

Herbal Therapy for the Treatment of Seborrhea Dermatitis

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Abstract: Seborrhea dermatitis is a skin disorder that usually appears on parts of the body that have high density of sebaceous glands, such as the face, chest, and scalp. Clinical manifestations that generally appear as scaly skin and erythema. Seborrhea dermatitis is also known as one of the causes of alopecia. Treatments that can be used for seborrhea dermatitis are antifungal, anti-inflammatory, keratolytic, and coal tar. There are concerns about poor adherence, resistance, and some side effects of drugs that have been used in the treatment of seborrhea dermatitis. Concerns regarding these issues increase the urgency for the development of new therapeutic agents in the treatment of seborrhea dermatitis. Research on medicinal plants has enormous potential to produce compounds with new structures and bioactivity. This review discusses clinical and in vitro studies related to the activity of several medicinal plants that have potential as a treatment for seborrhea dermatitis, as well as the compounds that play a role in these activities. Literature searches were carried out on the PubMed, Taylor & Francis, and SpringerLink databases using Boolean Operators to get 25 articles that match the keywords used. Of the 25 articles, six were clinical trials, while 19 were in vitro studies of Malassezia. Several plants have potential as promising therapeutic agents for the treatment of seborrhea dermatitis by inhibiting the growth of Malassezia, decreasing sebum secretion, and decreasing symptoms associated with seborrhea dermatitis such as itching, pain or burning sensation, and redness.

Keywords: seborrhea dermatitis, Malassezia, antifungal, medicinal plants

Introduction

Seborrhea dermatitis is a skin disorder that usually appears on parts of the body that have high density of sebaceous glands, such as the face, chest, and scalp.¹ The prevalence is 1–3% in the general population and 34–83% in people with compromised immune systems.² Risk factors for this disease include age, gender, increased activity of the sebaceous glands, immune deficiency, neurological and psychiatric diseases, use of certain drugs, and low humidity or ambient temperature.^{3,4}

Clinical manifestations of scaly skin, erythema, and itching associated with seborrhea dermatitis are caused by changes in skin cell function. Malassezia is strongly suspected to cause a nonspecific immune response that can trigger changes in skin function in seborrhea dermatitis patients.⁵ Malassezia is a component of the normal flora of the skin, but in patients with seborrhea dermatitis, this fungus attacks the stratum corneum, thereby releasing lipase which can result in the formation of free fatty acid compounds and cause an inflammatory process. Fatty acids can also increase the growth of this fungus.⁶

Inflammation that occurs can cause stratum corneum hyperproliferation and incomplete differentiation of corneocytes, thereby altering and impairing the function of the stratum corneum barrier, facilitating access to Malassezia and causing water to leave the cells more easily.⁶ Treatments for seborrhea dermatitis include keratolytic agents that can help remove the outer layer of the stratum hyperproliferative corneum. In addition, coal tar is thought to reduce the rate of

production of the stratum corneum.⁷ Antifungals can overcome Malassezia, while anti-inflammatory such as corticosteroids are useful for reducing the inflammatory response.⁸

There are concerns about poor adherence, resistance, and some side effects of the drugs already used. The use of corticosteroids for a long time can cause side effects and can lead to poor patient compliance.^{2,9} There are several side effects that can be associated with the use of antifungals including a burning sensation, redness of the skin, and hair loss/alopecia.¹⁰

Research has shown that Malassezia is less susceptible to fluconazole and voriconazole.¹¹ In addition, several strains of Malassezia are resistant to ketoconazole.^{12,13} These problems increase the urgency for the development of new therapeutic agents in the treatment of seborrhea dermatitis.

Research on medicinal plants has enormous potential to produce compounds with new structures and bioactivity. A number of studies have been published over the years regarding the potential of plants as new therapeutic agents in the treatment of seborrhea dermatitis. In addition, several compounds have been identified and tested for their activities related to the treatment of seborrhea dermatitis. Therefore, it is necessary to review the clinical and in vitro test data regarding the activity of several medicinal plants that have the potential to treat seborrhea dermatitis, as well as what compounds play a role in these activities.

It is often thought that plants and herbs, as “natural” and widely used in many sectors, do not present side effects, contraindications or interactions. Unfortunately, this is not the case, just think that in nature there are also toxic and poisonous plants, which can even be lethal. Gupta and Raina,⁷³ for example, reported list of 21 side effects of medicinal plants. The reported plants mainly used for oral uses. These include *tylophora asthmatica* (asthma), *prunus virginiana* (inflammation), *allium sativum* (cough), *vica rosea* (chemotherapeutics and diabetes), *colchicum autumnale* (gout, rheumatism), *matricaria recutita* (travel wickness), and *cassia alata* (constipation). It is hardly to find list of side effects of plants used for local uses, such as seborrheic dermatitis.

Seborrhea dermatitis is a common inflammatory condition of skin regions with a high density of sebaceous glands (eg, face, scalp, sternum). The cause is unknown, but species of Malassezia, a normal skin yeast, play an important role. Seborrhea dermatitis occurs with increased frequency in patients with HIV and in those with certain neurologic disorders. Seborrhea dermatitis causes occasional pruritus, dandruff, and yellow, greasy scaling on the scalp, along the hairline, and on the face. Diagnosis is made by examination. Treatment is with antifungals, topical corticosteroids, tar, and keratolytics. Seborrhea dermatitis is a common inflammatory condition of skin regions with a high density of sebaceous glands (eg, face, scalp, sternum). The cause is unknown, but species of Malassezia, a normal skin yeast, play an important role. Seborrhea dermatitis occurs with increased frequency in patients with HIV and in those with certain neurologic disorders. Seborrhea dermatitis causes occasional pruritus, dandruff, and yellow, greasy scaling on the scalp, along the hairline, and on the face. Diagnosis is made by examination. Treatment is with antifungals, topical corticosteroids, tar, and keratolytics.⁷⁴ The process of the formation of seborrhea dermatitis is shown in Figure 1.

