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THERAPEUTIC POTENTIAL OF INDONESIAN PLANT FOR POLYCYSTIC OVARY SYNDROME (PCOS): A NARATIVE REVIEW

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Abstract

Polycystic ovary syndrome (PCOS) is a very common, complex, and heterogeneous female endocrine disorder involving a combination of environmental and genetic factors. PCOS is defined by elevated androgen levels and an imbalance of the LH and FSH hormones, which results in anovulation, infertility, and irregular menstrual periods. PCOS is linked to a variety of endocrine and metabolic diseases, including obesity, hirsutism, acne, diabetes, and insulin resistance. Drug treatment for PCOS might have negative side effects, thus herbal therapy is regarded as a viable approach. Several studies have explored the use of herbs in the treatment of PCOS, but no one has specifically discussed Indonesian plants, which have historically been used for therapeutic purposes. This narrative review explores the therapeutic potential of Indonesian herbal plants in the management and treatment of PCOS, in addition to how chemicals found in Indonesian plants may influence PCOS risk factors such as obesity, insulin resistance, glucose intolerance, and dyslipidaemia. This review uses a literature search, with the method of collecting library data through searching several databases with the keywords: “PCOS, herbal therapy, clinical therapy and potential therapy for insulin resistance and the reproductive system”, in the period 2013 - 2023. Various studies show that drugs herbal medicines play a role in changing lipid and hormone profiles, increasing insulin sensitivity and blood glucose levels, and enhance ovarian tissue health through increasing gene and receptor expression, increasing and inhibiting the action of related enzymes. The herbal plant that has been most studied both in vivo, in vitro and in human trials is cinnamon. However, there are plenty more Indonesian plants that have the potential to treat PCOS. The emphasis is on the need for comprehensive research to determine the safety and efficacy of plant-based treatments in Indonesia, through pharmacokinetic, pharmacodynamic, bioavailability and toxicity studies to obtain complementary herbal medicines for conventional pharmaceutical therapy for PCOS that are more holistic, thereby potentially enhancing their quality of life and mitigating the occurrence of comorbid conditions.

Keywords: PCOS, Indonesia Plants, Insulin Resistance, Herbal Medicines.

INTRODUCTION

Polycystic ovary syndrome is a hormonal imbalance characterized by elevated male hormone levels in women of reproductive age. It is linked to a spectrum of clinical manifestations including sporadic periods, fertility difficulties, excessive hair growth, hirsutism, increased resistance to insulin, acne, weight gain, and the development of numerous cysts on the ovaries [1]. PCOS impacts women globally from the beginning to the end of their reproductive years, with the prevalence differing across races and ethnicities. It is more commonly observed in South Asian women compared to Caucasians. The proportion of Asian women with PCOS (52%) is significantly higher than that of Western Caucasian women (20%-25%). The World Health Organization reported that in 2012, PCOS affected 116 million women worldwide, which is between

4% to 12% of the female population. By 2020, the prevalence had sharply risen to 26%.[2]. Changes in neuroendocrine function, steroidogenesis, ovarian folliculogenesis, metabolism, insulin production and insulin resistance are potential factors involved in the etiology of PCOS. PCOS is also linked to several types of cancer, including ovarian cancer and cervical cancer. PCOS is also categorized as an endocrine dysfunction, because it can cause type II diabetes, obesity, ovarian cancer, abnormal uterine bleeding, high cholesterol levels, and cardiovascular abnormality [3].

