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THE EFFECTS OF CURCUMIN SUPPLEMENTATION ON GLYCAEMIC PROFILE IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME: AN EVIDENCE BASED CASE REPORT

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is the most common cause of infertility in the world. It is associated with impaired glucose tolerance and higher tendency to develop type 2 diabetes. Curcumin, which is known for its anti-inflammatory, antioxidant, and antidiabetic properties, may show promising effect in regulating blood glucose.
Objective: This study aims to evaluate the effect of curcumin supplementation on improving glycaemic profile in women with PCOS.
Methods: Literature searching was conducted by advanced searching in Pubmed, Cochrane Library, Scopus, and ProQuest database using MeSH Terms combined with Title/Abstract. After removing duplicates, the literatures were screened based on the eligibility criteria. Critical appraisal and level of evidence of the selected literatures were determined based on Oxford Centre for Evidence-Based Medicine.
Results: Two selected literatures were relevant to answer our clinical question. The first literature is a systematic review/meta-analysis study by Chien et al (2021) and the latter is a randomized controlled trial by Asan et al (2020). Both literatures show that curcumin supplementation is beneficial in improving glycaemic profile in PCOS patients. These effects were marked by lower fasting blood glucose, insulin level, and HOMA-IR in curcumin group compared to the control group. Curcumin supplementation for at least 6 weeks significantly improve glycaemic profile in women with PCOS.
Conclusion: Curcumin supplementation ranging from 93,42 mg to 500 mg until 1500 mg per day orally for at least 6 weeks significantly improve glycaemic profile in women with PCOS. It is also considered safe and well tolerable. However, more studies are needed to investigate further regarding the long-term effects of curcumin supplementation.

Clinical Scenario

A 26-year-old, unmarried woman was referred by her obstetrician and gynecologist (OBGYN) to the clinical nutrition physician. She was diagnosed with polycystic ovarian syndrome (PCOS). She had been struggling with her irregular menstrual cycle for years, along with acne breakouts and weight gain. All vital signs and general examination were within normal limits. Her current body mass index was 27.8 kg/m^2. Based on the laboratory examination, her fasting blood the glucose was 108 mg/dL and the HbA1C was 5.6%.

She refused to consume any medication from her OBGYN as she read on the internet that healthy lifestyle, especially eating unprocessed food, was the most essential in PCOS treatment. Then she asked about the beneficial effect of curcumin for PCOS patients like her, because she also got an information from her relatives that consuming curcumin would help to regulate her menstrual cycle and blood glucose.

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Introduction

Polycystic ovarian syndrome (PCOS) is one of the most prevalent disorders that affects 4% to 21% women of reproductive age and contributes to 70–80% of infertility cases globally.[1,2] PCOS is characterized by chronic anovulation and excessive androgen secretion by ovarian and/or adrenal glands. This was due to many factors, one of them is insulin resistant-hyperinsulinemia.[3] Besides the reproductive disorders, PCOS is associated with other metabolic features, including impaired glucose tolerance, type 2 diabetes, cardiovascular disease, and cardiovascular risk factors like dyslipidemia. Approximately 50% of the PCOS patients develop these conditions and metabolic syndrome as well. Another hypothesis also found that oxidative stress and inflammation have roles in PCOS pathogenesis.[4] Even though some medications, like metformin, are used to treat PCOS, healthy lifestyle is the mainstay of PCOS management. Recent developments in PCOS management are concentrating on some nutraceuticals, especially curcumin.

Curcumin is an active phytochemical that derived naturally from turmeric or *Curcuma longa,* an herbal plant that widely used in Asia, including Indonesia, as spices and natural yellow colouring in food and herbal medicine, known as *jamu.* Curcumin exhibits antioxidant and anti-inflammatory properties. As an antioxidant, curcumin can increase the gene expression of superoxide dismutase (SOD) and glutathione peroxidase (GPx). Curcumin can also reduce the pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), IL2, IL-6, IL-8, and IL-12.[5] Curcumin also has antidiabetic effect by increasing glucose uptake, glycolysis, and glycogen synthesis in the skeletal muscle. Moreover, curcumin can also affect the liver to increase glycolysis and glycogen synthesis while decreasing gluconeogenesis.[2] Due to these promising effects, curcumin is expected to help improving PCOS complications and regulating blood glucose.

From previous studies, curcumin has been shown to improve fasting blood glucose in patients with metabolic syndrome. However, the effects of curcumin on glycaemic control and insulin resistance in PCOS patients remain inconclusive. This evidence-based case report aims to evaluate the effect of curcumin supplementation on PCOS patients' glycaemic profile.