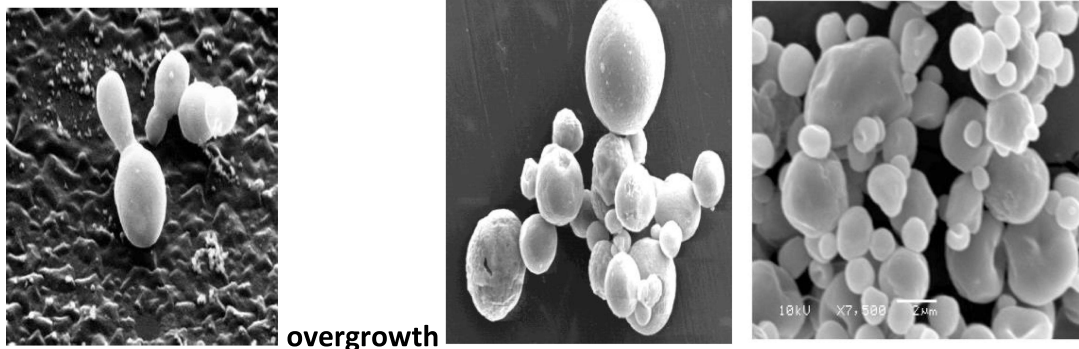
Materials and Methods

Data Source

A literature search was performed on the PubMed, Taylor & Francis, and SpringerLink databases covering the period from 2011 to the present. The keywords used were “seborrheic”, “Malassezia”, “plant”, “extract”, “essential oil”, and “volatile oil”. Inclusion criteria for the study materials used were articles with relevant titles and abstracts, articles containing at least in vitro testing of Malassezia species; and articles published in 2011–2021. While the exclusion criteria included duplicate articles found in two or more databases, articles with the type of publication in the form of reviews, and articles that did not use English.

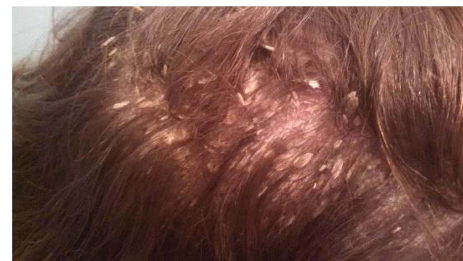
Study Selection

Literature search yielded 345 studies (173 from PubMed, 125 from Taylor & Francis, and 47 from SpringerLink), during 2011–2021. After removing duplication and screening titles and abstracts, 58 articles were selected and 277 articles were included in the exclusion criteria. After screening



Malassezia sp.

Growing on hairy head



Seborrhea dermatitis⁷⁴

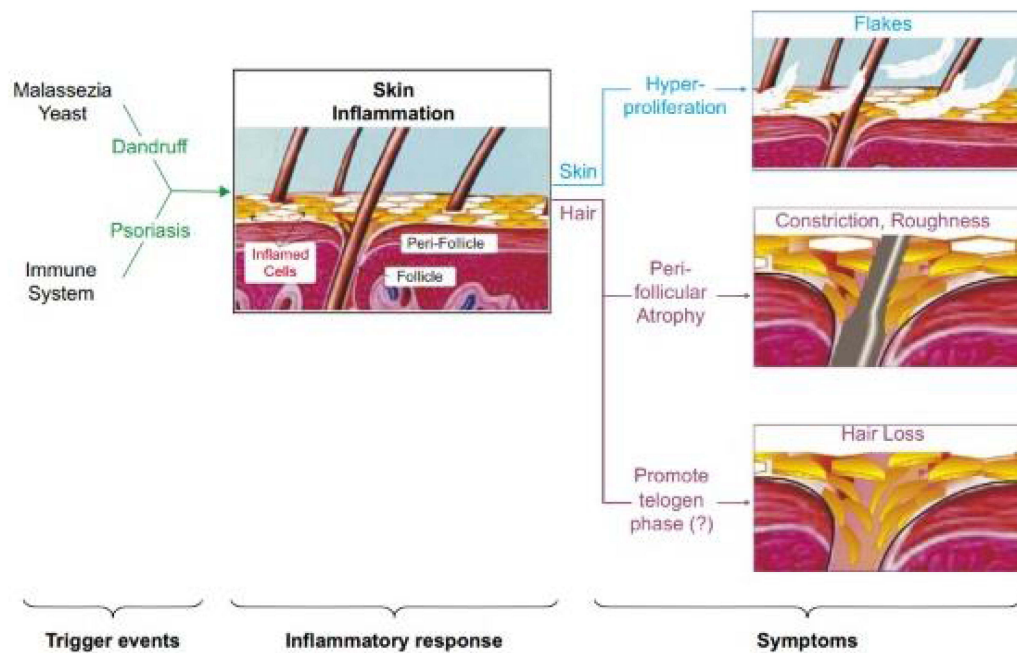


Figure 1 Metabolism of Seborrhea dermatitis.

based on the inclusion of result scores and descriptions of research methods, 25 articles were selected for review, while 33 studies were included in the exclusion criteria (Figure 2).