Imbalances of several hormones also play a role in PCOS, such as gonadotropin release hormone (GnRH), insulin, LH and FSH ratio, androgen, estrogen, parathyroid hormone (PTH), growth hormone (GH), cortisol, calcitonin, and all these hormones are involved in bone metabolism and its imbalance can promote osteoporosis. Therefore this syndrome has relevance to bone function abnormalities [3, 4]. Excessive secretion of adrenal precursor androgens has been demonstrated in PCOS women [5]. It is possible that hyperandrogenism may have a significant pathological influence on the onset of severe endocrine and metabolic disorders linked to Polycystic Ovary Syndrome (PCOS). Sex hormone-binding globulin (SHBG) is a glycoprotein known for its ability to modulate the availability of sex steroid hormones, and there exists a relationship between SHBG levels and the susceptibility to polycystic ovary syndrome (PCOS). Women with polycystic ovary syndrome (PCOS) who have reduced sex hormone-binding globulin (SHBG) levels exhibit a higher susceptibility to various health issues including excess androgen levels, type 2 diabetes, insulin resistance, impaired glucose tolerance, obesity, infertility, and cardiovascular disease (CVD)[6] due to the presence of insulin resistance [7]. PCOS is categorized into three distinct phenotypes: Classic PCOS comprising Phenotypes A and B, Ovulatory PCOS as represented by Phenotype C, and Nonhyperandrogenic PCOS denoted by Phenotype D [8]. Individualized treatment plans should be designed based on the unique characteristics and preferences of each patient, including factors like their specific phenotype and goals regarding fertility. [9].

Several treatment options have been utilized for patients with polycystic ovary syndrome (PCOS), including lifestyle modification, induction of ovulation, high testosterone therapy, insulin sensitizers, supplementation with myoinositol, folic acid, and vitamin D, assisted reproductive technology therapy, and surgical interventions. The primary therapeutic approach for managing insulin resistance and glucose intolerance in women diagnosed with Polycystic Ovary Syndrome (PCOS) is utilizing the medication metformin [7, 11, 12]. However, research findings indicate that pioglitazone may offer superior benefits in terms of enhancing menstrual regularity and promoting ovulation in individuals with PCOS when compared to metformin. [13]. Clomiphene Citrate (CC), a non-steroidal selective estrogen receptor modulator, is another pharmaceutical prescribed for inducing ovulation. Despite its efficacy in stimulating ovulation, the resulting pregnancy rate is considered inadequate. Several traditional therapies for PCOS only provide relief for the symptoms. Minimal side effects have been documented in relation to current drugs used to treat PCOS. However, there is a significantly increased risk of venous thromboembolism in patients with obesity, hypertension, and hypercholesterolemia who are undergoing PCOS treatment, with the risk ranging from three to six times higher(15). Hence, alternative herbal medicine is being recognized as a novel therapeutic approach for addressing this issue. The rise in popularity of herbal remedies can be attributed to the growing awareness of the adverse effects of pharmaceutical drugs [13, 14]. Herbal infusions

are a critical component in the management of Polycystic Ovary Syndrome (PCOS). The herbal infusion exhibits a steroidogenic effect and demonstrates the presence of estrogen receptor protein, decreases androgens levels, enhances glucose uptake, and ameliorates symptoms in individuals with polycystic ovary syndrome (PCOS) [16, 17]. Herbal medicine has been a longstanding tradition in Indonesia, where the use of medicinal plants has been passed down through generations as a method of addressing a range of health concerns. Indonesia is renowned for its exceptional variety of natural resources. Indonesia possesses jurisdiction over approximately 80% of the global plant species. National Geographic Indonesia (2019) reports that Indonesia's biodiversity on its mainland is ranked as second globally, behind only Brazil. Indonesia is home to a total of 31,750 identified plant species, with approximately 9,600 of these known to possess medicinal qualities. Regrettably, not all of the aforementioned have been utilized for medicinal purposes. Only a limited number of species, totaling 200, have been utilized as primary resources within the traditional medicine sector (18). The plant species found in Indonesia are diverse and have significant potential for serving as valuable sources of natural compounds that may offer effective solutions for individuals grappling with metabolic and endocrine-related ailments. Initial studies suggest that indigenous plants cultivated in Indonesia possess chemical elements that have the potential to enhance the functionality of both the reproductive and endocrine systems. Various herbs have been recognized as potential alternatives for the treatment of Polycystic Ovary Syndrome (PCOS). Certain herbs have been found to be effective in the treatment of Polycystic Ovary Syndrome (PCOS), including aloe vera, Cinnamon, Foeniculum vulgare (fennel), Licorice Root, turmeric (Curcuma longa) rhizome leaves, Mahogany leaves, and Moringa oleifera.

