

A Review: An *In-silico* Docking Studies of Herbal Compounds for the Treatment of Polycystic Ovarian Syndrome (PCOS)

Sushma Ghuge¹, Prajakta Kothawade², Shashikant Dhole³, Kranti Biradar¹

¹ PES Modern College of Pharmacy, (for ladies), Moshi, Pune; sushmavghuge10@gmail.com (S.G.); krantibiradar30@gmail.com (K.B.);

² Department of Chemistry, PES Modern College of Pharmacy, (for ladies), Moshi, Pune; prajaktakothawade12@gmail.com

³ Principal, Department of Pharmaceutics, PES Modern College of Pharmacy, (for ladies), Moshi, Pune; shashikantdhole27@gmail.com;

* Correspondence: sushmavghuge10@gmail.com;

Scopus Author ID 57208720012

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Abstract: Polycystic ovarian syndrome is a common hormonal condition that affects females of reproductive age, which causes hormonal imbalances, irregular periods, excess androgen levels, and cysts in the ovaries. PCOS is the leading cause of infertility in females. Herbal drugs have special importance in the treatment of PCOS. Different herbal phytoconstituents show great results in the treatment of PCOS. As PCOS is the leading cause of infertility in females, a promising herbal treatment must be discovered for future use. However, very little work is done in herbal *in-silico* studies for PCOS. So, the present review focuses on *in-silico* studies of phytoconstituents of herbal drugs that can be used for the treatment of PCOS. Rumphioside I in *Tinospora cordifolia*, the anethole in *Foeniculum vulgare*, quercetin and naringenin in *Hinguvachadi Choornam*, Carvone in *Mentha piperita* L and *Mentha spicata*, rutin in *Embilica officinalis*, 6-di-o-glloyl-d glucose in *Cordyceps*, quercetin in *Fenugreek*, NCGC00169066-01 in *Syzygium polyanthum*, quercetin and kaempferol in *Leonuri Herba*, Racemosol, Hyperoside in *Asparagus racemosus* showed good binding activity with different receptors like IRS 1, IRS 2, 3 RUK, 1E3G and 1XUN etc. compare to other constituents present in herbal plants. However, in the future, herbal phytoconstituents can be used to treat PCOS conditions after preclinical and clinical evaluation. From this survey, it can be concluded that flavonoids such as quercetin, racemose, Hyperoside, etc., can improve hormonal imbalance and ovulation for regularity of the menstrual cycle.

Keywords: PCOS; docking studies; phytoconstituents; molecular dynamics.

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1. Introduction

Polycystic ovary syndrome (PCOS) is a very common hormonal condition that affects women of reproductive age and causes hormonal imbalances, irregular periods, excess androgen levels, and cysts in the ovaries, with a lack of ovulation. PCOS is a leading cause of infertility [1].

The World Health Organization (WHO) stated that PCOS affected over 116 million women worldwide in 2012. One in five Indian women are affected by PCOS [2]. Globally, 1.55 million incident cases of PCOS in women of reproductive age (15-49 years) were

reported, representing an increase in the rate of 4.47% (2.86-6.37%) from 2007 to 2017 [3,4]. A large-scale survey conducted across India in 2020 showed that around 16% of female respondents between the ages of 20 and 29 years suffered from PCOS [5]. PCOS is also known as Stein-Leventhal [6].

The ovaries have a lifetime supply of immature eggs stored in tiny fluid-filled follicles. The adenohypophysis part of the pituitary gland located at the base of the brain produces various hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are secreted into the bloodstream to direct the function of ovaries [7,8].

When LH and FSH reach the ovaries, several hundred immature eggs start maturing, expanding the size of follicles, which simultaneously secretes estrogen. Once the level of estrogen reaches a certain level, the pituitary gland senses the sudden increase of LH in the ovaries, causing the most mature follicle to release the egg, which is called ovulation. The free egg travels to the fallopian tube, where it awaits fertilization. Eventually, the remaining other follicles and eggs dissolve. If the egg is not fertilized, the lining of the uterus breaks down during menstruation [9,10]. A typical menstrual cycle is about 28 days and consists of various phases, including the menses, follicular, ovulation, and luteal phases [11-14].

In PCOS, the pituitary gland releases a high amount of LH in the bloodstream, disturbing normal menstruation and leading to anovulation. The immature follicle remains as fluid-filled sacs or cysts that do not dissolve. Because of an increased amount of testosterone, the cysts lead to a hormonal imbalance, which can result in irregular periods. A high amount of testosterone in the ovaries prevents ovulation, which can lead to infertility [15-17].

