

Potential Herbal Medicine for Alopecia Areata Treatment : A Systematic Review

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Abstract

Alopecia areata is a clinical manifestation of baldness with the pathogenesis of an immune system disorder that damages hair follicles without scar tissue formation, characterized by the presence of round, hairless areas on the scalp. Treatment for alopecia areata includes glucocorticoids (topical, intralesional and systemic), minoxidil, anthralin, other immunosuppressive agents, and immunotherapy in severe cases. Other treatments include methotrexate (immune suppressants) and cyclosporine (calcineurin inhibitors) but their benefit may be too small and inconsistent to justify their use given their possible side effects. Currently there are only 2 drugs approved by the Food and Drug Administration to be given as alopecia drugs, namely Minoxidil and Finasteride. Although alopecia areata is a common condition in dermatological practice, the management of this disease can be challenging because of the degree of severity and susceptibility to treatment resistance that patients can experience. This study aims to present the potential of herbal medicine as a treatment for alopecia areata. This literature review uses secondary data in the form of research journals related to the topic through PubMed, Google Scholar and Sciencedirect for a period of 5 years from 2018 to 2022. Herbal medicine has the potential as an alternative in cases of alopecia areata and can improve patient recovery.

Kata kunci: alopecia areata, herbal medicine

INTRODUCTION

Alopecia areata is a clinical manifestation of baldness with the pathogenesis of an immune system disorder that damages hair follicles without scar tissue formation, characterized by the presence of round, hairless areas on the scalp whether seen at multiple areas (patchy alopecia areata) or complete baldness (alopecia totalis) or generalize (alopecia universalis).^{1,2} Alopecia areata is a fairly common manifestation of hair growth disorder with an incidence ranging from 1.7-2.1% of the world's population. Alopecia universalis, totalis, and ophiasis occur with an incidence of <0.01%, although there has been a significant increase in cases of these types of alopecia in recent years. The incidence of alopecia areata is not influenced by gender and mostly occurs in children or in 20% of cases. Most people are aware of their baldness or alopecia before the onset of age 30 years.^{3,4,5}

Most of alopecia areata is idiopathic. The pathogenesis of alopecia areata is theorized to be related to autoimmune and environmental factors that are not yet known with certainty. On the other hand, psychological stress is also associated with the pathogenesis of alopecia areata with a prevalence of up to 23% in cases of alopecia areata. However, this is not entirely the case considering that newborns and babies can suffer from this disease. Therefore, other factors, such as infection, toxins, and even food, are thought to be related to the process of autoimmune dysregulation, which is suspected as a trigger for the disease.⁴ Alcohol consumption, smoking and sleep disorders can affect the incidence of alopecia areata. On the other hand, Alopecia areata is associated with several co-morbidities. Alopecia areata is associated with atopic dermatitis and rhinitis as well as Helicobacter infection, insulin elevation, metabolic disorders, lupus, anemia due to iron deficiency, thyroid disease associated with autoimmune and psychiatric disorders such as depression, anxiety and obsessive-compulsive disorder. In addition, patients with alopecia areata also have a higher risk of developing psoriasis, immune-related arthritis and other autoimmune diseases.^{4,5}

Alopecia areata can be classified into several types, including patchy alopecia areata (which involves a localized area), totalis (involves the entire scalp), and universalis which affects the whole body. Other classifications of alopecia areata include ophiasis (bands over the occipital and temporal scalp), sisipho (abnormality of the hair in the center without involving the lateral margins), and diffuse. The severity of this disorder can be divided into mild (≤ 3 patches), moderate (≥ 3 patches but no alopecia totalis or universalis), and severe (alopecia totalis, universalis, and ophiasis).^{6,3} The diagnosis of this disease is established by the presence of round or oval bald patches of hair and the presence of exclamation mark hairs at the border of these lesions, non-