Nevertheless, despite the considerable natural resources present in Indonesia, the utilization of herbal remedies in the management of PCOS remains insufficiently acknowledged. This phenomenon could be attributed to the insufficient depth of scientific inquiry into these herbal remedies, in conjunction with the multifaceted mechanisms underlying polycystic ovary syndrome (PCOS) that necessitate thorough investigation across multiple systems. Hence, there is a need to analyze a range of research findings that demonstrate the effectiveness of herbal remedies in Indonesia for treating Polycystic Ovary Syndrome (PCOS). Previous reviews by several researchers have discussed the role of herbal plants in PCOS but to date no review has been found that discusses Indonesian plants that can play a role in treating PCOS. Therefore, this review was prepared for those who analyze the potential of Indonesian plants for PCOS considering that the benefits that can be obtained from the use of herbs are enormous, both from an economic perspective because of their low cost and from a health perspective because they contain nutritious substances that provide effects that can be used to overcome health problems. to society.

MATERIALS AND METHODS

This study utilizes a literature review approach to gather information from various academic databases such as PubMed, Science Direct, and Google Scholar, Frontiers, along with some other validated websites. The focus of the study is on original research and review articles related to the keywords PCOS, “herbal therapy, clinical therapy, potential therapy for insulin resistance, and the reproductive system”. Articles published between 2013 and 2023 that are readily accessible were included in the analysis. Following the retrieval of articles from the database based on specified

keywords, those that fail to meet the criteria are excluded. Subsequently, a filtering process is conducted to carefully analyze the complete content of the selected articles. Articles that do not share the same concept will not be analyzed in detail.

Sources of Active Compounds From Several Plants

Sources of active compounds from several plants that have benefits in treating PCOS can be seen in Table 1.

Table 1: Sources of Active Compounds from Various Plants and their Mechanisms

No	Plants	Active Compounds	Work Mechanism	Reference
1	Aloe vera (lidah buaya)	Fitosterol, sitosterol	alters steroidogenic response and expresses estrogen receptor protein, reduces androgens, increases estrogen, lowers serum cholesterol levels and normalizes 3βHSD (3β-Hydroxysteroid dehydrogenase) activity	Gholamalizadeh M, et al, 2018; Radha M, Padamnabhi N, Laxmipriya N., 2014
2	Cinnamomum/Cinnamon (Kayu Manis)	flavonoid dan polifenol	increases glycogen synthesis, increases insulin signaling at the post-receptor level increases Phosphoinositide 3 (PI3) kinase activity, increases glucose uptake via increased GLUT4 glucose transporter, inhibits glycogen hypoglycemic effect, possibly downregulates serum testosterone and insulin levels thereby reducing insulin-like growth factor -1 and increases the levels of insulin-like growth factor binding protein 1 (IGF) in plasma as well as in the ovaries in PCOS	Kort DH, Lobo RA, 2014; Borzoei A, Rafraf M, Asghari-Jafarabadi M, 2018; Dou L, Zheng Y, Li L, Gui X, Chen Y, Yu M, et al;2018
3	Foeniculum vulgare/ Fennel (Adas)	asam linoleat, asam palmitat dan asam oleat.	acts as an antiandrogenic by inhibiting the formation of the dihydrotestosterone receptor complex, increasing the activity of the aromatase enzyme so that it can reduce testosterone levels	Sadrefozalayi S et al, 2014; Karampoor P, et al, 2014; Fozalaee SS, Farokhi F 2015; Mokaberinejad R,et al, 2019.
4	Glycyrrhiza (Licorice/sweet root)	saponin, tanin, alkaloid dan steroid	inhibits 17-hydroxyl esterase activity, affects α5 and β5 reductase impairs 11β-hydroxysteroid dehydrogenase activity and increases aromatase activity (has) progesterron-like activity	Nazari S et al, 2017; Faghihi G et al, 2015; Yang H, et al, 2018
5	Curcuma/ Turmeric Rhizome (Kunyit)	curcumin	Increases PPAR-ɣ gene expression which has pleiotropic effects in improving insulin sensitivity, glucose homeostasis, and modulating gene expression. Increased GLUT4 and ERα gene expression. Decreased cholesterol biosynthesis via downregulation of HMG-CoA reductase and increased cholesterol clearance by stimulating bile secretion. The phytoestrogen effect of curcumin increases the secretion of the hormones estrogen and progesterone.	Jamilian M, et al, 2020;
6	Swietenia /	Flavonoid, sterol,	Inhibition of enzymes (α-glucosidase, α-amylase), glycogen phosphorylase and	Hasibuan et al, 2020;

