Combination of topical and oral glutathione as a skin-whitening agent: a double-blind randomized controlled clinical trial

by Anis Irawan Anwar

Submission date: 04-Apr-2022 07:52PM (UTC+0700)
Submission ID: 1801345956
File name: a_Double_Blind_Randomized_Controlled_Clinical_Trial_-_Copy1.pdf (250.25K)
Word count: 3806
Character count: 20018

International Journal of Dermatology

Pharmacology and Therapeutics

Combination of topical and oral glutathione as a skin-whitening agent: a double-blind randomized controlled clinical trial

Siswanto Wahab, MD, PhD, Anis I. Anwar, MD, PhD, Andi N. Zainuddin, MD, Emma N. Hutabarat, MD, Asvina A. Anwar, MD and Ivan Kurniadi, MD, BmedSci (Hons)

Department of Dermatology and Venereology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

Correspondence
Siswanto Wahab, MD, PHD
Department of Dermatology and Venereology
Faculty of Medicine
Hasanuddin University
Jl. Perintis Kemerdekaan Km. 10
Makassar
South Sulawesi
Indonesia
E-mail: siswantowahab64@gmail.com

Conflict of interest: None.

Funding source: None.

doi: 10.1111/ijd.15573

Abstract

Background The antimelanogenesis effect of topical and oral glutathione has been shown in several in vitro and clinical studies. However, whether combination of topical and oral glutathione is superior to topical or oral monotherapy is unknown. This study aimed to compare the skin-whitening effect of topical and oral glutathione combination therapy against topical and oral monotherapy.

Methods This double-blind randomized controlled study was done on 46 participants who were divided into two equal groups. Each group received oral placebo and oral glutathione, respectively. All participants were also instructed to apply topical placebo and glutathione to each facial side, respectively. Colorimeter examination was done biweekly using mexameter and chromameter for 8 weeks. One-way ANOVA test was used to compare the results of all groups.

Results The combination group showed significantly lower melanin index (MI) and L* score to placebo ($P < 0.05$). The mean MI and L* score of the combination group were the highest of all groups. Statistical significance of difference in L* score was reached when the combination group was compared to the oral placebo and topical glutathione group ($P < 0.05$).

Conclusion This study showed that topical and oral glutathione were effective skin-lightening agents. Furthermore, combination of topical and oral glutathione might be superior to monotherapy.

Introduction

Fair and flawless skin is often the standard of beauty in many countries and cultures, especially in people with skin of color, making the skin-whitening products market a vast growing market which continues to expand.[1] This desire has led to a plethora of skin-whitening products, both in topical and oral preparations that flood the market.

In terms of topical agent, hydroquinone is still regarded the gold standard treatment.[2,3] However, its use has been associated with adverse effects such as irritation, leukoderma, and malignancy,[4] resulting in its ban as a cosmetic agent in Europe, the Unites States of America, and some Asian countries.[5] Oral tranexamic acid, on the other hand, is popular among those who aim for a generalized whitening effect. However, the long-term safety profile of this plasmin inhibitor is yet to be clearly elucidated.[6] Thus, new agents with a good safety profile continue to need to be developed.

Glutathione is a tripeptide that consists of cysteine, glutamate, and glutamine that is well-known for its antioxidant effect.[7] It protects cells from oxidative stress and damage such as drug and hydrogen peroxide detoxification.[8] In addition, in vitro studies have shown that glutathione alters melanogenesis[9] through several proposed mechanisms such as increased pheomelanin production, tyrosinase inhibitory effect, and indirectly through its antioxidative effects.[10,11]

Despite the popular use of this agent in countries such as Singapore, Thailand, Malaysia, and Indonesia in various preparations, the evidence is still limited. To our knowledge, only two and three studies are available on topical[12,13] and oral[6,8,14] preparations, respectively. Furthermore, the efficacy of a combination of topical and oral therapy, despite its widely advertised use, has never been assessed and compared to monotherapy.

