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A REVIEW ON DRUG DISCOVERY AND DEVELOPMENT FOR THE TREATMENT OF POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Polycystic Ovarian Syndrome (PCOS), an endocrine disorder with the association of hyperandrogenism and anovulation, is the most common reproductive disorder in women. The condition further generates a constellation of different metabolic abnormalities worsening the situation more. The current treatment strategy for PCOS is rather symptomatic including drug therapy like anti-diabetic, anti-hirsutism, ovulation-inducing agents and others. However, in the past few years, there had been extensive studies on finding exact pathogenesis of PCOS and developing drugs that are curative rather than just being symptomatic. A few drugs which act as GnRH antagonist are under clinical trials for PCOS treatment. Also, NK3 receptor, extrasynaptic GABAA receptors are few other novel targets that are under investigation. An overview of pathogenesis, symptoms, treatment strategy and some novel targets has been presented in this paper.

KEYWORDS: Polycystic Ovarian Syndrome, PCOD, NK3 Receptor, Extra synaptic GABAA receptor, Anti-Mullerian Hormone, Atrial Natriuretic Peptide, Stress.

INTRODUCTION

The polycystic ovarian syndrome is one of the most common endocrine disorders among women of reproductive age with the association of hyperandrogenism and chronic anovulation in its most typical form. It is one of the most common metabolic and reproductive disorders and the most frequent cause of anovulation and hirsutism. Women plagued by PCOS are present with an array of symptoms associated with menstrual dysfunction and androgenic hormone excess, which significantly impacts their quality of life. Patients might also be at redoubled risk of multiple morbidities, including obesity, insulin resistance, Type II diabetes mellitus, cardiovascular diseases (CVD), infertility, cancer, and psychological disorders. It is a condition that occurs in approximately 5 to 10 percent of women of childbearing age.[1–3]

The well-accepted clinical definition of polycystic ovarian syndrome is the association of hyperandrogenism with chronic anovulation in women without specific underlying diseases of the adrenal or pituitary glands.[1] Not all the women with PCOS exhibit all of the symptoms and each symptom can vary from mild to severe. Many women only experience menstrual problems and/or are unable to conceive. Common symptoms of PCOS include oligomenorrhea or amenorrhea, infertility, acne, hirsutism and obesity.[2,4]

The onset of PCOS also increases chances of developing other health problems in later life. For example, women with PCOS are at a higher risk of developing Type II Diabetes (a lifelong condition that causes a person's glucose level to become too high), depression and mood swings (because the symptoms of PCOS may have an impact on one's confidence and self-esteem), high blood pressure and high cholesterol (which can lead to heart disease and stroke), sleep apnoea (overweight women may also develop sleep apnoea, a condition that causes interrupted breathing during sleep), endometrial cancer (women with absent or irregular menstruation for many years have a higher than average risk of developing cancer of the uterine lining).[5]

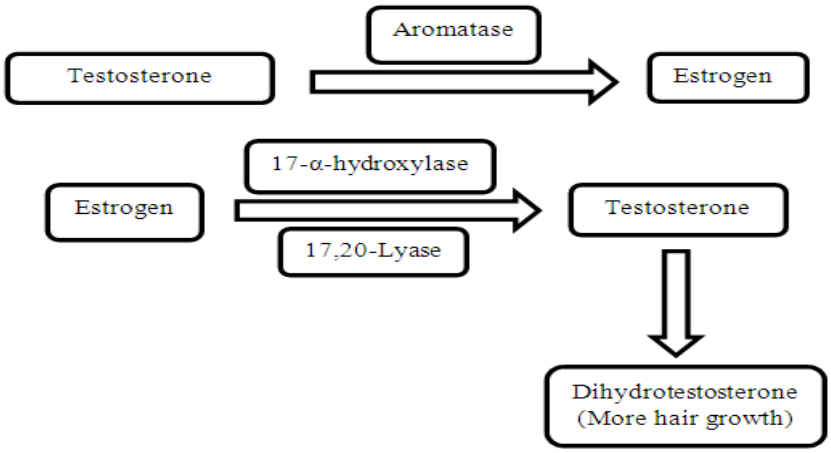
The pathogenesis of some complications has been studied and suggested in some of the studies. Some of them are:

Obesity in PCOS: Some possible reasons hypothesized for obesity in PCOS patients are-1) Mutations in the peroxisome proliferator-activated receptor-γ (PPAR- γ) gene.[6,7] 2) Reduced secretion of the gastrointestinal satiety peptide *cholecystokinin* and dysregulated secretion of the appetite-regulating gut hormone *ghrelin* that is independent of diet.[6,8]

Insulin Resistance in PCOS: A few possible reasons hypothesized for insulin resistance in PCOS patients are, post binding decrease in the phosphorylation of the tyrosine residues and an increase in the phosphorylation of the serine residues of the intracellular domain of the insulin receptor cause resistance to insulin's metabolic actions.[9] Elevation in serine phosphorylation enhances the activity of $CYP_{450}C17$, the key enzyme of adrenal and ovarian steroid synthesis is also a possible cause of insulin resistance.[10]