The science of Ayurveda makes use of herbal remedies for various treatments. Many herbal remedies have been used to treat PCOS. The World Health Organization (WHO) supports using plant-based medications to treat a number of illnesses, including PCOS. In the design and layout of novel medications, *in-silico* studies and molecular docking are crucial methodologies [18,19].

In-silico investigations of a few herbal phytoconstituents of herbs that have demonstrated strong binding affinities with various receptors have been enlisted in the present review. *In-silico* PCOS investigations may be carried out using a variety of drug design approaches, such as molecular docking, dynamics, and homology modeling. For the molecular docking study, various software is used, such as Pymol, Autodock vina, Autodock tools, Pyrx, Schrodinger maestro, MOE software, FRED Software, Pdb Databank, Pubchem, Discovery Studio visualizer [1922].

In the present review, we have listed different herbal phytoconstituents, their molecular docking interactions with various receptors, their molecular dynamic studies, etc., that are responsible for PCOS activity.

2. *Tinospora cordifolia* (Guduchi)

Tinospora cordifolia is an important traditional, ayurvedic medicine used from ancient days to treat various conditions. *Tinospora cordifolia* belongs to the family menispermaceae [23]. Cysts in the ovaries and insulin disturbance are the main causes of inflammation in the various tissues. *Tinospora cordifolia* (Guduchi) is believed to have an anti-inflammatory effect and can be used as a natural immunity booster [24].

Devi *et al.* [25] concluded that *Tinospora cordifolia* would be beneficial for treating PCOS. Leaves of the *Tinospora cordifolia* were selected for *in-silico* study. The Insulin Receptor Substrate (IRS1 and IRS2) was chosen as a target protein molecule for the study.

The protein structure was retrieved in the PDB format. The 3D structures of the IRS1 and IRS2 receptors were obtained from SWISS-MODEL [26].

Singh *et al.* [27] and Sinha *et al.* [28] conducted (GC-MS) studies on *Tinospora cordifolia* leaves that revealed the presence of alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics compounds in *Tinospora* leaves. Alkaloid and terpenoid categories such as berberine, palmatine, magnoflorine, tembetarine, rumphioside 1, syringin, ecdysterone, makisterone A, tinocordiside, and octacosanol were selected for the docking analysis with the IRS1 and IRS2 receptor using patch dock type of molecular docking.

Docking was performed using the patch dock server, and based on the ligand and receptor interaction, the docking score was computed. The docking score of ligand and receptor interaction was computed based on their binding energies in kJmol^{-1} . The ligands that showed a low binding energy compared to the receptor were selected as the best ligands. Through *in-silico* investigations, results showed significant inhibition of IRS1 and IRS 2 receptors by the antagonistic ligands Rumphioside and berberine. It can be concluded that rumphioside I and berberine can be used to treat PCOS after the completion of preclinical and clinical evaluation. Rumphioside I flavanol of the flavonoid category showed the best antagonistic potential in inhibiting IRS1 and IRS2 receptors with the lowest binding energy of -0.09 kcal/mol for IRS1 and -0.02 kcal/mol IRS2.

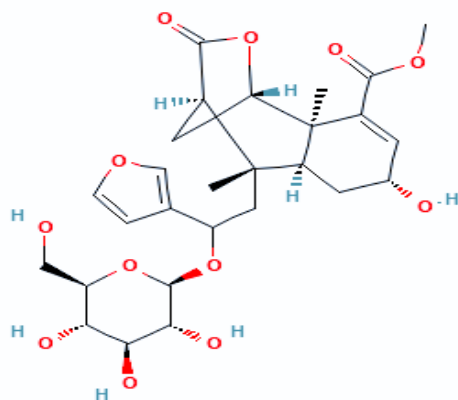


Figure 1. Structure of Rumphioside I from Pubchem database [29].

3. *Foeniculum vulgare* (Fennel)

Foeniculum vulgare, commonly called fennel, belongs to the Umbelliferae (Apiaceae) family [30]. Fennel contains 50-60% anethole, phenolic esters, 18-22% fenchone, fixed oils, and proteins, as well as vitamins such as α -tocopherol, ascorbic acid, β -tocopherol, γ -tocopherol and 6-tocopherol [31,32]. Anethole promotes menstruation, facilitates birth, and also induces estrogenic properties in the ovarian follicle [33,34]. *Foeniculum vulgare* shows various pharmacological activities, including antimicrobial activity, gastrointestinal effect, estrogenic property, antispasmodic activity, and antioxidant and antifungal activity [35].

