

REVIEW

# Putting It All Together to Understand the Role of *Malassezia* spp. in Dandruff Etiology

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**Abstract** Dandruff is a common scalp condition causing both a discomfort and an undesired social image. Various studies dating from early 1900s have investigated the condition, but understanding of underlying mechanisms and etiology of the condition is still in its infancy. Formation of dandruff is a common but complex event which has been associated with numerous causal factors. Physiological conditions such as pH, water content, or sebum secretion are some of the host-related factors. An imbalance between these factors can disturb the physiological equilibrium of the scalp that can lead to dandruff formation. However, severity of the condition is strongly related to the lipophilic yeast of the skin microbiota, *Malassezia* spp. On the other hand, there are recent publications highlighting the role of other scalp microbiota members on dandruff formation. This review investigates the processes leading to the formation of dandruff to provide an etiological description of the condition, with a focus on *Malassezia* spp.

**Keywords** Dandruff · *Malassezia* · Lipase · Scalp · Microbiota

## Introduction

Dandruff is a scalp condition that presents with the scaling of the skin (Fig. 1). This is usually accompanied with redness on the scalp which can extend to the neck with further symptoms including loosely attached oily flakes on the skin because of pruritus [1]. These flakes can be described as separated cells of keratinised layer with shorter renewal period [2]. The visible symptoms of dandruff are associated with a bad social image, which causes loss of confidence in individuals suffering from the condition [3].

Study of dandruff generally appears together with seborrheic dermatitis (SD) in studies where their relationship is discussed. Dandruff is mainly studied as a condition related to SD in studies where the main focus is the latter. The link between the two is strong, where both diseases cause scaling on the scalp and are thought to be associated with the *Malassezia* yeast for more than a century [4]. Indeed, they have been suggested to be the same disorder, differing only in severity [5]. In this context, dandruff is thought to be a milder, non-inflammatory form of SD [3, 6]. Unlike SD, dandruff is limited to the scalp.

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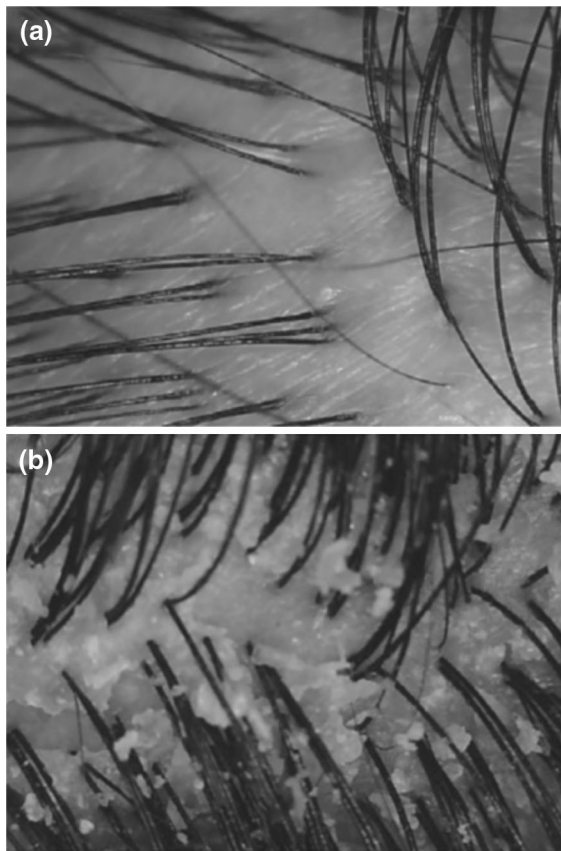


**Fig. 1** Clinical appearance of dandruff: close-up of **a** healthy scalp (dandruff free); **b** dandruff scalp showing characteristic flaking. (Reprinted with permission from Turner et al. [7])

Dandruff development has been linked to three main reasons which are *Malassezia* colonization, abnormal sebum production (with other stratum corneum dysfunctioning related abnormalities), and individual susceptibility [7, 8]. However, recent studies reported that the altered population of bacterial species (especially between *Propionibacterium* spp. and *Staphylococcus* spp.—which become dominant in dandruff cases) of scalp flora is another strong factor contributing to dandruff [9, 10]. Mutual dependence of colonization and sebum production defines the roots of timing and structure of dandruff or SD (D/SD) development. *Malassezia* is a lipophilic yeast that uses sebum lipids as a nutrient source. During puberty, sebaceous glands (SG) reach to maturity which results in increased sebum production [11]. Lipid levels of the scalp also show seasonal fluctuations [12]. As such, the condition of the lesions formed on the skin gets worse during winter compared to summer, where sunlight

appears to improve the clinical appearance of the condition [1].

Another factor that affects dandruff is individual susceptibility, depending on the nature of the stratum corneum of the scalp. On a scalp with dandruff, stratum corneum barrier lipids are observed to be reduced causing the healthy nature of the scalp to be altered. This leads to an increased transepidermal water loss, followed by an increased tendency for hyperproliferation, altered corneocyte maturation, and subclinical inflammation [7]. As formation of dandruff has been related with maximum levels of sebaceous activity earlier, further descriptive studies are needed to understand the influence of impaired sebaceous activity on dandruff.

Each part of the skin provides a different environment for microbial growth. Scalp is also one of these environments, and has distinct conditions such as thick terminal hair, large numbers of sweat glands and sebaceous glands, and humidity which provide a suitable environment for microbial growth. Stratum corneum, which is the outer layer of epidermis, favours this environment by constantly supplying amino acids, by secreting minerals from sweat glands and by secreting sebum from SG [13]. As a result, a nutrient-rich environment is provided to microorganisms. *Malassezia* yeast, one of these organisms, uses sebum and particularly saturated fatty acids as sources of nutrients. This leaves an increased amount of unsaturated free acids behind which is an irritant for the host [8]. Apart from the *Malassezia* effect, the barrier function could be altered by external factors such as temperature, humidity, or surfactants. These factors could result in dryness and irritation of the stratum corneum.