	Mahogany (Mahoni)	terpen, Katechin, Saponin, Berberin, Limonoid	glucose 6-phosphatase, Activation of Acetyl CoA, inhibits lipid peroxidation, stimulates insulin secretion, β cell function, regeneration of protective cells, activates AMPK, Increasing the expression level of GLUT4 transporter, inhibition of glycogen phosphorylase and glucose 6-phosphatase. Acting as phytoestrogens—which are structurally similar to the estrogen hormone estradiol and can bind to both estrogen receptors alpha and beta, their estrogen-like structure are able to counteract estrogen deficiency	Sukardiman, Martha Ervina, 2020 (46)
7	Moringa leaves (Daun Kelor)	quercetin	Decreases CYP17A1 gene expression in theca cells which may be responsible for decreasing 17a-hydroxylase activation, reducing FIS levels, FBG levels, HOMA-IR, cholesterol levels, TG levels, T levels, LH levels, LH/FSH ratio, VEGF levels and MDA in women with PCOS and increased SOD levels and GLUT4 mRNA expression.	Wang, Z.;et al, 2017; Shah, K.N.; Patel, S.S, 2016; Rosenfield RL, Ehrmann DA, 2016
8	Laportea/ Nettle (Jelatang)	polyphenols, triterpens, sterols, flavonoids, and lectin	increase of NO, inhibition of α-amylase and α-glycosidase, modulation of GLUT4 and protection of pancreatic β-cells, inhibit the binding of androgens to the SHBG (Sex Hormone Binding Globulin) transporter protein, reduces estrogen synthesis and conversion of androgens to estrogens through blocking aromatase	Bhusal KK et al. 2022; Bhusal KK et al, 2022; El Haouari M, Rosado JA, 2019
9	Andrographis (Sambiloto)	Flavonoid, lactones andrographolide, saponins and tanin	Acts as a diuretic resulting in lower blood sugar levels, decreasing androgen levels, makes the aromatization process of the androgen hormone converted into estrogen, increases expression of β estrogen receptors. Phytoestrogens contained in Sambiloto cause anti-estrogenic effects when high estrogen concentration senvironment, and vice versa cause estrogenic effects when low estrogen concentration senvironment. This estrogenic effect can result decreasing androgens.	Rahayu H.K, 2021

Clinical and Preclinical Evidence

1. Aloe Vera (Lidah Buaya)

Aloe vera is recognized for its medicinal properties, including hypoglycemic effects, due to its rich fiber content which promotes gastrointestinal transit, absorption, and influences hemostasis. Additionally, aloe vera possesses numerous compounds with varying potential biological activities. The presence of phytosterols in aloe vera can alter the steroidogenic response by influencing the expression of estrogen receptor proteins. This can lead to a decrease in androgens, an increase in estrogen levels, and ultimately result in improvements in the symptoms associated with polycystic ovary syndrome (PCOS). Aloe vera phytosterols, including sitosterol, were found to decrease serum cholesterol levels and restore 3βHSD (3β-Hydroxysteroid dehydrogenase) activity in mice with polycystic ovary syndrome (PCOS) [22,23].

Radha et al. conducted a study to see how aloe vera gel affected mice with PCOS. In this study, mice in each group were given different doses of aloe vera (5 mg/kg, 10 mg/kg, and 15 mg/kg) for 60 days, and it was discovered that aloe vera might increase glucose tolerance in a dose-dependent manner. High-dose aloe vera treatment reduces atretic follicles and activates 3βHSD and 17β-Hydroxysteroid dehydrogenase (17βHSD). In all groups, serum insulin levels and insulin resistance decreased significantly, while dosages of 10 and 15 mg significantly reduced testosterone levels [22,23]. From 45-day clinical experiment in mice found that 1 ml of aloe vera gel improved insulin sensitivity, 3βHSD activity, and 17βHSD activity without affecting biomarker enzymes[18]. Several studies report that aloe vera can reduce atretic follicles, and improve glucose intolerance and lipid metabolizing enzyme activity, reduce triglyceride (TG) and low-density lipoprotein (LDL-C) levels [22,23]. Faisal [20] found a significant decrease in plasma glucose, insulin, and TG to high-density lipoprotein (HDL) ratio with oral aloe vera treatment in rats. Aloe vera is an insulin sensitizer that affects pancreatic beta cells [21).