Chandran *et al.* [36,37] concluded that fennel would be a great source for regulating the menstrual cycle. Anethole phytoconstituent present in the fennel was selected for the *in-silico* study.

The three-dimensional crystal structure of insulin receptor substrate (IRS 1), androgen receptor, and follicle-stimulating hormone (FSH) (PDB ID 1IRS, 1E3G, and 1XUN) was downloaded from the RCSB Protein Data Bank. The chemical structure of the ligand was obtained from the PubChem compound database. It was prepared by Chem Bio Draw and

MOL. The atomic coordinate was generated by converting the SDF format of the ligand to a PDBQT file using the PyRx tool.

The ADME (absorption, distribution, metabolism, and excretion) properties were calculated using the Swiss ADME web-based tool, and the molecular properties bioavailability scores were calculated using the Molinspiration web-based tool. Molecular docking is used to recognize molecular interactions between ligands and target macromolecules. Autodock software was used for the molecular docking. Anethole has the best docking capability with the androgen receptor, FSH receptor, and IRS1 receptor. The binding affinity for anethole with androgen receptor was shown to be (-6.0 kcal/mol), which is higher than (-5.6 kcal/mol) and (-4.2 kcal/mol) for FSH and IRS1 receptors, respectively. Anethole has a great binding affinity with the androgen receptor compared to the IRS1 receptor and FSH receptor. Anethole is a phenylpropanoid organic compound that shows great binding affinity with androgen receptors (1E3G) (-6.0 kcal/mol), FSH receptor 1XUN (-5.6 kcal/mol), and IRS1 (-4.2 kcal/mol).

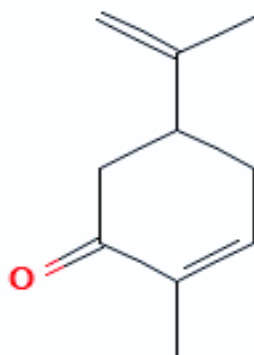


Figure 2. Structure of anethole from Pubchem database [38].

4. Hinguvachadi Choornam

Hinguvachadi Choornam is a combination of effective, potent herbs, including *Ferula asafoetida*, *Acorus calamus*, *Punica granatum*, *Inula racemosa*, *Zingiber officinale*, and *Tamarindus indica* [39].

Ferula asafoetida (Hing), a member of the family *Umbelliferae*, is considered useful in treating unusually painful, difficult, and excessive menstruation and leucorrhoea [40]. *Acorus calamus* (vacha) belongs to the family *Acoraceae*, a traditional Indian medicinal herb used for various problems, including neurological, gastrointestinal, respiratory, metabolic, kidney, and liver disorders [41]. *Punica granatum* is a well-known member of the *Punicaceae* family of leaves and pericarp of herbs. *Punica granatum* contains flavonols and flavones such as catechin, epicatechin, gallic acid, kaempferol, quercetin, and apigenin, identified by IR and NMR [42,43].

Inula racemosa (Pohkarmool) belongs to the family *Asteraceae*. The plant extract of *Inula racemosa* and its isolated active constituents show promising activity against abdominal pain, acute enteritis, bacillary dysentery, expectorant, and tonic [44]. Ginger, a member of the *Zingiberaceae* family, is consumed worldwide as a spice and flavoring agent and is featured to have many medicinal properties such as cardioprotective, anti-inflammatory, antimicrobial, antioxidant, antiulcer, and anticancer properties [45]. Ginger's phytoestrogen component can balance the estrogen-to-progesterone ratio, and thus, it could be used to treat PCOS [46]. *Tamarindus indica* of the family *Leguminosae* were reported to possess antidiabetic activity,

antimicrobial activity, antivenom activity, antioxidant activity, antimalarial activity, antiasthmatic activity, laxative activity, and anti-hyperlipidemic activity [47,48].

Divya Raj *et al.* [49] concluded that *Hinguvachadi Choornam* would be a great choice for treating PCOS. The phytoconstituents, including ferulic acid, asarone, quercetin, alantolactone, gingerol, and naringenin, were selected for the *in-silico* study.

The three-dimensional structure of the FSH receptor (PDB ID- 4AY9) and androgen receptor (PDB ID-2PIV) are retrieved from the RCSB protein data bank. Protein processing was done through PyMOL viewer by removing co-crystallized ligands and water molecules and adding hydrogen atoms to produce the processed 3D protein structure in PDB format. Absorption, distribution, metabolism, and elimination properties were analyzed using Swiss ADME, an online ADME prediction tool.

