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Efficacy of adjuvant therapy gingko biloba extract on vitiligo treated by topical desoximetasone to melanin index and vasi score

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***Abstract*---**Ginkgo biloba (GB) has anxiolytic properties, which can help to prevent the spread of vitiligo lesions. The purpose of this study was to examine the efficacy of adding orally and placebo GB extract as adjuvant therapy in treating depigmented lesions in vitiligo patients. This research is an experimental study with samples of vitiligo patients at the Dermatology and Venereology Polyclinic, RSUD Dr. Moewardi, Surakarta, Central Java, Indonesia. This study involved 23 patients aged 18-60 years. The sample met the inclusion criteria: routine control patients with stable non-segmental vitiligo with less than 20% lesions and not receiving therapy for the past four weeks.

Research subjects were divided into two groups using a capsule containing 60 mg of GB extract and a placebo. The data were processed by statistical analysis using the SPSS and the Mann-Whitney test with a significance P-value <0.05. The results showed that the administration of GB was able to significantly reduce the melanin index in vitiligo patients at week 12 ($p = 0.003 < 0.05$). In addition, administration of GB at week 8 and week 12 significantly reduced the erythema index in vitiligo patients with $p = 0.005$ and $p = 0.019$, compared to patients given placebo (significant value if $p < 0.05$). The effectiveness of the addition of GB extract can affect the clinical improvement of lesions in vitiligo patients with relatively faster repigmentation than the addition of placebo therapy for vitiligo so that the administration of GB extract can be recommended as adjuvant therapy.

***Keywords*---**ginkgo biloba, vitiligo, herbal medicine, adjuvant, skin health.

Introduction

Depigmentation of the skin, mucosa, and hair is a symptom of vitiligo [1]. Vitiligo can occur at any age. However, the prevalence of vitiligo in India is 4%, while it is around 0.19% [2,3]. The principle of vitiligo therapy is to reduce the destruction of melanocytes and increase the repopulation of epidermal melanocytes. In addition, vitiligo therapy stimulates [4,5]. Ginkgo biloba is rich in antioxidants that can counteract free radicals and prevent skin damage due to oxidation, including vitiligo [6]. According to the vitiligo area scoring index (VASI) score, giving 60 mg of GB twice a day for 12 weeks reduced the number of new lesions and repigmentation by 15% [7,8]. In addition, GB extract effectively protects melanocyte cells from apoptosis induced by oxidative stress by reducing reactive oxygen species (ROS) and lipid peroxidation processes so that it can be a potential therapy for vitiligo [9–11].

Topical corticosteroids are the first line of therapy, especially for localized vitiligo in children. Topical corticosteroids used are potent/potent, one of which is desoximetasone 0.25% cream which is most often used in this therapy [12]. Dexamethasone is a potent topical corticosteroid that can activate zinc-α2 to increase melanocyte proliferation and adhesion and prevent depigmentation in vitiligo [13]. In addition, dexamethasone also inhibits Langerhans cells (LC) cytotoxic to melanocytes [14]. Studies comparing the addition of oral GB extract as adjuvant therapy in vitiligo have never been done before. As a result, the purpose of this study was to see if adding oral GB extract as an adjuvant therapy to topical corticosteroid therapy improved the clinical appearance of vitiligo lesions.

Research Method

This study used a cross-sectional study design and was an experimental analytic investigation. The study took place between August 2020 and July 2021 at the

Dermatology and Venereology Clinic, Dr. Moewardi Surakarta. The research samples were vitiligo patients who received outpatient treatment and met the inclusion and exclusion criteria. The inclusion criteria used in this study were non-segmental stable vitiligo patients with lesions <20%, aged 18-58 years, and patients who had not received therapy for the last four weeks. As for the exclusion criteria in the form of a history of bleeding disorders, gastrointestinal system disorders, autoimmune diseases, occupational risks of exposure to sunlight, and drop outpatients. Patients were separated into two groups after being selected based on inclusion and exclusion criteria: those who received topical corticosteroid therapy and an oral form of GB capsules, and those who received topical corticosteroid therapy and a placebo. In both groups, the VASI score and Vitiligo index were examined using Mexameter MDD4®, measured before and after the administration of GB capsules. The procedure for packaging capsules containing GB 60 mg and placebo was carried out at the Dermatology and Venereology Polyclinic Laboratory, Dr. Moewardi Hospital, Surakarta. The Ethics Commission of RSUD, Dr. Moewardi Surakarta has given their approval to this study.