The yeast *Malassezia* are eukaryotic organisms forming a part of the microbial flora of the skin [14]. There are many lipophilic *Malassezia* species under the *Malassezia* genus as part of the human and animal skin microbiota. The common feature of these species is their lipid dependence, including *Malassezia pachydermatis* which was known as an exception until latest genome sequencing studies [15]. There are many studies that agree on the relation between *Malassezia*, sebum lipids, and dandruff [16–18]. The correlation between numbers of *Malassezia* and severity of dandruff provides an evidence of such causal link [1]. It has been shown that the amount of *Malassezia* on the scalp of a person with dandruff is higher

compared to a person who does not have dandruff [19]. Not all studies in the literature agree on such link as described above. An increase in the numbers of *Malassezia* yeast on the host is suggested to be not enough for dandruff formation. Further evidence against a causal link suggests that dandruff is formed as a result of an abnormal host immune response. Interestingly, hosts with dandruff appear not to have a higher total anti-body level, compared to the hosts with healthy scalps [5].

Apart from the microbiological, immunological, environmental, and hormonal factors, there are neurological abnormality, lifestyle, and diet factors that affect dandruff formation which is then associated with depression, stress, microtrauma, inappropriate skin care, poor nutrition, and alcoholism [20]. As the influence of *Malassezia* on dandruff production is rather poorly understood, this review aims to summarise our current understanding of the role of the skin microbiota, with a focus on *Malassezia*, and other causal factors on dandruff formation.

#### Link Between *Malassezia* and Dandruff

Dandruff is the one of the most common dermal disorders. The linkage between dandruff and *Malassezia* comes out mostly from epidemiological studies basically showing an increased incidence of *Malassezia*. This correlation makes the basis of *Malassezia* and dandruff relationship. Dandruff occurs in up to half of the healthy and up to 75–90% of immunocompromised people [1, 5]. Data on the epidemiology of dandruff in published literature are limited to the information coming from community-based surveys. The main body of clinical data comes from severe cases of the condition such as Atopic dermatitis (AD), SD, which is our main source of information on the epidemiology of dandruff in the general population. On the other hand; *Malassezia* is a yeast responsible for a range of skin infections such as Seborrhea, pityriasis versicolor, AD, and folliculitis. It has also been linked to other diseases of the skin such as psoriasis, adult and infantile SD, AD, Confluent and Reticulate Papillomatosis, Intertrigo, and Erythema Annulare Centrifugum [21]. *Malassezia* spp. are considered as etiopathological agents that are responsible from dandruff cases in such reports [22–24].

Dandruff is most common in the African-American ethnic group (81–95%) followed by the Caucasians

(66–82%) and Chinese (30–42%) [25]. Among the people who have SD infection, *Malassezia* yeast is the most common fungal genus found on the skin [26, 27]. In terms of most prevalent species within the genus; there are conflicting studies either suggesting the most prevalent species to be *Malassezia globosa* or *Malassezia restricta* among Dandruff or SD sufferers [17, 28–32]. However, new developments in molecular methods revealed that *M. restricta* is more abundant on skin suffering from Dandruff [9, 10, 33, 34]. *Malassezia* could also be observed in AD patients. A study conducted on 241 AD patients in Lithuania showed that the second most prevalent agent was *Malassezia* spp. (6.6%) after *Candida* spp. (27.4%) which were followed by *Rhodotorula* spp. (2.9%) [35].

When this yeast was marked as the possible active cause of dandruff, it was also marked as the possible agent to control this condition. More research started to take place and more products taking antifungal treatment into focus started to appear in the market to overcome this problem [36]. The treatment protocols mainly rely on antifungal drugs such as azoles and pyrithione zinc, but novel molecules targeting different fungal targets are being tested [37]. Coal tar, lithium gluconate/succinate, and phototherapy are other widely used alternative treatment options. In more severe cases, anti-inflammatory agents like steroids can be added to prescription. Besides, resistance to azoles and other antifungals is growing, and efficacy of antifungal treatment options for dandruff is decreasing [38]. Therefore, the efficacy achieved by antifungal therapies (or decrease in the efficacy because of resistance) appears to be an indicator of the important role of *Malassezia* in Dandruff production.

#### What is the Role of *Malassezia* in Dandruff Production?

The link between *Malassezia* colonization and dandruff formation comes from the lipid metabolism of *Malassezia* and the metabolites concerned. Among all *Malassezia* species, *M. globosa* and *M. restricta* are the ones with stronger association with dandruff [23].

Studies have shown that excessive proliferation of the *Malassezia* population due to various causes correlates with increased fat gland activity [28]. Of note, human sebum, which is the main lipid source for

the microorganism, mainly consists of free fatty acids, triacylglycerides, wax esters, diacylglycerides, monoacylglycerides, and 16–18 carbon length fatty acids (predominantly stearic, oleic, linoleic, palmitic, sapienic, and palmitoleic acid) [16].

Except for *M. pachydermatis*, all *Malassezia* species require an exogenous source of lipids. Lipids are the required substrates for *Malassezia* to contribute to the inflammation, hyperproliferation, and scaling reactions seen in patients with dandruff by the activity of lipases [39]. Furthermore, the cell wall of the yeast *Malassezia* boasts a rich and complex lipid content, which forms the basis for lipid dependence of the organism. This lipid-rich cell wall also acts as a shield to protect cell from phagocytosis.

Lipases are potential virulence factors for some pathogenic bacteria as well as fungi [40]. Lipases, secreted by *Malassezia*, perform the hydrolysis of sebum and ester bonds of triacylglycerols, and thus release free fatty acids which lead to inflammation. As sebum is consumed by *Malassezia* cells, the skin

produces more sebum. As sebum is consumed, free fatty acid concentration increases, leading to elevated release of irritants like oleic acid. It is known that oleic acid by itself can be responsible for the flaking of the scalp [41–43]. To sum up, after proliferation, lipase activity increases and this results in the release of free fatty acids such as oleic acid, which is an irritant. These mechanisms highlight the potential of lipases/phospholipases as therapeutic targets for D/SD.

