



REVIEW ON EFFICACY AND SAFETY OF NATURAL AND SYNTHETIC ANTI-DANDRUFF AGENTS

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ABSTRACT

Dandruff (*Pityriasis capitis*), characterized by loosely adherent white flakes on the scalp affects up to 50% of the human population. It is caused by numerous host factors in conjunction with fungi *Malassezia furfur*. Hair, a derivative of the epidermis consists of the follicle and hair shaft. The visible part, shaft sticks out of the skin. The hair root in the skin extends down to the deeper layers of the skin which is connected to the sebaceous gland. Blood vessels nourish the cells in the hair bulb and deliver hormones for hair health. Hair condition is directly linked to the condition of the scalp which is a host for various microorganisms due to the delicate structure and more sebaceous glands on the scalp than any other parts of the skin. Dandruff on the scalp extends to hair and clothing, even affects individual social esteem and confidence. The rising issues of scalp disorders including dandruff, seborrheic dermatitis, psoriasis, scalp folliculitis, etc. have led the cosmetic industry to focus on effective treatments to fight- off the root cause. This article gives an insight on the scalp condition- Dandruff, reflecting the idea of potential causes, effective treatments and the comparative study of synthetic and natural anti-dandruff treatments for effective dandruff control.

Keywords - *Malassezia furfur*, Dandruff, Darunaka, Seborrheic Dermatitis, Corneocytes, cellular toxicity.

INTRODUCTION

The scalp is one of the delicate areas of human skin. Rich in blood vessels, it is characterized by a thick skin layer with high follicular density and abundance of sebaceous glands. It has a lower barrier function, thus not very proficient at maintaining and replenishing hydration compared to the skin on other sites. This extremely delicate nature of the scalp, unfortunately, invites all sorts of skin problems including dandruff, seborrheic dermatitis, and other parasitic infections. The pH of the scalp is 5.5 and that of the hair shaft is 3.67. ^[1] The scalp, similar to other skin, sheds dead cells. The scalp skin renews itself about once a month. A small amount of dead skin flaking is normal; about 487,000 cells/cm² are released normally after shampooing. Dandruff occurs when this rate speeds up. These are clusters of corneocytes, which retains a large degree of cohesion with one another and which becomes detached as such from the surface of the stratum corneum. The faster the scalp releases dead skin, the worse dandruff becomes. ^[2, 3]

Acharya Vagbhata and Sharangadara believed *darunaka* (dandruff) as a *Kapalagata Roga* (Seborrheic Dermatitis), but Acharya Sushruta has described this disease as a *Kshudra Roga* as Vata and Kapha Doshas are affected with symptoms like *Kandu* (itching on the scalp), *Keshachyuti* (falling of hair), *Swapa* (abnormalities of touch sensation on the scalp), *Rookshata* (roughness or dryness of the scalp) and *Twaksphutana* (breaking or cracking of the scalp skin). As per Ayurveda, non-application of Kesha Taila i.e. oiling of the head, improper cleaning, sleeping during daytime, exposure to dust, hot weather, etc. are causative factors for *Darunaka*.^[4] Ayurvedic classics have dealt with various procedures and medications including *Shamana chikitsa* to manage the disease *Darunaka*. *Shiro abhyanga* i.e. massaging of the head, neck, and shoulders with taila is said to be effective due to its properties such as *Snigdha Guna* i.e. unctuousness quality, which acts through its *Vatahara* and properties. It performs the actions like *Snehana* (treatment process of oleation), *Kledana* (moistening), and *Vishyandana* at the cellular level of the body. ^[5]

The earliest known case of dandruff is identified in a small feathered dinosaur which lived on earth 125 million years ago. The study of fossilized feathers of the dinosaurs revealed the presence of tiny flakes. Paleontologists have found tiny flakes of fossilized skin on a crow-sized Microraptor-a meat-eating dinosaur. ^[6] (Fig.2)

