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REVIEW OF ADJUVANTS IN PCOS MANAGEMENT

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ABSTRACT

Background: PCOS (polycystic ovarian syndrome) is a multisystem condition that is common and affects 8–13% of women worldwide. The main pathogenic processes behind the development and course of this condition are unknown. Although there is currently no established cure for PCOS, symptoms are managed with lifestyle changes, menstrual cycle control, androgen reduction, and metabolic improvement. Resveratrol, Quercetin, and Curcumin are believed to have therapeutic benefits for PCOS. In order to find evidence-based information about Resveratrol, Quercetin, and Curcumin for PCOS, this meta-analysis was carried out.

Objective: To determine whether managing individuals who have polycystic ovary syndrome (PCOS) with resveratrol, quercetin, and curcumin improves the condition, despite the fact that the only proven treatments for PCOS are symptomatic measures like hormone medication, menstrual cycle management, lifestyle modification, androgen reduction and metabolic improvement.

Methods: This investigation used the PubMed and Google Scholar databases to find original research articles. The primary information source for this study was articles published between 2016 and 2024.

Results and Conclusions: A total of thirty-two studies were assessed as suitable for inclusion in the meta-analysis. Out of thirty-two research articles that were included, seventeen research articles dealt with human subjects and fifteen research articles with animal subjects. We investigated the pool of article's means and standard deviations. Resveratrol, quercetin, and curcumin may have positive therapeutic benefits in PCOS, according to the findings of these studies. As an instance, this meta-analysis additionally offers insights into the outcomes of each specified research article.

KEYWORDS: Resveratrol, Quercetin, Curcumin, PCOS, FSH, LH, Estrogen, Progesterone

INTRODUCTION

PCOS (polycystic ovarian syndrome) is a prevalent multisystem illness which impacts more than 8–13% of women globally. It causes abnormalities in reproduction, metabolism, and psychosocial functioning (1). PCOS affects more than 10% of women who are fertile, a prevalent endocrine illness It has been connected to an increased prevalence of cardiovascular risk factors such dyslipidaemia, hypertension, and insulin resistance, as well as metabolic syndrome and cardiovascular disorders (2). Numerous studies indicate that Metabolic dysfunction-associated steatotic liver disease (MASLD) a hepatic manifestation of the metabolic syndrome may also be more prevalent in PCOS-afflicted women. MASLD is a group of illnesses that progress cirrhosis eventually follows metabolic dysfunction-associated steato hepatitis (MASH) and simple steatosis. (1)(3). There is uncertainty on the primary pathogenic mechanisms that underlie the onset and progression of this illness (4). Patients with PCOS can be identified early using metabolic testing and ultrasound screening. Medical treatment for PCOS patients was developed, including hormone therapy, metformin, and oral contraceptive pills. However, due to side effects and ineffectiveness in certain cases, researchers are still looking for alternative, more successful treatment approaches (5). As of now, there is no proven treatment for PCOS; instead, symptomatic measures such as lifestyle modification, menstrual cycle management, androgen decrease, and metabolic improvement are employed. The most typical treatments for PCOS with ovulatory failure were combination short-acting oral contraceptives or second-half cycle progesterone; however, these treatments were prone to relapse following medication withdrawal and were unable to restore spontaneous ovulation in PCOS patients (6). Polyphenols are naturally occurring substances that have garnered interest recently as a PCOS treatment option with excellent treatment success and little negative effects. The most significant naturally occurring antioxidants in the human diet are thought to be polyphenols (7). Because of its apparent therapeutic potential in a variety of disease states, quercetin, resveratrol, and curcumin are being studied more and more (8-10). Flavonol quercetin is widely distributed and may be discovered in the majority of most terrestrial plants, foods, and nutritional supplements. It has been shown to have beneficial effects on immunological and inflammatory disorders, such as stress, cancer, asthma, and allergies, as well as cardiovascular disease (11). Natural sources of the stilbenoid resveratrol include Japanese knotweed (Fallopia japonica) and, additional notably, the red grape's skin (Vitis vinifera). Resveratrol has been shown to have anti-inflammatory, antioxidant, and anticarcinogenic properties (12). Lastly, curcumin, a naturally occurring phenolic molecule (diarylheptanoid) present in turmeric (Curcuma longa), is a thoroughly investigated inhibitor of IκBα kinase, a critical activator of nuclear factor κB (NF-κB). When this important mediator is inhibited in a variety of inflammatory disease states, such as tumerogenesis,