Discussion

Serratula coronata

Side effects reported during testing anterior hairline. It had also been reported the identification and quantification of ecdysteroid compounds contained in the dried herbs of this plant. In the initial extraction process, the solvent used was methanol, then continued with fractionation using ethyl acetate. Furthermore, the separation was carried out by chromatography using a mixed eluent of n-hexane and Me₂CO, and a mixed eluent of dichloromethane (CH₂Cl₂) and MeOH. The compounds that were successfully identified were ajugasterone C, polypodine B, and 20-hydroxyecdysone.¹⁴

Phytoecdysteroids could be associated with normalization of keratinocyte differentiation process because data in the literature suggest that phytoecdysone might cause normalization of keratinocyte differentiation in vitro.³⁹ The significant activity towards reducing inflammation might be due to its immunomodulatory function and modulation of proinflammatory cytokines (IL-6 and TNF-).⁴⁰

Cirsium eriophorum

C. eriophorum belonged to the Asteraceae family. This plant was spread in Central Europe, such as England, France, and the Netherlands to the Balkans. Creams containing *Cirsium eriophorum* cell culture extract were found to restore average sebum levels, reduce pore size, and improve the barrier function of the epidermis (Table 1). Some of the compounds contained include p-hydroxybenzoic acid, vanillic acid, balanophonin, apigenin, taraxasterol, -Sitosterol, and kaempferol-3-O-β-D-glucopyranosid.⁴¹ *Cirsium eriophorum* cell culture extract had been investigated for its role in sebum regulation, stratum corneum desquamation, and anti-inflammation. The extract could regulate important markers related to sebum secretion and pore enlargement, such as the enzyme 5α-reductase which plays a role in sebum production, and KLLK5 (Kallikrein-related peptidase 5) which plays a role in exfoliation and antimicrobial response.¹⁵

Myrtus communis

M.communis belonged to the Myrtaceae family. This plant was spread in the region of Southern Europe to West Asia. This plant had different components such as terpinolene, linalool, limonene, myrtenyl acetate, and -pinene. *M.communis*

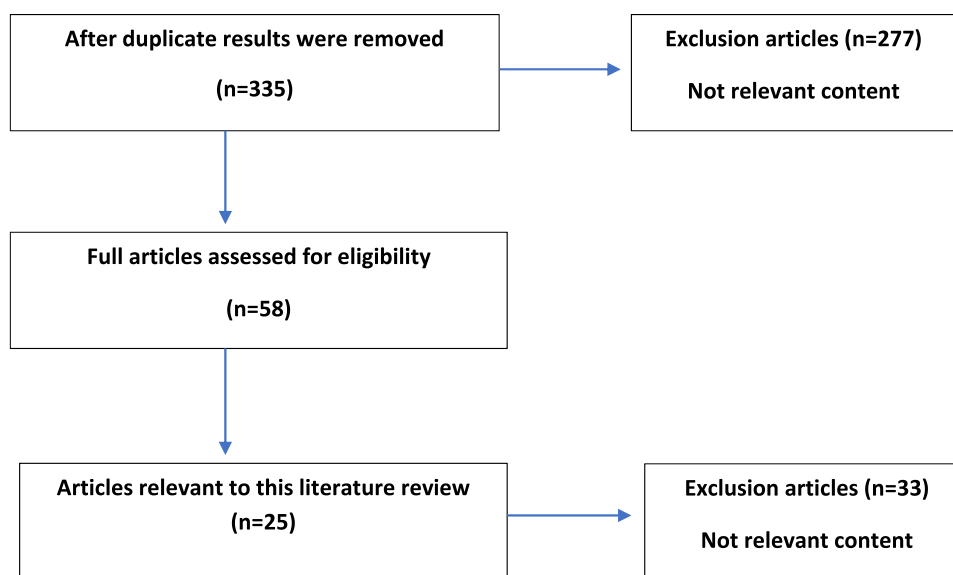


Figure 2 Literature search.

Table 1 Clinical Trials and Comparative Studies in vitro of Medicinal Plants That Have the Potential to Treat Seborrhea Dermatitis

Plants Name	Solvent for Extraction	Preparation Type	Concentration in Formulation	Subject	Duration of Treatment Formulation	Results	Ref.
<i>Serratula coronata</i>	Ethanol	Cream	2%	36 subjects (17 women and 19 men with age of 18–65 years)	2 times a week (for 6 weeks)	There was a significant reduction in symptoms ($p < 0.05$), especially in terms of pain or burning sensation, as well as itching in the affected area compared to the previous symptoms.	[14]
<i>Cirsium eriophorum</i>	–	Cream	0.5% plant extract	40 subjects (20–40 years)	2 times a day for 4 weeks	Cream containing <i>Cirsium eriophorum</i> cell culture extract could restore the average sebum level, reduced pore size, and improved the barrier function of the epidermis significantly ($p < 0.05$)	[15]
<i>Myrtus communis</i>	–	Cream	0.5% plant extract	90 subjects	Once every 3–4 days for 30 days	<i>Myrtus communis</i> group showing significant improvement in itching ($p = 0.004$) - After using antidandruff products, all dandruff indices increased significantly ($p < 0.001$) compared to the baseline value	[16]
<i>Apium graveolens</i>	–	Shampoo	3%	60 subjects	3 times a week for 3 weeks	The senkyunolide-A isolate significantly reduced dandruff intensity, histamine content, itching, and scalp redness compared with placebo and initial treatment.	[17]
<i>Quassia amara</i>	–	Gel	4% (hydroglycolic extract)	60 subjects	2 times a day for 4 weeks	-There was a significant decrease in mean seborrhea dermatitis score after 4 weeks of treatment, similar to or higher than that observed with ciclopiroxolamine and ketoconazole. - In follow-up control 4 weeks after discontinuation of treatment, quassia showed a better reduction than the cyclopyroxolamine and ketoconazole groups.	[18]
<i>Ananas comosus</i>	Methanol	Cream	2%	11 subjects	2 times a day for 12 weeks	Treatment with cream was superior to placebo because at the end of the study reduced: - Erythema index = $-20.76 \pm 0.89\%$ - Sebum secretion = $-40.71 \pm 0.75\%$	[19]

was used for seborrhea dermatitis in herbal medicine and has been shown to be effective in the treatment of dandruff without severe side effects.¹⁶

