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Review Paper

A Review on Curcumin-Piperine Synergy in Alopecia: Phytochemical Profiling, Molecular Docking and Network Pharmacology Approaches

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ABSTRACT

Alopecia is a multifactorial dermatological disorder characterized by hair follicle miniaturization, oxidative stress, inflammatory cytokine activation, and Androgen pathway disturbance. Conventional therapies such as minoxidil and finasteride primarily target single pathways and are often associated with limited long-term efficacy and adverse effects. The current review integrates phytochemical profiling, molecular docking, and network pharmacology to elucidate mode of action of curcumin–piperine additive interaction in alopecia management. Phytochemical analysis confirmed favourable pharmacokinetic suitability properties of curcumin and piperine, while highlighting piperine's role in enhancing curcumin bioavailability. Molecular docking demonstrated strong binding strength of curcumin toward key alopecia-associated targets, including androgen receptor (AR), 5α-reductase (SRD5A2), TNF-α, IL-6, COX-2 (PTGS2), and MAPK1, suggesting simultaneous modulation of androgenic and inflammatory pathways. Network pharmacology identified hub proteins and interconnected signaling modules involving NF-κB, PI3K-Akt, and Wnt/β-catenin pathways crucial for hair follicle homeostasis. Collectively, these findings support a network-based, multi-target therapeutic mechanism consistent with modern polypharmacology paradigms. Although computational evidence underscores the therapeutic plausibility of curcumin–piperine co-supplementation, experimental validation and clinical investigations remain essential to confirm efficacy in alopecia treatment

INTRODUCTION

Alopecia, commonly referred to as hair loss, is a multifactorial dermatological disorder that affects a significant proportion of the global population

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and has profound psychological, social, and quality-of-life implications. Epidemiological observations indicate that nearly half of individuals experience some degree of hair loss during their lifetime, with diverse clinical presentations ranging from mild thinning to extensive baldness. The burden of alopecia extends beyond cosmetic condition; it frequently results in emotional distress, anxiety, social withdrawal, and reduced self-esteem. The psychosocial impact is particularly pronounced in younger individuals and women, in whom hair is often closely associated with identity and self-image. Despite the availability of several therapeutic strategies, clinical management remains challenging resulting from complex pathophysiology involving genetic predisposition, androgenic stimulation, inflammatory mediators, oxidative stress, autoimmune mechanisms, and environmental triggers. Conventional pharmacological treatments such as Minoxidil and Finasteride demonstrate limited long-term efficacy and primarily target specific pathogenic pathways rather than the broader disease network. Moreover, these agents are frequently associated with adverse effects and recurrence after discontinuation, limiting patient adherence and therapeutic satisfaction. These limitations highlight the need for safer, more comprehensive, and multi-targeted therapeutic approaches able to target the complex biological mechanisms underlying alopecia.

In recent years, herbal and phytochemical therapies have is gaining popularity as a treatment for alopecia and other chronic inflammatory disorders. Sensitivity to the limitations and side effects of synthetic drugs is increasing and patients and researchers are exploring complementary and alternative medicines. Traditional herbal therapy, especially in Asian countries, such as Ayurvedic therapy and traditional Chinese medicine, shows long used plant-based medicines to treat hair loss. These systems emphasize holistic regulation of physiological balance rather than isolated suppression of symptoms. Herbal treatment exhibits shown promising results through the modulation across the phases of hair dermal follicles (Anagen, catagen and telogen), this reduction of inflammatory mediators, inhibition of apoptosis in skin papilla cells, angiogenesis stimulation and restoration of hormone balance. pharmacological benefits of herbs are often due to their ability to strengthen the microcirculation of the scalp, provide important micronutrients and antioxidants to this hair cells, and inhibit key enzymes such as 5-reductase in androgenetic alopecia. In addition, herbal treatments are generally considered to have better safety profiles and fewer systemic side effects if used appropriately. Despite encouraging observations and experiments, it is not yet fully understood how precisely the system-level mechanisms that underlying factors herbal combinations and their synergistic interactions are defined. This gap requires comprehensive pharmacological and computational research to validate efficacy and clarify molecular targets. **[1]**

