022). Clitoriaternatea extract has shown potential in modulating gut microbiota and improving overall hormonal balance (Liang et al., 2020).

Clitoriaternatea, also known as butterfly pea flower, has been studied for its potential therapeutic effects in PCOS. It contains compounds such as flavonoids, alkaloids, saponins, and tannins (Gejalakshmi.S&Harikrishnan, 2023), which have antioxidant and anti-inflammatory properties

(Wang et al., 2022). Studies have shown that Clitoriaternatea extract can inhibit the production of pro-inflammatory cytokines, reduce oxidative stress, and protect against liver and kidney damage. It may also help regulate lipid metabolism, lower cholesterol levels, and improve insulin sensitivity (Hakam Maulidy et al., 2022).

PCOS is a complex hormonal disorder that involves inflammation, oxidative stress, and metabolic dysfunction. Clitoriaternatea, with its antioxidant and anti-inflammatory properties, shows promise as a potential therapeutic agent for managing PCOS symptoms(Goh et al., 2021a; Widowati et al., 2023). Further research is needed to fully understand its mechanisms of action and determine its efficacy in clinical settings.

2. Material and Methods

Research articles were searched using three databases, namely PubMed, ScienceDirect, and Google Scholar in (2019- 2023) of publication and written in Indonesian and English. The keywords used in the article search have been matched to Medical Subject Titles (MeSH) including “Apple Flowers”, “Butterfly Pea, “Asian pigeonwing” (t/n: ClitoriaTernatea)”, “Antidiabetic”, "Anti glucose", "Cholesterol regulative", "Antinflammatory", “hepatoprotective”, "Anti-depressant", according to PICOTs (Population, Intervention, Comparators, Outcome, Time).

Table1. *Inclusion and Exclusion Criteria*

Criteria	Inclusion	Exclusion
Population	Human, rattus norvegicus, mus musculus, rats, mice, murrine	In vitro
Intervention	Clitoriaternatea	Clitoriaternatea combination with other herbs
Comparators	With control group	Without control group
Outcomes	Research shows the effects of clitoriaternatea as antidiabetic, anti-glucose, antioxidant, anti-obesity, cholesterol regulatie, anti-inflammatory, hepatoprotective, anti-depressant	Research shows other effects of clitoriaternatea
Time	2018-2023	<2018
Study design	Experimental research	Analytical observational research
Language	Indonesian, English	Besides Indonesian and English

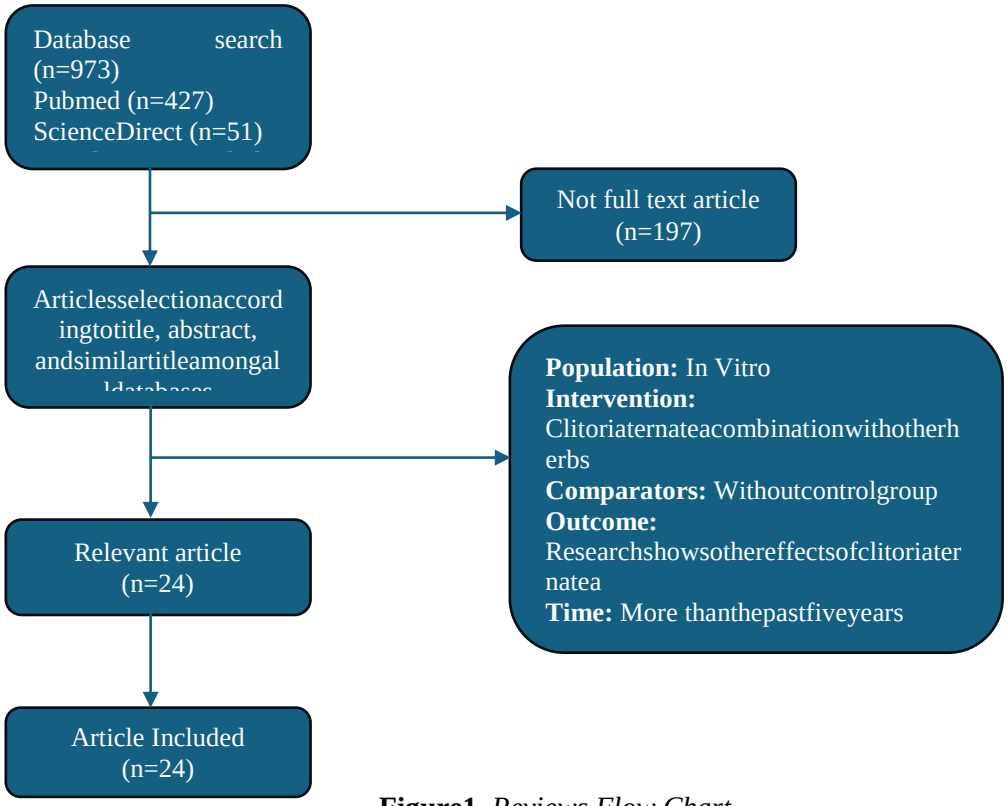

Figure1. *Reviews Flow Chart*

3. RESULTS AND DISCUSSION

Twenty-four research articles included studies. Table 2 reports a summary of each in this article in a systematic review of the potential bioactivity of clitoriaternatea as a PCOS herbal drug candidate.