Result

The data on the characteristics of the research subjects were grouped by age, gender, and occupation of vitiligo patients who were routinely controlled at the dermatology clinic of RSUD Dr. Moewardi Surakarta in the period August 2020-July 2021. Table 1 describes in full the characteristics of the research sample.

Table 1. Characteristics of the research sample

Characteristic	Group		Total	p-Value
	Group of GB	Group of Plasebo		
Age				0.653
Mean±SD	39.71±14.46	35.40±26.71		
Sex				0.363
Male	6 (42.9%)	1 (12.5%)	7 (36.8%)	
Female	8 (57.1%)	4 (80.0%)	12 (63.2%)	
VASI Initial Follow UP Score	4.05±3.60	2.75±3.99		1.000
VASI Score Follow Up 1	1.63±3.60	2.75±4.10		0.775
VASI Score Follow Up 2	1.95±3.33	2.75±4.06		0.559
VASI Score Follow Up 3	1.83±3.21	2.75±4.27		0.391

Based on Table 1, the GB group had a mean age of 39.71±14.46, and the placebo group was 35.40±26.71. In the T-test results, p-value = 0.653 (> 0.05) indicates no difference between the GB and placebo groups. There were six men in the GB group (42.9%) and eight women (57.1%). In the placebo group, there was only one man (20.0%) and four women (80.0%) with a p-value of 0.363 (>0.05), which revealed no difference between the GB and placebo groups. In the initial VASI follow-up score for the GB group, the median value was 4.05 ± 3.81, and in the placebo group, the median value was 1.63 ± 3.60 and p-value = 1.00 (> 0.05). The

VASI follow-up score-1 in the GB group had a median value of 1.63 ± 3.60 and the placebo group of 2.75 ± 4.58 with a p-value of 0.775 (> 0.05). The VASI score follow-up-2 in the GB group had a mean value of 1.95 ± 3.33 and the placebo group of 2.75 ± 4.55 with a p-value of 0.559 (> 0.05). The VASI follow-up score-3 in the GB group had a mean value of 1.83±3.21 and the placebo group of 2.75±4.27 with a p-value of 0.391 (>0.05). The early follow-up VASI scores of 1, 2, and 3 revealed no change in the number of lesions or repigmentation between the GB and placebo groups.

Table 2. Repair value of melanin index in both groups

Treatment	Melanin Index Mean			
	M-2	M-4	M-8	M-12
Kel.GB	195.14 + 56.61	195.53 + 52.63	206.86 + 54.06	243.07 + 56.07
Kel. Plasebo	151.68 + 70.97	143.06 ±66,51	141.20 + 87.13	135.40 + 69.49
Signifikan	0.184	0.091	0.063	0.003

* Significant value if ip<0.05

Based on Table 2, the mean value for the second week of the GB group was 195.14 ± 56.61, which was higher than the placebo group, which was 151.68 ± 70.97 with a p-value = 0.184 (> 0.05). In the second week, there was no significant difference. Week 4, the mean value of the GB group was 195.53 ± 52.63, and the mean value of the placebo group was 143.06 ± 66.51 with p-value = 0.091 (> 0.05), showed no difference at week 4. Eighth week, there was no difference (p=0.063), with the GB group having a mean score of 206.8654.06 and the placebo group having a mean score of 141.2087.12. At week 12 there was a significant difference with p-value = 0.003 (0.05), and the mean value in the GB group was 243.07 + 56.07, while the placebo group was 135.40 + 69.49.