This study aimed to assess the whitening effect of a combination of topical and oral glutathione on otherwise healthy, unaffected skin and how it compared with monotherapy and placebo.

Methods

Study design

This double-blind randomized controlled clinical trial was done at Hasanuddin University Hospital, Makassar, South Sulawesi, Indonesia, between January and March 2020.

Participants

Healthy females aged 25–50 years with Fitzpatrick skin type IV and V were included in this study. Subjects with a history of skin cancer, especially melanoma, glutathione intake in the past 1 month, presence of dermatoses on the face, pregnancy, those who smoked, and breastfeeding mothers were excluded from this study. In addition, subjects were required to work indoors or avoid intense sun exposure for a minimum of 8 hours per day.

Study protocol

Subjects were equally divided into two groups and were given oral placebo and oral glutathione. Participants in each group were then instructed to apply topical glutathione and placebo on the right and left cheeks in a blinded manner. This divided the participants into four groups: topical and oral placebo (group 1), topical glutathione and oral placebo (group 2), topical placebo and oral glutathione (group 3), and topical and oral glutathione (group 4). The oral preparation contained 600 mg glutathione, 50 mg alpha lipoic acid, and 4 mg zinc picolinate while the topical preparation was in a serum preparation containing 2% glutathione and vitamin C. The oral and topical placebo preparations were indistinguishable from those containing active ingredients.

The oral preparations were taken twice daily in the morning and evening with a 12 -hour interval, while each serum was applied on the right and left sides of the face, respectively, in the morning and evening after face cleansing for a total of 8 weeks. Participants were instructed to avoid consuming any supplements or applying other topical preparations except for an SPF 35 broad-spectrum sunscreen in the morning, which was applied one minute after the serum.

The skin brightness assessment was done at baseline and every 2 weeks for 8 weeks (T0, T2, T4, T6, and T8) using Chromameter (Konica Minolta, Tokyo, Japan) and Mexameter® MX 16 (Courage+Khazaka, Electronic GmbH, Cologne, Germany). Adverse events were recorded at each meeting.

This study was done after ethical clearance had been obtained from the local ethical board committee. The protocols were done in line with the Declaration of Helsinki guideline.

Quantitative skin color examination

Mexameter

The probe of this device emitted light at 568 (green), 660 (red), and 880 (infrared) nm wavelengths. A computerized assessment of the reflected light resulted in melanin index (MI), which corresponded with the skin melanin level.[15]

Chromameter

The fundamental principle of this device is to emit three wavelengths of 450, 560, and 600 nm to the skin surface which, upon reflection, were absorbed by the probe of the device and produced three scores, one of which was the L* score, which represented skin brightness and ranged from 0 (black) to 100 (white).[16]

Safety profile assessment

Participants were asked to report the occurrence of erythema, stinging sensation, pruritus, or any discomfort experienced during the study. In case of severe effects, participants were encouraged to contact the researchers anytime.

Statistical analysis

Demographic characteristics for both groups were described descriptively by calculating mean, standard deviation, and percentage. One-way ANOVA test was conducted to assess intergroup difference in each follow-up period. The MI and L* scores of each group were plotted into graphs to visualize the data pattern. All analyses were performed using SPSS version 22 (SPSS Inc. Chicago, IL, USA).

Result

Demographic data

A total of 46 participants took part in this study and were randomly divided into two groups, each containing 23 participants (Table 1). There was no significant difference in age nor Fitzpatrick skin type between both groups.

Efficacy analysis

Melanin index analyses of all groups at baseline and each follow-up meeting were expressed in Table 2. After 8 weeks of treatment, the highest MI was shown by group 1, while the

Table 1 Demographic characteristics

Characteristic	Oral placebo	Oral glutathione
Age (years)[a]		
Mean ± SD	29.7 ± 8.3	30.2 ± 7.8
Range	20–44	20–43
Gender (%)		
Male	0 (0)	0 (0)
Female	23 (100)	23 (100)
Fitzpatrick skin type (%)[a]		
Type IV	13 (56.5)	10 (43.5)
Type V	10 (43.5)	13 (56.5)

[a]No significant difference between both groups ($P > 0.05$).

