Review Article

The effect of Vitamin C on melanin pigmentation – A systematic review

Rizwan M Sanadi[1], Revati S Deshmukh[2]

[1]Department of Periodontics, Dr GD Pol Foundation's YMT Dental College, Kharghar, Sector - 4, Navi Mumbai and PhD Student,
[2]Department of Oral Pathology and Microbiology, Bharati Vidyapeeth Deemed to be University, Dental College and Hospital, Satara Road, Katraj, Dhankawadi, Pune, Maharashtra, India

Abstract

Vitamin C, also known as ascorbic acid, is used as a treatment modality in depigmentation of hyperpigmented spots on the skin and gingiva. This systematic review discusses the studies conducted to assess the effect of Vitamin C on melanin pigmentation. The primary objective was to evaluate the effect of Vitamin C on melanin pigmentation. The secondary objective was to analyze the effect of Vitamin C administration on melanin pigmentation. An electronic database search was conducted from the following databases: PubMed, EBSCOhost, ScienceOpen, EMBASE and Google Scholar. Randomized controlled trials, experimental studies, case–control studies and cohort studies published in peer-reviewed journals in English language were included. Case reports, case series, animal model studies, *in vitro* studies, studies where Vitamin C was used along with other agents and unpublished research were excluded. Out of 22,580 studies, only 7 studies satisfied the selection criteria. Data extraction sheet was prepared, and the studies were analyzed. Out of the 7 studies analyzed, 1 was a randomized controlled trial and 6 were experimental studies. Vitamin C has been used widely as a depigmenting agent in dermatology. However, there are limited studies conducted on the use of Vitamin C for gingival depigmentation.

Keywords: Ascorbic acid, depigmentation, gingival melanin hyperpigmentation, melanin pigmentation, melanogenesis, tyrosinase, Vitamin C

Address for correspondence: Dr. Rizwan M Sanadi, Bharati Vidyapeeth Deemed to be University, Dental College and Hospital, Satara Road, Katraj, Dhankawadi, Pune - 411 043, Maharashtra, India.
Department of Periodontics, Dr. G D Pol Foundation's, YMT Dental College, Kharghar, Sector – 4, Navi Mumbai - 410 210, Maharashtra, India.
E-mail: drriz28@yahoo.com

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INTRODUCTION

Vitamin C, also known as ascorbic acid (AA) and ascorbate, abounds in nature and is highly labile. It is a water-soluble vitamin that is lost in large amounts during food processing.[1] AA is vital for the growth and maintenance of healthy bones, teeth, gums, ligaments and blood vessels and is involved in important metabolic functions. The minimal daily requirement for AA in healthy adults is 40–60 mg.[2]

Vitamin C plays significant functions in the body. The biochemical functions of Vitamin C include stimulation of certain enzymes, collagen biosynthesis, hormonal activation, antioxidant, detoxification of histamine, phagocytic functions of leukocytes, formation of nitrosamine and proline hydroxylation.[1]

AA is required for the hydroxylation of prolyl and lysyl residues during collagen biosynthesis, which is essential

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for wound healing. Vitamin C has been associated with reduction in incidence of cancer. Vitamin C is effective in protecting against oxidative damage in tissues and also suppresses the formation of carcinogens like nitrosamines. Vitamin C increases the levels of antibodies that fight against germs and viruses. Vitamin C regulates the urinary excretion of hydroxyproline.[1]

This vitamin is needed for the proper metabolism of drugs in the body through adequate hepatic mixed-function oxidase system. There is an inverse relationship with blood pressure and Vitamin C. Vitamin C has a lowering effect on blood pressure, especially on systolic pressure more than diastolic pressure. Low levels of plasma Vitamin C are associated with stroke and with an increased risk of mortality.[1]

Vitamin C (AA) is synthesized by all plants and most animals.[3] It is an essential vitamin for humans because the gene for gulonolactone oxidase, the terminal enzyme in the AA synthesis pathway, has undergone mutations that make it nonfunctional in humans.[4] Therefore, humans obtain this vitamin from diet and/or vitamin supplements.[2] It is an essential nutrient for the biosynthesis of collagen, L-carnitine and the conversion of dopamine to norepinephrine.[5]

Under physiological conditions, Vitamin C plays a role in photoprotection, skin strengthening, immunomodulation and cancer therapy and is used for the removal of hyperpigmented spots. It is also a potent antioxidant.[6]