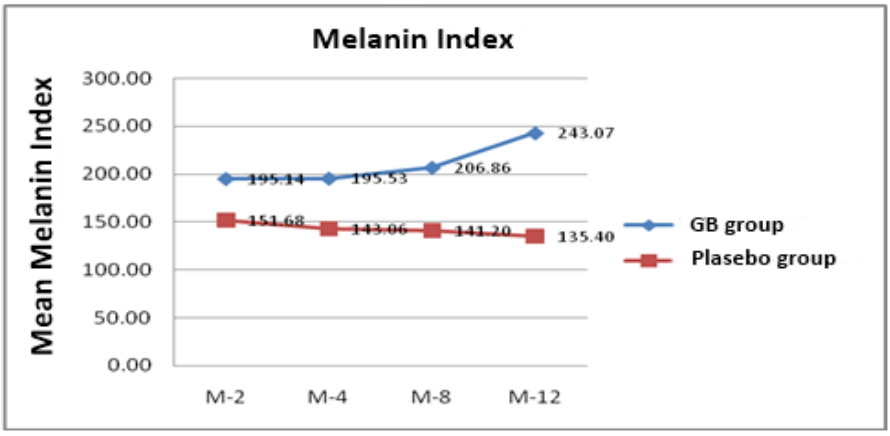

Figure 1. Changes in the mean melanin index in both groups. M2= Week 2, M4 = Week 4, M8 = Week 8, M12 = Week 12

Based on Figure 1, it shows an increase in the melanin index in the GB group, while in the placebo group there is no increase in the melanin index.

Table 3. Repair value of erythema index in both groups

Treatment	Mean Erythema Index							
	M-2		M-4		M-8		M-12	
KGroup GB	211.01 + 176.77		234.39 + 128.45		289.74 + 138.07		358.80 + 139.72	
Group Plasebo	169.06 + 49.32		163.96 ± 55.99		129.54 + 32.26		168.36 + 80.17	
p Value	0.500		0.343		0.005		0.019	

Based on Table 3, the mean erythema index for the second week of the GB group was 211.01±176.77, which was higher than the placebo group, which was 169.06±49.32 with p=0.500 (>0.05). At week 4, the mean value of the GB group was 234.39±128.45, and the mean value of the placebo group was 163.96±55.99 with p=0.343 (>0.05). The results at weeks 2 and 4 showed no difference in erythema index between the GB and placebo groups. At week eight, there was a difference between the GB and placebo groups with p = 0.005 (<0.05), the mean value in the GB group was 289.74 ± 138.07, and the placebo group was 129.54 ± 32.26. However, at week 12, the p-value for the difference between the GB and placebo groups was 0.019 (0.05), and the mean value in the GB group was 358.80 + 139.72, whereas the placebo group was 168.36 + 80.17.

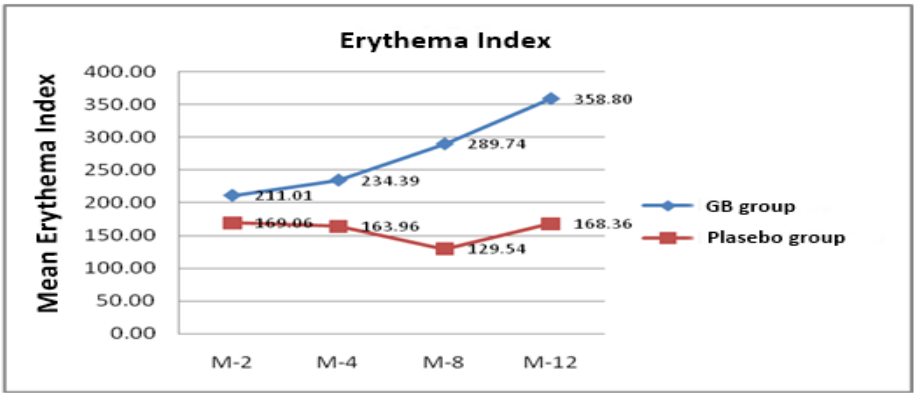

Figure 2. Changes in the mean erythema index in both groups. M2= Week 2, M4 = Week 4, M8 = Week 8, M12 = Week 12

Based on Figure 2, it was found that there was a change in the mean erythema index in the GB group and the placebo group. This shows an improvement in the erythema index in the GB and placebo groups, where the GB group experienced a higher increase than the placebo group.

Discussion

The findings of this study, as well as those of Jeong KH, Kim SK, Seo JK, et al. (2021) and de Menezes AF, Oliveira de Carvalho F, Barreto RSS, et al. (2017), indicate that vitiligo is most common in women over 36 [15,16]. Vitiligo disease most often affects 10-40 years, with a female predominance. The global prevalence of vitiligo ranges from 0.06 percent to 2.28 percent, but the distribution varies by area [17]. In addition, vitiligo can affect all ages, races, and genders [18].