Originally named *Malassezia* by Malassez in 1898, this genus was renamed as - *Pityrosporum* during the 20th century. The members of *Malassezia* at one time were classified into two species: a lipid-dependent species - *Malassezia furfur*, and a non-lipid-dependent species - *Malassezia pachydermatis*. In the mid-1990s studies of morphological, ultra structural, physiological, and genomic differences in *Malassezia* led to the identification of multiple. lipid-dependent species including *M. globosa*, *M. restricta*, *M. furfur*, *M. obtusa*, *M. slooffiae*, *M. sympodialis*, *M. japonica*, *M. nana*, *M. dermatitis*, and *M. yamatoensis*, and the non-lipid-dependent, primarily zoophilic, species, *M. pachydermatis*.^[7]



Figure 1. The fossils of a microcraptor.^[8]

To maintain healthy-looking hair, scalp health is equally and of utmost importance. The focus on scalp health is limited, however, the disorders such as dandruff and seborrheic dermatitis have been much studied and many treatments are emerging in research and development concerning effective scalp care, which is ultimately the root of healthy hair.

PREVALENCE

Dandruff is more prevalent in males compared to females. There is more loss of protein in men's scalp. The average sebum amount in men's scalp is 1.5 times higher than that of the women's. The ceramide, a component of stratum corneum, in the horny layer of men's scalp is lesser which plays a key role in skin barrier function. Thus, the skin barrier function in men's scalp is weaker than that of women's. This phenomenon states that the men's scalp is more susceptible to dandruff compared to women's, accompanied by a more itchy and oily scalp.^[9]

Dandruff is not contagious or harmful but can be embarrassing which also affects the self-esteem and self-confidence of an individual. It has become the main concern due to the delicate and infectious nature of the scalp. It often begins at puberty and peaks around age 20, becoming far less prevalent among the population of 50 yrs age. The dandruff severity affects depending on the season, becoming worse during winters.^[10]

TYPES OF DANDRUFF

Dandruff flakes are dead cells that fall naturally from the scalp. Either a dry scalp or too greasy scalp may cause excess cells to clump together and fall, forming flaky dandruff.. There are two types of Dandruff: Dry dandruff and oily dandruff.

1) Dry Dandruff - This type is faced by individuals having a dry scalp. It is more common during winters. Also, hot water dries out the scalp, which can cause flakes. More hair loss is observed in this type of dandruff. The best and most effective way to cure dry scalp is to increase hydration and moisturize the scalp regularly.^[11, 12]

2) Oily Dandruff - This occurs from an overproduction of sebum by hair follicles on the scalp and scalp build-up. The result is the clumping together of sebum and dead skin cells on the scalp which form itchy flakes on the scalp. Excess sebum production may result from high stress and anxiety. Forehead acne results from oily dandruff due to clogging of pores on the skin site. The microbes then leave behind a substance called oleic acid that causes blackheads, whiteheads, milia, and acne.^[13, 14]

DANDRUFF AND SEBORRHEIC DERMATITIS

The relation of dandruff to seborrheic dermatitis has been controversial from time to time. Dandruff has the clinical characteristic of small white or gray flakes which build up diffusely on the scalp in localized spots. It does not have any recognisable inflammation and is confined to the scalp.^[15]

In seborrheic dermatitis, the flakes are greasy with a yellow colour. Seborrheic dermatitis flakes are common enough to appear as sticky mounds with inflammatory changes. Seborrheic dermatitis varies in appearance, appearing as patches of red, scaly, oily skin and differs from dandruff in that it may appear beyond the scalp, particularly the nasolabial folds, ears, eyebrows, and chest.^[16] (Fig.2)



Fig 2. Dandruff versus Seborrheic Dermatitis. ^[17]

CAUSES OF DANDRUFF

There is still lot more to confirm the exact causes of dandruff. However, many research and findings are coming up with the possible, yet few confirmed causes to offer anti-dandruff preparations to discard the causes or symptoms of dandruff. The potential causes of dandruff discussed below focuses on Microbial and Non-microbial factors.

