

Review

# Nutrition Strategy and Life Style in Polycystic Ovary Syndrome—Narrative Review

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**Abstract:** Here we present an extensive narrative review of the broadly understood modifications to the lifestyles of women with polycystic ovary syndrome (PCOS). The PubMed database was analyzed, combining PCOS entries with causes, diseases, diet supplementation, lifestyle, physical activity, and use of herbs. The metabolic pathways leading to disturbances in lipid, carbohydrate, and hormonal metabolism in targeted patients are described. The article refers to sleep disorders, changes in mental health parameters, and causes of oxidative stress and inflammation. These conditions consistently lead to the occurrence of severe diseases in patients suffering from diabetes, the fatty degeneration of internal organs, infertility, atherosclerosis, cardiovascular diseases, dysbiosis, and cancer. The modification of lifestyles, diet patterns and proper selection of nutrients, pharmacological and natural supplementation in the form of herbs, and physical activity have been proposed. The progress and consequences of PCOS are largely modifiable and depend on the patient's approach, although we have to take into account also the genetic determinants.

**Keywords:** PCOS; reproduction; lifestyle; diet; sleep; supplementation; herbs supporting

## 1. Introduction

Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy, affecting as many as 15% to 18% of women of reproductive age [1]. The definition of PCOS changed in 2003, when representatives of the European Society of Human Reproduction and American Society of Reproductive Medicine met in Rotterdam, The Netherlands. Currently, it is defined as a heterogeneous group with different phenotypes, which pose challenges in its treatment [2]. It seems, however, that some dependences and the tendency of the occurrence of the similar metabolic disorders are comparable [3].

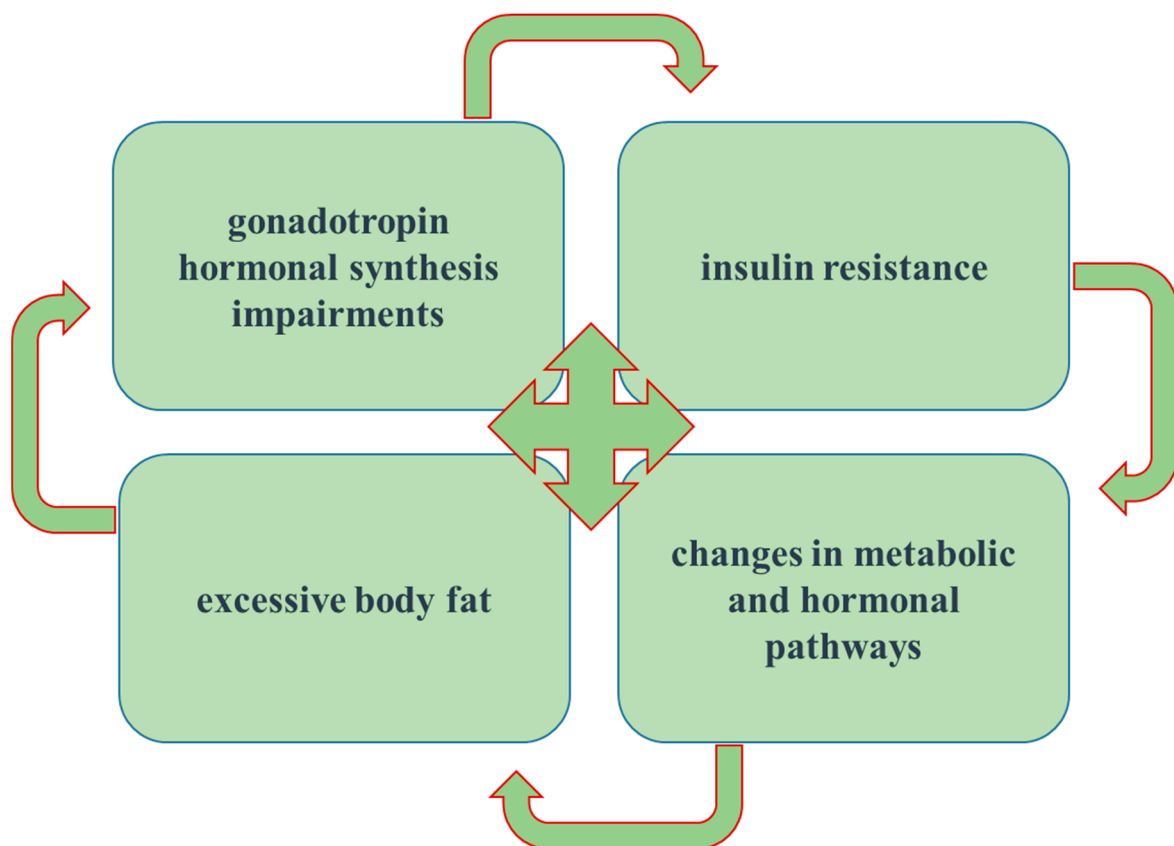
Many studies have shown that higher hormone levels, gut microbiome composition, and plasma metabolomics are new parameters related to the PCOS phenotypes [4]. The clinical phenotypes can change over the life span with weight gain, and can coexist in the same patient. Individualized treatment remains the main approach, but grouping the phenotypes and following therapeutic recommendations may also prove to be clinically suitable. Precise recommendations should be implemented long before metabolic complications occur, which is particularly important for women with PCOS as they are predisposed

to developing endometrial and ovarian cancer [5,6]. Therefore, the therapeutic approaches aimed at using anti-inflammatory remedies in supplementing and supporting anticancer therapy are crucial. They can help in inactivating the cascade of the deteriorating signaling pathways. Through these, better survival, faster recovery, and the improvement of the patients' quality of life can be achieved.