In the last decade, many studies have taken place to characterize lipases and to understand their structure–function relationship (Table 1). Many of these studies focused on two dandruff-related species (*M. restricta* and *M. globosa*) and the whole-genome sequencing with proteomic approaches enabled a deeper understanding of the role of lipases in dandruff formation. It has been revealed recently that there are different numbers of lipase-encoding genes for each species of *Malassezia* [44]. *M. restricta* have 12 lipase-encoding genes, while *M. globosa* have 14 lipase-encoding genes. Furthermore, among *M. globosa* lipases, 13 are

**Table 1** Selected key studies from the literature highlighting the role of *Malassezia* on dandruff production

| Source                   | Sampling/population                                                                                               | Disease         | Year | Key findings                                                                                                                                               |
|--------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clavaud et al. [10]      | France; <i>N</i> = 49                                                                                             | Dandruff        | 2013 | Major fungal species found on the scalp is <i>M. restricta</i> and dandruff is linked to the balance between bacteria and fungi of the host scalp surface. |
| Paulino et al. [14]      | USA; <i>N</i> = 2 (total skin sample 54: six healthy body locations and two psoriatic lesions)                    | Psoriasis       | 2007 | <i>M. restricta</i> is the most abundant species in the majority of samples, and high amounts of <i>M. globosa</i> also detected                           |
| Deangelis et al. [18]    | USA, <i>N</i> = 40 (20 non-dandruff subjects and 20 dandruff sufferers)                                           | Dandruff        | 2005 | Dandruff is mediated by <i>Malassezia</i> metabolites, specifically irritating free fatty acids released from sebaceous triglycerides                      |
| Sommer et al. [23]       | Canada; <i>N</i> = 1 ( <i>M. restricta</i> )                                                                      | Dandruff        | 2015 | <i>Malassezia</i> lipases are responsible for the hydrolysis of triacylglycerols, the main component of human sebum                                        |
| Honnavar et al. [69]     | India, <i>N</i> = 20 <i>Malassezia</i> isolates (five each of the two species from patients and healthy controls) | Dandruff and SD | 2016 | After $\beta$ -endorphin exposure, the isolates have significantly higher phospholipase activity compared to the healthy control isolates                  |
| Bigliardi-Qi et al. [70] | Switzerland; <i>N</i> = Skin culture samples from three different epidermal regions                               | Psoriasis       | 2000 | $\mu$ -opiate receptor system and its ligand $\beta$ -endorphin are involved in the pathogenesis of psoriasis, especially in terms of differentiation      |
| Xu et al. [9]            | China; <i>N</i> = 179                                                                                             | Dandruff        | 2016 | Severity of dandruff was closely associated with the interactions between the host and microorganisms including <i>Malassezia</i>                          |
| Park et al. [17]         | Korea; <i>N</i> = 56                                                                                              | Dandruff        | 2017 | <i>M. restricta</i> lipases have an effect in the progression of dandruff                                                                                  |
| Rosenthal et al. [6]     | Canada; <i>N</i> = 246                                                                                            | Dandruff        | 1994 | Antifungal shampoos have a significant effect on dandruff                                                                                                  |

predicted to be secreted and 7 of the lipase orthologues of *M. restricta* are identified to have a signal peptide involved in secretion [17, 45]. *Malassezia sympodialis* and *M. furfur* genome sequences contain lipase genes too despite having a weaker relation with D/SD.

Comparing lipase activities of different *Malassezia* species revealed *M. globosa* as the species with the highest lipase activity [46]. Ability of *M. globosa* to fully degrade unsaturated fatty acids is ambiguous [43]. Furthermore, the role of level of secretion in dandruff development is still not clear as *M. restricta* is known to be more abundant, but *M. globosa* have higher lipase activity. Some of the lipases may be expressed more than others and the level of expression of different enzyme groups can be different. For example, Park et al. studied the expression levels of the 12 lipase genes in *M. restricta* with a clinical perspective and reported that one of the enzymes (MRES\_03670-*LIP5*) was predominant [17]. Similarly, MgLip2 and MgLip3 were found to be highly secreted enzymes in contrast to other *M. globosa* lipases [23].

In terms of function and substrate specificity, each lipase can have its unique features. For instance, a successfully isolated and expressed lipase, MgLip1, of *M. globosa* shows specific activity against mono- and diacylglycerols, whereas no activity against triacylglycerols was detected [45]. Another lipase of *M. globosa*, MgLip2, was identified and purified in a study, but no substrate specificity for mono-, di-, and triacylglycerols was detected [46, 47]. Despite a significant effort to characterize lipases, there is still need for studies, for mapping the crystal structure of lipases which can be a gateway for a complete understanding of enzyme function and for treatment of dandruff and related skin diseases.

Unlike lipases, phospholipases are not essential enzymes for *Malassezia* for successful growth or in pathogenicity of the yeast. A few lipases can hydrolyse both lipids and phospholipids. However, phospholipids are mainly hydrolysed by phospholipases with the highest activity reported in *M. pachydermatis*, followed by *M. sympodialis* (reported to be in very low activity/barely detectable in contrast to *M. pachydermatis*), *M. restricta*, and *M. globosa*, respectively [48]. For *M. globosa*, it was reported that six of the nine phospholipases are predicted to be secreted [41]. Thus, the literature suggests that the role of *Malassezia* phospholipases in dandruff is not as clear as lipases.

*Malassezia* is associated with the peroxidation of squalene which is a major sebum component on the scalp. A recent study reported that squalene was significantly more peroxidized in dandruff-affected scalps [49]. Peroxidation of squalene can increase the hyperproliferation and immunological response of keratinocytes on scalp.

Other *Malassezia* metabolites with potential roles in dandruff formation are aryl hydrocarbon receptor (AhR/dioxin receptor) ligands. AhRs are receptors proteins expressed by human cells which regulate cellular responses to certain chemicals through regulation of gene expression. Some of the *Malassezia*-related AhR ligands are malassezin, indirubin, indolo[3,2-b] carbazole, pityriacetrin, tryptanthrin, and 6-formyl-indol [50, 51]. It was shown that patients with *Malassezia*-related conditions display a 10–1000-fold increase in AhR activation capacity compared to healthy control groups [51]. The production of AhR ligands by *Malassezia* strains isolated from SD patients correlates with the pathogenic potential of this fungus in dandruff etiology [52]. Furthermore, there are studies, hypothesizing that *Malassezia*-related AhR ligands are associated with UV damage, apoptosis, cell cycle, and even carcinogenesis through various mechanisms [50]. Taking into consideration the complexity of these mechanisms, future studies are required to provide insights into AhR ligands and their effects on dandruff formation, particularly in dandruff-related species.