The pathophysiology of PCOS has not been yet completely established however many different mechanisms ultimately give rise to the cluster of complications associated with PCOS. Despite the heterogeneity of clinical presentations of women with polycystic ovaries, there is a common thread of biochemical features that are associated with the spectrum of symptoms and signs. The endocrine hallmarks are hyperandrogenemia and hypersecretion of luteinizing hormone. However, abnormal gonadotropin secretion is a result, rather than the cause, of ovarian dysfunction.[1]

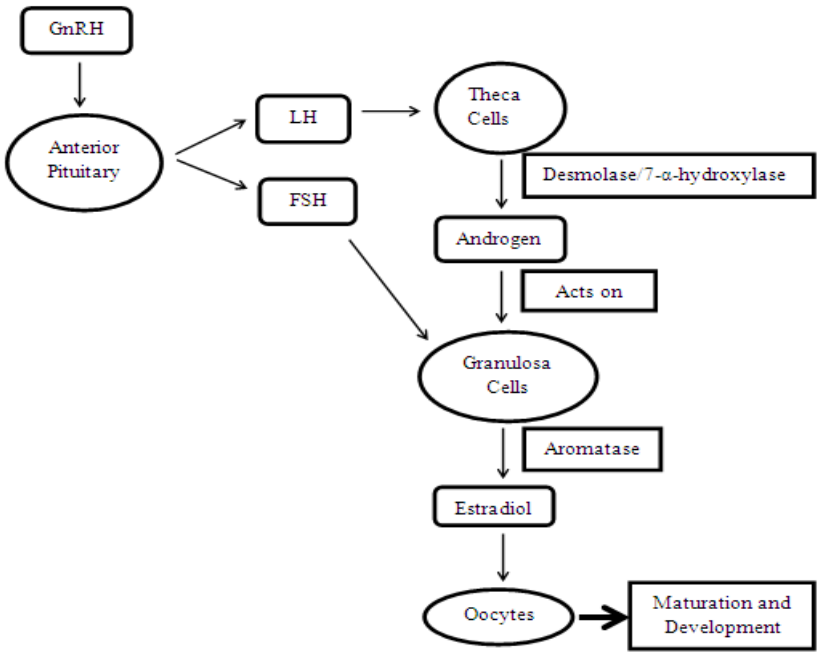
Clinical and in vitro studies of human ovarian theca cells provide evidence regarding dysregulation of the rate-limiting enzyme in androgen biosynthesis, cytochrome P-450c17α, which catalyzes both 17α-hydroxylase and 17, 20-lyase activities that may lead to PCOS.[11] Some important conversions in this regard are indicated in scheme I:



Scheme I: Hormonal imbalance in PCOS.

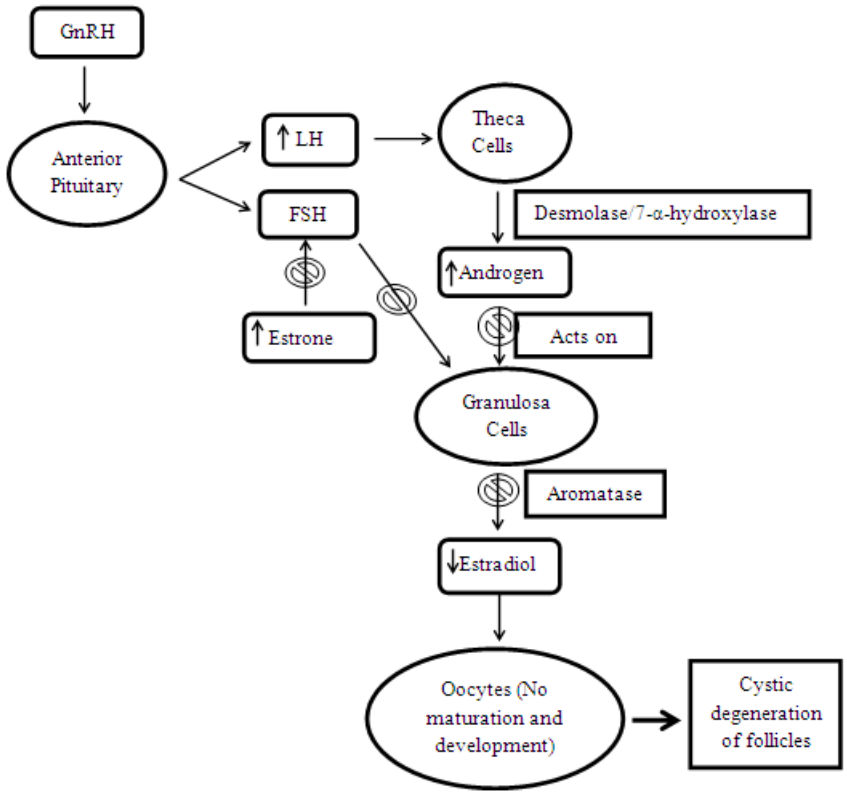
Pathogenesis of PCOS[12]