### 1.1. Physiological Basis

The four main causes of the physiological basis of PCOS include:

- disorders of gonadotropin hormonal synthesis;
- the appearance of insulin resistance;
- the influence of the present excessive body fat; and finally,
- the metabolic pathways involved in PCOS (the secretion and activity of insulin, encoding for steroidogenesis, and other metabolic and hormonal pathways) (Figure 1) [7].



**Figure 1.** Main pathophysiological basis of polycystic ovary syndrome (PCOS)—disorders of gonadotropin hormonal synthesis, the appearance of insulin resistance, the influence of the present excessive body fat and oblique metabolic pathways involved in PCOS.

Appropriate functioning of the mechanisms responsible for the maturation of the ovarian follicle and its ovulation depends on the proper physiological activity of three organs: the hypothalamus, pituitary gland, and ovaries.

The mechanisms of hormonal regulation in the hypothalamic-pituitary-ovarian system take place through the axes of negative feedback: long, short and ultra short feedback. In the suprachiasmatic nucleus of the hypothalamus there are neurons synthesizing gonadotropin-releasing hormone (GnRH), which is released into the pituitary portal circulation in the median eminence. GnRH release is regulated by a network of interconnected neurons. Gonadoliberin is an example of a hormone secreted in a pulsatile rhythm, and the frequency of this rhythm determines the type of gonadotropin released. A low frequency of

gonadoliberein pulses results in the secretion of follicle-stimulating hormone (FSH), while a high frequency results in the secretion of luteinizing hormone (LH) from the anterior lobe of the pituitary gland. LH is responsible for the luteinization of the corpus luteum, i.e., the transformation of granulosa cells into theca lutein cells which produce progesterone. In turn, FSH stimulates ovarian follicle maturation and estrogen secretion in the granulosa cells of ovarian follicles. It also increases the activity of aromatase, the enzyme responsible for converting androgens (testosterone and androstendion) to estrogens. When the concentration of luteinizing hormone increases relative to FSH, excessive androgen production occurs, which is more common in women with PCOS [8].

Insulin, both directly and indirectly, affects the pathogenesis of PCOS. It acts synergistically with luteinizing hormone, increasing the production of androgens (theca cells) and decreasing the liver synthesis of the main binding testosterone protein (SHBG), which results in testosterone circulating in the unbound, active form [8]. Excess body fat is involved in the development of PCOS in many ways. Adipose tissue cells (adipocytes) produce peptide hormones like resistin and leptin, as well as some inflammatory cytokines (IL-beta, TNF-alpha) [9].

The activity of leptin affects the function of the hypothalamus–pituitary gland–ovary axis by modifying the secretion of GnRH, LH, and FSH. Leptin is a signal for the hypothalamus to release LH, causing the secretion of pituitary GnRH, as well. This can result in excessive androgen synthesis. Adipose tissue, by secreting pro-inflammatory factors such as mentioned cytokines, contributes to the development of inflammation in PCOS and an increased amount of free radicals caused by hyperglycemia; excess adipose tissue and androgens contribute to the formation of chronic inflammation in PCOS [8].

The various clinical symptoms of the disease indicate that many metabolic pathways participate in PCOS development, including: secretion and activity of insulin, with genes encoding for insulin receptor (IR), insulin (INS), and insulin-like growth factor (IGF) and its receptor; genes encoding for steroidogenesis; genes responsible for the activity of cytochrome P450 (CYP 17, CYP 11 alpha); and other metabolic and hormonal pathways, with genes for androgenic receptor (AR), LH receptor, leptin, and follistatin [10]. Moderate adherence to an anti-inflammatory dietary pattern and the low glycemic index (GI) and low-fat dietary pattern, have protective effect on the odds of developing PCOS [11,12].

## 1.2. Improvement in Metabolic Pathways

### 1.2.1. Insulin Resistance

Weight gain mediates most of its direct medical sequelae through worsening insulin sensitivity.

Insulin resistance (IR) plays a key role in the development of metabolic dysfunction, including hypertension, dysglycemia, and dyslipidemia. A large amount of evidence supports a role of mitochondrial dysfunction in the development of IR, stimulated through ectopic fat deposition. Lipid-induced production of reactive oxygen species (ROS) within skeletal muscle promotes mitochondrial dysfunction and the development of IR [13]. Ultimately, IR underlies obesity-related conditions such as polycystic ovary syndrome (PCOS).