Gene families that have been recently discovered following the sequencing of *Malassezia* genome appear to be potential important factors that can contribute to dandruff etiology. Among those gene families are aspartyl protease, glucose methanol choline oxidoreductase (GMCO), and acid sphingomyelinase in addition to allergens [41]. Importantly, a recent study documented that aspartyl protease of *M. globosa* has an anti-biofilm activity on *Staphylococcus aureus* biofilms [53]. This finding is concurrent with the study of Clavaud et al., which discusses the interactions between host and different bacteria. It can, therefore, be hypothesized that *Malassezia* may have an effect on the balance between beneficial and harmful bacteria. Obviously, these newly discovered gene families might have key roles in *Malassezia*-related skin conditions which warrant further investigation.

Following the introduction of whole-genome sequencing methods, our understanding of *Malassezia* and pathogenic mechanisms which lead to dandruff formation has significantly improved. Importantly, we now know that all species of *Malassezia* genus have lost the genes involving in lipid metabolism. Complete genome sequencing of *Malassezia* isolates revealed that *Malassezia* genomes have a unique adaptation capacity to environmental conditions like skin's carbohydrate lacking environment [44]. Genomic studies showed that pathogenicity of *Malassezia* is mainly related to unique metabolic limitations and capabilities [41]. Main metabolic limitation of the yeast *Malassezia* is their lipid dependence, but the genome has the capability to synthesize genes like lipases and phospholipases to overcome this limitation [17]. For instance, a recent molecular study demonstrated the assimilation incapability of *M. globosa* strains for palmitic acid [54]. Because of their lipid dependence, *Malassezia* cells prefer to reside in lipid-rich environments like scalp, and as soon as they start to proliferate, they cause damage due to the activity of their metabolites [43]. This advances to dandruff by disruption of microbial equilibrium, generating immune response and causing inflammation, consequently leading to flaking of the scalp.

#### Factors Other than *Malassezia* in Dandruff Formation

The barrier function of the stratum corneum comes from patterned lipid lamellas localized on extracellular spaces between corneocytes [55]. It acts as the first line of immunological defense against environmental or microbiological antigens and allergens [4]. In physiological equilibrium, the approximate lipid composition of the epidermis is 50% ceramide, 25% cholesterol, and 10–20% free fatty acids [56]. AD, a dandruff-like skin disorder, is known to cause a decline in all three major lipids, especially ceramides, which is found in lesioned and non-lesioned skin [57]. A healthy stratum corneum structure acts as a barrier to provide protection against extreme water loss, disease-producing microorganisms including *Malassezia*, and carries out external neutralisation of toxic materials [7]. Any damage or abnormal physiological change from such a reason (explained through section) on the epidermal barrier may contribute to increase the number of *Malassezia* cells on scalp, and this may

prepare the basis for the start of dandruff production process.

Maintaining a balanced scalp physiology is the key for prevention from dandruff. SGs are the sebum factories of the scalp, maintaining optimum levels of sebum inside the hair follicles for lubrication. Physiological equilibrium of the scalp is dependent on the activity level of SGs through an altered sebum-to-water ratio in the epidermal barrier [9]. Level of activity of SG is also age-dependent which explains the link between aging and incidence of dandruff [42]. On the other hand, an imbalanced SG activity and increased sebum secretion may pave the way for overpopulation of *Malassezia* cells as this will make the scalp surface a nutrient-rich media for lipophilic yeasts.

A number of factors damaging the physiological balance of skin have been studied. Mostly, behavioral factors seem to constitute this imbalance. For instance, poor personal hygiene is linked to facilitate dandruff formation previously [58]. Likewise, being exposed to sun rays is reported to trigger dandruff [59]. Young age and male sex are found to be other risk factors for dandruff [60]. Temperature-related changes on scalp like bathing with over-heated water may also trigger dandruff formation. Over-combing and over-shampooing are the other non-specific, behavioral causes of dandruff formation [2].

A characteristic of epidermal barrier which is linked to dandruff formation is pH. The pH range of the human skin is 4.5–6.0, with higher pH values in the intertriginous regions. Increased skin alkalinity has been associated with susceptibility to cutaneous infections [61]. The logic of acidification of the skin by antifungal products is based on the acid mantle theory which suggests that cutaneous microorganisms found in human skin with reduced pH form a protective barrier against infection [62]. This can be thought as an evidence for the effect of *Malassezia* in dandruff formation and can also suggest the increase of skin pH (because of such reason) as a risk factor for dandruff formation.

Immune response of the host tissue is another host-related factor that can determine the severity of dandruff. Since *Malassezia* species are a part of skin's resident flora, the host immune system is regularly exposed to fungi, and *Malassezia*-specific IgG and IgM can be detected in healthy individuals [63]. One study found that approximately 50% of adult atopic

eczema patients were susceptible to *Malassezia* and allergen-specific IgE and T cells showed positive results in the reactivity and/or mantle atopy patch test [64]. *Malassezia* can release antigens that penetrate deeply and are captured by an antigen-presenting cell (APC). APC can then present antigens to T-lymphocytes. The cytokines present in the medium determine the T-cell subset that will be produced from Th0 cells. IL-12 stimulates the development of T-helper 1 (Th1) cells; IL-4 and IL-13 support the production of T-helper 2 (Th2) cells. Th1 cells secrete IL-2 and IFN- $\gamma$  that induce IgG responses. *Malassezia*-specific IgG can act as a protective or activating complement to provoke inflammation. Th2 cells secrete IL-4 and IL-13 which induce allergen-specific IgE responses. IgE anti-bodies bind to mast cells. Subsequent triggering of degranulation by allergens can lead to clinical features of type I hypersensitivity reactions [4]. On the whole, host immunologic response to *Malassezia* and other possible contributory microorganisms involving in dandruff formation is related with the severity of dandruff.

Immunological response to *Malassezia* metabolites like lipases and consecutive formation of short-chain fatty acids can be thought as another indirect host-related factor. In-vitro studies revealed that short-chain fatty acids have an anti-bacterial and anti-mycotic activity. For example, azelaic acid, a known anti-bacterial agent, has been showed to have anti-mycotic activity at a well-defined pH range (4.8–5.5) [65]. The balanced anti-bacterial and anti-mycotic activity of these short-chain fatty acids may contribute to microbiota equilibrium in a healthy scalp. Short-chain fatty acids can also be present in colon (which are produced by some commensal members of the gastrointestinal tract as a side-product of fermentation or taken by nutritional intake) as well and they encourage the synthesis of colonic regulatory T cells. Interestingly, Wheeler et al. suggest that *Malassezia* fatty acid metabolism in the skin results in a similar immunological response [66].

