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In Silico Evaluation of Phytoestrogens as Targeted Modulators of Hormonal Receptors (ESR1 and PGR) in Amenorrhea: A Comprehensive Bioinformatics and Molecular Docking Approach.

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Abstract

Amenorrhea is a condition where a woman does not get her period. This condition is often related to problems with the pituitary-ovarian axis. The pituitary-ovarian axis is a system that helps control when a woman gets her period. Amenorrhea is also associated with changes in the way that hormonal receptors work. These hormonal receptors, such as Estrogen Receptor alpha and Progesterone Receptor are important for a woman to have a menstrual cycle.

Hormone replacement therapy is one way that doctors treat Amenorrhea. However using hormone replacement therapy for a time can cause problems with a womans metabolism. Because of this doctors need to find ways to treat Amenorrhea.

This study looked at how certain phytoestrogens, such as Quercetin, Genistein, Diosgenin, Apigenin and Vitexin might be used to treat Amenorrhea. The study used computers to analyze the information, which is called a bioinformatics-based approach. The researchers wanted to see if these phytoestrogens, such as Quercetin, Genistein, Diosgenin, Apigenin and Vitexin could be used as an alternative, to hormone replacement therapy. The molecular docking analysis was performed using AutoDock Vina for determining their binding interactions with ESR1 (PDB ID: 1A52) and PGR (PDB ID: 1A28). Docking studies revealed that Quercetin exhibited the highest binding affinity for PGR at -9.74 kcal / mol, and Diosgenin exhibited the strongest binding with ESR1 at -8.88 kcal / mol.

The team did research on how these compounds work in the body and if they are safe. They used tools like SwissADME and pkCSM to see how well the body absorbs these compounds and if they are toxic. The results showed that these compounds are absorbed well in the stomach and are generally safe.

In the end the team thinks that these natural compounds could work like steroids to affect hormone levels and might be options to study for new treatments, for amenorrhea.

Keywords: Amenorrhea, HPO axis, ESR1, PGR, molecular docking, phytochemicals, ADMET, bioinformatics.

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1. Introduction

The menstrual cycle is a process that the female body goes through. It is a sign of how healthy the female reproductive system's. When a female does not get her period this is called amenorrhea. Amenorrhea is not a disease. It can be a sign of something else going on. There are reasons why a female might not get her period, such as problems with her genes problems with her body or problems with her hormones.

The menstrual cycle is controlled by a system that involves the brain and the reproductive organs. This system is called the pituitary-ovarian axis or the menstrual cycle system. The brain sends signals to the organs to help control the menstrual cycle. One important part of this system is the release of a hormone called gonadotropin-releasing hormone or GnRH from the brain. The way that GnRH is released is very important. It helps control the release of two hormones called luteinizing hormone or LH and follicle stimulating hormone or FSH from the pituitary. The menstrual cycle system is very important for the female body to work properly. The pituitary-ovarian axis and the release of GnRH and other hormones, like luteinizing hormone and follicle stimulating hormone all work together to control the menstrual cycle.Such variations in the frequency or amplitude of these pulses may disturb the normal hormonal balance. Such disturbances can be caused by stress, metabolic imbalance, chronic disease or structural abnormality. These eventually result in primary or secondary amenorrhoea. So when a girl does not get her period by the time she is supposed to that's called primary amenorrhea. This usually happens because of problems with the chromosomes. Because of some issue with the way the body developed like with Turners syndrome or Mullerian agenesis.

Then there is amenorrhea, which is more common. This is when a girl stops getting her period after she had been getting them. This can happen to girls with ovary syndrome or PCOS or if their ovaries stop working too early or if they have a functional hypothalamic disorder.

The menstrual cycle is controlled by things in our cells called nuclear hormone receptors. The main ones are estrogen receptor alpha or ESR1 and progesterone receptor or PGR. These receptors are, like helpers that get turned on by hormones and they help our genes do what they need to do.

They do this by using their natural hormones, estrogen and progesterone, which cause structural changes that allow them to bind to specific sequences of DNA, controlling the gene expression responsible for growth and differentiation of the endometrium. In amenorrheic patients, the low hormone levels are responsible for poor receptor activation leading to insufficient endometrial development and disturbed menstrual function. Hormone replacement therapy is an established clinical practice but its long-term use has been associated with possible risks, such as thromboembolic events and hormone-sensitive cancers. Such restrictions have increased the interest in safer alternative approaches , especially plant-derived compounds called phytoestrogens .