Table2. *List of Research Articles, Journals in Review*

Reference	Sample	Intervention (type, Dose, Duration)	Result	Potentialeffecton PCOS
(Gunawan etal., 2023)	30 whiterats (Rattusnorvegicus) withmetabolicsyndrome	The dosesadministeredwere dose I (100 mg/kgBW), dose II (200 mg/kgBW), anddose III (400 mg/kgBW) for a durationof 28 days	The mosteffectivedoseofbutterflypea extractinterventionforloweringblood glucoselevels in whiteratswithmetabolicsyndrome isdose III, whichis 400 mg/kgBW	Antiglucose Antidiabetic
(Putri etal., 2022)	20 male Albino Wistarrats, inducedwithstreptozotocinandnicotinamidetogeneratetype 2 diabetes	(T1) wasgivenacarboseat a doseof 1.8 mg/kg bodyweight. (T2) wasgivenanethanolextract CT flowerat a doseof 150 mg/kg bodyweight. The durationoftheinterventionwas 21 days.	Clitoriaternateaextractat a doseof 150 mg/kg bodyweightcanincreasebodyweightandreduce MDA levels in diabeticrats	Antidiabetic Antiobesity
(Minelkoe tal., 2020)	25 miceDiabetes wasinducedbyintraperitonealinjectionofalloxanatincreasingdosesof 80, 100, and 150 mg/kg bodyweight in 3-day intervals.	Normal control (phosphatebuffersaline, normal mice), negativecontrol (AlloxanInduced (AI), phosphatebuffersaline), AI + 100 mg/kg BW PCT, AI + 500mg/kg BW PCT, AI + 100 mg/kg BW metformin, dailydosetreatmentfor a durationof 30 days.	The Maximumreduction in bloodglucose level wasachievedthroughtheadministrationof 500 mg/kg BW PCT andmodulatedtheexpressionof diabetes-relatedgenes in adiposetissue, skeletalmuscletissue, andpancreas	Antidiabetic Antiglucose
(Widowati etal., 2023)	40 rats (rattusnorvegicus) a high-fat diet and a substancecalledpropylthiouracil (PTU) in theirdrinkingwater. Streptozotocin (STZ) andnicotinamide (NA) were injectedtoinduce DM	The negativecontrolgroup (I) receiveddistilledwater, whilethepositivecontrolgroup (II) receivedglibenclamideandsimvastatin. InterventionGroups: The dosesincluded CTE 200 mg/kg ofbodyweight (III), CTE 400 mg/kg ofbodyweight (IV), and CTE 800 mg/kg ofbodyweight (V). The durationoftheinterventionwas 28 days	CTE treatmentsignificantlyreducedblodglucoselevels in diabeticrats, withthemosteffectivedosebeing 400 mg/kg bodyweight, increased insulin levels in diabeticrats, increased CAT and SOD levels. Reduced MDA and IL-18 levels, which are markersofoxidativedamageandinflammation.	Antidiabetic Antioxidant Anti-inflammatory
(Ginting etal., 2022)	25 male whiterats, inducedwithalloxantoinduce diabetes	Controlgroupwithoutalloxaninduction, a positivecontrolgroupreceivingglibenclamide. The extractdoses: 200 mg/kg BW, 400 mg/kg BW, and 600 mg/kg BW, everydayfor a durationof 7 days	The bestdecreasewasobserved in thegroupthatreceived a doseof 400 mg/kg bodyweight, withblood sugar levelsdecreasingfrom 322.8 mg/dl to 31.2 mg/dl	Antiglucose Antidiabetic
(Fani Temarwute	15 male rats Alloxan 150 mg/kg BW) ondays 6 inducedgives a	The controlhealthygroup, theplacebogroupandtheextracttreatedgroupthatreceived	The highestdoseofClitoriaternateaextract (450 mg/kg)	Antidiabetic Antiglu

