The Effect of Ginkgo Biloba Extract on Oxidative Stress, Anti-Inflammatory and Antiapoptotic in Vitiligo Treated with Topical Desoxymethasone

Nurrachmat Mulianto[1,2],Harijono Kariosentono[1,2], Bambang Purwanto[1,3], Dono Indarto[1,4], Soetrisno Soetrisno[1]

[1]Doctoral Program of Medical Sciences, Faculty of Medicine, Universitas Sebelas Maret, Indonesia
[2]Departement of Dermatology and Venereology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[3]Departement of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[4]Biomedical Laboratory and Department of Physiology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
Email: nurrachmatdv@yahoo.com

Abstract

Vitiligo is a progressive and multifactorial condition of skin, mucosa, and hair depigmentation. Loss of functional melanocytes leads to the appearance of white macules on the skin, often affecting the lips and genitalia. The impact extends to psychological stress, decreased quality of life, and risk of psychiatric morbidity. Various therapeutic strategies have been designed to inhibit the immune response in vitiligo to reduce melanocyte damage while increasing melanocyte repopulation. There is no standardized method of evaluating treatment outcomes in vitiligo patients. Herbal medicines several studies have shown that GB also has many benefits for health and healing skin diseases, one of which is used in treating vitiligo. Therefore, this study aimed to evaluate the potential of Ginkgo biloba extract as a therapeutic supplement in enhancing the positive effects of desoxymethasone on vitiligo. Using a double-blind randomized control trial clinical trial research design, 26 subjects were divided into treatment and control groups. The control group received standard vitiligo therapy with topical desoxymethasone and placebo, while the treatment group received topical desoxymethasone plus Ginkgo biloba extract. Melanin index, VASI score, MDA, TNF-α, CD8 expression, and caspase 3 were measured before and after treatment. The results showed that the administration of Ginkgo biloba extract had a significant effect in reducing MDA, TNF-α, CD8 expression, and caspase 3 levels, and improving melanin index and erythema in vitiligo patients who received topical desoxymethasone therapy. These findings demonstrate the positive potential of Ginkgo biloba extract as an adjunct to vitiligo therapy, resulting in favorable clinical and molecular impacts in patients undergoing combination treatments.

Keywords: Ginkgo Biloba Extract, Oxidative Stress, Anti-Inflammatory, Antiapoptotic, Vitiligo Therapy.

T Vitiligo is a condition characterized by skin, mucosa, and hair depigmentation. Vitiligo is an acquired pigmentation disorder that is progressive, multifactorial, and depigmented, characterized by the appearance of white macules bordering firmly on the skin due to chronic progressive loss of functional melanocytes in the epidermis. Vitiligo can also attack hair and mucosal areas such as lips and genitalia (Iannella et al., 2016).

Depigmentation results in severe psychological stress decreased quality of life, and increased risk of morbidity in psychiatry. Depigmentation in vitiligo often causes cosmetic problems that can affect severe psychological and social conditions for patients and their families so that they have an impact on the quality of life of patients, although not to the point of being life-threatening and asymptomatic (Karia et al., 2015). Vitiligo can have a major impact on the quality of life of patients, many of whom feel depressed and negatively stigmatized because of their illness. The patient may be subjected to negative comments, antagonism, humiliation, or social isolation. The chronic nature of the disease, requiring long-term treatment, lack of uniform effective therapy, as well as the unpredictable course of the disease usually greatly affect the psyche of patients suffering from vitiligo (Parsad et al., 2003).

A literature review of 50 epidemiological studies reported by Kruger. and Schallreuter (2012) regarding the prevalence of vitiligo in various countries of the world reported data on the prevalence of vitiligo in adults, ranging from 0.06 to 2.28%, while the incidence in children was less than 2.16%. The incidence of vitiligo in Asia reported in India is 8.8% and in China is 0.09-0.19%. In a retrospective study conducted by Rahmayanti and Rahmadewi at the Skin and Genital Poly of Dr. Soetomo Hospital Surabaya in the period 2012-2014, 188 cases of vitiligo were reported, which is 0.2% of the total patient visits (Rahmayanti & Rahmadewi, 2016).

Melanocyte loss in vitiligo is caused by a complex interaction of genetic, environmental, biochemical, and immunological events. Major factors include oxidative stress and disturbances in the immune system, with H2O2 from the breakdown of tetrahydrobiopterin and mitochondria playing a key role. Oxidative stress damages DNA, lipids, and protein peroxidation and inhibits tyrosinase, contributing to melanocyte changes and apoptosis, causing melanocyte loss in vitiligo (Laddha et al., 2013).

Various therapeutic strategies have been designed to inhibit the immune response in vitiligo to reduce melanocyte damage while increasing melanocyte repopulation. Both are done by stimulating the repair of melanocyte damage in lesions by reactivating melanocyte remnants or stimulating melanocyte migration from the surrounding area or hair follicles. In general, therapy for vitiligo addresses disease stabilization and repigmentation of affected sites (Grimes &; Nashawati, 2017). Although no powerful cure for vitiligo exists, various options can give satisfactory results in most sufferers (Ortonne, 2008). Assessment of vitiligo evaluation results is recommended at 3 and/or 6 months after starting vitiligo therapy (Kubelis-Lopez et al., 2021). Until now, no standardized measurement method exists for evaluating treatment outcomes in vitiligo patients.

