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FORMULATION AND EVALUATION OF DUAL HERBAL TRANSDERMAL PATCHES ON POLYCYSTIC OVARIAN SYNDROME

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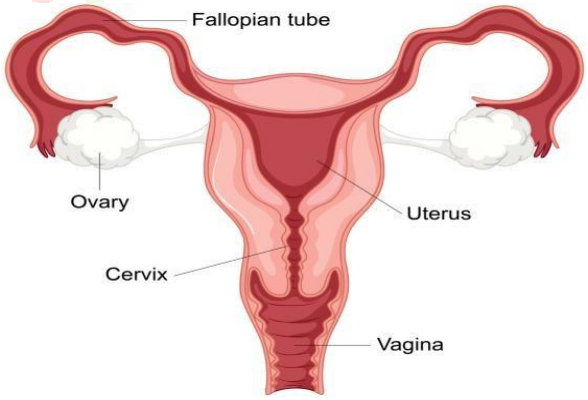
Abstract: Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder characterized by hormonal imbalance, chronic inflammation, and metabolic irregularities. Conventional treatments often present limitations, including side effects and poor patient compliance. In this study, a novel **herbal transdermal patch technology** was developed as a non-invasive approach to support hormonal regulation and symptom management in PCOS. The formulations incorporated standardized herbal extracts of **Ashwagandha (Withania somnifera)**, **Fenugreek (Trigonella foenum-graecum)**, **Cinnamon (Cinnamomum verum)**, and **Spearmint (Mentha spicata)** plants known for their phytochemicals with adaptogenic, insulin-modulating, anti-androgenic, and anti-inflammatory actions. Their **chemical constituents**, including withanolides, trigonelline, cinnamaldehyde, and rosmarinic acid, play a crucial role in restoring hormonal balance, particularly by regulating cortisol levels, improving insulin sensitivity, and reducing excess androgens associated with PCOS.Two types of transdermal patches were formulated: a **pre-period patch**, designed to mitigate premenstrual discomfort and early hormonal fluctuations, and a **continuous-period patch**, intended for sustained support throughout the menstrual cycle. The patches were prepared using suitable polymers and evaluated for **drug–polymer compatibility**, physicochemical properties, and stability. Compatibility studies confirmed the absence of major interactions between the herbal extracts and excipients, ensuring effective transdermal permeation. Preliminary observations indicated favorable mechanical strength, uniform drug distribution, and potential for controlled release.Overall, the developed **herbal transdermal patches** demonstrate promise as an innovative and effective delivery system for PCOS management by providing targeted hormone- balancing support through natural phytochemicals. Further in vitro and in vivo studies are recommended to validate therapeutic efficacy and long-term safety.

Keywords: Polycystic Ovary Syndrome (PCOS), Herbal transdermal patches, Ashwagandha, Fenugreek, Cinnamon, Spearmint, Curcumin, Hormonal balance.

INTRODUCTION

The female reproductive system is a complex network of organs responsible for the production of ova, hormonal regulation, fertilization, and supporting the development of a fetus. It includes external structures such as the vulva and internal organs including the vagina, uterus, fallopian tubes, and ovaries. The ovaries produce gametes and secrete essential hormones like estrogen and progesterone, which regulate the menstrual cycle and reproductive function. The fallopian tubes facilitate the transport of