Vitamin C interacts with the copper (Cu) ions at the tyrosinase active site and inhibits action of the enzyme tyrosinase, thereby reducing melanin formation. It also acts on the perifollicular pigment. However, it is an unstable compound. Therefore, it is used in combination with soy and liquorice for depigmentation in dermatology.[7]

Vitamin C is used as a treatment modality in depigmentation of hyperpigmented spots on the skin. It can be used topically, transdermally as well as intravenously. It is a water-soluble antioxidant and an essential nutrient for cells.[8] Despite its tremendous significance, humans are unable to synthesize this vitamin due to mutation of the gene needed for its synthesis.[9]

It also plays a significant role in collagen synthesis,[10] provides photoprotection[11] and reduces the melanin,[12] scavenger (free radicals)[13] and immunomodulation.[14]

Vitamin C was found to be effective in depigmentation as a result of its direct effect on melanogenesis. Melanin is said to be a reservoir for reactive oxygen species (ROS), Cu and calcium (Ca) within the cells. Following its entry into the target tissue, it binds to melanin. This causes a deficiency of the ROS, Cu and Ca, resulting in reduction of melanin production.[15]

RATIONALE

Studies have been conducted to determine the effect of Vitamin C on melanin pigmentation on skin and gingiva. Different formulations were used either in the form of oral administration or topical application or intravenous injection or intraepithelial injection. Although the use of Vitamin C as a depigmenting agent is common in dermatology, there is limited documentation on the use of Vitamin C as a depigmenting agent for gingival melanin hyperpigmentation. Therefore, this systematic review attempts to analyze the existing evidence on the effect of Vitamin C on melanin pigmentation on the skin and gingiva.

Focused question

Is there a possible effect of Vitamin C on melanin pigmentation?

Another research question

Does administration of Vitamin C reduce melanin pigmentation?

Primary objective

To evaluate the effect of Vitamin C on melanin pigmentation.

Secondary objective

To analyze the effect of Vitamin C administration on melanin pigmentation.

MATERIALS AND METHODS

Study design

This is a systematic review of randomized controlled trials, experimental studies, case–control studies and cohort studies which aims to analyze the effect of Vitamin C on melanin pigmentation and administration of Vitamin C as a depigmenting agent.

Inclusion criteria

1. Randomized controlled trials, experimental studies, case–control studies and cohort studies
2. Full-text articles published in peer-reviewed journals in English language
3. Vitamin C levels, tyrosinase levels or melanin pigmentation index scores assessed.

Exclusion criteria

1. Case reports and case series
2. Animal model studies and *in vitro* studies
3. Studies where Vitamin C was used along with other agents or in conjunction with other treatment modality
4. Unpublished research.

Search strategy

An electronic database search for randomized controlled trials, experimental studies, case–control studies and cohort studies published in peer-reviewed journals in English was conducted from the following databases: PubMed, EBSCOhost, ScienceOpen, EMBASE and Google Scholar.

The search terms used were:

Vitamin C OR Ascorbic acid OR

AND Melanin pigmentation OR Melanin synthesis OR

Melanin production OR melanocyte activity OR

Melanin hyperpigmentation AND Depigmentation

Study selection

Study selection was carried out in two phases:

i. Assessment of titles and abstracts
ii. Assessment of full text.

Data collection process

Data extraction sheet was prepared based on variables associated, and the articles were analyzed. Using data extraction sheet, the following data were collected: authors, year of publication, country, aim, tissue assessed, type of study, sample size, comparison group and control group, methodology and conclusion.

RESULTS

A total of 22,580 articles were found after electronic search. 22,100 articles, which were of other languages and duplicates, were excluded leaving 480 articles. 450 articles were excluded as they did not fulfill the eligibility criteria leaving 30 articles. Figure 1 shows the Flow chart of literature search results and study selection.

Studies included for the analysis

Seven studies were included for the qualitative synthesis. Out of the 7 studies, 1 was a randomized controlled trial and 6 were experimental studies. In all, 7 studies suggested that Vitamin C has a role in melanin pigmentation. An overview of the included studies for the analysis is presented in Table 1.

Assessment of risk of bias in included studies

This assessment was conducted using the recommended approach for assessing the risk of bias in studies included in Cochrane Reviews (Higgins 2011)22 using the tool RevMan 5.0.