Compounds were reprocessed from PubChem databases, i.e., ferulic acid (CID-445858), alantolactone (CID 72724), gingerol (CID-442793), asarone (CID-636822), naringenin (CID-932) and quercetin (5280343). The compounds in SDF format were converted into PDB format using online smile translators. Docking was performed in order to analyze and evaluate the binding affinity of phytoconstituents present in the choornam with FSH and androgen receptors with the help of the Auto dock Vina program in PyRx software and visualized using PyMol software. All six constituents showed good docking scores. Among them, quercetin possesses the highest binding affinity with the FSH receptor (-10.0 kcal/mol), and for the androgen receptor, naringenin showed the highest binding affinity (-9.1 kcal/mol) [47]. Naringenin is a flavonoid that showed the highest binding affinity (-9.1 kcal/mol) for the androgen receptor (2PIV).

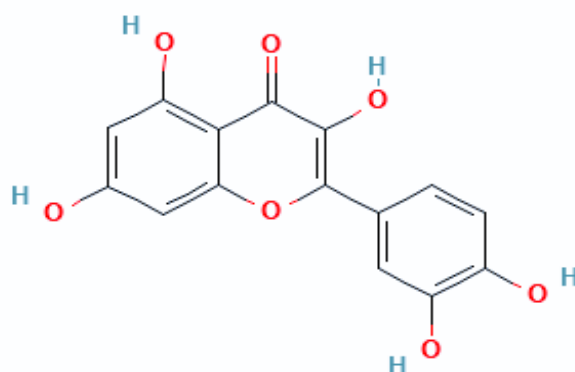


Figure 3. Structure of naringenin from Pubchem database [50].

Quercetin is a potent antioxidant flavonoid that showed the highest binding affinity (-10.0 kcal/mol) with FSH receptor (4AY9).

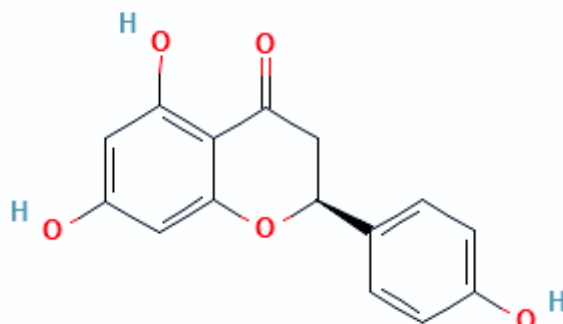


Figure 4. Structure of quercetin Pubchem database [51].

5. *Mentha piperita* L. (Peppermint) and *Mentha spicata* (Spearmint)

Mentha piperita L and *Mentha spicata* belong to the *Mentha* species of the *Lamiaceae* family. They can be used as antioxidant, antidiabetic, antimicrobial, anti-inflammatory, and anti-carcinogenic [52]. Spearmint improves ovarian cysts in PCOS by reducing atretic follicles and enhancing Graafian follicles [53]. *Mentha* regulates the blood ratio of LH and FSH. Based on this regulation of LH/FSH in the blood, it could be useful for treating PCOS. Some studies have shown that spearmint has anti-androgen properties [54]. Essential oils of *Mentha* species include basic components such as menthol, menthone, isomenthone, cineol (eucalyptols), menthyl acetate, menthofuran, β -myrcene, β -caryophyllene, limonene, pulegone and carvone [55].

Nickavar *et al.* [56] concluded that essential oils and their volatile constituents from *Mentha piperita* L.(peppermint) and *Mentha spicata* (spearmint) can be used against polycystic ovary syndrome. In this research, essential oils from two *mentha* species were used to assess the binding of constituents of the oils to the androgen receptor as well as their pharmacokinetic features.

The essential oils were isolated by water distillation and then analyzed using GC-FID and GC-MS. GC analyses showed the presence of 19 and 23 constituents out of the total components, with menthol (29.3%), menthone (33.1%), and carvone (73.0%), and as the major compounds in spearmint and peppermint oils, respectively [57].

In silico, binding studies were performed on the main volatile constituents and human androgen receptors using Autodock Vina, and the pharmacokinetic properties were evaluated using Swiss ADME. Molecular docking studies revealed that carvone has the lowest binding energy to the androgen receptor, indicating that the main volatile constituent in the spearmint oil, i.e., carvone, could probably cause a beneficial effect on PCOS. Carvone is a terpenoid that showed the highest binding affinity with androgen receptors compared with other phytoconstituents.

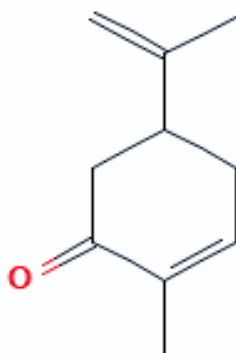


Figure 5. Structure of carvone Pubchem database[58].

