Endocrine and Metabolic Science 14 (2024) 100162

Contents lists available at ScienceDirect

Endocrine and Metabolic Science

journal homepage: www.elsevier.com/locate/endmts

Review

A review on critical appraisal and pathogenesis of polycystic ovarian syndrome

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ARTICLE INFO

Keywords:
PCOS
Pathogenesis
Complications
Gonadotropins
Irregularities
Infertility

ABSTRACT

Polycystic Ovarian Syndrome (PCOS) is a complex endocrine disorder affecting reproductive-aged women, characterized by clinical manifestations such as hyperandrogenism, menstrual irregularities, and polycystic ovaries. Despite its prevalence and impact on women's health, the pathogenesis of PCOS remains incompletely understood. This review provides a comprehensive critical appraisal of existing literature on PCOS pathogenesis, addressing knowledge gaps and highlighting its multifactorial nature. A systematic literature review identified relevant articles published up to the knowledge cutoff date in 2023, focusing on molecular, genetic, hormonal, and environmental factors contributing to PCOS pathogenesis. Electronic databases, including PubMed, MEDLINE, and Embase, were systematically searched using predefined terms. Eligible studies investigated molecular, genetic, hormonal, and environmental factors associated with PCOS pathogenesis. The critical appraisal revealed diverse studies enriching our understanding of PCOS. Molecular and genetic studies highlighted alterations in signaling pathways, hormonal dysregulation, and the role of insulin resistance. Environmental factors, including lifestyle and exposure to endocrine-disrupting chemicals, were implicated. Heterogeneity in study designs and methodologies underscored the need for standardized approaches to enhance comparability. This review synthesizes current evidence on PCOS critical appraisal and pathogenesis, emphasizing its multifaceted nature. Standardization of study designs and methodologies will facilitate future comparisons, enabling the development of targeted therapeutic interventions and personalized management strategies for women affected by PCOS.

1. Introduction

Reproductive health for females encompasses a broad spectrum of physical, mental, and social well-being associated with their reproductive system and processes. It involves the holistic care and support necessary to maintain optimal reproductive function throughout a woman's life, from adolescence to adulthood and through the various stages of reproductive development. Key aspects of female reproductive health include menstrual health, fertility, prenatal and maternal care. Female reproductive health concerns include organ mutilations controlled by estrogen, hormonal irregularities and diseases like endometriosis, polycystic ovary syndrome (PCOS), fibroids, and cancers affect women due to increased exposure to endocrine toxicants. PCOS, a common endocrine disorder, often goes undiagnosed initially. Its prevalence ranges from 5 to 25 %, and leading to infertility and various clinical and metabolic disorders, posing an economic burden on healthcare.

Polycystic Ovarian Syndrome (PCOS) is a prevalent and enigmatic endocrine disorder affecting women of reproductive age, characterized by a spectrum of clinical manifestations that include hyperandrogenism, menstrual irregularities, and the presence of polycystic ovaries. Despite being recognized as one of the most common endocrinopathies, the precise etiology and pathogenesis of PCOS remain elusive, posing significant challenges to effective diagnosis and targeted therapeutic

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https://doi.org/10.1016/j.endmts.2024.100162
Received 1 December 2023; Received in revised form 10 January 2024; Accepted 25 January 2024
Available online 30 January 2024

interventions. The increasing prevalence of PCOS is attributed to a complex interplay of genetic susceptibility, environmental factors, and lifestyle changes. Elevated insulin resistance, sedentary behavior, and dietary patterns, coupled with genetic predisposition, contribute to the rising incidence of PCOS. Emerging research suggests that environmental endocrine disruptors may also play a role. This review undertakes a meticulous exploration of the critical appraisal and underlying pathogenic mechanisms of PCOS, aiming to shed light on the intricate web of factors contributing to its manifestation. The complexity of PCOS arises not only from its heterogeneous clinical presentation but also from the intricate interplay of genetic, hormonal, environmental, and lifestyle factors. Understanding the multifactorial nature of PCOS is pivotal for unraveling its pathogenesis and devising tailored strategies for management. In navigating the ever-growing body of literature addressing various facets of PCOS, this review systematically examines the existing knowledge landscape, consolidating and critically evaluating diverse findings. Molecular and genetic studies play a crucial role in elucidating the pathogenesis, offering valuable insights into aberrations in signaling pathways, hormonal dysregulation, and the pivotal role of insulin resistance. As advances in genomic research continue, uncovering the intricate genetic underpinnings of PCOS has become a focal point, providing potential biomarkers and therapeutic targets. Simultaneously, the influence of environmental factors, including lifestyle choices and exposure to endocrine-disrupting chemicals, adds another layer of complexity to the syndrome's origin. The critical appraisal of existing literature is essential in recognizing methodological strengths and limitations, navigating through conflicting findings, and advocating for standardized approaches to enhance comparability. By synthesizing and critically evaluating this body of evidence, this review aims to contribute to a nuanced understanding of PCOS pathogenesis.

Compared to a normal female ovary, a polycystic ovary has multiple small cysts, a result of disturbances in the menstrual cycle. Enlarged ovaries in this condition lead to excessive production of androgen and estrogenic hormones, potentially causing infertility due to anovulation. Ever since, with the advancements in healthcare, the development of PCOS management of PCOS starts from 19th century. The first case of bilateral polycystic ovaries was detailed by Stein and Leventhal in 1935, defining the condition now known as Stein and Leventhal syndrome (Azziz and Adashi, 2016). Hormonal and biochemical measurements became possible in the 1960s and 1970s. High-resolution ultrasound in the 1980s allowed the study of typical polycystic ovaries containing over 10 follicles of diameter 2–10 mm (Cheong et al., 2016). In the 1990s, two key features emerged: a genetic component to PCOS and elevated insulin levels in affected women, increasing their risk of diabetes later in life (Diamanti-Kandarakis et al., 2006). This review embarks on a journey through the intricate landscape of PCOS, delving into the critical appraisal of existing literature and dissecting the multifaceted nature of its pathogenesis, with the ultimate goal of paving the way for more effective diagnostics, targeted therapeutic interventions, and personalized management strategies for women grappling with the complexities of Polycystic Ovarian Syndrome.

1.1. Criteria for diagnosis

Various terms have been used to describe PCOS, such as polycystic ovarian syndrome, poly follicular ovarian disease, syndrome O, functional ovarian hyperandrogenism, and ovarian dysmetabolic syndrome. The National Institute of Health established the diagnostic criteria (NIH criteria) in 1990, encompassing ovulatory dysfunctions and hyperandrogenism (Dumesic et al., 2016). Subsequently, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) established the Rotterdam criteria in 2003, revised in 2004, requiring two of three criteria: hyperandrogenism, ovulatory dysfunction, or polycystic ovarian morphology on ultrasound (Fig. 1). Additionally, the Androgen Excess and Polycystic Ovary Syndrome Society (AES) set another criterion in 2006, mandating hyperandrogenism combined with ovarian dysfunction (Azziz et al., 2006). (See Figs. 2 and 3.)

2. Development of PCOS

2.1. Hormonal dysfunction and development of PCOS

Hormonal imbalances are central to PCOS pathogenesis, featuring elevated androgens, disrupted gonadotropin secretion, and insulin resistance. Hyperandrogenism drives irregular menstrual cycles and contributes to the characteristic symptoms of PCOS, including hirsutism and acne. Dysregulated gonadotropins disrupt ovarian function, leading to follicular cyst formation. Insulin resistance amplifies androgen production, creating a feedback loop. Recent studies underscore the intricate hormonal interplay, emphasizing the pivotal role of hormonal dysregulation in PCOS development and manifestation. Hormonal imbalance causes the formation of cysts in the antral follicles of the ovary, preventing ovulation and disturbing the menstrual cycle,

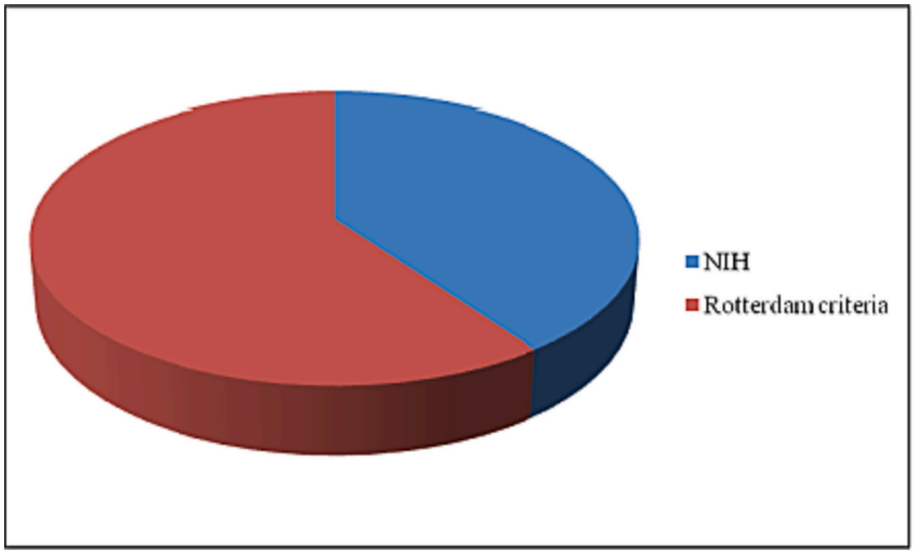

Fig. 1. Showing the criteria (NIH and Rotterdam) based prevalence of PCOS. Applying the Rotterdam criteria for the diagnosis of PCOS, showed higher prevalence of PCOS in comparison to the NIH criteria.

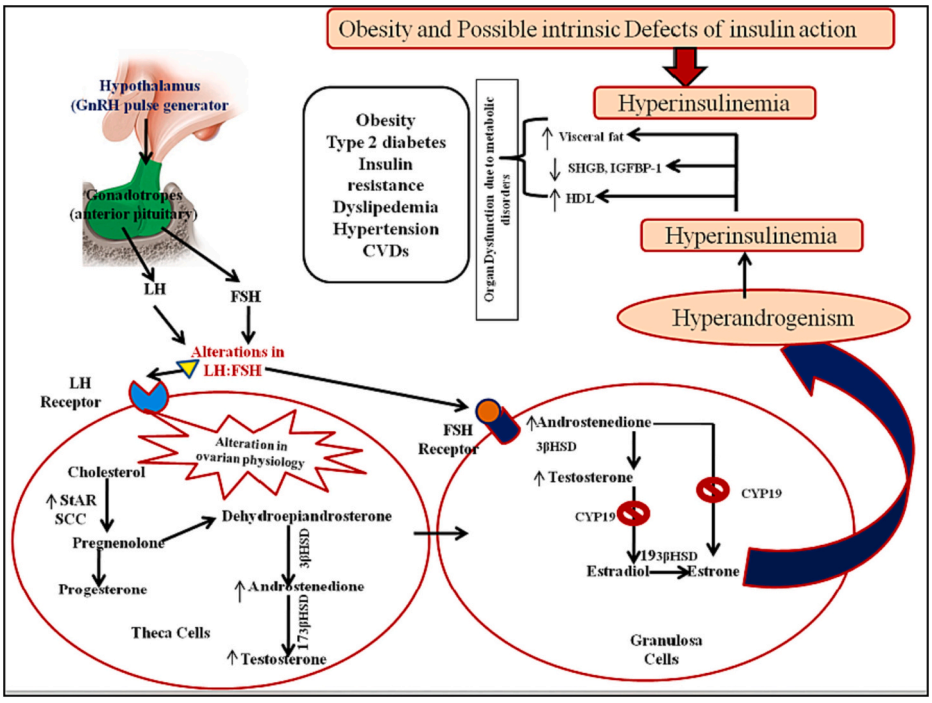

Fig. 2. Showing the development of PCOS and its pathogenesis. Disruption and irregular function of hypothalamic-pituitary-gonadal axis, desynchronizes the whole hormone circuit. Like structural changes in receptors of LH and FSH due to physiological dysfunction, interrupts the steroidogenic pathway, results in the hyperandrogenism in theca cells. The excess androgens are transported into the granulosa cells were the androgens are converted into estradiol and progesterone, but due to the dysfunctioning of α-aromatase enzymes, androgens are not converted into the estradiol, which in turn causes excess of androgens and the development of cysts, hormonal imbalance etc.