We used the two-part tool to address the six specific domains (namely random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias). Each domain includes one or more specific entries in a risk of bias table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry: either low risk, unclear risk or high risk.

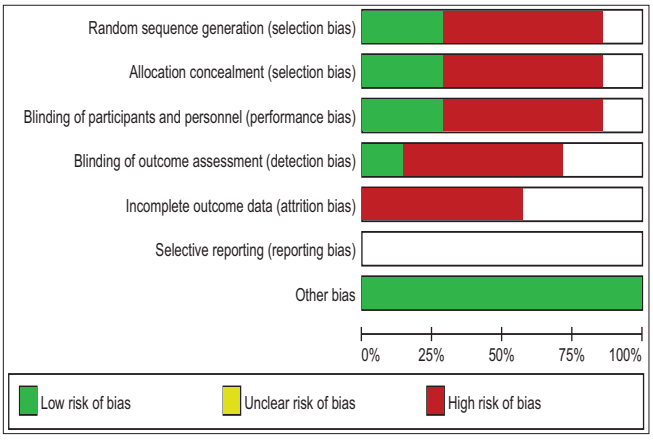
The domains of random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting are addressed in the tool by a single entry for each study. We completed a "risk of bias' table for each included study. The risk of bias of the included studies is presented in Table 2 and Graphs 1, 2.

Studies excluded from the analysis

Twenty-three studies were excluded, in which 2 were animal studies, 8 were *in vitro* studies, 2 were case reports, 7 were studies where Vitamin C was used along with other agents, 2 were studies where Vitamin C was used for the purpose of scar reduction, 1 study where Vitamin C was used in conjunction with iontophoresis and 1 study where Vitamin C was used in conjunction with fluorescent pulsed light (FPL). An overview of the excluded studies is presented in Table 3.

DISCUSSION

Skin pigmentation is the result of melanin synthesis in the



Graph 1: Risk of bias

Table 1: Characteristics of the studies included in the Systematic Review

Authors & Year of Publication	Country	Aim	Tissue assessed Gingiva/Skin	Type of study	Sample size, Comparison group & control group	Methodology	Conclusion
Shimada Y, Tai H, Tanak A, Suzuki I, Takagi K (2009) 16	Japan	To investigate the inhibitory effects of a gel containing ascorbic acid 2-glucoside (AS-G gel) on gingival melanin pigmentation.	Gingiva	Double-masked placebo-controlled clinical trial, split-mouth design (randomised controlled trial)	73 subjects with symmetric gingival melanin pigmentation. (22 males and 51 females). The mean age was 37.2±1.0 years (range, 25 to 57 years).	AS-G test gel was applied to left the side and placebo gel was applied to the right side of the gingiva. Using a spectrophotometer the color of the keratinized gingiva was measured at four points (canine and lateral incisor; and between lateral incisor and incisor) in each subject. Three consecutive measurements were taken at one site, and the mean of individual measurements was calculated at 0 weeks, 4 weeks, 8 weeks and 12 weeks.	Ascorbic acid (AS-G) seems to have potential for the treatment of gingival melanin pigmentation at home.
Yussif NM, Zayed SO, Hasan SA, Sadek SS (2016) 5	Cairo University, Egypt	To evaluate the efficiency of injectable Vitamin C as a depigmenting agent in physiologic gingival hyperpigmentation	Gingiva	Experimental Study	40 patients in age range of 20-44 years with physiologic gingival melanin hyperpigmentation	A 200-300mg (1-1.5 ml) ascorbic acid (ampoule) was injected in the gingival tissues once per week until no visible pigmentation. The patients were recalled after 1, 3& 6 months for follow up. Decrease in pigmentation indices scores & reduction in area of pigmentation was assessed.	Vitamin C injection is a safe, minimally invasive non-surgical depigmenting technique for gingival tissue.
Yussif NM, Abdel Rahman AR, Elbarbary E (2019) 17	Cairo University, Egypt	To evaluate the efficacy of intra-epidermal vitamin C injection in comparison to the conventional surgical technique in gingival hyperpigmentation	Gingiva	Experimental Study	30 patients with mild to severe hyperpigmented gingival tissues were divided into Group 1(Control group-conventional scalpel depigmentation performed) & Group 2(Test group- Vitamin C was injected intra-epidermal)	Maximum 0.1 ml of ascorbic acid was recommended for each point with 2-3 mm apart. The same dose was repeated once per week for maximum 4 visits till no further color improvement gained. The same operator performed all the surgical procedures. For gingival ablation, epithelial layer and part of the connective tissue layer were removed using 15c blades till the pigment disappeared. Caution was taken at the canine region to avoid bone exposure. Two different color assessment indices (Takashi and Kumar indices) were assessed. The pain and itching grades were reported using VAS Scale.	Usage of vitamin C injection for depigmentation showed comparative results to the conventional surgical technique.