The cellular effects of insulin occur through two main post-receptor pathways: the phosphatidylinositol 3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) pathways [14]. The PI3K pathway regulates cellular intermediary metabolism, whereas the MAPK pathway controls growth processes and mitoses [14]. AKR1C3 expression in adipocytes leads to the occurrence of insulin resistance and hyperinsulinemia, then drives a vicious circle of intra-adipose androgen activation, lipid accumulation, and hyperinsulinemia [15]. Kauffman et al. suggested that ethnicity plays an additive effect on insulin resistance in PCOS. Mexican American women showed significantly higher insulin resistance compared with Caucasian American women [16].

### 1.2.2. Oxidative Stress and Chronic Inflammation

The association between body weight and IR is mediated through inflammatory pathways [17]. Obesity causes changes in the release of key cytokines and adipokines, which in turn manifest in paracrine and endocrine effects. The increased levels of leptin and plasminogen activator inhibitor-1 and the reduced release of adiponectin result in a generalized low-grade inflammatory response. This process is mediated by macrophages and other immune cells.

Increases in ROS generation, p47phox gene expression, and circulating thiobarbituric acid-reactive substances (TBARS) occur in PCOS in response to saturated fat ingestion independent of obesity. A diet rich in simple sugars, as well as saturated fatty acids additionally enhances the production of ROS by different mechanisms, including the influence on gut microbiota [18]. Circulating mononuclear cells and excess adipose tissue are separate and distinct contributors to oxidative stress in this disorder [19]. Lipid-stimulated oxidative stress may be a key driver of insulin resistance and hyperandrogenism in PCOS. Excess adipose tissue is a contributor to the pro-oxidant burden and an additional regulator of insulin action [19]. Moreover, the chronic exposure to androgens results in an increase in oxidative stress in islet cells, inducing mitochondrial dysfunction [20,21].

Superoxide is a ROS produced when NADPH is oxidized by membrane-bound NADPH oxidase [22]. Dysregulated ROS production from NADPH oxidase has been implicated in a variety of cardiovascular disorders, including endothelial dysfunction, atherosclerosis, and hypertension, which are observed in women with PCOS [23]. Peroxide-induced oxidative stress activates nuclear factor- $\kappa$ B (NF- $\kappa$ B), which is a cardinal inflammatory signal that increases tumor necrosis factor (TNF)- $\alpha$  gene transcription [24]. Oxidative stress in response to saturated fat ingestion is an intermediate step in stimulating TNF- $\alpha$  secretion from circulating leukocytes [19,25]. In our investigations, we also showed that women with PCOS exhibit increased TNF- $\alpha$  synthesis [4]. Women with PCOS with normal and low levels of androgens measured by the level of testosterone and free androgen index (FAI) were more susceptible to the development of oxidative stress and inflammation induced by TNF- $\alpha$  [26].

### 1.2.3. Anticancer Protection

Many studies have targeted the inactivation of the transcription factor (NRF2) as a therapeutic approach in various types of cancer [27]. NRF2 was first recognized in anticancer research as an inducer of several antioxidant enzymes. It can protect cells and tissues against many types of toxicant that interrupt essential biochemical processes and carcinogens by increasing the expression of cytoprotective genes [28]. NRF2 can act as a double-edged sword, being able to mediate both tumor-suppressive or pro-oncogenic functions depending on the specific biological context of its activation [29]. In line with this principle, the controlled activation of NRF2 might reduce the risk of cancer initiation and development in normal cells by scavenging ROS and by preventing genomic instability through decreased DNA damage. In contrast, already transformed cells with constitutive or prolonged activation of NRF2 signaling might represent a major clinical hurdle and exhibit an aggressive phenotype characterized by therapy resistance and unfavorable prognosis, requiring the use of NRF2 inhibitors [29].

It has been found that there are at least three pathways controlling the stability of NRF2. The first one depends on the cytosolic repressor KEAP1 [30]; the second is connected with the  $\beta$ -transducin repeat-containing protein ( $\beta$ -TrCP) [31]; while the third is related to the protein HRD1, which is an E3 ubiquitin ligase associated with the endoplasmic reticulum [32].

The abnormal activation of the NRF2/KEAP1 pathway promotes cancer development [33], metastasis formation [34], and even resistance to ovarian cancer therapy [35]. Mutations in the KEAP1 gene induce the hyper activation of the NRF2/KEAP1 pathway. Notably, KEAP1 missense or nonsense mutations were reported in endometrial carcinomas [36], as well as gall bladder [37], breast [38,39], cervical [40], and ovarian [41,42]

cancers. MicroRNA miR-141 was the first-identified miRNA to directly repress KEAP1 levels in ovarian carcinoma cell lines [43].

### 1.3. Gut Microbiota Dysbiosis

The structural and functional dysbiosis of the gut microbiota in high-fat diet (HFD)-induced obesity was demonstrated in a mouse model [44]. The microbiota, through its metabolites, has multiple and complex effects on appetite, lipids, and carbohydrate metabolism and may influence body weight [44,45]. The gut microbiota can regulate about 10% of the host's transcriptome and genes involved in the immune response, proliferation, and metabolism [46]. Interest in dietary fiber, gut fermentation, and probiotics has led to extensive research in this field [47]. The role of dietary fiber was demonstrated to modulate gut microbiota dysbiosis in patients with type 2 diabetes [48]. The growth of *Bifidobacteria* correlates with insulin secretion and increased glucose tolerance, regulates IR, and helps reduce inflammation. Short-chain fatty acids (SCFAs) such as acetate and butyrate produced by the beneficial gut flora influence glycemia through glucagon-like peptide 1 (GLP-1) and pancreatic polypeptide (PPY), which are intestinal hormones [45]. The hormone PYY is a peptide that acts as a paracrine substance to stimulate the feelings of satiety or hunger in the control center [49]. Due to the absolute role of metabolites such as SCFAs in the metabolism of lipids and carbohydrates, ensuring the good condition of the microbiota is one of the therapeutic goals [50] in combating inflammation at local and systemic levels [51], as well as infections of the urogenital tract [52].