These naturally occurring compounds have structural similarities to endogenous estrogens and can interact to varying degrees with estrogen and progesterone receptors. However, the large diversity of phytochemicals makes experimental screening time- and cost-consuming. Computational methods such as molecular docking have become useful tools in modern drug discovery. These methods allow researchers to predict how small molecules bind to target proteins, including the orientation and affinity of the binding. We can also use computer models to predict how drugs will work in the body like how they will be absorbed, distributed, changed and removed. This helps us figure out if a drug is safe and will work well.

In this study we looked at some compounds like Quercetin, Genistein, Diosgenin, Apigenin and Vitexin to see if they can affect the HPO axis. Our goal, with this study is to find out if these natural compounds can help with amenorrhea by targeting ESR1 and PGR and we used computer analysis to do this.

2. Amenorrhea: Pathophysiology, Types, And Causes

2.1 Classification: Primary and Secondary Amenorrhea

Amenorrhea has two types.

* Primary amenorrhea is when you have never had a period.

* Secondary amenorrhea is when your periods stop after they have started.

Primary amenorrhea is defined as the lack of menstruation by the age of puberty. It is usually considered when there is no menarche by age 13 in the absence of secondary sexual characteristics or at 15 years despite normal growth and pubertal development. This situation is usually linked to congenital issues and structural problems with the reproductive system. Common causes include dysgenesis, such as Turner syndrome and Müllerian agenesis that affects normal ovarian development or the development of reproductive tract structures.

Secondary amenorrhea is when a woman misses her periods for a while even though she had periods before. Amenorrhea is when a woman does not get her periods for 3 months if she usually has cycles and for 6 months if her cycles are irregular. This type of amenorrhea is often seen in practice and is commonly linked to hormonal and metabolic disorders. The main causes are Polycystic Ovary Syndrome, also known as PCOS, Functional Hypothalamic Amenorrhea, Premature Ovarian Insufficiency or POI that affect ovulation due to abnormal hormone function or problems with the ovaries, such, as PCOS, FHA and POI.

