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Extracellular Lipase of Malassezia as Anti Dandruff Drug Target: A Review

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ABSTRACT
This review seeks to answer how is the adaptation of Malassezia spp. for their indwelling life in scalp; what are the roles of extracellular enzymes as a virulence factor in the pathogenesis of Malassezia for dandruff/seborrheic dermatitis; and how can Indonesian herbal materials be screened as potential anti-dandruff drug by observing their ability to inhibit extracellular lipase of Malassezia. Three species of Malassezia (*M. furfur, M. globosa* and *M. restrica*) are commonly indwelling in the scalp-skin either in normal healthy individuals, or in patients with dandruff/seborrheic dermatitis. The infectious lipolytic Malassezia spp. are adapted with the scalp-skin environment and depend significantly on fatty acid supplement. To be able to live in the scalp, extracellular lipases are produced by Malassezia. Their invasive pathogenicity is dependent on high activities and production of extracellular lipases which plays a significant role in the survival and virulence of Malassezia. Therefore, these lipases may become the main target in screening for anti-dandruff drugs. For this purpose, several Indonesian herbal materials can be screened due to their potentials as lipase inhibitor.

Keywords: Dandruff Lipase, Herbal material, Malassezia, Seborrheic dermatitis

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Dandruff causes discomfort in scalp and creates an undesired social image. Two factors are important for the aetiology of Dandruff and Seborrheic Dermatitis (D/SD): physiological factors (sebum, pH, water content, and individual susceptibility) and microbial metabolism (especially Malassezia spp.). The lipophilic yeast of the skin microbiome, Malassezia spp., determine the severity of the D/SD. (1, 2). Several species of Malassezia are involved in skin/scalp disorders including D/SD, which together affect >50% of humans (3)

In this review, three research questions are discussed. The first research question is how the predominant species of Malassezia adapt to the D/SD scalp and whether there are differences between Malassezia as natural flora of the skin and as D/SD causing pathogen. The second research question is about the extracellular enzymes as a virulence factor of Malassezia. Malassezia species, even though acts as a natural inhabitant of the healthy skin, can cause several skin diseases. Its infection and colony formation are a result of complex interactions between the Malassezia and its extracellular enzymes as its virulence factor (4). The third research question is whether extracellular lipases of Malassezia can become target of anti-dandruff drug. The interaction between these enzyme and their inhibitor(s) is important to be understood(5-7) because this alternative approach can lead to the discovery of potential novel anti-dandruff drugs in the future. So far, the treatment of dandruff relies mainly on azole anti-fungal drugs, which are nowadays characterized by emerging resistance, poor compliance, clinical inefficacy and several side effects. It is necessary to promote the alternative for potential novel anti-dandruff drugs (8-10). Several Indonesian herbal materials have potential in anti-lipase activity and therefore can be used as anti-dandruff drug in the future.

The aims of this study were to find characteristics of the scalp predominant indwelling Malassezia spp. which cause D/SD, and to describe their extracellular enzymes as a virulence factor which determines the survival and pathogenesis of Malassezia; and to select Indonesian herbal materials which have potential as anti-lipase activity and are prospective to become anti-dandruff drugs. After the introduction, the following sections are presented: the adaptation of Malassezia to the scalp environment (D/SD); the extracellular enzymes as a virulence factor of Malassezia; and Indonesian herbal materials as a source of lipase inhibitors. At the end, are sections for conclusions and recommendations.

THE ADAPTATION OF MALASSEZIA TO THE SCALP ENVIRONMENT

Scalp environment[1]

The scalp is characterized with rich sebum production and carbohydrate deficient environment. The pH of the scalp plays an important physiological role. The pH of the stratum corneum is acidic, between 4.1 to 5.8. This pH is determined by several mechanisms/factors, such as the amount of fatty acids produced, products of filaggrin degradation, activated sodium-hydrogen exchanger, and released melanosome. The acidic pH of the stratum corneum of the scalp inhibits the formation of microbial colony (e.g. by *Staphylococcus aureus* and Malassezia). However, the acidic pH also influences skin condition, lipid biosynthesis, cells aggregation, epidermal differentiation and/or desquamation. The disturbance of skin barrier by the increased pH can cause skin inflammation and other epidermal diseases. Topical treatment to normalize the pH helps to maintain a healthy physiological microbiota, as well as the condition of the skin barrier, the induction of epidermal differentiation and avoiding skin inflammation (11).