## 2. Lifestyle Changes

Lifestyle change is the first line of treatment for the management of women with PCOS but is not an alternative to its pharmacological treatment [7]. Regular physical activity, maintaining appropriate body weight, following healthy dietary patterns and avoiding tobacco use is vital in prevention and treatment of metabolic disorders, and is included in clinical guidelines for various conditions. Focusing on overall wellbeing and mental health is a personal choice, and while it is not an immediate fix, it is an important step towards a more fulfilling life.

Nutritional counseling for PCOS patients has been one of the treatment methods for many years. However, strict caloric restrictions do not produce the expected long-term effects [53,54], and the isocaloric diet did not significantly improve the biochemical and anthropometric parameters even in combination with physical activity [55].

### 2.1. Diet

Analysis of the impact of lifestyle modification related to the share of energy from macronutrients (protein, fat, and carbohydrates) showed no significant differences in the levels of the analyzed parameters. However, a significant factor in these changes was the reduction in the caloric content of the diet [56] and the introduction of a reduced-calorie diet with a low GI [57]. Low GI (LGI) diets decreased homeostatic model assessment for insulin resistance (HOMA-IR), fasting insulin, total and low-density lipoprotein (LDL) cholesterol, triglycerides, waist circumference, and total testosterone compared with high GI (HGI) diets without affecting fasting glucose, HDL cholesterol, weight, or the free androgen index [58]. In addition, the inclusion of the LGI diet, punitive restrictions, and/or physical activity, and the supplementation of omega-3 increased HDL, sex hormone binding globulin (SHBG) synthesis, and reduction in body fat [8]. Gonzales et al. found that saturated fat acid (SFA) ingestion stimulates increases in circulating TNF- $\alpha$  and peripheral leukocytic suppressor of cytokine-3 (SOCS-3) expression [25]. Therefore, eliminating SFA from the diets of these patients is imperative. Dietary  $\alpha$ -linolenic acid-rich flaxseed oil exerted beneficial effects on polycystic ovary syndrome through the sex steroid hormones–microbiota–inflammation axis in rats, but other sources of  $\alpha$ -linolenic acid will probably produce an equally good effect [59].



The effects of soluble dietary fiber on SCFAs were demonstrated. Fermentable fiber has positive metabolic benefits on the gut microbiome with subsequent release of SCFAs [60]. Diets with a low GI may influence appetite-regulating hormones including ghrelin and glucagon [12,61]. Low-GI meals reduced ghrelin and increased glucagon in women with PCOS [61]. High fructose consumption (HFC) synergistically aggravated endocrine but not metabolic changes in PCOS, suggesting that (HFC) might deteriorate endocrine-related phenotypes in PCOS [62]. A meta-analysis and systematic review showed that the LGI diet is an effective, acceptable, and safe intervention for relieving IR, and professional dietary advice should be offered to all PCOS patients [63,64].

It seems that another reduced-GI diet modification is the ketogenic diet, which limits the consumption of total carbohydrates in favor of plant-based fat. The ketogenic diet (KD) improves the menstrual cycle, reducing blood glucose and body weight, improving liver function, and treating fatty liver in women with PCOS and liver dysfunction who were obese [65]. Even more interesting results were reported by Paoli et al. after using the KD for 12 weeks in women with PCOS [66]. The anthropometric and body composition measurements revealed a significant reduction in body weight (−9.43 kg), body mass index (BMI; −3.35), and fat-free body mass (8.29 kg). A significant decrease in glucose and insulin blood levels was observed, together with a significant improvement in HOMA-IR scores. A significant decrease of triglycerides, total cholesterol and LDL were observed along with a rise in HDL levels. The LH/FSH ratio, LH total and free testosterone, and DHEAS blood levels were also significantly reduced. Estradiol, progesterone and SHBG increased. The Ferriman Gallwey Score was slightly, although not significantly, reduced [66]. There was no significant association between parameters of hirsutism and the visceral adiposity index (VAI). Hirsutism is unlikely to be due to visceral adipocyte dysfunction [67]. Therefore, in PCOS patients with advanced obesity and/or obesity accompanied by full-blown metabolic syndrome, the introduction of a ketogenic diet may provide even better results than a diet with a LGI. Nonetheless, a general conclusion is that by following the main principles of a healthy diet, the physiological homeostasis can be managed, as well as faster recovery from disease achieved.

## 2.2. Physical Activity

Exercise training in the management of PCOS is becoming more recognized and accepted among professionals in the health sector and the patients. Physical training potentiates the effects caused by insulin sensitivity through the optimization of glucose transport and metabolism [68].