arthritic conditions, cardiovascular disorders, metabolism-related illnesses, and degeneration of neurons, curcumin becomes therapeutically active (13). By focusing on their pharmacodynamics and effects on different hormone levels and related symptoms, we conducted a meta-analysis of the data gathered to examine the advantages of resveratrol, quercetin, and curcumin for managing and treating PCOS. We pursued this threshold by carefully examining the relevant scientific literature.

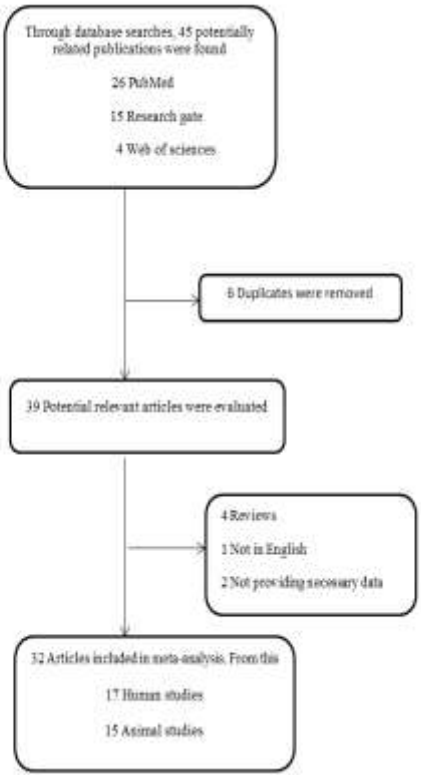

Figure 2: Schematic diagram of search flow

Table 1: Features of seventeen research projects on PCOS in humans

s.No	Author Name	Year	Study Type	Sample Size	Variable	Mean	Sd
1	Ardehjani, N. A.et al	2024	RCT	56	Resveratrol	3	33.4
2	Hashemi Taheri, A. P. et al	2021	RCT	41	Resveratrol	15.6	3.4
3	Sima Vaez et al.,	2022	RCT	72	Quercetin	15.19	1.96
4	N. Rezvan et al.,	2017	RCT	84	Quercetin	3.06	1.43
5	Rezvan, N et al.,	2018	RCT	84	Quercetin	21.1	4.24
6	Beata Banaszewska et al	2016	RCT	41	Resveratrol	12.17	1.59
7	Ghanbarzadeh-Ghashti et al	2023	RCT	54	Curcumin	13	22.004
8	Sabiha Ataç Asan et al.,	2020	RCT	30	Curcumin	54.43	27.45
9	A. MALVASI et al.,	2022	Pilot study	6	Curcumin	14.34	4.61
10	Tayebeh Zohrabi et al.,	2023	RCT	104	Curcumin	15.46	20.44
11	Ainehchi, N et al.,	2019	RCT	60	Quercetin	0.004	0.0001
					Curcumin	7.2	0.9
12	Jamilian, M et al.,	2020	RCT	60	Curcumin	-0.1	0.3
13	Khorshidi et al.,	2018	RCT	78	Quercetin	4.76	1.99
14	Bahramrezaie, M et al	2019	RCT	62	Resveratrol	303.9	120.8
15	Mendes da Silva, D et al.,	2017	RCT	44	Resveratrol	11.85	4.6
16	Mansour, A.,et al	2021	RCT	78	Resveratrol	-0.084	4.49
17	Brenjian, S et al.,	2020	RCT	40	Resveratrol	-1.23	2.59

(RCT-Randomized Control Trial)