In normal conditions, mechanism, as illustrated in scheme II, is followed for oocyte development and maturation,



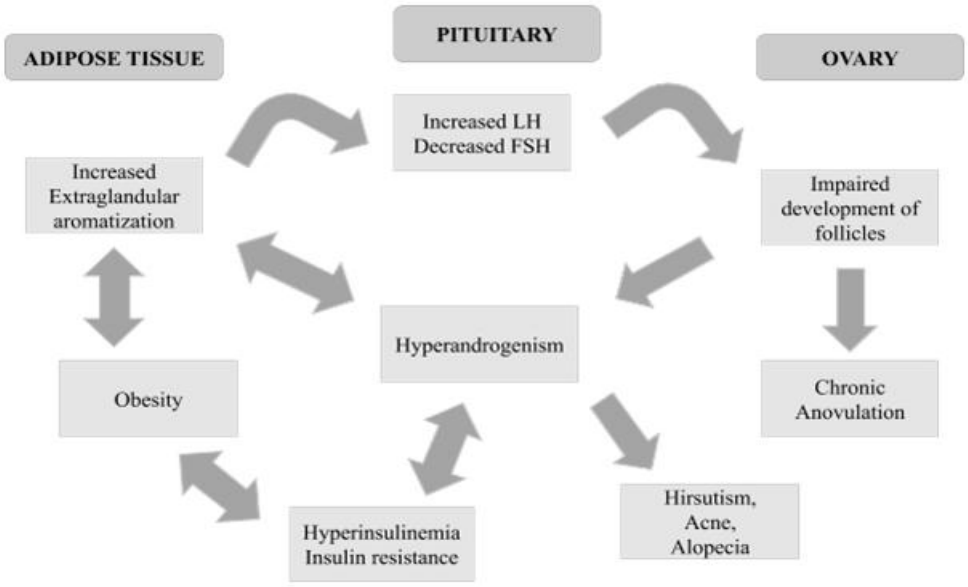
Scheme II: Normal Oocyte Development Cycle.

However, in PCOS, this physiology is altered due to increased levels of LH. As a result, it raises androgen levels leading to hirsutism. This increased androgen triggers adipose leading to increased estrone secretion. Also, decreased estradiol leads to cystic degeneration of follicles. The aftermath of increased LH levels are summarized in the flowchart below in scheme III:



Scheme III: Aftermath of increased levels of LH.

PCOS and other complications: An Inter-relation[13,14]
PCOS has been found to be related to several other metabolic disorders owing to the underlying cause of androgen increase. The inter-relation can be observed in between three organs, the Pituitary gland, Adipose tissue, and Ovaries. A cascade of interrelating diseases is followed once there is an androgen excess in body, especially in ovary. The flowchart below (scheme IV) represents different inter-related disease conditions in PCOS.



Scheme IV: Inter-relation of PCOS and other metabolic disorders.

DIAGNOSIS of PCOS

The diagnosis of PCOS depends on several criteria. Three different sets of diagnostic criteria as prescribed by the National Institutes of Health (NIH), Rotterdam and the Androgen Excess and PCOS Society (AE-PCOS Society) are being summarized below:

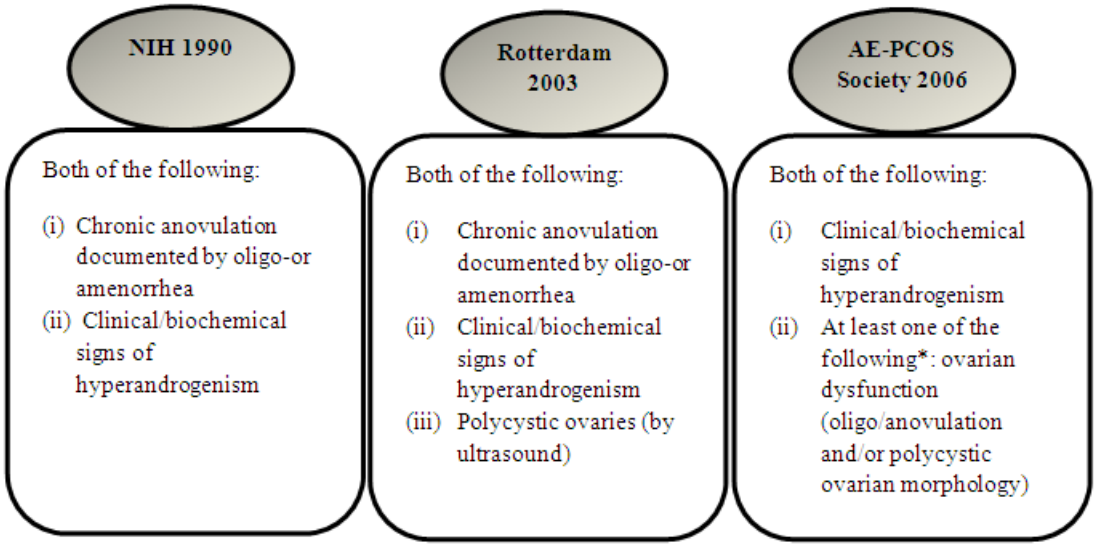


Figure 1: Diagnostic Criteria for PCOS.