Lipid-dependence of Malassezia

Human pathogenic Malassezia spp. is lipid-dependent and are adapted to the narrow niche on sebum-rich skin. Most of the Malassezia showed an absolute requirement for long fatty acid chains. In the case of the three predominant dandruff-causing species of *M. furfur*, *M. globosa* and *M. restricta*, oleic acid alone can initiate dandruff-like desquamation (1, 12). The lipid dependence of *Malassezia* can be understood because of the absence of fatty acid synthase gene. Their incapability in fatty acids biosynthesis are complemented by the presence of multiple secreted lipases to aid in degrading host lipid and harvesting the resulted fatty acids. Therefore, high levels of lipase is a probable importance in their pathogenicity, and expressed on human scalp (1, 13). Malassezia has many genes encoding the secretion of hydrolases (e.g., acid sphingomyelinase, aspartyl protease, lipase, phospholipase) which are important indicators of host-specific adaptation (3). Therefore, it can be concluded that the presence and activity of multiple secreted lipases are important to harvest the host's lipids (14).

The genomic analysis shows that a larger set of genes are lost. This evidence is concordant with the adaptation of Malassezia to skin's carbohydrate-deficient scalp environment. Therefore, it is important for Malassezia to produce and secrete extracellularly for the several key enzymes, such as aspartyl protease, lipases, phospholipases, and other peptidases. A unique genomic resource explained the development of Malassezia niche-specificity and potential virulence, as well as the abundance and distribution in the environment and on human skin(15).

The long-chain fatty acids are not synthesized by Malassezia. Therefore, the biosynthesis of myristic acid requires the addition of preformed fatty acids as its precursor. The growth media of Malassezia needs to be supported by the addition fatty acids with a carbon chain length of greater than 10. The additional supply, including the fatty acids are odd- or even-numbered carbon chain lengths. The kind of added lipid that is used during growth, affects the fatty acid composition of the Malassezia. This means that the fatty acids are used as energy sources and also incorporated directly into cellular lipids. The lipids present on normal human scalps are able to fulfill the lipid requirement of the Malassezia (3).

Inability of Malassezia to ferment glucose/carbohydrate

Malassezia is unable to ferment sugars as the sole source of carbon but are able to use lipid. Beside sebum production, scalp environment is characterized by carbohydrate deficient environment. Carbohydrates, electrolytes, vitamins and trace elements are not required for the growth of Malassezia. Malassezia is normally able to grow in vitro under aerobic, microaerophilic as well as anaerobic conditions (11).

THE EXTRACELLULAR LIPASE OF MALASSEZIA AS MAIN INVASIVE VIRULENCE FACTORS AND AS TARGET OF NEW ANTI-DANDRUFF DRUG

Main invasive virulence factors

The pathogenesis of Malassezia depends on several virulence factors, namely its ability to produce reactive oxygen species (ROS) (16), allergens (17), metabolites (indole and azelaic acid) (18, 19), unique volatile gamma lactones, and extracellular enzymes (Lipase, Carbonic anhydrase, and Protease). The survival and growth of Malassezia in the scalp, as well as subsequent scalp damage, are mediated by its virulence factors which set them apart from harmless microbiota. The host–fungus interactions lead to the development of D/SD(20). The pathogenic role of Malassezia are determined by the host immune system and the virulence factors. Several virulence factors in Malassezia are their enzymatic lipolytic activity that result in the production of distinct metabolites, special cell wall features, and irritant metabolic by products including bioactive indole derivatives (21, 22). Compared with lipase, carbonic anhydrase and protease are less important factors to be used as target of the anti-dandruff drug. The first attention should be given to lipase which enables Malassezia to use triglyceride sebum in the scalp. The secretion of enzymes by Malassezia is considered as an important factor in the invasion and dissemination in the host. Therefore, it is suggested that secreted lipases are responsible for the pathogenicity of Malassezia spp. However, the expression of these genes is not yet investigated during the development of the disease. The *M. globosa* lipase gene expression on human scalp is still in the early step. (3). The role of lipase activity is very crucial in the pathogenicity of *M. globosa* towards dandruff and seborrheic dermatitis (D/SD).