Depigmentation in vitiligo frequently creates cosmetic issues, which can have serious psychological and social consequences for sufferers and their families. Even though it is asymptomatic and not life-threatening, it has an influence on the patient's quality of life. The stigma associated with vitiligo has a significant impact on patients' quality of life, making them feel disheartened and alienated.[19]. Patients can target whispering comments, hatred, contempt, or isolation from society [20]. In addition, the characteristics of the disease as a chronic disease with long-term treatment, lack of uniform effective therapy, and unpredictable disease course usually significantly affect the psyche of patients suffering from vitiligo [21].

At week 12, there was a significant difference between the GB group and the placebo group ($p = 0.003$), and the mean value in the GB group was 245.65 + 61.34, where this value reduced more than the placebo group, which was 147.00 + 68.34. These results indicate that the administration of GB extract affects decreasing the melanin index. This study supports the research conducted regarding the use of GB as adjuvant therapy for vitiligo which has proven its effectiveness by looking at the improvement in the clinical prognosis of vitiligo.

Topical or systemic antioxidant administration aims to counteract cellular oxidative stress that occurs during the development of vitiligo. For example, GB which is rich in flavonoids, polyphenols, vitamin C, CoQ10, and alpha lipoic acid works as an antioxidant. Antioxidants can counteract free radicals and prevent skin damage due to oxidation by inhibiting the decrease in keratinocyte-melanocyte crosstalk. Keratinocytes can produce growth factors such stem cell factor (SCF), endothelin (ET), and basic fibroblast growth factor (bFGF), all of which help melanocytes grow in a continuous manner during melanogenesis. In the end, GB may be able to prevent the onset of vitiligo [22–24].

Melanocytes are highly sensitive to toxic substances or injuries mediated by immune reactions to keratinocytes or fibroblasts. TRP-1 and TRP-2 (tyrosinase and tyrosinase-related proteins-1 and 2) are located on melanosomes and are necessary for melanin formation. An increase in the number of circulating CD8+ lymphocytes that are reactive to Melan-A/Mart-1 (a melanoma antigen recognized by T cells), glycoprotein 100 (gp100), and tyrosinase. Activated CD8+ cells can be found in the skin around vitiligo lesions [25,26].

According to [27], 0.25% desoximetasone cream is a class 2 topical corticosteroid class, which is strong potency and can treat vitiligo. Furthermore, desoximetasone is a potent topical corticosteroid that can activate zinc-α2 to

increase the proliferation and adhesion of melanocytes and prevent depigmentation in vitiligo [28]. In addition, dexamethasone also inhibits Langerhans cells (LC) cytotoxic to melanocytes [29]. Furthermore, it is known that GB can inhibit melanocyte apoptosis due to oxidative effects, so it can be hypothesized that GB can activate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway and protect melanocytes from oxidative damage [30].

This study showed no significant difference at week two and week 4. In contrast, at week eight and week 12, there was a significant difference between GB treatment and placebo, where GB treatment was more effective in improving erythema than with placebo. GB in vitiligo can be used as a therapy that can inhibit the expansion of the lesion and accelerate the occurrence of repigmentation [31]. Ginkgo biloba and its components have been demonstrated to lower oxidative stress in macrophages and endothelial cells, bind superoxide, and protect against UVB-induced toxicity [8]. Furthermore, GB can slow the evolution of vitiligo through an anxiolytic action, where stress contributes to the spread of vitiligo lesions. Ginkgo biloba as an antioxidant also has immunomodulatory and anti-inflammatory effects [32].

Conclusion

At week 2, week 4, and week 8, there was no significant difference in the melanin index of vitiligo patients who received GB versus those who received placebo. However, giving GB for the 12th week reduced the melanin index in patients with vitiligo significantly. There was no significant difference in the erythema index between the administration of GB and placebo at weeks two and four, indicating that there was no decrease in the erythema index in vitiligo patients. In patients with vitiligo, however, administering GB at weeks eight and twelve dramatically lowered the erythema index. The use of GB extract can influence the clinical improvement of lesions in vitiligo patients with relatively faster repigmentation than placebo therapy, therefore it can be recommended as adjuvant therapy.

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