PCOS is also acknowledged as a metabolic disorder. Cardiometabolic features of PCOS can be summarized as visceral obesity, insulin resistance, and hyperinsulinemia, risk of type II diabetes, disturbed secretion from adipocytes (adipokines, pro-inflammatory, and macrophage-derived factors), dyslipidemia, vascular endothelium dysfunction, prothrombotic state, atherosclerosis.[6]

The different diagnostic criteria create several phenotypes of PCOS. For simplification, these phenotypes were divided into four diagnostic groups namely phenotype A, phenotype B, phenotype C, phenotype D as summarized in Table 1:[6,15]

Table 1: Diagnostic Phenotypes of PCOS.

Phenotype A	NIH PCOS: hyperandrogenism and oligo/anovulation with PCO
Phenotype B	NIH PCOS: hyperandrogenism and oligo/anovulation without PCO
Phenotype C	Non-NIH PCOS: hyperandrogenism with PCO but with normal ovulation
Phenotype D	Non-NIH PCOS: no hyperandrogenism but with oligo/anovulation and with PCO

CURRENT STATUS OF TREATMENT STRATEGY

There is currently no permanent cure for PCOS. For women with PCOS not seeking pregnancy, combined oral contraceptive pills (OCPs) are the first line of treatment. These pills regulate the menstrual cycle and decrease the production of adrenal androgens. A healthy lifestyle helps to control associated health conditions such as obesity, cardiovascular disease, and infertility. Hirsutism is treated using OCPs along with anti-androgen. Laser-hair removal is also a way of controlling hirsutism among PCOS patients.[16]

Conventional targets for treatment line of PCOS can be stated as Ovulation Inducing Agents, Antiandrogens, Oral Contraceptives, Insulin Sensitizing Agents, Anti-Hirsuitics and Lipid-Lowering Agents.

OVULATION INDUCING AGENTS

Clomiphene Citrate (1): Clomiphene citrate is considered as the first-line treatment for the management of anovulation seen in PCOS. It is a selective estrogen receptor modulator (SERM) that binds to and acts as an estrogen antagonist at the Hypothalamo pituitary estrogen receptors. It thus abrogates the estrogen-mediated suppression of pituitary gonadotropins which leads to an increase in the endogenous release of follicle-stimulating hormone (FSH) which is responsible for initiating and maintaining ovarian follicle recruitment, growth, and subsequent ovulation.[17]

ANTI-ANDROGENS

Spironolactone (2): It is an aldosterone antagonist used as an antihypertensive and potassium-sparing diuretic. Its use in the treatment of PCOS comprises mechanisms of action that include a reduction of adrenal gland testosterone production by depleting microsomal cytochrome P-450, the competitive inhibition of the androgen receptors in target tissue, and the inhibition of 5-alpha reductase (the enzyme responsible for the conversion of testosterone into more potent dihydrotestosterone [DHT]).[17]

ORAL CONTRACEPTIVES

Desogestrel (3) is used in PCOS due to its low androgenic effects.[3]

INSULIN SENSITIZING AGENTS

Metformin (4): A safe and well-tolerated drug of proven efficacy in the management of type 2 diabetes, metformin is one of the insulin-sensitizing drugs mostly used in the management of PCOS. Its mechanism of action includes a metabolic pathway through decrease in hepatic gluconeogenesis via activation of the AMP-kinase pathway.[17]

ANTI-HIRSUITICS

Eflornithine hydrochloride (5) inhibits enzyme ornithine decarboxylase in human skin. Its topical application slows down the growth of hair in treated areas.[17]

LIPID LOWERING AGENTS

Women with PCOS are often observed with elevated serum LDL and triglycerides and suppressed high-density lipoprotein levels. Statins like **Simvastatin (6)** inhibit cholesterol biosynthesis, decreasing circulating LDL cholesterol, thus reducing cardiovascular risks associated with PCOS. Statins are also found to inhibit ovarian theca-interstitial cell proliferation and ovarian steroidogenesis *in vitro*, thus hold potential for improving the hyperandrogenemia of PCOS.[17]