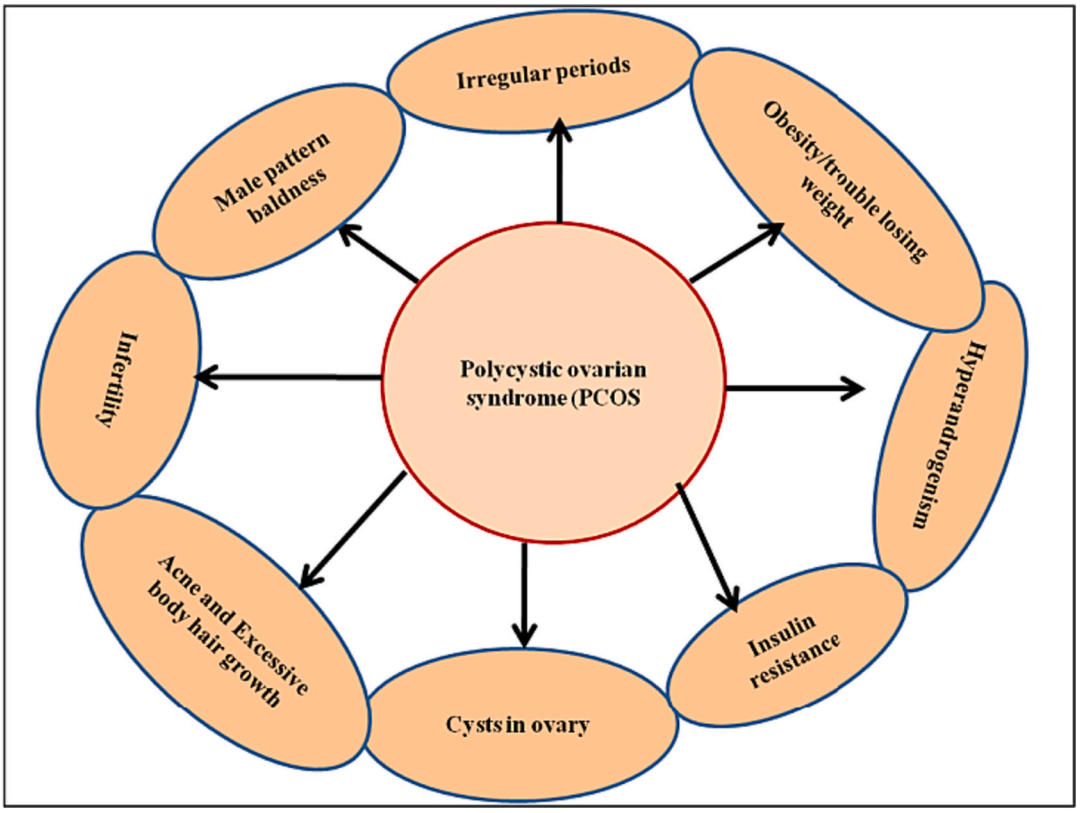

Fig. 3. Showing the various diagnostic symptoms of PCOS such as irregular menstrual cycle, hyperandrogenism, insulin resistance, cysts in ovaries, male baldness, infertility etc.

resulting in amenorrhea. These cysts can be as large as 10 mm, and the ovaries can swell up to 10 cm in width, hindering fertilization and making conception complicated (Bulmer, 2014). PCOS is linked to pregnancy-related problems like gestational diabetes and pregnancy-induced hypertension, elevating risks for eclampsia and small-for-gestational-age babies (McDonnell and Hart, 2017). Theca cells, which support growing follicles, respond excessively to insulin in PCOS patients, leading to elevated androgen levels. The distressed secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus is a key feature of PCOS, disrupting the menstrual cycle and causing amenorrhea (Roberts et al., 2020). This condition can be classified into primary amenorrhea, where menarche doesn't occur, and secondary amenorrhea, where menstrual cycles are absent for three or more consecutive months. The presence of an increased amount of lactotropin hormone blocks the activity of gonadotropin-releasing hormone.

2.2. Dysfunction of hypothalamus/pituitary-ovarian axis

PCOS involves an imbalance in sex hormones, leading to cyst formation in the ovaries. Elevated luteinizing hormone (LH) levels and a decreased follicle-stimulating hormone (FSH) level result in a higher LH/FSH ratio, which is often associated with an abnormal BMI in PCOS women. Excess androgen secretion inside the ovary is a significant factor in PCOS development, caused by hyperinsulinemia and altered steroidogenesis. In PCOS, there are more growing follicles than in normal controls, and the dynamics between various factors regulating follicle maturation remain unclear. PCOS is linked to disturbed follicular development, abnormal morphology, and dysregulation in the ovaries. Follicle density and the balance of factors affect the follicular growth continuum, with anti-mullerian hormone playing a crucial role in regulating follicular reserve. Androgens, mediated by androgen receptors, support the expression of essential enzymes and receptors in the follicles. The dominant follicle compensates for the loss of FSH stimulation, resulting in luteinizing hormone surge and subsequent ovulation. PCOS impacts the ovarian stroma, making it more rigid and less conducive to follicular growth. Abnormal growth during the early stages of follicular development contributes to the ovarian characteristics seen in PCOS (Franks et al., 2008).

2.3. Steroidogenesis in PCOS

2.3.1. Ovarian Steroidogenesis

The normal functioning of the ovary depends on the coordinated action of luteinizing hormone (LH) on the theca interstitial stromal cells and follicle-stimulating hormone (FSH) on granulosa cells (Orsi et al., 2014). Theca cells secrete androstenedione in response to LH, which is then converted to estrogen in granulosa cells under the influence of FSH (Richards et al., 2018). Maintaining an optimal level of androgen synthesis is crucial for follicle development, as excessive androgens can interfere with follicular maturation (Franks and Hardy, 2018). In PCOS, excessive androgen production is common. PCOS women exhibit hyperresponsiveness to gonadotropin-releasing hormones and human chorionic gonadotropin drugs, leading to increased ovarian androgen production. Insulin plays a significant role in augmenting ovarian androgen production by synergizing with LH.

The steroidogenic pathway involves multiple proteins and enzymes that convert cholesterol into biologically active steroid hormones. Steroidogenic acute regulatory protein (StAR) facilitates the translocation of cholesterol across the mitochondrial membrane, a crucial step in this pathway. Various enzymes, including cytochrome P450s, catalyze the conversion of cholesterol into pregnenolone and further into androgens like dehydroepiandrosterone and androstenedione. These androgens are produced in the theca cells and are converted into estrogens in granulosa cells under the influence of FSH. In summary, maintaining the right balance of androgen synthesis is crucial for proper follicle development, and disruptions in this balance, often seen in PCOS, can impact ovarian function and fertility.

3. Prevalence of PCOS associated comorbidities

PCOS is marked by hormonal imbalances, excess androgen production, menstrual irregularities, and fertility challenges. Diagnostic criteria encompass NIH 1990, Rotterdam 2003, and AE PCOS 2006, with higher prevalence using Rotterdam criteria. Global prevalence ranges from 5 % to 10 % (Mishra et al., 2021) (Figs. 4 & 5). Insulin resistance in PCOS affects follicular growth and ovulation (Huber-Buchholz et al., 1999). Lifestyle changes and weight loss improve insulin sensitivity and ovulation (Huber-Buchholz et al., 1999). PCOS significantly affects fertility and is a major cause of ovulatory disorders, also increasing the risk of miscarriage. Women with PCOS experience a substantial impact on health-related quality of life, affecting physical, emotional, and social aspects (Behboodi Moghadam et al., 2018). PCOS incidence varies based on factors like body weight, diet, lifestyle, and ethnicity, with obesity being a significant concern (Sendur and Yildiz, 2021). Hirsutism is distressing for about 70 % of women with PCOS. Infertility and irregular periods have a negative psychological impact on affected women (Behboodi Moghadam et al., 2018).

3.1. Pathogenesis of PCOS

Various factors are associated with the pathogenesis of PCOS, which involves the interactions among hormones, genes and environmental stressors.

3.1.1. Hyperandrogenism

Hyperandrogenism (HA) typically leads to a decrease in SHBG levels and an increase in free testosterone concentration. In PCOS women, elevated testosterone levels in plasma can be converted into estrone in adipose tissue. Disruptions in the conversion of estrone to estradiol affect follicle growth and disrupt the LH to FSH ratio, causing ovulatory dysfunction (Li et al., 2019). HA also up-regulates AMH levels, suppressing ovulation and follicle development through various mechanisms. Additionally, IGF-II levels, positively influencing follicle diameter and estradiol concentration in follicular fluid, are negatively associated with androgen, which HA decreases in follicular fluid (Li et al., 2018). HA indirectly increases LH levels (Moore and Campbell, 2017). Both estradiol and progesterone control GnRH and LH secretion through negative feedback mechanisms (Coyle and Campbell, 2019; Ruddenklau and Campbell, 2019). Hyperandrogenism disrupts this negative feedback, leading to increased LH levels (Ruddenklau and Campbell, 2019).

The interaction of androgen with its receptor interferes with progesterone receptor transcription. This receptor is associated with the conversion of higher androgens into compounds that alter GABA-A receptors, activate GnRH neurons, and weaken the response to negative progesterone feedback. Additionally, androgens can reduce hepatic nuclear-4 (HNF-4) levels by inhibiting lipogenesis. HNF-4 stimulates SHBG expression by binding to its promoter (Zhu et al., 2019). HA contributes to the progression of other PCOS factors such as insulin resistance (IR), inflammation, and oxidative stress. It intensifies IR through various pathways, decreasing insulin sensitivity, GLUT-4 expression, and suppressing insulin breakdown in hepatocytes (Li et al., 2018). Furthermore, HA accelerates a type of skeletal muscle fibers that have lower insulin sensitivity. However, HA exacerbates central obesity associated with IR.

Studies indicate that testosterone accelerates the production of inflammatory chemicals, including lipopolysaccharide-induced IL-6 in 3 T3-L1 cells, by activating specific signaling pathways (Li et al., 2018). HA-induced oxidative stress increases mononuclear cell sensitivity to glucose and worsens glucose-stimulated oxidative stress (Sanchez-Garrido and Tena-Sempere, 2020). It's important to note that dehydroepiandrosterone, an androgen, reduces interferon-γ (IFN-γ), a crucial

regulator for maintaining ovarian physiology and cellular functions (Li et al., 2018). Additionally, PCOS women resemble the fatty tissue of men, and HA affect adipocyte dysfunction (Escobar-Morreale, 2018). HA is a major cause of adipocyte hypertrophy and significantly impairs adipokine secretion (Fig. 8).

Understanding the role that hyperandrogenemia plays in the pathophysiology of polycystic ovarian syndrome (PCOS), given the generally high levels of circulating androgens in women with the condition, is crucial. One of the main debates centers around whether the elevated androgens in PCOS women are simply a result of the ovary being driven by an overactive gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion, or if the elevated androgens themselves act in the brain (or pituitary) during development and/or adulthood, thus shaping and maintaining the hypersecretion of GnRH and LH. Uncertainty persists regarding the processes through which increased androgens may modulate alterations in the neuroendocrine axis. Pinpointing the brain regions where androgen action occurs could provide crucial insights for the development of PCOS therapies.

3.2. Neuroendocrine implications: cellular and molecular mechanisms in PCOS

Clinical studies suggest that PCOS may have a neuroendocrine basis, with women with psychiatric conditions such as bipolar disorder and epilepsy being more susceptible to developing the syndrome (Qadri et al., 2018; Herzog et al., 1984). It has been postulated that altered GABA action and levels, which may be modulated by drugs like valproate, impact the hypothalamus-pituitary-gonadal (HPG) axis and contribute to the development of PCOS (Joe et al., 2001; Viswanathan et al., 2016; Zhang et al., 2016; Ghodke-Puranik et al., 2013). Collectively, these findings underscore the potential involvement of the neuroendocrine axis in the onset of PCOS.

Both the pituitary gonadotrope and the brain (GnRH output) have the capacity to regulate the amplitude of LH pulses. Changes at either tissue may be implicated in variations in the amplitude of the LH pulse or in basal LH levels. However, the timing of GnRH pulse secretion wholly determines the frequency of LH pulses and can be influenced by changes in the GnRH neurons themselves or modifications to the upstream GnRH pulse generator (Clarkson et al., 2017). The observation that LH pulse frequency changes in women with PCOS directly points to upstream alterations in GnRH pulse frequency and associated neuronal networks. In the following sections, we will highlight evidence suggesting that alterations in the brain, particularly in GnRH neurons and afferent hypothalamic GABA and/or kisspeptin neurons, may contribute to the neuroendocrine pathways underlying PCOS (Fig. 6).

3.3. GABAergic neurons

GABA serves as the primary inhibitory neurotransmitter in the forebrain and various other regions of the brain. However, GABA actually activates, rather than inhibits, GnRH neurons due to their high intracellular chloride concentration. The GABAA receptor facilitates GABA activation of GnRH neurons (DeFazio et al., 2002). Recent studies have revealed that women with PCOS exhibit elevated levels of gamma-aminobutyric acid (GABA) in their cerebrospinal fluid (Kawwass et al., 2017). While this remains speculative, the observed increase in GABA levels, known to stimulate gonadotropin-releasing hormone (GnRH) neurons, might contribute to the heightened GnRH secretion in women with PCOS. Additionally, research utilizing prenatally androgenized (PNA) and prenatally androgenized prenatally metyrapone-treated (PAMH) mice has demonstrated an augmentation in GABA neuron axon inputs to GnRH neurons, primarily originating from cells in the arcuate nucleus (ARN) (Moore et al., 2015; Tata et al., 2018). GABA neurons may play a role in the hyperactivity of GnRH neurons in PCOS, particularly in the PNA and PAMH models, as findings from investigations in PNA mice have indicated an increase in GABAergic postsynaptic currents onto the GnRH neurons (Sullivan and Moenter, 2004).