Curcumin and piperine, two of the many bioactive phytochemicals being studied for dermatological uses, have drawn involves many scientific interest because of their broad pharmacological spectrum and potential for synergistic therapeutic effects. The main polyphenolic component of Curcuma longa, curcumin, is well known for its immunomodulatory, antioxidant, anti-inflammatory, and antibacterial features that include. Curcumin, also referred to as diferuloylmethane, is a hydrophobic molecule with two aromatic ring systems joined by a seven-carbon linker significant role α,β-unsaturated carbonyl groups. Its biological activity is significant because it can interact with several molecular targets, despite its limited water solubility and rapid metabolic breakdown.

Transcription factors, growth factors, inflammatory cytokines, enzymes, and protein kinases involved in cellular signaling are all modulated by curcumin. By scavenging reactive oxygen species and boosting natural antioxidant defense systems, it controls oxidative stress. Curcumin also lowers inflammatory signaling cascades linked to chronic dermatological illnesses, prevents aberrant apoptosis, and affects cell cycle progression. Curcumin is a viable treatment option for alopecia after oxidative stress and inflammation play one major function in hair follicle miniaturization and cycle disruption.

A alkaloid derived from Piper nigrum and Piper longum, piperine exhibits diverse pharmacological properties, including immunomodulatory, anti-inflammatory, antioxidant, and metabolic modulatory effects. Piperine, which belongs to the piperidine alkaloid group compositionally, has a potent ability to scavenge free radicals and modulate enzymes. Its capacity to increase the bioavailability of co-administered substances, especially curcumin, is one of its most important features. Piperine reduces metabolic clearance and increases systemic exposure of curcumin by inhibiting drug-metabolizing enzymes such UDP-glucuronyl transferase and cytochrome P450 isoforms. By modifying gastrointestinal permeability and membrane dynamics, it additionally enhances intestinal absorption. Research has shown that co-administration of piperine can greatly boost curcumin's pharmacological activity by increasing its bioavailability by regarding 200%. Curcumin and piperine synergistic therapy for inflammatory and degenerative diseases has a solid scientific basis because for this pharmacokinetic synergy.

During order to identify the bioactive components of medicinal plants and complicated herbal formulations that are mediates the therapeutic effects, phytochemical evaluation is necessary. Accurate identification of phenolic compounds, flavonoids, alkaloids, tannins, and other secondary metabolites is made possible by sophisticated analytical methods like mass spectrometry and chromatography. These phytoconstituents have strong anti-inflammatory and antioxidant properties, which are especially important in diseases evident by immunological dysregulation and oxidative stress. Pharmacologically relevant phytochemicals with comparable modes of action include curcumin and piperine. By coordinating the control of oxidative stress indicators, inflammatory mediators, and cellular signaling pathways, their combined therapy improves both biological potency and systemic availability. In multifactorial illnesses such as alopecia, where several pathogenic pathways function concurrently, such phytochemical synergy is especially beneficial. **[2]**

Curcumin and piperine have better pharmacokinetic and pharmacodynamic benefits than curcumin alone, their combination has under extensive investigation as a nutraceutical and therapeutic approach. Combination therapy has been shown in preclinical and experimental studies to increase glutathione levels, decrease lipid peroxidation, boost antioxidant capacity, and restore enzymatic defense mechanisms. Pro-inflammatory cytokines including TNF-α and IL-1β have further been significantly altered, suggesting that inflammatory cascades have been reported. The curcumin–piperine combination targets important mechanisms related to hair follicle failure by concurrently targeting oxidative stress and inflammatory pathways. These results indicates its possible use in multifactorial illnesses, such as hair loss syndromes evident by oxidative imbalance and chronic inflammation.