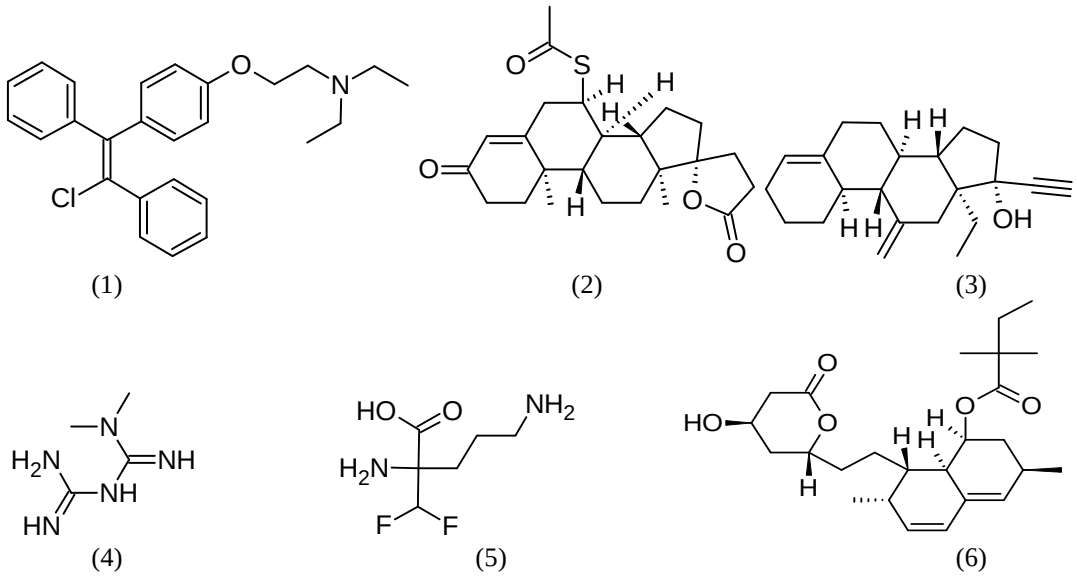


Figure 2: Currently used drugs in the treatment of PCOS.

DRUGS IN CLINICAL TRIALS

Though there are specific medications developed for targeting irregular or no ovulation, acne, excess facial or body hair, mood swings and other symptoms of PCOS individually, there doesn't really exist one single therapy that reliably addresses the array of symptoms observed in PCOS. Hence, there is always much interest when a new drug in the research and development phase holds promise for a broader positive impact on women with PCOS. Different herbal plants and certain chemical entities had been subjected to clinical research for their applicability in the treatment of PCOS. Among allopathic medicines, drug shown in Table 2 are under clinical trials:

Table 2: Synthetic Drugs in Clinical Trials (as reported in the year 2017).

Drug Name/ Code	Category	Proposed Mode of Action
MLE4901	NK-3 Receptor Antagonist	Downregulation of LH
Elagolix	Gonadotropin Receptor Antagonist	Downregulation of GnRH

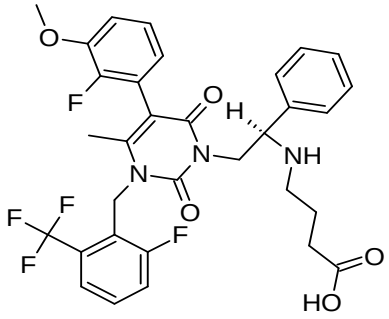
SYNTHETIC DRUGS IN CLINICAL TRIALS FOR PCOS TREATMENT

Elagolix

Elagolix (7) is a gonadotropin-releasing hormone antagonist (GnRH antagonist) medication that is used in the treatment of pain associated with endometriosis in women. It is also under development for the treatment of uterine fibroids in women. The pharmaceutical company behind this compound, Neurocrine (in collaboration with Abbvie), has also suggested a variety of other women's health conditions that the drug could benefit, including PCOS. However, its effect on the release of GnRH would shut down the complete reproductive axis which may lead to severe consequences. Hence, as reported in literature, the studies are being carried out to minimize the side effects.[18–20]

MLE4901

The compound MLE4901, now known as **Pavinetant (8),** was initially undertaken for trials as a treatment for schizophrenia. It was then identified as a downregulator of LH. It was identified as an orally active, selective neurokinin-3 (NK_3) receptor antagonist which downregulated LH secretion selectively, not shutting down the whole reproductive axis, which would otherwise create a pseudo-menopausal state. It was initially developed by AstraZeneca, as compound AZD4901. Phase I studies explored the safety of the drug. Phase IIa study, done by AstraZeneca, established the drug's efficacy when compared to placebo. The AZD4901 Phase IIa study included 65 women of age 18-40 with PCOS. A randomized double-blinded trial was conducted with the primary outcome of looking at the ratio of LH concentrations after 7 days of treatment, compared to baseline. The placebo and lower two treatment doses showed no significant difference from baseline to day 7. The third arm, though, with 40mg AZD4901 twice daily, demonstrated a statistically significant 46.4% decrease in the LH concentration. It was then taken up by another pharmaceutical company Millendo Therapeutics, Inc., which conducted Phase III trials. However, In November 2017, development of the medication for hot flashes and PCOS was terminated after its developer assessed the clinical risks and benefits.[18,21–23]



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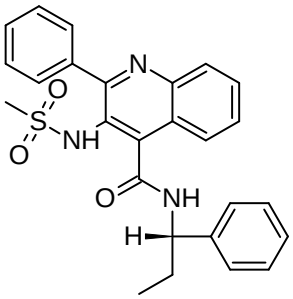

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Figure 3: Synthetic Drugs in Clinical Trials for PCOS.