A recent meta-analysis found that improvements in health outcomes are more dependent on exercise intensity than dose. The results from this analysis support the use of exercise and that vigorous intensity exercise may have the greatest impact on cardiorespiratory fitness, insulin resistance, and body composition [69]. Insulin resistance, measured using the HOMA-IR and BMI showed a significant decrease with moderate and high certainty (MD-0.57; 95% confidence interval (CI), −0.98 to −0.16, and  $p = 0.01$ ; MD-1.90, 95% CI −3.37, −0.42, and  $p = 0.01$ ), respectively [70]. Other authors in a systematic review found that vigorous aerobic exercise and resistance training to improve insulin sensitivity and androgen measurements are warranted for women with PCOS. [71]. The minimum aerobic activity per week should be 120 min [69].

## 2.3. Sleep

Mental health disorders are highly prevalent in PCOS cases, which are associated with significantly more frequently experienced states of anxiety and depression, as well as sleep disorders [72]. Sleep disorders impact the etiology and development of the anxiety and depression seen in PCOS, so treating sleep-related conditions should be an integral part of treating women with PCOS [72]. Sleep deprivation has been connected with increased risk of IR, obesity, and type 2 diabetes (T2D) [73–75]. Although incompletely understood, the factors that mediate IR in response to sleep deprivation, likely implicated

centrally regulated autonomic pathways, endocrine responses (e.g., changes in the key appetite hormones ghrelin and leptin), and inflammatory status. Mice experiencing sleep fragmentation (SF) showed white adipose tissue (WAT) inflammation and worsened IR, which resulted from enhanced disruption to the colonic epithelial barrier [76] and “gut leakage” syndrome which leads to LPS mediated inflammation [51]. Thus, SF-induced metabolic alterations may be mediated in part by concurrent changes in the gut microbiota, thereby providing an opportunity for gut-microbiome-targeted therapeutics [76]. The main pineal gland hormone melatonin is involved in the regulation of the circadian rhythm. In recent years, it was observed that a reduction in the melatonin levels of follicular fluid occurs in PCOS patients [77]. Melatonin receptors in the ovary and intrafollicular fluid adjust sex steroid secretion at different phases of ovarian follicular maturation. Melatonin is a strong antioxidant and an effective free-radical scavenger, which protects ovarian follicles during follicular maturation [77].

Based on current knowledge, it is plausible to conclude that sleep disorders can be considered as one of the first symptoms leading to the weakening of the body’s protective properties and intensification of the pathways associated with insulin resistance in the course of PCOS.

#### 2.4. Supplementation

The research showed that the vast majority of women with PCOS consume an improperly balanced diet, involving deficiencies in fiber, omega 3, calcium, magnesium, zinc, and vitamins (folic acid, vitamin C, vitamin B12, and vitamin D) [8]. An excess of nutrients was also noted in sucrose, sodium, total fats, saturated fatty acids, and cholesterol [8]. It was examined whether the deficiencies can be balanced with a correct calories-reduction diet with a lowered GI and it resulted positive regarding influence on the water-soluble vitamins [78,79]. In the case of most vitamin B, the increase in its supply with the diet led to the expected result in the form of its increased level in the plasma of women with PCOS. This effect was not observed for vitamin B3, and the levels of B2 and thiamine were not as satisfactory as in the case of the other, related vitamins [79]. It was documented that the insufficient supply of vitamin B3 is associated with the development of inflammatory conditions, leading to the associated diseases [80] as well as the increased risk of cardiovascular syndromes [81]. Women with PCOS may be treated with metformin, which normalizes glycemia, but its chronic intake is additionally associated with deficiencies in thiamine and cobalamin [82]. Therefore, it is a good idea to supplement with thiamine, which, by activating transketolase, contributing to the inhibition of mechanisms damaging blood vessels, reducing the risk of cardiovascular diseases [83,84].

While drawing attention to the potential properties of blood vessel protection in PCOS, supplementation with coenzyme Q10 also requires consideration. CoQ10 supplementation for 8 weeks had a beneficial effect on inflammatory and endothelial dysfunction markers in overweight and obese patients with PCOS [85].

When analyzing the available literature on supplementation in PCOS, attention should be paid to vitamin D, which increases insulin synthesis and release, increases insulin receptor expression, and increases insulin response to glucose transport [86]. Vitamin D indirectly influences carbohydrate metabolism by normalizing extracellular calcium and parathyroid hormone concentration. It also affects the expression of the genes of the metabolic pathways affecting systemic inflammation by inhibiting the synthesis of pro-inflammatory cytokines, which may contribute to the occurrence of IR [87]. Women with PCOS receiving 20,000 IU of cholecalciferol weekly benefited from improved carbohydrate metabolism. Decreases in fasting glucose, triglycerides, and estradiol were observed. Although no changes in androgen levels were observed, improvements in menstrual frequency were noted [88]. Combined magnesium, zinc, calcium, and vitamin D supplementation in another study led to a significant reduction in hirsutism and total testosterone compared with the placebo, but supplementation did not affect SHBG levels or the free androgen index (FAI) [89]. Conversely, the combination of vitamin D and fish oil reduced the parameters of inflam-

mation in the body (serum C-reactive protein (CRP), downregulation of interleukin (IL)-1 genes) and total testosterone levels and has beneficial effect on mental health parameters measured by Beck's Depression Questionnaire [90].