6. *Emblica Officinalis* (Amla)

Emblica officinalis (amla) belongs to the family *Euphorbiaceae* [59]. *Emblica officinalis* (amla) is useful in hepatoprotective, gastroprotective, cytoprotective, antitumor, antifungal, and antiulcer activity. *Emblica officinalis* is the richest source of vitamin C, along with phyllembin, rutin, chebulagic acid, tannins, and emblicol [60,61].

Kamboj *et al.*[62] concluded that *Emblica officinalis* can be used as a potential de novo drug to treat infertility in PCOS. The raw X-ray crystal structure of the enzyme human cytochrome CYP17 (PDB ID: 3RUK) was retrieved from RCSB. The 3D structures of

phytochemicals were retrieved from the Pub Chem database. The ligands were further converted into PDBQT format using the PyRx open babel wizard.

Molecular binding affinity was predicted from docking analysis. Protein-ligand docking was done with the help of PyRx. A virtual screening software for in silico drug discovery is used to screen compounds against a potential drug target. Analysis of molecular docking revealed that all the constituents of *Embllica officinalis*, vitamin C (-5.2 kcal/mol), phyllembin (-5.5 kcal/mol), rutin (-9.5 kcal/mol), chebulagic acid (-8.2 kcal/mol) showed good docking scores. Among them, rutin showed great binding affinity towards the 3RUK receptor. Rutin, flavonoid glycoside, showed binding affinity (-9.5 kcal/mol) towards human cytochrome P450 CYP17A1 (3RUK).

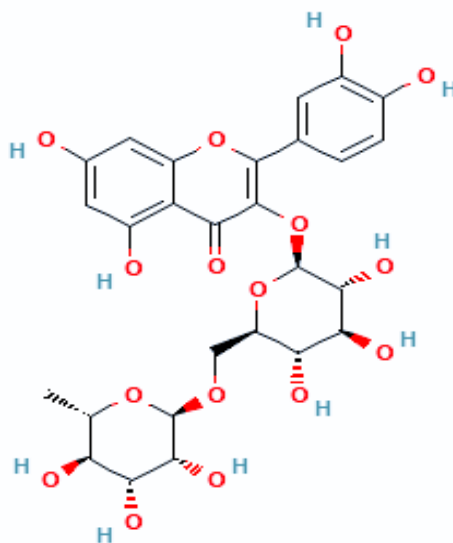


Figure 6. Structure of rutin Pubchem database[63].

7. Cordyceps (Vegetable Caterpillar)

Cordyceps species belongs to the family *Cordycipitaceae* [64]. *Cordyceps* and their extracts have fantastic medical effects, including a motion on cardiovascular, immunological systems, hepatic, renal, respiratory, nervous, anti-cancer, antioxidants, anti-inflammatory, and antimicrobial [65,66].

Kumar *et al.* [67] concluded that *Cordyceps* would be a great source for the treatment of PCOS. Ligand preparation was done by using the application Ligrep wizard of Maestro 12.0. Protein preparation was done using Schrodinger Maestro software. The PDB for the X-ray crystallographic structure of Human Cytochrome P450 CYP17A1 (PDB ID: 3-RUK) was obtained from the Protein Data Bank. Ligand bound within the X-ray crystal structure of a protein was utilized by Glide molecular docking for the identification of the active site receptor grid. Thus, the ligands were assisted by grid-based molecular docking to bind in more than one possible conformation.

The docking score was obtained, and the ligand-protein interaction pose was formed on the basis of the evaluation of the results of the docking study. Results indicated that all the ligands have a strong binding affinity for the human cytochrome P450 CYP17A1 receptor, as indicated by their docking score values that were found to be comparable with the docking score of the molecules 1,6-di-o-glloyl-d glucose (-12.172), isoquercitrin acid (-11.366), isoguaicin (-8.04), ellagic acid (-7.938), linoleic acid (-5.463) and 3,4,6-tri-o-glloyl-d-glucose (-5.079).

Analysis of molecular docking results reveals that 1,6-di o-glloyl-d-glucose was found to have the highest affinity towards the human cytochrome P450 CYP17A1 receptor (docking score = -12.172 Kcal/mol). 1,6-di o-glloyl-d-glucose a flavonoid showed highest affinity towards the human cytochrome P450 CYP17A1 3RUK (-12.172 Kcal/mol).