Microbial factors include fungal and bacterial causes. The main microbial culprit for the cause of dandruff is the fungus *Malassezia furfur*. The *Malassezia* genus consists of a group of lipophilic yeasts which lack the metabolism necessary for fatty acid synthesis. The levels of *M.furfur* increase by 1.5 to 2 times their normal level in the case of dandruff. ^[18]

One of the mechanisms involves stimulation of lipase by *M.furfur* on the scalp. The oxidation of triglycerides of sebum is caused by this enzyme which produces saturated and unsaturated fatty acids. Fungi consume saturated fatty acids for growth and self-proliferation. Oleic acid and arachidonic acid are unsaturated fatty acids present on the scalp. Oleic acid irritates human skin whereas arachidonic acid is involved in inflammatory responses. Thus, the degradation of fatty acids on scalp skin causes irritation, inflammation, itching, and fungal growth. Further, this causes dry yellowish flaky scales, known as dandruff. ^[19] The other mechanism states that, few of the enzymes on the scalp eat up bondings between dead skin cells and slough them off individually. *Malassezia* causes modification of this mechanism of enzymes and inhibits cutting off the connections between dead skin cells. Thus, the aggregation of corneocytes takes place and is shed off in clusters instead of shedding off individually. Thus, *Malassezia* alters the normal shedding of dead skin cells. ^[20]

Besides fungal cause, individuals with dandruff have higher amounts of Staphylococcus, and much less of a different type of bacteria – *Propionibacterium*. Microbial balance on the scalp determines the presence of dandruff. When there is disequilibrium in the proportion of main bacterial populations - *Propionibacterium acnes* and *Staphylococcus epidermidis*, dandruff formation takes place. ^[21, 22]

Non-microbial factors include, excessive exposure to sunlight reported to cause desquamation of the scalp. Irritation of scalp due to over-shampooing, frequent combing, use of certain cosmetic products, dust and dirt, sensitivity to oleic acid, oily skin, dry scalp, damage to stratum corneum to some extent, cause dandruff. ^[23, 24]

THE ROLE OF SEBUM IN DANDRUFF

The role of sebum in dandruff is characterized by the strong temporal correlation with the sebaceous gland activity. This includes increased incidence during infancy (cradle cap), low incidence from infancy to puberty, an increase in adolescence and young adulthood, and a decrease later in life. Dandruff occurs exclusively on skin areas with high sebum levels. Human sebum is a complex mixture of triglycerides, fatty acids, sterol esters, cholesterol esters, cholesterol, wax esters, and squalene. When secreted, sebum consists of triglycerides and esters which are broken down into monoglycerides, diglycerides, and free fatty acids by microbes. The free fatty acids play a role in initiation of the irritant response, which is further involved in scalp hyperproliferation. The role of sebaceous secretion also depends upon the stress and hormones which is directly linked to dandruff. ^[25, 26]

THE ROLE OF FUNGUS IN DANDRUFF

The strongest contributing factor in dandruff cause is *Malassezia furfur* which thrives when it is fed by saturated fatty acids in sebum. A greasy scalp is therefore a perfect host for the fungus to grow. The natural skin cells renewal is disturbed when *Malassezia* grows too quickly. Hence, current dandruff treatments focus on anti-fungal ingredients that focus on removal of *Malassezia* causing cellular toxicity of the fungal cells.^[27]

In a research carried out by the Unilever research team, a detailed genetic investigation of scalp microbiome was studied using a new technology called next-generation sequencing (NGS). More than 100 people were tested with healthy and dandruff-affected scalps, all of whom had refrained from using anti-dandruff shampoo for six months. Research has shown that there is 10 times more *Malassezia* on the dandruff scalp than a healthy scalp. However, beyond the fungal cause of dandruff, the research also found insights on the bacterial causes. Using a qPCR technique, the bacteria were accurately counted. The study found that the bacteria -*Staphylococcus capitis*, were 100 times more abundant on dandruff-affected scalps. The research concluded that *Malassezia* is not the sole microbial culprit of dandruff. Both fungi and bacteria have a part in the development and progression of dandruff.^[28]

There is a tendency for people to use anti-dandruff shampoos until the condition resolves. However, clinical studies showed that there can be a reoccurrence of dandruff if switched to non-anti-dandruff shampoos. The regular use of a good anti-dandruff shampoo is the key to the long-term elimination of dandruff.