Current results showed that myo-inositol is as effective as metformin in improving the clinical and metabolic profile of women with PCOS and the metabolic disorders associated with diabetes [91]. However, the administration of metformin is associated with side effects that are not experienced with inositol [92]. Inositol increases insulin sensitivity, normalizes androgens in the blood, improves glycemia, and affects numerous features of metabolic syndrome [93,94]. PCOS appears to involve increased epimerization of myo-inositol (MI) to d-chiro-inositol (DCI) in the ovary by insulin, the consequence of which is overproduction of DCI and deficiency of MI, which in turn affects the disturbance of FSH signaling and deterioration of the quality of oocytes [95]. Inositols (both isomers, both given separately and in combination) also have the potential to restore spontaneous ovulation and improve fertility in women with PCOS. An analysis of the literature showed supplementation with inositol as being a safe and, importantly, effective form of PCOS therapy, improving the development of ovarian follicles, oocyte maturation, and stimulation of pregnancy [96].

As in traditional medicine, natural substances such as isoquinoline alkaloids have been used to regulate the synthesis of androgens and the metabolism of lipids and carbohydrates, the introduction of berberine in patients with PCOS has been considered [97–99]. As with metformin, the beneficial metabolic effects of berberine in type II diabetes are related to the activation of adenosine monophosphate-activated protein kinase (AMPK). Berberine has good hypoglycemic and hypolipidemic effects, reduces body weight, and is an effective insulin sensitizer [100]. It also reduces the synthesis of steroid hormones and the expression of ovarian aromatase by acting on the hypothalamic–pituitary–ovarian axis, and improves the ovulation rate and the regulation of menstruation, thus increasing the pregnancy and live birth rates. In addition, studies showed that even with long-term use of berberine, its side effects are transient and mild (constipation, nausea) [101], which suggests that berberine may be a safe and promising compound for the treatment of PCOS patients [98,102].

Chromium is the basic element involved in the metabolism of carbohydrates and lipids; therefore, it has become one of the most commonly consumed dietary supplements in the USA [103]. The indications for its supplementation were once very broad; however, chrome is currently one of the most controversial components by which its influence is strongly undermined [104,105]. It was argued that it is not an essential micronutrient, but has potential benefits and/or side effects. By enhancing the insulin signaling pathway, increasing the activity of AMPK, and increasing cellular glucose uptake, it has a beneficial effect in PCOS patients in improving diabetes [106]. Decreases in the expressions of  $3\beta$ -hydroxysteroid dehydrogenase and  $17\beta$ -hydroxysteroid dehydrogenase were identified in adipose tissue, which were related to dehydroepiandrosterone [107].

The research, and the available literature, show that supplementation with zinc and selenium to counter deficiencies may be indicated in the case of at least some patients with PCOS. Due to intracellular signaling and structural functions, zinc plays a role in lipid and glucose metabolism and fertility [108]. Low zinc intake in obese people is associated with hyperinsulinemia, increased low-grade inflammation, and a worsened lipid profile. In addition, zinc ions can act in an insulin-mimetic manner in adipocytes, stimulating lipogenesis and glucose transport through the translocation of glucose transporter 4 (GLUT4) to the plasma membrane [109]. Zinc deficiency may play a significant role in the pathogenesis of PCOS and may be a prognostic marker of PCOS. Studies showed that the average serum zinc levels of PCOS patients are significantly lower compared with healthy controls [110]. In addition, serum zinc levels were shown to be lower in PCOS patients with impaired glucose tolerance than in PCOS patients with normal glucose tolerance. [110]. Selenium is associated with a lower level of CRP. It has anti-inflammatory and antioxidant properties [111]. Finally, it is necessary to supplement the omega-3 fatty acids, which tend to lack in the diet of PCOS women. However, with the balanced diet, supplementation can be regarded as a seasonal intervention [112]. Polyunsaturated fatty acids (PUFAs) enhance



the reproductive performance in PCOS by increasing the expression of steroidogenesis enzymes, which are related to hormone secretion and ovarian functions, and the protein levels of CYP51, CYP19, StAR, and 3 $\beta$ -HSD [113]. In summary, supplementing the diet is an individual subject that requires dietary consultation with the patient, and its active participation and compliance is desirable for the overall improvement of the metabolic equilibrium. A properly balanced diet and a healthy lifestyle should be the first element of PCOS therapy.

### 2.5. Herbs Supporting Treatment

A balanced diet to support insulin management is the most important treatment for PCOS; drinking infusions of some herbs would therefore be a very good complement to the therapy, such as *Aloe vera*, cinnamon (*Cinnamomum verum*), green tea (*Camellia sinensis*), and chamomile (*Matricaria chamomilla*), and white mulberry (*Morus alba*) [114]. There are medical herbs can affect the lipid profile, blood glucose, and IR [115]. Because these herbs have properties of regulating lipid and carbohydrate metabolism they can be used by all phenotypes of PCOS women. Several of the herbs also have endocrine properties, these were the ones mentioned earlier: green tea [116] and marjoram (*Maiorana hortensis*) are some of the herbs whose effects include improvements in hormonal levels, ovaries weight, insulin sensitivity, antioxidants, and anti-inflammatory parameters [117,118].