Apium graveolens

This plant with the Indonesian name celery belongs to the Apiaceae family. This plant was spread in the area of central and southern Europe, to Africa and Asia, including Indonesia. Senkyunolide A was one of the active compounds in *A. graveolens*.¹⁷

Senkyunolide-A could be isolated from seed oil of *A. graveolens* by supercritical CO₂ extraction method. Senkyunolide-A and several of its parent compounds, trigger pathways associated with skin protection, scalp barrier and anti-inflammatory, and detoxification activities.¹⁷

Ananas comosus

This plant with the Indonesian name nanas belonged to the Bromeliaceae family. This plant came from the South American region, namely Brazil. Studies related to treatment with *A.comosus* cream that could reduce the erythema index and sebum secretion had been reported (Table 1). *A.comosus* extract contained several phenolic compounds, namely flavonoids, isoflavones, flavones, anthocyanins, catechins, and other phenolics.¹⁹

The decrease in erythema value after application of the active cream was thought to be due to the presence of phenolic content. Phenolic content was thought to play a role in photoprotection and reduce the inflammatory process. In addition, phenolic compounds, namely myrecetin, kempferol, quercetin, rutin, toxifoline, emodin, and caffeic acid had the potential to inhibit 5 α -reductase and reduce sebum secretion.¹⁹

Quassia amara

Q. amara belonged to the Simaroubaceae family. This plant was spread in the northern part of South America such as Guyana, northern Brazil, and Venezuela. The gel containing the ethanolic extract of this plant showed a significant reduction in symptoms of seborrhea dermatitis (Table 1).¹⁸

This plant extract contained several terpene compounds, including quassin and neoquassin, and picrasinoside B.⁴² Natural triterpenoids were thought to be compounds that play a role in activities related to reducing seborrhea dermatitis scores because they had been reported to reduce skin inflammation in a psoriasis mouse model.⁴³

In vitro Study of Medicinal Plants That Have the Potential to Treat Seborrhea dermatitis *Cinnamomum zeylanicum*

This plant with the Indonesian name kayu manis belongs to the Lauraceae family. This plant was spread in East Asia such as India and Sri Lanka, but was also widely cultivated throughout the Tropics, including Indonesia. SFE extract (extraction of supercritical fluid with methanol cosolvent) and ethyl acetate extract from the plant *Cinnamomum zeylanicum* have shown significant antimicrobial activity (Table 2). Extraction with SFE (Super Fluid Extract) was preferred over conventional extraction due to shorter extraction time, non-toxicity, low cost, low critical temperature, and higher selectivity.¹⁴

Some of the compounds contained in this plant extract included cinnamaldehyde, eugenol, and caffeic acid. GC-MS analysis showed that the most abundant compound was cinnamaldehyde or phenylpropanoid with a peak area of 75.58%.¹⁴ Cinnamaldehyde in extracts had been reported to have antifungal activity against different skin pathogens namely *M. pachydermatis*, *M. furfur*, *Trichophyton rubrum*.^{44,45}

Eugenol compounds were reported to have anti-inflammatory activity by suppressing the expression of TNF- α , IL-1 β , and IL-6 at concentrations 150 mg/kg.⁴⁶ Hydroumbelic acid or caffeic acid is a polyphenol that exhibits antimicrobial activity by disrupting the ionic balance in microbial cell membranes.⁴⁷

Table 2 In vitro Studies of Medicinal Plants That Have the Potential to Treat Seborrhea Dermatitis