Figure 1: Aloe Vera

2. Cinnamomum/Cinnamon (Kayu Manis)

Cinnamon is a botanical species categorized as an herbaceous plant within the Lauraceae plant family. Numerous studies have been documented. It has been observed that cinnamon has the ability to enhance the sensitivity of insulin. Cinnamon is comprised of a range of flavonoids and polyphenols that exhibit properties of scavenging free radicals and functioning as antioxidants. [24]. Several studies reported that Type-A polymers and their synthesis, as well as increasing the synthesis of glycogen and polyphenol procyanidin in cinnamon extract increased insulin signaling at the post-receptor level increased Phosphoinositide 3 (PI3) kinase activity, increased glucose absorption through increased GLUT4 glucose transporter, inhibited glycogen hypoglycemic effect [24, 25].

Research conducted by Wang and colleagues. Examined the impact of cinnamon extract on insulin resistance among individuals diagnosed with Polycystic Ovary Syndrome (PCOS). Within this research project, participants in the control group were provided with three meals a day alongside one placebo capsule per meal, while those in the intervention group were administered capsules containing 333 mg of cinnamon extract three times daily. The intervention group experienced significant reductions in fasting blood sugar (FBS) and insulin resistance. Cinnamon improved insulin sensitivity and reduced oral glucose tolerance tests in this study [24]. In a study conducted by Kort and associates, participants in the test group were given 1.5 grams of cinnamon supplements daily for half a year, while the control group was given a

placebo. The study noted regular menstrual cycles in those taking cinnamon, indicating normal progesterone secretion during their menstrual cycle's luteal phase. However, there was no significant difference in androgen levels or insulin resistance when compared to the control group (24). Additionally, Borzoei and colleagues found that consuming 500 mg of cinnamon for three days a week over a period of eight weeks resulted in improved fasting blood sugar, insulin levels, and total cholesterol in patients with Polycystic Ovary Syndrome. [25]. A study involving 66 women with Polycystic Ovary Syndrome divided participants into two groups; the experimental group received capsules of cinnamon powder totaling 1.5 grams per day in three separate doses for three months, while the control group was given a placebo. The findings suggested that cinnamon markedly decreased insulin resistance and fasting insulin levels in women with PCOS. Further research indicated that a group treated with metformin exhibited lower levels of anti-Müllerian hormone, which is related to PCOS and diminishes follicular responsiveness to Follicle-Stimulating Hormone, in comparison to the group receiving cinnamon [26].

Nonetheless, the group receiving metformin experienced a higher incidence of side effects than those taking cinnamon. Supplementation with ginger and cinnamon was associated with elevated levels of antioxidant enzymes, including catalase, glutathione peroxidase, and superoxide dismutase (28). Dou and colleagues noted that cinnamon supplementation was beneficial in reducing insulin resistance and enhancing the overall health condition of individuals with Polycystic Ovary Syndrome [29]. Cinnamon might work to lower serum testosterone and insulin amounts, which could lead to a decrease in insulin-like growth factor-1 and a rise in insulin-like growth factor-binding protein 1 levels within both the blood and ovaries of those with PCOS. This suggests that cinnamon could be a promising treatment option for Polycystic Ovary Syndrome [29].

Figure 2: Cinnamon

3. Foeniculum vulgare/Fennel (Adas)

Fennel, scientifically known as Foeniculum vulgare, is traditionally used to address hormonal and metabolic imbalances in women suffering from polycystic ovary syndrome. Recognized for its phytoestrogenic properties, fennel also offers defense against oxidative damage (30). It's noted for its antimicrobial and antioxidative actions derived from its essential oil (30, 31).