HERBAL DRUGS IN CLINICAL TRIALS FOR PCOS TREATMENT

With increasing interest in herbal medications, there has been a vast exploration of herbal drugs which can be promising for the treatment of PCOS. Few of them are enlisted below in Tables 3 and 4.[24]

According to the evidence, herbal extracts containing phytoestrogens can effectively help in decreasing androgen levels, insulin resistance, and ovary weight as well as in increasing ovulation rate. Therefore, these plants and their phyto-constituents (Tables 3 and 4) can be partially effective in PCOS by altering the serum levels of different hormones and ovarian weight and morphology thus presenting an opportunity to investigate and discover new bioactive products.

Table 3: Medicinal Plants in Clinical Studies (Human Trials).

Medicinal plants (Scientific & English Name)	Family	Mechanism of action	Outcomes
Mentha spicata/ Spearmint	Lamiaceae	Not clear	Reduced levels of total and free testosterone in *M. spicata* treated group after 1-month treatment increased FSH and LH, and decrease in degree of hirsutism.[25]
Cinnamomum zeylanicum/ Cinnamon	Lauraceae	Improved insulin sensitivity	Significant reduction in insulin resistance in *C. zeylanicum* treated group.[26]
Grifola frondosa/ Maitake or Hen-of the-wood	Meripilaceae	Improved insulin sensitivity	Observation of ovulation induction in the patients of all groups.[27]
Trigonella Foenum-graceum/ Fenugreek	Leguminosae	Improved insulin sensitivity	A decrease in the polycystic ovaries and improvement of menstrual cycle in the women.[28]
Phoenix dactylifera/ Date palm	Arecacae	Anti-androgen	Decreased levels of estrogen and LH, increased levels of progesterone and FSH, decreased number of cystic follicles, increased number of primary and antral follicles and Grafian such as corpus luteum.[29]

Table 4: Medicinal Plants in Pre-clinical Studies (Animal Studies).

Medicinal plants (Scientific & English Name)	Family	Mechanism of action	Outcomes
Punica granatum L. Pomegranate Juice	Lythraceae	Antioxidant property	Improvement in the levels of testosterone, androstenedione, and estrogen in the treated groups.[30]
Cocos nucifera Coconut palm	Arecaceae	Antiandrogen And Phytoestrogen	Regulation of menstrual cycle and increasing uterus weight.[31]
Pergularia daemia Trellis – vine	Apocynaceae	Management of obesity	Normalization of the irregular menstrual cycle in patients with PCOS after treatment with the extract.[32]
Camellia sinensis Green Tea	Theaceae	Antioxidant property	Significant decrease in serum LH levels, decrease in the body's and ovarian weight and insulin resistance; changes in the number of follicles and the thickness of theca layer in histomorphometric studies.[33]
Bambusa vulgaris Bamboo	Poaceae	Antioxidant and anti-diabetic	Improving the estrous cycle and exerting hypolipidemic and hypoglycemic effects. Decreasing blood glucose and the levels of cholesterol, LDL, and triglyceride, improving cystic ovaries and ovulation.[34]
Glycine max Soybean	Fabaceae	Antiandrogen, Phytoestrogen, Antioxidant	100 mg/kg of soybean significantly changed PCOS symptoms through the body's weight loss and reducing testosterone, the activities of 3 beta-hydroxysteroid dehydrogenase and 17beta-hydroxysteroid dehydrogenase, and oxidative stress.[35]

NOVEL TARGETS FOR PCOS TREATMENT

The occurrence of PCOS is a combined result of malfunctioning of the endocrine system and reproductive system. However, in recent years, a relationship between insulin levels and androgen synthesis has been established at the level of genetic interaction. Several other aspects of interrelation in different organ malfunctioning leading to PCOS have been unfolded in the past years. Table 5 below enlists few targets, widely studied for PCOS:

Table 5: Novel Targets for PCOS Treatment.

Target	Category	Relation With PCOS
Anti Mullerian Hormone	Hormone	Increased AMH leads to Hyperandrogenism
Atrial Natriuretic Peptide	Hormone	Prevents ovarian cell apoptosis by forming NPRA/PGRMC1/EGFR complex, prevents ovarian cell degradation in PCOS.
$CYP_{450}17A1$	Enzyme	An important enzyme in steroidal biogenesis, dysregulation of enzyme activity (increase in activity) leads to hyperandrogenism
Neurokinin-3 Receptor (NK_3R)	Receptor	Hypothalamic regulation of GnRH release
$GABA_A$	Receptor	Activation of hypothalamic arcuate nucleus GABA neurons promotes LH secretion and reproductive dysfunction.