Another group of herbs is indicated especially for women with PCOS with biochemical evidence of increased levels of androgens: green mint (*Mentha spicata* L.), which has an antiandrogenic effect and restores follicular development in ovarian tissue [119,120]; licorice smooth (*Glycyrrhiza glabra*) has been used in the treatment of PCOS because of its antiandrogen and estrogen-like activity. Licorice root appears to be effective in reducing excess testosterone as it blocks the conversion of androstenedione. Glycyrrhetic acid and metabolites block 11 beta-hydroxysteroid dehydrogenase type 2 and bind mineralocorticoid receptors directly, acting as agonists [121,122]. However, licorice is not a flawless solution, having the potential to induce hypertension, hypokalemia, and metabolic alkalosis [123]. People with high cortisol levels should, therefore, avoid this preparation. The available literature suggests a role of herbal drugs in the action against 5-alpha-reductase enzyme, inhibiting it and reducing hair loss [124]. *Serenoa repens*, *Camellia sinensis*, *Rosmarinus officinalis*, and *Glycyrrhiza glabra* can also lower androgen levels and inhibit androgenetic alopecia [124]. *Vitex agnus-castus* is a good regulator of the menstrual cycle and has been used in traditional medicine for centuries [125]. The best-studied dietary phytoestrogens are the flaxseed lignans [126]. The lignan content of flax-seed (*Linum usitatissimum*) may alter the activity of key enzymes involved in estrogen synthesis (e.g., aromatase) to modulate relative levels of circulating sex hormones and their metabolites [127].

Turmeric (*Curcuma longa*), and specifically curcumin, is a biologically active phytochemical ingredient [128,129]. Curcumin seems to be an efficient reducer of oxidative-stress-related complications in patients with PCOS [130,131]. Moreover, curcumin attenuates proangiogenic and proinflammatory factors in human eutopic endometrial stromal cells through the NF- $\kappa$ B signaling pathway [132]. Nettle (*Urtica dioica*) is a multipurpose herb in medicine for which some antioxidative, anti-inflammatory, antimutation, and antitumor properties were identified [133,134]. The flavonoids are a family of compounds with antioxidant activities that can modify specific enzymes, so they can inactivate some agents such as nitrite peroxide and hydroxide radicals [135].

Ultimately, in advanced PCOS with accompanying disease associated with metabolic syndrome and the steatosis of internal organs (especially non-alcoholic fatty liver disease), herbs and their extracts with proven properties should be considered for their hepatoprotective activities [136]. These substances include the silymarin contained in milk thistle (*Silybum marianum*) [137,138] and sesquiterpenes and antioxidant-active ingredients in artichoke (*Cynara Cardunculus*) extract [139,140]. Dandelion (*Taraxacum officinale*) and its component taraxasterol may silence the gene of SIRT1, preventing the disruption of hepatic cells [141]. Black cumin (*Nigella sativa*) also has similar properties, which should be

included in the diet of obese PCOS patients [142]. To summarize, herbs and the substances they contain offer many possibilities for interventions supporting the treatment of PCOS at various stages of disease. The selection of the appropriate mixture may be individualized depending on the occurrence of symptoms. Summary information has been added in Table 1.

