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A Review On Formulations, Efficacy, And Mechanisms Of Herbal Anti-Dandruff Shampoos

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Abstract: Dandruff is a common scalp disorder primarily associated with Malassezia species, abnormal keratinization, and inflammatory responses. Although synthetic agents such as ketoconazole, zinc pyrithione, and selenium sulfide remain standard treatments, their long-term use is often limited by irritation and microbiome disruption. This review summarizes current research on the formulations, mechanisms, and efficacy of herbal anti-dandruff shampoos, highlighting their growing relevance as safer and multifunctional alternatives. Key herbal ingredients including neem, tea tree oil, rosemary, Aloe vera, hibiscus, amla, and tulsi demonstrate significant antifungal, anti-inflammatory, antioxidant, and sebum-regulating activities supported by in-vitro and clinical findings.Formulation strategies emphasize mild surfactant systems, standardized extracts, and optimized physicochemical properties to ensure stability and bioactivity. Comparative studies show that polyherbal shampoos can achieve reductions in dandruff severity similar to synthetic agents while offering superior scalp tolerance and user acceptability. Despite these advantages, gaps remain in extract standardization, large-scale clinical validation, and advanced delivery technologies. Overall, herbal anti-dandruff shampoos present an effective and sustainable approach for long-term scalp care, warranting further research to refine their therapeutic potential.

Index Terms - Herbal shampoos, dandruff, Malassezia, antidandruff agents, phytochemicals, scalp microbiome

1. INTRODUCTION

Dandruff is a chronic scalp disorder marked by excessive corneocyte shedding and mild inflammation. Clinical studies show that its onset is strongly associated with the overgrowth of *Malassezia* yeasts, particularly *M. restricta* and *M. globosa*, which metabolize sebum lipids and trigger an inflammatory response on the scalp [1]. Conventional antidandruff ingredients such as zinc pyrithione and ketoconazole are effective but often linked with irritation, altered scalp microbiota, and regulatory restrictions on long-term use [2].

Because of these limitations, recent research has shifted toward herbal antidandruff shampoos. Plant-derived agents such as neem, tea tree oil, *Aloe vera*, rosemary, and hibiscus contain bioactive compounds terpenoids, flavonoids, phenolics, and limonoids shown to exert antifungal, anti-inflammatory, and keratolytic actions against dandruff-associated pathways [3]. Several formulation studies report that herbal shampoos can achieve

comparable or even superior reductions in *Malassezia* colony counts and symptom scores while maintaining better scalp tolerance [4].

This review compiles evidence from published formulation and efficacy studies to summarize the mechanisms, performance, and practical considerations in developing herbal anti-dandruff shampoos.

2. Pathophysiology of Dandruff

Dandruff develops through the interaction of three key factors: *Malassezia* proliferation, excessive sebaceous secretion, and abnormal epidermal differentiation. *Malassezia* species hydrolyze triglycerides in sebum, releasing unsaturated fatty acids such as oleic acid, which penetrate the stratum corneum and disrupt barrier integrity, leading to increased cell turnover and flaking [1,5]. Clinical biopsy studies show accelerated keratinocyte renewal and reduced corneodesmosome density in affected individuals, supporting a keratinization defect rather than simple dryness [6].

Inflammation also contributes to symptom severity. Research indicates that *Malassezia*-derived metabolites induce cytokine responses involving IL-1α, IL-6, and TNF-α, which aggravate itching and erythema [7]. Oxidative stress further amplifies this process, as dandruff scalps show higher lipid peroxidation levels and reduced antioxidant enzyme activity [8].

These mechanistic insights highlight why herbal actives containing antifungal molecules (e.g., terpinen-4-ol), anti-inflammatory compounds (e.g., nimbidin, rosmarinic acid), and antioxidants play a meaningful therapeutic role in dandruff management.

3. Herbal Ingredients Used in Anti-Dandruff Shampoos

Herbal antidandruff formulations commonly rely on plant extracts with proven antifungal, anti-inflammatory, keratolytic, or antioxidant actions. Many of these extracts directly inhibit *Malassezia* species or reduce the inflammatory cascade triggered during dandruff progression. Key ingredients supported by experimental data are summarized below.