Plants Name	Test Sample	Plant Parts	Solvent for Extraction	Test Method	Test Control	Results	Ref:
<i>Cinnamomum zeylanicum</i> Blume	Ethyl acetate extract and supercritical fluid extraction	Bark	Methanol and Ethyl acetate	Well diffusion and microdilution	-	Supercritical fluid extraction: - Inhibition Zone = 18.22 mm - MIC = 390 g/mL Ethyl acetate extract: - Inhibition Zone = 18 mm	[20]
<i>Boswellia sacra</i>	Essential oil	Gum resin	Water	Microdilution	-	- MIC of Najdi cultivar: 252 g/mL - Sahli cultivar MIC: 252 g/mL - Houjri cultivar MIC: 240 g/mL	[21]
<i>Eugenia pyriformis</i>	Essential oil	Leaves and twigs	Water	Microdilution	Fluconazole	MIC = 30 µg/mL	[22]
<i>Scutellaria scordifolia</i>	Methanol extract	Aerial parts	Methanol		-	MIC50 = 64 µg/mL MIC80 = 64 µg/mL MIC100 = 128 µg/mL	[23]
<i>Origanum vulgare</i>	Essential oil	Aerial parts	Water		Fluconazole and carvacrol	MIC50 = 390 µg/mL MIC90 = 1560 µg/mL MICM = 780±490.73 µg/mL	[24]
<i>Thymus vulgaris</i>	Essential oil	Aerial parts	Water	Microdilution	Fluconazole and carvacrol	MIC50 = 780 µg/mL MIC90 = 1560 µg/mL MICM = 920±490.73 µg/mL	[24]
<i>Deverra tortuosa</i>	Essential oil	Stems and Flowers	Water	Microdilution	Itraconazole	Flower essential oil: - MIC = 3–6 µL/mL - MFC = 3–12 µL/mL Minyak asiri batang: - MIC = 6–12 µL/mL - MFC = 12 µL/mL	[25]
<i>Thapsia villosa</i>	Essential oil	Aerial parts	Water	Microdilution	Flukonazole	- MIC = 2.5 µL/mL - MFC = 2.5 µL/mL	[26]
<i>Embelia ribes</i>	Isolate embelin	Fruit	Hexane	Microdilution	Embelin	MIC = 400 µg/mL	[27]
<i>Castanea crenata</i>	Extract	Shell	-	Microdilution	Ketoconazole	<i>M. restricta</i> : - MIC = 62.5–125 µg/mL <i>M. globosa</i> : - MIC = 500–1000 µg/mL:	[28]
<i>Glycyrrhiza glabra</i>	Soluble extract	-	-	Microdilution	Ketoconazole	<i>M. restricta</i> : - MIC = 62.5–125 µg/mL <i>M. globosa</i> : - MIC = 250–1000 µg/mL	[29]
<i>Caryocar coriaceum</i>	Ethanol extract	Fruit pulp and skin	Ethanol -96%	Microdilution	-	Pulp extract: - MIC = 19.53 µg/mL - MFC = 39.06 µg/mL fruit peel extract - MIC = 9.77 µg/mL MFC = 39.06 µg/mL	[30]
<i>Vitis vinifera</i>	Ethanol extract	Seed	Ethanol -70%	Microdilution	Ketoconazole	Kultivar Michelia Palieri: - GM MIC50 = 32–161 µg/mL - GM MIC100 = 64–256 µg/mL Kultivar Italia: - GM MIC50 = 32–81 µg/mL - GM MIC100 = 81–256 µg/mL	[31]
<i>Hypericum perforatum</i>	Methanol fraction	Root	Methanol	Microdilution	-	- MIC = 16 µg/mL - MIC90 = 32 µg/mL	[31]
<i>Kunzea ericoides</i>	Essential oil	Leaves	Water	Microdilution	-	MIC = 7.800 µL/mL	[32]

(Continued)

Table 2 (Continued).

Plants Name	Test Sample	Plant Parts	Solvent for Extraction	Test Method	Test Control	Results	Ref:
<i>Leptospermum scoparium</i>	Essential oil	Leaves	WaterAir	Microdilution	-	MIC = 10.560 µL/mL	[32]
<i>Asparagus racemosus</i>	Saponin-enriched extract	Root	Hexane, ethanol (95%), and methanol	Microdilution	Ketoconazole and Zinc pyrithione	- MIC = 300 and 190 µg/mL - MFC = 780 dan 300 µg/mL	[33]
<i>Diospyros canaliculata</i>	Isolate Plumbagin	Bark	Methanol	Microdilution	Ketoconazole	MIC = 1.56 µg/mL	[34]
<i>Cymbopogon citratus</i>	Essential oil	Leaf sheath	Water	Liquid dilution	Citral standard	- MIC = 6.25 µg/mL - MFC = 6.25 µg/mL	[35]
<i>Cymbopogon citratus</i>	Isolate Hibicuslide	Aerial parts	Methanol	Liquid dilution	Amphotericin B	MIC = 5 µg/mL	[36]
<i>Cannabis sativa</i>	Essential oil	Aerial parts	Water	Microdilution	-	MIC >12.460 µg/mL	[37]
<i>Dittrichia viscosa</i>	Methanol extract	Leaves	Methanol	Disc diffusion	-	Konsentrasi 10 mg/mL:	[38]

Abbreviations: MIC, minimum inhibitory concentration; MFC, minimum fungicidal concentration; MIC50, lowest drug concentration that prevented 50% of growth with respect to the untreated control; GM, geometric mean.

Boswellia sacra

B.sacra belonged to the family Burseraceae. This plant was spread from tropical regions of Northeast Africa such as Somalia, to areas of Yemen and Oman. The main part of this plant was the sap, which was where the essential oil could be obtained. A comparative study of the oil extracted from the resins of three different *B.sacra* cultivars (Najdi, Sahli and Houjri) had been carried out (Table 2).²¹

Essential oils from various cultivars of *B. sacra* were obtained by hydrodistillation method. After 2 hours of hydrodistillation, grade 1 essential oil from each oleogum resin was collected, while grade 2 and grade 3 essential oils were collected after 4 and 6 hours. The highest content of essential oil compounds of all grades (grade 1–3) is -pinene with levels ranging from 61.82% to 79.59%. The activity against the fungal pathogen *Malassezia* was thought to be due to the high percentage of -pinene in Grade 1 essential oil and generally in monoterpenes.²¹

Eugenia pyriformis

E.pyriformis belonged to the Myrtaceae family. This plant was spread in the southern part of South America such as Argentina, Paraguay, Uruguay, and Brazil. Assays on the anti-*Malassezia* activity of essential oils obtained from the leaves and twigs of this plant had been reported (Table 2).²²