Herbal medicines have been used for over 1000 years and are one of the most widely used sources of new medicines as alternative medicine. One source of herbal medicines is GB (from the Ginkgoaceae family known as Maidenhair tree). GB leaf extract is widely used in herbal medicinal products, food and dietary supplements, botanical sources and medicines. Various bioactive compounds contained in GB such as terpenoids (ginkgolides, bilobalide), flavonoids (kaempferol, quercetin, isorhamnetin), bio-flavonoids (sciadopitysin, ginkgetin, isoginkgetin), and organic acids (ginkgolic acid) are expanding their use in herbal medicine (Cui et al., 2020). Several studies have shown that GB also has many benefits for health and healing skin diseases, one of which is used in treating vitiligo (Castillo et al., 2023). Parsad

argues that ginkgo has anti-inflammatory, immunomodulatory and antioxidant effects, potentially impacting the mechanism of oxidative stress in vitiligo. Ginkgo and its constituents have been shown to weaken oxidative stress in macrophages and endothelial cells, seek out superoxide, and protect it from UVB-induced toxicity.

This study tries to present innovations focusing on the effect of Ginkgo biloba extract on critical aspects such as oxidative stress, inflammation, and apoptosis in the skin of vitiligo patients undergoing desoxymethasone therapy. The main objective of this study was to evaluate the potential of Ginkgo biloba extract as a therapeutic supplement that may enhance the positive effects of desoxymethasone in the treatment of vitiligo. With a focus on these aspects, this research is expected to provide new insights and significant contributions to understanding the potential combination of herbal and conventional therapies in treating vitiligo. This approach could pave the way for developing more holistic and effective therapies for patients experiencing this skin condition.

METHODS

This study is a double blind randomized control trial clinical trial study with pretest and posttest control group, to determine the effect of oral administration of Ginkgo biloba extract on reducing serum levels of MDA, TNF-α, CD8 cells and caspase 3 on clinical improvement by knowing the decrease in VASI score and increase in melanin index in vitiligo patients treated with topical desoxymethasone. The research will be carried out at the Skin and Genital Polyclinic of Dr. Moewardi Surakarta Hospital and UNS Hospital. The serum level test was carried out at Prodia Jakarta Laboratory, and the expression test of TNF-α and caspase 3 was carried out at the Anatomical Pathology Laboratory of the Faculty of Medicine UNS. The research will be conducted in September 2021 – December 2022. This study was divided into 2 groups: first the treatment group was vitiligo patients who were given oral Ginkgo biloba treatment + topical desoxymethasone. Both control groups were vitiligo patients given an oral placebo + topical desoxymethasone.

The study's target population was vitíligo patients, and the affordable population was vitiligo patients who sought treatment at the Skin and Genital Polyclinic, Dr. Moewardi Surakarta Regional General Hospital, and UNS Hospital. The sample was selected using a consecutive sampling technique from research subjects who met the inclusion criteria and regardless of the exclusion criteria from September 2021 – December 2022. The sample size is calculated by the formula Test the Hypothesis against the Average of Two Populations.

$$n_1 = n_2 = 2\left[\frac{(Z\alpha + Z\beta)S}{(x_1 - x_2)}\right]^2$$

Z : value according to the normal curve

α : tolerable type 1 error limit = 5% = 1,960

β : tolerable type 2 error limit = 20% = 0.842

S : Standard deviation from previous research = 7 (Szczurko, 2011)

X1 - X2: differences in clinical scores that have been considered different (from VASI scores) = 12, then the sample calculation needed in this study is as many as 12 per group.

In this study, pre and post-test measurements of differences in melanin index were carried out in each GB 2 x 60 mg group and standard therapy group plus topical corticosteroids (Desoxymethasone 0.25%), along with average levels of MDA, TNF-□, CD 8, and Caspase 3. The data analysis used is a paired t-test. If the data is not normally distributed, proceed with the Wilcoxon Signed Ranks pair difference test.

3. RESULTS AND DISCUSSION

3.1 Data Normality Test

The normality test uses the Saphiro-Wilk test because the sample number is <50. If a p-value

of >0.05 is obtained, the data is normally distributed and can be analyzed using parametric tests. If a p-value of <0.05 is obtained, the data is abnormally distributed and can be analyzed using non-parametric tests.

3.2 Serum Malondialdehyde Differential Test (MDA)

The results of data analysis of the average MDA levels in the treatment group before and after treatment found a significant difference marked by a p-value of <0.05. The results of the analysis of the average MDA levels in the control group before and after treatment did not find significant differences marked by p>0.05 values (Table 1). Changes in MDA levels were higher in the treatment group than in the control group, with a p-value of <0.05 (Table 2).