pigmented hairs can be found in the abnormal lesions. The management of alopecia areata can be affected by the severity and type of alopecia. Generally mild severity and less than 12 months can heal on its own but moderate-severe degrees of severity may require treatment. Current management of alopecia includes glucocorticoids (topical, intralesional and systemic), minoxidil, anthralin, other immunosuppressive agents, and contact immunotherapy in severe cases. Other treatments include methotrexate (immune suppressants) and cyclosporine (calcineurin inhibitors) but their benefit may be too small and inconsistent to justify their use given their possible side effects. Currently there are only 2 drugs approved by the Food and Drug Administration to be given as alopecia drugs, namely Minoxidil and Finasteride. Although alopecia areata is a common condition in dermatological practice, the management of this disease can be challenging because of the degree of severity and susceptibility to treatment resistance that patients can experience.^{6,7,8,9} Herbal medicine can be used as an alternative treatment for cases of alopecia areata. There have been several studies to find herbal plants that have anti-alopecia properties. However, there are not many of them, so the data obtained for developing alternative herbal medicines is still not enough. Therefore, this journal review was made to serve as an additional reference regarding efficacious herbal plants that have potential as a treatment for cases of alopecia areata.

METHOD

The data used for this literature review is secondary data in the form of research journals related to the topic through PubMed, Google Scholar and Sciencedirect. The research journal that will be used as a source for this literature review is an English-language journal and published within 5 years, namely between 2018-2022. The research journal search keywords used in this study were "alopecia areata" AND "herbs" AND "treatment". The inclusion criteria in this literature review are English or Indonesian language journals, with a period of 5 years, namely between 2018-2022, journals are research articles or case reports. On the other hand, journals in the form of reviews and meta-analyses or comments and letters to editors, book chapters, journals in languages other than Indonesian and English, journals with non-human populations are excluded from this study. Based on the results of a literature search, the researcher found 1314 journals that matched these keywords. Journals were then excluded from the study prior to screening for reasons of journal duplication and inappropriate topics so that in the next stage there were only 921 research journals which were then screened through titles and abstracts and a total of 289 journals were excluded from the study. A search for full text journals was carried out on the remaining 632 journals and there were only 525 journals with full text. Research in the form of reviews, books, articles which are comments or letters to editors and journals not in English or Indonesian as well as journals with animal populations are then excluded from this study, so that 4 journals will be analyzed. The journal screening chart for this literature review can be seen in Figure 1.