Contd...

Ratnam AV, Sastry PB, Satyanarayana BV (1977)18	India	To estimate the content of ascorbic acid in normal pigmented skin in comparison to the depigmented skin of vitiligo.	Skin	Experimental study	Control group-10 subjects with normal pigmented skin. Study group-12 vitiligo cases with variable loss of pigmentation and 1 was albino.	The estimations of ascorbic acid levels were repeated after saturation with daily doses of 70 mg ascorbic acid per stone body weight. The skin samples were obtained from the lateral aspect of the leg in all the subjects and extracts were prepared from full thickness skin. The ascorbic acid contents of skin, plasma and urine were assessed	Ascorbic acid has an important role to play in the metabolic functions of the epidermis, the most important of these being keratinization and melanogenesis.
Kameyama K, Sakai C, Kondoh S, Yonemoto K, Nishiyama S, Tagawa M (1996)19	California	To examine the effect on pigmentation of magnesium-L-ascorbyl-2-phosphate (VC-PMG), a stable derivative of Ascorbic acid.	Skin	Experimental study	34 patients with phelides. chloasma, senile freckles, nevus of Ota, or healthy skin	VC-PMG cream 10% was applied twice a day to the skin. The effectiveness of the lightening of the pigmentation was judged by a color-difference meter	VC-PMG was effective in lightening the skin of some patients with hyperpigmentation disorders and some subjects with normally pigmented healthy skin.
Kim HM, An HS, Bae JS, Kim JY, Choi CH, Kim JY (2017)20	Korea	To investigate the effects of palmitoyl-KVK-L-ascorbic acid on skin aging, the anti-wrinkle and depigmentation.	Skin	Experimental study	21 healthy Korean women aged between 41 and 55 years	The cream with 0.075% (0.75 mg/mL) of Palm-KVK-AA or without Palm-KVK-AA was applied to each half of the participant's face, twice daily for 12 weeks. The allocation of the cream was based on a double-blind randomized method. Skin replica images were evaluated using a visiometer. Visual assessment was performed using the global photodamage score at baseline, 4, 8 and 12 weeks after the application of the cream	Palmitoyl-KVK-L-ascorbic acid is an effective anti-aging agent that reduces wrinkles and abnormal skin pigmentation.
Jaros A, Zasada M, Budzisz E, Debowska R, Rzepka MG, Rotsztejn H (2019)21	Poland	To evaluate selected capillary skin parameters after applying 5% vitamin C concentrate.	Skin	Experimental study	(50.1 ± 3.9 years) 30 women of 30-60 years of age with capillary skin indicating visible signs of erythematous plaques. Control group of 11 patients	The participants were instructed to use 5% Vitamin C concentrate once a day during the evening and apply it on their facial skin. The participants were asked to fill out a questionnaire where they evaluated the properties of the applied concentrate throughout the period of 6 weeks	5% Vitamin C concentrate is very effective in treating Erythema as well as decreasing the visibility of telangiectasia

Table 2: Risk of Bias of the studies included in the Systematic Review

Author (Year)	Type of study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome	Incomplete outcome data	Selective reporting
Shimada Y, Tai H, Tanak A, Suzuki I, Takagi K (2009)[16]	Randomized controlled clinical trail	yes	yes	yes	not clear	not clear	not clear
Yussif NM, Zayed SO, Hasan SA, Sadek SS (2016)[5]	Experimental study	yes	yes	not clear	not clear	not clear	not clear
Yussif NM, Abdel Rahman AR, Elbarbary E (2019)[17]	Experimental study	no	no	no	no	no	not clear
Ratnam AV, Sastry PB, Satyanarayana BV (1977)[18]	Experimental study	no	no	no	no	no	not clear
Kameyama K, Sakai C, Kondoh S, Yonemoto K, Nishiyama S, Tagawa M (1996)[19]	Experimental study	no	no	no	no	no	not clear
Kim HM, An HS, Bae JS, Kim JY, Choi CH, Kim JY (2017)[20]	Experimental study	not clear	not clear	yes	yes	not clear	not clear
Jaros A, Zasada M, Budzisz E, Debowska R, Rzepka MG, Rotsztejn H (2019)[21]	Experimental study	no	no	no	no	no	not clear