Table 2: Features of fifteen studies on animal research in PCOS

s.No	Author Name	Year	Study Type	Sample Size	Variable	Mean	Sd
1	Sarwat Jahan et al.,	2018	a histological and a biochemical study	24	Quercetin	14.7	0.66

2	Furat Rencber et al.,	2018	ES	63	Resveratrol	33.4	2.65
3	Shah, M. Z. U. H et al.,	2023	ES	18	Quercetin	86.7	1.46
4	OMNIA E. MAAMOUN et al,	2022	ES	40	Quercetin	1.98	0.37
5	Zhang, Y et al.,	2021	ES	50	Curcumin	10.3	1.51
6	Raja, M. A et al.,	2021	ES	32	Curcumin	24	1.32
7	Mohammadi, S et al.,	2017	ES	72	Curcumin	305.4	8.51
8	P. Sushma Reddy et al.,	2016	ES	30	Curcumin	35.8	4.67
9	Shima Mohammadi et al.,	2017	ES	90	Curcumin	18.8	0.13
10	Suaad M. Abd-Alqade et al.,r	2023	ES	56	Curcumin	10.9	0.52
11	Nasiri Bari, Y et al.,	2021	ES	60	Curcumin	22.9	8.48
12	Amini et al	2018	ES	60	Curcumin	1.21	11.76
13	Maria Yarmolinskaya et al.,	2021	ES	24	Curcumin	488.9	78
14	Shah, K. N et al.,	2016	ES	12	Quercetin	8.46	0.22
15	Eman Aly Sadeek Fadlalla	2022	ES	32	Quercetin	12.5	0.18

(Es-Experimental Study)

METHODS

Search Strategy

For original papers from databases, this study searched the PubMed and Google Scholar databases. The current study's research technique was restricted to full-text publications written in English. To get pertinent literature to create a list of relevant variables, pursuit across it using Google Scholar. For this study, articles released from 2016 to 2024 were the primary source of information. The following research terminology were used: PCOS, or polycystic ovarian syndrome; quercetin, resveratrol, curcumin, TSH, and FSH.

Literature selection criteria

Articles that satisfied each of the subsequent inclusion constraints were listed:
(1) PCOS women enrolled in randomized controlled clinical trials treated with quercetin, resveratrol, and curcumin. (2) Research using animals to test quercetin, resveratrol, and curcumin for PCOS treatment has been included.
(3) the study used the Rotterdam criteria, the National Institutes of Health (NIH) criteria for PCOS diagnosis; (4) this reported means and standard deviations (SDs) or enough information about PCOS hormones to calculate its mean and SDs; (5) Articles which issued in full text edition in English and has featured. Articles that were published as case reports, expert comments, letters, reviews, abstracts, editor's opinions, or animal research were excluded.

Data extraction

The publications found in databases were filtered using the titles, abstracts, and keywords. To systematically collect relevant data from every trial, a pre-existing and consistent data extraction was done. This included information about the study's design, sample composition, study site, publication year, and indication of quercetin, resveratrol, and curcumin administered in PCOS participants, among other associated characteristics. It also disclosed the name of the first author. Data extraction was carried out from the qualifying articles following evaluation of the relevant ones. The data was stored in Microsoft Excel after collection.

RESULTS

Study selection

Figure 1 displays a flowchart with pertinent research articles categorized. 45 articles were found using Google Scholar and PubMed's electronic databases, according to the search strategy. Following the removal of duplicates (n = 6), reviewers went through the titles and abstracts and chose 39 papers. Of the 39 articles, 7 were disqualified due to the following reasons: Four reviews; two lacks the required information and one is not in English. Consequently, the eligibility of 32 complete papers was evaluated. 37 human studies and 15 animal studies were selected from a total of 32 articles.

Study characteristics

A total of thirty-two publications were deemed suitable for inclusion in the meta-analysis. On the thirty-two included research, seventeen articles focused on humans, and fifteen research articles focused on animals. In human investigations, seventeen research papers examined 994 women with PCOS. 15 publications in the field of animal studies examined 663 model rats.