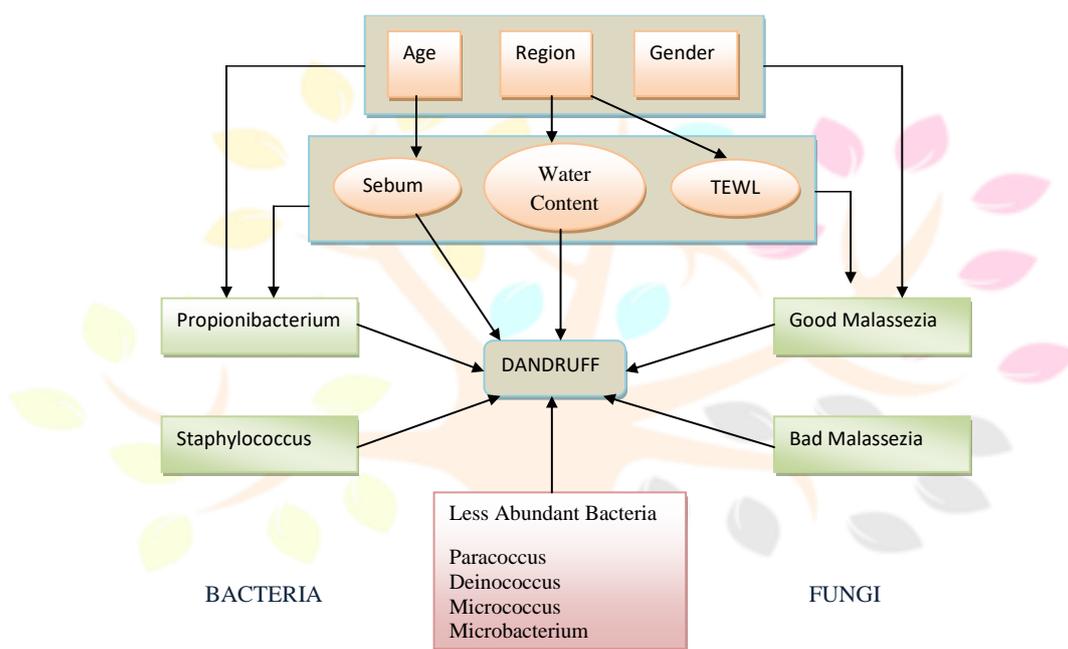


Fig 3. Causative factors of dandruff^[28]

TREATMENT OF DANDRUFF:

Malassezia, sebum, and individual susceptibility are the three factors involved in dandruff etiology, there are several potential avenues for treatment. Thus, one may treat the causes or one may treat the symptoms

I) Anti-dandruff formulations containing Synthetic actives.

Treatment can be done by one or both the following strategies; treatments of causes and symptoms. Treatment of the cause involves the removal of the fungi with antifungal treatments or suppressing the sebum secretion. Treatment of symptoms involve calming the inflammation with anti-inflammatory steroidal agents, minimizing cell proliferation with anti-proliferative, or by simply grooming away the resultant flakes.