Lipases are produced by Malassezia with the help of lipoxygenase and are used to digest triglyceride of the sebum. These enzymes are located on the cell wall and the cytoplasmic membrane. The greatest lipase activity is observed during logarithmic phase where the cells are active growing. The activity is influenced by the concentration of the substrate. (23) At least three different extracellular lipases are known as essential for the growth of Malassezia. In vitro growth of Malassezia species also produce a phospholipase. Activity of phospholipase releases arachidonic acid that are involved in inflammation of the skin. The activity of phospholipase is the basic mechanism by which Malassezia species may trigger inflammation. Isolates of *M. furfur, M. globosa,* and *M. restricta,* also produce esterase, phosphatase-acid and Naphtol-AS-BI-phosphohydrolase in significant amounts from most isolates excepted for *M. restricta. M. restricta has* limited enzymatic activity compared to other species. Five extracellular enzymes including keratinase (protease), lipase and phospholipase are produced (24, 25). Genetic analysis of the *M. restricta* genome identified at least eight lipase sequences. The lipases MrLip1, MrLip2 and MrLip3 are tested for their activity using mono-, di- and triacylglycerol substrates. Hydrolysis by the *M. restricta* lipase MrLip1 and MrLip2 are limited to the mono- and diacylglycerol. Meanwhile, MrLip3 hydrolyses all three substrates. Lipases are responsible for the hydrolysis of triacylglycerols, the main component of human sebum. The information regarding lipases from *M. restricta* may aid in the search for anti-dandruff agents (26). Even though most lipases of Malassezia are considered to be active against triacylglycerides, there is a small group of lipases that are active only on mono- and diacylglycerides (27) (Table 1).

Lipase of M. furfur

The activity of lipase can be measured in the extract of the soluble and insoluble cells, as well as in the supernatant of the culture. The enzymatic activity and cell growth are first induced and later inhibited by increasing concentrations of Tween-80 (polyethylene-sorbitan-monooleate). The characters of the lipolytic system explained the incremental growth of *M. furfur* that alter the surface lipid in the scalp, such as seborrheic dermatitis. The lipolytic system is induced by the substrate and influenced by the environmental pH and/or different cations). (23). The growth of *M. furfur* is totally dependent on the external lipid supply. With the lipolytic activity, Malassezia hydrolyses lipid and release fatty acids that are necessary for both growth and pathogenicity. The sequence similarity of the gene MfLIP1 is high compared with the other known extracellular lipases (28). The hyphal form of Malassezia shows higher lipase activities than those of the yeast form (29).

Lipase of M. globosa

Malassezia globosa is characterised by its highest lipase activity compared to the rest of the Malassezia species. It has 6 phospholipase-C encoding genes which secrete lipases, and two phospholipase-D genes and one phospholipase-B gene which do not secrete. (3). MgLIP1 and MgLIP2 are found in *M. globosa*. The activity of lipase from of *M. globosa* (SMG1) is special because of its specific activity on hydrolysis mono- and diacylglycerol, but not on triacylglycerol (29).*M. globosa* lipase (SMG1) has an unusual activity in which it is capable in catalysing epoxidation of alkenes. The long chain carboxylic acids are catalysed to peroxides that subsequently react with double bonds of alkenes to produce epoxides. SMG1 is selectively reactive to carboxylic acids. Since the activity of SMG1 lipase is regulated by allosteric mechanism upon binding to the lipophilic-hydrophilic phase interface, it is used to drive the epoxidation in the lipophilic phase exclusively (30). SMG1 is one of the few members in the fungal lipase family that strictly specific for mono- and diacylglycerol (31).The diglyceride-hydrolyzing lipase of *M. globosa* can be isolated. It is able to degrade diolein, but not triolein. But the lipase of the intact cells show activity against both substrates. This evidence indicates that the presence of at least another lipase is necessary. The lipase-gene expression can be detected on the human scalp by reverse transcription-PCR. This step is important in molecular description of lipid metabolism on the scalp, ultimately leading toward a test of its role in D/SD aetiology (32).