In addition to alterations in GABA transmission to GnRH neurons, PCOS animal models exhibit changes in GABA neuron regulation. Specifically, the expression of the progesterone receptor (PR) is less frequent in the ARN GABA neurons of PNA females, potentially contributing to the impaired steroid hormone feedback observed in this PCOS model (Moore et al., 2013; Moore et al., 2015). This finding aligns with certain PCOS women displaying a diminished progesterone feedback phenotype (Chhabra et al., 2005). Similarly, reduced PR mRNA expression in the ARN region has been observed in the LET mice model of PCOS, suggesting the possibility of reduced progesterone feedback in this model as well (Kauman et al., 2015). More research is needed to identify the specific neuron types exhibiting decreased PR expression in the ARN region and to confirm whether they include GABA neurons, as seen in the PNA animals. However, the lower PR levels in LET mice imply that GABA neurons, specifically ARN GABA neurons, may play a crucial role in mediating the normal progesterone negative feedback to the GnRH system, which is disrupted in a PCOS-like condition (Fig. 6).

Surprisingly, there is a limited number of publications focusing on ARN GABA levels, the quantity of GABA neurons, or GABA signaling to GnRH neurons in other animal models of PCOS, apart from the PNA and PAMH mice. Lower GABA mRNA levels were observed in the hypothalamus and other brain regions in a distinct LET model with elevated luteinizing hormone (LH) levels in rats treated with LET via oral gavage (Chaudhari et al., 2018). Moreover, compared to animals administered LET alone, co-administration of GABA and LET in this same LET model led to lower testosterone levels and body weight, suggesting that GABA may indeed inhibit the reproductive axis and that reduced inhibitory GABA signaling may be a component of PCOS (Ullah et al., 2017). This indicates that GABA can have both stimulatory and inhibitory effects on various cell populations in the brain, which contradicts the stimulatory GABA narrative in the PNA animal model. Afferent neurons known to stimulate GnRH neurons, such as kisspeptin neurons, might become more active due to a decrease in GABA levels. However, further research is necessary to test this theory. Therefore, the precise locations of GABA action in most in vivo investigations remain ambiguous and need to be elucidated (Fig. 6).

The Kiss1 gene encodes the 54-amino-acid protein kisspeptin, which operates through the membrane receptor kiss1r (Gottsch et al., 2006; Messager et al., 2005). It acts as a potent stimulator of neurons releasing gonadotropin (GnRH). In women with polycystic ovary syndrome (PCOS), there is a positive correlation between high blood levels of luteinizing hormone (LH) and circulating kisspeptin. These findings suggest that kisspeptin-Kiss1r signaling may be a promising candidate for a modified brain mechanism in the PCOS state, along with data from kisspeptin or Kiss1r knockout experiments demonstrating the significant role of kisspeptin and Kiss1r in GnRH/LH secretion (D'Anglemont de Tassigny et al., 2007; Lapatto et al., 2007).

Kisspeptin neurons found in distinctive regions of brain in different animals have been reported to have role in PCOS. In human females, these neurons are located in the rostral periventricular zone might resemble the rodent AVPV/PeN kisspeptin neurons that mediate positive steroid feedback. Most PCOS animal investigations have focused on the ARN kisspeptin neurons, akin to the human infundibular kisspeptin neurons, as women with PCOS exhibit aberrant elevations in LH pulse secretion. Immunohistochemistry revealed a significant increase in ARN kisspeptin- and NKB-positive cells in PNA female rats compared to control females (Osuka et al., 2016). Similarly, another study using PNA rats demonstrated increased ARN mRNA expression of Kiss1 and Tac2 (the gene for NKB) (Yan et al., 2014). In PNA sheep, the size of kisspeptin neurons increased, although the number of kisspeptin cells remained unchanged (Cernea et al., 2015). The heightened GnRH neuron activity and LH secretion observed in this PNA model of PCOS may be partially explained by the reported increase in kisspeptin cells or Kiss1 mRNA, given that kisspeptin typically activates GnRH neurons (Fig. 6).

The impact of dihydrotestosterone (DHT) or letrozole (LET) on kisspeptin neurons in postnatally treated models of PCOS has been investigated. In rats subjected to postnatal DHT treatment, both kisspeptin-immunoreactive (IR) cells in the ARN and Kiss1 mRNA in the hypothalamus were reduced (Brown et al., 2012). This corresponds to a lower LH level in this model compared to controls, as opposed to the higher LH level observed in PCOS (Osuka et al., 2016). Conversely, in the rat LET PCOS model characterized by females with elevated LH levels (Aliabadi et al., 2017), a similar increase in the number of ARN kisspeptin cells was observed compared to control females.

Overall, in mouse PCOS models, the quantity of kisspeptin cells and the levels of Kiss1 and Tac2 mRNA in the ARN positively correlate with LH levels. Since NKB stimulates kisspeptin neurons via the NK3 receptor and kisspeptin neurons are stimulated by kisspeptin (Ruka et al., 2013), findings in the PCOS models suggest the involvement of ARN KNDy neurons in promoting GnRH hyperactivity and thus increased LH pulse secretion. Recent clinical research in women with PCOS sought to inhibit KNDy neuron activity to reduce LH secretion. An NK3 receptor antagonist (George et al., 2016) was employed in the trial for a 28-day treatment of PCOS women. The results demonstrated a significant decrease in LH pulsatility and, consequently, in serum testosterone concentrations. The kisspeptin-NKB system presents a promising therapeutic target for lowering LH and testosterone levels in women with PCOS, as indicated by this phase 2 clinical trial (Fig. 6). However, long-term post-treatment blood LH or testosterone levels and ovulation were not evaluated.

Flutamide therapy led to a comparable decrease in LH levels in PCOS women as in control women following the administration of progesterone (P) and estradiol (E2) (Eagleson et al., 2000). This finding is significant because it suggests that hyperandrogenemia contributes to the poor steroid (E2 or P) hormone feedback observed in PCOS, as the same E2 and P administration failed to reduce LH in PCOS women not undergoing flutamide treatment [58]. These findings are supported by a recent study utilizing the prenatally androgenized (PNA) PCOS model, which demonstrated that treatment with the androgen receptor antagonist flutamide could reduce testosterone levels, reverse aberrant GnRH neuron morphology, and restore estrous cyclicity in PNA mice (Silva et al., 2018). This indicates that some of the GnRH abnormalities may be caused by hyperandrogenemia, either directly or indirectly (other aspects of GnRH physiology or upstream afferent pathways were not examined). This finding underscores the potential of anti-androgenic medications in the treatment of PCOS. However, it remains unknown whether the androgen blockade affecting the brain directly or other tissues was responsible for restoring these reproductive characteristics, and if it was in the brain, whether specific cell targets were involved, as the study only employed peripheral administration of flutamide.

A recent study using postnatally androgenised mice demonstrated that androgen receptor (AR) knockout in the brain (using Cre/lox technology) improved ovarian morphology and function and reduced obesity, supporting the significance of androgen signaling specifically in the brain (Caldwell et al., 2017). As it was assumed in that study that AR had been disrupted in every neuron, it remains unclear which precise brain region or regions, as well as which specific types of neurons, are involved. However, these findings suggest that androgen-induced changes in the GnRH neural network are likely critical in the pathophysiology of many PCOS cases and that androgen effects in the brain may contribute to the symptoms of PCOS.

The notion that androgens cause hyper-gonadal hormone secretion is fiercely debated, given that androgens, particularly in females, typically exhibit a negative feedback loop on the hypothalamic-pituitary-gonadal (HPG) axis. Consequently, elevated androgen levels would be expected to induce more negative feedback, leading to decreased GnRH/LH secretion, as opposed to reducing negative feedback and promoting increased GnRH/LH secretion. Indeed, androgen therapies reduce ARN Kiss1 levels in addition to LH secretion in vivo (Smith et al., 2005; Eagleson et al., 2000), thereby further diminishing GnRH production. Future research suggesting a role for androgens in driving the hypersecretion of GnRH in PCOS must address this inconsistency with the known negative feedback actions of androgen activities.

3.4. Hormones

Gonadotrophic hormones such as LH and FSH hormones, Estrogen, Progesterone and Testosterone mainly contribute to the pathogenesis of PCOS. High levels of androgens and luteinizing hormone in women with PCOS have been associated with reproductive issues, driven by the overproduction of sex steroids and hyperandrogenemia. Dysregulated release of gonadotropin-releasing hormone in the hypothalamus, as well as brain androgen signaling, potentially affected by changes in upstream regulators such as kisspeptin and gamma-aminobutyric acid (GABA) (Carmel et al., 1976), may contribute to the pathophysiology of PCOS.

The involvement of abnormal gonadotropin secretion and signaling in PCOS has also been supported by genetic evidence; LH and LH receptor (LHR) gene polymorphisms are closely associated with the syndrome (Deswal et al., 2019). Additionally, genome-wide association studies have revealed variations in or near the follicle-stimulating hormone receptor (FSHR), FSH subunit, and LH/choriogonadotropin receptor (LHCGR) genes, suggesting a potential role for these genes in the etiology of PCOS (Day et al., 2015; Mutharasan et al., 2013; Du et al., 2010).

3.5. GnRH neurons

Women affected by PCOS exhibit high LH pulse frequency and amplitude (Lizneva et al., 2016b; Kazer et al., 1987). The latter observation suggests alterations in the brain, the pituitary, or both. Conversely, the former indicates an increase specifically within the brain, either in GnRH neurons or in the upstream regulators of GnRH secretion.

Studies conducted in female mice with PNA have demonstrated higher GnRH neuron action potential firing activity compared to that in control females (Roland and Moenter, 2014), which aligns with the hypothesis of altered brain function. Additionally, GABAergic postsynaptic currents (PSCs) to GnRH neurons are more substantial and more frequent in PNA females, indicating an amplified GABAergic drive to these neurons. Likewise, another study revealed an increase in GABAergic synapses on GnRH neurons in PNA mice (Moore et al., 2015). Similarly, GnRH neuron firing increased in female PAMH mice, which was associated with a rise in GABA inputs onto GnRH neurons (Tata et al., 2018). These findings suggest that the heightened activity of GnRH neurons is responsible for the elevated LH secretion observed in these PCOS-like animals, given that GABA acts as an excitatory signal to GnRH neurons through the activation of GABAA receptors (DeFazio et al., 2002) (Fig. 4).

The increased GnRH activity is believed to be caused by a reduction in inhibitory steroid hormone feedback along with an increase in excitatory GABAergic inputs to the GnRH neurons. This is supported by research demonstrating that, compared to healthy control women, women with PCOS require larger doses of estradiol and progesterone to reduce mean LH levels, LH pulse frequency, and LH pulse amplitude. Furthermore, the PNA PCOS model strongly supports impaired steroid hormone feedback (Moore et al., 2013; Moore et al., 2015). After ovariectomy and estradiol (E2) administration, PNA mice exhibited a diminished LH response, indicating impaired E2 negative feedback modulation of GnRH/LH secretion in PNA animals. The defective steroid feedback is likely mediated by afferent neurons since GnRH neurons only express estrogen receptor (ER) β (Hrabovszky et al., 2001), not the main receptors providing negative feedback, such as the androgen receptor (AR) (Huang and Harlan, 1993) or classical ERα (Herbison et al., 2001). Therefore, the heightened activity of GnRH neurons may stem from changes in afferent neurons in the GnRH neural circuit that express steroid hormone receptors.

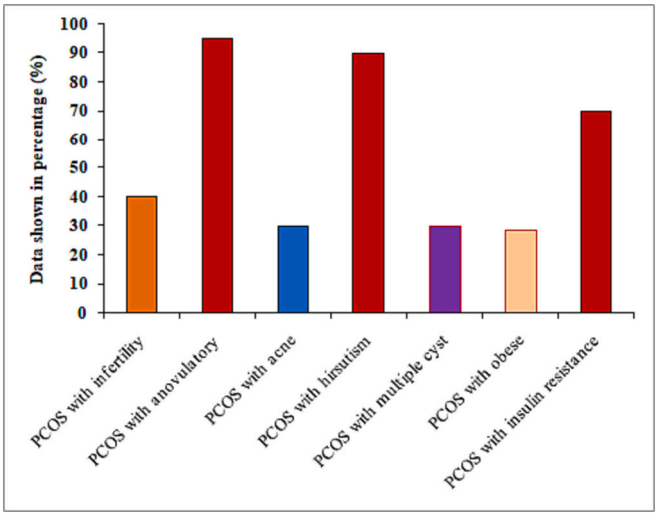

Fig. 4. Showing the occurrence of different diagnostic symptoms in PCOS women. Figures show that in most of the PCOS women show ovaries with multiple cysts along with anovulatory condition. Secondly With advancement in PCOS female shows growth of hairs on face and other parts of the body which gives her male like appearance. PCOS women develop insulin resistance followed by infertility, acne, and obesity.