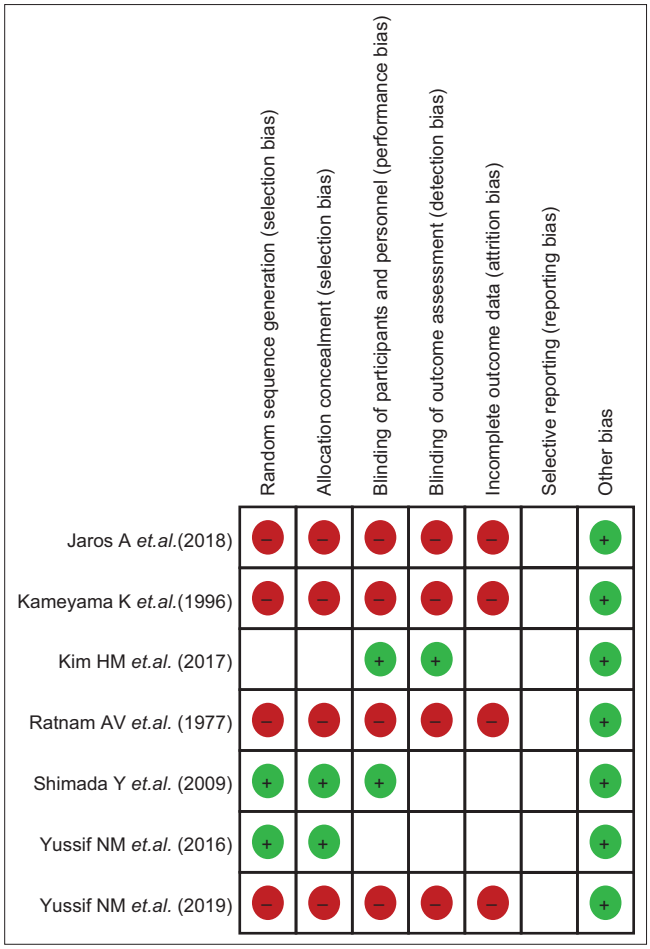
Table 3: Characteristics of Excluded Studies

Authors (Year)	Reason for Exclusion
Takenouchi K, Aso K (1964)[23]	Animal study
Yussif NM, Koranayb NS, Abbass MMS (2017)[24]	Animal study
Matsuda S, Shibayama H, Hisama M, Ohtsuki M, Iwaki M (2008)[25]	*In-vitro* study
Panich U, Tangsupaanan V, Onkoksoong T, Kongtaphan K, Kasetsinsombat K, Akarasereenont P *et al* (2011)[11]	*In-vitro* study
Lee SA, Son YO, Kook SH, Choi KC, Lee JC. (2011)[26]	*In-vitro* study
Taira N, Katsuyama Y, Yoshioka M, Okano Y, Masaki H (2017)[27]	*In-vitro* study
Katsuyama Y, Taira N, Yoshioka M, Okano Y, Masaki H (2018)[28]	*In-vitro* study
Taira N, Katsuyama Y, Yoshioka M, Okano Y, Morikawa T (2018)[29]	*In-vitro* study
Yim S, Lee J, Jo H, Scholten J, Willingham R, Nicoll J, Baswan SM (2019)[30]	*In-vitro* study
Miao F, Su MY, Jiang S, Luo LF, Shi Y, Lei TC (2019)[31]	*In-vitro* study
Lee (2008)[32]	Case report
Sheel V, Purwar P, Dixit J. and Rai P (2015)[33]	Case report
Postaire E, Jungmann H, Bejot M, Heinrich U, Tronnier H. (1997)[34]	Used along with other agents
Broekmans WM, Vink AA, Boelsma E, Klöpping-Ketelaars WA, Tijburg LB, van't Veer P, van Poppel G, Kardinaal AF. (2003)[35]	Used along with other agents
Hwang SW, Oh DJ, Lee D, Kim JW, Park SW (2009)[36]	Used along with other agent
Dormael RD, Bastien P, Sextius P, Gueniche A, Ye D, Tran C, *et al* (2019)[37]	Used along with other agent
Ishikawa Y, Niwano T, Hirano S, Numano K, Takasima K, Imokawa G (2019)[38]	Used along with other agents
Kim J, Kim J, Lee YI, Almurayshid A, Jung JY, Lee JH. (2020)[39]	Used along with other agents
Rattanawiwatpong P, Wanitphakdeedecha R, Bumrungpert A, Maiprasert M (2020)[40]	Used along with other agents
Huh CH, Seo KI, Park JY, Lim JG, Eun HC, Park KC (2003)[41]	Used in conjunction with Iontophoresis
Shaikh I, Mashood AA (2014)[42]	Used in conjunction with fluorescent pulsed light (FLP)
Yun IS, Yoo HS, Kim YO, Rah DK (2013)[43]	Used for scar reduction
Amirlak B, Mahedia M, Shah N (2016)[44]	Used for scar reduction