Lipase of M. restricta

The presence of lipases and phospholipases have significant contribution in the virulence of *M. restricta* as being the most frequently isolated Malassezia spp. from the human skin. These lipases in the host scalp environment are significantly able to produce free fatty acids for Malassezia (33). Therefore, extracellular lipases of Malassezia play a critical role in its survival on the host skin surface.

Targeting Malassezia lipase for discovering new anti-dandruff drugs

Two approaches are known in discovering anti-dandruff drugs which have inhibitory activity on the extracellular lipase of Malassezia, namely with docking analysis and screening bioactivity compounds from herbal materials. In order to improve the eradication rate of Malassezia, the use of extracellular enzymes, such as lipase and /or carbonic anhydrase (MgCA), is carried out. This topic is important in dealing with the latest discoveries of herbal medicine for the management of Malassezia spp.-related diseases. New opportunities are open for discovering innovative and alternative anti-dandruff drugs in the future (8). In this review, we focus on herbal materials, mainly from Indonesia, which have anti-lipase activity since lipase is the most important target.

The resistance to single and/or multi-drug is greatly hampering patient management. Additionally, drug resistance mechanisms include altered drug-target interactions, reduced cellular drug concentrations mediated by drug efflux transporters, and permeability barriers are associated with the presence of biofilms. Therefore, the development of better diagnostic tools and approaches that allow targeted use of antifungals are essential to enhance drug efficacy (28)

Currently, the most utilized anti-dandruff drug is the Azole group, such as ketoconazole and climbazole. Ketoconazole significantly inhibits fungal filamentation or mycelia formation. Since mycelia typify the pathogenic form of Malassezia infection, the capacity of ketoconazole to block morphogenesis may represent an additional important effect of the antifungal(29). Climbazole is an example of an imidazole antifungal agent that can provide anti-dandruff benefits when incorporated into a hair shampoo. Azole antifungals are able to prevent the ergosterol synthesis (30). However, anti-fungal therapies, as in the case of Malassezia related dandruff, are considered less effective due to of chronic character of Malassezia infections and high percentage of relapses. Therefore, there is a urgent need to develop new approach for Malassezia therapies, in this case, with novel inhibitors of lipase of Malassezia (31).

THE INDONESIAN HERBAL MATERIALS WITH ANTI-LIPASE POTENTIAL

Natural remedies for treating dandruff are becoming more popular. Natural antimicrobials/antifungal are importance in recent times to combat the global challenge of antibiotic resistance. Herbal antimicrobial materials are gaining importance in therapy because their ability to encounter minimal challenges of emergence of resistance. As example, embelin of *Embelia ribes* was identified as an anti-lipase and fungi static agent. Embelin exhibits a synergistic effect with the anti-fungal drug ketoconazole (KTZ) against Malassezia spp. (9). Several Indonesian herbal materials that have the potential as anti-dandruff agents are listed in table 2.

- *Aloe vera* is known for hair growth, acne, wound healing, and shampoo. It is able to inhibit adipose lipase activities. And therefore, *Aloe vera* has great potential as functional foods in the activation adipose lipolysis and the prevention of obesity-related metabolic alterations. *Aloe vera* gel has inhibitory potential against pancreatic lipase activity, and significant inhibition on pancreatic lipase (32, 33).
- *Azadirachta indica* (neem tree) contains azadirachtin as its main constituent in various parts of the tree. Azadirachtin, a tetranortriterpenoid, is remarkable for its chemical complexity and for its biological activity. It is reported that azadirachtin inhibit the rice bran lipase, an esterase, which is a versatile enzyme that catalyzes the hydrolysis of ester linkages, primarily in neutral lipids such as triglycerides (34, 35)
- *Centella asiatica* is used to as a remedy for acne because of its ability to inhibit lipase produced by the bacteria responsible for acne formation. It is reported that pancreatic lipase inhibitory activity of *C. asiatica* extract was significantly higher than rutin but lower than orlistat, an anti-obesity drug(36).
- *Nigella sativa* is known for its anti-fungal capacity. Ethanol seed extract of *Nigella sativa* has anti-fungal capacity against *M. furfur*. It was identified that *N. sativa* contains bioactive constituents which it

stimulates further studies on the dermatological effects and application of *N. sativa*(37).