Table 2 Melanin index of each group

	Group 1 Topical and oral placebo	Group 2 Topical glutathione and oral placebo	Group 3 Topical placebo and oral glutathione	Group 4 Topical and oral glutathione	*P*-value[a]
Baseline	378.83 ± 85.33	370.87 ± 85.00	353.87 ± 80.44	347.09 ± 78.49	0.535
Week 2	377.57 ± 86.05	365.09 ± 87.74	354.78 ± 71.51	335.57 ± 72.44	0.338
Week 4	382.57 ± 87.29	359.13 ± 92.40	345.30 ± 77.97	320.04 ± 74.27	0.086
Week 6	385.65 ± 85.70	343.87 ± 92.81	339.04 ± 91.25	319.00 ± 78.01	0.076
Week 8	385.69 ± 94.38	330.69 ± 87.90	347.00 ± 81.77	314.35 ± 70.13	**0.033**

Bold values represent statistically significant, $P < 0.05$.
[a]Significant if $P < 0.05$ (one-way ANOVA).

Table 3 Melanin index comparison between all groups at week 8

	Group 1 Topical and oral placebo	Group 2 Topical glutathione and oral placebo	Group 3 Topical placebo and oral glutathione	Group 4 Topical and oral glutathione
Group 1 Topical and oral placebo		**0.029**	0.122	**0.005**
Group 2 Topical glutathione and oral placebo			0.512	0.511
Group 3 Topical placebo and oral glutathione				0.191
Group 4 Topical and oral glutathione				

Bold values represent statistically significant, $P < 0.05$.

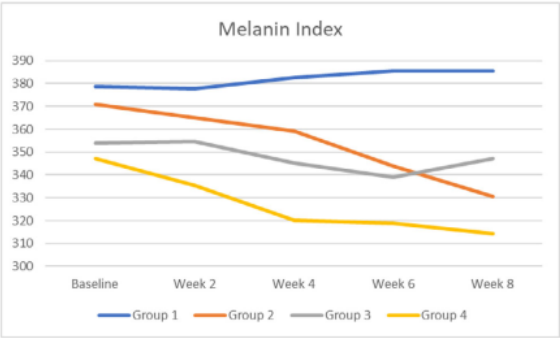

Figure 1 Melanin index in each group during the study

lowest MI was shown by group 4. One-way ANOVA analysis showed no significant MI difference among groups at baseline and a significant difference at week 8 ($P < 0.05$). Post-hoc analysis at week 8 showed significant difference between group 1 and group 2 and between group 1 and group 4 ($P < 0.05$) (Table 3). Figure 1 shows the trend of MI change during 8 weeks of treatment in all groups. Group 1 showed a stable trend, while all treatment groups showed a decreasing trend, with the lowest result shown by group 4.

The L* scores of all groups at baseline and each follow-up were expressed in Table 4. At the end of the study, the highest and lowest L* scores were shown by group 4 and group 1,

Table 4 L* score of each group

	Group 1 Topical and oral placebo	Group 2 Topical glutathione and oral placebo	Group 3 Topical placebo and oral glutathione	Group 4 Topical and oral glutathione	*P*-value[a]
Baseline	47.68 ± 3.15	48.13 ± 4.08	49.87 ± 3.88	49.78 ± 3.31	0.092
Week 2	47.71 ± 3.45	47.83 ± 5.12	49.03 ± 3.26	49.62 ± 3.31	0.269
Week 4	46.85 ± 3.52	48.20 ± 4.61	49.65 ± 6.37	50.30 ± 3.12	0.057
Week 6	46.78 ± 3.54	48.59 ± 4.73	49.68 ± 3.99	51.01 ± 3.29	**0.040**
Week 8	46.39 ± 2.99	49.07 ± 4.42	50.16 ± 3.38	51.21 ± 3.35	**0.001**

Bold values represent statistically significant, $P < 0.05$.
[a]Significant if $P < 0.05$ (one-way ANOVA).