The test used a broth microdilution test method with modifications. The microdilution test was carried out according to the M27-A3 guidelines issued by CLSI in 2008. The positive control used was fluconazole.²² The fungal suspension was adjusted by spectrophotometer (530 nm) to reach an initial concentration of 0.5–2.5×10³ cells/mL. Tests were carried out on 96-well microplates and incubation was carried out on 35°C for 48 hours, with constant agitation. The reading was done by the plate reader on 490 nm and the minimum inhibitory concentration (MIC) was defined as the lowest concentration capable of inhibiting 50% of fungi. The main constituents were -pinene (7.1%), caryophyllene oxide (9.9%), -cadinol (10.3%), nerolidol (11.0%), and limonene (14.8%).²² The anti-*Malassezia* activity exhibited by these plants could result from the activity of their main compounds, because antifungal activity had been previously reported, namely the terpene limonene,⁴⁸ nerolidol,⁴⁹ -cadinol,⁵⁰ caryophyllene oxide,⁵¹ and -pinene.⁵²

Scutellaria scordifolia

S. scordifolia belonged to the Lamiaceae family. This plant was spread from Siberia to mainland China. Anti-Malassezia activity assays of methanol extract (extraction at room temperature) obtained from aerial parts of this plant have been reported (Table 2).²³ Some of the compounds contained in this plant are flavones, luteolin, and apigenin.²³ Another study showed that *S. barbata* essential oil inhibited the growth of *Candida albicans*, *Candida tropicalis*, and *Staphylococcus aureus*.⁵³

Origanum Vulgare and Thymus Vulgaris

Both of these plants belong to the Lamiaceae family. *O.vulgare* plants spread from most of Europe, including England, to northern Asia and west. While the *T.vulgaris* plant is spread in the southern part of Europe. Assays on the anti-Malassezia activity of essential oils obtained from aerial parts of these two plants had been reported (Table 2).²⁴ The content of *O.vulgare* essential oil was characterized by a high content of -Terpinene (23.69%) and thymol (45.43%) compounds. While the content of *T.vulgaris* essential oil was characterized by a high content of thymol (24.35%) and p-cymene (36.36%) compounds. In addition, there was also a carvakrol content of 0.52% for *O.vulgare* and 2.91% for *T.vulgaris*. Carvakrol was thought to be a compound that plays a role in inhibitory activity against Malassezia, because the single compound test of carvakrol showed a better MIC value than *O.vulgare* essential oil and *T.vulgaris*.²⁴

Deverra tortuosa

D.tortuosa belonged to the Apiaceae family. This plant was native to the territory of Tunisia to Israel and the Arabian Peninsula. Assays on the anti-Malassezia activity of essential oils obtained from the stem and flower parts of this plant have been reported (Table 2). Some of the compounds contained in the essential oil extract of this plant were -terpinene, -cymene, -phellandren, apiol, elemycin, and widdrol.²⁵ Apiol was the main constituent of essential oils in *D.tortuosa* (65.73–74.41%). Other components that had high enough concentrations include elemycin (5.38–6.96%) and -selinol (7.44% in roots). The antimicrobial activity of this plant was thought to be due to the compound content in the essential oil of this plant. In addition, the widdrol compound extracted from *Juniperus lucayana* was reported to exhibit an inhibitory effect against the necrotrophic plant fungus *Botrytis cinerea*.⁵⁴ Cymene-derived compounds had been reported to have antimicrobial activity against several strains of bacteria and fungi.^{55,56} In addition, phellandrene compounds were reported to have antifungal activity against *Candida* species.⁵⁷

Thapsia villosa

T.villosa belonged to the Apiaceae family. This plant was native to the southwestern region of Europe and the northwestern region of Africa that surrounds the Mediterranean Sea. Assays on the anti-Malassezia activity of essential oils obtained from aerial parts of this plant had been reported (Table 2). The main components of *Thapsia villosa* essential oil isolated by hydrodistillation method were limonene (56% and 57.5%) and methyleugenol (35% and 35.9%).²⁶

The high content of phenylpropanoid compounds (36.3% and 37.0%) and monoterpene hydrocarbons (57.4% and 58.6%) was the hallmark of this plant. Limonene compounds were thought to play a role in anti-Malassezia activity because previous studies on plants with high limonene content, namely *Citrus aurantifolia*, showed inhibitory activity against Malassezia.⁵⁸

Embelia ribes

E.ribes belonged to the family Primulaceae. This plant was spread from Sri Lanka, India and southern China to Papua New Guinea. Embellin compounds had been isolated from this plant (Table 2).²⁷ In a nutshell, the embelin isolation process was that the fine powder of dry *E. ribes* fruit (20 g) was extracted using 100 mL of hexane twice. The extracts were then thoroughly mixed with equal volumes of 2% NaOH solution. Then the aqueous phase was separated and acidified using HCl to pH 6.0.⁵⁹ Subsequently, the acidified solution was extracted using hexane twice and then washed with distilled water twice to remove the salt. Next, the organic phase was separated and evaporated at 55°C followed by

vacuum evaporation. Finally, the extract was washed using cold chloroform.⁵⁹ Several other compounds contained in this plant extract include gallic acid, catechol, caffeic acid, rutin, quercetin, quercitrin, and kaempferol.⁶⁰ The active compound that plays a role in the inhibitory activity against *Malassezia* was embelin.²⁷

Castanea crenata

C.crenata belonged to the Fagaceae family. This plant came from Korea and Japan. Some of the compounds contained in this plant extract include gallic acid, catechol, caffeic acid, ferulic acid, kaempferol, and apigenin.⁶¹ Inhibition against microbes occurred in the area of flavonol glycosides and several terpenoids were detected, the correlation indicates that this group of compounds might be responsible for antimicrobial activity.²⁸