ANTI-MULLERIAN HORMONE

Anti-Mullerian hormone (AMH) is also known as the Müllerian-inhibiting hormone (MIH). It is a glycoprotein hormone structurally related to inhibin and activin from the transforming growth factor beta superfamily, whose important roles are in growth differentiation and folliculogenesis.[36,37]

In PCOS, there is an increase in AMH levels by nearly two to three times higher than normal. This is attributed to the increased follicle count number characteristic of PCOS, indicating an increase in granulosa cells since they surround each individual egg. However, increased AMH levels have also been attributed to an increased amount of AMH produced per follicle.[38,39]

It has been found that the serum AMH level helps in early and accurate diagnosis of antral follicles in the ovary. Therefore, in cases where ultrasonography is not possible, AMH can be incorporated as the diagnostic parameter.[37,40]

The high levels of androgens, which are a characteristic of PCOS, also stimulate and provide feedback for increased production of AMH. In this way, AMH can be considered to be a tool or biomarker that can be used to diagnose or indicate PCOS.

A strong inverse relationship has been observed between AMH and estrogen levels in serum. AMH can decrease aromatase activity leading to dysregulation of steroidogenesis.[41]

AMH is also found to reduce the number of LH receptors in granulosa cells, also an FSH induced process. Thus, it is established that AMH is involved in the regulation of follicle growth initiation and in the threshold for follicle FSH sensitivity.[42]

Studies suggest that AMH levels ultimately regulate the release of GnRH.[43] In future, AMH may prove not only as a diagnostic tool for PCOS but also a potential target for treatment of the same.

ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic peptide (ANP) (H_2N-Ser-Leu-Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Met-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr-COOH, Disulfide bridge:7-23) is a small peptide with natriuretic and diuretic functions, and its availability to be used in PCOS treatment is not completely known. However, in a study conducted by Zheng et al.[44], the potential role of ANP in reversing PCOS was identified.

It was found that the serum ANP level decreased in PCOS patients and also in the RU486-induced (Mifepristone induced) PCOS rats by ELISA assay. Also, through in vivo and in vitro experiments, it was found that ANP positively regulated the ovarian functions by promoting proliferation and inhibiting apoptosis of ovarian granulosa cells. The data suggested that ANP may be a potential therapeutic target for PCOS.

ANP promotes the growth and inhibits the apoptosis of ovarian granulosa cells by the formation of NPRA/PGRMC1/EGFR complex. It was studied that ANP upregulated NPRA (Natriuretic Peptide Receptor A) expression and promoted proliferation and inhibited apoptosis and co-expression of NPRA and PGRMC1 (Progesterone Receptor Membrane Component 1) in human ovarian granulosa cells and ovarian tissues of PCOS rats. Furthermore, inhibition of PGRMC1 expression by RU486 could be restored by addition of ANP. The above data suggest the co-existence of molecular interaction between NPRA and PGRMC1. EGFR (Epidermal Growth Factor Receptor) plays an important role in cell growth and differentiation and is involved in many reproductive processes, including implantation.

RU486 decreased the formation of NPRA/PGRMC1/EGFR complex. However, ANP could reverse the effects of RU486 on complex formation. The NPRA/PGRMC1/EGFR complex was further found to activate the MAPK/ERK signaling pathway and induced transcription factor AP1 expression and activation, which facilitated proliferation and inhibited apoptosis of granulosa cells.[44,45]

These findings thus demonstrate that ANP improves ovarian functions via the NPRA/PGRMC1/EGFR complex, which is involved in the pathogenesis and treatment strategy of PCOS. Therefore, ANP can be a novel option as a non-steroid hormonal drug for PCOS treatment.

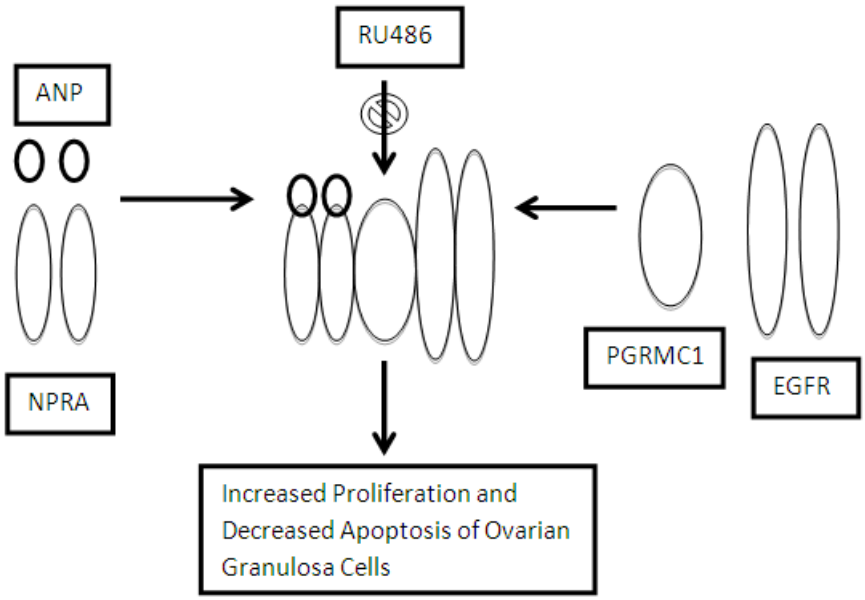


Figure 4: Effect of ANP on Ovarian Granulosa Cells.