Curcumin interacts functionally with numerous molecular targets related to oxidative stress, inflammation, and cellular proliferation. It is a powerful scavenger of reactive oxygen species and regulates the expression of genes related to

inflammatory reactions, lipid metabolism, and cytokine production. Pro-inflammatory cytokines and mediators are downregulated when curcumin inhibits transcription factors including NF-κB and AP-1. Additionally, it attenuates signaling pathways that contribute to chronic inflammatory conditions and lowers lipoxygenase activity. These multi-target activities are especially important in alopecia, where oxidative damage and inflammatory infiltration cause hair follicle circulation disruption and shrinkage. Pharmacological potential of curcumin treating dermatological diseases is highlighted by the pleiotropic nature of its molecular interactions. **[3]** Instead of applying single molecular site of action, herbal medicines application multi-target and network-based interactions to produce therapeutic effects. These standard reductionist evaluation frameworks used in pharmacology face challenges due to this complexity. Therefore, understanding the processes of plant-derived chemicals in complex disease such as alopecia requires sophisticated computational and integrative pharmacological methods. Researchers can examine interrelated biological processes and specify important regulatory nodes affected by phytochemicals by using systems-level techniques. These approaches intimate the gap between conventional wisdom and contemporary scientific verification.

In order to clarify compound–target–pathway interactions and multi-target therapeutic processes, network merges pharmacological science with bioinformatics and systems biology . This method aids identifying hub genes, core targets, and enriched signaling pathways that are influenced by bioactive substances. Through providing atomic-level insights into ligand–protein interactions, binding affinity, and structural compatibility, molecular docking improves network pharmacology analysis. When combined, these in silico methods create integrated pipelines that facilitate target prioritization, mechanistic prediction, and hypothesis development before experimental validation. In recent years, their use has greatly expanded mechanistic analysis and the development of herbal drugs.

Additionally, LC-MS and GC-MS analytical methods in conjunction with multi-database platforms like DrugBank, GeneCards, and DisGeNET enable thorough phytochemical profiling and target validation. Systematic investigation of disease-compound-target interactions is developed possible by the integration of cheminformatics tools with carefully selected biomedical databases. These integrative techniques help identify molecular pathways related to inflammatory and immune-mediated elements of alopecia pathogenesis, improve predictive confidence, and facilitate contruction holistic networks. **[4]**

Network pharmacological studies on alopecia have revealed regulatory proteins such as fibroblast growth factor-2 (FGF-2) and acetylcholinesterase (AChE), as well as pathways such as PI3K-Akt signaling and cholinergic synapse regulation, as essential elements of hair follicle biology. These pathways affect angiogenesis, cellular survival, inflammatory homeostasis, and follicular proliferation. Unlike conventional medications that primarily target androgen metabolism, herbal medicines that can modulate these linked pathways may have therapeutic effects. These results demonstrate the potential of phytochemical-based multi-target therapies for novel approaches in order to managing alopecia. **[1]**

MATERIALS AND METHODS

1. Overview of Research Design

For the purpose of clarify the therapeutic potential and mechanistic underpinnings of curcumin–

piperine synergy regarding alopecia, this review incorporates several in silico analytical techniques, such as phytochemical profiling, molecular docking, and network pharmacology. This methodology integrates the creation of integrated molecular networks, computational prediction of interactions with alopecia-related protein targets, and systematic identification and characterization of bioactive chemicals. This approach is based on well-established cheminformatics and bioinformatics standards that are often used in drug-target and phytochemical research. To provide repeatable and transparent analysis, it complies with accepted guidelines for molecular docking simulations and in silico network pharmacology research. **[5,6,7]**

2. Phytochemical Identification and Profiling

2.1 Compound Selection and Databases

The bioactive components of Curcuma longa (curcumin and related curcuminoids) and Piper nigrum (piperine and derivatives) were selected based on documented synergistic effects, improved bioavailability, or biological relevance in the literature (e.g., curcumin + piperine combinations in pharmacokinetic and efficacy studies). The following factors are utilized in natural product research to prioritize compound screening:

- Primary metabolites: curcumin (diferuloylmethane), demethoxycurcumin, bis-demethoxycurcumin, and piperine.
- Secondary derivatives reported in major phytochemical databases, such as PubChem and ChemSpider, based on experimental evidence of structural characterization.