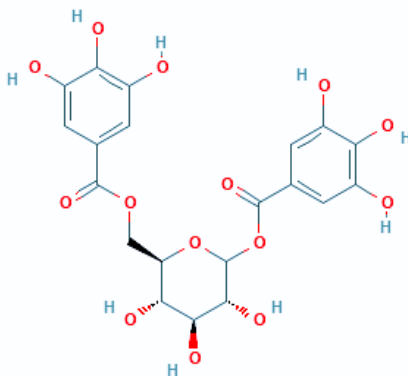


Figure 7. Structure of 1,6-di o-glloyl-d-glucose Pubchem database [68].

8. *Trigonella Foenum-Graecum* (Fenugreek)

Trigonella foenum-graecum (L.) belongs to the family *Fabaceae*. It is commonly known as Fenugreek [69]. It is one of the most promising medicinal herbs and has nutritional value. *Trigonella foenum-graecum* (Fenugreek) plant contains various components, i.e., alkaloids, glycosides, polyphenols, steroids, amino acids, and volatile components [70]. Fenugreek is used for reproductive health problems, improved digestion, and hepatoprotective properties. Studies have shown it has anti-cancerous, anti-helminthic, antiparasitic cardioprotective, anti-sterility, antimicrobial, and neuroprotective properties [71,72].

Zahid *et al.* [73] concluded that quercetin can be considered for the treatment of PCOS. The three-dimensional crystal structure of insulin receptor substrate (IRS 1), androgen receptor, and follicle-stimulating hormone (FSH) receptor (PDB ID IRS1, 1E3G, and 1XUN) were downloaded from the RCSB Protein Data Bank. The chemical structure of the ligands was obtained from the PubChem compound database. Chem-Bio Draw prepared the ligand, and the MOL SDF format of this ligand was converted to a PDBQT file using the PyRx tool to generate atomic coordinates. The ADMET properties were calculated using smile notation in the Swiss ADME web-based tool.

Molecular docking of quercetin with insulin receptors substrate 1, follicle-stimulating hormone receptors, and androgen receptors was performed using Autodock4. Quercetin showed a great binding affinity towards insulin receptor substrate (IRS 1), androgen receptor (1E3G), and follicle-stimulating hormone receptors (1XUN). Quercetin is a flavanol that showed a potent binding affinity towards insulin receptors substrate (IRS 1), androgen receptor (1E3G), and follicle-stimulating hormone receptors (1XUN).

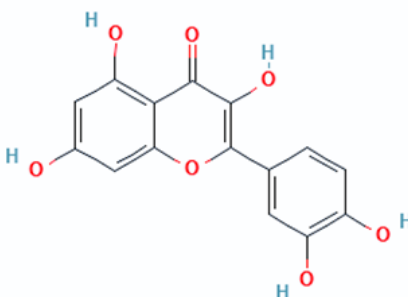


Figure 8. Structure of quercetin Pubchem database[74].

9. Syzygium Polyanthum (Bay Leaves)

Syzygium polyanthum belongs to the genus *Syzygium*, which comprises 1200–1800 species belonging to the family *Myrtaceae* [75]. The leaves of *Syzygium polyanthum* were traditionally used in Indonesian cuisine as traditional medicine for diabetes and hypertension [76,77].

Aditya *et al.* [78] concluded that *Syzygium polyanthum* can be used for PCOS activity. *Syzygium polyanthum* leaf is used for this research because it is rich in pharmacological potentials, such as anti-cholesterol antitumor, anti-diabetic, antimicrobial, and anti-inflammatory. The protein was prepared using Discovery Studio Software. Protein targets (TNF α , SOD NF- κ B, and KEAP1) were retrieved from RSCB Protein Data Bank with ID of 2AZ5, 1CB4 3DO7, and 4ZY3, respectively. The *S. polyanthum* was extracted using the ultrasound-assisted extraction (UAE) method, and the bioactive compounds of *S. polyanthum* were screened using liquid chromatography high-resolution mass spectrometry (LC-HRMS) analysis. The ligands were prepared using an open babel at PyRx Software.

The analysis of protein-protein interactions was done through the STRING webserver. Protein-protein interactions (PPIs) network of TNF α , NF- κ B, SOD, and KEAP1 Were analyzed. This analysis was done to evaluate the interaction of each protein. Some bioactive compounds were found in *S. polyanthum*, and 3 were selected, including deoxyphomalone, NCGC00169066-01, and phloretin, for *in-silico* study. The molecular docking was done using Autodock Vina in PyRx software and visualized using Discovery Studio.