Reference	Sample	Intervention (type, Dose, Duration)	Result	Potentialeffecton PCOS
tal., 2023)	significantincrease in glucoseand albumin level	150 mg/kg BW (group I), 300 mg/kg BW (group II) and 450 mg/kg BW (group III) orally. Placebo (Na-CMC) andextract were givenfor 5 days	wasabletopreventtheelevationofthesebiomarkers, indicating a protectiveeffectonthefunctionand structureofthepancreas.	cose
(Sa etal., 2023)	24 rats	Controlgroupwhichreceived normal saline (10 ml/kg) byintraperitoneal (i.p.) route; Group II streptozotocin (65 mg/kg) dissolved in normal salineintraperitoneal, Group III CT extract (100 mg/kg), Group IV and V wasadministeredwiththenano particlesi.e. CT-AuNPs (25 mg/kg) and CT- Co3O4 NPs (25 mg/kg) respectively. Time: 21 daysby oral route.	The CT-C3O4 NPsbetteractivitydecrease in thebloodglucose level fromday 8. CT-AuNPs a moresignificantlyreduction in serum cholesterolandtriglycerids. CT, change in serum HDL and BUN, serum creatinine level, significantincrease in SOD CAT and GSH, reduce MDA-lipid peroxidation level, preventedoxidativestress.	Antidiabetic Antiglucose Antioxidant
(Goh etal., 2021 b)	32 femalemice	Vehiclecontrol (VC) group: 0.15 mL/kg BW ofoliveoil. BPA group: 5 mg/kg BW of BPA. CTE group: 100 mg/kg BW of CTE. CTE + BPA group: 100 mg/kg BW of CTE followedby 5 mg/kg bodyweightof BPA. Time: sixweeks	Maternal feedingwith C. ternateaflowerextract (CTE) resulted in a higherpercentageof male offspringand had a protectiveeffectagainstthenegativeeffectsofbisphenol-A (BPA) on maternal weight, uterus weight, pregnancy, andlittersize. C. ternateaextractshowedhighantioxidantactivityandexpertpotentialprotectiveeffectsagainst BPA.	Antioxidant
(Thilavech etal., 2021)	16 participants (9 overweightand 7 obese)	Participantsconsumed a high-fat (HF) meal, an HF meal plus 1 g of CTE, HF meal plus 2 g of CTE. Participants were askedtoconsumethemealwithin 10 min.	FRAP (FerricReducingAntioxidant Power): The high-fatmealcaused a decrease in postprandial FRAP levels, indicating a reduction in antioxidantactivity. CTE improvedpostprandial FRAP levels, suggestinganenhancement in antioxidantcapacity.	Antioxidant
(Wang etal., 2022)	40 miceinducedbya high-fat, high-fructose diet	The dosesoftheextractadministered were 0.25%, 0.5%, and 2% (w/w) oftheextract in drinkingwater. Duration: The interventionlastedfor a total of 16 consecutiveweeks.	C. ternateablue petal extractcanreduceblood lipid levels, as demonstratedbydecreased plasma TC, FFA, and LDL-C levels in themice, reducedthebodyweightofobesemiceand lipid accumulation in theirliverandadiposetissues, significantlyincreasedthe plasma levelsofthecirculating anti-inflammatorycyto- kines IL-4 and IL-10 in the HFFD-fedobesemice.	Antidiabetic Antiobesity Anti-inflammatory
(Hakam Maulidy etal.,	30 miceinducehypercholesterolemia (high-fatfeedcontainingbeeflard, duckegg yolk,	Control Group: healthymice, Group (S): simvastatin 10 mg/time (0.36 mg/day/head). Group 1: ethanolextract CT 25 mg/Kg BW/day. Group 2:	The optimum doseofbutterflypeaextractbyaddingevenhigherdosevariations (> 100 mg/Kg BW/day).	Cholesterolregulatie