Table 1. Synthetic agents in anti-dandruff treatments of cause. ⁽²⁹⁻³²⁾

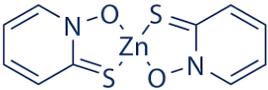
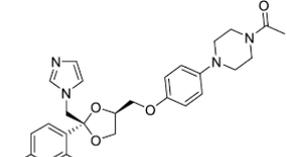
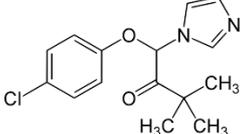
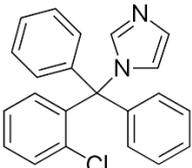
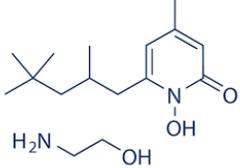
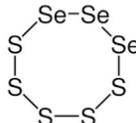
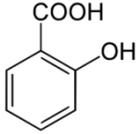
Treatments	Synthetic Anti-dandruff agents	Concentration used in anti-dandruff shampoos	Mechanisms	Side Effects
TREATMENTS OF CAUSE	Zinc Pyrithione 	0.3-2.0%	Increase of intracellular copper reserves in fungal cell. ↓ Forms endogenous Copper Pyrithione. ↓ Loss of Iron-Sulphur loading activity. ↓ Deactivates enzyme Aconitase. ↓ Cellular toxicity.	<ul style="list-style-type: none"> ➤ No common side effects. ➤ Rare, but allergic conditions include irritation to scalp area, stinging and burning of scalp, etc.
	Ketoconazole 	0.25 – 2.0%	Ketaconazole inhibits enzyme cytochrome-450 (responsible for conversion of lanosterol to ergosterol). ↓ Ergosterol synthesis does not take place. ↓ Disruption of membrane function, increases cell permeability.	<ul style="list-style-type: none"> ➤ No serious side effects. ➤ Mild irritation, or pimples like bumps on the scalp.
	Climbazole 	0.25 – 2%	Similar to other azoles	Localized irritation of skin, redness and itching.
	Clotrimazole 	1.0%	Similar to other azoles	Peeling, pruritus, burning, skin irritation, cramps due to overdose.
	Piroctone olamine 	0.5 – 1.0%	Inhibits mechanism of degradation of sebum triglycerides to unsaturated fatty acids	Irritation, swelling, bruising, wrinkling of skin.
	Selenium sulphide 	1.0 – 2.5%	Anti-mitotic mechanism involving reduction in the incorporation rate of thymidine into DNA of dermal epithelial cells. ↓ Reduction in epidermal cell turnover.	<ul style="list-style-type: none"> ➤ Unusual oiliness/ dryness of hair/ scalp may occur. ➤ Increase in normal hair loss, scalp discoloration may occur.

Table 1. Synthetic agents in anti-dandruff treatments of symptoms. ^(33, 34)

Treatments	Synthetic Anti-dandruff agents	Concentration used in anti-dandruff shampoos	Mechanisms	Side Effects
TREATMENT OF SYMPTOMS	Salicylic acid (Keratolytic agent) 	1.5-6.0%	Causes shedding of dead skin cells by increasing moisture in the skin. ↓ Dissolve substance that clumps cell together	➤ Dry, peeling, red, or scaling skin. ➤ A very serious allergic reaction to this agent is rare.
	Coal Tar (Anti-proliferative agent)	0.5-3.0%	Suppress hyper plastic skin.	➤ Sunburn, skin cancer.

Comparative studies:

- 1) Ketoconazole was statistically noted superior to selenium sulfide in a study. However, both ketoconazole (2%) and selenium sulphide (2.5%) were found equally effective but, ketoconazole proved to be better tolerated. ^[35]
- 2) Studies found that the combination of Piroctone Olamine (0.55%) and Climbazole (0.45%) was equally effective when compared with Zinc Pyrithione (1%). ^[36]
- 3) Comparative studies of anti-dandruff efficacy between tar and a non-tar shampoo concludes that the non-coal tar shampoo with 2% salicylic acid and 0.75% Piroctone olamine proved to have a greater reduction in dandruff. ^[37]

II) Anti-dandruff formulations containing natural actives.