Another compound that may have an effect on dandruff production is B-endorphin. Morphine is a substance found in *Papaver somniferum* and has been known for many years for its analgesic effect. The human body produces compounds that have similar properties to this substance and are termed as endogenous opioids. Beta-endorphin, enkephalin, and dynorphin are few of those endogenous opioids,

also known as the peptide hormone group. It was shown previously that *M. pachydermatis* produce more phospholipases in lesions of dogs in contrast to non-lesioned regions and this was linked to increased presence of B-endorphin that elevates the production of phospholipases [67, 68]. Recent studies documented the enhancement of phospholipase activity of *M. globosa* and *M. restricta* by B-endorphins present in human skin [69]. Furthermore, B-endorphin concentration regulates  $\mu$ -opiate receptor expression in keratinocytes, which affects the pathogenesis of skin conditions including dandruff [70].

### Collective Description of Dandruff Etiology

The idea that microorganisms, in general, have a role in dandruff formation is not a novel one. By the first half of 1900s, the presence of coagulase negative cocci and *Propionibacterium acnes* in dandruff patients had already been investigated [71]. On the other hand, a link between dandruff and *Malassezia* has been a hot topic for decades. In their recent report; Xu et al. suggest that dandruff is more related with bacteria than it is with *Malassezia* as they detected an increase in *Staphylococcus* cells after dandruff starts where no significant increase in *Malassezia* cells was observed [9]. This may have to do with the state of the condition after the start of dandruff such as the severity of dandruff or the inflammatory response. Investigation of the relationship between microbiota and host factors reveals significant interactions between microbiota, host demographics (age, region, and gender), and host physiological conditions (sebum level, water content, and transepidermal water loss) [9, 10]. Nevertheless, besides studies featuring physiological/demographical factors, numerous epidemiological studies found strong evidences of links between *Malassezia* and dandruff [7, 16, 18, 28]. Indeed, a mechanism for dandruff production as a result of *Malassezia* lipid metabolism has been resolved [42]. Main mechanism of *Malassezia* effect on dandruff production seems to be the secretion of lipases. Lipid molecules found in sebum makes the scalp a suitable environment for lipid-dependent *Malassezia*, and lipases are the main enzymes used to hydrolyse sebum lipids as nutrients. As soon as an abnormal change occurs in the physiological state of scalp surface, (1) with the existence of appropriate host-related conditions, *Malassezia* overpopulates the scalp microbiota

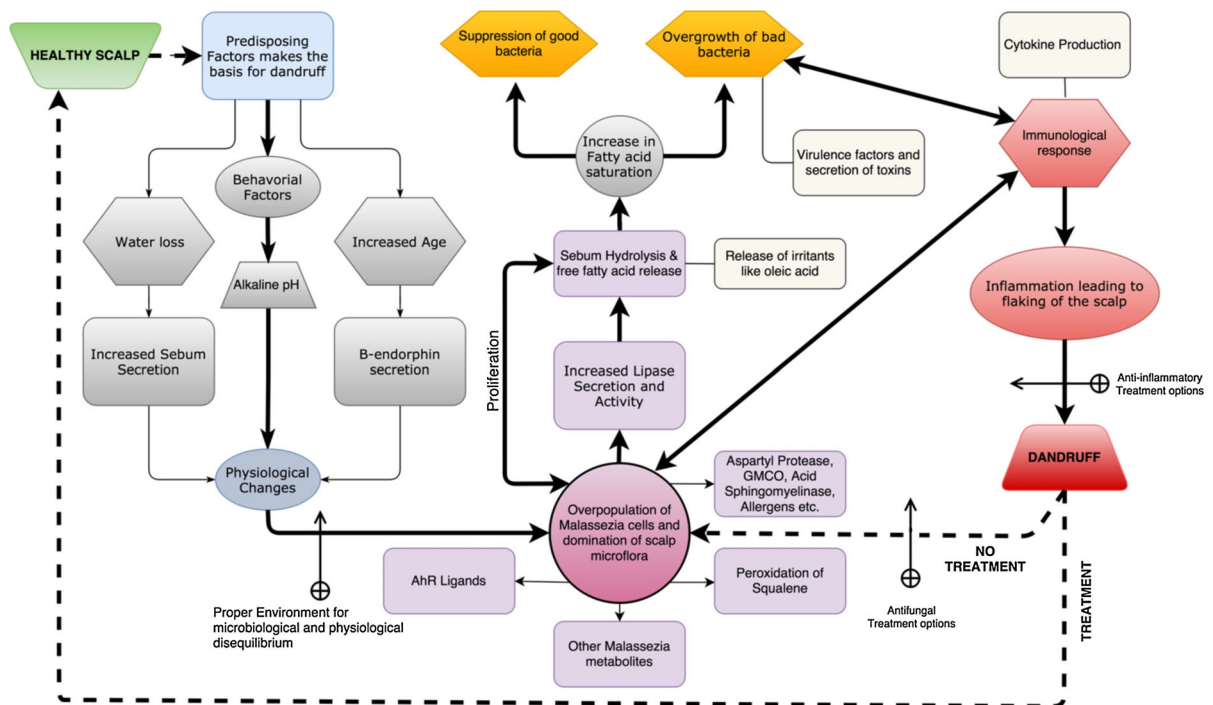


**Fig. 2** Flowchart (without colour/shape coding) summarising the etiology of dandruff that research to date produced

and breaks down the sebum, (2) healthy bacterial balance is altered and microbiota of the scalp becomes invaded by opportunistic bacteria, and (3) disruption of healthy nature of scalp yields the subclinical symptoms of dandruff that can lead to be more severe. Taken together, *Malassezia* and bacteria always seem to be present on the scalp as part of the microbiota, but a disruption of the structure and the physiological equilibrium of the epidermal barrier provide an optimal environment for *Malassezia* to dominate. This increase in *Malassezia* cell numbers, and thus, their metabolites harm the skin which sets the scene for bacteria to worsen the case (Fig. 2). Future systematic cohort studies tracking the changes in physiological conditions and microbiota deviations from the healthy scalp state to dandruff state would suggest new consecutive models.