Reference	Sample	Intervention (type, Dose, Duration)	Result	Potentialeffecton PCOS
2022)	andlard)	ethanolextract CT 50 mg/Kg BW/day. Group 3: ethanolextract CT 100 mg/Kg BW/day. Time: 14 days.		
(Arifah & Prabandari, 2022)	30 male rats (Rattusnorvegicus)	The extractwasgivenatthreedifferentdoses: dose I (100 mg/kg bodyweight), dose II (200 mg/kg bodyweight), anddose III (400 mg/kg bodyweight).	The resultsshowedthattheextractwasabletoreduce total cholesteroland LDL cholesterollevels, whileincreasing HDL cholesterollevels. The mosteffectivedosewasfoundtobe 400 mg/kg bodyweight.	Cholesterolregulatie
(Pratiwi Irawan etal., 2023)	The respondents were 15, agedbetween 30-60 years, havingbloodcholesterollevels ≥ 200 mg/dL	The doseofbutterflypeaflowerteagiventotherespondentswas 1 gram ofdriedflowerboiledwith 250 ml ofwater, tobeconsumed once a dayfor 7 consecutivedays, consumingbutterflypeaflowertea once a dayforthisperiod	The average level ofcholesterolbefore a teais 258,06 ± 47,093 mg/dL, whileafterteais 245,13 ± 42,746 mg/ dL. There's a significantdifference in total cholesterollevelsbeforeandafter.	Cholesterolregulatie
(Nadya Audina etal., 2023)	22 subjectsparticipated in theresearch	The doseofClitoriaternateaflowerextractcapsulesgiventothetreatmentgroupwas 2000 mg/day. The treatmentwithClitoriaternateaflowerextractcapsuleswascarriedoutforonemonth	The resultsshowed a significantdecrease in IL-6 levels in thetreatmentgroupcomparedtothecontrolgroup.	Anti-inflammatory
(Saengnak etal., 2021)	Total 32 rats, l-NAME inducedhypertensiverats	The rats were dividedintofourgroups: control + vehicle, l-NAME + vehicle, l-NAME + CT flowerextract, and l-NAME + lisinopril. The CT flowerextractwasgivenorally at a doseof 300 mg/kg/day, andlisinoprilwasgivenorallyat a doseof 1 mg/kg/day. The durationoftheinterventionwas 5 weeks.	Treatmentwith CT flowerextractorlisinoprilsignificantlyreduced SBP and DBP. Significantlydecreased plasma Ang II levels, inhibited Nox4 protein overexpression. Significantlyalleviatedoxidativestressproductionbydecreasing plasma MDA.	Anti-inflammatory
(Maneesai etal., 2021)	32 male SpragueDawleyrats	Controlgroup (thecontrolgroupreceivedonlythevehicle (drinkingwater, 1.5 mL/kg), L-NAME group, L-NAME + CT extractgroup, and L-NAME + lisinoprilgroup. CTE 300 mg/kg BW + 2.5 mg/kg BW. The interventionlastedfor 5 weeks	The resultsshowedthattreatmentwith CT extractreducedsuperoxidegenerationand plasma lipid peroxidation, decreasedtheexpressionof p-NF-κB protein and tumor necrosisfactor-alpha (TNF-α).	Anti-inflammatory
(Safhietal., 2022)	25 albino rats	CT groupreceived a dailydoseof 400 mg/kg of Asian pigeonwingextractby oral gavage, 21 days.	The combinationofMSCsandtheextractwasfoundtobethemosteffectivetreatment, significantdecrease in	Anti-inflammatory Antioxi

Reference	Sample	Intervention (type, Dose, Duration)	Result	Potentialeffecton PCOS
			thelevelsofcreatinine, urea, anduricacid, reducing MDA levels, increase in SOD levels, increasing GSH levels.	dant
(Swathietal., 2021)	24 rats	Group II wastreatedwithdiclofenac (20 mg/kg), group III and IV were treatedwith 200 and 400 mg/kg of EECT (ethanolicextractofClitoriaternatea) respectively, andgroup I served as thecontrol, 21 days.	The treatmentof EECT (200 and 400 mg/kg), diclofenac sodium (10 mg/kg) significantlyrestoredthelevelsof GSH, SOD andcatalase	Antioxidant Anti-inflammatory
(Chandra etal., 2019)	25 healthy male & female rats (wistar albino)	Negativecontrol: Normal saline. Positivecontrol: CCl4 (1ml/kg/day). Standard treatment: Silymarin(100 mg/kg/day) + CCl4. Treatments 1 and 2: (MethanolicextractofClitoriaternatea (500 mg/kg/day) and (1000 mg/kg/day)+ CCl4(1ml/kg/day) for 9 days	The resultsshowedthattheextractat a doseof 1000 mg/kg reducedthelevelsoftheseenzymes, reducedthelevelsof urea andcreatinine, indicatingitsnephroprotectiveeffect.	Hepatoprotective
(Pebiansyah etal., 2022)	30 rats	positivecontrolgroup: curliv 37 mg/200 g BW, testdoses 1, 2, and 3 were givenethanolextractof telang flower, respectively 123 mg/200 g BW, 247 mg/200 g BW, and 370 mg/200g BW onday 1 until the 7th day	2 doseethanolextract (247 mg/200 g BB) has thepotential as aneffectivehepatoprotectiveagent in preventingliverdamagecausedby paracetamol.	Hepatoprotective
(Mittaletal., 2021)	24 albino mice	Clitoriaternateaextractattwodifferentdoses - 200 mg/kg and 400 mg/kg via intra-peritonealinjection	The extract (400 mg/kg) wasfoundtobeeffectiveanditexhibitedactivitysimilartothatofthestanderddrugImipramine	Antidepressant
(Margretetal., 2019)	30 adultfemale albino Swissmice were usedtoinducedepression	AqueousextractoftheplantClitoriaternateaatdosesof 50 mg/kg and 100 mg/kg. The durationofthetreatmentphase wasoneweek. The extractwascomparedto a controlgroupreceivingsalineorally.	The extract (100 mg/kg) wasfoundtobeeffectiveanditexhibitedactivitysimilartothatofthestanderddrug	Antidepressant
(Permatasarietal., 2022)	40 male albino Swiss	The lowdosegroup (SG-L) received 65 mg/kg bodyweightof KBPF, whilethehighdosegroup (SG-H) received 130 mg/kg bodyweightof KBPF. The othertwogroupsserved as controlgroupsanddid not receive KBPF.	KBPF at a doseof 65 mg/kg BW wasmoreeffective in increasing PGC-1α levels. The additionof KBPF tothe diet preventedanincrease in bodyweight in mice.	Anti-inflammatory Anti-obesity
(Sunartietal., 2023)	30 mouse	Normal controlwithouttreatment, negativecontrol (mouse given CMC-Na 0.5%), positivecontrol (Mouse	The 14th dayofanadvancedtrial in a positivecontrolgroupwithanethylacetatefractiongroupandan n-hexanefractionshowednosignific	Antiglucose Antidiabetic