Synthesis of Results

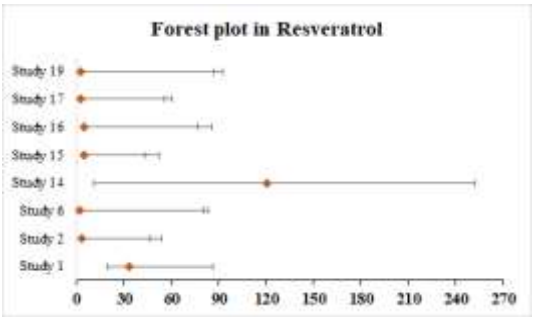

Figure 2: Resveratrol's Impact on PCOS in Human and Animal Research

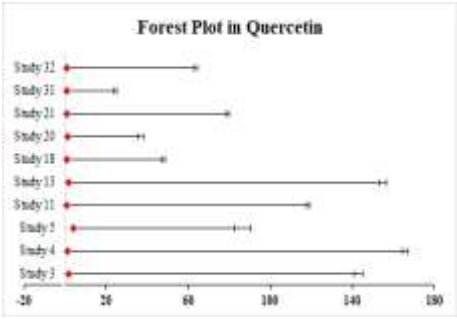

Figure 3: Quercetin's Impact on PCOS in Human and Animal Research

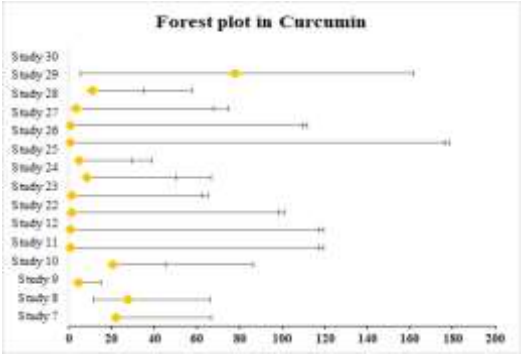

Figure 4: Curcumin's Impact on PCOS in Human and Animal Research

A comprehensive assessment of thirty-two papers was done as part of the literature evaluation that covered the years 2016–2024. This led to the analysis of 17 research articles followed by human studies involving 994 PCOS women. To analyze the data from different publications, we are using the forest plot. The data gathered indicated that resveratrol, quercetin, and curcumin has benefits for both PCOS-related hormone changes and symptoms, though some of the articles did not provide proof that these compounds show any potential changes in PCOS hormones. 15 research articles followed by animal experiments were conducted on 663 rat models, demonstrating improvements in PCOS-related hormonal alterations and symptoms. The outcome is meta-analysis displayed that resveratrol notably enhanced the condition of PCOS patients. Figure 2 from Bahramrezaie, M. (2019) illustrates the deviations in resveratrol between various research. It demonstrates that most likely by altering the expression of the VEGF and HIF1 genes in the granulosa cell's angiogenesis pathway and the blood levels of certain sex hormones (14). Rezvan, N. (2018) found that there was only a slight deviation in quercetin use in PCOS patients when compared to existing research (figure 3). Their findings demonstrate that oral quercetin supplementation enhances PCOS patients' metabolic characteristics in PCOS.
Figure 4 illustrates how Sabiha Ataç Asan's (2020) study deviates from the other articles which assertions that curcumin may be helpful for PCOS.

DISCUSSION

As previously mentioned, symptomatic approaches including hormone medication, menstrual cycle management, lifestyle adjustment, androgen reduction, and metabolic improvement are the only treatments for PCOS that have been shown to be effective (6). However, evidence indicates that curcumin, resveratrol, and quercetin may have therapeutic value in a range of illness situations even in PCOS (8-10). The N. A. Ardehjani et al., (2024) this study recommends that resveratrol could be a useful treatment for PCOS patients undergoing reproduction. By examining the parameters of FSH (Follicular Stimulating Hormone) , LH (Lueitenzing Hormone), Prolactin, TSH (Thyroid Stimulating Hormone), and testosterone, it also demonstrates improved condition in PCOS condition (17). The study, conducted by Hashemi Taheri, A. P., (2024), finds that resveratrol therapy groups dramatically reduced polycystic ovarian shape and ovarian volume, indicating a