the ovum and serve as the typical site of fertilization. The uterus provides the environment for implantation and fetal development, while the vagina functions as the canal for intercourse, childbirth, and menstrual flow. Together, these structures work in coordination to enable reproduction and maintain overall reproductive health[1,2] Normal hormonal regulation in females occurs through the HPO axis. The hypothalamus releases GnRH, which stimulates the pituitary to produce FSH and LH. FSH helps follicles grow, and rising estrogen leads to an LH surge that triggers ovulation. After ovulation, the corpus luteum produces progesterone to prepare the uterus. When pregnancy does not occur, hormone levels drop and menstruation begins, restarting the cycle.[2] The menstrual cycle is a monthly sequence of hormonal and physiological changes that prepare the female body for pregnancy. It typically lasts 28 days and has three main phases: Follicular phase (Days 1-14): FSH stimulates follicle growth; estrogen thickens the uterine lining.Ovulation(Around day 14): An LH surge releases the mature egg.Luteal phase(Days 15-28): The corpus luteum produces progesterone to prepare the uterus. If pregnancy doesn't occur, hormone levels fall and menstruation begins.[3] PCOS is a common endocrine disorder in women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. It involves HPO axis dysregulation and often insulin resistance, leading to irregular menstrual cycles, infertility, hirsutism, acne, and metabolic disturbances. Diagnosis is based on Rotterdam criteria, and management includes lifestyle modification, hormonal therapy, insulin sensitizers, and fertility treatments. PCOS affects reproductive, metabolic, and psychological health, requiring individualized care.[4]PCOS commonly presents with irregular menstrual cycles, anovulatory infertility, and signs of hyperandrogenism such as hirsutism, acne, and scalp hair thinning, often accompanied by metabolic issues like weight gain and psychological effects including anxiety and low self-esteem.The risk of PCOS is increased by genetic predisposition, insulin resistance, obesity, sedentary lifestyle, and hormonal imbalances, with environmental and ethnic factors also influencing its development and severity.[5] Dual transdermal patches offer a useful and effective approach for managing PCOS by providing controlled and sustained hormone delivery that helps regulate menstrual cycles, reduce hyperandrogenic symptoms, and improve metabolic parameters. Cyclic or "pre- period" patches mimic the natural menstrual cycle, delivering estrogen and progesti during specific phases to support endometrial health and induce regular bleeding. Continuous patches maintain steady hormone levels, minimizing fluctuations, reducing withdrawal bleeding, and potentially improving mood and compliance. Compared to oral therapy, transdermal delivery avoids first-pass liver metabolism, lowering the risk of thromboembolism and metabolic side effects, which is particularly advantageous in PCOS patients with obesity or insulin resistance. These features make dual transdermal patches a promising non-oral therapeutic option for both reproductive and metabolic management in PCOS.



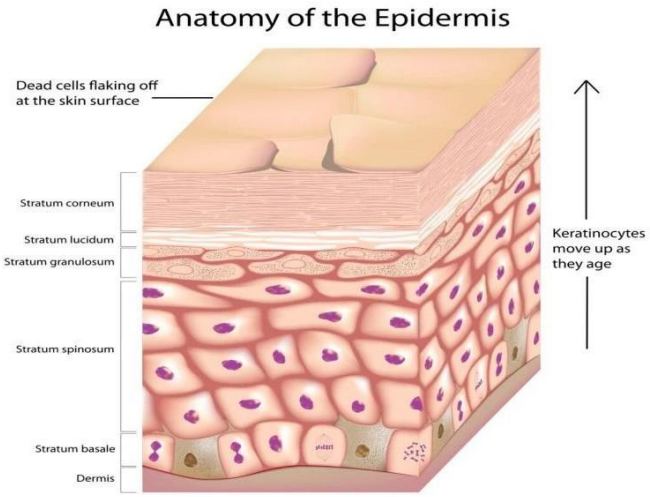
LITERATURE REVIEW:

Sr. No.	Title	Author	Year
1.	The last update on polycystic ovary syndrome (PCOS), diagnosis criteria, and novel treatment.	Arghavan Ghafari a, Malihe Maftoohi b.	2025
2.	Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics.	Samradhi Singh, Swasti Shubha Devojit Kumar Sarma.	2023
3.	Prevalence and Risk Factors of Polycystic Ovarian Syndrome PCOS: Cross-sectional Study.	Fawaz Eldirdiri Satti Mohmed, Raghad Mubarak Aljuhaysh.	2023

Skin Anatomy and Physiology

It is important to understand the layers of our skin so that we can understand how healing occurs differently he skin has two principal layers, the epidermis and the dermis. The hypodermis is considered an extension of the skin by some sources, but not by others.[1]

Epidermis:



Composed of five layers

- It is avascular
- Its thickness varies based on location. For example, it is thickest on the heels and thinnest on the eyelids. Areas that have increased use from friction or weight bearing can build up thicker layers of skin (e.g., where a pencil rubs your writing finger or shoe rubs against your foot).
- It has no nerves, but free nerve endings from the dermis do extend into the mid layers of the epidermis.