Glycyrrhiza glabra

This plant with the Indonesian name akar manis was included in the Fabaceae family. This plant came from the southern part of Europe (Mediterranean region) and some parts of Asia. Some of the compounds contained in this plant were glycerin, butin, quercetin, and glabridin.⁶² These compounds thought to play a role in the inhibitory activity against *Malassezia* was glabridin. Previous studies had shown that glabridine isolates trigger the overexpression of apoptosis-inducing factor genes in *Candida albicans*.⁶³

Caryocar coriaceum

C.coriaceum belonged to the Caryocaraceae family. This plant was native to the eastern and northern parts of Brazil. Assays on the anti-*Malassezia* activity of ethanolic extracts obtained from the pulp and rind of this plant have been reported (Table 2).³⁰ The content of total flavonoids and total phenol contained in the fruit peel extract was higher than the pulp extract. Isoquercitrin was the main flavonoid in the pulp and skin. Flavonoid compounds such as quercetin, rutin, and isoquercitrin were thought to be important indicators of inhibitory activity against *Malassezia*.³⁰

Vitis vinifera

This plant with the Indonesian name grape belongs to the Vitaceae family. This plant was native to central and southern Europe to Central Asia and northern Iran. Test. Anti-*Malassezia* activity of ethanolic extracts obtained from the seeds of this plant has been reported (Table 2).³¹

Grape seed or *V.vinifera* contained a complex mixture of monomers, oligomers, and flavan-3-ol polymers.^{64–67} The flavan-3-ol compound is thought to play a role in the inhibitory activity against *Malassezia*.³¹

Hypericum perforatum

The plant, known as St John's-wort, belonged to the Hypericaceae family. This plant came from the Macaronian region, Europe to China, as well as some parts of Africa. Assays on the anti-*Malassezia* activity of methanol extracts obtained from root cultures of this plant have been reported (Table 2).³¹ Some of the compounds contained in this plant extract include hyperforin, hypericin, rutin, quercetin, and chlorogenic acid.⁶⁷ The methanol fraction has the largest xanthone content compared to the chloroform and ethyl acetate fractions. In addition, the data obtained showed a positive correlation between the concentration of xanthenes in the extract and antifungal activity against *M. furfur* planktonic cells.³¹

Kunzea ericoides and Leptospermum scoparium

K. ericoides and *L.scoparium* were members of the Myrtaceae family. The *k.ericoides* plant was native to New Zealand. While the plant *L.scoparium* came from Australia and New Zealand. Assays on the anti-*Malassezia* activity of essential oils obtained from the leaves of this plant by steam distillation method had been reported (Table 2).³² Some of the compounds contained in these two plants were -pinene, -pinene, limonene, terpinolen, ledol, and viridiflorol.⁶⁸ The essential oils of these two plants exhibited a strong inhibitory effect on inflammation. In THP-1 cells, essential oils from these two plants decreased TNF- released after lipopolysaccharide stimulation.³²

Asparagus racemosus

Thapsia villosa belongs to the Apiaceae family. This plant was spread in East Asia such as China, Japan, and India. Assays on the anti-Malassezia activity of Saponin-enriched extracts obtained from the root parts of this plant have been reported (Table 2). Saponin-enriched extract contained the highest saponins equivalent to IV shatavarin at 38.34%. To obtain the saponin-enriched extract, dry root powder of *A. racemosus* (150 g) was extracted by percolation method using acetone (500 mL) for 10 minutes. Then the residue was macerated with methanol (500 mL) 3 times at room temperature and filtered. Then the methanol filtrate was combined and concentrated. The concentrated extract was then precipitated with acetone (1500 mL)³³ Furthermore, the precipitate was dissolved in distilled water (25 mL) and partitioned with n-butanol (400 mL). The organic layer was collected, and the solvent was removed to obtain a dark brown saponin-enriched extract. Saponins were thought to play a role in Malassezia-related activities, because the MIC value of Saponin-enriched extract showed better results than Defatted ethanolic extract.³³

Diospyros canaliculata

D. canaliculata belonged to the Ebenaceae family. This plant was native to tropical West Africa to North Angola. The compound plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) and two known pentacyclic triterpene compounds (lupeol and lupenone) had been isolated from the bark extract.³⁴

Plumbagin isolate had been reported to produce MIC values against *Malassezia spp.* the best was 1.56 g/mL compared to crude extract (12.5 g/mL), hexane fraction (3.12 g/mL), and fraction eluted with 100% hexane (3.12 g/mL). In addition, the acute toxicity test showed the extract was not toxic to rats after oral administration.³⁴

Cymbopogon citratus

C. citratus belongs to the Poaceae family. This plant came from Sri Lanka which then spread to tropical countries including Indonesia. Assays on the anti-Malassezia activity of essential oils obtained from the leaf midrib parts of this plant had been reported (Table 2).³⁵ Some of the compounds contained in this plant were geraniol, citral, vanillin, adamantana, phytol, stigmaterol, and cannabidiol. Compounds that were thought to play a role in the inhibitory activity against Malassezia were citral compounds. Based on the test results using a thin layer chromatographic plate, the Rf value of the essential oils tested for activity correlated with the standard Rf value of citral compounds.³⁵