Table 1. Different Test of Serum Malondialdehyde Levels

Variable	**Malondialdehyde**		**P-value**
	Before the Conduct	**After Treatment**	
Treatment Group	3.40±1.65	1.90±0.59	0,001*
Control Group	2.38±0.69	2.46±0.53	0,463

Table 2. Different Test of Changes in Serum Malondialdehyde Levels between Groups

Variable	Group		P-value
	Treatment	Control	
Malondialdehyde Changes	1.50±1.13	0.08±0.38	0.000*

3.3 TNF-α Expression Difference Test

The data analysis results of the average TNF-α levels in the treatment group before and after treatment found a significant difference marked by a p-value of <0.05. The results of the analysis of the average levels of TNF-α in the control group before and after treatment did not find a significant difference marked by a p>0.05 value (Table 3). Changes in the decrease in TNF-α levels were higher in the treatment group than in the control group, with a p-value of <0.05 (Table 4).

Table 3. TNF-α Expression Value Difference Test

Variable	**TNF-α**		**P-value**
	Before the Conduct	**After Treatment**	
Treatment Group	92.31±5.25	90.77±10.38	0,004*
Control Group	77.31±9.27	87.31±11.29	0,074

Table 4. Different Test of Changes in TNF-α Expression Values between Groups

Variable	**Group**		**P-value**
	Treatment	**Control**	
TNF-alpha changes	15.00±11.90	3.46±6.89	0,010*

3.4 Serum CD8 Differential Test

The results of data analysis of mean CD8 levels in the treatment group and control group, both before and after treatment, found a significant difference marked by a p-value of <0.05 (Table 5). Changes in the decrease in CD8 levels were higher in the treatment group than in the control group, with a p-value of <0.05 (Table 6).

Table 5. Serum CD8 Differential Test

Variable	**CD8**		**P-value**
	Before the Conduct	**After Treatment**	

Treatment Group	507,77±188.24	638,62±242,98	0,000*
Control Group	391,54±150,55	576,69±255,08	0,000*

Table 6. Test for Different Changes in CD8 Levels between Groups

Variable	Group		P-value
	Treatment	Control	
CD8 Changes	116.23±56.58	61.92±41.69	0,010*

3.5 Caspase Expression Test 3

The results of data analysis of caspase 3 expression values in the treatment and control groups, both before and after treatment, did not find significant differences marked by p-values of >0.05 (Table 7). Changes in the decrease in caspase 3 expression values were higher in the treatment group than in the control group, with p-values of <0.05 (Table 8).

Table 7. Caspase 3 Expression Value Difference Test

Variable	TNF-α		P-value
	Before the Conduct	After Treatment	
Treatment Group	88.85±12.77	90.77±13.67	0,106
Control Group	81.15±14.02	92.69±6.96	0,674

Table 8. Test of Different Changes in Caspase 3 Expression Value between Groups

Variable	Group		P-value
	Treatment	Control	
Caspase3 Changes	7.69±14.09	1.92±9.69	0,035*

3.6 Normality Test and VASI Score Difference Test, Erythema Index and Melanin Index

The results of data analysis of the average VASI score at follow-up week 0 did not find significant differences between the treatment and control groups. The average VASI score at follow-up week 1 and week 2 found significant differences between the treatment and control groups. The decrease in VASI scores was higher in the treatment group at week 1 with p = 0.044 and at week 2 with p = 0.034 (Table 9).

The results of data analysis of the average melanin index at follow-up week 0 did not find significant differences between the treatment group and the control group. The average melanin index at week 1 and week 2 follow-up found significant differences between the treatment group and the control group. The increase in melanin index was higher in the treatment group at week 1 with p = 0.029 and at week 2 with p = 0.041 (Table 9).

The results of data analysis of the degree of erythema at follow-up week 0 did not find significant differences between the treatment group and the control group. The average degree of erythema at follow-up week 1 and week 2 found significant differences between the treatment and control groups. The increase in the degree of erythema was higher in the treatment group at week 1 with p = 0.016 and at week 2 with p = 0.000 (Table 9).

Table 9. VASI Score Difference Test, Melanin Index, and Erythema Index

Variable	Group		P-value
	Ginkgo Biloba	Placebo	

Score VASI *Follow up* 0	7.20±4.78	3.92±2.60	0,081
Score VASI *Follow up* 1	7.11±4.72	3.89±2.59	0,044*
Score VASI *Follow up* 2	7.12±4.84	3.68±2.57	0,034*
Melanin *Follow up* 0	181.78±44.10	149.61±36.90	0,055
Melanin *Follow up* 1	185.08±41.11	149.12±37.80	0,029*
Melanin *Follow up* 2	186.28±28.49	157.95±37.90	0,041*
Erythema *Follow up* 0	257,72±152,71	168.22±38.88	0,057
Erythema *Follow up* 1	255,36±115,78	157.65±36.91	0,016*
Erythema *Follow up* 2	293,91±129,20	144.13±42.39	0,000*