disease-modifying effect (18). Beata Banaszewska et al., (2016) suggests that the Resveratrol dramatically lowered adrenal and ovarian androgens. This impact may be partially explained by better sensitivity to insulin and decreased insulin levels. Additionally, it is associated with improved PCOS hormone levels, including total testosterone, LH, FSH, prolactin, and insulin index. Overall, this indicates that reveratrol helped in PCOS (19). According to a study by Bahramrezaie, M., (2019) resveratrol may help PCOS patients with certain outcomes. Resveratrol was also found to improve levels of AMH, Estradiol, Progesterone, Total testosterone, FSH, LH, Prolactin, and TSH in PCOS conditions. (14)

According to Mendes da Silva, D. (2017), resveratrol does not seem superior to a placebo in treating endometriosis pain, based on prolactin levels and available evidence (20). Mansour, A., (2021) suggests that While amount of androgens, insulin, and lipids stayed constant, resveratrol improved menstrual cyclicity and hair loss. (21). According to Brenjian, S. (2020), resveratrol may be able to control the expression of genes related to the unfolded protein response (UPR) mechanism, therefore modifying ER (Endoplasmic Reticulum) stress in granulosa cells (GCs). According to their research, ER stress may be a focus for PCOS patients' treatment. Additionally, data shows that resveratrol alleviated PCOS symptoms (22). Maria Yarmolinskaya's (2021) investigation on female wistar rats indicates that the outcomes of their animal research indicate that resveratrol is a promising treatment for PCOS. This could also extend the range of medications available and help to personalize the treatment of this condition (23). The study, which was carried out on female wistar albino rats by Furat Rencber, S. (2018), suggests that the combination of metformin and resveratrol therapy might develop the ovarian follicular cell architecture, hormone profile, and weight gain in PCOS patients by triggering the antioxidant and anti-inflammatory systems via SIRT1 and AMPK (AMP-activated protein kinase activation). It also demonstrates that the resveratrol group by itself improves PCOS conditions more than the control group (24).

According to a study by Sima Vaez and Kazem Parivr (2022) on 72 PCOS-afflicted women, quercetin consumption improves oocyte and embryo grade as well as the pregnancy rate in PCOS patients. Consequently, it has been demonstrated that consistent Quercetin consumption lowers LH and inflammatory markers, which makes it useful in the treatment of PCOS and associated conditions (25). Rezvan, N. (2017) the study's findings demonstrated that giving PCOS patients quercetin supplements raises adiponectin while lowerings HOMA-IR (Homeostatic model assessment values for insulin resistance), testosterone, LH, FBS (Fasting Blood Sugar), and insulin levels. Given its relatively encouraging effects on adiponectin and HMW adiponectin levels in PCOS, quercetin may be a useful supplement for the condition (26).

According to Rezvan, N. (2018), oral quercetin supplementation enhances PCOS patients' metabolic characteristics by up regulating the expression of AMPK and adiponectin receptors. It also demonstrates a general improvement in PCOS (15). Quercetin administration reduced resisting plasma levels and gene expression, as well as the concentration of testosterone and LH, in overweight or obese PCOS women, according to Masoud Khorshidi (2018). Furthermore, evidence suggests that quercetin helps in PCOS (27). According to a study by Jahan, S. (2018) using female SD rats, quercetin can be utilized to treat PCOS either on its own or as an adjuvant medication (28). When 18 Parkes strain mice were used in a study by Mohd Zahoor ul haq Shah (2023), it became evident that the pituitary-ovary axis was the target of the quercetin effect because it reversed normal levels and ratios of LH/FSH, the two primary gonadotropic hormones. It’s concluded that Quercetin improves PCOS in a systematic, histological, and molecular way (29). In accordance to research done on female wister rats by FATEN ABBAS MOHAMED (2022), quercetin treatment dramatically reduced testosterone and TNF-a while increasing FSH, LH, estrogen, progesterone, and catalase. Both body weight and the spread of body hair decreased. Additionally, it enhanced insulin sensitivity and the ovary's histological structure. When it came to the metrics we tested, the dose of 100 mg/kg of quercetin outperformed than the together of 50 mg/kg of quercetin and metformin. The effects of metformin and quercetin at 50 mg/kg were similar (30). According to Eman Aly Sadeek Fadlalla's (2022) research, melatonin significantly improved hormone levels, morphology, and oxidative stress more than quercetin did. In contrast, quercetin showed some moderate improvements with regard to ovarian and uterine morphology as well as hormone features (31).