Chemical analysis reveals that fennel's primary constituents are linoleic, palmitic, and oleic acids. Specifically, the beta-oxidation of palmitic acid is known for its anti-androgenic action, which includes the inhibition of dihydrotestosterone receptor complex formation and the reduction of testosterone. Fennel has been observed to promote the activity of aromatase enzymes, leading to lower testosterone levels (30).

With prolonged use, fennel can impact the luteinizing hormone and testosterone, potentially restoring natural menstrual cycles in PCOS sufferers through negative feedback mechanisms. It's been found that a significant dose of fennel administered in animal studies can raise follicle-stimulating hormone levels while reducing testosterone and LH levels (31). Additionally, fennel has been reported to lower progesterone levels at modest doses and, comparable to metformin, it can shorten the interval between menstrual cycles as well as alleviate pain associated with dysmenorrhea in those with PCOS (32, 33).

Figure 3: Foeniculum vulgare/Fennel (Adas)

4. Glycyrrhiza (Licorice/sweet root)

Licorice is believed to act similarly to estrogen and might mildly obstruct the body's own hormone metabolism (34). It inhibits certain enzymes involved in hormone processing and is used to manage menopausal symptoms due to its estrogen-mimicking effects. It can also address excessive hair growth by impacting the enzymatic cycle of melatonin production and possibly curtailing tyrosinase activity. Furthermore, licorice may diminish hormone levels in the bloodstream by disrupting 11β-hydroxysteroid dehydrogenase function while promoting activities similar to aromatase or progesterone (34, 35). A study by Faghihi and colleagues observed that combining licorice gel with laser treatments was substantially more beneficial than laser treatment by itself (35). Another research indicated that licorice along with spironolactone lessened the renin-angiotensin system's activity without altering blood pressure in subjects. Additionally, Yang and collaborators discovered that licorice extract mitigated symptoms of PCOS by regulating serum FSH levels, the LH/FSH ratio, and abnormal ovarian follicles [36].

Figure 4: Glycyrrhiza (Licorice/sweet root)

5. Curcuma/Turmeric Rhizome (Kunyit)

The use of curcumin has been found to help improve various metabolic issues in patients with polycystic ovary syndrome (37). The connection between curcumin and better glycemic control is explained by several molecular mechanisms. Curcumin may lower levels of lipids and glucose in the blood by boosting the expression of the PPAR-γ gene, which enhances insulin sensitivity, controls blood sugar balance, and influences the expression of genes essential for fat and glucose metabolism, ultimately leading to better insulin secretion and lipid stability (38). Curcumin could also enhance insulin release from beta cells in response to glucose in a concentration-dependent manner, and it may promote glucose absorption by stimulating the phosphorylation of AMP-activated protein kinase. Furthermore, it might reduce glucose production in the liver, which in turn decreases glycogen breakdown (glycogenolysis) and new glucose creation (gluconeogenesis) (39). Preclinical studies have revealed significant metabolic improvements in PCOS mice models treated with different doses of curcumin, showing its positive impact on metabolic markers. Curcumin administration in these models led to lowered fasting plasma glucose, fasting insulin, HOMA-IR, and an elevation in QUICKI, potentially due to the upregulation of GLUT4 and ERα gene expression, which enhances insulin resistance and normalizes the glycemic index (40). Additionally, curcumin can significantly lower serum lipid levels by decreasing cholesterol synthesis via the suppression of HMG-CoA reductase and by promoting cholesterol elimination through increased bile production. The phytoestrogen properties of curcumin may also elevate levels of sex hormones such as estrogen and progesterone, leading to an increase in ovulation, as evidenced by the presence of oocytes in ovary histological examinations (41, 42).

Figure 5: Curcuma

6. Swietenia /Mahogany (Mahoni)

Mahogany seeds have demonstrated capabilities in regenerating beta cells and lessening insulin resistance owing to their richness in secondary metabolites like flavonoids, glycosides, and saponins (43). Flavonoids are one of these metabolites, acting as phytoestrogens—which are structurally similar to the estrogen hormone estradiol and can bind to both estrogen receptors alpha and beta (44). Research has identified the presence of flavonoids such as isoflavones, which due to their estrogen-like structure are able to counteract estrogen deficiency. Administration of mahogany extract has been shown to encourage uterine growth, increase bone density, and promote mammary gland proliferation in ovariectomized mice (45). Furthermore, limonoids are recognized as hypoglycemic bioactive components. Specifically, limonoid compounds in the hexane extract of S. humilis have shown hypoglycemic effects, diminishing serum triglycerides and uric acid levels. These findings point to potential mechanisms like insulin sensitization, glycogen synthesis activation, reduction of abdominal fat, as well as elevated glucose uptake by adipose tissue (48).