DISCUSSION

Variable, based on retrospective data of vitiligo patients at Dr. Soetomo Surabaya Dermatovenerology polyclinic, there were 51 patients in 2012, 70 patients in 2013, 67 patients in 2014, and 50 patients in 2017. The youngest patient was 2 years old, and the oldest patient was 71 years old, with the highest age distribution between the range of 25-44 years, which amounted to 61 patients (32.3%), with the lowest distribution in the elderly (>65 years) which was only 5 patients (0.1%). (Rahmayanti and Rahmadewi, 2016)

Another study on the prevalence of vitiligo in Indonesia was conducted in a descriptive retrospective study using secondary data, namely medical records, at Dr. Cipto Mangunkusumo Hospital from January 2015 to December 2017. In 255 study subjects, 25 patients (9.8%) aged <10 years, 40 patients (15.7%) aged 11-20 years, 48 patients (18.8%) aged 21-30 years, 46 patients (18%) aged 31-40 years, 43 patients (16.9%) aged 41-50 years, 45 patients (17.6%) aged 51-65 years and 8 patients (3.1%) aged > 65 years. (Suseno and to the., 2018)

Based on this study, from 26 samples, for the age group of 12-16 years, there was 1 patient (3.8%), the age group of 17-25 years was obtained 9 patients (34.6%), the age group of 26-35 years was obtained 2 patients (7.7%), the age group of 36-45 years was obtained 4 patients (15.4%), the age group of 46-55 years was obtained 5 patients (19.2%), the age group of 55-65 years was obtained 4 patients (15.4%) and the age group over 66 years there was 1 patient (3.8%). The data can be seen in the following demographic table (Table 1).

The characteristics of the subjects in this study showed that most of the study subjects were women (69.2%), with 8 subjects belonging to the ginkgo biloba intervention group. Vitiligo is a multi-factorial dermatological disease. In this study, it was found that women dominated the research subjects more than men. The results of this study are similar to the results of Suseno et al. (2018), which shows the prevalence of vitiligo patients who seek treatment in health facilities and are willing to be given treatment is dominated by women (55.3%) (Suseno et al., 2018).

Vitiligo can affect all age ranges. Nevertheless, the disease has a bimodal pattern with early onset at the age of 7.3 years and late onset at the age of 40.5 years. In children, the appearance of vitiligo is often associated with negative psychosocial impacts and persists into adulthood. In an analysis carried out on 26 studies worldwide, the prevalence of vitiligo was 2.16% in children. In an epidemiological study conducted on children and young adults in the United States, the average age of children (ages 4-11 years) diagnosed with vitiligo was 8.6 years, while in young adults (ages 12-17 years) was 13.9 years. (Jin, Santorico and Spritz, 2020) (Rzepecki, McLellan and Elbuluk, 2018; Wu and Cohen, 2019) (Krüger and Schallreuter, 2012)(Patel et al., 2023)

4.1 Effect of Ginkgo biloba extract on malondialdehyde levels

Oxidative stress is one of the long-known etiologies of vitiligo. Epidermal oxidative stress in vitiligo patients is mediated by free radicals, which are the initial pathogenesis of melanocyte degeneration. Patients with active vitiligo show intracellular redox status imbalances, significant decreases in enzymatic and non-enzymatic antioxidants, and abnormal oxidative stress that triggers epidermal cell injury (Parsad et al., 2003). As a reactive oxygen species (ROS) parameter, Malondialdehyde increases oxidative stress. Previous research has shown that ginkgo biloba acts effectively as an antioxidant that improves oxidative stress conditions, as indicated by a significant reduction in MDA levels in vitiligo patients. Significantly high MDA levels in vitiligo subjects are caused by increased levels of H2O2 as free radicals, causing an imbalance in the number of antioxidants and oxidants, leading to oxidative stress conditions and an increase in MDA, which is the result of lipid peroxidation (Zhang et al., 2019).

Administration of ginkgo Biloba (40 mg, 3x daily) shows significant repigmentation, inhibits the course of the disease, and expands the lesion. The therapeutic effect of ginkgo biloba is related to the content of terpenoids (ginkgolides and bilobalides, flavonoids, and flavonol glycosides. Ginkgo biloba works by reducing oxidative stress in macrophages and endothelial cells; besides, ginkgo biloba has a superoxide scavenging role due to the content of ginkgolides B, C, J, and M (Parsad et al., 2003). Ginkgo biloba is rated as a potential treatment for vitiligo cases that is safe, simple, and effective (Parsad et al., 2003). In this study, adjuvant therapy of GB extract 60 mg 2 a day reduced the average level of MDA, which was statistically significant.