Herbal actives or their formulations are viable alternative to synthetic formulations. The need and awareness of herbal cosmetics is on the rise, primarily because it is believed that these products are safe and free from side effects. Plant products contain many phytochemical compounds like alkaloids, flavanoids, tannins, terpenoids etc which have efficient antifungal activity. These compounds can be used as combination of polyherbal mixtures for dandruff control. Natural botanicals can be used in their crude form, purified extracts, or derivatives to get desired effect. Number of plants have been reported to have beneficial results on hair and scalp and introduced in the hair and scalp care formulations.

Ethanol extract of *Ocimum sanctum* (tulsi) and *Azadirachta indica* (neem) leaves have good antimicrobial activity due to the presence of flavonoids, it is found to be effective, harmless and economic. The reported values showed that 50% and above level of concentration of neem extract has optimal level of inhibition on the dandruff growth. ^[38] and that of tulsi extract showed the concentration of 2% and above for antidandruff activity. ^[39] Herbal extracts of number of plants have been used for antidandruff shampoos and oils preparation like, *Glycine max* (soyabean), *Rosmarinus officinalis* (rosemary), *Arctium lappa* (burdock), *Zingiber officinalis* (ginger), *Salvia officinalis* (sage), *Mentha piperata* (mint), *Plantago major* (greater plantain), *Melaleuca spp* (tea tree), *Camellia chinensis* (tea), *Thymus vulgaris* (thyme), *Glycerriza glabra* (yashtimadhu). The inhibitory effect of the fruit extracts of *Terminalia bellerica* (baheda) consists of chemical substances gallic acid and ethyl gallate present in the fruits. ^[39] *Terminalia chebula* (haritaki) contain tannins like beta-sitosterol, gallic acid, ellagic acid, gallate, galloyl glucose, chebulagic acid. ^[40,41] Crude and methanolic extracts of dry fruit of *Terminalia bellerica* possess a broad spectrum of antimicrobial activity.

Among the herbal ingredients, tea tree oil is recorded to have significant antifungal activity. Tea tree oil is an essential oil of the leaves of the Australian *Melaleuca alternifolia*. It is a mixture of hydrocarbons and terpenes, consisting of almost 100 substances of different concentrations. The major component of tea tree oil is terpinen-4-ol which is found to have a significant antimicrobial activity. Concentration of 0.25% to 5% tea tree oil appears to be effective and well-tolerated in the treatment of dandruff. Tea tree oil represents a good alternative for patients with dandruff who prefer a natural product and are willing to shampoo their hair on daily basis. ^[42, 43]

Basil oil and Coleus oil are known to have the highest activity among the herbal ingredients. Other herbs include *Nyctanthes arbortristis* (Harshingar), *Hibiscus rosasinensis* (Gurhal), *Azadirachta indica* (Neem), *Emblca officinalis* (Amalki), *Casytha filiformis* (Amar Bel), *Cinnamomum, camphora* (Karpoor), *Curcuma longa* (Haldi), *Rubia cordifolia* (Majistha). Herbal ingredients like rosemary oil, clove oil, pepper extract, neem extract, rosemary oil, henna, and lemon also recorded good anti-pityrosporum activity. ^[44]

Henna (*Lawsonia inermis*) has strong fungicidal as well as anti-inflammatory, analgesic, and antibacterial properties. The chemical constituents of this plant extract include naphthalene derivatives, quinoids, beta-sitosterol, gallic acid, and flavonoids.^[45] It also acts as a very good conditioner for the hair. The study of antifungal effects of chloroformic, methanolic and aqueous extracts of henna leaves on *Malassezia furfur* showed the complete inhibition of *M. furfur* by chloroformic extract of henna.^[46,47]

The study was conducted to differentiate the maximum and minimum inhibition of growth of *M. furfur* in which Plant extracts were prepared from *Citrus limon*(lemon), *Emblca officinalis* (amla),*Trigonella foenum graecum* (fenugreek), *Vitis vinifera*(grape vine), *Papaver somniferum*(poppy)and *Allium cepa*(onion) in different concentration. The aqueous plant extracts were added to the wells of *Malassezia furfur* inoculated plates. Results showed that Citrus limon extract had maximum zone of inhibition than other plant extracts and Papaver somniferum and Allium cepa extracts showed no inhibition zone.^[48]