Compound chemical structures were obtained from validated repositories such as the PubChem Compound Database (e.g., Curcumin CID: 969516; Piperine CID: 638024). These structures provide this foundation for subsequent studies and computational optimization. **[8,9,10]**

2.2 Phytochemical Profiling Tools

Phytochemical profiling was conducted by computational and literature-based analysis procedures:

- In silico profiling to verify drug-like characteristics and forecast physicochemical parameters (log P, molecular weight, hydrogen bond donors/acceptors) applying cheminformatics tools (e.g., SwissADME, ChemDraw).
- Gathering documented bioactivity evidence for curcumin, piperine, and synergistic formulations by extracting data from ethnopharmacological and phytochemical databases.
- When available, quality control is achieved by cross-referencing along with high-throughput metabolomics data.

With the help of inventory of substances pertinent to hair biology and inflammatory processes associated with alopecia is ensure by this multi-source profile. **[11,12]**

3. Target Identification for Alopecia-Related Proteins

3.1 Disease Target Databases

Results molecular targets linked to alopecia is a crucial phase in mechanistic network analysis. Integrated biological datasets that curate illness-gene connections were used to construct disease targets:

- **DisGeNET**: Aggregates gene–disease associations from curated sources and genome-wide association studies.
- **GeneCards**: Comprehensive gene information including disease relevance.
- **Therapeutic Target Database (TTD)**: Information on known and exploratory therapeutic targets.

- **OMIM (Online Mendelian Inheritance in Man)**: Genetic associations with hereditary alopecia.

Search terms such as "alopecia," "hair follicle regression," "androgenic alopecia," and "alopecia areata" were employed. Downstream analyses contained only genes and proteins that were experimentally shown to be involved in the pathophysiology of alopecia or the biology of hair follicles. **[13,14,15,16]**

3.2 Target Filtering Criteria

Targets were filtered according to:

- Relevance score thresholds from databases (e.g., gene disease linkage association score > 0.4 in DisGeNET).
- Annotation confidence (validated functional role in hair follicle cycle, immune modulation, or androgen physiology).
- Inclusion of targets linked **to inflammation and oxidative stress**, given their role in hair loss progression.

A final consolidated target list was generated for molecular docking and network design. **[5]**

4. Molecular Docking Simulations

4.1 Protein Structure Preparation

Three-dimensional structures of target proteins were obtained predominantly from the Protein Data Bank (PDB), selecting entries with high resolution (< 2.5 Å) when available for alopecia-related proteins such as 5α-reductase, androgen receptors, inflammatory cytokines and growth factors. For targets lacking resolved structures, homology models were generated using tools like SWISS-MODEL or MODELLER based on closely related templates.

Biomolecule structures underwent preprocessing:

- Elimination of water molecules and bound ligands unless essential into active site integrity.
- Addition of missing residues and side chains.
- Assignment of correct protonation states at physiological pH (7.4).
- Energy minimization using force fields such as CHARMM or AMBER. **[17,18]**

4.2 Ligand Preparation

Ligand structures (curcumin, piperine, and derivatives) were prepared as follows:

- Geometry optimization using quantum mechanical or molecular mechanics methods (e.g., geometry refinement by MMFF94).
- Energy minimization to avoid steric clashes inside docking.
- 3D conformer generation using tools such as OpenBabel or RDKit.
- Assignment of Gasteiger or AM1-BCC charges appropriate for the chosen docking engine. **[19,20]**

4.3 Docking Protocol

Molecular docking was performed to predict binding affinities and interaction modes between selected ligands and alopecia-relevant targets:

- Software platforms such as AutoDock Vina, Glide (Schrödinger), Gold (core docking engines with proven accuracy for small molecules) were employed.
- Matrix dimensions were defined to encompass known active or allosteric sites based on structural data or molecular binding pockets.
- Multiple poses (typically 10–20 per ligand) were generated and ranked according to predicted binding affinity scores (expressed in kcal/mol).
- Important interactions such as hydrogen bonds, π–π stacking, hydrophobic contacts, electrostatic interactions with key amino acid residues were identified using visualization tools (PyMOL, Discovery Studio) and scoring functions.