According to a study by Ghanbarzadeh-Ghashti, N. (2023) on women with PCOS, curcumin improved menstrual features (amenorrhea, oligomenorrhea, and abnormalities) and decreased FBS levels in these women, but it had no effect on other metabolic, hormonal, or hirsutism indices. Additionally, they came to the conclusion that curcumin has beneficial qualities for PCOS patients (32). Studies conducted by Sabiha Ataç Asan (2020) provide evidence that supplements containing curcumin may help PCOS-affected women regulate their weight and improve their glucose metabolism. In addition, they asserted that in order to conclusively identify a clear change in the clinical circumstances, more research with more patient populations, longer treatment durations, and diverse genetic backgrounds is needed (16). A. MALVASI., (2022) carried out the pilot study on humans, which indicates that a curcumin and teopolioside nutraceutical together is benefits for enhancing a number of PCOS symptoms linked to aberrant hormonal parameters in PCOS affiliated women, as well as indications and symptoms linked to hyperandrogenism (33). Zohrabi Tayebeh., (2023) the randomized clinical trials concluded that there was a significant impact on insulin levels and HOMA-IR from the co-administration of curcumin with the DASH diet. Nevertheless, curcumin, the DASH diet, and its combination had no discernible positive effects on the QUICKI (Quantitative insulin-sensitivity check index) or FBS (34). Ainehchi, N. (2019) studied women with PCOS and found that taking a herbal mixture (Curcumene) as a supplement in addition to CC (clomiphene citrate) can help PCOS patients' glycemic status, antioxidant activity, and likelihood of getting pregnant. For those with PCOS, it could therefore be regarded as a helpful adjunct medication (35). According to Mehri Jamilian's., (2020) findings, giving women with PCOS 12 weeks of cur cumin treatment improved their body weight, glycemic management, blood lipid levels (apart from triglycerides and VLDL cholesterol), and the expression of the PPAR-γ and LDLR genes (36).

Yaling Zhang (2021) studied 50 female Sprague Dawley (SD) rats that were specifically pathogen-free (SPF) and 21 days old. They promoted overall PCOS symptoms (37). Raja MA. (2021) studied 32 PCOS rat models. According to the study, many of the symptoms of PCOS may be reversed by treating the nanoparticles. Consequently, a promising new option for

the administration of curcumin to treat PCOS may be these nanoparticles (38). The study was carried out on 72 adult female Wistar rats by Mohammadi, S. (2017).