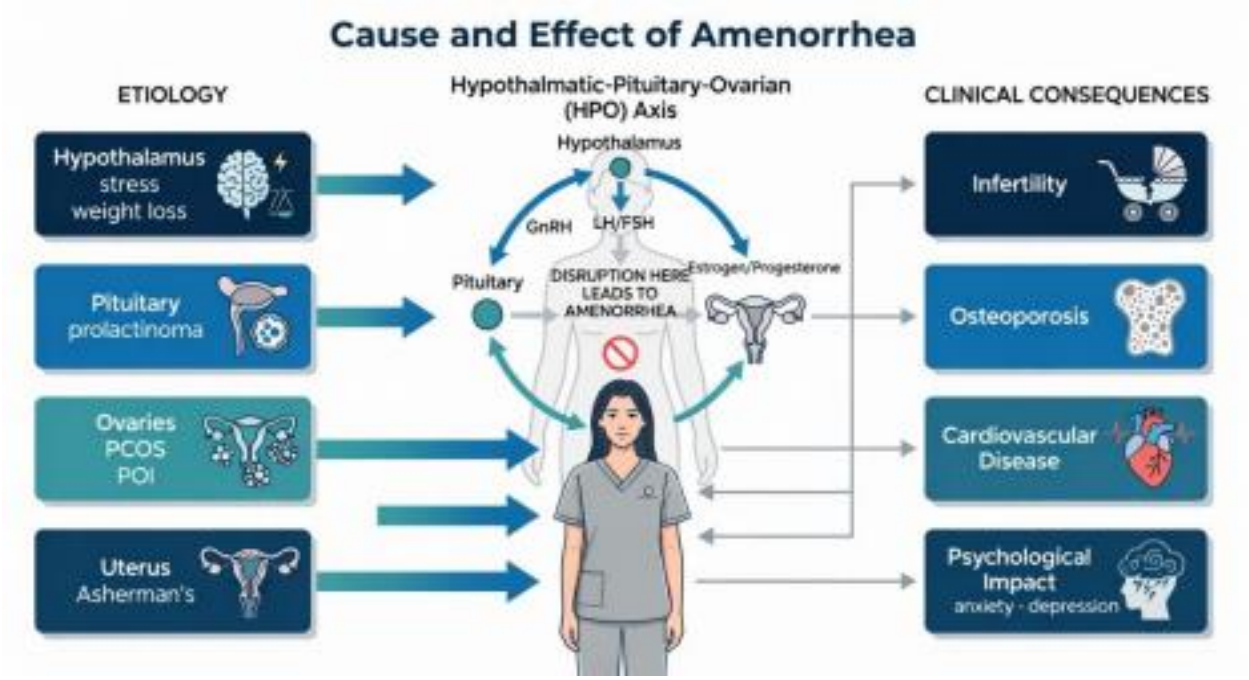

Figure 1: The cause and effect of Amenorrhea in women

2.2 Role of the HPO Axis

The hypothalamic-pituitary-ovarian (HPO) axis is the main regulatory network controlling the female reproductive function. Gonadotropin-releasing hormone (GnRH) is released by the hypothalamus as part of a coordinated hormonal network. This hormone causes the anterior pituitary to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which regulate ovarian function like follicular development and ovulation. The pulsatile secretion of GnRH is critical for the maintenance of normal reproductive physiology.Any alteration in the frequency or amplitude of the pulses may disturb the balance of secretion of FSH and LH, which may lead to irregular menstruation and poor ovulation. Such changes may be caused by psychological stress, bad diet, too much physical exercise, chronic illness or metabolic imbalance.

This process is particularly evident in Functional Hypothalamic Amenorrhea, where changes in energy balance and stress lead to direct decreases in hypothalamic signals. Pathological diseases such as pituitary tumors, systemic endocrine abnormalities, also interfere with the HPO axis, further decreasing estrogen production and preventing normal endometrial development and cyclic changes during menstruation.

2.3 Molecular Targets: ESR1 and PGR

ESR1-At the molecular level, regulation of the menstrual cycle is mediated by estrogen and progesterone via their nuclear receptors, ESR1 and PGR, respectively . These receptors are crucial for the regulation of gene expression necessary for the proper development and function of the endometrium.

The ESR1 gene is really important because it helps our bodies make something called estrogen receptor alpha. This estrogen receptor alpha is found in a lot of our organs like the uterus, ovaries and mammary glands.

When the ESR1 gene is working properly during the time of the month when our bodies are getting ready for a pregnancy it helps the cells in the uterus grow and the tissue get thicker.

But if something goes wrong with the ESR1 gene the uterus does not develop like it should and the lining becomes thin and does not work like it is supposed to so we might have problems with our periods. The ESR1 gene plays a role in all of this because it helps our bodies get ready for a pregnancy every month. The ESR1 gene is crucial, for the estrogen receptor alpha to work correctly.