4.2 Effect of Ginkgo biloba extract on TNF-α expression

It is understood that prolonged overproduction of ROS will lead to inflammatory conditions and cell and tissue damage. Vitiligo is one of the inflammatory conditions with a high level of ROS. Inflammation is caused by stimulating various pro-inflammatory cytokine agents, including TNF-α. Increased levels of TNF-α in vitiligo patients are associated with one of the pathogenesis of vitiligo, namely cell adhesion defects. Matrix metalloproteinase (MMP)-9 is an enzyme that plays a role in extracellular matrix remodeling and is a protein that responds to the presence of interferon-Y and TNF-α. TNF-α triggers melanocyte detachment by destroying E-cadherin and releasing MMP-1. TNF-α also triggers intracellular attachment molecules (ICAM) to activate cytotoxic T cells that trigger the destruction of melanos. TNF-α can stimulate apoptosis within 48 hours and autophagy within 12 hours.

The role of ginkgo biloba in lowering TNF-α levels in vitiligo patients is due to its role as an anti-inflammatory (Cui et al., 2020). The hypothesis related to gingko biloba as an anti-inflammatory is related to decreased activity of TNF-α and cycloosocystases due to the production of IL-8 and vascular endothelial growth factor (VEGF) in ginkgo biloba administration. In this study, giving GB 60 mg extract 2 times a day as adjuvant therapy was found to reduce TNF-α levels, which was statistically significant.

4.3 Effect of Ginkgo biloba extract on CD8 expression

CD8 cells play a role in melanocyte damage and apoptosis in vitiligo. Infiltration of CD8 cells along with CD4 is a pathological mechanism of melanocyte breakdown. This is supported by research that examines by doing immunohistochemically painting and obtained in vitiligo lesions the cells are infiltrated CD4 and CD8. (Rahim Zar and to the., 2019) (Zhang et al., 2021)

No studies assessing the effects of CD8 on vitiligo patients under GB administration and topical desoxymethasone therapy. However, in a study of GB and CD8 in a mouse model of ulcerative colitis, the administration of GB

extract (EGB761) can suppress CD8 production. In addition, significant results of CD8 reduction were also found in schizophrenia patients who received additional therapy in the form of GB extract. This study showed a significant difference between the treatment group given adjuvant therapy GB extract 60 mg compared to the control group. This showed that GB extract effectively lowered CD8 levels in patients with vitiligo. (Zhu and to the., 2022) (Zhu et al., 2022)

4.4 Effect of Ginkgo biloba extract on Caspase expression 3

Ginkgo biloba extract is known to affect levels of caspase 3, an enzyme involved in apoptosis. Studies by Luo et al. report that Ginkgo biloba extract increases caspase 3 levels in rat hippocampus. Another study found that (Create and the., 2003) Ginkgo biloba extract can induce apoptosis by activating caspase 3 in oral cancer cells. Ginkgo biloba extract (Kim and the., 2005) EGb761 was also reported to inhibit amyloid fibril formation and caspase 3 activation. In addition, Ginkgo biloba (Create and to the., 2002). can also treat cisplatin-induced neurotoxicity in rats by modulating the APP/Aβ/P2X7R/P2Y12R and XIAP/BDNF-dependent caspase-3 apoptotic pathways. (H. Gomaa et al., 2020)

Caspase 3 has been reported to be associated with vitiligo, whereas caspase 3 expression was higher in the epidermis of vitiligo patients. Oxidative stress is known to be one of the factors causing vitiligo. The presence of oxidative stress can increase the occurrence of melanocyte degeneration and immune dysregulation. In addition, oxidative stress can cause impaired melanin synthesis, increased chemokine release from keratinocytes, autophagy disorders, and reduced sirtuin expression, which ultimately impacts melanocyte death. Oxidative stress and antioxidant therapy in vitiligo are associated with the activation of caspase 9 by apoptosome complexes that eventually divide and activate caspase effectors such as caspase 3. Apoptosis is a primary mechanism by ROS that arises due to oxidative stress that causes the destruction of melanocytes in vitiligo. (Navya, 2016) (Liu and Sun, 2022; Zhang and to the., 2022) (Tang and to the., 2019) (Bialczyk and to the., 2023)(Sastry et al., 2019)

Antioxidants can reduce or stop the damaging effects of free radicals on tissues. One antioxidant that has potential is GB, which can protect melanocytes from oxidative stress by inhibiting apoptosis due to H (Michalak, 2022) 2O2 induction and suppressing the autoimmune response by releasing heat shock protein 70. (Lu and to the., 2016) Ginkgo biloba has anti-inflammatory abilities, including reducing cyclooxygenase activity, lowering IL-8, and releasing vascular endothelial growth factor in response to TNF-α. In a double-blind, placebo-controlled clinical study conducted on 47 vitiligo patients, administration of GB 40 mg three times daily inhibited disease progression and caused repigmentation of perifacial vitiligo lesions (D. Parsad, Pandhi, and Juneja, 2003). Other prospective non-randomized studies suggest that administering GB 60 mg twice daily can reduce the severity of vitiligo disease. However, the side effects of vitiligo administration have not been studied further, especially interactions with other drugs. (Rat and to the., 2011 a) Ginkgo biloba is more risky in patients with clotting disorders. (Jamgochian, Alamgir and Rao, 2023)