Clinical Question

The clinical question is "in women with polycystic ovarian syndrome, could curcumin improve the patients' glycaemic profile?" From this question, we can state that the population is women with polycystic ovarian syndrome, the intervention is

curcumin supplementation, the comparison is placebo, and the outcome is glycaemic profile.

Methods

Searching Strategy

Literature searching was conducted by advanced searching using combination of both MeSH Terms and Title/Abstract in four databases: Pubmed, Cochrane Library, Scopus, and Proquest. Keywords that were used include *"Polycystic Ovarian Syndrome", "PCOS", "Stein Leventhal Syndrome", "Curcumin*", "Curcuma longa", "Turmeric", "Turmeric Yellow", "Placebo", "Glycaemic Profile", "Glycaemic Control"*. Authors used the guideline from Oxford Centre for Evidence-Based Medicine to critically appraise the literature and determine the level of evidence.

Eligibility Criteria

Some inclusion and exclusion criteria are set to select the suitable articles. The inclusion criteria are: 1) women diagnosed with PCOS; 2) patients received curcumin supplementation; 3) the study output was PCOS patients' glycaemic profile, including fasting blood glucose, glycated hemoglobin (HbA1C), HOMA-IR, or insulin resistance level; 4) the study design is randomized controlled trial or systematic review/meta-analysis of randomized controlled trials; 5) articles were published in English. The exclusion criteria are: 1) studies that were not conducted on humans; 2) the published article was not available in full text.

Results

The authors found 2 articles from Pubmed database, 3 articles from Cochrane Library, 4 articles from Scopus, and 1 article from ProQuest using searching strategy that shown in Table 1. Duplicated articles were removed first, then remaining articles were assessed for eligibility based on Population, Intervention, Comparison, and Outcomes (PICO) and eligibility criteria (Figure 1). We eventually selected 2 articles from Chien et al and Asan et al, whose details are shown in Table 2.[4,5] The level of evidence for each article is 1A and 2, respectively. Both articles were valid and relevant to answer our clinical question (Table 3, Table 4).

Discussion

One of the common complications related to PCOS is glucose tolerance impairment that eventually can lead to type 2 diabetes. Forslund et al found that women with PCOS develop type 2 diabetes more frequently than women without PCOS (19%, compared with 1% in control group).[6] Curcumin, which is known to have anti-inflammatory, antioxidant, and antidiabetic properties, has been proposed to be beneficial in regulating blood glucose in PCOS patients.

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Table 1. Literature Searching Strategy

Database	Search Strategy		Hits
Pubmed	("polycystic ovarian syndrome"[Title/Abstract] OR "polycystic ovary syndrome"[MeSH Terms] OR "PCOS"[Title/Abstract] OR "stein leventhal syndrome"[Title/Abstract]) AND ("curcumin"[MeSH Terms] OR "curcum*"[Title/Abstract] OR "curcuma longa"[Title/Abstract] OR "turmeric"[Title/Abstract]) AND ("placebo*"[Title/Abstract] OR "placebo*"[MeSH Terms]) AND ("glycaemic profile"[Title/Abstract] OR "glycaemic control"[MeSH Terms])		2
Cochrane	#1	("polycystic ovary syndrome"):ti,ab,kw (Word variations have been searched)	3
	#2	(PCOS):ti,ab,kw (Word variations have been searched)	
	#3	MeSH descriptor: [Polycystic Ovary Syndrome] explode all trees	
	#4	("Stein Leventhal syndrome"):ti,ab,kw (Word variations have been searched)	
	#5	#1 OR #2 OR #3 OR #4	
	#6	(curcumin):ti,ab,kw (Word variations have been searched)	
	#7	MeSH descriptor: [Curcumin] explode all trees	
	#8	(curcuma longa):ti,ab,kw (Word variations have been searched)	
	#9	MeSH descriptor: [Curcuma] explode all trees	
	#10	(turmeric):ti,ab,kw (Word variations have been searched)	
	#11	#6 OR #7 OR #8 OR #9 OR #10	
	#12	MeSH descriptor: [Placebos] explode all trees	
	#13	(placebo):ti,ab,kw (Word variations have been searched)	
	#14	#12 OR #13	
	#15	(glycaemic profile):ti,ab,kw (Word variations have been searched)	
	#16	MeSH descriptor: [Glycaemic Control] explode all trees	
	#17	#15 OR #16	
	#18	#5 AND #11 AND #14 AND #17	
Scopus	(TITLE-ABS-KEY(pcos) OR TITLE-ABS-KEY(polycystic AND ovarian AND syndrome) OR TITLE-ABS-KEY(stein AND leventhal AND syndrome)) AND (TITLE-ABS-KEY(curcum*) OR TITLE-ABS-KEY(curcuma AND longa) OR TITLE-ABS-KEY(turmeric)) AND TITLE-ABS-KEY(placebo) AND (TITLE-ABS-KEY(glycaemic AND control) OR TITLE-ABS-KEY(glycaemic AND profile))		4
ProQuest	(ti(Polycystic Ovary Syndrome) OR ti(PCOS) OR ti(stein leventhal syndrome)) AND (ti(Curcumin) OR ti(curcuma longa) OR ti(Turmeric)) AND (ti(placebo)) AND (ti(glycaemic control) OR ti(glycaemic profile))		1