Figure 6: Mahogany

7. Moringa leaves (Daun Kelor)

The compound flavonol quercetin is present in elevated levels within the leaves of the Moringa oleifera plant. The predominant compound found in Moringa oleifera leaves is identified as quercetin 3, 3', 4', 5, 7-pentahydroxyflavone(51). Quercetin is a flavonoid possessing potent bioactive properties, including antioxidant, anti-inflammatory, anti-cancer, anti-hyperlipidemic, and antiplatelet activities. Studies have demonstrated that quercetin has the ability to inhibit PI3K. Quercetin, through its inhibition of the PI3K pathway, reduces the expression of the CYP17A1 gene in theca cells. This reduction in gene expression is believed to attenuate the activity of 17α-hydroxylase, a crucial enzyme in the pathogenesis of polycystic ovary syndrome (PCOS) [52]. Quercetin provides a range of beneficial effects on the multiple facets of polycystic ovary syndrome. In women with PCOS, quercetin has been shown to effectively lower fasting insulin and blood glucose levels, insulin resistance as measured by HOMA-IR, along with levels of cholesterol, triglycerides, testosterone (T), luteinizing hormone, and the ratio of LH to follicle-stimulating hormone. Additionally, it reduces vascular endothelial growth factor and malondialdehyde levels while increasing superoxide dismutase activity and the expression of the GLUT4 messenger RNA. The therapeutic impact of quercetin on PCOS operates through several biological pathways including metabolic aspects, as evidenced by changes in insulin, blood sugar, cholesterol, and TG levels; endocrine functions, indicated by alterations in hormones from the pituitary gland and ovaries; and on a molecular scale, it manages GLUT4 gene expression and oxidative stress. Lastly, quercetin influences the CYP17A1 gene, which produces cytochrome P450c17—a key enzyme in

androgen synthesis that operates as both a 17-hydroxylase and a 17, 20-lyase [54]. Quercetin has been found to affect androgen synthesis in granulosa cells by impacting cytochrome P450c17 activity, which is significant in the development of PCOS. It does so by managing this enzyme's action, inhibiting the phosphatidylinositide 3-kinase (PI3K) pathway, and suppressing the CYP17A1 gene (28). Such effects highlight quercetin's potential usefulness in treating disorders tied to excess androgens, especially within the context of PCOS (52).

Figure 7: Moringa leaves

8. Laportea/Nettle (Jelatang)

Nettle's chemical compounds offers a variety of health benefits for women, including the ability to treat unpleasant premenstrual symptoms such as cramps and bloating, and also to reduce blood flow during menstruation. Nettle may ease the transition and act as a restorative remedy for women experiencing menopause, lowering the intensity of hormonal changes in the body(55). In sufferers of polycystic ovary syndrome, sex hormone binding globulin (SHBG) levels are very low and testosterone production is greater. Nettle is used to lower testosterone levels and increase SHBG production, thereby correcting hormonal imbalances in PCOS patients. The phytochemicals that cause these effects are found in the roots of the nettle plant. Long-term use of this plant may cause hypotension (56).

Several researchers say that lignans from nettle extract function to inhibit the binding of androgens to the SHBG (Sex Hormone Binding Globulin) transporter protein. Root extract reduces estrogen synthesis and conversion of androgens to estrogens through blocking aromatase (55). U. dioica contains compounds, such as polyphenols, triterpenes, sterols, flavonoids and lectins that reduce blood glucose levels by interfering with different cellular signaling pathways, among others, including increasing NO, inhibiting α-amylase and α-glycosidase, modulating GLUT4 and protecting pancreatic β cells. This can also reduce the condition of insulin resistance (57) In research conducted by previous researchers. Nettle has been established to provide an anti-androgen effect via inhibiting SHBG (58). In this trial, nettle was used to treat women with hyperandrogenism. According to research, this plant has the potential to impact sex hormones and androgen levels. As a result, it can lessen the effects or levels of these hormones in the body, helping to regulate and alleviate symptoms.