Table 5 Post-hoc analysis of L* score comparison among all groups at week 8

	Group 1 Topical and oral placebo	Group 2 Topical glutathione and oral placebo	Group 3 Topical placebo and oral glutathione	Group 4 Topical and oral glutathione
Group 1 Topical and oral placebo		**0.046**	**0.003**	**0.000**
Group 2 Topical glutathione and oral placebo			0.301	**0.045**
Group 3 Topical placebo and oral glutathione				0.324
Group 4 Topical and oral glutathione				

Bold values represent statistically significant, $P < 0.05$.

respectively. One-way ANOVA analysis showed no significant difference of L* score among groups at baseline ($P > 0.05$). A significant difference started to appear at week 6 and was maintained at week 8 ($P < 0.05$). Post-hoc analysis at week 8 showed significant difference between group 1 and groups 2, 3, and 4 and between group 2 and group 4 ($P < 0.05$) (Table 5). All treatment groups showed a consistent increasing pattern throughout the study, while the placebo group showed a decreasing pattern (Fig. 2).

Tolerability

Erythema, edema, stinging, and pruritus were not observed nor reported by any of the participants. No systemic side effects were observed nor complained during this study.

Discussion

This study evaluated the efficacy of topical and oral glutathione and combination of both in improving skin brightness of healthy Indonesian women. Both topical and oral glutathione were effective skin-lightening agents and that combination of both agents might result in a superior outcome compared to monotherapy.

Analysis of the results showed that, compared to placebo, the administration of glutathione, through topical, oral, or combination of both methods, resulted in a significant MI and L* score improvement after 8 weeks of treatment ($P < 0.05$). In contrast with the placebo group, all treatment groups also showed consistently decreasing and increasing trend of the MI and L* score values, respectively, throughout the study. An exception was shown by MI of group 3 (topical placebo and oral glutathione), which did not show a statistically significant difference compared to placebo. However, the mean MI at week 8 of group 3 was considerably higher to that of placebo. These results were in line with previous studies on topical[12,13] or oral[6,8,14] monotherapy, which all showed a consistent skin-lightening effect. An exception was shown by the study conducted by Weschawalit *et al*[8] which did not demonstrate beneficial effects of oral glutathione, both in reduced and oxidized form, in most of the assessed parameters.[8] However, this result might be attributed to the significantly lower dose of glutathione administered (250 mg/day) as compared to the other two studies by Handog[14] and Arjinpathana,[6] which administered 500 mg glutathione.

To our knowledge, studies assessing the skin-lightening effect of oral and topical glutathione combination therapy are yet to be available. We attempted to take a step further by

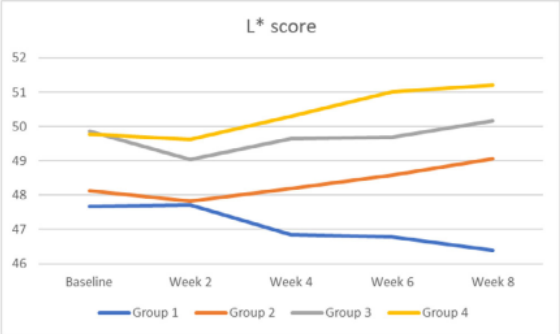

Figure 2 L* score of each group during the study

comparing the efficacy of combination topical and oral glutathione to monotherapy using two devices, the chromameter and mexameter. Our results suggested that a combination of oral and topical glutathione showed the most consistent result when compared to oral and topical glutathione monotherapy. The combination treatment group showed the lowest and highest MI and L* scores, respectively, and significantly higher L* score compared to topical glutathione monotherapy after 8 weeks of treatment. Although based on L* score analysis, oral glutathione monotherapy seemed to show a comparable efficacy to combination therapy, MI analysis showed less superior result of oral glutathione monotherapy when compared to combination treatment, where oral glutathione monotherapy did not reach statistical significance when compared to placebo. Taken together, our results indicated that combination of both routes of administration might be superior to monotherapy. In addition, the use of two different colorimeters further strengthened and affirmed our findings.