Reference	Sample	Intervention (type, Dose, Duration)	Result	Potentialeffecton PCOS
		givenglibenclamide 0.09 mg/200gr BB rats), ratsgiven n-hexanefractionofethanolextractof CT flowers (400mg/KgBB), ratsreceivedethylacetatefractionfrom CT extracts (400 mg/K gBB), micereceived a waterfrationof etanol extractedfrom CT (400mgs/kgBB), 14 daysintervention.	antdifference, meaningthatthe n-heksanefractionsandtheethylacid fractiongroups had antidiabeticabilitiesthat were almostequivalenttothoseofglibenclamide.	

Potential of ClitoriaTernatea as a PCOS Insulin Sensitizer Agent

Clitoriaternatea has several mechanisms that can reduce glucose in the body. One such mechanism is through the inhibition of the formation of advanced glycation end products (AGEs), which are one of the main pathways leading to diabetes complications. Water extract and ethanol extracts have been shown in vitro to inhibit the formation of AGEs by reducing the protein carbonyl content and preventing the deployment of thiol protein(Indriyati et al., 2022). Clitoriaternatea has been shown to have potential in increasing insulin sensitivity. C. ternatea flower extracts contain active compounds that can enhance the expression of genes associated with insulin sensitivity, such as PPARɣ, Glut2, Tcf7l2, and Capn10, in addition, c. ternatea can also reduce hyper insulin-related inflammation by reducing the MCP1 gene expression. This mechanism helps improve the body's ability to use insulin and regulate blood glucose levels(Indriyati et al., 2022).

Flavonoid compounds in butterfly peas that can protect cells from hyperglycemic stress. Flavonoids can prevent further decreases in NAD+ and NADH levels by inhibiting PARP-1 overactivation. In addition, flavonoids also have antioxidant properties that can reduce the adverse effects of oxidative stress. With this mechanism, c. ternatea can help lower blood glucose levels in rats with metabolic syndrome(Gunawan et al., 2023). Protein extracts from c. ternatea have been shown to have inhibitory activity against the α-amylase enzyme, which is responsible for digesting carbohydrates into glucose. By inhibiting the activity of these enzymes, c. ternatea can help reduce the absorption of glucose from food into the blood. C. ternatea has anti-inflammatoryassociated with insulin resistance andincrease the body's sensitivity to insulin(Minelko et al., 2020).

C. ternatea increase the expression of insulin protein in the pancreas, reduces the activity of the GSK-3b enzyme in the liver, which inhibits the conversion of glucose to glycogen, which helps keep blood glucose levels stableand potentially as a therapy for hyper insulin(Widowati et al., 2023). C. ternatea can increase the activity of antioxidant enzymes such as CAT and SOD, as well as reduce the level of MDA, which is a sign of oxidative stress, can also lower IL18 levels associated with inflammation(Widowati et al., 2023). Flavonoid compounds c. ternatea can protect the pancreatic cells from oxidative damage caused by Oxidative Stress, by protecting the pancreas cells, normal pancreas function in producing insulin(FaniTemarwut et al., 2023). C. ternatea significant decrease levels of diabetic enzymes (α-amylase, α-glucosidase, and xanthine oxidase) at levels in vitro and in vivo, increasing the activity of antioxidant defense enzymes such as SOD, GSH, and CAT, protect the body from oxidative stress associated with diabetes(Sa et al., 2023).

Clitoria extract ternatea had anti-diabetic effects in rats given high fat and fructose diets. CT extracts can increase insulin sensitivity and reduce insulin resistance caused by foods high in fat and fructose. In addition, CT extracts can also reduce blood glucose levels and improve blood lipid profiles by reducing free fatty acids, total cholesterol, and LDL levels. CT can increase levels of adiponectin, which is a hormone involved in regulating lipid metabolism and insulin sensitivity. Therefore, CT water extract can potentially reduce insulin resistance through improved lipid profile and increased adiponectin(Wang et al., 2022).The ethanol extract from the flower of Clitoriaternatea L. also has a

significant hypoglycemic effect, by lowering blood sugar levels in rats induced by alloxan(Ginting et al., 2022). The fractions of n-hexane, ethyl acetate, and water from clitoriaternatea have antidiabetic abilities that are almost equivalent to the synthetic drug glibenclamide. Clitoriaternatea fraction n-hexane have the potential as a natural ingredient that can be used in antidiabetic therapy with fewer side effects compared to synthetic drugs such as glibenclamide(Sunarti et al., 2023).