- *Musa paradisiaca* is popular for its fruit everywhere in the world. Anti-fungal and antibiotic principles are found in the peel and pulp of fully ripe bananas. It can be used effectively for a beauty treatment either for skin or hair. Bananas have the ability to improve manageability and shine while moisturizing our skin and helping to prevent dandruff. Therefore, it is good to use it an excellent treatment for in addressing the dandruff's problem and in retaining moisture on our scalp(38).
- *Eleusine indica* showed pancreatic lipase inhibitory activity with no significant difference between its methanol extract and the standard drug Orlistat. It is a good component of anti-dandruff shampoo(39).
- *Ruta angustifolia* is reported as herbal material for various diseases, including dandruff. the antibacterial and antifungal effects of four traditional plants essential oils(40)

CONCLUSIONS AND FUTURE DIRECTIONS (RECOMMENDATIONS)

Conclusions

- The lipolytic Malassezia is adapted to the scalp environment, in order to transform their existence as skin flora normal to a pathogenic agent. They have lost their lipid biosynthetic genes and are significantly dependent on fatty acid supplement.
- As one of the virulence factors of Malassezia, extracellular lipase is important for its survival in the scalp environment. Therefore, key extracellular lipases of Malassezia can become target of dandruff drugs.
- Indonesian herbal materials are potential and promising as a source of novel discovered anti-dandruff drugs.

Recommendation for future direction

- Further research on interaction host-microbe in the scalp environment is recommended.
- Lipase as virulence factors of Malassezia should be understood properly in order to support the effort to search novel anti-Malassezia, especially anti-dandruff drugs. The additional information on lipase formation in needed to aid the screening of anti-dandruff agents.
- Extracellular lipase produced by Malassezia is a good target of seeking novel anti-dandruff drug. Searching and screening natural bioactive compounds can be started by exploring lipase inhibitors. Investigation about lipase inhibitor on fungal virulence factors is necessary in order to identify the precise mechanism of antifungal activity and to do clinical trials on Malassezia

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Table 1. List of lipases produced by Malassezia

Producer	Type of lipase	Substrate	pH	Ref.
M.furfur	MfLIP1	MAGs, TAGs	Opt. 4.5-5.8 Range 3.5-7.0 Inactive >6.5	(41) (42)
M.globosa	MgLIP1 MgLIP2 MgLIP3	MAGs, DAGs MAGs, DAGs MAGs, DAGs, TAGs	Opt. 5.5 No at 8	(43) (44) (45)
M.restricta	MrLip1 MrLip2 MrLip3 MrLip4 MrLIP5	MAGs, DAGs MAGs, DAGs MAGs, DAGs, TAGs	Opt. 5,5	(26) (46)

Table 2. List of Indonesian herbal materials which are potential candidate for lipase inhibitor

Name of plant	Local name	Part used	Ref.
Aloe vera,	*Lidah buaya*	Leaf	(47)
Azadirachta indica,	*Neem, nimba*	Leaf	(35, 47)
Centella asiatica	*Goto kola, Pegagan*	Leaf	(36)
Coriandum sativum	*Coriander, Ketumbar*	Leaf	(47)
Dolichos lablab	*Daun komak*	Leaf	(48)
Eleusine indica	*Goose grass, Rumput belulang*		(39)
Mentha asiatica	*Mint*	Leaf	(47)
Musa paradisiaca	*Pisang*	Fruit, peel	(38)
Nigella sativa	*Biji jintan hitam*	Seed	(37) (49)
Ocimum tenuiflorum	*Tulsi*	Leaf	(47)
Piper bettle	*Betel leaf*	Leaf	(47)
Punica granatum	*Delima*	Leaf	(50)
Ruta angustifolia	*Daun inggu*	Leaf	(40)