$CYP_{450}17A1$

Cytochrome P450c17 (*CYP17A1*) is the rate-limiting enzyme for the formation of androgens in the gonads and in the adrenal cortex. Its expression is totally dependent upon tropic hormone stimulation, LH in the ovary and ACTH in the adrenal cortex in a dose-dependent manner.

This one enzyme possesses both 17-hydroxylase and 17, 20-lyase activities. The 17α-hydroxylase activity of CYP17A1 is required for the generation of glucocorticoids such as cortisol, but both the hydroxylase and 17,20-lyase activities of CYP17A1 are required for the production of androgenic and estrogenic sex steroids by converting 17α-hydroxypregnenolone to dehydroepiandrosterone (DHEA).[46,47]

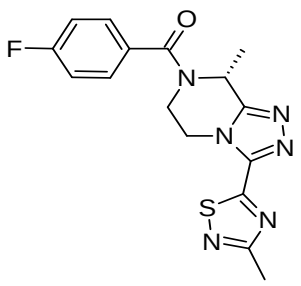
Dysregulation of steroidogenesis especially at the level of the 17-hydroxylase/17, 20-lyase activities of P450c17, constitutes two-thirds of PCOS. Increased P450c17 gene expression and enzymatic activity in ovarian theca cells in women with PCOS as well as increased transactivation of the CYP17 promoter has been previously reported. Moreover, it was also revealed that CYP17 expression is dysregulated at the level of mRNA stability in PCOS theca cells. Thus this particular enzyme can be studied and investigated further to develop a potential target for treatment of PCOS.[48]

NEUROKININ-3 RECEPTOR

The regulation of GnRH release in the body is governed through a complex network of neurotransmitters and neuropeptides from CNS and hypothalamus. Neurokinin-3 and kisspeptin are two such neuropeptides that have emerged as important in modulating the tonic pulsatile gonadotropin-releasing hormone (GnRH) release. NK3R is expressed on the so-called kisspeptin-NKB-Dyn (dynorphin A) neurons (KNDy neurons for short) located in the hypothalamic arcuate nucleus (ARC). An increase in GnRH leads to binding of NKB to NK3R (on KNDy neurons) thus inducing kisspeptin secretion, which acts on GPR54 (on GnRH neurons) with attendant impact on the GnRH pulse regulator.[22,49]

Based on this hypothesis, Hovyeda et.al developed a novel N-acyl triazolopiperazine derivative as an NK3 receptor antagonist. Further optimization and pharmacokinetic and pharmacodynamic studies of developed compounds gave a novel NK3 receptor antagonist.[50,51]

The compound has been named **Fezolinetant (9)** which is under development by Ogeda. As of March 2018, it has completed phase IIa clinical trials for PCOS.



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GABA RECEPTOR

The pathogenesis of PCOS has been a matter of debate for a long time now. Whether the syndrome arises due to abnormalities in brain or in ovaries is still controversial. However, in the past few decades, the role of brain especially the HPG axis has been extensively studied. After NK3 receptor, another receptor found to have control over GnRH release is GABA. GnRH neurons have been found sensitive to tonic GABAergic signaling which is modulated by 4,5,6,7-tetrahydroisoxazol0[5,4-c]pyridine-3-ol (THIP). THIP is an agonist with highest selectivity and efficacy for δ containing $GABA_A$ receptors. This indicates an involvement of δ containing $GABA_A$ receptors in GnRH regulation. Extra synaptic $GABA_A$ receptors have been indicated to be pharmacologically and functionally distinct from their synaptic counterparts.[52,53]

It was initially unclear whether GABA had an excitatory or inhibitory effect on GnRH neurons. However, the most recent studies regarding the effects of endogenous GABA release on GnRH neurons indicate that the predominant action is that of excitation.[54,55]

Recently, a study by Silva et. al demonstrated the role of GABA neurons of the arcuate nucleus in hypothalamus in increasing LH levels and causing reproductive dysfunction. The study conducted on PRN mice proved that ARN GABA neurons played an important role in regulation of HPG axis and chronic activation of GABA neurons gave PCOS like symptoms.[56] Thus, with proper investigations, GABAA receptor can also be an option for therapy of PCOS.

CONCLUSIONS

Polycystic Ovarian Syndrome is gaining wide attention due to its increasing prevalence in women. The strategies conventionally available for the treatment of PCOS are rather symptomatic, treating a single complication associated with PCOS at a time. Also, long-term therapy with these drugs leads to severe consequences of adverse effects. Newer and novel treatment strategies are an ardent need for the treatment of PCOS. A single drug entity that could give the best possible outcomes at suitable doses is required to be developed.

Drug discovery data in the past few years reveals that not much development has occurred in this field. Thus, a wide scope for the discovery of new and novel molecules for the treatment of PCOS is available. With the advances in drug development strategies, a comparatively superior drug molecule can be developed that provides a selectively targeted activity. Currently, NK-3 receptor, GnRH and several other targets are being seen as a potential target for PCO treatment. More is still required to be investigated in this field for development of a novel drug for PCOS treatment.

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