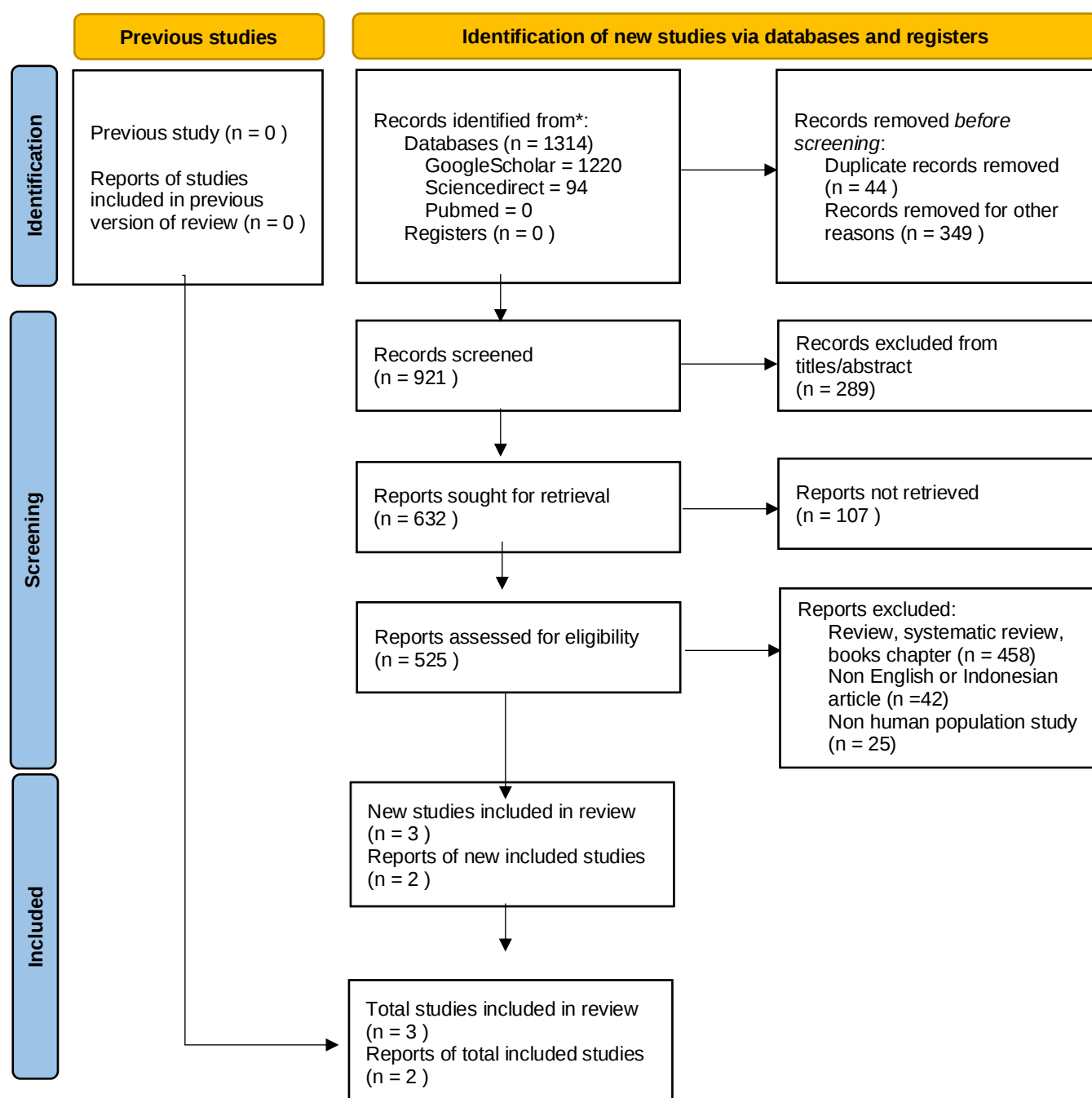


Figure 1. PRISMA Flow Diagram

RESULT

The results of the literature review found that treatment with plants and herbal compounds can be beneficial in resolution and cure of alopecia areata and reduce the risk of recurrence. In addition, this review journal found that herbal medicine also plays a role in significantly improving the antioxidant/oxidant balance of the erythrocytes and lymphocytes in alopecia areata patients. The related journals are as follows:

Table 1. Journal Analysis of Literature Review

Author	Title	Study Design	Subject	Method	Outcomes
(Kawashima et al., 2021) ¹⁰	A combination of herbal formulas, acupuncture, and novel pine-needle stimulation for recurrent alopecia	Case Report	34 year old male with sudden baldness on the top of his head measuring 5-6cm with minimum	The patient received herbal treatment from 2 herbal forms, namely JKM (saikokaryukotsuboreito and shichimotsukokato)	Improved clinical condition 50% from baseline after herbal treatment for 4 months. The patient achieved complete remission at 5 months.