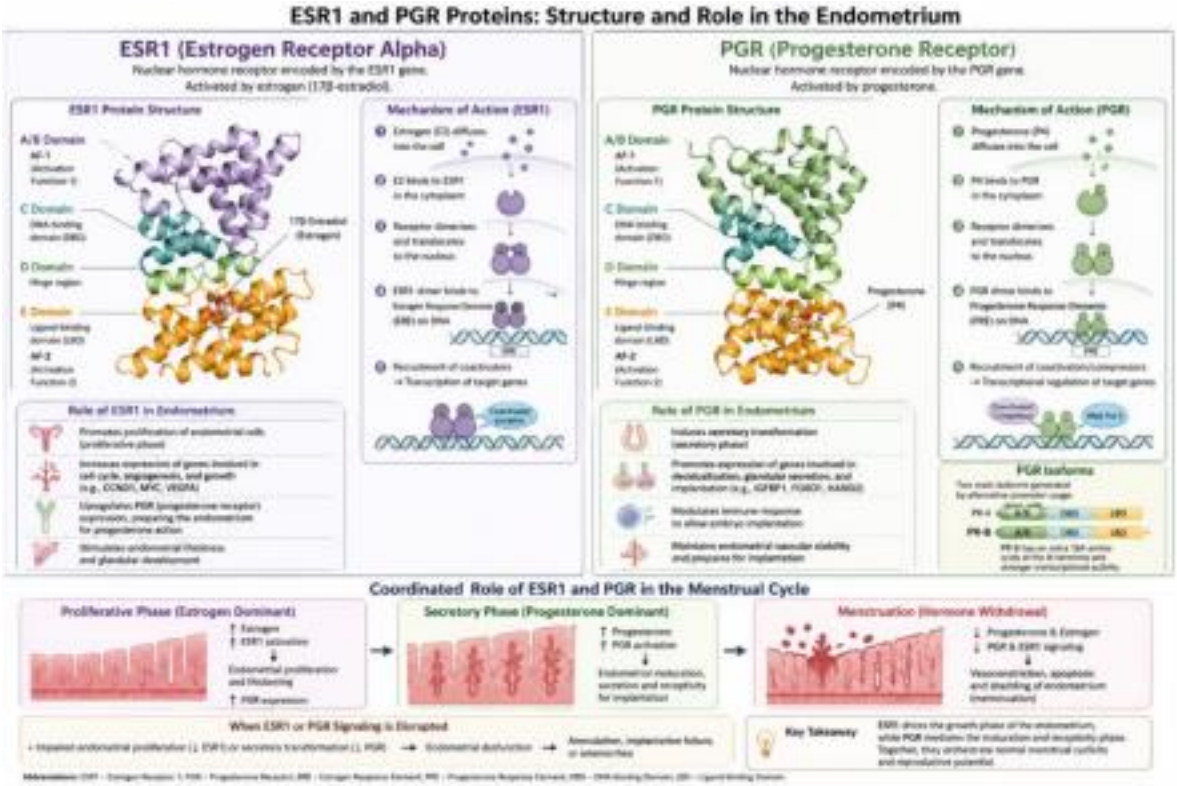

Figure 2: Structure and Role of ESR1 and PGR during menstrual cycle

PGR (Progesterone Receptor)

During the secretory phase, progesterone responses are mediated by two major isoforms of the progesterone receptor, PR-A and PR-B, both of which are required. Progesterone after ovulation makes the endometrium stable and differentiated. The natural metamorphosis of the endometrium for menstruation cannot take place if PGR activation is blocked. Any malfunction in ESR1 or PGR aggravates amenorrhea, providing the molecular basis for hormone responsiveness in the endometrium.

2.4 Etiological Factors and Clinical Markers

Amenorrhea is linked to problems with the endocrine system and metabolism that are important clues for diagnosis.

Hyperprolactinemia is one issue. When prolactin levels are high it stops the hypothalamus from releasing Gonadotropin Releasing Hormone, which means that Follicle Stimulating Hormone and Luteinizing Hormone levels are low. This affects the hormones that control menstruation and ovulation. People with this issue may have periods and galactorrhea.

A common reason for this is a prolactin-secreting adenoma.

Thyroid problems are another issue. Changes in gonadotropins and sex hormone-binding globulin because of hyperthyroidism or hypothyroidism can affect cycles. Thyroid hormones have an effect on the ovaries and any change can cause irregular periods and reproductive issues.

Polycystic Ovary Syndrome is a cause of amenorrhea that happens after someone has had periods. Polycystic Ovary Syndrome is characterized by androgen levels and chronic anovulation.

When someone has Polycystic Ovary Syndrome they may have ovaries. High androgen levels can cause symptoms like hair growth, acne and irregular periods. Insulin resistance is also common in people with Polycystic Ovary Syndrome, which makes hormonal imbalance worse and contributes to problems in people, with Polycystic Ovary Syndrome.

Table 1: Summary of Amenorrhea Dynamics

Category	Primary Drivers	Major Systemic Effect
Functional	Stress, Nutrition, Exercise	GnRH suppression →→ Low Estrogen
Endocrine	PCOS, Thyroid dysfunction	Hormonal imbalance →→ Anovulation
Structural	Adhesions, Obstructions	Outflow tract blockage
Consequence	Hypoestrogenism	Bone loss, Infertility, Cardiac risk

3. Methodology

3.1 Protein Target Acquisition

The 3D structures of the target proteins were downloaded from the RCSB Protein Data Bank (PDB) For this study, two major hormone regulating receptors were selected:
• ESR1: PDB ID 1A52, ligand-binding domain of human estrogen receptor alpha

• PGR: Human Progesterone Receptor ligand-binding domain (PDB ID 1A28) Protein structures were prepared using AutoDock Tools (ADT) prior to the docking analysis. This preparation procedure involved removal of crystallographic water molecules, addition of Gasteiger charges and merging of non-polar hydrogens for proper optimization of the receptor for docking experiments.