The molecular docking analysis showed that deoxyphomalone, NCGC00169066-01, and phloretin had inhibition potential against TNF α and NF- κ B and activation potential against SOD due to several residues involved in the interaction of compounds-protein was the same as the interaction of inhibitor (SPD-304 and MG-132) and activator (gallic acid) control against the protein. NCGC00169066-01 has shown potential inhibition against TNF α , NF- κ B, SOD, and KEA.

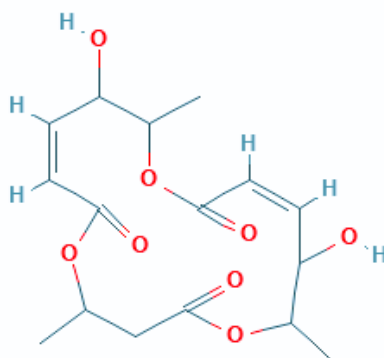


Figure 9. Structure of NCGC00169066-01 Pubchem database [79].

10. Leonuri Herba

Leonuri herba is naturally found in plants and has traditionally been used in China for thousands of years for uterine contractions, postpartum congestion, breast tenderness, and other gynecological disorders [80,81]. *Leonuri herba* contains several active components, including alkaloids, flavonoids, diterpenes compounds, and fatty acids [82,83].

Wu *et al.* [84] concluded that *Leonuri herba* can be used to treat PCOS.

The structure of the receptors AKT1, IL6, EGFR, and MMP9 was downloaded from the PDB Protein Database. Quercetin (MOL000098) and kaempferol (MOL000422) were

selected as ligands, and molecular structures were from the TCMSP database. The binding affinity between molecules and proteins is predicted based on the docking minimum free energy. The lower the free energy, the higher the affinity. Molecular docking verification was carried out by AutoDock Vina, and the results are saved in the PDBQT file.

Finally, the results were analyzed and demonstrated by PyMOL. The results showed that the minimum free energy of quercetin (MOL000098), kaempferol (MOL000422), and key targets AKT1, IL6, EGFR, and MMP9. Quercetin is a flavonoid that shows great binding affinity with AKT1 (−6.1 kcal/mol), IL6 (−6.9 kcal/mol), EGFR (−8.6 kcal/mol)

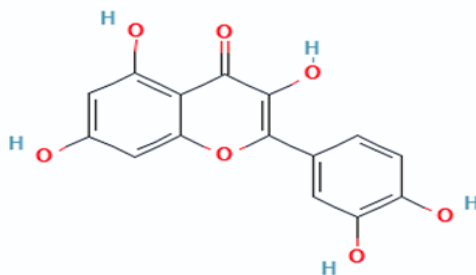


Figure 10. Structure of quercetin Pubchem database [85].

Kaempferol is a natural flavanol that has shown the best affinity with MMP9 (−9.6 kcal/mol).

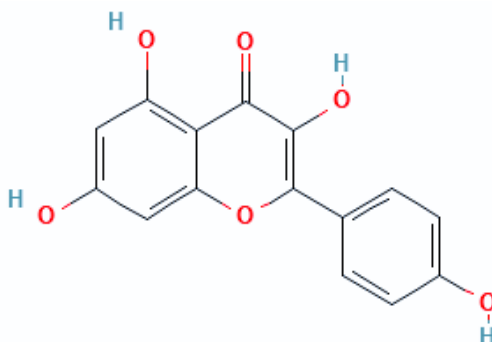


Figure 11. Structure of kaempferol Pubchem database [86].

11. *Asparagus Racemosus* (Shatavari)

Asparagus racemosus (Shatavari) is a member of the family *Liliaceae*. Shatavari is the one that implies its potency in treating all women's health issues [87]. Hormonal balances can also be corrected using Shatavari because of the presence of phytoestrogen, which helps regulate the ovarian cycle in women of reproductive age. Heavy bleeding and pre-menstrual symptoms are also corrected by the herb [88]. *Asparagus racemosus* constitutes oligosaccharides, flavonoids, steroidal saponins, and sulfur-containing amino acids. It has been used for the treatment of diarrhea, dysentery, nervous breakdown, rheumatism, and microbial infection due to its various medicinal properties [89,90].

The phytochemical compounds of the plant were known from the GC-MS studies of Hayes *et al.* [91]. The 3D structure of the receptors was downloaded from PDB (Protein data bank). The 2D structure of *A. racemosus* phytochemicals was retrieved from PubChem. The score of ligand and receptor interaction was obtained from the patch dock server.