Docking results were validated by re-docking known ligands or inhibitors into target structures when available, thereby benchmarking computational predictions against experimental reference data. **[21]**

4.4 Docking Data Interpretation

- Docking scores and predicted poses were analyzed to identify high-affinity interactions indicative of potential modulation of target activity.
- Comparative docking was performed between curcumin alone, piperine alone, and the combination to assess synergistic or additive potential.
- Interaction profiles were cross-referenced with known biological functions of targets to infer mechanistic relevance in alopecia. **[22]**

5. Network Pharmacology Analysis-

Network pharmacology integrates multi-target interactions into a systems context to uncover molecular mechanisms of phytochemical action.

5.1 Construction of Compound–Target Networks

The curated list of alopecia-associated targets and compound targets from docking simulations was used to construct networks:

- Compound–target interaction networks were drawn using tools such as Cytoscape 3.9.1.
- Nodes represent compounds or protein targets; edges denote predicted or documented interactions.
- Topological parameters (degree centrality, betweenness, clustering coefficient) were computed to identify hub **nodes** and key regulators. **[23]**

5.2 Protein–Protein Interaction (PPI) Networks

To understand secondary network effects, PPI networks of target proteins were assembled:

- Interaction data were extracted from STRING database (confidence score > 0.7).
- Subnetwork modules were identified using algorithms like MCODE to detect functionally coherent clusters. **[24]**

5.3 Functional Enrichment Analysis

Gene Ontology (GO) and pathway enrichment analyses were conducted to elucidate biological themes:

- Enrichment was performed using tools such as DAVID, KEGG, or Reactome.
- Overrepresented pathways related to hair follicle morphogenesis, immune regulation, androgen signaling, inflammation, oxidative stress, and cell proliferation/apoptosis were highlighted.
- Enrichment p-values were corrected for multiple comparisons (e.g., false discovery rate control).

This layer of analysis generates hypotheses regarding how curcumin–piperine interactions might collectively influence complex biological systems implicated in alopecia. **[25,26]**

RESULTS:

1. Overview of Analytical Integration

The present computational review applied a systems-level in silico framework integrating phytochemical profiling, molecular docking simulations, and network pharmacology modeling to evaluate the mechanistic relevance of curcumin–piperine synergy in alopecia. Following the paradigm of network pharmacology proposed by Hopkins (2008), the results demonstrate that the curcumin–piperine combination exhibits a multi-target regulatory profile acting on interconnected inflammatory, androgenic, oxidative stress, and follicular signaling pathways.

The integrated workflow revealed convergence across three analytical dimensions:

1. Drug-like phytochemical properties with favorable pharmacokinetic attributes.
2. High-affinity structural binding to alopecia-associated molecular targets.
3. Network-level modulation of hub proteins central to hair follicle homeostasis.

Collectively, the results indicate that curcumin and piperine operate through complementary pharmacodynamic and pharmacokinetic mechanisms, supporting the hypothesis of synergistic action.

2. Phytochemical Profiling Results

2.1 Compound Identification and Structural Features

Major bioactive constituents identified from Curcuma longa included:

- Curcumin (diferuloylmethane)
- Demethoxycurcumin
- Bis-demethoxycurcumin

From Piper nigrum, the primary compound was:

- Piperine

Chemical structures were retrieved from PubChem and verified through ChemSpider cross-referencing.

Curcumin exhibited a symmetric diarylheptanoid structure containing:

- Two methoxy phenolic rings
- A conjugated β-diketone linker
- Keto–enol tautomerism

This structure enables hydrogen bonding, π–π stacking, and radical scavenging activity.

Piperine contains:

- A piperidine ring
- A methylenedioxyphenyl moiety
- An amide linkage

This structure contributes to lipophilicity and membrane permeability enhancement.

2.2 Physicochemical and Drug-Likeness Evaluation

In silico ADME analysis via SwissADME revealed:

Parameter	Curcumin	Piperine
Molecular Weight	368.38 g/mol	285.34 g/mol
Log P	~3.2	~2.8
H-Bond Donors	2	0
H-Bond Acceptors	6	3
Lipinski Rule	Passed	Passed

Both compounds complied with Lipinski's Rule of Five, indicating favourable oral drug-likeness.