*3.1 Tea Tree Oil (*Melaleuca alternifolia*)*

Tea tree oil is widely documented for its strong antifungal action, primarily due to terpinen-4-ol, which disrupts fungal membrane integrity. A clinical trial using 5% tea tree oil shampoo observed a 41% reduction in dandruff severity score, significantly higher than the placebo group [1]. In vitro assays also show clear inhibition zones against *M. furfur* and *M. globosa* at low concentrations [2]. These findings support its inclusion as a primary active in herbal shampoos.

*3.2 Neem (*Azadirachta indica*)*

Neem leaves and seed extracts contain nimbidin, azadirachtin, and quercetin, which collectively exhibit antifungal and anti-inflammatory activity. Ethanolic neem extract demonstrated complete inhibition of *Malassezia* growth at 2–4 mg/mL, according to antimicrobial plate assays [3]. Another formulation study reported improved symptom scores and reduced scalp erythema when neem extract was incorporated into a polyherbal shampoo base [4]. Neem's multi-target action makes it effective for both microbial control and scalp soothing.

*3.3 Aloe vera (*Aloe barbadensis Miller*)*

Aloe vera gel contains polysaccharides and phenolic compounds with proven anti-inflammatory and wound-healing effects. Studies report that Aloe vera extracts suppress IL-1β and TNF-α levels in inflamed scalp tissue, helping reduce itching and irritation associated with dandruff [5]. In shampoo formulations, Aloe vera enhances moisturization and supports barrier repair while improving user tolerance [6].

*3.4 Rosemary (*Rosmarinus officinalis*)*

Rosemary extract, rich in rosmarinic acid and essential oils, demonstrates potent antifungal activity. In vitro studies show significant inhibition of *Malassezia* species, with MIC values ranging from 0.5–1 mg/mL [7]. Its antioxidant properties also help counter lipid peroxidation, a documented contributor to dandruff pathology.

*3.5 Hibiscus (*Hibiscus rosa-sinensis*)*

Hibiscus extracts exhibit keratolytic and scalp-conditioning benefits. Research indicates that flavonoids in hibiscus can reduce excess corneocyte accumulation and improve hair shaft texture [8]. When incorporated into shampoo formulations, hibiscus contributes to improved foam quality and reduced scalp flaking.

*3.6 Shikakai (*Acacia concinna*)*

Shikakai pods contain natural saponins that act as mild surfactants. Formulation studies highlight its ability to cleanse sebum without disrupting scalp pH, making it suitable for dandruff-prone individuals [9]. Combined with antifungal herbs, shikakai supports a gentle, non-irritating shampoo base.

*3.7 Amla (*Phyllanthus emblica*)*

Amla fruits are rich in vitamin C and phenolic antioxidants. Extracts have shown inhibitory activity against *Malassezia* in broth dilution assays and significantly reduce oxidative stress markers in scalp models [10]. In herbal shampoos, amla improves hair strength while supporting antimicrobial action.

*3.8 Tulsi (*Ocimum sanctum*)*

Tulsi essential oil contains eugenol and ursolic acid, which exhibit broad antifungal activity. Studies report dose-dependent inhibition of *M. furfur* and reduced inflammatory markers in treated tissue samples [11]. Tulsi also enhances fragrance and preservative properties in shampoos.

4. FORMULATION APPROACHES IN HERBAL ANTI-DANDRUFF SHAMPOOS

Developing an effective herbal anti-dandruff shampoo requires careful alignment of cleansing efficiency, stability, extract compatibility, and scalp tolerance. Recent studies provide formulation strategies that improve both antifungal activity and consumer performance.

4.1 Surfactant Systems

Herbal shampoos commonly rely on mild surfactants to minimize irritation and maintain scalp microbiota balance. Research shows that SLES combined with cocamidopropyl betaine offers good foam quality with reduced irritation compared to SLS-based systems [12]. Some formulations replace synthetic surfactants with natural saponins such as shikakai and soapnut, which provide gentler cleansing while remaining compatible with plant extracts [13].

4.2 Incorporation of Herbal Extracts

Herbal actives are typically added as aqueous, ethanolic, or hydroalcoholic extracts depending on the solubility of major phytochemicals. Ethanolic neem and rosemary extracts demonstrate significantly stronger antifungal activity due to higher extraction of phenolics and terpenoids [14]. Hydroalcoholic tea tree oil systems, when thickened with carbomer or HPMC, maintain viscosity and show improved antifungal stability [15].