	areata A case report		symptoms. The patient has a previous history of asthma. The patient had undergone topical immunotherapy but developed an exacerbation of her hairless lesions.	combined with acupuncture.	
(Abbas, 2020) ¹¹	Ginger (Zingiber officinale (L.) Rosc) Improves Oxidative Stress and Trace Elements Status in Patients with Alopecia Areata	open-label pilot clinical study	Twenty patients (9 girls and 11 boys) had a mean age of 26.0 ± 8.0 years with stable alopecia areata localized to the scalp.	The patient was treated with ginger powder 500 mg once daily for 60 days. Blood samples were taken on day zero, day 30 and day 60 to evaluate the content of reduced glutathione (GSH), malondialdehyde (MDA) and total antioxidant status (TAS) as well as serum zinc (Zn) and copper (Cu) levels.	Treatment of AA patients with ginger significantly increased the antioxidant/oxidant balance of erythrocytes and lymphocytes. Treatment also increased zinc and copper levels in the treatment group at the end of the treatment period.
(Vasco 2022) ¹²	The Treatment of Non-Scarring Alopecia with Acupuncture, Plum Blossom Hammer, and Chinese Herbs: A Case Report	Case report	A 29-year-old woman has been experiencing patch-shaped baldness since four years ago. Initially there were 4 patches measuring 2 cm. There is no evidence of fungal infection or other causes of blindness	Patients were given Polygonum 14 herbs containing Bai Shao (Radix Paeoniae Alba), Chuan Xiong (Rhizoma Chuanxiong), Da Zao (Fructus Jujubae), Dang Gui (Radix Angelicae Sinensis), Gan Cao (Radix et Rhizoma Glycyrrhizae), Ge Gen (Radix Puerariae Lobatae), Gui Zhi (Ramulus Cinnamomi), Hei Zhi Ma (Semen Sesami Nigrum), Huang Qi (Radix Astragali), Mo Han Lian (Herba Ecliptae), Nu Zhen Zi (Fructus Ligustri Lucidi), Sang Shen (Fructus Mori), Shu Di Huang (Radix Rehmanniae Preparata) and Zhi He Shou Wu (Radix Polygoni Multiflori Praeparata) at a dose of 10 grams a day	Resolution of the lesion was 75% after 3 months of treatment. After a follow-up of five and again eight months later, the lesion had completely healed with no apparent recurrence
(Moosavi, et al. 2019) ¹³	The comparison of therapeutic effect of Clobetasol propionate lotion and squill extract in alopecia areata: a randomized,	randomized, double-blind clinical trial	This test was conducted on 42 alopecia areata patients with inclusion criteria of five years of patients with at least 25% of scalp hair loss	The patient received topical squill treatment for 12 weeks which was used twice	The hair growth rate increased significantly in the herbal medicine group. The use of herbal medicine with Lotion 2% of U.maritima tuber extract showed a positive effect in 45% of patients with patchy alopecia areata and showed

	double-blind clinical trial		caused by alopecia areata. On the other hand, the exclusion criteria for this study were the presence of digoxin or calcium treatment. The patient has heart failure, kidney disease, liver dysfunction, is pregnant or breastfeeding, is taking other medicinal plants or any treatment for alopecia areata within the past month.		a moderate effect on terminal hair regrowth.
(Masoud et al., 2020) ¹⁴	Efficacy and safety of a novel herbal solution for the treatment of androgenetic alopecia and comparison with 5% minoxidil: A Double-blind, Randomized Controlled Trial study	randomized, double-blind controlled trial w	There were 24 male patients with an average age of 33.04 years from a total population of 44 people.	Patients were then grouped into 2 groups with a 1:1 ratio by administering 1 mL of the herbal drug at morning and evening intervals for nine months.	The herbal treatment combination group was significantly superior to the MTS group after 36 weeks of therapy as measured by growth in hair growth diameter and hair density.

DISCUSSION

Alopecia areata is a common form of immune-mediated alopecia in which autoimmune attack of the hair follicles causes hair loss without scarring, which is characterized by the appearance of round, hairless areas on the scalp.^{8,4} Alopecia areata (AA) known as hair disorder without scarring that presents with solitary or multiple well-demarcated patches of round or oval non-sicatricial or oval patches with characteristic "exclamation mark hairs" on the marginal side.¹⁵ Alopecia areata can be classified based on its presentation: partial or limited scalp hair loss of a few circular bald areas (patchy alopecia areata), complete scalp hair loss (alopecia totalis), or complete body hair loss (alopecia universalis). Other relatively rare variants include: ophiasis which is a band-like loss of hair in the parieto-temporo-occipital region; ophiasis inversus or siaipho which appears as ribbon-like hair loss in the fronto-parieto-temporal area; diffuse thinning of part or all of the scalp; and reticular patches of hair loss. The disease can be diagnosed clinically as round or oval patches of loose hair with normal smooth skin and exclamation mark hairs at the border of the lesion; non-pigmented hairs may be seen scattered throughout the lesion.^{3,15,7}