3.2 Ligand Selection and Library Preparation

Five special plant substances were chosen because they are found in plants that have been used for a time to help womens health:

*** Quercetin, a flavonoid that you can find in many fruits and vegetables**

*** Genistein, an isoflavone that's very common in soy products**

*** Diosgenin, a steroidal sapogenin that comes from wild yam plants**

*** Apigenin, a flavonol that is found in chamomile**

*** Vitexin, a flavone glycoside that's present in Vitex agnus-castus.**

The chemical structure of these substances was downloaded from the PubChem database, in SDF format. These structures were then changed to PDBQT format using the Open Babel software for studying how they dock with molecules.

3.3 Molecular Docking Workflow

Molecular docking studies were conducted using AutoDock Vina to investigate the binding interactions of selected ligands with target receptors. The grid box was designed in a way that the active site area of each receptor including the binding pocket where natural ligands such as progesterone and estradiol bind was occupied.
The following docking parameters were used:
• Exhaustiveness: 8, to ensure adequate sampling of potential binding orientations and ligand conformations
• Scoring Function: AutoDock Vina uses a hybrid empirical and knowledge-based scoring function to predict binding affinity.

This method can be used to predict the binding energies and the binding poses of ligand–receptor interactions.

3.4 ADMET and Pharmacokinetic Profiling

The drug like-ness and safety profile of the selected compounds was assessed by computational ADMET analysis using established online tools.

• SwissADME: Used to evaluate pharmacokinetic properties, such as compliance with Lipinski's Rule of Five and the potential for gastrointestinal absorption

• pkCSM: For prediction of toxicity related parameters like AMES mutagenicity and Hepatotoxicity
The selected phytochemicals were analyzed to determine if they have favorable characteristics for possible therapeutic development.

4. Results

4.1 Molecular Docking Results

The binding energy (ΔG) was used to evaluate the interactions of the selected ligands with target receptors as a measure of the stability of the ligand-receptor complex. More negative values of the binding energy correspond to stronger and more persistent binding interactions between the ligand and the protein target . Molecular docking analysis was carried out to compare the binding affinities of all selected phytochemicals with ESR1 and PGR receptors. Data were used to identify the drugs with the greatest theoretical potential to effectively modify receptor function in the setting of hormonal imbalance associated with amenorrhea.

Table 2: Molecular Docking Scores (Binding Affinity in kcal/mol)

Ligand	ESR1 (Binding Energy)	PGR (Binding Energy)
Diosgenin	**-8.88**	-9.38
Quercetin	-8.58	**-9.74**
Genistein	-8.64	-9.30
Apigenin	-8.20	-8.90
Vitexin	-7.90	-8.50

The docking data revealed that quercetin had the highest binding affinity to the progesterone receptor and was better than all the other phytochemicals studied with a binding energy of -9.74 kcal/mol. This suggests that quercetin may have a higher affinity to the active site of the receptor and may also interact with signaling pathways related to progesterone.

On the other hand, Diosgenin showed the most favorable interaction with an estrogen receptor with a binding value of -8.88 kcal/mol. This finding suggests that diosgenin could have a stronger tendency to bind within the estrogen receptor binding pocket, and in theory could act as an estrogen-like modulator.