The bioactivity of the flower of Clitoriaternatea as an antiglucose and potential antidiabetic is exploited as a candidate drug for PCOS through insulin sensitivity mechanisms. The mechanism of insulin sensitizing aims to increase the sensitivity of body cells to insulin and reduce insulin resistance. By increasing the insulin sensitivity, the body can use existing insulin more efficiently, thereby reducing excess insulin production. Thus, the various negative effects of hyperinsulinemia on ovarian follicle development can be reduced or prevented. The use of this insulin sensitizing agent can help regulate glucose metabolism, reduce hyperinsulinemia, reduce excess androgen production, and thus, contribute to the development of normal ovarian follicles(Chappell et al., 2022).

Potential of ClitoriaTernatea as Anti-inflammatory in Low-Grade Chronic Inflammation of PCOS

Low-grade chronic inflammation is an inflammatory process that lasts over a long period of time with a low, but persistent rate of inflammasome reaction. Low-degree chronic inflammation can contribute to the development of diseases such as diabetes, heart disease, and obesity. Low-degree chronic inflammation can affect many aspects of this disorder, including hormone production, ovulation, insulin resistance, and ovary follicle development. In conditions of PCOS, body cells and ovary tissue can produce pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha. (TNF-alpha). These cytokines stimulate a sustained inflammatory reaction in the ovaries. Low-degree chronic inflammation can contribute to insulin resistance, which is one of the main characteristics of PCOS. Pro-inflammatory cytokines can inhibit normal insulin signal pathways, making the body cells less responsive to insulin, causing the body to produce more insulin to cope with high blood glucose levels, which further leads to hyperinsulinemia (Aboeldalyl et al., 2021).

Pro-inflammatory cytokines can affect the production of luteinizing hormone (LH) and follicle-stimulating hormones (FSH), which are important for ovulation regulation. As a result, ovulation becomes irregular or even does not occur at all. The ovary follicle is a structure that contains a mature egg cell. Inflammation can cause damage to the follicle cells and interfere with its development, it can lead to the formation of ovarian cysts, which is one of the characteristic features of PCOS. Low-degree chronic inflammation can also increase oxidative stress in the body. Oxidative stress occurs when the balance between free radical production and the body's antioxidant system is disrupted. Oxidative stress can damage ovarian cells and affect follicle development(Mohammadi, 2019).

MDA (malondialdehyde) is a lipid oxidation product that is formed when oxidative stress occurs in the body. Oxidative stress can cause inflammation, and MDA can play a role in the inflammatory process. MDA can damage cell membranes and activate immune responses, which can lead to chronic inflammation. Flavonoids and anthocyanin compounds can protect cells from oxidative damage and reduce the production of free radicals, it contributes to a decrease in the levels of MDA, which is an indicator of Oxidative Damage in the body. The antioxidant content in the flower of ClitoriaTernatea can affect glucose metabolism and reduce oxidative damage, which can contribute to weight gain. C ternatea extract can reduce inflammation by inhibiting the production of inflammatory mediators and reducing the activity of pro-inflammatory enzymes(Putri et al., 2022; Sa et al., 2023; Widowati et al., 2023).

Antioxidants play an important role in fighting inflammation in the body. The main mechanism involves the capture of free radicals that can lead to damage to cells and tissues, by neutralizing free radicals, antioxidants help reduce inflammation and prevent further damage. In addition, antioxidants can also inhibit the production of inflammatory molecules such as cytokines and prostaglandins, which can exacerbate inflammation. The antioxidants can protect the reproductive system from oxidative damage caused by endocrine disruptive compounds such as BPA. It can increase the percentage of pregnancies and the size of litter in experimental animals. Although there are no visible histopathological changes, can also reduce the ratio of uterine weight to body weight, which is an indicator of protection against the negative effects of BPA on reproduction (Goh et al., 2021).

C. ternateawith a high-fat (HF) diet, increase plasma antioxidant capacity by increasing the activity of the enzyme glutathione peroxidase (Gpx) and maintain plasma protein thiol levels, protect antioxidant enzymes from oxidative damage and reduce inflammation associated with high-fat diets(Thilavech et al., 2021). C. ternatea increases the levels of anti-inflammatory cytokines IL-4 and IL-10 in rat plasma, as well as decreases the production of pro- inflammatory cytokines, can help in reducing the risk of metabolic syndrome and insulin resistance associated with obesity (Gunawan et al., 2023). The mechanism of c. ternatea in inflammation involves pressure against Ang II/Nox4/oxidative stress cascade, can reduce Ang II levels and suppress Nox4 expression, which in turn reduces oxidative stress(Saengnak et al., 2021).