3.5.1. *Environmental stressors, epigenetic mechanism and xenobiotics*

Hyperandrogenism and obesity are two significant factors contributing to the development of PCOS. Various genetic and environmental factors play a role in the progression of this condition. Some studies suggest that exposure to androgens during pregnancy may contribute to the development of PCOS in the fetus. Oxidative stress is also considered a potential cause of PCOS development. Consequently, antioxidant therapies are being explored for the treatment of PCOS. The use of herbal and Ayurvedic treatments has gained traction, reducing reliance on allopathic drugs to minimize secondary complications. Plants, rich in beneficial bioactive components, offer potential in the treatment of PCOS and associated disorders (Fig. 7;Tables 1 and 2).

3.6. *Environmental toxicants*

The United States Environmental Protection Agency (USEPA) defines endocrine-disrupting chemicals (EDCs) as exogenous molecules that interfere with the synthesis, secretion, transport, binding, or removal of natural hormones essential for maintaining homeostatic conditions, reproduction, development and behavior (Rocha et al., 2013). EDCs can act as hormone agonists or antagonists by binding to their respective receptors (Jones and Regan, 2019). These chemicals are found in everyday items and are structurally composed of phenols or halogens like chlorine and bromine, mimicking the action of steroid hormones (Rutkowska and Diamanti-Kandarakis, 2016). Long-term and continuous exposure to EDCs from prenatal stages to adolescence can increase the susceptibility to PCOS (Rutkowska and Diamanti-Kandarakis, 2016). One such EDC is bisphenol A (BPA), a synthetic compound used in polycarbonate plastics, epoxy resins, dental fillings, food and drink packaging, baby bottles, and polyvinyl chloride (PVC), all of which interfere with metabolic activities through different pathways. BPA directly impacts oogenesis by interacting with estrogen receptors (ER) and non-classical membrane ER, as well as G-protein-coupled receptor 30 (GPCR30). It activates androgen secretion and inhibits testosterone breakdown in theca cells (Rutkowska and Diamanti-Kandarakis, 2016; Soave et al., 2020). Additionally, BPA down regulates the activity of 17-hydroxylase (P450c17), leading to excessive androgen production in interstitial theca cells, and it also downregulates the activities of cholesterol side-chain cleavage enzyme (P450scc) and steroidogenic acute regulatory protein (Palioura and Diamanti-Kandarakis, 2013). BPA's effects on granulose cells down-regulate aromatase enzyme expression and estrogen production, ultimately disrupting the follicular environment and arresting oocyte progression and maturation (Palioura and Diamanti-Kandarakis, 2013). Indirectly, BPA affects hyperandrogenism by reducing the regulation of testosterone 2a-hydroxylase and testosterone 6b-hydroxylase enzymes in hepatocytes, increasing testosterone concentration. BPA is a strong ligand for sex hormone-binding globulin (SHBG) and replaces testosterone, further elevating free testosterone levels (Fig. 7). This reciprocal relationship between androgen and BPA inhibits uridine disphosphate-glucuronosyl transferase enzyme activity, leading to increased levels of free BPA in the bloodstream and worsening its adverse effects on the ovaries (Palioura and Diamanti-Kandarakis, 2013).

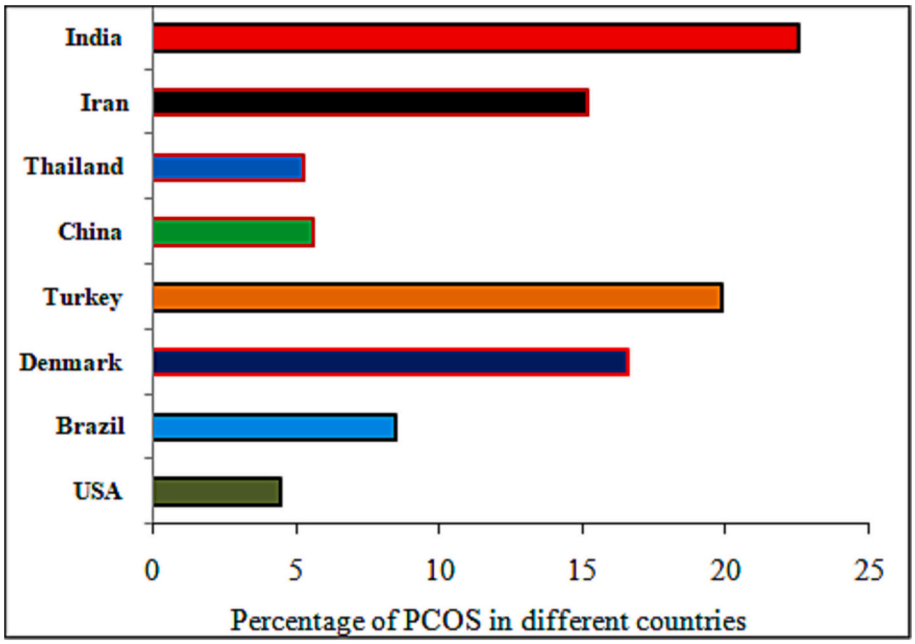

Fig. 5. Showing the country wise data of PCOS, India stands on the top of the list. Followed by Iran, Turkey, Denmark and Brazil respectively.

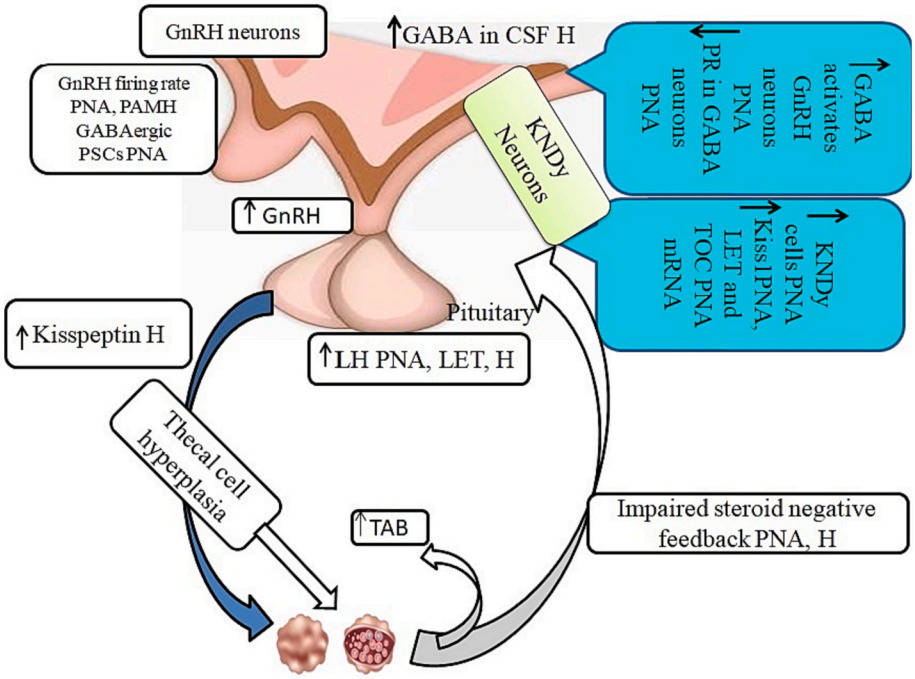

Fig. 6. Represents the cellular insights responsible for PCOS neuroendocrine disturbances.

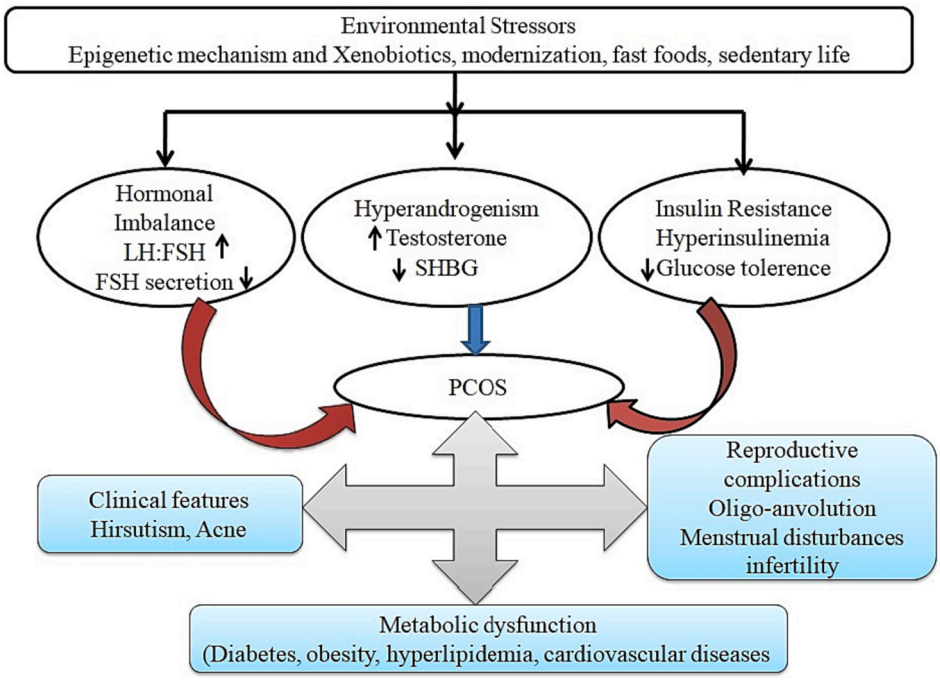

Fig. 7. Represents the role of different environmental factors for the induction of PCOS, reproductive, ovulatory, menstrual and metabolic dysfunctions.

Another group of chemicals affecting body health is advanced glycation end products (AGEs), also known as glycotoxins. AGEs are pro-inflammatory molecules interacting with their cell surface receptor, RAGE (receptor for AGE), stimulating pro-inflammatory cascades and oxidative stress (Soave et al., 2020; Wang et al., 2020). The body can absorb AGEs as exogenous compounds or derived from non-enzymatic glycation and oxidation of proteins and lipids (Rutkowska and Diamanti-Kandarakis, 2016). PCOS women often exhibit higher levels of AGEs in circulating serum. AGEs interfere with pre-ovulatory follicular growth through the ERK1/MAPK pathway and damage developing follicles through oxidative stress caused by their interaction with RAGEs. This association raises intracellular molecule levels. In vitro studies reveal that glycotoxins trigger adipogenesis in 3T3-L1 cell lines. Interestingly, increased body mass index corresponds to decreased levels of soluble RAGEs, responsible for glycotoxin clearance and accumulation of AGEs in the reproductive system, particularly in ovaries (Soave et al., 2020). AGEs contribute to IR by disrupting glucose transport in human granulose KGN cell lines and decreasing glucose uptake by adipocytes. Additionally, they are associated with IR by inducing oxidative stress, inflammation, and protein glycation, significantly reducing

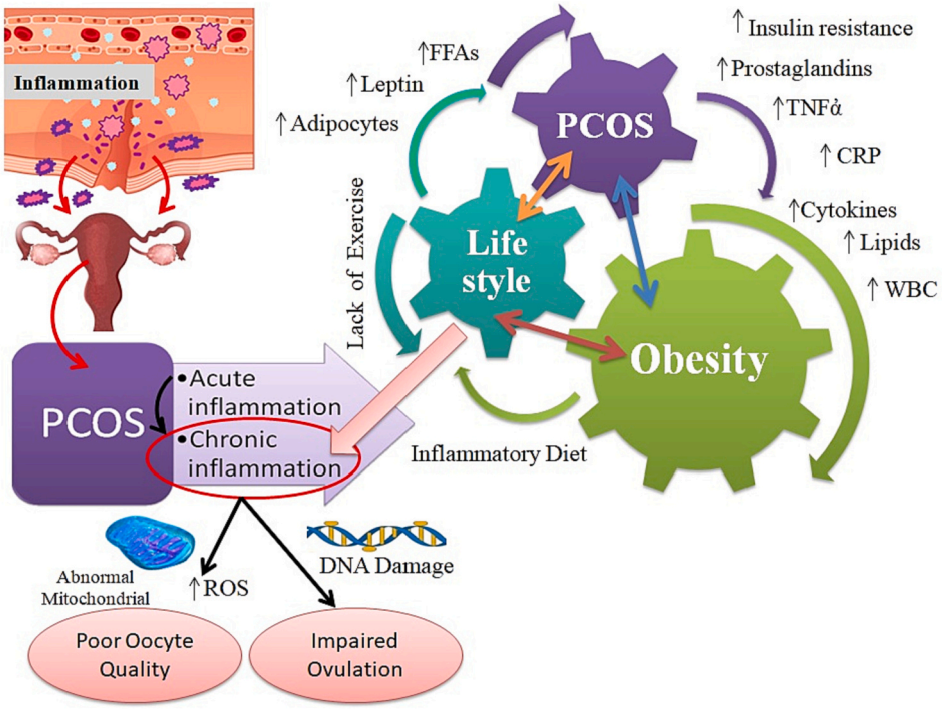

Fig. 8. Showing the various biological activities and factors responsible for the causation of inflammation in PCOS.

insulin sensitivity. Higher levels of AGEs modulate the insulin signaling pathway and interfere with glucose transporter-4 (GLUT4) translocation.