Hair follicles are characterized by areas of specificity related to immunity (IP) as well as those of the brain, eye, gonads and placenta. IP is the main mechanism for preventing the occurrence of autoantigen potential in human tissues. In hair follicles, this IP mechanism plays a role in providing protection to stem cells and their derivatives. There are several mechanisms of IP protection in normal hair conditions, including through physical barriers to prevent infiltration of the immune system into the hair. In addition, in the hair follicle area, decreased expression of major histocompatibility complex (MHC) class I molecules and class II MHC molecules was found in Langerhans cells, which are a type of dendritic cell in the skin, resulting in disruption of antigen presenting function, thereby reducing the secretion of pro-inflammatory cytokines. Damage to the immune system of the hair follicles has been considered to be a major driver of alopecia areata. Low expression of class I and II MHC molecules and high expression of macrophage migration inhibitory factor (MIF), an inhibitor of NK cells, prevents infiltration of a subset of T lymphocytes — CD56+/NKG2D+ NK cells — from hair follicles of healthy individuals, but reduced CD56+/NKG2D+ NK cell aggregation in cases of alopecia areata. In patients with alopecia areata there is also impaired expression of receptors for vasoactive intestinal peptides (VIPR1 and VIPR2) which are characterized by their downregulation which could reflect that the patient has defects in VIPR-mediated signaling.⁵

There are several treatments for alopecia areata, including minoxidil, anthralin (dithranol), corticosteroids and tretinoin. However, this treatment has some drawbacks. Currently available minoxidil and tretinoin cannot be combined in one regimen, so patients must use several types of solutions that are considered less effective and increase the discontinuation of self-medication. Finasteride as a synthetic 4-azasteroid compound used to induce growth is given 1 mg per day but the treatment must be applied for a long period of time, which is around 6-12 months until hair growth can recover. On the other hand, these drugs are known to decrease libido and ejaculate volume and/or cause erectile dysfunction in men. Finasteride is not indicated for women and is contraindicated in pregnant women, because it may increase the risk of feminizing a male fetus and discontinuation of treatment may result in exacerbations even after prolonged treatment. Hence a large number of herbal topical formulations are being developed and marketed worldwide to treat hair loss or promote hair growth. These herbal remedies have a variety of benefits including patient compliance, less side effects, easy availability, low cost and more than a biochemical mode of action for hair loss treatment. Herbal medicines may provide promising new hair loss treatments.¹⁶

In this study, each journal used different types of herbs, but the outcomes of each journal were similar, namely the use of herbal medicines could potentially be an alternative treatment for alopecia areata patients. The herbal plants in this study also have several different mechanisms of action related to their potential as a therapy for cases of alopecia areata, such as anti-inflammation so that redness on the skin surface reduces and increases the ability of hair regrowth (*U. maritima* or squill), induction of vasodilation by increasing nitric oxide which can increase local circulation of the scalp (*hichimotsukokato*), inhibit 5 α -reductase enzymes (*Rosmarinus officinalis* and LSEsr), inhibit the binding of dihydrotestosterone to its androgen receptors (*Rosmarinus officinalis*), increase the anagen phase and decrease the catagen phase of the hair growth cycle (*Olea europaea*) and inhibit hair cell apoptosis process (LSEsr).^{13,14,10}

CONCLUSION

There are quite a number of herbal plants which are efficacious as anti-alopecia and have the potential to be developed into alternative herbal medicines. Further research is needed regarding the mechanism and effective dosage of each plant in the management of alopecia areata. This improvement will provide a better quality of evidence for the effectiveness of herbs and compounds used to treat alopecia.