4.3 Stability, pH, and Viscosity Considerations

Herbal shampoos are generally optimized to a pH of 5.0–6.0, which helps sustain scalp barrier function. Stability testing of polyherbal formulations under accelerated conditions (40°C, 75% RH) confirms that properly buffered and preserved shampoos remain stable without phase separation [16]. Viscosity is regulated using thickeners such as guar gum and xanthan gum, while antioxidants like vitamin E are added to protect essential oils from oxidation.

4.4 Preservation and Foam-Building Agents

Because herbal extracts introduce microbial load, low-toxicity preservatives such as phenoxyethanol, sodium benzoate, or potassium sorbate are often used, and studies confirm they maintain microbial stability without interfering with antifungal performance [17]. Foam-building agents particularly betaine surfactants and saponin blends—enhance foam richness and improve user acceptance [18].

4.5 Physical and Sensory Optimization

Sensory quality is a key determinant of user satisfaction. Essential oils like tea tree and rosemary provide natural fragrance and therapeutic activity. Conditioning agents such as polyquaternium-7 or Aloe vera mucilage improve slip, reduce roughness, and enhance post-wash feel in herbal shampoos [19].

5. EFFICACY EVALUATION METHODS IN HERBAL ANTI-DANDRUFF SHAMPOOS

Assessing the performance of herbal anti-dandruff shampoos requires a combination of in-vitro, ex-vivo, and in-vivo methods that measure antifungal activity, scalp improvement, and formulation quality. Research studies commonly adopt the following evaluation techniques.

*5.1 In-Vitro Anti-*Malassezia *Assays*

The most widely used method is the agar well diffusion assay, where zones of inhibition around herbal extracts or formulated shampoos are measured against *Malassezia globosa* or *M. furfur*. Neem, rosemary, and tea tree oil–based shampoos frequently show clear dose-dependent inhibition zones in these assays [20].

Minimum Inhibitory Concentration (MIC) testing is also used to determine the lowest concentration at which a herbal ingredient suppresses fungal growth. Studies report MIC values of 0.5–4 mg/mL for neem, rosemary, and tulsi extracts against dandruff-causing species [21].

5.2 Ex-Vivo and In-Vivo Scalp Studies

Clinical trials typically assess dandruff severity using standardized scoring systems such as Adherent Scalp Flaking Score (ASFS) or Dandruff Severity Score (DSS). Polyherbal shampoos containing neem, tea tree oil, and Aloe vera have demonstrated significant reductions in ASFS within 2–4 weeks of application [22].

Ex-vivo studies using isolated human scalp tissue evaluate inflammation markers and barrier recovery after treatment. Herbal actives like Aloe vera and rosemary reduce IL-1β and TNF-α expression, supporting their anti-inflammatory potential [23].

5.3 Physicochemical Evaluation of Shampoos

Herbal shampoo quality greatly influences user acceptance and therapeutic performance. Standard evaluation parameters include:

- **pH**: Ideally maintained at 5.0–6.0 for scalp compatibility.
- **Surface tension**: Effective shampoos reduce surface tension to enhance cleansing efficiency.
- **Foam height and stability**: Saponins and betaine surfactants produce stable foam, confirmed through Ross–Miles testing [24].

- **Viscosity**: Rheology studies ensure that the product spreads uniformly and maintains stability during storage.
- **Solid content**: Influences strength and concentration of herbal actives.

These physicochemical assessments ensure that herbal actives remain stable and bioavailable throughout the product's shelf life.

5.4 Sensory and User Acceptability Studies

User perception plays an important role in the success of herbal shampoos. Sensory evaluation panels measure fragrance, spreadability, lather quality, and post-wash feel. Studies show that formulations enriched with Aloe vera, shikakai, or conditioning polymers achieve higher user acceptability scores than non-conditioned herbal shampoos [25].

6. MECHANISMS OF ACTION OF HERBAL ANTI-DANDRUFF AGENTS

Herbal anti-dandruff shampoos act through multiple biological pathways that collectively reduce *Malassezia* proliferation, scalp inflammation, abnormal keratinization, and oxidative stress. These multi-target mechanisms explain why many herbal formulations demonstrate strong efficacy with lower irritation compared to synthetic agents.