3.7. Stress

While there's limited information on stress directly causing PCOS, it's known that PCOS can adversely affect self-esteem and mental health. Prolonged stress triggers excessive growth and enlargement of adipocytes, initiated by the hypersecretion of glucocorticoids and their impact on pre-adipocyte maturation. Stress also leads to negative effects such as adipokine secretion, attraction, and activation of stromal fat immune cells (Stefanaki et al., 2018). Glucocorticoid-induced stress induces inflammation, evidenced by increased levels of inflammatory cytokines like IL-6 and TNF-α, and disrupts the activity of antioxidant enzymes (Stefanaki et al., 2018). Stress negatively activates the hypothalamic-pituitary-adrenal (HPA) axis, releasing cortisol, which contributes to the development of insulin resistance (IR) by stimulating fat accumulation in visceral organs, gluconeogenesis, and lipolysis (Yang et al., 2018a). Cortisol also increases glucose generation in hepatocytes (Yang et al., 2018a). Additionally, stress is associated with hypersecretion of insulin levels in the circulatory blood. Other stress-induced factors linked to PCOS development include interference with anti-mullerian hormone (AMH) and alterations in reproductive hormonal levels (Yang et al., 2018b; Steegers-Theunissen et al., 2020).

3.8. Genetic factors

Familial clustering in PCOS suggests genetic factors play a role (Diamanti-Kandarakis et al., 2006). Studies, including those on genetically identical twins, confirm a genetic origin of PCOS (Vink et al., 2006). However, it remains uncertain whether genes related to testosterone and insulin synthesis and metabolism are inherited (Jones et al., 2010).

3.9. Epigenetic mechanism

Epigenetics modifications can involve the addition or deletion of chemical components on DNA or histones (Fig. 7). PCOS women often exhibit hyperactivity of LH, which may be linked to follicular and HA development dysfunctions (Ibáñez et al., 2017). The LH/choriogonadotropin receptor (LHCGR) regulates the steroidogenic process in theca cells (Fenichel et al., 2017). However, due to receptor hypomethylation, gene expression increases along with LH sensitivity (Ibáñez et al., 2017; Abbott et al., 2019). The hypomethylated sequences are associated with the over-expression of LHCGR on the surface of theca cells. Additionally, the active epoxide hydrolase 1 (EPHX1) enzyme is crucial for the degradation of aromatic compounds (Ilie and Georgescu, 2015; Fenichel et al., 2017; Rutkowska and Diamanti-Kandarakis, 2016). Gene promoter hypomethylation of EPHX1 leads to increased enzyme expression (Ilie and Georgescu, 2015). Excessive EPHX1 production reduces the conversion of testosterone to estradiol, contributing to PCOS development. Peroxisome proliferator-activated receptor gamma (PPAR) is vital for proper ovarian functioning (Ilie and Georgescu, 2015; Fenichel et al., 2017; Ibáñez et al., 2017; Qu et al., 2012). However, in PCOS women, hypermethylation of PPAR, hypomethylation of nuclear co-repressor 1, and modulation of histone deacetylase 3 acetylation (which acts as co-repressors for PPAR) have been observed, revealing HA (Ilie and Georgescu, 2015; Fenichel et al., 2017; Ibáñez et al., 2017; Qu et al., 2012). These modifications were observed in the granulose cells of PCOS patients (Ibáñez et al., 2017; Li et al., 2019).

3.10. Diet

Although clear evidence regarding the role of nutrition in PCOS is lacking, previous studies have indicated a connection between nutrition and PCOS indicators (Fig. 7). The consumption of saturated fatty acids (SFAs) has been linked to PCOS development by promoting inflammatory cytokines and reducing insulin sensitivity (Szczuko et al., 2021). SFAs induce inflammation by elevating TNF-α levels in the circulatory serum and expression of specific cytokine-suppressing genes (Szczuko et al., 2021). Additionally, a deficiency of vitamin D may exacerbate

Table 1
Factors, Sources, and Roles in PCOS Development.

S. No.	Factor	Source	Role in PCOS development	References
1	Change in diet	Intake of sugar drinks, fried foods, processed meat Refined carbohydrates (e.g. white bread, sweetened yogurt, ice creams with surplus sugar	All these factors triggers the development of PCOS	Lydic and Juturu, 2008
2	Geography and Economic and social status	Use of synthetic fertilizers, pesticides and insecticides.	All these chemicals disrupts the environmental toxins	Pathak (2023), Galt and Asprooth (2021)
3	Stress	Stress is one of the main causes in the development of PCOS. PCOS in turn results in anxiety, depression and severe mental health issues.		Damone et al., 2019
4	Xenobiotic exposure	Various toxins such as pesticides, bisphenols A (BPA) or phthalates, a weakened immune system, poor diet, and family history of PCOS are the major contributes causing this syndrome	EDCs might act as hormones agonists or antagonists and binds with their receptors BPA directly induces negative impacts on oogenesis by interacting with estrogen receptor (ER) and non-classical membrane ER, and G-protein coupled receptor 30 (GPCR30)	Dunn, 2021
5	Life style modification	Obesity, lack of exercise and weight gain leads to metabolic imbalances, such as insulin resistance Lack of nutritional food and sedentary lifestyle also contributes in the development of the PCOS	Deskbound lifestyle and a diet of fried foods, processed meats, sausages, hot dogs, and a diet rich in fat and carbohydrates, such as intake of too much sugar and carbonated drinks, cause obesity and insulin and hormonal imbalance that cause PCOS by stimulates androgen receptors present outside the ovary	Smyka et al., 2017
6	Ethnic background and Race	All races and ethnic groups are influenced by affected PCOS, but black women are mostly affected in comparison other ethnic groups e.g., hirsutism is more prevailing in black women having PCOS Different race possesses various features e.g., most severe phenotype is exhibited by Hispanic women	**In Asian countries** 6.3 % women have been diagnosed with PCOS 52 % Asian women living in the Indian subcontinent. **Hispanic women** showed excessive hair growth (93.8 % vs. 86.8 %), abnormal free androgen index (75.8 % vs. 56.5 %), abnormal homeostasis model assessment (52.3 % vs. 38.4 %), and hyperglycemia (14.8 % vs. 6.5 %) living in the Indian subcontinent **African women** having incidence of 8.0 % for Black women and 4.8 %	Zhao and Qiao, 2013
7	Genetic variations	PCOS is a genetic syndrome it involves CYP11a, CYP21, CYP17 and CYP19 genes	Inhibition of aromatization of androgen into estrogen and progesterone in theca and granulosa cells	Chaudhary et al., 2021
	Contraceptives	Birth control pills and other unprescribed drugs	Disturbs the hormonal homeostasis, disrupts hypothalamic-pituitary-ovarian axis.	Riddell et al., 2018

PCOS and its comorbidities (Muscogiuri et al., 2017). Calcitriol, an active form of vitamin D, up-regulates insulin receptor expression at both mRNA and protein levels, enhancing insulin sensitivity directly and indirectly (Fig. 7). The indirect effect involves stimulating PPAR-γ, a receptor associated with fatty acid metabolism in adipocytes and skeletal muscles, and regulating intracellular calcium crucial for insulin-mediated signaling in adipocytes and muscles (Muscogiuri et al., 2017). Conversely, a deficiency in vitamin D is associated with insulin resistance through an inflammatory reaction (Ciebiera et al., 2021). Moreover, a lack of vitamin D has been reported to down-regulate the expression of the anti-Mullerian hormone (AMH) promoter (Ciebiera et al., 2021).

3.11. Insulin resistance (IR)

Insulin resistance (IR) is characterized by an inadequate and improper response to insulin (Greenwood and Huddleston, 2019). IR is not dependent on factors like adiposity, body fat distribution, and androgen levels (Petrakis et al., 2017) and can affect lean patients as well (Shang et al., 2020). In PCOS women, IR is tissue-specific (Dabadghao, 2019), with various tissues losing their insulin sensitivity, including skeletal muscles, adipocytes, and hepatocytes (Dabadghao, 2019; Rosenfield and Ehrmann, 2016), while the adrenal gland and ovaries retain their sensitivity (Dabadghao, 2019; Rothenberg et al., 2018). Insulin directly activates androgen production and follicle growth in ovaries (Rosenfield and Ehrmann, 2016; Jeanes and Reeves, 2017; Polak et al., 2017; Zhang et al., 2020) by stimulating receptors in follicular cells (He and Li, 2020). It also enhances enzymes like P450c17 and P450scc involved in steroidogenesis (Bannigida et al., 2018; Avery et al., 2011) in synergy with LH and insulin-like growth factor 1 (IGF-1) (Rothenberg et al., 2018). Hyperinsulinemia amplifies LH-binding sites and androgen response to LH (Rosenfield and Ehrmann, 2016),

Table 2

Table 2a: Showing different factors involved in the development of Polycystic Ovarian Syndrome and associated complications. 2b-Represents various therapies, remedies and biomolecules used for the treatment of PCOS and their side defects and associated comorbidities. 2b- various herbal formulation used for the treatment of PCOS in different experimental animals models. 2c-various bioactive compound used for the treatment of PCOS and 2d-depicts role of biomolecules for the management of PCOS.

Name of drug	Effect	Side defect	Experimental animals/women	Treatment doses	Experiment duration	References
Table 2a: Showing different factors involved in the development of Polycystic Ovarian Syndrome and associated complications						
Clomiphene Citrate	Antagonist of estrogen receptors, Considered as a first-line agent for ovulation induction in PCOS patients Initiates Ovulation by stimulating growth of ovarian follicles and secretes FSH and LH from the brain's pituitary gland	Risk factors, including the elevated blood pressure level, smoking and clotting history, and obesity.	Female albino Rats and Human female	50 mg orally/day	5 days	Legro et al., 2007 Sovino et al., 2002 Chang et al., 2019
Tamoxifen	Tamoxifen blocks estrogen receptors in the hypothalamus, which causes ovarian stimulation	Increased bone or tumor pain, pain or reddening around the tumor site. Hot flashes, nausea. Excessive tiredness, dizziness, depression, headache.	Female albino Rats and Human female	60 mg orally/day	5 days	Dhaliwal et al., 2011.
Aromatase Inhibitors	Very potent in inducing ovulation (e.g., anestrazole and letrozole) Aromatase is necessary for the production of follicles	Aromatase inhibitors (letrozole causes hyperandrogenism	Human female and Female albino Rats and	2.5 mg/day & 1 mg/kg	21 days	Nugent et al., 2015; Basheer et al., 2023; Rani et al., 2022; Torjesen, 2016
Gonadotropins	Exogenous gonadotropins are considered second-line therapy for ovulation in PCOS patients These help to induce ovulation, proper growth, and maturation of oocytes and makes them capable to be fertilized.	Multiple pregnancies, multiple follicles development, and ovarian hyperstimulation syndrome (hCG-mediated production of vasoactive mediator)	Human females	150 U/d	4 days	Nugent et al., 2000 Lunenfeld et al., 2019 Zong et al., 2022
Metformin	Antidiabetic agent for type II diabetes weight loss and has a lesser effect on lowering Testosterone levels. It improves ovulation and decreases androgen levels. Reduces insulin level increases insulin sensitivity.	Bloating, Gas Diarrhea, Belly pain Constipation, Little appetite	Human females	1500–2550 mg/day (500 or 850 mg three times daily	3 months	McCreight et al., 2016
Troglitazone	Antidiabetic Having promising effects on testosterone levels	Infection, headache. runny or stuffy nose. urinary tract infection. Diarrhea, weakness. Dizziness, swelling of the extremities.	Mice/Human	200 mg or 400 mg daily.	1 to 6 (weeks) or 4 to 6 (weeks)	Dunaif et al., 1996
Spironolactone (an Aldosterone Antagonist)	Single-drug therapy decreases hirsutism (up to 40 %) Its combination with oral contraceptives further augments the effects up to 75 % with a fall in hirsutism upto 45 %.	General complaints of nausea and menstrual irregularities It also inhibits adrenal and ovarian steroidogenesis	Human Female	50 mg bid on days 5–25 of menstrual cycle	9 months	Cappelli et al., 2017 Layton et al., 2017; van Westerloo et al., 2005
Flutamide	Nonsteroidal antiandrogens and It block the action of both endogenous and exogenous testosterone. Combination of flutamide and metformin shows a synergistic effect. It is also effective against hirsutism.	Dry skin and teratogenicity, limit its use in women with PCOS	Human Female	250 mg	0.5–3 months	Gambineri et al., 2006 Layton et al., 2017; van Westerloo et al., 2005
Finasteride	Finasteride is a 5-reductase inhibitor. Blocks the production of androgens by inhibiting its isoenzyme. Blocking androgens in the hair follicles, it lessens the PCOS-related hair loss	Risk for teratogenicity in male fetuses	Human females	5 mg (mg) once a day	Varies according to the disease	Swiglo et al., 2008
Statins	Very effective in cardiovascular and endocrine support for PCOS patients Reduces inflammation and decreases lipid levels and hyperandrogenism.	Teratogenicity is also associated with their use in PCOS patients	Human females	5–80 mg	12 weeks	Cassidy-Vu et al., 2016 Unluhizarci et al., 2009; Wüster et al., 2023;