Five layers of the epidermis (most to least superficial):

1. *Stratum corneum*
   - Composed of 15 to 30 layers of keratinocytes called squames or corneocytes. These are dead keratinocytes. They contain a high concentration of keratin which provides a waterproof barrier for the skin, hair, and nails.
   - This layer is continually being shed from the body. Shed cells are replaced via the process of skin cell migration from the stratum basale. This process takes an average of 30 days, but this varies based on age and certain health conditions.[1]
2. *Stratum lucidum*
   - Contains two to three layers of keratinocytes and is not living. It can be penetrated or shaved off without awareness.
   - It is only found in areas of thick skin, like the palms of the hand and the soles of the feet. Present in calluses.[1]
3. *Stratum granulosum*

This layer contains the greatest concentration of free nerve endings that extend from the dermis. Free nerve endings are unencapsulated dendrites originating from a sensory neuron. They are the most common nerve endings in skin and provide sensory information about painful stimuli, hot and cold, and light touch. However, they are less sensitive to abrupt changes in stimulation.[13]

   - This is the most superficial layer of the epidermis which contains living cells.[1]
4. *Stratum spinosum*
   - Contains Langerhans cells and lymphocytes which play an important role in the immune system.[1]
5. *Stratum basale*
   - The only layer that undergoes continuous mitosis to produce new cells.[1]
   - Keratinocytes are constantly being produced in the stratum basale and they move up through the layers until they reach the outermost layer.[1] Keratinocytes are the most dominant cell

type in the skin. They play a critical role in wound healing as they are structural cells and they perform important immune functions.[14]

- This layer also contains Merkel cells which can perform both nervous and endocrine actions. They can synthesise and store locally produced hormones and neurotransmitters. They function as mechanoreceptors[1] for light and selective tactile perception, but not for hard touch and vibration.[15]

Two layers of the dermis (most to least superficial):

1. **Papillary layer**

Interdigitates with the epidermis

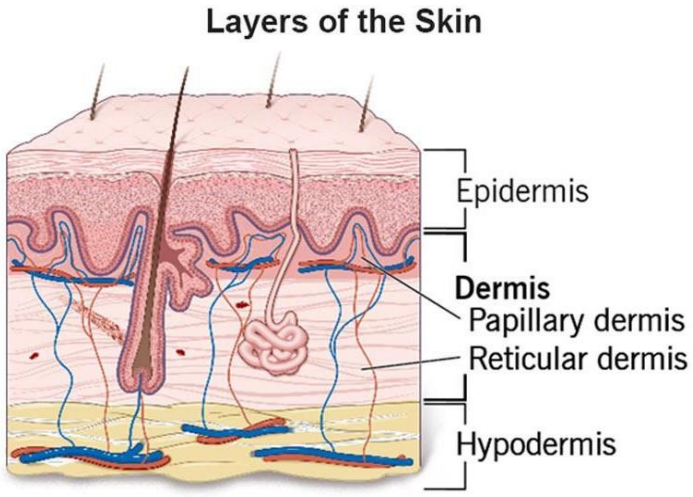
- The ridges of this layer give rise to our unique fingerprints.
- Contains fibroblasts which are responsible for the production of collagen, elastin, and proteins. These qualities give skin strength and flexibility.
- Contains mast cells which produce heparin and histamine, important factors in clot formation and the inflammatory response.
- Contains macrophages which play an important role in the immune response, wound repair, cancer defence, salt balance, and hair regeneration. They are known for destroying foreign invaders through phagocytosis[1] (the process by which a phagocyte, a type of white blood cell, engulfs and digests foreign cells and removes dead cells[1][16]).
- Contains leukocytes[1] which are crucial to the inflammatory response following an injury to the skin. Leukocytes are essential for clearing infection and normal wound healing.[17]