## Conclusions

A significant effort has been put in understanding the underlying cause and mechanisms of the condition to discover treatments. Herein, we provided a hypothetical etiologic description of dandruff formation with a

focus on the role of the yeast, *Malassezia* by collectively discussing the findings that research to date has produced. Substantial evidence accumulated so far suggest that microbial communities on skin certainly have an influence on dandruff formation besides other physiological factors. Among all microorganisms, the strongest link between dandruff formation and microorganisms has been observed with *Malassezia*. Many comparative studies clarified that *Malassezia* numbers and the severity of dandruff correlate. In addition, bacteria can participate in increased severity of dandruff in addition to host-related physiological factors and *Malassezia*.

Greater understanding of such underlying mechanisms and their potential interactions may allow the development of new therapeutic approaches of re-establishing the healthy balance of scalp microbiota and in turn regaining the healthy physiological state of the scalp. Wide-scale, omic studies are required for a better understanding of the association between microbiota and dandruff formation.

**Author Contributions** YM and DG have contributed in acquisition of data and drafting the manuscript. MG have

conceived the presented idea and contributed in drafting and finalising the manuscript.

### Compliance with Ethical Standards

**Conflict of interest** The authors have no conflict of interest to report.

### References

- Gupta AK, Batra R, Bluhm R, Boekhout T, Dawson TL. Skin diseases associated with *Malassezia* species. *J Am Acad Dermatol*. 2004;51:785–98.
- Manuel F, Ranganathan S. A new postulate on two stages of dandruff: a clinical perspective. *Int J Trichol*. [Internet]. India: Medknow Publications; 2011;3:3–6. Available from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3129121/>.
- Warner RR, Schwartz JR, Boissy Y, Dawson TL. Dandruff has an altered stratum corneum ultrastructure that is improved with zinc pyrithione shampoo. *J Am Acad Dermatol*. 2001;45:897–903.
- Chen TA, Hill PB. The biology of *Malassezia* organisms and their ability to induce immune responses and skin disease. *Vet Dermatol*. 2005;16:4–26.
- White TC, Findley K, Dawson TL, Scheynius A, Boekhout T, Cuomo CA, et al. Fungi on the skin: dermatophytes and malassezia. *Cold Spring Harb Perspect Med*. 2014;4:a019802.
- Rosenthal D, Margesson LJ. A randomized, double-blind, placebo-controlled trial of ketoconazole 2% shampoo versus selenium sulfide 2.5% shampoo in the treatment of moderate to severe dandruff. *J Am Acad Dermatol*. [Internet]. American Academy of Dermatology, Inc.; 1993;29:1008–12. Available from [http://dx.doi.org/10.1016/0190-9622\(93\)70282-X](http://dx.doi.org/10.1016/0190-9622(93)70282-X).
- Turner GA, Hoptroff M, Harding CR. Stratum corneum dysfunction in dandruff. *Int J Cosmet Sci*. 2012;34:298–306.
- Schwartz JR, DeAngelis YM, Dawson Jr. TL. Dandruff and seborrheic dermatitis: a head scratcher. *Pract Mod Hair Sci*. 2012;562.
- Xu Z, Wang Z, Yuan C, Liu X, Yang F, Wang T, et al. Dandruff is associated with the conjoined interactions between host and microorganisms. *Sci Rep*. [Internet]. Nature Publishing Group; 2016;6:24877. Available from <http://www.nature.com/articles/srep24877>.
- Clavaud C, Jourdain R, Bar-Hen A, Tichit M, Bouchier C, Pouradier F, et al. Dandruff is associated with disequilibrium in the proportion of the major bacterial and fungal populations colonizing the scalp. *PLoS One*. 2013;8.
- Pochi PE, Strauss JS. Studies on the sebaceous glands in acne and endocrine disorders. *Bull N Y Acad Med*. 1977;53:359–67.
- Rogers J, Harding C, Mayo A, Banks J. Stratum corneum lipids: the effect of aging and seasons. *Arch Dermatol Res*. 1996;288:765–70.
- Jang SJ, Lim SH, Ko JH, Oh BH, Kim SM, Song YC, et al. The investigation on the distribution of *Malassezia* yeasts on the normal Korean skin by 26S rDNA PCR-RFLP. *Ann Dermatol*. 2009;21:18–26.
- Paulino LC, Tseng CH, Blaser MJ. Analysis of *Malassezia* microbiota in healthy superficial human skin and in psoriatic lesions by multiplex real-time PCR. *FEMS Yeast Res*. 2008;8:460–71.
- Gaitanis G, Magiatis P, Hantschke M, Bassukas ID, Velegraki A. The *Malassezia* genus in skin and systemic diseases. *Clin Microbiol Rev*. 2012;25:106–41.
- Ro BI, Dawson TL. The role of sebaceous gland activity and scalp microfloral metabolism in the etiology of seborrheic dermatitis and dandruff. *J Invest Dermatol Symp Proc*. [Internet]. Elsevier Masson SAS; 2005;10:194–7. Available from <http://www.sciencedirect.com/science/article/pii/S0022202X15525864>.
- Park M, Cho Y-J, Lee YW, Jung WH. Whole genome sequencing analysis of the cutaneous pathogenic yeast *Malassezia restricta* and identification of the major lipase expressed on the scalp of patients with dandruff. *Mycoses*. Germany. 2017;60:188–97.
- DeAngelis YM, Gemmer CM, Kaczvinsky JR, Kenneally DC, Schwartz JR, Dawson TL. Three etiologic facets of dandruff and seborrheic dermatitis: *Malassezia* fungi, sebaceous lipids, and individual sensitivity. *J Invest Dermatol Symp Proc*. [Internet]. Elsevier Masson SAS; 2005;10:295–7. Available from <http://dx.doi.org/10.1111/j.1087-0024.2005.10119.x>.
- Mcginley KJ, Leyden JJ, Marples RR, Path MRC, Kligman AM. Quantitative microbiology of the scalp in non-dandruff, dandruff, and seborrheic dermatitis. *J Invest Dermatol*. 1975;64:401–5.
- Adamski Z, Mycology M, Science M, Hospital P, Head SD. The treatment of dandruff of the scalp. 2006;49–56.
- Marcon MJ, Powell DA. Human infections due to *Malassezia* spp. *Clin Microbiol Rev*. 1992;5:101–19.
- Guillot J, Hadina S, Gueho E. The genus *Malassezia*: old facts and new concepts. *Parassitologia*. Italy. 2008;50:77–9.
- Sommer B, Overy DP, Kerr RG. Identification and characterization of lipases from *Malassezia restricta*, a causative agent of dandruff. *FEMS Yeast Res*. 2015;15:1–8.
- Cafarchia C, Otranto D. The pathogenesis of *Malassezia* yeasts. *Parassitologia*. Italy. 2008;50:65–7.
- Hay RJ. *Malassezia*, dandruff and seborrheic dermatitis: an overview. *Br J Dermatol*. 2011;165:2–8.
- Sampai ALSB, Mameri ACACA, Vargas TJDS, Ramos-e-Silva M, Nunes AP, Carneiro SCSDS, et al. Seborrheic dermatitis. *An Bras Dermatol*. 2011;86:1061–74.
- Otomi Cho AT. Molecular characterization of the skin fungal microbiota in patients with seborrheic dermatitis. *J Clin Exp Dermatol Res*. [Internet]. 2014;5:5–8. Available from <http://www.omicsonline.org/open-access/molecular-characterization-of-the-skin-fungal-microbiota-in-patients-with-seborrheic-dermatitis-2155-9554.1000239.php?aid=32995>.
- Gupta AK, Kohli Y, Summerbell RC, Faergemann J. Quantitative culture of *Malassezia* species from different body sites of individuals with or without dermatoses. *Med Mycol*. [Internet]. 2001;39:243–51. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11446527](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11446527).