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Table 2 (*continued*)

Name of drug	Effect	Side defect	Experimental animals/women	Treatment doses	Experiment duration	References
IVF (In Vitro Fertilization) Techniques	IVF for patients unable to get pregnant using the single-embryo transfer technique Risk of multiple gestations be overcome	None	NA	NA	NA	Badawy and Elnashar, 2011
Glycyrrhiza glabra L	Decreases level of Testosterone Used against hirsutism in PCOS patients	None	Mouse model	100 mg/kg	3 months	Yang et al., −2018
	Reduces Testosterone (T) level Suppresses transformation of androstenedione to T and might be useful for expressions of androgenization		Human trial (seven men)	Commercial preparation of licorice tablets	1 wk	Bergner, 2016
Aloe vera (L.) Burm. f.	It restores the steroid status in ovaries and modulates the steroidogenic activity and estrus cyclicity	None	Rats/letrozole induced PCOS	1 ml of *aloe vera* gel 100, 200&400 mg/kg of yellow aloe extract intraperitoneally	45 days	(Maharjan et al., 2010; Radha et al., 2016 Moini Jazani et al., 2019
Linum usitatissimum L. (Flaxseed)	1. Reduces level of androgen, hirsutism, obesity, and insulin Decreases volume of ovaries, number of follicles. 2. Improves th e cyclicity the menstrual cycles but did not alter the body weight, blood sugar or hirsutism" 3. Positive effect on PCOS, due to the reduction in T, E2, LH and insulin levels essential for the maturation of follicles maturation, and the anti-inflammatory actions to the 4. Decrease in ovarian volume"	None	Open-label interventional study (32 women with PCOS)	Orally 15 g flax seed powder	3 months	Nowak et al., 2007 Fatima Farzana et al., 2015
Cinnamomum verum (Cinnamon)	Very effective to IR and increases insulin action activates insulin-signaling pathway by increasing P13—K activity and hence decreases insulin resistance	None	Human female	1 g (1capsule contains 333 mg of cinnamon extract 3times/day) 3 capsules of cinnamon (500 mg/capsule)	8 weeks	Sun et al., 2004 Borzoei et al., 2018; Wang et al., 2020
	Improves insulin resistance by suppression of tyrosine phosphatase and improves insulin sensitivity, renovate ciclicity, reduces IGF-1, increases IGFBP-1 and down-regulated T in PCOS rats 2. Hepatoprotective, antioxidant, anti-obesity, antihyperlipidemic and antidiabetic activities	None	Rats/dehydroepiandrosterone	10 mg/100 g	20 days	Dou et al., 2018 (34)
Anise (Pimpinella anisum)	1. Decreased signs of PCOS in rats by effects on the histo-morphologies of the ovarian tissue 2. Ameliorated the hormonal profile of PCOS (FSH, LH, P4)	None	Rats/estradiol valerate induced PCOS	200 mg/kg, 400 mg/kg	15 days	Mahood, 2012
Curcuma longa L. (Curcumin)	Decrease androgens level and improves ovulation	None	Estradiol-valerate injected Wistar rats	100, 200, 300&400 mg/kg	14 days	(Nabiuni et al., 2015; Amini et al., 2018;
			Letrozole administered Wistar rats	100 and 200 mg/kg	6–12 weeks	Alibraheemi et al., 2021; Chien et al., 2021
			Women with PCOS	500–1500 mg/day		
Berberine (BBR), a major active component of the Chinese herbal medicines Rhizoma Coptidis, Cortex Phellodendri, and Cortex Berberidis	1. decreases level of LDL, triglycerides, cholesterol, glucose, insulin and insulin resistance levels as well as increased HDL and SHBG 2. Combination of BBR with Chinese prescription Cang Fu Dao Tan Tang reduced BMI, HOMA-IR, FIN-D2D, T, LH, and LH: FSH, LDL-C, and the effect on TG, LDL-C, and HDL-C"	None	Human trial (89 women)	BBR at a dosage of 3 × 500 mg daily	3 month	Wei et al., 2012 Cai, 2012 Wang, 2015
Dodder (Cuscuta)	1.Reduces ovario-uterine viscera indexes 2.Reduces LH:FSH ratio, serum PPRL and INS levels, IGF-1andTNF-α 2. Restores the pathologic alteration of uterus and (like endometrial glandular hyperplasia, irregular or tubular arrangement)	None	Rats/ dehydroepiandrosterone, combined human chorionic gonadotropin	200 mg/kg,100 mg/kg,50 mg/kg	3 weeks	Miao et al., 2019 (41)

(*continued on next page*)

Table 2 (*continued*)

Name of drug	Effect	Side defect	Experimental animals/women	Treatment doses	Experiment duration	References
Pomegranate (Punica granatum	1. Presence of phenolic in the pomegranate extract compounds reduces the effect of Testosterone 2. Decreases the impedimens related with PCOS and increases the level of f female sex hormones by decreasing the concentration of E2, free T, and andrestandion hormones in PCOS	None	Rats/estradiol valerate induced PCOS	100 mg/kg, 200 mg/kg, 400 mg/kg,	81 days	Kargar Jahromi et al., 2015 (18)
Pergularia (Pergularia daemia	1. Upgrade the level of fundamental female hormones in the menstrual cycle: FSH, LH, E2, P4 and T. Hence used for the treatment in infertility. 2. Decreases level of lipids (LDL, triglycerides, cholesterol) and glucose levels in the serum. Hence might be helpful to manage obesity pattern in PCOS rats	None	Rats/testosterone propionate induced PCOS	1 ml fresh Pergularia leaves extract every day	15 days	Poornima et al., 2015 (19); Bhuvaneshwari et al., 2015 (20
Combination of Paeonia spp. and *Glycyrrhiza glabra*	Synergistic effects on polycystic ovary Improvement of follicles in the ovaries	None	NMRI mice	50, 100 mg/kg/day	20 days	(Takahashi and Kitao, 1994; Westphal et al., 2006 Sadinpour et al., 2020
Vitex agnus-castus L. (Chaste Berry	Used for the treatment of PCOS. Reduction of PCOS risk symptoms like anovulation, amenorrhea, and pelvic pain Regulates hormonal level. **1.** Maintains the profile of sex steroid, LH: FSH ratio, steroidogenic enzymes in serum. Regulates glucose level and estrous cycles 2. Induces its protective impact by restoring the level of serological indicators associated with PCOS due to presence of phyto-components.	None	Rats/letrozole induced PCOS	200, 400 mg/kg	66 day	Zeng et al., 2022 Ammar and Salem, 2021 Kakadia et al., 2019 (40)
Urtica dioica L. (Stinging Nettle)	Reduces the level of testosterone. Increase the production of SHBG. Corrects the hormonal imbalance in PCOS Improvement of reproductive function	Prolonged treatment causes hypotension	NMRI mice	(1) 200, 400 mg/kg (2) 125, 250 mg/kg (3) Combination 200 & 125 mg/kg;	30 days	(Najafipour et al., 2014; Zare et al., 2015)
	Effective in decreasing some common symptoms of metabolic syndrome and type 2 diabetes in PCOS relating to its ability in adjusting the lipid profile and increasing the sensitivity to insulin, because of its flavonoid compounds" 2. "Increased insulin sensitivity, reduced hepatic necrosis and may reduce inflammation and improve metabolic symptoms in PCOS rats"	None	Rats/letrozole induced PCOS	150 mg/kg, 250 mg/kg, 450 mg/kg,	21 days	Zare et al., 2015 (22)
Camellia sinensis (L.) Kuntze (Green Tea)	Green tea modulates level of Gonadotrophins and other metabolic hormones (glucose, insulin, progesterone, LH, and testosterone) Decreases IR and weight in rats. Improves morphology of ovary Green tea is a generally used herbal remedy for weight loss Decreases the number of cysts in ovaries	None	Rat model/Human females	500 mg/day 540 mg of	12 weeks and 45 days 3 months	(Ghafurniyan et al., 2015) Raheleh and Damoon (2022); Mombaini et al., 2017; Chan et al., 2006
Licorice (Glycyrrhiza glabra)	1. Decreased T 2. Inhibited conversion of androstenedione to T and might be useful for expressions of androgenization	None	Human trial (seven men)	7 g of a commercial preparation of licorice tablets	1 week	Bergner, 2016
Hazelnut (Corylus avellana)	1. "Ability to regulate gonadotropins, steroids, serum lipid parameters, and also it had antioxidant activity in PCOS, which could be attributed to the relatively high total phenol content of the extract" 2. Decreased leptin and glucose concentration	None	Rats/letrozole induced PCOS	2 ml	45 days	Demirel et al., 2016
Palm pollen (Phoenix dactylifera)	1. Reduced the number of cystic follicles, improved tissue symptoms and adjusted the levels of sex hormones in PCOS	None	Rats/estradiol valerate induced PCOS	200 mg/kg, 400 mg/kg	21 days	Karimi Jashni et al., 2016 (25)

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Table 2 (*continued*)

Name of drug	Effect	Side defect	Experimental animals/women	Treatment doses	Experiment duration	References
	2. "Increased the number of primary, antral and graaffian follicles as well as the corpus luteum"					
Silybum marianum (L.) Gaertn. (Milk Thistle)	Very effective to regulate level of hormones regulation Combined treatment of metformin and *Silybum marianum* were found more beneficial in for the treatment of PCOS symptoms, like anovulation.	None	Rat model	420 mg/day orally 12 to 15 g	41 months	Rani et al., 2022 Zeng et al., 2022 Milić et al., 2013 van Wyk and Wink, 2004
Gymnema sylvestre (Retz.) R. Br. ex Sm. (Gymnema)	Antidiabetic and lipid-lowering action Regulates insulin activity	None	Mice model	500 mg/kg	28 days	Zeng et al., 2022 Jangam et al., 2024
Trifolium pratense L. (Red Clover)	Used for the treatment of acne and associated symptom of PCOS used for the treatment of Endometriosis, breast cancer, and ovarian cancer It increases the level of progesterone	None	Rat model	500 or 750 mg/kg	30 days	Abbasian et al., 2020
Cucurbita pepo L. (Pumpkin Seeds)	Presence of omega 3 fatty acids make its use for hyperinsulinemia and decrease cholesterol levels. Beta-sitosterol present in *Cucurbita pepo* used to reduce excess testosterone levels Used also for the treatment of other symptoms of PCOS, such as acne, hirsutism, and obesity.	None	Rat model	20, 50,100 mg/kg	21 days	(Szczuko et al., 2017) Zeng et al., 2022 Motamed-Jahromi and Niami-Jahromi (2019)
Oenothera biennis L. (Evening Primrose Oil)	oil of ***Oenothera biennis*** is used to lower luteinizing hormone/FSH and testosterone levels Phytoestrogenic chemicals present in the Evening primrose effectively acts on the hypothalamic-pituitary axis.	None	Women	70–140 mg of Gamolenic Acid (GLA) containing primrose (*Oenothera biennis*) seeds with concentrations of 7–14 %	8 weeks	Zand Vakili et al., 2018).
Calligonum polygonoides	1.As an antioxidant, decreased ovary cysts, oxidative stress and ROS, and eliminated free radicals in PCOS model 2. Improved invitro fertilization rat and reduced weight	None	Rats/estradiol valerate induced PCOS	20 mg/kg	2 months	Tahmasebi et al., 2018 (37)
Tribulus terrestris L. (Puncture Vine)	Used for the treatment of menstrual irregularities, increases ovulation, used as Antidiabetic agent	None	*Invitro* studies	1 or 10 μg/ml	3–5 days	(Arentz et al., 2014; Parikha and Krishna, 2019). Sirotkin et al., 2020
Mentha spicata L. (Spearmint Tea)	Reduces hirsutism and testosterone levels after 30 days of treatment and simultaneously increases LH and FSH levels	None	Rat model	(500 mg/kg)	20 days	Grant, 2010; Goswami et al., 2012). Alaee et al., 2020
Matricaria chamomilla L. (Chamomile)	*Matricaria chamomilla* L. reduces the testosterone level No lipid parameters, LH/ FSH ratio, and DHEAS level	None	Rat model	75 mg/kg	30 days	(Amir et al., 2007
Astragalus dasyanthus Pall. (Astragalus Polysaccharide)	Decreases insulin resistance, lipid metabolism, and reduces the incidence of high testosterone levels. After treatment of treatment it decrease fasting serum insulin and LH/FSH level	None	Rat model	25, 50, 75 (mg/kg)	10 days	Luo et al., 2009; Goswami et al., 2012
Foeniculum vulgare Mill. [Apiaceae]	Traditionally used for the treatment of anovulation/infertility it is used as strong anti-inflammatory, estrogenic, and antioxidant agent, hence might be potential treatment option for PCOS Regulates hormonal level like it increases FSH, while as it decreases LH and testosterone.	None	Rats/estradiol valerate induced PCOS	250,500,1000 mg/kgBW,	4–10 days	(Karampoor et al., 2014).
Welsh onion (*Allium fistulosum*).	LedtoalowplasmaLH:FSHratio,highE2levels, ovarianmorphology, folliculogenesis-relatedgene expression" 2. InfluencedaromataseproductionandenhancedE2 synthesis 3."Restoredtheestrogenicfeedbackmechanismin thepituitary-ovarysystem"	None	Rats/letrozole induced PCOS	500 mg/kg	2 wk	Lee et al., 2018
Guggul (Commiphora wightii)	Had a potential role in reducing DHEA-induced PCOS by reducing the morphological abnormalities of ovarian follicles and restoring hormonal levels to normal in adult rats"	None	Rats/dehydroepiandrosterone (DHEA)	100 mg/kg	15 days	Kavitha et al., 2016