The mechanism of skin-lightening effect of glutathione has been well documented and described. It has long been known as an antioxidant[7] and mediates its effect by scavenging free radicals during hydrogen peroxide and lipid peroxide detoxification process.[17] Its melanogenesis inhibition activity is thought to occur through tyrosinase inhibition, both directly by chelating copper ions on the active site of tyrosinase and indirectly through the antioxidative property described above and by shifting eumelanin, the darker pigment, to pheomelanin, the lighter pigment, production.[14,18] The production of reactive oxygen species and free radicals has been known to induce tyrosinase activity; glutathione has been shown to suppress reactive oxygen species (ROS) production, thus preventing melanogenesis.[14,19] Production shift to pheomelanin occurs as a result of spontaneous conjugation of glutathione and cysteine (one of the components of the glutathione tripeptide) with L-dopaquinone to produce glutathionyldopa and cysteinyldopa, respectively, which are precursors for pheomelanin.[10,20]

Although some studies were skeptical about the effectivity of oral glutathione due to its reported low bioavailability based on whole blood examination,[21] a study has shown that glutathione can be detected in its protein-bound form in human blood following oral administration.[22] This finding is further supported by the above-mentioned clinical trials. On the other hand, clinical efficacy of topical administration is more well-established as topical preparation may directly penetrate the skin and exert its effect on melanocytes.[13] Thus, based on the results of this study, we believe that the skin-whitening effect of combined topical and oral glutathione may be superior to topical or oral glutathione monotherapy.

Although the colorimeter results improvement in this study might not seem to be clinically apparent, it has to be emphasized that the findings of this study were neither to confirm nor promote the use of glutathione as a skin-whitening agent but rather provide additional supportive data on the melanogenesis inhibitory effect of glutathione. The seemingly not-so-intense difference might occur as it is more challenging to drastically change the facultative skin color and hence this difference might have not been clinically obvious in the course of our study. To the very least, if the clinical effect of glutathione was not found to be clinically significant, it still can be considered as an adjuvant or alternative therapy where conventional therapy does not result in an expected outcome or a more optimal result is desired.

Future studies with larger scale and longer follow-up duration that incorporate patient perception are needed to better delineate the efficacy and safety of glutathione. In addition, the presence of other antioxidants in the ingredient might have contributed in the observed effect through ROS scavenging and the possible tyrosinase inhibitory activity. However, this scenario might better suit daily clinical practice setting where glutathione is commonly combined with other supporting agents and we believe these data will be valuable for daily practice.

Conclusion

This study showed that topical and oral glutathione were promising skin-lightening agents. Furthermore, combination of topical and oral glutathione might be superior to monotherapy alone.

Acknowledgments

The authors thank all subjects for their participation in this study. The serum and oral preparations were manufactured by PT. LipWih SynergyLab, Indonesia.