melanosomes of melanocytes (MCs), followed by the progressive transfer of this melanin to keratinocytes. Melanin is the pigment responsible for skin color and plays normal physiological roles within the skin.[20] It is worthwhile to note that the antimelanogenic mechanism employed by most skin-lightening agents mediates the suppression of tyrosinase activity at various levels.[31]

When choosing a depigmenting agent, it is important to differentiate between substances that are toxic to the MC and substances that interrupt the key steps of melanogenesis. Vitamin C falls into the latter category of depigmenting agents.[31]

Vitamin C is essential for a number of processes in human skin, such as dermal collagen synthesis, antiaging and antioxidation. It is a weak acid and is only slightly stronger than vinegar. The acidification of MCs by Vitamin C could inhibit the catalytic activity of tyrosinase, the rate-limiting enzyme required for melanin biosynthesis.[31]



Graph 2: Risk of bias summary

Vitamin C and its derivatives inhibit tyrosinase activity and melanin content in a dose-dependent manner.[7] It is highly unstable in aqueous solution. The instability of AA is due to its oxidation to dehydroascorbic acid, which is a reversible reaction, and subsequently to 2,3-diketo-L-gulonic acid. The latter reaction is irreversible,[45] thereby resulting in loss of its physiological properties.

It has good photoprotective ability against ultraviolet A-mediated phototoxicity. Effective delivery of AA through topical preparations is a major factor, as it may be dependent on the nature or type of the formulation. The pH of the formulation should be on the acidic side (pH 3.5) for effective penetration of the vitamin in the skin.[2]

Vitamin C is available in the market as a variety of creams, serum and transdermal patches. It is in an almost colorless form and unstable. On exposure to light, gets oxidized to dehydro-AA, which imparts a yellow color. Topical AA formulations have been used in the concentration range of 1%–20%.[46]

From a clinical point of view, it is important to note that the efficacy of the Vitamin C serum is proportional to

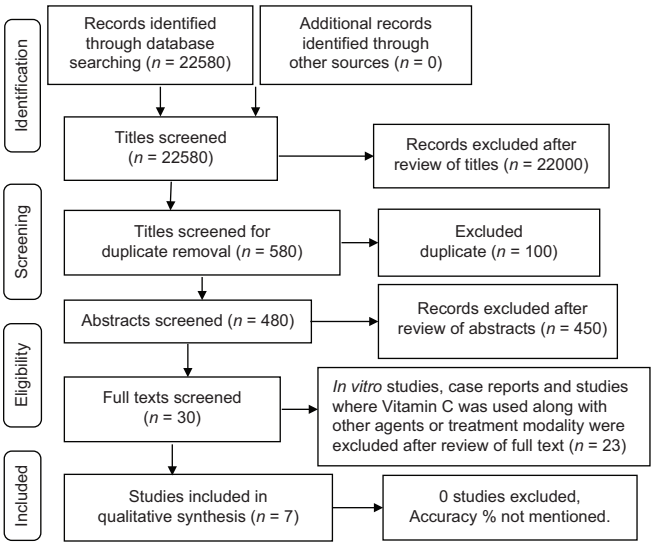


Figure 1: Flow chart of literature search results and study selection

the concentration but only up to 20%. The half-life in the skin after achieving maximum concentration is 4 days. A persistent reservoir of Vitamin C is important for adequate photoprotection and can be achieved by regular 8-hourly applications. A combination of tyrosine, zinc and Vitamin C has been shown to increase the bioavailability of Vitamin C 20-times vis-a-vis using just Vitamin C.[47]