**Table 1.** Table summarizing described interventions of herbs and their effects.

A Symptom Accompanying PCOS	Diet	Physical Activity	Sleep Regulation	Supplementation	Microbiota	Herbs
Hirsutism	reduced diet [26,44,45,54,58]			magnesium, zinc, calcium [89,108–111], and vitamin D [86–90], myo-inositol [93–96]		green mint [120,121], licorice smooth [122], <i>Serenoa repens</i> , <i>Camellia sinensis</i> , <i>Rosmarinus officinalis</i> , and <i>Glycyrrhiza glabra</i>
The androgens levels	diet with reduced GI and calorie [26,44,45,54,58], Ketogenic diet [64]			magnesium, zinc, calcium [89,108–111], and vitamin D [86–90], berberine [97–102], chromium [105–107], zinc [110]		green mint [120,121], licorice smooth [122], <i>Serenoa repens</i> , <i>Camellia sinensis</i> , <i>Rosmarinus officinalis</i> , and <i>Glycyrrhiza glabra</i> [124]
Ovulation disorders	diet with reduced GI and calorie [26,44,45,54,58], Ketogenic diet [64]			vitamin D [86–90], myo-inositol [97,98] berberine [99], zinc [108], PUFAs [112,113]		green mint [120,121], licorice smooth [121], <i>Vitex agnus-castus</i> [124], flax-seed [59,125,126]
Fat mass reduction	high-fiber diet with reduced GI and calorie [28,46,47,56,60], ketogenic diet [64] elimination SFA [22,58]	daily physical activity [68–71]	improving sleep [72–77]		microbiota and metabolites [46,47]	
Carbohydrate metabolism disorders	high-fiber diet with reduced GI and calorie [26,44,45,54,58], ketogenic diet [64]	daily physical activity [68–71]	improving sleep [72–77]	vitamin B1 [82–84], vitamin D [86–90], myo-inositol [91–96], berberine [97–102], chromium [105–107], zinc [109]	SCFA [47,52], microbiota and metabolites [50]	Aloe vera, cinnamon green tea [115], chamomile and white mulberry [117]
Insulin resistance	high-fiber diet with reduced GI and calorie [26,44,45,54,58], elimination SFA [22,58]	daily physical activity [71–74]	improving sleep [72–77] melatonin [77]	vitamin D [86–90], myo-inositol [91–96], berberine [97–102]	Bifidobacteria [45,50]	Aloe vera, cinnamon, green tea, chamomile and white mulberry [117]
Lipids metabolism disorders	high-fiber diet with reduced GI and calorie [26,44,45,54,58], elimination SFA [25,60]	daily physical activity [68–71]		omega 3 [112,113], berberine [97–102], zinc [110]	SCFA [47,52]; microbiota and metabolites [50]	milk thistle [137,138] artichoke extract [139,140]. Dandelion [141], Black cumin [142]
Steatosis of organs-liver profile	high-fiber diet with reduced GI and calorie [46,47,56,60]			silymarin [137,138], sesquiterpenes [139,140], taraxasterol [141]		milk thistle [137,138] artichoke extract [139,140]. Dandelion [141], Black cumin [142]
Cardiovascular diseases	high-fiber diet with reduced GI and calorie [46,47,56,60]	intensity exercise [72]		$\alpha$ -linolenic acid [59], vitamin B3 [80,81], vitamin B1 [82–84], coenzyme Q10 [85]		
Intestinal dysbiosis	high-fiber diet [49,50]				Bifidobacteria [45,50]	

Table 1. Cont.

A Symptom Accompanying PCOS	Diet	Physical Activity	Sleep Regulation	Supplementation	Microbiota	Herbs
Chronic inflammation	high-fiber diet with reduced GI and calorie [28,46,47,56,60]		melatonin [79]	$\alpha$ -linolenic acid [59], vitamin B3 [80,81], coenzyme Q10 [85], vitamin D [88,89], selenium [112], flavonoids [135]	Bifidobacteria [45,50]	Green tea and Marjoram [117–119], Turmeric [128–131], Nettle [133,134], milk thistle [137,138] Artichoke extract [139,140]. Dandelion [141], Black cumin [142]
Limiting predisposition to cancer	elimination SFA [25,27]; high-fiber diet [49,50]			$\alpha$ -linolenic acid [59]		Turmeric [128–131], Nettle [133,134]
Mental health disorders		daily physical activity [71–74]	improving sleep [75]	vitamin D [86–90], omega 3 (fish oil) [72,90]		

SCFA—short-chain fatty acids; GI—glycemic index; SFA—saturated fat acids; PUFA—Polyunsaturated fatty acid.

### 3. Conclusions

The analysis of metabolic symptoms occurring in the course of PCOS points to the need for a multidirectional therapeutic approach. The metabolic pathways leading to the abnormalities are presented, which requires focusing on the improvement of parameters related to fertility, hirsutism, the occurrence of carbohydrate-lipid disturbances and the reduction of insulin resistance. One of the most important pathways for blocking carcinogenesis is presented. It has been shown that significant improvement of these parameters depends on modifiable factors related to the improvement of lifestyle, the introduction of a diet, especially a low-calorie diet with reduced GI, normalization of sleep and the introduction of daily physical activity. In addition, supplementing the diet with antioxidants and herbs seems to be highly effective in combating the chronic inflammation (*Curcuma longa*), improving liver steatosis (*Silybum marianum*, *Nigella sativa*) and the frequently occurring intestinal dysbiosis (probiotic therapy). Conducting our own research in this area, we examined how increasing the supply of vitamins and minerals with the diet affects the supply of these components in patients, so we also searched the literature and described suggested supplementation (inositol, thiamine, coenzyme Q10, vitamin D, zinc, selenium). Undoubtedly there is a need for further research to be undertaken to determine the efficacy and applicability of the ingredients described as a support for traditional PCOS management.

### 4. Methods of Searching

In this study, we reviewed the literature focused on PCOS therapy, unrelated to medical therapy, by searching the records of international PubMed and Embase (Elsevier) databases from the last 20 years.

All articles collected through the electronic search process used in this article were reviewed from the abstract. Articles unrelated to the main topic, duplicate papers in both databases (PubMed and Embase), and conference abstracts were excluded from the review process. Only articles published in English were considered.

The main core of the issue was the authors' own 10 years of experience and research in this patient group. From the authors' own studies, those that corresponded sequentially to the intervention steps discussed were selected. The physiological basis was discussed (searching the database for PCOS and insulin resistance or chronic inflammation or endocrine disorders or cancer or microbiota). Lifestyle changes were then discussed. Studies that examined the association between PCOS and diet or supplementation (pcos + inositol; PCOS + berberine; PCOS + vitamin D; PCOS + chromium; PCOS + zinc; PCOS + selenium; PCOS + melatonin) or adjunctive herbs were included in the review. In the case of dupli-

cation of information in publications, those that contribute most to the main topic were selected.

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