References

1 Shroff H, Diedrichs PC, Craddock N. Skin color, cultural capital, and beauty products: an investigation of the use of skin fairness products in Mumbai, India. *Front Public Health* 2018; **5**: 365.
2 Haddad AL, Matos LF, Brunstein F, *et al.* A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone vs. placebo in the treatment of melasma. *Int J Dermatol* 2003; **42**: 153–156.
3 Gupta AK, Gover MD, Nouri K, *et al.* The treatment of melasma: a review of clinical trials. *J Am Acad Dermatol* 2006; **55**: 1048–1065.
4 Gillbro J, Olsson M. The melanogenesis and mechanisms of skin-lightening agents–existing and new approaches. *Int J Cosmet Sci* 2011; **33**: 210–221.
5 Desmedt B, Courselle P, De Beer JO, *et al.* Overview of skin whitening agents with an insight into the illegal cosmetic market in Europe. *J Eur Acad Dermatol Venereol* 2016; **30**: 943–950.
6 Arjinpathana N, Asawanonda P. Glutathione as an oral whitening agent: a randomized, double-blind, placebo-controlled study. *J Dermatol Treat* 2012; **23**: 97–102.
7 Exner R, Wessner B, Manhart N, Roth E. Therapeutic potential of glutathione. *Wien Klin Wochenschr* 2000; **112**: 610.
8 Weschawalit S, Thongthip S, Phutrakool P, Asawanonda P. Glutathione and its antiaging and antimelanogenic effects. *Clin Cosmet Investig Dermatol* 2017; **10**: 147.
9 Imokawa G. Analysis of initial melanogenesis including tyrosinase transfer and melanosome differentiation though interrupted melanization by glutathione. *J Invest Dermatol* 1989; **93**: 100–107.
10 Villarama C, Maibach H. Glutathione as a depigmenting agent: an overview. *Int J Cosmet Sci* 2005; **27**: 147–153.
11 Nakajima H, Nagata T, Koga S, *et al.* Reduced glutathione disrupts the intracellular trafficking of tyrosinase and tyrosinase-related protein-1 but not dopachrome tautomerase and Pmel17 to melanosomes, which results in the attenuation of melanization. *Arch Dermatol* 2014; **306**: 37–49.
12 Etnawati K, Adiwinarni DR, Susetiati DA, *et al.* The efficacy of skin care products containing glutathione in delivering skin lightening in Indonesian women. *Dermatol Rep* 2019. https://doi.org/10.4081/dr.2019.8013.
13 Watanabe F, Hashizume E, Chan GP, *et al.* Skin-whitening and skin-condition-improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women. *Clin Cosmet Investig Dermatol* 2014; **7**: 267–274.
14 Handog EB, Datuin MS, Singzon IA. An open-label, single-arm trial of the safety and efficacy of a novel preparation of glutathione as a skin-lightening agent in Filipino women. *Int J Dermatol* 2016; **55**: 153–157.
15 Baquié M, Kasraee B. Discrimination between cutaneous pigmentation and erythema: comparison of the skin colorimeters Dermacatch and Mexameter. *Skin Res Tech* 2014; **20**: 218–227.
16 Clarys P, Alewaeters K, Lambrecht R, *et al.* Skin color measurements: comparison between three instruments: the Chromameter®, the DermaSpectrometer® and the Mexameter®. *Skin Res Tech* 2000; **6**: 230–238.
17 Lu SC. Regulation of glutathione synthesis. *Mol Aspects Med* 2009; **30**(1–2): 42–59.
18 Sonthalia S, Jha AK, Lallas A, *et al.* Glutathione for skin lightening: a regnant myth or evidence-based verity? *Dermatol Pract Concept* 2018; **8**: 15–21.
19 Hong S-Y, Gil H-W, Yang J-O, *et al.* Pharmacokinetics of glutathione and its metabolites in normal subjects. *J Korean Med Sci* 2005; **20**: 721–726.
20 Ebanks JP, Wickett RR, Boissy RE. Mechanisms regulating skin pigmentation: the rise and fall of complexion coloration. *Int J Mol Sci* 2009; **10**: 4066–4087.
21 Witschi A, Reddy S, Stofer B, *et al.* The systemic availability of oral glutathione. *Eur J Clin Pharmacol* 1992; **43**: 667–669.
22 Park EY, Shimura N, Konishi T, *et al.* Increase in the protein-bound form of glutathione in human blood after the oral administration of glutathione. *J Agric Food Chem* 2014; **62**: 6183–6189.