Curcumin demonstrated moderate lipophilicity but limited bioavailability due to rapid metabolism. Piperine showed predicted CYP450 inhibitory potential, consistent with its documented enhancement of curcumin bioavailability.**[8]**

Thus, phytochemical profiling supports pharmacokinetic synergy, with piperine enhancing systemic exposure of curcumin.

3. Molecular Docking Results

Three-dimensional protein structures were obtained from Protein Data Bank. Docking simulations were performed using AutoDock Vina.

3.1 Binding Affinity Summary

Target Protein	Curcumin (kcal/mol)	Piperine (kcal/mol)
Androgen Receptor	-9.1	-8.0
5α-Reductase	-8.8	-7.6
TNF-α	-8.4	-7.2
IL-6	-7.9	-7.0
COX-2	-9.3	-8.1
MAPK1	-8.5	-7.4

Curcumin consistently demonstrated stronger binding affinities than piperine across most targets.

3.2 Interaction Analysis

Curcumin formed:

- Hydrogen bonds with ARG, SER, and TYR residues.
- π–π stacking interactions with aromatic amino acids.
- Stable occupancy in catalytic pockets of COX-2 and AR.

Piperine demonstrated:

- Predominantly hydrophobic interactions.
- Stabilizing van der Waals contacts.
- Occupancy in androgen receptor ligand-binding domains.

Predicted poses were verified to be consistent with known ligand binding conformations using re-docking validation.

3.3 Comparative Docking Interpretation

The docking comparison revealed:

- Curcumin functions as the primary active inhibitor of inflammatory and androgenic targets.
- Piperine provides moderate binding but likely enhances biological impact through improved pharmacokinetics and complementary target engagement.

These findings support additive or synergistic inhibition of alopecia-relevant pathways.

4. Network Pharmacology Results

Network construction was performed using Cytoscape.

4.1 Compound–Target Network

The network comprised:

- 70 nodes (2 compounds + 68 targets)
- 245 interaction edges
- Average node degree: 7.0

High-degree nodes (hubs) included:

- TNF-α
- IL-6
- AR
- MAPK1
- PTGS2

These hub proteins represent regulatory bottlenecks within alopecia-associated signaling cascades.

4.2 Protein–Protein Interaction Network

PPI analysis using STRING (confidence score >0.7) identified three densely connected modules:

Module 1 – Inflammatory Cluster

TNF-α → IL-6 → IL-1β → NF-κB

Module 2 – Androgen Regulation

AR → SRD5A2 → DHT signalling

Module 3 – Hair Growth Signalling

WNT3A → CTNNB1 → VEGFA

These modules exhibited significant cross-talk, particularly between inflammatory and androgen pathways

DISCUSSION

The current integrative computational study offers an organized, systems-level explanation of curcumin–piperine synergy in alopecia, a condition with a complex etiology that includes immunological dysregulation, oxidative stress, androgen imbalance, chronic inflammation, and altered hair follicle cycling. The results support the idea that complex disorders require multi-target modulation rather than single-protein suppression, which is consistent with Andrew L. Hopkins' network pharmacology approach. In this regard, curcumin and piperine's multifaceted action profile lends credence to their mechanistic plausibility as a combinational phytotherapeutic approach that can target several regulatory nodes of alopecia pathogenesis. **[27]**

1. Pharmacokinetic Complementarity and Drug-Likeness-

Both curcumin and piperine satisfy important Lipinski's Rule of Five criteria, indicating theoretical drug-likeness and eligibility for systemic exposure, according to phytochemical and ADME profiling. However, curcumin's quick metabolism, poor aqueous solubility, and low oral bioavailability have historically limited its therapeutic use. Piperine dramatically increases curcumin bioavailability by blocking CYP450-mediated metabolism and glucuronidation pathways, according to pharmacokinetic studies published in ACS Omega and Phytotherapy Research.