Ocimum sanctum has a high content of flavonoids. The principle ingredients of *Ocimum sanctum* are fatty acids including stearic, palmitic, oleic, and linoleic acid. It has significant anti-inflammatory activity against prostaglandin, leukotriene, and arachidonic acid and also acts as a microbial agent. The 100% extract of neem leaves produced the widest zone of inhibition. It can also cure skin epidermal problems ranging from dandruff, acne, psoriasis and ringworm infection.^[49]

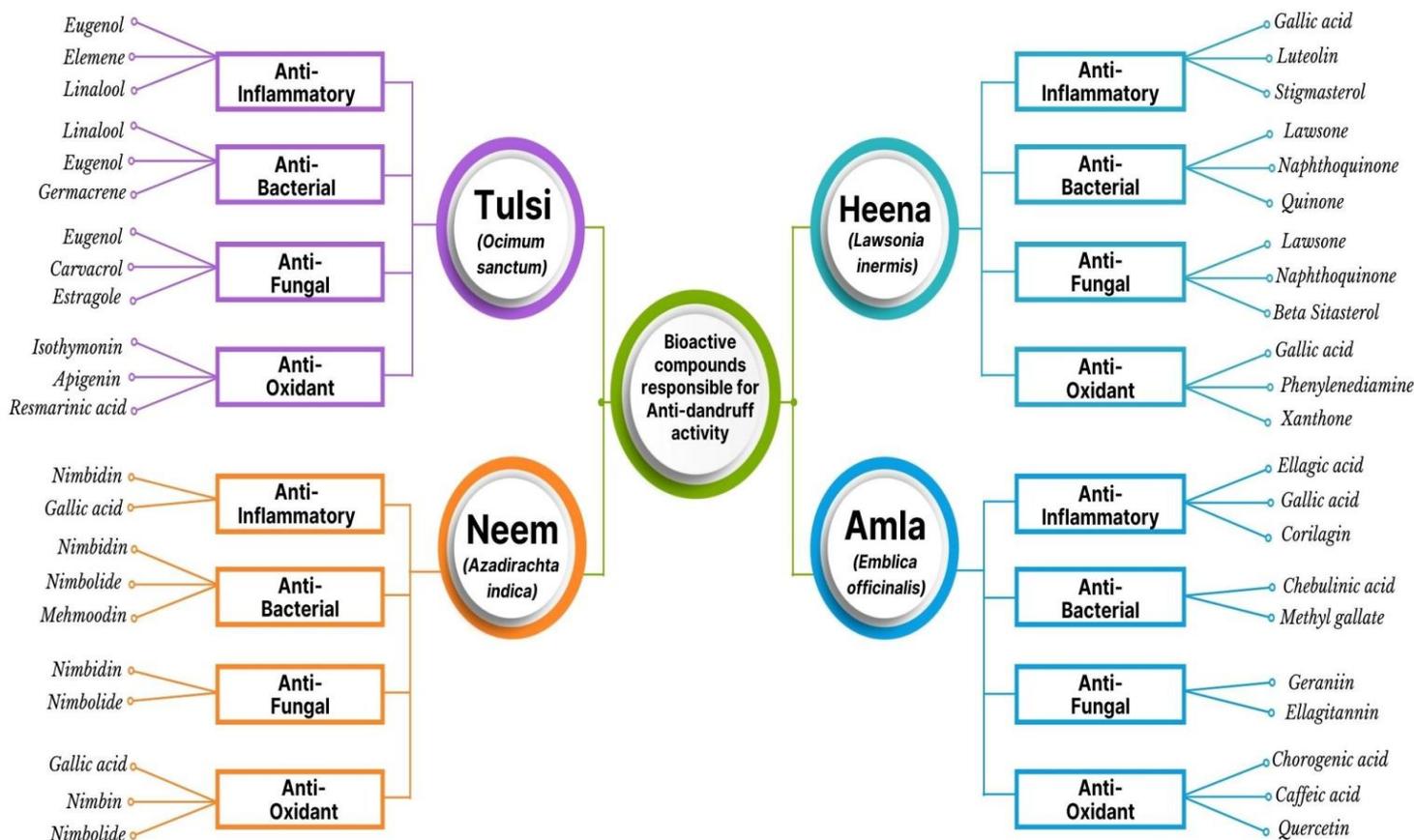


Fig 4. Bio-active compounds responsible for anti-dandruff activity.

EFFECTIVITY OF SYNTHETIC AND NATURAL ACTIVES IN ANTI-DANDRUFF TREATMENT

Herbal ingredients like tea tree oil, rosemary oil, coleus oil, clove oil, pepper extract, neem extract, and basil extract also have anti-pityrosporum activity, but their MIC (Minimum Inhibitory Concentration) is much higher than the synthetic ingredients. These ingredients can be exploited for their anti-dandruff activity individually or in combination in anti-dandruff shampoos. The commercial shampoos with tea tree oil, rosemary oil, henna, and lemon have good anti-pityrosporum activity in vitro but are not better than shampoos with synthetic ingredients in both MIC and ZOI (Zone of Inhibition) assays. But for regular usage, even shampoos with herbal anti-dandruff ingredients may suffice the purpose.^[50]

Ketoconazole and Zinc Pyrithione based shampoos are used more by the consumers for common dandruff problems. The shampoos with Zinc Pyrithione are preferred by the majority of the consumers not only because the shampoo brands with Zinc Pyrithione are cheaper but also provide the desired functional benefits and better management of dandruff. However, in very severe cases of dandruff, ketoconazole-based shampoos are preferred despite their relatively higher costs.^[51]

Many studies concluded that most of the plant extracts show good antifungal activity almost equivalent to that of commercially available shampoos. The use of herbal actives is not only cost-effective but also has negligible side effects.^[52]

A NEW APPROACH