Combination of topical and oral glutathione as a skin-whitening agent: a double-blind randomized controlled clinical trial

ORIGINALITY REPORT

15%	12%	9%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.amedeo.com Internet Source	2%
2	Submitted to University of Glamorgan Student Paper	2%
3	www.mdpi.com Internet Source	1%
4	www.koreascience.or.kr Internet Source	1%
5	"Agache's Measuring the Skin", Springer Science and Business Media LLC, 2017 Publication	1%
6	www.tjogonline.com Internet Source	1%
7	Anis I. Anwar, Siswanto Wahab, Widya Widita, Airin R. Nurdin, Suci Budhiani, Arifin Seweng. "Randomized control trial outcomes of tranexamic acid combination serum as a	1%

depigmenting agent for the use in healthy individuals", Dermatologic Therapy, 2019
Publication

8	Submitted to University of Wisconsin, La Crosse Student Paper	1 %
9	Submitted to Marquette University Student Paper	1 %
10	downloads.hindawi.com Internet Source	<1 %
11	pb.merck.de Internet Source	<1 %
12	www.panafrican-med-journal.com Internet Source	<1 %
13	Submitted to Georgia Gwinnett College Student Paper	<1 %
14	onlinelibrary.wiley.com Internet Source	<1 %
15	Khalid M. AlGhamdi, Ashok Kumar, Ammar C. AL‐Rikabi, Mohammed Mubarak. "Safety and efficacy of parenteral glutathione as a promising skin lightening agent: A controlled assessor blinded pharmacohistologic and ultrastructural study in an animal model", Dermatologic Therapy, 2020 Publication	<1 %

16	akademik.unsoed.ac.id Internet Source	<1 %
17	core.ac.uk Internet Source	<1 %
18	ijdvl.com Internet Source	<1 %
19	Ibrahim, Zeinab A, Shereen F Gheida, Gamal M El Maghraby, and Zeinab E Farag. "Evaluation of the efficacy and safety of combinations of hydroquinone, glycolic acid, and hyaluronic acid in the treatment of melasma", Journal of Cosmetic Dermatology, 2015. Publication	<1 %
20	Joël Duperray, Renaud Sergheraert, Kunyanatt Chalothorn, Preeyanuch Tachalerdmanee, Fabrice Perin. "The effects of the oral supplementation of L - Cystine associated with reduced L - Glutathione - GSH on human skin pigmentation: a randomized, double - blinded, benchmark - and placebo - controlled clinical trial", Journal of Cosmetic Dermatology, 2021 Publication	<1 %
21	Salem, Ahmed, Hend Gamil, Ali Ramadan, Mona Harras, and Amin Amer. "Melasma:	<1 %

Treatment evaluation", Journal of Cosmetic and Laser Therapy, 2009.
Publication

22	cyberleninka.org Internet Source	<1 %
23	jcadonline.com Internet Source	<1 %
24	journals.plos.org Internet Source	<1 %
25	www.ijdvl.com Internet Source	<1 %
26	www.lifeextension.com Internet Source	<1 %
27	Fumiko Watanabe, Erika Hashizume, Gertrude P Chan, Ayako Kamimura. "Skin-whitening and skin-condition-improving effects of topical oxidized glutathione: a double-blind and placebo-controlled clinical trial in healthy women", Clinical, Cosmetic and Investigational Dermatology, 2014 Publication	<1 %
28	SE-YEONG JEONG, JAE-BIN SHIN, UN-CHEOL YEO, WON-SERK KIM, IL-HWAN KIM. "Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet Laser for Melasma with Pre- or Post-Treatment Triple	<1 %

Combination Cream", Dermatologic Surgery, 2010
Publication

29	dpcj.org Internet Source	<1%

Exclude quotes	On	Exclude matches	< 5 words
Exclude bibliography	On		