The present systematic review summarizes the results of the studies that assessed the effect of Vitamin C on melanin pigmentation on the skin as well as the gingiva. There are limited studies available, which assessed the effect of Vitamin C alone on melanin pigmentation. *In vitro* studies, animal studies and case reports were excluded due to the low level of evidence of these studies.

Lee[32] reported the management of a case of postlaser hyperpigmentation in a woman suffering from melasma. He concluded that intravenous administration of Vitamin C appears to be useful in treating postlaser hyperpigmentation. Sheel *et al.*[33] evaluated the efficacy of Vitamin C as a depigmenting agent after surgical scalpel depigmentation on the gingiva. They reported satisfactory esthetic results with low subjective pain levels, and no recurrence was observed after 9 months of follow-up. However, as case reports have a level low of evidence, they were excluded.

In the present review, studies in which Vitamin C was used along with other agents were excluded. As Vitamin C is highly unstable, it is often used in combination with other agents such as Vitamin E, Vitamin B, lycopene and β-carotene.[34] We excluded those studies, as we wanted to analyze the effect of Vitamin C alone on melanin pigmentation.

Vitamin C has been used in conjunction with other treatment modalities. Huh *et al*.[41] used Vitamin C in conjunction with iontophoresis so as to enhance the penetration of Vitamin C into the skin tissue with a favorable outcome. Shaikh and Mashood[42] used Vitamin C in conjunction with FPL for treating refractory melasma in Asian patients and reported a favorable outcome. However, isolated effect of Vitamin C was not assessed; hence, these studies were excluded.

Seven studies were included for the qualitative synthesis. Out of the 7 studies, 1 was a randomized controlled trial and 6 were experimental studies. Three of the studies analyzed assessed the effect of Vitamin C on the gingiva and 4 studies assessed the effect of Vitamin C on skin.

Shimada *et al*.[16] investigated the inhibitory effect of AA gel on gingival melanin pigmentation in a double-masked placebo-controlled trial with a split-mouth design and reported that AA gel inhibited the gingival melanin pigmentation. As this study was a randomized controlled trial, when the risk of bias was assessed, the lowest risk of bias was observed.

Intraepithelial injections were used on gingiva (Yussif *et al*., 2016, and Yussif *et al*., 2019), which helps in direct delivery of Vitamin C at the site. This provides for assessment of effect of Vitamin C alone on melanin pigmentation. However, when the risk of bias was assessed, a higher risk of bias was observed in the study conducted by Yussif *et al*., 2019.

Vitamin C has been used in dermatology for skin depigmentation in the form of tablets (Ratnam *et al*., 1977), cream (Kameyama *et al*., 1996, and Kim *et al*., 2017) and Vitamin C concentrate (Jaros A *et al*., 2018). The authors have reported a favorable outcome, suggesting the possible effect of Vitamin C on melanin pigmentation. However, when the risk of bias was assessed, these studies showed a higher risk of bias.

Except for one study, the risk of bias existed in the studies as randomization of study participants and blinding was not performed. This could have influenced the outcome of the studies. However, based on the studies analyzed, it was observed that Vitamin C did have an effect on reducing melanin pigmentation and has been used as a depigmenting agent on the skin as well as gingiva. There remains a future scope for randomized controlled studies to be conducted

CONCLUSION

Vitamin C is a naturally occurring substance and an essential nutrient. It has various biological and pharmaceutical functions. It inhibits melanin synthesis through downregulation of tyrosinase enzyme activity. It is widely used in dermatology as a treatment modality in depigmentation of hyperpigmented spots on the skin. It has also been used for treatment of gingival melanin hyperpigmentation. However, there is limited documentation on the use of Vitamin C as a depigmenting agent for gingival melanin hyperpigmentation, although it has shown promising results.

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Conflicts of interest
There are no conflicts of interest.

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