This study demonstrated how curcumin can enhance the histologic characteristics of polycystic ovary and move it closer to having an active and healthy ovary by inhibiting TNF-α and IL-6, lowering the follicular sheath, and increasing ovulation and corpus luteum (39). A study by P. Sushma Reddy (2016) on thirty female Albino Wistar rats reveals that curcumin has several positive benefits on PCOS treatment and ovulation induction that are comparable to those of clomiphene citrate. In PCOS rats given letrozole, curcumin normalized the hormone and lipid profile, antioxidant status, glucose metabolism, and ovarian morphology (40). According to a 2017 study by S. Mohammadi on 90 adult Wistar rats which says Curcumin may therefore be regarded as a preventive factor against the inflammatory condition associated with PCOS (41). The study, conducted on 56 virgin female (Wister albino) rats by Suaad M. Abd-Alqader in 2023, demonstrates the therapeutic benefit of zinc and curcumin supplements for rats with PCOS. Reversing the PCOS-related alterations represents this value. Considerable restoration of FSH, LH, and testosterone levels to baseline values. In addition to its capacity to raise progesterone and estrogen levels while lowering prolactin (42). Researchers Yousef Nasiri Bari (2021) found a study involving sixty female mice. So, which is advised to utilize the curcumin to accelerate the development of embryos during in vitro fertilization as well as to improve PCOS (43). An investigation by Raoofi, A. (2018) on sixty female Wistar rats led to the conclusion that the antioxidant and anti-inflammatory qualities of curcumin and ziziphora extract could effectively reduce cysts and alter hormone levels in polycystic ovarian syndrome (44). Shah, K. N., & Patel, S. S. (2015) studied 12 female pre-pubertal Sprague-Dawley rats and came to the conclusion that quercetin might be beneficial to PCOS patients because it inhibits PI3K, which lowers the CYP17A1 gene expression, which is important for steroidogenesis (45). Pallavi Dubey et al. (2022) concluded that although animal models demonstrated higher rates of improvement in terms of ovarian morphology and hormone balance, changes in ovarian morphology were observed with the use of resveratrol, and in a few patient trials, there was a slight improvement in androgen homeostasis (46). The research was done by Pingping Su et al. in 2024, and the findings showed that quercetin had a substantial therapeutic effect on PCOS. The following are some of the ways that quercetin can work. Quercetin can systematically lower blood sugar, cholesterol, triglycerides, and insulin levels in metabolic pathways. A decrease in these markers may assist in modifying the patients' metabolic milieu and mitigating PCOS. Quercetin can lower T and LH levels, lower the LH/FSH ratio, and modulate the pituitary-ovarian axis activity in endocrine pathways. This regulating impact helps patients' endocrine levels return to normal and helps to improve PCOS. One of the major genes involved in the metabolism of glucose, GLUT4, can also have its expression regulated at the molecular level by quercetin (47). The study by Hammad Ali Fadlalmola et al. (2023) found that because resveratrol affects the levels of DHEAS, LH, and testosterone, it is a promising and useful medication for treating PCOS in women. To improve the outcome for women with PCOS, combinations with various treatments are necessary, particularly for hyperlipidemia (48). According to a study by Zheng S et al. (2020) on 101 PCOS women, the controlled attenuation parameter shows an independent correlation between the lipid accumulation product and hepatic steatosis in these women. This implies that the lipid accumulation product could be a helpful indicator for determining liver fat in this group (49). According to the results of a pilot study by Chakraborty, S. (2020), which included 70 women with PCOS and 60 women who appeared to be in good health (controls), women with PCOS were more likely to Metabolic dysfunction-associated steatotic liver disease (MASLD) early in the course of the disease. According to the study's first results, CAP and LSM on fibroscan may be examined as possible indicators of MASH in these women. The right connections might be shown via a comprehensive, well-designed study that follows PCOS women over an extended period of time using liver biopsy, liver function tests, ultrasonography, and TE (50).

CONCLUSION

The above-rated research papers indicate that there is potential for the use of resveratrol, quercetin, and curcumin in PCOS conditions, even though the only proven treatments for PCOS are symptomatic approaches such as hormone medication, menstrual cycle management, lifestyle modification, androgen reduction and metabolic improvement. Thus, it is clear that resveratrol, quercetin, and curcumin improved the PCOS condition's histological features, menstrual cycles, and hormone alterations. However, a small amount of data exists to bolster the claims that curcumin, quercetin, and resveratrol can treat PCOS. Research indicates that in order to provide definitive evaluations, larger sample sizes and a range of genetic backgrounds are necessary. However, it is generally proven to be helpful for PCOS. The analysis therefore recommends that further research is necessary to develop PCOS treatment in order to address potential problems in PCOS condition.

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