Recently, the treatment focuses more on the equilibrium of the population of microbes on the scalp, which includes the sum of all microorganisms including bacteria, viruses, fungi that inhabit in the area, called as Scalp microbiome. Global studies have revealed that the scalp microbiome is characterized by a rather low bacterial diversity as compared to other body sites and it is dominated by *Cutibacterium acnes*, *Staphylococcus epidermis*, and *Malassezia spp.* [53] Due to the high volume of vitamin-rich sebum production on the scalp and humid environment, the scalp gives rise to cutaneous bacteria, pathogens, bio film, and microbes that are not found anywhere else. Disequilibrium in the proportion of main bacterial populations on the scalp i.e. Propionibacterium acnes and Staphylococcus epidermidis also lead to the occurrence of dandruff. [54]

Many recent products target re-balancing the scalp microbiome containing ingredients that restore the equilibrium of the scalp microbiome, nourish the scalp, and alleviate the itch associated with dandruff scalps which makes it an easier and more effective solution to fight dandruff and other scalp related issues.

CONCLUSION:

Anti-dandruff shampoos and other scalp care products are widely used to get rid of the condition which is not contagious or serious but can be irritating and can also affect social behaviour which also affects the health of the scalp. The treatment strategy varies, as the cause of dandruff depends on individual susceptibility. The healthy microbiome has to be taken into consideration, the disequilibrium of which is directly linked to scalp problems in an individual. Herbal treatment is however cost-effective with no side-effects, but synthetic actives are proven to be more effective in action. The recent focus to provide solutions for maintaining the balance of scalp microbiome is emerging and as much research has revealed that both fungi and bacteria have a part in the development and progression, future developments will possibly target the two together. Knowing both fungi and bacteria have a role will help further to improve our scalp care and anti-dandruff solution offerings.

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