Molecular docking was carried out using patch dock analysis to find a fitting ligand of the plant compound as a competitive inhibitor for the receptor IRS 1 and IRS 2. The best docking score was selected, and the inhibitory potential of the phytoconstituents of *A. racemosus* was analyzed. The receptors IRS 1 and IRS 2 inhibitory activity with the

phytochemicals was performed using Ligplot. Based on their docking score, I was selected from the 14 phytochemicals: quercetin, hyperoside, racemosol, rutin, and Shatavari.

According to molecular docking analysis, five ligands, quercetin, racemosol, rutin, hyperoside, and Shatavari I, have an antagonistic action against IRS receptor protein. These ligands can act as a competitive inhibitor for insulin binding to IRS receptors of theca cells in the ovary [92]. Racemosol showed the highest binding affinity towards the IRS2 receptor; for IRS1, Hyperoside showed the highest docking score. Racemosol showed the highest binding affinity towards the IRS2 receptor compared with selected ligands.

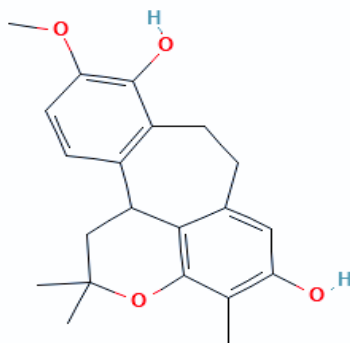


Figure 12. Structure of racemosol Pubchem database [93].

Hyperoside flavonoid showed the highest docking score with IRS1.

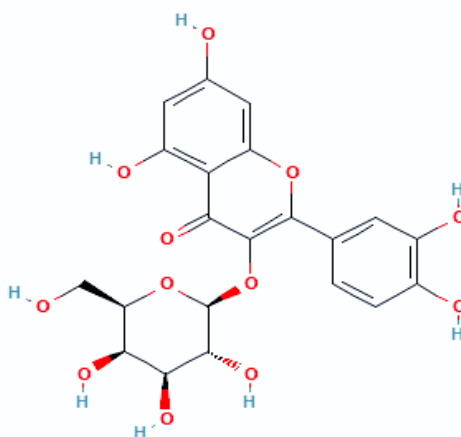


Figure 13. Structure of hyperoside Pubchem database [94].

12. Conclusions

Herbal drugs are the best remedies for various diseases and disorders with nearly no side effects. Herbal medicines play an important role in the improvement of PCOS. PCOS is the primary cause of infertility in females, so to overcome infertility due to PCOS, we need the best and most promising treatment against PCOS for the future. From various *in-silico* studies carried out on plants, it is suggested that the herbal compounds show significant binding properties with different target proteins and, hence, can be used to develop newer drugs. Modern scientific studies like docking, homology modeling, molecular dynamics, and 3D QSAR have become more popular recently. The present review focuses on plants studied by docking methods against PCOS in recent years.

Autodock software is used for most docking studies. Targets for the docking studies were IRS1, IRS2, 1XUN, 3 RUK, etc. Docking studies suggest that phytoconstituents such as quercetin, rumphioside I, anethole, racemosol, hyperoside, kaempferol, NCGC00169066-

01,1,6-di-o-galloyl-d glucose RUTIN, carvone, naringenin. The current review may be useful for the design of novel lead molecules for PCOS.

Table 1. Chemical constituents of some herbal compounds used for PCOS.

Sr.no	Plant	Chemical constituent	Receptor	Software used
1	<i>Tinospora cordifolia</i>	Rumphioside I	IRS1 and IRS2	patch dock server
2	<i>Foeniculum vulgare</i>	Anethole	1IRS, 1E3G and 1XUN	Auto dock
3	<i>Hinguvachadi Choornam</i>	Quercetin And naringenin	4AY9 and 2PIV	Auto dock Vina
4	<i>Mentha species</i>	Carvone	1E3G	Autodock Vina
5	<i>Emblica officinalis</i>	Rutin	3 RUK	Autodock vina
6	<i>Cordyceps</i>	1,6-di-o-galloyl-d glucose	3-RUK	Maestro 12.0 (Schrodinger 2020)
7	<i>Trigonella foenum-graecum</i>	Quercetin	1IRS, 1E3G and 1XUN	Autodock4
8	<i>Syzygium polyanthum</i>	NCGC00169066-01	2AZ5, 1CB4 3DO7 and 4ZY3	AutoDock Vina at PyRx
9	<i>Leonuri Herba</i>	quercetin and kaempferol	AKT1, IL6, EGFR and MMP9	Autodock Vina
10	<i>Asparagus racemosus</i>	Racemosol and Hyperoside	IRS 1 and IRS 2	Patch dock server

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Conflicts of Interest

The authors declare no conflict of interest.

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