2. **Reticular layer**

- Located between the papillary layer and the subcutaneous layer or hypodermis.
- It is made up of collagen, blood vessels, nerve endings, T-cells, hair follicles and glands.
- The hair follicles contain stem cells that produce keratinocytes that will become hair. They play an important role in wound healing by contributing epithelial cells for wound closure.
- Nerves located within the dermis detect sensations such as itching, touch, pressure, vibration, pain, and temperature.
- Injuries which reach into the dermis can result in pain due to nerve exposure and or damage. There will be an absence of pain if the nerves are completely destroyed and or severed by an injury. [1]

The Hypodermis

- Located below the dermis and contains subcutaneous tissue.
- It is made up of loose connective tissue, adipose tissue. It is well vascularised and well innervated.
- It helps to attach the skin to the muscles and bones through superficial fascia, and provides insulation and cushioning through fat storage.

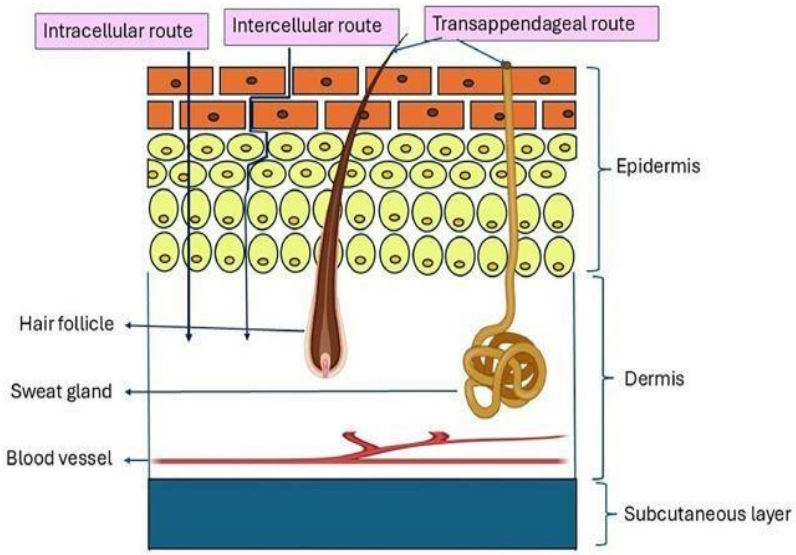


Drug penetration route:

There are two possible routes of drug penetration across the intact skin, namely the transepidermal and transappendegeal pathways, which have been diagrammatically presented in Figure 2. The transepidermal pathway involves the passage of molecules through the stratum corneum, an architecturally diverse, multi-layered and multi-cellular barrier. Transepidermal penetration can be termed intra- or inter-cellular [29]. The intra-cellular route through corneocytes, terminally differentiated keratinocytes, allows the transport of hydrophilic or polar solutes. Transport via inter-cellular spaces allows diffusion of lipophilic or non-polar solutes through the continuous lipid matrix. The transappendegeal route involves the passage of molecules through sweat glands and across the hair follicles [5 30]

An understanding of the kinetics of skin permeation is necessary for development of successful TDD systems. In order to evaluate any TDD, the assessment of percutaneous absorption of molecules is a very important step. Percutaneous absorption is the penetration of substances into various layers of skin and permeation across the skin into the systemic circulation [8,31,32,33]. Percutaneous absorption of molecules is a step wise process involving:

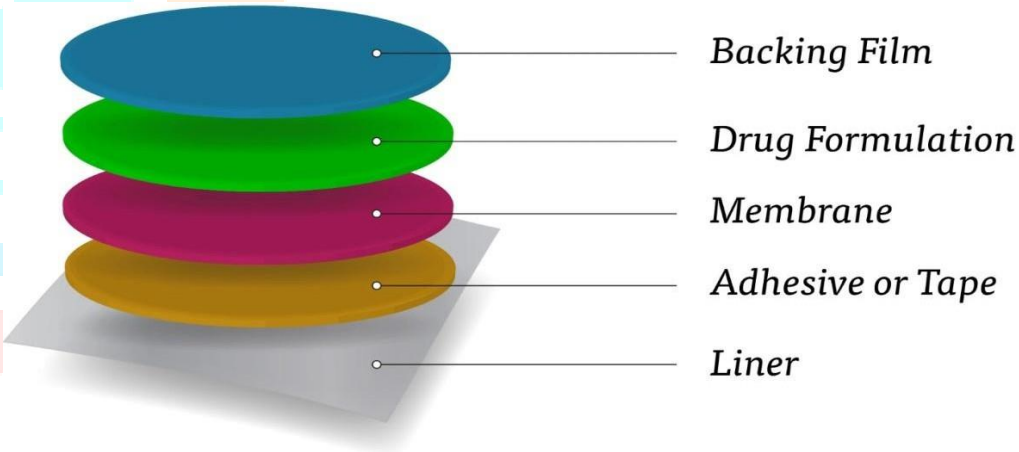
i. Penetration: The entry of a substance into a particular layer of the skin;
ii. Partitioning from the stratum corneum into the aqueous viable epidermis;
iii. Diffusion through the viable epidermis and into the upper dermis;
iv. Permeation: The penetration of molecules from one layer into another, which is different both functionally and structurally from the first layer;
v. Absorption: The uptake of a substance into the systemic circulation.



An Overview OF Tansdermal Patches :

Dual transdermal patches for PCOS are an emerging therapeutic approach designed to deliver two complementary herbal or hormonal agents through the skin to help regulate menstrual cycles, reduce pre-menstrual discomfort, and support long-term hormonal balance. These patches are typically used in two patterns: pre-period patches, applied a few days before the expected menstrual cycle to manage symptoms like pain, inflammation, mood swings, and bloating; and continuous patches, applied throughout the cycle to provide steady support for insulin sensitivity, androgen regulation, and ovarian function. By delivering two actives together—such as anti-inflammatory and hormone-modulating herbs (e.g., Vitex + Curcumin) or insulin-sensitizing combinations (e.g., Cinnamon + Berberine)—dual patches offer synergistic benefits that target multiple PCOS pathways simultaneously. The transdermal route bypasses first-pass metabolism, improves bioavailability, and ensures controlled, sustained release, making it especially useful for chronic conditions like PCOS. These patches aim to reduce reliance on oral medications, minimize side effects, and offer a non-invasive, patient- friendly option for menstrual regulation and metabolic balance. While promising, key challenges include standardization of herbal actives, achieving effective skin permeation, and ensuring safety for long-term use.

Fig no. :- structure of transdermal patches



ADVANTAGES AND DISADVANTAGES OF TRANSDERMAL PATCHES:

ADVANTAGES:

- Avoids the digestive system, preventing stomach irritation.
- Bypasses first-pass liver metabolism, improving drug effectiveness.
- Provides steady and controlled drug release over long periods.
- Reduces dosing frequency, improving patient compliance.
- Offers painless drug administration compared to injections.
- Easy and convenient for patients to apply and remove.
- Maintains stable blood drug levels, reducing side-effect spikes.
- Allows immediate discontinuation by simply removing the patch.
- Useful for patients who have difficulty swallowing tablet **DISADVANTAGES:**

- Can cause skin irritation, redness, or allergic reactions.
- Only suitable for drugs that can pass through the skin barrier.
- Provides slower onset of action compared to oral or injectable routes.
- Patch adhesion may fail due to sweat, hair, or physical activity.
- Heat exposure can increase drug absorption unpredictably.
- Some patches are visible and may cause cosmetic concerns.
- Can be more expensive than oral dosage forms.
- Limited drug dose capacity, unsuitable for high-dose medications.
- Risk of accidental transfer if the patch touches another person.
- Improper application (wrong site or damaged skin) can reduce effectiveness

FACTORS AFFECTING SKIN PENETRATION:

i.Physiological Factors:

- Skin thickness
- Skin hydration
- Skin condition
- Site of application
- Blood flow to the skin.

ii.Physiochemical Factors:

- Partition coefficient.
- Molecular weight (less than 400 Dalton).
- Degree of ionization (only unionized drugs gets absorbed well).
- Effect of vehicles.