6.1 Antifungal Activity Against Malassezia *Species*

Many plant extracts—such as neem, tea tree oil, rosemary, and tulsi—contain bioactive compounds (terpenoids, phenolics, flavonoids) that directly disrupt fungal cell membranes. Terpinen-4-ol from tea tree oil increases membrane permeability and causes leakage of intracellular contents, resulting in growth inhibition of *M. globosa* and *M. furfur* [26]. Neem-derived nimbidin and azadirachtin also inhibit fungal mitochondrial activity, leading to reduced colony formation [27]. Rosemary essential oil components such as 1,8-cineole and camphor exhibit strong MIC values against dandruff-related yeasts [28].

6.2 Anti-Inflammatory Mechanisms

Inflammation plays a major role in dandruff severity due to cytokine release triggered by *Malassezia* metabolites. Herbal agents like Aloe vera, tulsi, and hibiscus reduce these inflammatory responses by downregulating IL-1β, IL-6, and TNF-α pathways. Experimental studies show that Aloe vera polysaccharides significantly decrease cytokine expression in inflamed scalp tissue, improving redness and itching [29]. Tulsi's active compound eugenol has been shown to inhibit COX-2 activity, reducing inflammatory mediator production [30].

6.3 Keratolytic and Desquamation-Regulating Effects

Dandruff is partly caused by accelerated turnover of corneocytes and improper desquamation. Hibiscus and amla extracts contain natural alpha-hydroxy acids and flavonoids that help normalize keratinocyte differentiation. Research shows that hibiscus extracts improve corneocyte cohesion and promote controlled desquamation without the irritation associated with synthetic keratolytics [31]. Meanwhile, amla's phenolic compounds help maintain scalp hydration, which is essential for healthy barrier function.

6.4 Sebum Regulation

Excess sebum contributes to the proliferation of *Malassezia*, which relies on lipase-mediated breakdown of lipids. Herbs like neem, rosemary, and shikakai exhibit mild sebum-normalizing activity. Studies indicate that neem extract reduces sebum triglycerides by inhibiting lipase activity associated with *Malassezia* metabolism [32]. Rosemary extract has also been shown to modulate sebaceous gland activity due to its phenolic antioxidants [33].

6.5 Antioxidant Defense and Barrier Protection

Oxidative stress is significantly elevated in dandruff-affected scalps, contributing to inflammation and barrier disruption. Amla, rosemary, Aloe vera, and tulsi deliver strong antioxidant defense by scavenging free radicals and boosting endogenous antioxidant enzymes. Amla extract, for example, significantly reduces lipid peroxidation markers in scalp models [34]. Rosemary polyphenols also protect the scalp barrier by enhancing antioxidant capacity and reducing oxidative degradation of sebum lipids [35].

6.6 Synergistic Effects in Polyherbal Formulations

Multiple studies report that combinations of herbal ingredients show synergistic effects greater than individual extracts. Polyherbal shampoos containing neem + tea tree oil + Aloe vera display enhanced antifungal activity and improved symptom reduction due to complementary mechanisms—antifungal action, inflammation control, and barrier repair [36]. This synergy is a key reason why polyherbal shampoos demonstrate quicker clinical improvement.

7. COMPARATIVE EFFICACY OF HERBAL VS SYNTHETIC ANTI-DANDRUFF AGENTS

Herbal anti-dandruff formulations are increasingly compared with conventional agents such as ketoconazole, zinc pyrithione (ZPT), and selenium sulfide. Evidence from clinical and laboratory studies indicates that while synthetic agents often produce rapid antifungal effects, herbal formulations can achieve comparable long-term outcomes with better tolerability and fewer adverse reactions.

7.1 Comparison with Ketoconazole

Ketoconazole (1–2%) shampoos remain a gold standard due to potent inhibition of ergosterol synthesis in *Malassezia*. However, prolonged use has been associated with scalp dryness, irritation, and disruption of the normal microbiome [37].

Clinical comparisons show that tea tree oil (5%) and polyherbal shampoos containing neem and Aloe vera achieve similar reductions in dandruff severity scores over four weeks, although with slower onset than ketoconazole [38]. Importantly, herbal formulations demonstrated significantly better user comfort and lower incidence of irritation.

7.2 Comparison with Zinc Pyrithione (ZPT)

ZPT is widely used for its broad-spectrum antifungal and anti-inflammatory effects. Although effective, concerns exist regarding long-term environmental impact and potential scalp sensitivity in some users [39].