29. Gaitanis G, Velegraki A, Alexopoulos EC, Chasapi V, Tsigonia A, Katsambas A. Distribution of *Malassezia* species in pityriasis versicolor and seborrheic dermatitis in Greece. Typing of the major pityriasis versicolor isolate *M. globosa*. *Br J Dermatol*. 2006;154:854–9.
30. Tajima M, Sugita T, Nishikawa A, Tsuboi R. Molecular analysis of *Malassezia* microflora in seborrheic dermatitis patients: comparison with other diseases and healthy subjects. *J Invest Dermatol*. 2008;128:345–51.
31. Prohic A, Jovovic Sadikovic T, Kuskunovic-Vlahovljak S, Baljic R. Distribution of *Malassezia* species in patients with different dermatological disorders and healthy individuals. *Acta Dermatovenerol Croat*. 2016;24:274–81.
32. Kamamoto CSL, Nishikaku AS, Gompertz OF, Melo AS, Hassun KM, Bagatin E. Cutaneous fungal microbiome: *Malassezia* yeasts in seborrheic dermatitis scalp in a randomized, comparative and therapeutic trial. *Dermatoendocrinol*. 2017;9:1361573.
33. Park M, Cho YJ, Lee YW, Jung WH. Whole genome sequencing analysis of the cutaneous pathogenic yeast *Malassezia restricta* and identification of the major lipase expressed on the scalp of patients with dandruff. *Mycoses*. 2017;60:188–97.
34. Wang L, Clavaud C, Bar-Hen A, Cui M, Gao J, Liu Y, et al. Characterization of the major bacterial-fungal populations colonizing dandruff scalps in Shanghai, China, shows microbial disequilibrium. *Exp Dermatol*. Denmark. 2015;24:398–400.
35. Czaika V, Nenoff P, Glöckner A, Fegeler W, Becker K, Schmalreck AF. Epidemiology and changes in patient-related factors from 1997 to 2009 in clinical yeast isolates related to dermatology, gynaecology, and paediatrics. *Int J Microbiol*. 2013;2013:2013.
36. Bulmer AC, Bulmer GS. The antifungal action of dandruff shampoos. *Mycopathologia*. 1999;147:63–5.
37. Angiolella L, Carradori S, Maccallini C, Giusiano G, Supuran CT. Targeting *Malassezia* species for novel synthetic and natural antidandruff agents. *Curr Med Chem*. Netherlands. 2017;24:2392–412.
38. Rojas FD, Córdoba SB, de los Angeles Sosa M, Zalazar LC, Fernández MS, Cattana ME, et al. Antifungal susceptibility testing of *Malassezia* yeast: comparison of two different methodologies. *Mycoses*. 2017;60:104–11.
39. Midgley G. The lipophilic yeasts: state of the art and prospects. *Med Mycol*. 2000;38:9–16.
40. Brunke S, Hube B. MfLIP1, a gene encoding an extracellular lipase of the lipid-dependent fungus *Malassezia furfur*. *Microbiology*. 2006;152:547–54.
41. Xu J, Saunders CW, Hu P, Grant RA, Boekhout T, Kuramae EE, et al. Dandruff-associated *Malassezia* genomes reveal convergent and divergent virulence traits shared with plant and human fungal pathogens. *Proc Natl Acad Sci*. [Internet]. 2007;104:18730–5. Available from <http://www.pnas.org/cgi/doi/10.1073/pnas.0706756104>.
42. Dawson TL. *Malassezia globosa* and *restricta*: breakthrough understanding of the etiology and treatment of dandruff and seborrheic dermatitis through whole-genome analysis. *J Invest Dermatol Symp Proc*. [Internet]. Elsevier Masson SAS; 2007;12:15–9. Available from <http://dx.doi.org/10.1038/sj.jidsymp.5650049>.
43. Gordon James A, Abraham KH, Cox DS, Moore AE, Pople JE. Metabolic analysis of the cutaneous fungi *Malassezia globosa* and *M. restricta* for insights on scalp condition and dandruff. *Int J Cosmet Sci*. 2013;35:169–75.
44. Wu G, Zhao H, Li C, Rajapakse MP, Wong WC, Xu J, et al. Genus-wide comparative genomics of *Malassezia* Delineates its phylogeny, physiology, and niche adaptation on human skin. *PLoS Genet*. United States. 2015;11:e1005614.
45. DeAngelis YM, Saunders CW, Johnstone KR, Reeder NL, Coleman CG, Kaczvinsky JR, et al. Isolation and expression of a *Malassezia globosa* lipase gene, LIP1. *J Invest Dermatol*. [Internet]. 2007;127:2138–46. Available from <https://www.sciencedirect.com/science/article/pii/S0022202X15335405?via%3Dihub>.
46. Juntachai W, Oura T, Kajiwarra S. Purification and characterization of a secretory lipolytic enzyme, MgLIP2, from *Malassezia globosa*. *Microbiology*. 2011;157:3492–9.
47. Xu H, Lan DM, Yang B, Wang YH. Biochemical properties and structure analysis of a DAG-like lipase from *Malassezia globosa*. *Int J Mol Sci*. 2015;16:4865–79.
48. Juntachai W, Oura T, Murayama SY, Kajiwarra S. The lipolytic enzymes activities of *Malassezia* species. *Med Mycol*. England. 2009;47:477–84.
49. Jourdain R, Moga A, Vingler P, El Rawadi C, Pouradier F, Souverain L, et al. Exploration of scalp surface lipids reveals squalene peroxide as a potential actor in dandruff condition. *Arch Dermatol Res*. Germany. 2016;308:153–63.
50. Gaitanis G, Velegraki A, Magiatis P, Pappas P, Bassukas ID. Could *Malassezia* yeasts be implicated in skin carcinogenesis through the production of aryl-hydrocarbon receptor ligands? *Med Hypotheses*. [Internet]. Elsevier Ltd; 2011;77:47–51. Available from <http://dx.doi.org/10.1016/j.mehy.2011.03.020>.
51. Magiatis P, Pappas P, Gaitanis G, Mexia N, Melliou E, Galanou M, et al. *Malassezia* yeasts produce a collection of exceptionally potent activators of the Ah (Dioxin) receptor detected in diseased human skin. *J. Invest. Dermatol*. [Internet]. 2013;133:2023–30. Available from <http://linkinghub.elsevier.com/retrieve/pii/S0022202X15363582>.
52. Gaitanis G, Magiatis P, Stathopoulou K, Bassukas ID, Alexopoulos EC, Velegraki A, et al. AhR ligands, malassezin, and indolo[3,2-b]carbazole are selectively produced by *Malassezia furfur* strains isolated from seborrheic dermatitis. *J Invest Dermatol*. [Internet]. 2008;128:1620–5. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18219281](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18219281).
53. Li H, Goh BN, Teh WK, Jiang Z, Goh JPZ, Goh A, et al. Skin commensal *Malassezia globosa* secreted protease attenuates *Staphylococcus aureus* biofilm formation. *J Invest Dermatol*. [Internet]. Elsevier; 2018; Available from <http://dx.doi.org/10.1016/j.jid.2017.11.034>.
54. Triana S, de Cock H, Ohm RA, Danies G, Wösten HAB, Restrepo S, et al. Lipid metabolic versatility in *Malassezia* spp. yeasts studied through metabolic modeling. *Front Microbiol*. 2017;8:1–18.
55. Madison KC. Barrier function of the skin: “La Raison d’Être” of the epidermis. *J Invest Dermatol*. [Internet]. Elsevier Masson SAS; 2003;121:231–41. Available from <http://dx.doi.org/10.1046/j.1523-1747.2003.12359.x>.