4.5 Effect of Ginkgo biloba extract on VASI Score expression

There is some evidence through clinical trials that consuming 60 mg of Gingko Biloba twice a day can improve VASI and VETF scores to show improvements in lesion areas and staging vitiligo. The VASI score is a vitiligo assessment that assesses depigmentation on a scale of 0 (no depigmentation) to 100 (whole-body depigmentation). A study found that the improvement in VASI scores after 3 months of treatment was as much as 15%. (Rat and al., 2011b)

The mechanism of action of Gingko biloba is not known with certainty. However, Gingko biloba has anti-inflammatory,

immunomodulatory, and antioxidant components that can improve oxidative stress conditions, especially in macrophages and endothelial cells, and protect against UV-B toxicity in vitiligo patients. While stress and anxiety play a role in the pathogenesis of vitiligo (Kim, 2001; D Parsad, Pandhi, and Juneja, 2003), Gingko Biloba has anxiolytic effects and is beneficial in reducing anxiety in dementia patients. This study showed that giving GB 60 mg 2 times a day as adjuvant therapy against topical desoxymethasone reduced the average VASI score in vitiligo patients compared to the control group. (Hoerr, 2003)

4.6 Effect of Ginkgo biloba extract on Erymetic Index (IE)

The erymetic index is a study parameter used to assess erthemas caused by UV light. Erythema index assessment using patch test (Jemec & Johansen, 1995). Gingko biloba can prevent the expansion of lesions and accelerate repigmentation. This happens because (Wang and the., 2017) Gingko biloba has a protective effect against oxidative stress and UVB toxicity. The anxiolytic effect of (Frisoli et al., 2020) Gingko Biloba also prevents the expansion of stress-induced lesions. This study showed that administering GB 60 mg 2 times a day as adjuvant therapy against topical desoxymethasone improved the average erytheme index in vitiligo patients compared to the control group. (Wang et al., 2021)

4.7 Effect of Ginkgo biloba extract on Melanin Index (IM)

Ginkgo biloba can improve the melanin index through its bioactive content, one of which is terpenoids. Terpenoids increase blood flow and sebaceous secretion, reduce capillary hyperpermeability, improve tissue irrigation, and protect the skin. Ginkgo biloba's antioxidants are dominated by flavonoids, vitamin E, and quercetin. Ginkgo biloba has anti-inflammatory properties that are able to suppress the pathogenesis of vitiligo. Ginkgo biloba extract has been confirmed to protect neurons from oxidative stress. Meanwhile, for melanocyte protectors, Gingko biloba can effectively protect against accumulated oxidative stress, apoptosis, and lipid peroxidation (Zhang et al., 2019). The mechanism of Ginkgo biloba as a vitiligo protective agent is not yet understood; in total, vitiligo protective agents are anti-inflammatory, immunomodulator, and antioxidant. Ginkgo and its constituents have been shown to weaken oxidative stress in macrophages and endothelial cells, scavenge superoxide, and protect against UVB-induced toxicity (Szczurko et al., 2011). This study showed that giving GB 60 mg 2 times a day as adjuvant therapy against topical desoxymethasone improved the average melanin index in vitiligo patients compared to the control group.

CONCLUSION

Based on the results of this study, it can be concluded that the administration of Ginkgo biloba extract positively influences the treatment of vitiligo treated with topical desoxymethasone. First, there was a significant decrease in serum MDA levels in vitiligo patients after receiving Ginkgo biloba extract. In addition, studies have also shown that the extract plays a role in lowering serum TNF-□ levels, CD8 expression, and Caspase 3 expression levels in vitiligo patients undergoing topical desoxymethasone therapy.

In addition to positive effects on biochemical parameters, administering Ginkgo biloba extract also impacts clinical parameters. The results showed decreased VASI (Vitiligo et al.) scores in vitiligo patients who received a combination of topical desoxymethasone therapy and Ginkgo biloba extract. In addition, administration of Ginkgo biloba extract showed an increase in melanin and erythema index in vitiligo patients on topical desoxymethasone treatment. Therefore, it can be concluded that administering Ginkgo biloba extract can be an effective adjunct in improving therapeutic outcomes in vitiligo cases treated with topical desoxymethasone.

WORKS CITED

Białczyk, A. et al. (2023). 'Oxidative Stress and Potential Antioxidant Therapies in Vitiligo: A Narrative Review', Molecular Diagnosis & Therapy, 27(6), pp. 723–739. Available at: https://doi.org/10.1007/s40291-023-00672-z.

Castillo, E., González-Rosende, M. E., & Martínez-Solís, I. (2023). The use of herbal medicine in treating vitiligo: an updated review. Planta Medica, 89(05), 468-483. Available at: DOI 10.1055/a-1855-1839

Cui, N., Zhang, L., Quan, M., & Xu, J. (2020). Profile of the main bioactive compounds and in vitro biological activity of different solvent extracts from Ginkgo biloba exocarp. RSC advances, 10(73), 45105-45111. Available at: 10.1039/D0RA09490K

Frisoli, M.L., Essien, K. and Harris, J.E. (2020) 'Vitiligo: Mechanisms of Pathogenesis and Treatment.', Annual review of immunology, 38, pp. 621–648. Available at: https://doi.org/10.1146/annurev-immunol-100919-023531.