In vitro tests revealed that neem, rosemary, and tulsi extracts showed inhibition zones comparable to ZPT against *M. globosa*, suggesting that properly formulated herbal agents can match ZPT's antifungal strength [40]. In vivo studies also found similar improvements in flaking and itching when users applied polyherbal shampoos for 2–3 weeks.

7.3 Comparison with Selenium Sulfide

Selenium sulfide acts by reducing cell turnover rates but is associated with odor issues, scalp discoloration, and residue formation [41]. Herbal shampoos containing hibiscus, Aloe vera, and amla reported similar improvements in desquamation scores but without these cosmetic drawbacks [42].

Herbal shampoos also offer additional antioxidant and barrier-repair properties not typically provided by selenium sulfide, contributing to improved scalp feel and hair manageability.

7.4 Consumer Acceptability and Long-Term Safety

A major advantage of herbal formulations is higher user acceptability. Studies consistently show better scores for fragrance, foam mildness, and post-wash feel in herbal shampoos compared to synthetic medicated shampoos [43].

Long-term use studies also report lower incidence of irritation, dryness, and hair roughness in herbal formulations due to the presence of conditioning agents and the absence of harsh surfactants [44].

7.5 Clinical Relevance

Although synthetic drugs offer rapid antifungal action, herbal shampoos provide a multifactorial therapeutic approach—addressing fungal load, inflammation, keratinization, oxidative stress, and scalp barrier health. This broader mechanistic profile makes herbal formulations an appealing alternative for individuals seeking sustained benefits with minimal side effects.

8. SAFETY, TOXICITY, AND REGULATORY CONSIDERATIONS

Safety remains a key factor in evaluating herbal anti-dandruff shampoos, as consumers increasingly prefer formulations that are gentle on the scalp and suitable for long-term use. Research generally supports the favorable safety profile of herbal extracts, although proper standardization and quality control remain essential.

8.1 Dermatological Safety and Irritation Potential

Unlike synthetic agents such as ketoconazole or selenium sulfide, herbal shampoos typically demonstrate lower irritation scores in patch-testing studies. Formulations containing Aloe vera, hibiscus, and amla have shown excellent dermal tolerance in 24–48-hour patch tests, with no significant erythema or itching reported among volunteers [45].

Tea tree oil and neem extracts can occasionally cause sensitivity in individuals allergic to essential oils, but when used at controlled concentrations (0.5–2%), clinical studies show minimal adverse effects [46].

8.2 Toxicity Studies of Herbal Extracts

Acute and sub-chronic toxicity assessments are commonly performed using animal or cell-line models. Neem, rosemary, tulsi, and hibiscus extracts demonstrate no signs of systemic toxicity at cosmetic-use concentrations, and LD50 values reported in literature are far higher than topical exposure levels [47].

Cytotoxicity assays (MTT tests) show that Aloe vera, amla, and shikakai extracts maintain high cell viability (>80%) even at relatively concentrated doses, supporting their safety in rinse-off applications [48].

8.3 Microbiological Safety and Preservation Requirements

Although plant extracts provide antimicrobial benefits, they may introduce microbial load and nutrients into formulations. Therefore, herbal shampoos require preservation systems that comply with international cosmetic safety guidelines. Studies indicate that combinations of phenoxyethanol, sodium benzoate, or potassium sorbate maintain microbial stability for up to 12 months without reducing herbal antifungal activity [49].

Regulatory frameworks generally mandate microbial load limits (<100 CFU/mL for bacteria; <10 CFU/mL for fungi), which well-preserved herbal shampoos can meet.

8.4 Regulatory Guidelines for Herbal Shampoos

Herbal shampoos fall under cosmetic regulations, not drug regulations, in most countries unless specific therapeutic claims are made.

- In India, they are regulated under the Drugs and Cosmetics Act, 1940, requiring ingredient safety data and labeling compliance.
- International guidelines (EU Cosmetics Regulation, FDA Cosmetic Guidelines) emphasize the need for stability testing, safety assessment, and proper allergen labeling for essential oils [50].

Standardization challenges remain, as variability in herbal extracts can affect consistency and efficacy. Regulatory bodies increasingly encourage validated analytical methods (HPLC, GC-MS) to ensure batch-to-batch uniformity.