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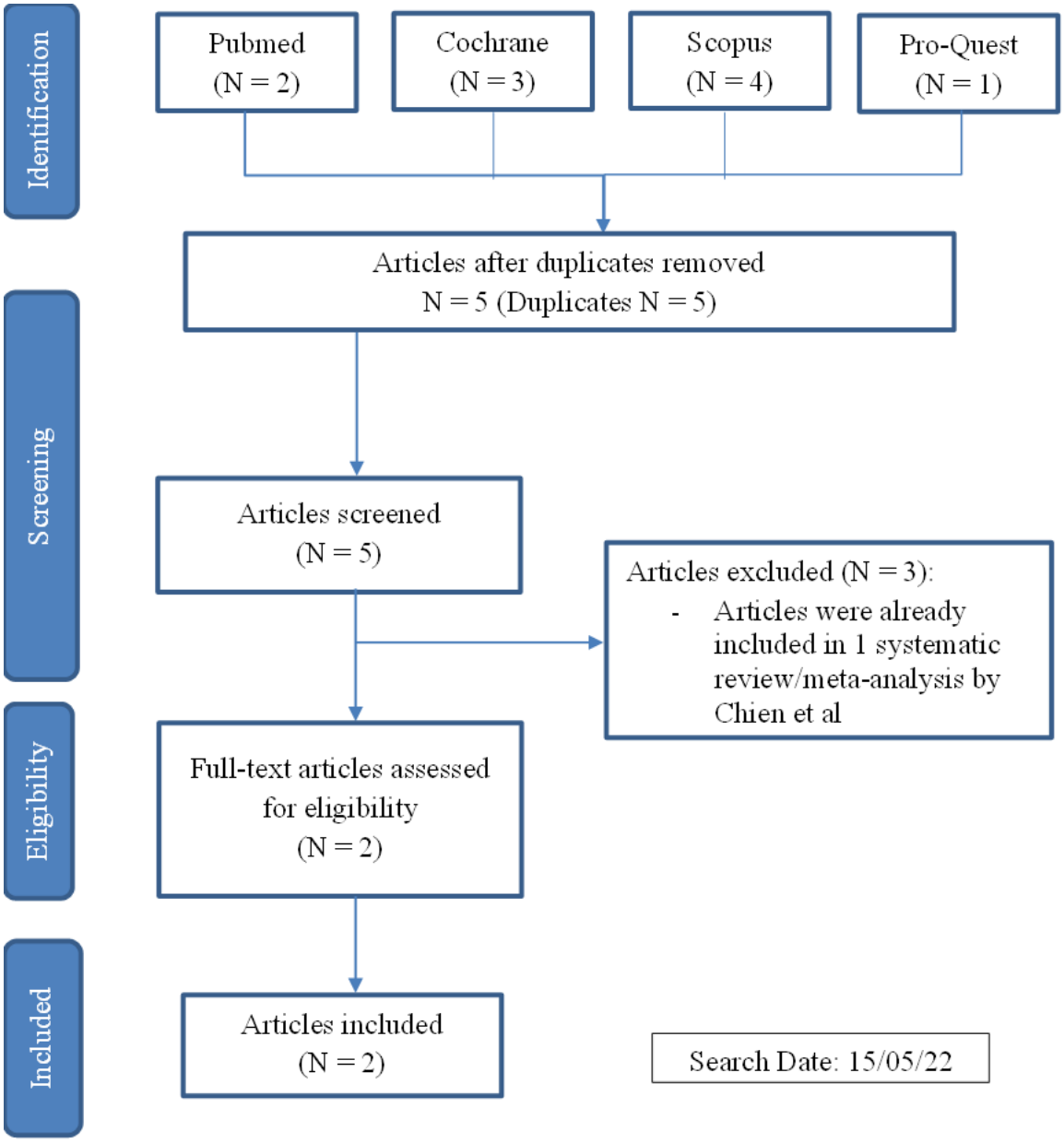