METHODOLOGY

1. Preparation of Herbal Extracts Using Soxhlet Extraction

➢ Weigh of the herbal Extract or Powder.

➢ Place the Herbal Extract or Powder into a flask and add a suitable solvent (such as ethanol or methanol)in a 1:10 plant material to solvent ratio.

➢ Allow the mixture to stand for 24-48 hours at room temperature with occasional stirring.

➢ Filter the mixture using Whatman filter paper and collect the filtrate in a clean container.

➢ Repeat the extraction process 2-3 times until the solvent has extracted all the desired compounds from the plant material.

➢ Concentrate the filtrate using a rotary evaporator until a thick syrup is obtained.

➢ Transfer the concentrated extract to a sterile container and store at 4°C for further use.

MATERIAL AND METHOD

Herbal Ingredients:

a. Ashwagandha extract – adaptogenic, hormone-regulating.
b. Fenugreek extract – improves insulin sensitivity, reduces androgen levels.
c. Cinnamon extract – regulates glucose and menstrual cycles.
d. Spearmint extract – reduces testosterone, improves PCOS symptoms.

Polymers & Excipients:

i. Hydroxypropyl methylcellulose (HPMC) – film-forming polymer.
ii. Polyvinylpyrrolidone (PVP) – improves flexibility and solubility.
iii. Ethyl cellulose (EC) – rate-controlling polymer for sustained release.
iv. Plasticizers: Glycerin, PEG 400 – to improve flexibility.
v. Permeation enhancers: Menthol, DMSO, or eucalyptus oil – to enhance skin penetration.
vi. Backing membrane: Aluminum foil or polyester film.
vii. Adhesive layer: Medical-grade adhesive tape (for patch stickiness).

Solvents:

Ethanol, distilled water or propylene glycol – for dissolving polymers and herbal extracts.

RESULT

Numerous herbal and nutraceutical products can positively influence metabolic, endocrine, and (in certain situations) reproductive outcomes in PCOS, according to an increasing amount of preclinical and clinical research. Agents that enhance insulin signaling (Cinnamon), lower oxidative stress and inflammation (curcumin), or alter steroidogenic pathways (Ashwagandha,Fenugreek,Cinnamon ,Spearmint) Moreover, there is insufficient information on the long-term safety, pregnancy safety, and interactions with traditional fertility drugs. When there is evidence to support their benefits, herbal remedies may be best used as supplements to traditional medical therapy and lifestyle changes, or as alternatives for patients who are intolerant of conventional medications. However, this should only be done after counseling regarding the scant evidence and problems with quality control. Clinical practice should emphasize individualized care: evaluate PCOS phenotype, metabolic risk, fertility desires, concomitant medications, and preferences; if herbal/nutraceutical therapy is considered, use standardized products with defined dosages, monitor metabolic/hormonal parameters, and avoid unmonitored combinations. Because the composition and danger of contamination of supplements can vary greatly, regulatory supervision and improved pharmacovigilance are required.

CONCLUSION:

Nutraceuticals and herbal medications have the potential to improve insulin resistance, metabolic profiles, and menstrual regularity in the treatment of PCOS. With supporting evidence for Curcumin,Cinnamon,Fenugreek,Ashwagandha,Spearmint has the most robust and reliable evidence basis. However, there are currently insufficient long-term safety data, inconsistent trial designs, and product standards that make it impossible to completely substitute proven treatments. To determine the best indications, dosage, safety, and clinical integration for CAM usage in PCOS, high-quality RCTs, standardized formulations, and integrated clinical guidelines are desperately needed

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