C. ternatea inhibits the activation of the nuclear transcription factor kappa B (NF-κB), which is one of the main mechanisms in inflammation, reduce the rate of tumor necrosis factor-alpha (TNF-α), which is an inflammatory mediator, thuscan reduce inflammation through inhibition of NF-κB and decrease of TNF -α (Maneesai et al., 2021). Combination c. ternatea and mesenchymal stem cells (MSCs) can rearrange the expression profile of the IL-6, IL-1β, and caspase-3 genes involved in the inflammatory response (Safhi et al., 2022). MSCs also have the effect of paracrine that can inhibit inflammatory responses(Swathi et al., 2021).

Obesity is a major risk factor for developing hypercholesterolemia. Excess weight and excess body fat can lead to increased production and accumulation of cholesterol in the body. In addition, obesity can also cause chronic inflammation that can affect lipid metabolism. Inflammation can also play a role in the development of hypercholesterolemia(Perovic Blagojevic et al., 2022). Chronic inflammatory processes can damage the walls of blood vessels and trigger the formation of atherosclerosis plaque, which in turn can increase the risk of heart disease and stroke(Shaaban et al., 2019). C. ternatea contains flavonoid compounds, alkaloids, saponins, and tannins that have antioxidant effects. These compounds can protect cells from damage from oxidative stress and reduce cholesterol synthesis by inhibiting the enzyme HMG-CoA reductase, can inhibit inflammation by reducing the production of pro-inflammatory cytokines and relieving excessive immune responses(Hakam Maulidy et al., 2022).

High LDL (Low-Density Lipoprotein) cholesterol in the blood can be oxidized. This oxidative cholesterol can cause the activation of macrophage cells, the immune cells that play a role in responding to inflammation. The activation of these macrophages can lead to the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and factor-alpha necrosis tumors (TNF-alpha), which stimulate low-degree chronic inflammation. High LDL cholesterol can damage endothelial function and reduce the production of anti-inflammatory molecules, such as nitric oxide (NO). This decrease in endothelial function can lead to an increase in chronic inflammation. High LDL cholesterol can contribute to oxidative stress, which is an imbalance between the production of free radicals and the body's antioxidant system. Oxidative stress can damage cells and tissues, as well as stimulate chronic inflammation(Rudnicka et al., 2021). The flavonoids found in eggplant flowers play an important role in lowering blood cholesterol levels. These flavonoid compounds can protect damaged arterial vessels and eliminate cholesterol accumulated on the surface of blood endothelial arteries. In addition, flavonoids can also enhance the synthesis of bile acid that requires cholesterol as a raw material, thereby helping to lower total cholesterol levelsand prevent inflammation(PratiwiIrawan et al., 2023).

In inflammatory conditions, such as PCOS, certain cells in the body, including macrophage cells and endothelial cells, produce IL-6 in response to inflammation stimuli. This release of IL-6 stimulates further inflammatory responses by attracting more inflammation cells and stimulating the production of other pro-inflammatory cytokines. IL-6 production by ovarian cells may increase due to hormonal imbalances and insulin resistance. Increased IL-6 in the ovaries can cause ovarian follicle development disruption and interfere with the ovulation process. IL-6 can affect insulin resistance by interfering with the insulin signal pathway. High levels of IL-6 can lead to worse insulin resistance, which is one of the main characteristics of PCOS. Insulin resistance contributes to low-degree chronic inflammation and plays a role in the development of PCOS symptoms and complications. IL-6 can also interact with sex hormones, including estrogen and androgen, which play a role in ovarian function regulation. Changes in sex hormone levels caused by PCOS can affect the production and response of IL-6 in the ovaries and other related tissues. Chronic inflammation and increased IL-6 can

affect the balance of reproductive hormones and ovarian function, it can affect ovulation and fertility in women with PCOS(Rudnicka et al., 2021).

The flavonoid and phenol content in the C. ternatea flower extract inhibits the cyclooxygenase enzyme, which helps prevent the inflammatory process by inhibiting the metabolism of arachidonic acid. This, in turn, reduces the formation of prostaglandins and significantly reduce IL-6 levels(Nadya Audina et al., 2023). The flavonoids in oatmeal are exogenous antioxidants that can protect cells from damage from oxidative stress. In addition, flavonoids can also inhibit LDL oxidation in vitro. In addition to flavonoids, the tannins contained in oatmeal flowers also have a positive effect on cholesterol levels. Tannins can reduce the oxidation of LDL cholesterol, as well as increase HDL, reduce body fat, and reduce the risk of cardiovascular disease(Arifah&Prabandari, 2022).