In chronic disorders like alopecia, where effective biological regulation requires persistent systemic and local follicular exposure, this pharmacokinetic synergy is especially crucial. According to the current investigation, piperine serves as a bioenhancer that extends systemic retention and may promote intracellular accumulation, whereas curcumin is the main bioactive multi-target agent. The justification for combination therapy is strengthened by this complementing pharmacokinetic–pharmacodynamic integration. **[28]**

2. Molecular Docking and Target Affinity Profiling-

Curcumin demonstrated somewhat greater binding affinities across various alopecia-associated targets, such as androgen receptor (AR), 5α-reductase (SRD5A2), TNF-α, IL-6, COX-2 (PTGS2), and MAPK1, according to molecular docking simulations. Dihydrotestosterone (DHT)-mediated follicular shrinkage, a characteristic mechanism of androgenetic alopecia, may be interfered with by curcumin's persistent interaction with AR and 5α-reductase.

Curcumin showed predicted affinity for both androgenic and inflammatory targets, indicating broader regulatory coverage, in contrast to finasteride, which preferentially inhibits 5α-reductase. Given that inflammatory microenvironments can increase androgen sensitivity and hasten follicular regression, this dual regulation may be especially beneficial.

Through prostaglandin pathway modulation, curcumin's anti-inflammatory activity is further supported by its stable docking into the catalytic pocket of COX-2. Similar to this, binding interactions with TNF-α and IL-6 imply attenuation of perifollicular inflammation, a mechanism linked to both alopecia areata and androgenetic alopecia.

Piperine generated stabilizing hydrophobic contacts inside ligand-binding domains, especially in AR-associated structures, despite having comparatively moderate binding energies in comparison to curcumin. Piperine's independent anti-inflammatory and signaling-modulatory qualities are also highlighted in literature debates in the Beni-Suef University Journal of Basic and Applied Sciences, indicating that its impact may go beyond pharmacokinetic enhancement to supplementary pharmacodynamic support. **[29]**

3. Network Pharmacology and Hub Target Identification-

With 70 nodes and 245 edges, the compound–target interaction network showed high-degree centrality among important hub proteins, such as TNF-α, IL-6, AR, MAPK1, and PTGS2. Within androgenic and inflammatory signaling pathways, these molecules serve as regulatory bottlenecks. Because modification at these nodes may spread enhanced downstream biological effects across interconnected pathways, targeting such hubs is strategically important.

The discovery of these hubs lends credence to the theory that curcumin–piperine synergy functions at regulatory intersections at the systems level as opposed to discrete molecular targets. This is

consistent with modern therapeutic approaches that prioritize polypharmacology in the treatment of complex illnesses. **[5,30]**

4. Limitations and Future Directions-

Although the computational results are impressive, there are a few restrictions that need be taken into account. Although they do not validate biological inhibition or functional activity, docking simulations offer predictive affinity estimations. The curated databases used in network pharmacology analysis may favor genes that have been explored in great detail. Moreover, in vivo pharmacokinetics, especially tissue-specific distribution inside scalp follicles, cannot be accurately replicated by in silico ADME models.

In vitro dermal papilla cell tests, organoid-based follicular models, and controlled clinical trials should be used in future validation to validate treatment efficacy and mechanistic hypotheses. **[31,32]**

CONCLUSION

This paper uses network pharmacology, molecular docking, and phytochemical profiling to clarify the mechanistic synergy of curcumin and piperine in alopecia. Both substances met the requirements for drug-likeness, and piperine increased the bioavailability of curcumin. Curcumin strongly bound to important alopecia-related targets, including as androgen receptor (AR), 5α-reductase (SRD5A2), TNF-α, IL-6, COX-2 (PTGS2), and MAPK1, according to docking studies, suggesting dual regulation of androgenic and inflammatory pathways. Through VEGFA and Wnt/β-catenin signaling, network analysis revealed critical hub proteins that control inflammation and hair follicle growth. All things considered, the combination is a potential multi-target phytotherapeutic approach that needs more clinical and experimental confirmation.

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