Figure 8: Laportea/Nettle (Jelatang)

9. Andrographis (Sambiloto)

Sambiloto (Andrographis paniculata Nees) contains andrographolide, a diterpenoid glycoside that can be utilized as a diuretic, analgesic, antipiretic, and antiulsergenic. In mice with diabetes induced by alloxan, sambiloto plant ethanol extract reduced blood glucose at a dose of 2.1 g / kg BW. Mice's estrus cycle pattern changed when treated with sambiloto extract therapy at different doses in groups of experimental animals. The alterations in mice's ovaries that follow the administration of sambiloto extract are tightly linked. The recurring process known as the estrus cycle denotes variations in the levels of reproductive hormones brought about by pituitary hormone-stimulated ovarian activity. Giving sambiloto extract has several benefits, including acting as a diuretic, which can lower blood insulin levels and prevent insulin resistance, which in turn lowers androgen levels. Decreased androgen levels cause the aromatization process of the androgen hormone to be converted into estrogen. As a result, folliculogenesis can occur, and mice will eventually experience a desire cycle. esearch conducted by Rahayu HK (2021), shows that the hyperandrogenous condition accompanied by insulin resistance after being given sambiloto extract for 15 days was able to change the hyperandrogenous condition which initially experienced a cessation of the estrous cycle (anestrus) to return to normal in experimental animals. This relates to the estrogen receptor, wherein the expression of the estrogen receptor increases with increasing doses of sambiloto extract (59).

Figure 9: Andrographis (Sambiloto)

CONCLUSION AND FUTURE PERSPECTIVE

Polycystic ovary syndrome is a disorder of the endocrine system that often attacks women during their fertile period. This is associated with various risk factors such as obesity, glucose intolerance, and abnormal lipid levels. Insulin resistance plays an important role in the mechanisms underlying PCOS. Several studies have examined herbs that show alternative treatment potential for treating PCOS. Various studies show that herbal medicines play a role in changing lipid and hormone profiles,

increasing insulin sensitivity and blood glucose levels, as well as impacting the health of ovarian tissue through increasing gene and receptor expression as well as increasing and inhibiting the action of related enzymes. The herbal plant that has been most studied both in vivo, in vitro and in human trials is cinnamon. However, there are still many other potential Indonesian plants that can overcome PCOS. The emphasis is on the need for comprehensive research to determine the effectiveness of herbal medicines in Indonesia safely and convincingly, through pharmacokinetic, pharmacodynamic, bioavailability and toxicity studies to obtain herbal medicines that are safe to use to treat PCOS. The effectiveness and safety of traditional medicines, especially Indonesian herbal ingredients, in treating PCOS is not yet fully known and requires broader and more thorough research in the future that could lead to better treatment plans, improve the quality of life for those affected by PCOS, and help prevent complications.

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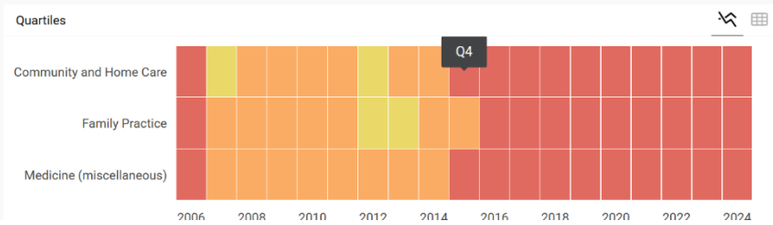

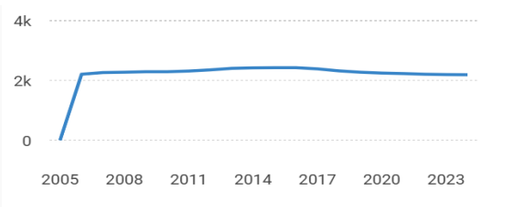

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