(*continued on next page*)

Table 2 (*continued*)

Name of drug	Effect	Side defect	Experimental animals/women	Treatment doses	Experiment duration	References
Mistletoe fig (extract of leaves of *Ficus* deltoidea)	1.Induced fewer cystic follicles with presence of a number of corpora lutea and various stages of developing follicles implying ovulation as compared to PCOS rats" 2. Decreased the ovarian wet weight and increased uterine wet weight of PCOS rats, and showed protective effects against ovaries and uterine in PCOS	None	Rats/letrozole induced PCOS	25, 125, 250 mg/kg	42 days	Suhaimi et al., 2016; Abdulrahman (2023)
Nishamalaki (a combination of *Curcuma longa* and *Emblica officinalis*)	1. Decreases body weight. 2. Reduces level of lipids, sugar and insulin in blood.	None	Rats/letrozole induced PCOS	0.9 g/kg	56 days	Dawane et al., 2017
Ginger (Zingiberofficinale)	1. Increased FSH but no significant effect on the level of E2 and T hormones 2. Increased primary follicles, primary and secondary graviflower and yellow corpuscles, and decreased atritic follicles	None	Rats/letrozole induced PCOS	100, 200 and 300 mg/kg	28 days	Foroozandeh and Hosseini, 2017
Ethanolic seed extract of *Tephrosia purpurea*	Ethanolic seed extract restores the alterations at biochemical, hormonal and histological level. Decreases blood plasma estradiol, progesterone leptin and ovarian tissue reduced glutathione and superoxide dismutase activities	None	Rats/letrozole induced PCOS	300 mg/kg bw	4 weeks	Rai et al., 2015; Basheer et al., 2018
Calligonum polygonoides	Antioxidant ability of Calligonum polygonoides, reduces production of ovarian cysts, ROS, and reduces oxidative stress in PCOS model. 2. Increases the chances of invitro fertilization and reduces body weight.	None	Rats/estradiol valerate induced PCOS	20 mg/kg	2 months	Tahmasebi et al., 2018 (37)
Brown alga (Ecklonia cava)	Repairs level of hormone T, E2, LH, FSH, and AMH 2. Regulates the ovarian cycles and suppeesses the symptoms of PCOS	None	Rats/letrozole induced PCOS	E. cava extract per os (P. O.)	2 wk	Yang et al., 2018a
Phyllanthus muellerianus (Euphorbiaceae	P. muellerianus regulates GnRH, LH, and FSH release, enhances androgen conversion into oestrogens, and increases estrogen production in adipocytes to restore estrus cyclicity and induce ovulation. Diet rich in E2, despite reducing LH, T, and cystic follicles, improved lipid profile, and alleviated reproductive, biochemical, and structural changes in PCOS rats.		Rats/letrozole induced PCOS	30, 60, 120 mg/kg	7 or 14 days	Ndeingang et al., 2019 (42)

Name of polyphenols	Treatment for PCOS	Molecular and biochemical modulations				References
Tanshinone IIA	Reverses insulin resistance, reversed the serum estradiol and testosterone level, antioxidant, anti-inflammatory and immunomodulatory	Decreases mRNA expression of ovarian aromatase, Increases FSHR, LHR and PPARγ, GSH, SOD, CAT function, cAMP level the isolated granulosa cells	Rats/estradiol induced PCOS	100 mg/kg/day	4 weeks	Chen and Xu, 2014; Fan et al., 2005; Komar, 2005; Jin et al., 2019)
Curcumin	Decreases the level of androgens abnormal Increases progesterone and estrodial blood serum level, profile, lipid profile, antioxidant, glycemic control and morphology of ovary Anti-inflammatory, antioxidant, Hypoglycaemic, Anti-hyperlipodemic, antiproliferative	Decreases TC, TG's, LSL and HDL, ROS, Decreases TC, TG's, LSL and HDL, ROS, Increases activities of GSH, SOD, CAT	Rats/letrozole induced PCOS	100 mg/kg, 200 mg/kg	15 days	(Pari and Murugan, 2007; Reddy et al., 2016, 2005)
Rutin	Decreases glucose level, Increases insulin-dependent receptor kinase activity, restoration and recovery in all the cellular	Down regulates expression of adipogenic genes, Decreases total protein content, reduces ROS Generation	Rats/letrozole induced PCOS	(100 mg/kg and150mg/kg, p.o)	15 days	(Jahan et al., 2016; Umar et al., 2012)

(*continued on next page*)

Table 2 (*continued*)

Name of polyphenols	Treatment for PCOS	Molecular and biochemical modulations				References
	changes in the ovarian follicles, decreases oxidative stress, up-regulates the antioxidant system					
Apigenin	Down-regulates the gene expression, Increases progesterone, decreases estrogen and LH/FSH ratio, Increases number of primary follicles, Graafian follicles, Decreases number of cystic and atretic follicles, reduces oxidative stress	Decreases FSH, TOS, TNF-α levels, IL-6, expression of NF-kB Increases TAC and SOD activity	Rats/Dehydroepiandrosterone (DHEA induced PCOS)	20 mg/kg po	21 days	Peng et al., 2022; Salmani et al., 2017; Darabi et al., 2020; Palacz-Wrobel et al., 2017)
Catechins	Modulates hormonal disorders, insulin resistance, and ovarian and uterine pathological changes, Decreases inflammation, incidence of IR, weight of uterus, regulates the level of sex hormones Increases glucose metabolism	Inhibits STAT3 signaling, upregulates the IRS1 and PI3K Signaling pathways, suppresses the expression of MMP2 and MMP9, Decreases expression of p-STAT3	Mice model induced by insulin combined with human chorionic gonadotropin (hCG).	25, 50 and 100 mg/kg	15 days	Hong et al., 2020; Fang et al., 2019)
Soy isoflavones	Regulates the menopausal symptoms, increases the expression of mRNA and proteins of ERb, down-regulates the androgen receptors, decreases testosterone level, decreases weight of ovaries Estrogenic activity, cardioprotective, antiinflammatory, Anticancer	Decreases expression of p-STAT3 Inhibits 3b-HSD and 17b-HSD, Decreases LPO and NO level Increases SOD, CAT, GPx activities and GSH content	Rats/letrozole induced PCOS	50 mg/kg, 100 mg/kg	14 days	Nynca et al., 2013, Rajan et al., 2017; Ortega et al., 2012; Hu et al., 2010
Resveratrol	Decreases low-grade chronic pro-inflammatory cytokines, Decreases inflammatory pathways and subsequently ↓ ER stress, decreases testosterone quantity as well as dehydroepiandrosterone sulphate Anti-inflammatory, antioxidative, anti-apoptotic and anti-tumor	Suppresses the secretion of IL-1β, IL-6, cyclooxygenase-2 (COX-2), TNF-α, IL-18, NF-κB, and CRP, down-regulates the expression of CHOP, decreases GRP78, and XBP1 mRNA	Rats/letrozole induced PCOS	20 mg/kg and 30 mg/kg	30 days.	Yarmolinskaya et al., 2021; Csaki et al., 2008; Shakibaei et al., 2007; Aggarwal and Shishodia, 2004
6-Gingerol	Decreases serum FSH, LH and estradiol and testosterone, inhibiting the cyclooxygenase pathways, alters pituitary-ovarian axis, inhibits the expression of lipoxygenases, NF-Kβ, nitric oxide synthase	Decreases ALT, AST, ALP Increases the activities of SOD, catalase and GPx, Increases mRNA level of COX-2, inhibition of ROS/NFkβ /COX-2 activation in H2H7 hepatocytes	Rat/Estradiol valerate – Induced polycystic ovary syndrome	200 and 400 μg/kg	14 days	(Jackson et al., 2000; Malekinejad et al., 2013; Kamato et al., 2013; Manasa et al., 2013; Kim et al., 2007)
Quercetin	Decreases Glut androgen, activation of AMPK dependent & insulin-independent pathways, down regulating the major enzymes responsible for gluconeogenesis, maintains the levels of testosterone, estrogen and progesterone, prevents loss of bone mass post-menopausal women Antioxidant, cardiovascular protection, anticancer, antidiabetic, anti-inflammatory, anti-androgenic Positive control can potentially reduce metabolic and hormonal imbalances associated with PCOS by restoring healthy follicles and regulating steroidogenesis.	Up-regulates the activities of CAT, SOD, GR and GSHPX, Blocking the PK13 pathways and also down-regulates the CYP17A1 gene, neutralizes free radicals	Rats/letrozole induced PCOS	30 mg/kg	21 days	(Jahan et al., 2018; Gambineri et al., 2002; Kleemann et al., 2011)
Melatonin	Melatonin act as anti-androgen reduces elevated level of testosterone prevents ovarian dysfunction in PCO rats. Directly scavenges free radicals Regulates the hormonal level	None	Rat/Letrozole induced PCOS	200 μg/kg	30 days	Rai et al., 2015; Rani et al., 2021
Myo-Inositol	Inositol could promote ovulation in PCOS patients Inositol supplement with myo-inositol, regulates the menstrual cycle, restores amenorrheic and oligomenorrheic Control insulin and reproductive hormonal balance	None None	Women	12–18 g/day	4–6 weeks	(Unfer et al., 2012; Bevilacqua et al., 2015; Kalra et al., 2016)

increasing steroidogenic enzyme expressions (Avery et al., 2011; Docea et al., 2017). This interaction boosts androgen synthesis through enzymes like CYP450c17 (Rosenfield and Ehrmann, 2016). Conversely, hyperinsulinemia reduces SHBG levels in the liver (Cassar et al., 2016; Condorelli et al., 2017; Lizneva et al., 2016a), inhibits IGF-1 binding protein synthesis, increasing androgen production in theca cells (Jeanes and Reeves, 2017). IGF-1 downregulation hampers granulosa cell survival and folliculogenesis, leading to inhibited follicle growth due to both hyperandrogenism and hyperinsulinemia (Jeanes and Reeves, 2017;Macut et al., 2017). Hyperinsulinemia also adversely affects the pituitary gland, stimulating LH release and influencing GnRH secretion (Baskind and Balen, 2016). Moreover, insulin plays a role in adipogenesis, lipid biogenesis, and fat accumulation (Shang et al., 2020). IR elevates fatty acid levels in plasma, impacting the liver and adipocytes (Wang et al., 2020). Additionally, IR decreases omentin levels, irrespective of patient BMI, and induces hyperglycemia, causing TNF-α-induced inflammation from mononuclear cells (MNCs) (Figs. 1 and 7).

3.12. Inflammation

Properly regulated inflammation is crucial for oocyte growth and ovulation. However, elevated levels of white blood cells (Liu et al., 2021a), C-reactive protein (CRP), and other inflammatory biomarkers in peripheral blood are linked to the development of PCOS (Liu et al., 2021b; Zuo et al., 2016; Rudnicka et al., 2021). Hyperandrogenism is a major contributor to this inflammation (Shorakae et al., 2018). TNF-α, a significant inflammatory cytokine, exacerbates insulin resistance (IR) by interfering with insulin signaling cascades (Zuo et al., 2016), reducing the expression of GLUT-4. Studies have shown that phosphorylation of insulin receptor substrate (IRS) serine residues suppresses insulin receptor signaling, preventing GLUT-4 transport and glucose uptake (Stepto et al., 2019). Additionally, TNF-α can proliferate theca cells under in vitro conditions (Mancini et al., 2021). IL-1 also inhibits the expression of FSH and LH receptors, suppressing follicle development and ovulation (Liu et al., 2021a). Both TNF-α and IL-1 hinder HNF stimulation through various mechanisms. Furthermore, NLRP3 inflammasomes induce pyroptosis of follicular cells, ovarian fibrosis, and disrupt the formation of follicular cells. Elevated CRP levels also contribute to the development of IR in insulin-sensitive tissues (Fig. 7).