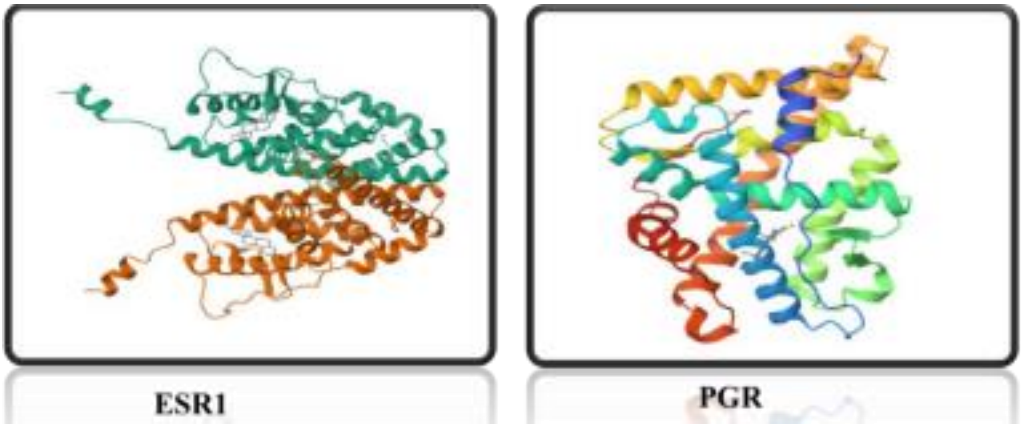

Figure 3: 3D REPRESENTATION OF RECEPTORS (PROTEIN) FROM PDB DATABASE

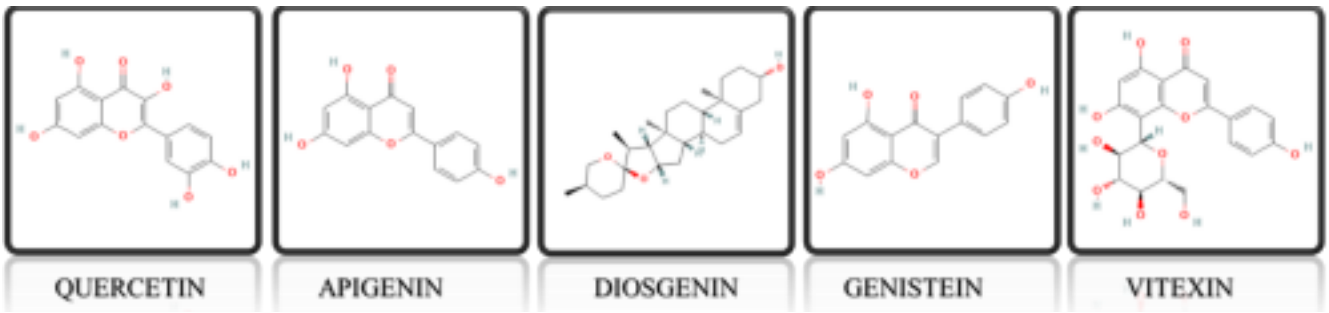

Figure 4: 2D REPRESENTATION OF PHYTOCHEMICALS FROM PUBCHEM DATABASE

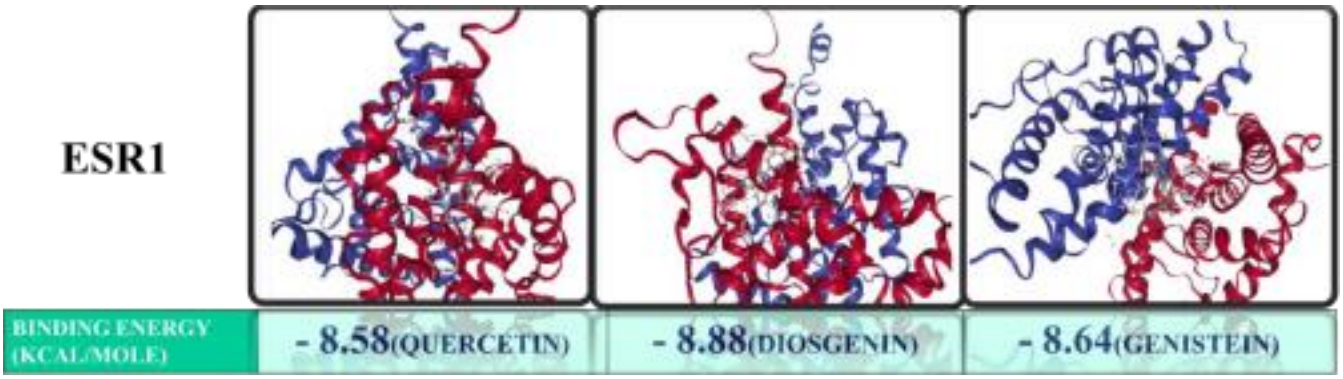

Figure 5a: 3D REPRESENTATION OF MOLECULAR DOCKING OF ESR1 PROTEINS WITH PHTOCHEMICALS

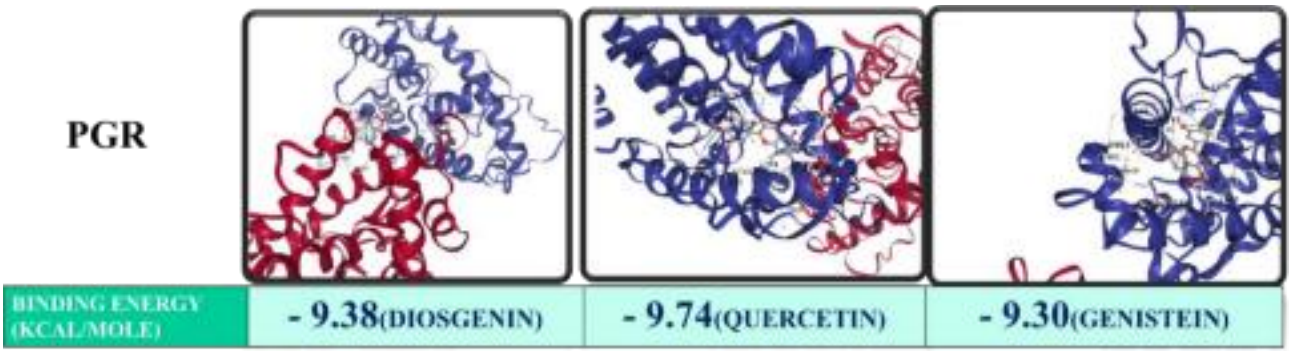

Figure 5b: 3D REPRESENTATION OF MOLECULAR DOCKING OF PGR PROTEINS WITH PHTOCHEMICALS

4.2 ADMET Findings

The ADMET study gave us a lot of information, about the safety characteristics of the selected phytochemicals. We found out that Quercetin and apigenin are well absorbed in the gastrointestinal system. This means that when we take Quercetin and apigenin by mouth our body will likely absorb them well. This is important to know about Quercetin and apigenin.This characteristic lends support to their potential suitability for formulation as oral medication. All the five selected compounds were found obeying Lipinski's Rule of Five suggesting good drug like properties. The parameters assessed such as molecular weight, LogP values, hydrogen bond donors and hydrogen bond acceptors were within the acceptable limits indicating a good potential for oral bioavailability.

In the toxicity assessment, one of the substances showed the expected skin sensitization or hepatotoxicity in the in silico models. The results suggest that the selected phytochemicals may have a relatively safe profile, further supporting the potential of these phytochemicals for future therapeutic investigation.