Potential of ClitoriaTernatea on The Dysbiosis Mechanism of Gut Microbiota (DOGMA) PCOS

Microorganisms in the digestive tract can affect hormone metabolism, including reproductive hormones such as estrogen. Estrogen plays an important role in ovarian follicle development. An imbalance in the production or metabolism of estrogen due to dysbiosis can affect the hormonal balance in the body and potentially affect the development of ovarian follicles. The gut microbiota affects the balance of the immune system. Inflammation caused by an improper immune response or a change in the balance of immune cells can affect the development of ovarian follicles(Liang et al., 2020).

Microorganisms in the digestive tract can produce a variety of metabolites, including short-chain fatty acids and long-chain fat acids. These metabolites can act as signals that affect the hormonal system and the development of ovarian follicles. The gut microbiota plays a role in synthesizing some vitamins and removing nutrients from the foods we consume. An imbalance of the intestinal microbiota can affect the availability of nutrients that are essential for the development of ovarian follicles(Liang et al., 2020).

The kombucha C.ternatea has a positive effect on intestinal microbiota dysbiosis. This kombucha contains bioactive compounds that can affect the intestinal microbial community, such as increasing the abundance of bacteria Blautia, Bacteroides, Parabacteroids, Pharscolarctobacterium, and Proteus. In addition, this kombucha can also improve lipid profiles, blood glucose, oxidative stress, metabolic enzymes, and inflammatory markers associated with metabolic syndrome. This mechanism is likely to involve interactions between bioactive compounds in kombucha with intestinal microbes and the body's immune system(Permatasari et al., 2022).

Potential of the ClitoriaTernatea on The Mechanisms of Psycho-Neuroimmunology

Psychological stress can affect the autonomic nervous system and spinal cord, which then affects the production of hormones by the adrenal glands, such as cortisol (hormone stress). High levels of cortisol due to chronic stress can affect the balance of sex hormones, including estrogen and androgen, which play a role in the development of ovarian follicles and can cause hormonal imbalances in the body. The immune system's response to psychological stress can also affect the development of PCOS. Increased inflammation caused by the activation of the immune system can contribute to insulin resistance and hormonal dysfunction associated with PCOS(Damone et al., 2019). Psychological stress can also affect eating behavior and lifestyle, such as poor diet and lack of physical activity. Unhealthy diet and unbalanced lifestyle habits can affect hormonal regulation and the immune system, as well as contribute to the development of PCOS and abnormal development of ovarian follicles(Xia & Du, 2022).

C. ternateareduce the standby time on both tests. The results of this study show that the antidepressant effect of Clitoriaternatea is mediated by increased levels of norepinephrine in the synapses, increasing the level of noradrenaline in the Synapse, which can contribute to the anti-depressive effect. C. ternatea also contains compounds such as flavonoids and triterpenoids that have antioxidant and anti-inflammatory effects. These compounds can play a role in reducing oxidative stress and inflammation, which can affect the nervous system, mentality, and immune system(Margret et al., 2019; Mittal et al., 2021).

Hepatoprotective in ClitoriaTernatea

Treatment for PCOS is often aimed at addressing symptoms and related health problems, such as hormonal imbalances, irregular menstrual cycles, and metabolic disorders. Regarding the long-term effects of such drugs on the liver (hepar), some of them may have side effects that affect liver health, especially if used for a long time or in high doses. Some drugs, such as spironolactone and metformin, can cause stress on the liver and cause inflammation or liver cell damage (hepatotoxicity), therefore, it is important to monitor liver function regularly during long-term use of the drug. Some medications can cause elevated levels of liver enzymes in the blood. If this increase is significant, it could be a sign of liver problems. Antiandrogenic drugs, have been associated with an increased risk of developing NAFLD in women with PCOS. NAFLD is a condition in which fat accumulates in the liver without being caused by alcohol consumption (Guan et al., 2020; Pedersen et al., 2018).

C. ternatea can reduce liver damage caused by CCl4 by reducing levels of SGPT, SGOT, ALP, and total bilirubin in the blood, can reduce kidney damage caused by cisplatin by reducing the levels of urea and creatinine in the blood. C.ternateacontains secondary metabolites such as flavonoids and anthocyanins, which act as antioxidants and can contribute electrons to stabilize free radicals that cause liver damage. In addition, flavonoids can interfere with oxidative reactions in cells, protect cells from oxidation stress, and increase the endogenous antioxidants of the body, thereby reducing the risk of liver damage. This hepatoprotective and nephroprotective activity(Pebiansyah et al., 2022).

4. CONCLUSION

Clitoriaternatea, has the potential as a potential drug candidate for PCOS. Clitoriaternatea flower extract has shown hepatoprotective and nephroprotective activity, which can help protect the liver and kidneys from damage caused by PCOS. In addition, the flower of Clitoriaternatea also has the potential to reduce insulin resistance and increase insulin sensitivity, which is a major problem in hyperandrogenPCOS. By understanding the potential of Clitoriaternatea as a potential cure for PCOS, we can develop more effective and natural therapies to deal with the problem of PCOS and prevent its complications.

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