Figure 1. Prisma's Flow Chart

Table 2. Study Characteristic

Articles	Study Design	Population/Intervention	Outcome
Chien et al (2021)[5]	Systematic review/Meta-Analysis of Randomized Controlled Trials	Three studies involving 168 patients with PCOS, based on Rotterdam Criteria, were included. Intervention group received curcumin supplementation doses range from 1x500 mg/day – 3x500 mg/day for 6–12 weeks. Control group received placebo.	Glycaemic control, including fasting glucose, fasting insulin, HOMA-IR, QUICKI. Lipid profile, including HDL, LDL, and total cholesterol.
Asan et al (2020)[4]	Randomized Single-Blinded Controlled Trial	Thirty PCOS patients were randomly assigned to curcumin group (n=15) or placebo group (n=15). Curcumin group received 93.34 mg (2 capsules) of curcumin per day for 8 weeks. Despite that, each group received same diet intervention.	Anthropometric characteristics, such as: weight, body mass index, body fat, waist circumference. Serum biochemical levels, such as: fasting blood glucose, insulin level, HOMA-IR, total cholesterol, triglyceride, LDL, and HDL level.

From the literature research, two studies by Chien et al and Asan et al showed that curcumin supplementation significantly improved glycaemic profiles in PCOS patients, including fasting blood glucose, fasting insulin, and HOMA-IR biomarker.[4,5]

The study by Chien et al found that curcumin supplementation, whose doses ranged from 500 mg to 1500 mg per day for 6–12 weeks, is useful to lower the fasting glucose (MD: –2.77, 95% CI: –4.16 to –1.38; $p < 0.001$; $I^2 = 0\%$), fasting insulin (MD: –1.33, 95% CI: –2.18 to –0.49, $p = 0.002$, $I^2 = 0\%$), HOMA-IR (MD: –0.32, 95% CI: –0.52 to –0.12; $p = 0.002$, $I^2 = 0\%$), and improve QUICKI (MD: –0.32, 95% CI: –0.52 to –0.12; $p = 0.005$, $I^2 = 69\%$), compared to placebo.[5] Asan et al also found that compared to the control group, administration of oral curcumin supplementation as much as 93.34 mg for 8 weeks in PCOS women revealed a significant effect on anthropometric status and glycaemic profile, that was marked by fasting blood glucose level, fasting insulin, and HOMA-IR.[4] Both studies only used curcumin supplementation and compared it with placebo. Chien et al as well as Asan et al did not mention any history of hormonal therapy such as metformin in their participants.

Curcumin affects glycaemic profile by various mechanisms. Curcumin can increase glucose uptake by upregulating the translocation of glucose transporter (GLUT4)

Table 3. Validity Criteria for Chien et al

Article	Study Design	Question	Find	Appraise	Inclusion	Total Up	Heterogenity	Result	Applicability
Chien et al[5]	Systematic Review / Meta-Analysis of Randomized Controlled Trials	+	+	+	+	+	+	A	+

A = There are significant improvement of fasting glucose (MD: –2.77, 95% CI: –4.16 to –1.38; $p < 0.001$; $I^2 = 0\%$), fasting insulin (MD: –1.33, 95% CI: –2.18 to –0.49, $p = 0.002$; $I^2 = 0\%$); HOMA-IR (MD: –0.32, 95% CI: –0.52 to –0.12; $p = 0.002$; $I^2 = 0\%$), and QUICKI (MD: 0.010, 95% CI: 0.003–0.018; $p = 0.005$; $I^2 = 69\%$) in patients taking curcumin than those taking placebo.

Table 4. Validity Criteria for Asan et al

Article	Study Design	Randomisation	Similarity	Equally treated	Intention to treat analysis	Blinding	Result	Applicability
Asan et al[4]	Randomized Controlled Trials	?	+	+	+	Single-blind	B	+

B = Fasting blood glucose level decreased by 6.8 ± 3.8 mg/dL after intervention in curcumin group ($p < 0.05$) and 1.2 ± 3.5 mg/dL in placebo group ($p > 0.05$). Fasting plasma insulin and HOMA-IR decreased only in curcumin group ($p < 0.05$). There were significant differences in fasting blood glucose level, fasting insulin level, and HOMA-IR in curcumin group ($p < 0.05$).