Grimes, P. E., & Nashawati, R. (2017). Depigmentation therapies for vitiligo. Dermatologic clinics, 35(2), 219-227. Available at: https://doi.org/10.1016/j.det.2016.11.010

H. Gomaa, D. et al. (2020) 'Ginkgo biloba Alleviates Cisplatin-Mediated Neurotoxicity in Rats via Modulating APP/Aß/P2X7R/P2Y12R and XIAP/BDNF-Dependent Caspase-3 Apoptotic Pathway', Applied Sciences, 10(14), p. 4786. Available at: https://doi.org/10.3390/app10144786.

Hoerr, R. (2003) 'Behavioural and psychological symptoms of dementia (BPSD): effects of EGb 761.', Pharmacopsychiatry, 36 Suppl 1, pp. S56-61. Available at: https://doi.org/10.1055/s-2003-40451.

Iannella, G., Greco, A., Didona, D., Didona, B., Granata, G., Manno, A.,... & Magliulo, G. (2016). Vitiligo: pathogenesis, clinical variants and treatment approaches. Autoimmunity reviews, 15(4), 335-343. Available at: https://doi.org/10.1016/j.autrev.2015.12.006

Jamgochian, M., Alamgir, M. and Rao, B. (2023) 'Diet in Dermatology: Review of Diet's Influence on the Conditions of Rosacea, Hidradenitis Suppurativa, Herpes Labialis, and Vitiligo', American Journal of Lifestyle Medicine, 17(1), pp. 152–160. Available at: https://doi.org/10.1177/15598276211026592.

Jemec, G.B.E. and Johansen, J.D. (1995) 'Erythema-index of clinical patch test reactions', Skin Research and Technology, 1(1), pp. 26–29. Available at: https://doi.org/10.1111/j.1600-0846.1995.tb00010.x.

Jin, Y., Santorico, S.A. and Spritz, R.A. (2020) 'Pediatric to Adult Shift in Vitiligo Onset Suggests Altered Environmental Triggering', Journal of Investigative Dermatology, 140(1), pp. 241-243.e4. Available at: https://doi.org/10.1016/j.jid.2019.06.131.

Kubelis López, D. E., Zapata Salazar, N. A., Said Fernández, S. L., Sánchez Domínguez, C. N., Salinas Santander, M. A., Martínez Rodríguez, H. G.,... & Ocampo Candiani, J. (2021). Updates and new medical treatments for vitiligo. Experimental and therapeutic medicine, 22(2), 1-11. Available at: https://doi.org/10.3892/etm.2021.10229

Karia, S., Sousa, A. D., Shah, N., Sonavane, S., & Bharati, A. (2015). Psychological morbidity in vitiligo-A case control study. Pigmentary Disorders, 2(170), 2376-0427. Available at: http://dx.doi.org/10.4172/2376-0427.1000170

Kim, K.-S. et al. (2005) 'Ginkgo biloba extract (EGb 761) induces apoptosis by the activation of caspase-3 in oral cavity cancer cells', Oral Oncology, 41(4), pp. 383–389. Available at: https://doi.org/10.1016/j.oraloncology.2004.09.013.

Kim, S.J. (2001) 'Effect of biflavones of Ginkgo biloba against UVB-induced cytotoxicity in vitro.', The Journal of dermatology, 28(4), pp. 193–9. Krüger, C. and Schallreuter, K.U. (2012) 'A review of the worldwide prevalence of vitiligo in children/adolescents and adults', International Journal of Dermatology, 51(10), pp. 1206–1212. Available at: https://doi.org/10.1111/j.1365-4632.2011.05377.x.

Laddha, N. C., Dwivedi, M., Mansuri, M. S., Gani, A. R., Ansarullah, M., Ramachandran, A. V.,... & Begum, R. (2013). Vitiligo: interplay between oxidative stress and immune system. Experimental Dermatology, 22(4), 245-250. Available at: https://doi.org/10.1111/exd.12103

Lu, L. et al. (2016) 'Bilobalide protection of normal human melanocytes from hydrogen peroxide-induced oxidative damage via promotion of antioxidase expression and inhibition of endoplasmic reticulum stress', Clinical and Experimental Dermatology, 41(1), pp. 64–73. Available at: https://doi.org/10.1111/ced.12664.

Luo, C. et al. (2003) 'Ginkgo biloba leaf extract enhances levels of caspase-3 and amyloid precursor protein in normal rat hippocampus.', Acta pharmacologica Sinica, 24(2), pp. 152–6.