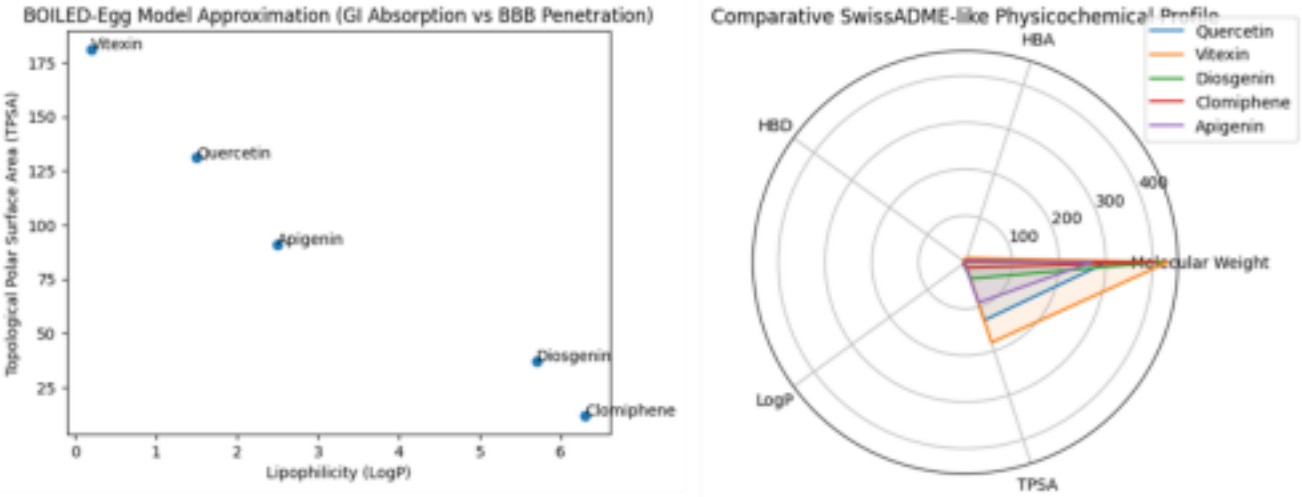

Figure 6: 3D REPRESENTATION OF MODEL SWISSADME OF PHYTOCHEMICALS

5. Interpretation and Discussion

5.1 Structural Basis of Binding

Structural basis for binding the steroid-like molecular scaffold of diosgenin similar to the unique four-ring structure of endogenous estrogen may contribute to its high binding affinity to ESR1. Computational study indicates that Diosgenin forms stable hydrophobic interactions with key amino acid residues in the ESR1 binding pocket such as Leu346 and Met388. Like agonist binding, these interactions probably serve to stabilize the receptor. However, quercetin had the highest binding affinity for the progesterone receptor (PGR).

This behaviour may be due to the large number of hydroxyl functional groups in its structure, which are able to form strong hydrogen bonds with active site residues like Gln725 and Arg766. These interactions imply that quercetin can bind efficiently at the receptor binding site and potentially have a physiological effect on progesterone signaling.

5.2 Clinical Implications for Amenorrhea

Based on their receptor binding characteristics, substances like quercetin and diosgenin could be useful as therapeutic support in clinical conditions such as Functional Hypothalamic Amenorrhea (FHA) and Primary Ovarian Insufficiency (POI) where estrogen levels are significantly low. Based on the predicted interactions, they might be involved in helping to regulate hormones and to stimulate the activity of the endometrium. Furthermore, good gastrointestinal absorption profile of Apigenin implies that these phytochemicals are amenable to oral administration and is an important aspect to be taken into consideration in future formulation strategies for medication.

5.3 Bioinformatics as a Predictive Tool

This study shows the efficiency of in silico methods to identify putative bioactive molecules from a wide range of phytochemicals. Computational docking can help us to discover a small number of interesting candidates with

a better theoretical affinity to relevant biological targets in amenorrhea instead of exhaustive experimental screening of different plant extracts.

6. Conclusion

In this work, a computational study on the potentiality of some phytoestrogens for the treatment of amenorrhea is made. Pharmacological knowledge and bioinformatics technologies were integrated, and allowed to identify important molecular candidates with interesting interactions with the hormone receptors involved in the control of the hypothalamic-pituitary-ovarian (HPO) axis. The results of the molecular docking showed that the chemicals being studied have a distinct order of binding affinities. Diosgenin showed a strong interaction with ESR1, indicating structural compatibility with the estrogen receptor binding site . Similarly, quercetin exhibited the highest affinity for PGR, indicating that it could have an efficient interaction with progesterone signaling pathways. These observations were further supported by ADMET analysis showing good gastrointestinal absorption and drug-likeness criteria compliance for most of the compounds especially for Quercetin and Apigenin. Importantly, the toxicity predictions reflected a safe profile in general and no major hepatotoxic or mutagenic risks were detected in silico.

Taken together, the results of this study suggest that these phytochemicals are promising natural agents for the modulation of hormone receptor activation. Moreover, the research points out the significance of classical medicinal herbs in modern drug discovery, giving a molecular basis to their use in therapy.

It should be noted, however, that the computational results are only the first stage in the prediction process. Biological efficacy needs to be confirmed by experimental validation with in vitro research, in vivo models, and molecular dynamics simulations. “Future research that integrates advanced drug delivery techniques and computational chemistry could lead to the development of more effective and safer amenorrhea therapies.”

7. Declaration

The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication.

The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript, including all revisions made in response to reviewer comments.

8. Ai Usage Statement

The authors declare that AI tools, if used, were solely employed to improve the clarity, grammar, and language of the manuscript. No data, results, or scientific content were generated or altered using AI.

9. Conflict of Interest And Ethical Compliance

All authors confirm that:

i) Any potential conflicts of interest, whether financial or non-financial, have been fully disclosed. – **Not Applicable**.
ii. All sources of funding and financial support received for the conduct of the study have been appropriately acknowledged, including any updates made during revision. - **Not Applicable**.
iii. Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable, and are clearly stated in the manuscript - **Not Applicable.**

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