Abutilon theophrasti

A. theophrasti belonged to the Malvaceae family. This plant was native to Central Asia to China. The active compound hibicuslide C had been isolated from the aerial parts of this plant.⁶⁹ In the isolation process aerial parts of *A. theophrasti* (1.6 kg) were cut and extracted with methanol (MeOH) at 80°C for 4 hours. MeOH extract (43.5 g) was suspended in water and then partitioned sequentially with equal volumes using dichloromethane (CH₂Cl₂), ethyl acetate (EtOAc), and n-butanol as solvents. The CH₂Cl₂ fraction (6.0 g) was continued by column chromatography on silica gel with a hexane: acetone gradient elution system (20:1/10:1/5:1/3:1/2:1/1:1). Based on the TLC pattern, the fractions were combined to produce five subfractions, which were named D1-D5. Subgroup D5 (37.5 mg) was then purified by column chromatography on silica gel eluted with Hexane: EtOAc (20:1) to produce hibicuslide C (27.1 mg). The chemical structure of the compound was determined as hibicuslide C by comparing its spectroscopic results (1H NMR and COSY) with results in the literature.⁶⁹

Cannabis sativa

C. sativa belonged to the Cannabaceae family. This plant was native to West Asia, Iran to India. Assays on the anti-Malassezia activity of essential oils obtained from aerial parts of this plant have been reported (Table 2).³⁷ Naringenin (706 g/mL) and naringin (83 g/mL) were the two most important metabolites which could further characterize this plant essential oil, together with the presence of compounds catechins (60 g/mL) and epicatechins (56 g/mL). Naringenin had been shown to act as an antioxidant, anti-inflammatory, anticancer, antidiabetic, and antiobesity agent.³⁷

Dittrichia viscosa

D. viscosa belonged to the Asteraceae family. This plant came from Europe which included the Mediterranean region. Anti-Malassezia activity assays of extracts of ethanol (80% and 100%), methanol, and butanol obtained from aerial parts of this plant have been reported (Table 2).³⁸ Some of the compounds contained in this plant were caffeoylquinic acid derivatives, chlorogenic acid, quercetin, luteolin derivatives, and coumaric acid derivatives.⁷⁰ The methanol extract had the highest phenol and caffeoylquinic acid content compared to other extracts. The extraction method with high polarity solvent (methanol) resulted in better inhibitory activity against Malassezia species than extraction using low polarity solvent (ethanol and butanol). The inhibitory activity against Malassezia is thought to be related to the high content of phenol and caffeoylquinic acid.³⁸ Based on the activity threshold value, the MIC value below 100 g/mL indicated that the plant showed significant activity.⁷¹ Based on these values, there were 12 out of 22 plants that had been tested in vitro that had significant activity, namely *Eugenia pyriformis*, *Scutellaria scordifolia*, *Deverra tortuosa*, *Thapsia villosa*, *Castanea crenata*, *Glycyrrhiza glabra*, *Caryocar coriaceum*, *Vitis vinifera*, *Hypericum perforatum*, *Didiotos*, *Cymbopogon citratus*, and *Abutilon theophrasti*.

The Mechanism of Inhibition of the Carbonic Anhydrase of the Fungus Malassezia

Carbonic anhydrase (CAs) were enzymes that catalyze fundamental reactions, for example the bidirectional conversion of carbon dioxide (CO₂) and water (H₂O) to bicarbonate (HCO₃⁻) and protons (H⁺). The mechanism of action related to the inhibitory activity against Malassezia was the inhibition mechanism against the carbonic anhydrase of the *M. fungus*. Several phenolic compounds had been investigated as carbonic anhydrase inhibitors (CAs) of the fungal parasite *M. globosa* (MgCA), the target of a validated anti-Malassezia drug. This inhibitory activity was compared with previously reported human isoforms of hCA I and II which were widely off-target.⁷² Research that had been conducted had shown that some of the tested phenolic compounds had better efficacy in inhibiting MgCA than the sulfonamide acetazolamide which was used clinically, with an inhibitory concentration of about 2.5–65 micromolar. The potential of carbonic anhydrase had also been proposed as a promising new target in the search for new agents (antibiotics, antifungals and antiprotozoa) that did not have cross-resistance to existing drugs.⁷² In silico studies of homologously fabricated MgCA models had also been used to understand the binding mode of phenol to fungal enzymes. Extensive hydrogen bonding networks and hydrophobic interactions between phenols and residual active sites have been demonstrated. The OH moiety of the inhibitor was observed to interact with water or hydroxide ions bound to zinc, as well as forming hydrogen bonds with Ser48 and Asp49. Some compounds Phenol exhibits effective MgCA inhibitory properties, but the inhibition of hCA I and II was rather low.⁷²

Many plants have promising potential as treatments for seborrhea dermatitis in the future. Most of the studies reviewed were the results of in vitro studies. Therefore, further studies with in vivo testing need to be carried out to ensure its safety and efficacy. As for the few clinical trials reviewed, further trials involving a larger number of respondents and longer treatment times were recommended to better evaluate this natural product.

Conclusion

Based on clinical trials and MIC values of less than 100 g/mL from in vitro studies, medicinal plants that had the potential to treat seborrhea dermatitis were *Serratula coronata*, *Cirsium eriophorum*, *Myrtus communis*, *Apium graveolens*, *Quassia amara*, *Ananas comosus*, *Eugenia pyriformis*, *Scutellaria scordifolia*, *Deverra tortuosa*, *Thapsia villosa*, *Castanea crenata*, *Glycyrrhiza glabra*, *Caryocar coriaceum*, *Vitis vinifera*, *Hypericum perforatum*, *Diospyros canaliculata*, *Cymbopogon citratus*, and *Abutilon theophrasti*.

In addition, compounds that play a role in the activity of medicinal plants related to seborrhea dermatitis had been identified, including limonene, xanthenes, plumbagin, citral, hibiscuslide C, ecdysteroids, senkyunolide-A, cinnamaldehyde, carvakrol, and naringenin compounds.

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