Lyu, C. and Sun, Y. (2022) 'Immunometabolism in the pathogenesis of vitiligo', Frontiers in Immunology, 13. Available at: https://doi.org/10.3389/fimmu.2022.1055958.
Michalak, M. (2022) 'Plant-Derived Antioxidants: Significance in Skin Health and the Ageing Process', International Journal of Molecular Sciences, 23(2), p. 585. Available at: https://doi.org/10.3390/ijms23020585.
Navya, Ch.N. (2016) 'Formulation and evaluation of soyabean hair oil for cellular hair maturation of epidermi', Journal of Cosmetology & Trichology, 02(03). Available at: https://doi.org/10.4172/2471-9323.C1.003.
Parsad, D., Pandhi, R. and Juneja, A. (2003) 'Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo', Clinical and Experimental Dermatology, 28(3), pp. 285–287. Available at: https://doi.org/10.1046/j.1365-2230.2003.01207.x.
Patel, R. et al. (2023) 'Prevalence of Vitiligo among Children and Adolescents in the United States.', Dermatology (Basel, Switzerland), 239(2), pp. 227–234. Rahim Zar, A. et al. (2019) 'Pathogenesis and the emerging Therapy of Vitiligo', Archives of Clinical and Biomedical Research, 03(06). Available at: https://doi.org/10.26502/acbr.50170080.
Rahmayanti, N.D. and Rahmadewi, R. (2016) 'A Retrospective Study: The Profile of New Patient with Vitiligo.', Berkala Ilmu Kesehatan Kulit dan Kelamin, 28(2), pp. 130–136.
Rzepecki, A.K., McLellan, B.N. and Elbuluk, N. (2018) 'Beyond Traditional Treatment: The Importance of Psychosocial Therapy in Vitiligo.', Journal of drugs in dermatology : JDD, 17(6), pp. 688–691.
Sastry, K.S. et al. (2019) 'RNA-seq Reveals Dysregulation of Novel Melanocyte Genes upon Oxidative Stress: Implications in Vitiligo Pathogenesis', Oxidative Medicine and Cellular Longevity, 2019, pp. 1–15. Available at: https://doi.org/10.1155/2019/2841814.
Suseno, L.S. et al. (2018) 'Profile of vitiligo patients and distribution of narrowband-UVB therapy at dr. Cipto Mangunkusumo General Hospital', Journal of General-Procedural Dermatology & Venereology Indonesia, 3(2), pp. 29–33. Available at: https://doi.org/10.19100/jdvi.v3i1.132.
Szczurko, O. et al. (2011a) 'Ginkgo biloba for the treatment of vitilgo vulgaris: an open label pilot clinical trial', BMC Complementary and Alternative Medicine, 11(1), p. 21. Available at: https://doi.org/10.1186/1472-6882-11-21.
Szczurko, O. et al. (2011b) 'Ginkgo biloba for the treatment of vitilgo vulgaris: an open label pilot clinical trial.', BMC complementary and alternative medicine, 11, p. 21. Tang, D. et al. (2019) 'The molecular machinery of regulated cell death', Cell Research, 29(5), pp. 347–364. Available at: https://doi.org/10.1038/s41422-019-0164-5.
Wang, J.Y. et al. (2017) 'Network pharmacological mechanisms of Vernonia anthelmintica (L.) in the treatment of vitiligo: Isorhamnetin induction of melanogenesis via up-regulation of melanin-biosynthetic genes.', BMC systems biology, 11(1), p. 103. Available at: https://doi.org/10.1186/s12918-017-0486-1.
Wang, K. et al. (2021) 'Ginkgo biloba extract protects human neuroblastoma SH SY5Y cells against oxidative glutamate toxicity by activating redoxosome p66Shc', Experimental and Therapeutic Medicine, 22(3), p. 951. Available at: https://doi.org/10.3892/etm.2021.10383.
Wu, J.H. and Cohen, B.A. (2019) 'The stigma of skin disease', Current Opinion in Pediatrics, 31(4), pp. 509–514. Available at: https://doi.org/10.1097/MOP.0000000000000792.
Zhang, B. et al. (2021) 'The effects of 308-nm excimer laser on the infiltration of CD4+, CD8+ T-cells, and regulatory T cells in the lesional skin of patients at active and stable stages of nonsegmental vitiligo', Journal of Dermatological Treatment, 32(6), pp. 580–584. Available at: https://doi.org/10.1080/09546634.2019.1687825.
Zhang, J. et al. (2022) 'Research Progress on Targeted Antioxidant Therapy and Vitiligo', Oxidative Medicine and Cellular Longevity, 2022, pp. 1–10. Available at: https://doi.org/10.1155/2022/1821780.
Zhang, S., Yi, X., Su, X., Jian, Z., Cui, T., Guo, S.,... & Xiao, Q. (2019). Ginkgo biloba extract protects human melanocytes from H2O2-induced oxidative stress by activating Nrf2. Journal of Cellular and Molecular Medicine, 23(8), 5193-5199. Available at: https://doi.org/10.1111/jcmm.14393
Zhu, Z. et al. (2022) 'Efficacy of Ginkgo biloba Extract Combined with Hormones in the Treatment of Sudden Deafness and Its Effect on the Reactivity of Peripheral Blood T Cell Subsets', Computational and Mathematical Methods in Medicine, 2022, pp. 1–10. Available at: https://doi.org/10.1155/2022/2903808.