3.13. Oxidative stress

Oxidative stress (OS) refers to the imbalance between pro-oxidants and antioxidants (Mancini et al., 2021;Mizgier et al., 2021; Zhang et al., 2017). Oxidative molecules encompass reactive oxygen species (ROS) (Zhang et al., 2017; Liu et al., 2021b; Di Segni et al., 2017) (O_2, H_2O_2, and $OH^{\bullet}$) and reactive nitrogen species (RNS) (Liu et al., 2021a; Di Segni et al., 2017) ROS play a role in various mechanisms such as signaling cascades (Lai et al., 2018), cellular growth (Mancini et al., 2021; Zhang et al., 2017), and differentiation. RONS also affect the functional physiology of ovaries, including steroidogenesis (Lu et al., 2018), and neurons important for feeding behavior to induce hunger. However, excessive production of free radicals can cause damage to crucial molecules like lipids, proteins, and DNA (Mancini et al., 2021; Zhang et al., 2017; Di Segni et al., 2017; Lai et al., 2018; Lu et al., 2018).

Elevated oxidative stress is linked to the pathogenesis of PCOS, as indicated by various studies (Uyanikoglu et al., 2017;Özer et al., 2016). Higher oxidative stress stimulates nuclear factor-kappa B (NF-B), associated with various inflammatory pathways, affecting the generation of pro-inflammatory cytokines such as TNF-α and IL-6. Increased OS levels also lead to the secretion and release of TNF-α (Lu et al., 2018). On the contrary, heightened OS activates various protein kinases that promote serine/threonine phosphorylation instead of normal tyrosine phosphorylation of IRS. Consequently, the insulin signaling cascade is suppressed, resulting in insulin resistance. Oxidative stress is also a factor in the development of obesity, increasing the size of mature adipocytes and subsequently promoting the multiplication and differentiation of pre-adipocytes.

3.14. Obesity

Obesity stands as a key initiator of chronic inflammation (Mizgier et al., 2021). Accumulation of adipocytes and fats in visceral organs leads to hypoxia and subsequent necrosis, triggering the production of inflammatory cytokines (Liu et al., 2021a). Hypertrophy results in the death of adipocytes and prompts inflammatory reactions (Shorakae et al., 2018). The mononuclear cells of adipocytes generate pro-inflammatory cytokines (Delitala et al., 2017; Glueck and Goldenberg, 2019). Fat deposition in the abdomen contributes to the development of an inflammatory state (Delitala et al., 2017; Glueck and Goldenberg, 2019). Additionally, obesity contributes to the onset of insulin resistance (IR) and hyperandrogenism (HA). Visceral obesity is induced by elevated levels of non-esterified fatty acids (NEFAs) in the bloodstream. Skeletal muscles utilize NEFAs as an energy source over glucose. Hyperglycemic conditions stimulate the pancreas, leading to hyperinsulinemia. Moreover, visceral fat and catecholamines induce lipolytic activity, causing lipotoxicity and impairing insulin clearance and activity (Delitala et al., 2017). FFA stimulates the phosphorylation of IRS-1 on serine/threonine and reduces tyrosine phosphorylation. With increased FFAs, intramyocellular lipid levels decrease glucose sensitivity and insulin uptake (Zeng et al., 2020).

Studies have shown that women genetically predisposed to developing PCOS often experience clinical and biochemical alterations due to weight gain and obesity, indicating a close association between obesity and the development of PCOS. A significant proportion of women with PCOS (38–88 %) were found to be either overweight or obese (Barber et al., 2006; Legro, 2000). The Northern Finland Birth Cohort (NFBC) 1966 revealed a notable correlation between body mass index (BMI) and PCOS characteristics across all age groups (Ollila et al., 2016). Additionally, modest weight loss of about 5 % can result in various clinically significant reproductive, hyperandrogenic, and metabolic features of PCOS (Kiddy et al., 1992; Holte et al., 1995).

Reports indicate that 50–90 % of women with PCOS suffer from insulin resistance (Dunaif et al., 1989; Dunaif, 1997). However, the exact reason for the origin of insulin resistance in PCOS and its mechanism remains poorly understood. It is assumed that testosterone and the CAG repeat number within the androgen receptor contribute to the development of insulin resistance in PCOS. One observed reason is a post-receptor defect specific to the phosphatidylinositol 2 kinase pathway (PI3-kinase), a pathway that plays a role in the metabolic effects of insulin, including glucose disposal into skeletal muscle (Barber et al., 2006). Insulin mediates steroidogenic effects and cellular growth through this pathway, while the mitogen-activated protein (MAP) kinase pathways remain normal via a distinct post-receptor pathway (Cusi et al., 2000). Compensatory hyperinsulinemia is another factor in PCOS pathogenesis, in addition to insulin resistance. It induces activating effects on the normal MAP kinase and impairs the PI3-kinase pathway to increase steroidogenesis (Rice et al., 2005).

3.15. PCOS and other related complications

Polycystic ovarian syndrome (PCOS) was defined by the National Institute of Health-National Institute of Child Health and Development in 1990. It is identified through clinical and biochemical signs of hyperandrogenism and exclusion of other known disorders such as hyperprolactinemia, thyroid gland disorders, adrenal gland hyperplasia, ovarian tumors, and chronic anovulation caused by androgens. Hirsutism, present in about 80 % of women with PCOS, indicates hyperandrogenism, which can be confirmed by measuring androgen levels in the blood. In PCOS, the most frequently found steroid in the blood is free testosterone. Elevated levels of circulatory hormones such as total testosterone, androstenedione, and Dehydroepiandrosterone are also

observed (Richardson, 2003). PCOS is associated with dyslipidemia, characterized by lower high-density lipoprotein (HDL) and high-density lipoprotein-2-cholesterol (HDL2-C), higher total and low-density lipoprotein-cholesterol (LDL-C), higher triglycerides (TG), and very low-density lipoprotein-cholesterol (VLDL-C) levels (Kim and Choi, 2013). Women with PCOS often experience obesity, and between 39 % and 86 % of them are overweight or obese (Sam, 2007). Obesity plays a significant role in PCOS, affecting clinical and endocrine aspects, and contributing to metabolic disorders such as insulin resistance, non-insulin dependent diabetes mellitus, hypertension, non-alcoholic fatty liver diseases, dyslipidemia and cardiovascular diseases.

PCOS is a common cause of menstrual irregularities and infertility (Dennett and Simon, 2015), and it presents challenges in pregnancy, including a higher risk of miscarriage, gestational diabetes, hypertension, and pre-eclampsia (Alfirevic et al., 2012). Epigenetic changes in genes responsible for reproduction and metabolism may result from maternal, placental, or fetal hyperandrogenism, potentially leading to various diseases like non-insulin dependent diabetes mellitus, autism spectrum disorder, hypertension, and PCOS (Kelley et al., 2019; Xita and Tsatsoulis, 2006). Women with PCOS have a higher risk of gestational diabetes (20–30 %) and pregnancy-induced hypertension (10–15 %) (Kamalanathan et al., 2013).

Obesity during pregnancy is associated with several complications, including miscarriage, preeclampsia, gestational diabetes, foetal macrosomia, and caesarean section. Adipocytes produce adipokines, such as leptin, adiponectin, tumor necrosis factor-α, interleukin-6, resistin, and visfatin, potentially activating insulin resistance in pregnancy and contributing to inflammatory responses (Kamalanathan et al., 2013) (Fig. 8).

3.16. Role of translational medicine

Translational medicine refers to a rapidly growing discipline in biomedical research that aims to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary, highly collaborative approach. The ultimate goal of translational medicine is to translate scientific findings into practical applications that improve human health and well-being. It bridges the gap between basic research and clinical applications, facilitating the translation of scientific knowledge into effective therapies and diagnostics.

Translational medicine is essential in comprehending, diagnosing, and treating complex conditions such as polycystic ovarian syndrome (PCOS). PCOS, affecting women of reproductive age, involves hormonal imbalances, cystic ovaries, and symptoms like irregular cycles, excess hair growth, acne, and infertility. It bridges the gap between basic research and clinical practice, aiding in the development of effective diagnostic and therapeutic approaches. By identifying biomarkers and diagnostic tools, it enables early detection and personalized treatments. Understanding PCOS's pathophysiology and molecular mechanisms is critical for targeted therapies, while translational research supports drug development and personalized medicine for distinct PCOS subtypes. Recent advancements include genetic studies uncovering relevant genes for personalized treatments, metabolomics and proteomics aiding in early diagnosis, and microbiome research exploring gut microbiota's role in PCOS progression. Precision medicine integrates patient-specific data to tailor treatment regimens, while lifestyle interventions, focusing on diet and exercise, alleviate symptoms and improve overall health in PCOS patients. Translational medicine, thus, contributes significantly to enhancing PCOS management by incorporating multifaceted approaches involving genetics, metabolomics, microbiome research, and precision medicine.

4. Conclusion

Polycystic Ovarian Syndrome (PCOS) remains a complex endocrine disorder characterized by a spectrum of clinical manifestations, including hyperandrogenism, anovulation, and polycystic ovarian morphology. The multifaceted pathogenesis of PCOS involves intricate interplays between genetic predisposition, environmental factors, and aberrant hormonal signaling, notably implicating dysregulation in the hypothalamic-pituitary-ovarian (HPO) axis, insulin resistance, and chronic low-grade inflammation. Notably, the emerging role of epigenetic modifications and their influence on gene expression underscores the need for further exploration into the epigenetic landscape of PCOS. Critical appraisal of the current diagnostic criteria and phenotypic heterogeneity underscores the necessity for a comprehensive and holistic approach in the diagnosis and management of PCOS, with personalized treatment strategies tailored to address the specific manifestations and underlying pathophysiological mechanisms. Future research efforts should focus on unraveling the intricate molecular mechanisms and identifying novel therapeutic targets, aiming to alleviate the burden of PCOS and improve the quality of life for affected individuals. Additionally, fostering interdisciplinary collaborations between researchers and clinicians will be pivotal in advancing our understanding and management of this prevalent yet enigmatic syndrome.

4.1. Limitations

Given the intricate interplay of genetic predisposition, environmental factors, and hormonal signaling pathways in the pathogenesis of PCOS, the review encountered challenges in fully dissecting the multifactorial etiology, possibly leading to an oversimplification of certain aspects of the syndrome's underlying mechanisms. Additionally, the lack of uniformity in diagnostic criteria and the existence of phenotypic variations among individuals with PCOS posed a challenge in accurately categorizing and comparing study populations, potentially impacting the generalizability of findings and the overall conclusions derived from the reviewed literature. Despite acknowledging the role of epigenetic modifications and environmental factors in the pathogenesis of PCOS, the review had limitations in fully addressing the complex interactions and contributions of these influences, emphasizing the need for more extensive research in these areas. Acknowledging and addressing these limitations will be essential for further enhancing the understanding and management of PCOS in future research endeavors.

4.2. Future directions

Future research should prioritize the integration of multi-omics approaches, encompassing genomics, transcriptomics, proteomics, and metabolomics, to unravel the intricate molecular mechanisms underpinning the pathogenesis of PCOS. This comprehensive understanding will illuminate the complex interplay between genetic predisposition and environmental influences, paving the way for more targeted and effective interventions. It is imperative to conduct large-scale longitudinal cohort studies with extended follow-up periods to elucidate the natural history, progression, and long-term health implications of PCOS. These studies can help identify critical intervention windows and facilitate the development of personalized management strategies. Standardizing diagnostic criteria and phenotypic classifications for PCOS, incorporating both clinical and biochemical parameters, is crucial to enhance the consistency and comparability of research findings and to foster a more nuanced understanding of the heterogeneity within the PCOS population. Additionally, further exploration into the epigenetic landscape of PCOS, including investigation into DNA methylation patterns, histone modifications and non-coding RNA regulation is essential for gaining insights into the role of epigenetic modulations in the syndrome's development and progression. These insights may reveal novel therapeutic targets and diagnostic biomarkers. Integrating advancements in non-invasive imaging techniques, such as high-resolution ultrasound and magnetic resonance imaging (MRI), can enable accurate and early detection of ovarian morphological changes, facilitating precise characterization of the structural alterations associated with PCOS.

This, in turn, can enhance diagnostic accuracy and enable better monitoring of treatment responses. Encouraging translational research efforts, including the development of targeted pharmacological interventions, lifestyle modifications, and innovative therapeutic modalities tailored to address specific pathophysiological mechanisms implicated in PCOS, will be crucial in improving clinical outcomes and enhancing the quality of life for individuals affected by this syndrome. Pursuing these future directions will significantly contribute to advancing our understanding of PCOS and foster the development of more effective diagnostic, preventive, and therapeutic strategies for managing this prevalent and complex endocrine disorder.

CRediT authorship contribution statement

Younis Ahmad Hajam: Formal analysis, Data curation, Conceptualization. **Hilal Ahmad Rather:** Writing – review & editing, Conceptualization. **Neelam:** Resources, Writing – original draft. **Rajesh Kumar:** Writing – review & editing. **Muddasir Basheer:** Conceptualization. **Mohd Salim Reshi:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

The authors gratefully acknowledge the Department of Life Sciences and Allied Health Sciences, Sant Baba Bhag Singh University, Jalandhar, Punjab, India for providing the requisite platform to complete this review.

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