to the membrane of adipocyte and skeletal muscle cells. This effect was mediated by stimulating the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and activating adenosine monophosphate-activated protein kinase (AMPK). This AMPK activation is also resulting in reduced hepatic glucose production and increased proliferator-activated receptor (PPAR) γ, which contributes to control the genes involved in glucose, lipid metabolism, and inflammatory response.[5,7,8] In addition to that, the anti-inflammatory and antioxidant properties of curcumin itself may also help in improving glucose metabolism. Curcumin's anti-inflammatory effect was mediated by inhibiting the induction of cyclooxygenase-2 and lipogeneses, which leads to suppression of prostaglandins. Moreover, curcumin also inhibit activation of TNF-α in the NF-kB pathway. Whereas as an antioxidant, curcumin can increase the activity of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase.[7,9]

Chien et al stated that PCOS patients are associated with higher oxidative stress and proinflammatory cytokines. Both will lead to insulin-resistant hyperinsulinemia, which contributes to an increase of luteinizing hormone by activating the cytochrome P450c17. High level of insulin and luteinizing hormone caused hyperandrogenism symptoms in PCOS patients.[5,9] Curcumin may play a role in improving hyperandrogenism by reducing cytochrome P450c17. This theory was successfully shown in a study by Heshmati et al, that administration of 1500 mg curcumin supplement per day for 12 weeks in patients with PCOS significantly reduced not only fasting blood glucose, but also dehydroepiandrosterone (DHEA), precursor of the androgens.[10] Moreover, curcumin is also considered safe, as Joint United Nations and World Health Organization Expert Committee on Food Additives recommended the daily intake of 0–3 mg/kg body weight of curcumin. Some clinical trials even show good tolerability and safety at doses from 4000 to 8000 mg/day.[9]

Both studies by Chien et al and Asan et al have strength and limitation. Some of the limitation in Chien's study: first, only a few studies are included in the meta-analysis. These studies also have different duration of curcumin intervention, ranging from 6–12 weeks. Second, studies included did not put thorough explanation regarding the preparation of the curcumin supplement formulation.[5] Curcumin is hydrophobic and has poor bioavailability, which is characterized by its poor absorption, rapid metabolism and elimination. In animal studies, oral administration of curcumin showed 40% excretion in rats' faeces. Therefore, various curcumin formulations are developed in order to prevent curcumin hydrolysis inactivation, such as nanocurcumin to increase its water solubility.[9] In contrast to Chien et al, Asan et al mentioned that they used a highly bioavailable formulation of curcumin. This was probably due to microemulsions formulation that increase curcumin solubility in duodenum.[4] Marked limitations in Asan's study are the small sample size and duration of the supplementation. Despite that, studies by Chien et al and Asan et al are valid to answer our clinical question. Chien et al show to us the effect of curcumin supplementation in improving glycaemic profile with a detailed forest plot, narrow confidence interval, and minimal heterogeneity. Furthermore, Asan et al also add new information about curcumin effects in improving anthropometrical status, such as lower the body weight, body fat mass, and waist circumference, compared to the placebo group ($p < 0.05$).[5,9] This effect was first studied by Asan et al during 8 weeks of

intervention. Effects of curcumin on anthropometrical and clinical status of PCOS patients are needed to be investigated further with longer duration. Curcumin is one of the nutraceuticals that could be recommended as an adjuvant therapy for women with PCOS, since PCOS women tend to have hyperglycaemia and higher risk to develop type 2 diabetes in later life.

Conclusions and Recommendation

Based on the critical review for both articles, it was found that curcumin supplementation, for at least 6 weeks of duration, could be considered in improving glycaemic profile in PCOS patients. We recommend taking the curcumin in a supplement form rather than consuming it from food or beverage, to ensure that we can get a proper dose to have the anti-inflammatory, antioxidant, and antidiabetic properties of curcumin. From both literatures, the recommended dosage for curcumin supplementation ranging from 93,42 mg to 500 until 1500 mg per day orally. Even though curcumin supplementation is well tolerable and considered safe in both studies, we still need more studies with longer duration and larger sample size to determine curcumin effects and possible side effects for at least a year. Curcumin effects on improving hyperandrogenism clinical symptoms may also be investigated later in the future.

Competing Interest

The authors declare that there are no competing interests related to the study

List Of Abbreviations

DHEA	: dehydroepiandrosterone
HbA1C	: glycated hemoglobin
HDL	: high-density lipoprotein
HOMA-IR	: Homeostatic Model Assessment Insulin Resistance
GLUT	: glucose transporter
GPx	: glutathione peroxidase
IL	: interleukin
LDL	: low-density lipoprotein
OBGYN	: Obstetrician and gynecologist
PCOS	: Polycystic Ovarian Syndrome
PPAR	: proliferator-activated receptor
QUICKI	: Quantitative Insulin Sensitivity Check Index
SOD	: superoxide dismutase
TNF-α	: tumor necrosis factor alpha

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