8.5 Long-Term Safety Considerations

Long-term use studies of polyherbal shampoos report minimal adverse events, with users experiencing less dryness and irritation compared to synthetic medicated shampoos [51]. The presence of natural conditioning agents such as Aloe vera gel and mucilage-rich herbs also contributes to improved hair softness and reduced breakage over extended use.

Overall, existing evidence suggests that herbal anti-dandruff shampoos offer a high safety margin, provided that formulations are standardized, allergen warnings are included, and appropriate preservation systems are used.

9. RESEARCH GAPS AND FUTURE DIRECTIONS

Despite strong interest in herbal anti-dandruff shampoos, several scientific and formulation-related gaps limit their full clinical and commercial potential. Addressing these issues will help develop more reliable, standardized, and globally accepted herbal antidandruff products.

9.1 Need for Standardized Herbal Extracts

One of the major challenges in herbal formulations is the lack of standardized phytochemical profiles. The concentration of active compounds (e.g., terpinen-4-ol in tea tree oil, azadirachtin in neem, rosmarinic acid in rosemary) can vary significantly due to differences in plant origin, extraction method, and storage conditions [52].

This variability affects batch-to-batch consistency, antifungal strength, and clinical outcomes, highlighting the need for validated analytical methods such as HPLC, GC–MS, and DNA barcoding for raw material authentication.

9.2 Limited Large-Scale Clinical Trials

Most clinical evaluations of herbal antidandruff shampoos involve small sample sizes and short study durations (2–4 weeks). While initial results are promising, large, multicenter trials comparing herbal formulations with established synthetic agents like ketoconazole or zinc pyrithione are still lacking [53].

Future studies should also examine long-term effects, recurrence rates, and responses in different age groups and scalp types.

9.3 Underexplored Multi-Herb Synergies

Many studies highlight strong synergistic interactions between herbs for example, neem + tea tree oil, or amla + hibiscus yet only a few formulations systematically evaluate synergy using in-vitro combination assays or fractional inhibitory concentration (FIC) indices [54].

9.4 Advances in Novel Delivery Systems

Conventional shampoo bases may not provide optimal penetration of herbal actives into the scalp. Modern delivery systems such as nanoemulsions, liposomes, solid lipid nanoparticles, and microgels have shown improved stability and enhanced penetration of essential oils and plant phenolics in preliminary research [55].

However, these technologies remain underexplored in herbal antidandruff formulations and warrant deeper investigation.

9.5 Need for Microbiome-Focused Studies

Dandruff is increasingly recognized as a microbiome-related disorder involving imbalances in bacterial and fungal communities on the scalp. Very few herbal studies evaluate shifts in microbiome diversity after treatment, despite evidence that botanicals can modulate microbial ecosystems [56].

Future research should integrate metagenomic sequencing to assess how herbal products restore microbial balance.

9.6 Sustainability and Regulatory Harmonization

As demand grows, sustainable sourcing of medicinal plants becomes important to prevent ecological pressure. Additionally, global regulatory differences in permissible levels of essential oils, preservatives, and labeling requirements pose challenges for product standardization [57]. Harmonizing guidelines can facilitate broader commercialization of evidence-based herbal shampoos.

10. CONCLUSION

Herbal anti-dandruff shampoos represent a promising alternative to synthetic agents due to their multi-target mechanisms, including antifungal activity, anti-inflammatory effects, regulation of keratinization, sebum control, and antioxidant protection. Evidence from formulation and clinical studies shows that well-designed herbal shampoos containing ingredients such as neem, tea tree oil, rosemary, Aloe vera, hibiscus, and amla can achieve comparable reductions in dandruff severity to conventional agents like ketoconazole and zinc pyrithione, while offering better scalp tolerance and user acceptability.

However, challenges remain, particularly regarding extract standardization, large-scale clinical validation, and the need for advanced delivery systems to improve penetration of herbal actives. As research progresses, integrating molecular profiling, microbiome analysis, and modern formulation technologies will help elevate herbal shampoos to evidence-based therapeutic options.

Overall, current findings support the potential of herbal formulations as safe, effective, and sustainable solutions for long-term dandruff management. Future advancements will depend on rigorous scientific validation, improved regulatory harmonization, and continued innovation in phytoformulation science [58].

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