REFERENCES

1. King B, Ohyama M, Kwon O, Zlotogorski A, Ko J, Mesinkovska NA, et al. Two Phase 3 Trials of Baricitinib for Alopecia Areata. *N Engl J Med*. 2022 May 5;386(18):1687–99.
2. Andersen YMF, Nymand L, DeLozier AM, Burge R, Edson-Heredia E, Egeberg A. Patient characteristics and disease burden of alopecia areata in the Danish Skin Cohort. *BMJ Open*. 2022 Feb;12(2):e053137.
3. Foitzik-Lau K. Alopecia Areata. In: Hoeger P, Kinsler V, Yan A, Harper J, Oranje A, Bodemer C, et al., editors. *Harper's Textbook of Pediatric Dermatology* [Internet]. 1st ed. Wiley; 2019 [cited 2022 Nov 22]. p. 2139–46. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/9781119142812.ch160>
4. Minokawa Y, Sawada Y, Nakamura M. Lifestyle Factors Involved in the Pathogenesis of Alopecia Areata. *IJMS*. 2022 Jan 18;23(3):1038.
5. Sánchez-Pellicer P, Navarro-Moratalla L, Núñez-Delegido E, Agüera-Santos J, Navarro-López V. How Our Microbiome Influences the Pathogenesis of Alopecia Areata. *Genes*. 2022 Oct 14;13(10):1860.
6. Alshahrani AA, Al-Tuwaijri R, Abuoliat ZA, Alyabsi M, AlJasser MI, Alkhodair R. Prevalence and Clinical Characteristics of Alopecia Areata at a Tertiary Care Center in Saudi Arabia. *Dermatology Research and Practice*. 2020 Mar 13;2020:1–4.
7. Al Chalabi Q, Al harbawi A, Al Salman H. Dermatoscopic evaluation of alopecia areata. *Ann Coll Med Mosul*. 2021 Dec 1;43(2):144–51.
8. Lin X, Meng X, Song Z. Vitamin D and alopecia areata: possible roles in pathogenesis and potential implications for therapy. :16.
9. Pratt CH, King LE, Messenger AG, Christiano AM, Sundberg JP. Alopecia areata. *Nat Rev Dis Primers*. 2017 Dec 21;3(1):17011.

10. Kawashima N, Hu X, Ishikawa N, Matsuhisa T, Sato J. A combination of herbal formulas, acupuncture, and novel pine-needle stimulation for recurrent alopecia areata: A case report. *Medicine*. 2021 May 21;100(20):e26084.
11. Abbas A. Ginger (*Zingiber officinale* (L.) Rosc) improves oxidative stress and trace elements status in patients with alopecia areata. *Niger J Clin Pract*. 2020;23(11):1555.
12. Vasco CT. The Treatment of Non-Scarring Alopecia with Acupuncture, Plum Blossom Hammer, and Chinese Herbs: A Case Report. 2022;1(2).
13. Moosavi ZB, Aliabdi M, Golfakhrabadi F, Namjoyan F. The comparison of therapeutic effect of Clobetasol propionate lotion and squill extract in alopecia areata: a randomized, double-blind clinical trial. *Arch Dermatol Res*. 2020 Apr;312(3):173–8.
14. Masoud F, Alamdari HA, Asnaashari S, Shokri J, Javadzadeh Y. Efficacy and safety of a novel herbal solution for the treatment of androgenetic alopecia and comparison with 5% minoxidil: A double-blind, randomized controlled trial study. *Dermatologic Therapy [Internet]*. 2020 Nov [cited 2022 Dec 25];33(6). Available from: <https://onlinelibrary.wiley.com/doi/10.1111/dth.14467>
15. Cua VCS, Villena JPDS, Lizarondo FPJ, Silva CY. Azathiopine for the Treatment of Extensive Forms of Alopecia Areata: A Systematic Review. *Acta Med Philipp [Internet]*. 2019 Apr 30 [cited 2022 Nov 22];53(2). Available from: <https://actamedicaphilippina.upm.edu.ph/index.php/acta/article/view/172>
16. Herman A, Herman AP. Topically used herbal products for the treatment of hair loss: preclinical and clinical studies. *Arch Dermatol Res*. 2017 Oct;309(8):595–610.