56. Sugarman JL. The epidermal barrier in atopic dermatitis. *Semin Cutan Med Surg.* 2008;27:108–14.
57. Danby S, Cork M. A new understanding of atopic dermatitis: the role of epidermal barrier dysfunction and sub-clinical inflammation. *J Clin Dermatol.* 2010;33–46.
58. Al-Saeed WY, Al-Dawood KM, Bukhari IA, Bahnassy AA. Risk factors and co-morbidity of skin disorders among female schoolchildren in Eastern Saudi Arabia. *Invest Clin. Venezuela.* 2007;48:199–212.
59. Ranganathan S, Mukhopadhyay T. Dandruff: the most commercially exploited skin disease. *Indian J Dermatol. India.* 2010;55:130–4.
60. Misery L, Rahhali N, Duhamel A, Taieb C. Epidemiology of dandruff, scalp pruritus and associated symptoms. *Acta Derm Venereol.* 2013;93:80–1.
61. Chikakane K, Takahashi H. Measurement of skin pH and its significance in cutaneous diseases. *Clin Dermatol.* 1995;13:299–306.
62. Schmid MH, Korting HC. The concept of the acid mantle of the skin: its relevance for the choice of skin cleansers. *Dermatology.* 1995;191:276–80.
63. Ashbee R, Bignell EM, editors. *The yeast handbook: pathogenic yeasts.* Berlin: Springer; 2010.
64. Hay RJ, Midgley G. Introduction: *Malassezia* yeasts from a historical perspective. *Pract: Malassezia Ski Sci Clin;* 2010.
65. Brasch J, Christophers E. Azelaic acid has antimycotic properties in vitro. *Dermatology. Switzerland.* 1993;186:55–8.
66. Wheeler ML, Limon JJ, Underhill DM. Immunity to commensal fungi: detente and disease. *Annu Rev Pathol. United States.* 2017;12:359–85.
67. Cafarchia C, Otranto D. Association between phospholipase production by *Malassezia pachydermatis* and skin lesions. *J Clin Microbiol.* 2004;42:4868–9.
68. Cafarchia C, Dell'Aquila ME, Capelli G, Minoia P, Otranto D. Role of beta-endorphin on phospholipase production in *Malassezia pachydermatis* in dogs: new insights into the pathogenesis of this yeast. *Med Mycol. [Internet].* 2007;45:11–5. Available from <http://www.ncbi.nlm.nih.gov/pubmed/17325939>.
69. Honnavar P, Chakrabarti A, Prasad GS, Singh P, Dogra S, Rudramurthy SM. Beta-Endorphin enhances the phospholipase activity of the dandruff causing fungi *Malassezia globosa* and *Malassezia restricta*. *Med Mycol. England.* 2017;55:150–4.
70. Bigliardi-Qi M, Eberle AN, Büchner S, Ruffi T, Bigliardi-Qi M. Beta-endorphin stimulates cytokeratin 16 expression and downregulates Mu-opiate receptor expression in human epidermis. *J Invest Dermatol.* 2000;114:527–32.
71. Leyden JJ, McGinley KJ, Kligman AM. Role of microorganisms in dandruff. *Arch Dermatol. [Internet].* 1976;112:333–8. Available from <http://dx.doi.org/10.1001/archderm.1976.01630270013003>.