

The reporting quality of randomized controlled trial abstracts on topical vitamin C

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**UNIVERSITY OF SPLIT
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**THE REPORTING QUALITY OF RANDOMIZED CONTROLLED TRIAL
ABSTRACTS ON TOPICAL VITAMIN C**

Diploma thesis

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LIST OF ABBREVIATIONS

RCT - randomized controlled trial

UV - ultraviolet

DEJ - dermo-epidermal junction

DNA - deoxyribonucleic acid

TGF - Transforming growth factor

MMP - metalloproteinase

TSP-1 - thrombospondin-1

VEGF - vascular endothelial growth factor

PIH - post-inflammatory hyperpigmentation

YAG - yttrium-aluminum-garnet

LED - light-emitting diode

NIR - near-infrared

CONSORT - Consolidated Standards of Reporting Trials

NOS - Newcastle-Ottawa Scale

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analysis

IQR - interquartile range

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The harder it is for me now to celebrate this journey without you.

Tata, volim te.

1. INTRODUCTION

1.1. Pathophysiology of skin aging

Maturing of the skin is a course that affects everyone. The phenotypic changes that the aging process brings are one of the first impressions of our environment. Skin aging is characterized by features such as wrinkles and a rough and dry appearance of the skin, mostly on the face, that results from a decrease in elasticity. Both external variables - primarily ultraviolet (UV) solar radiation, which leads to photoaging - and intrinsic factors, which are mainly physiological changes over time, contribute to this process (1).

Shrinking skin, loss of elasticity and low metabolic activity are some of the symptoms of intrinsic aging. In addition to fine wrinkles, thin, translucent, and dry skin, lack of background fat, thinning of facial bones, inability to adequately cool the face through sweating, hair loss, and unwanted hair growth, are other signs of intrinsic aging (2). Notable external factors leading to intrinsic aging are toxic irritants and air pollution, while genes, the metabolism of our cells, and hormonal changes play a role as endogenous factors (3).

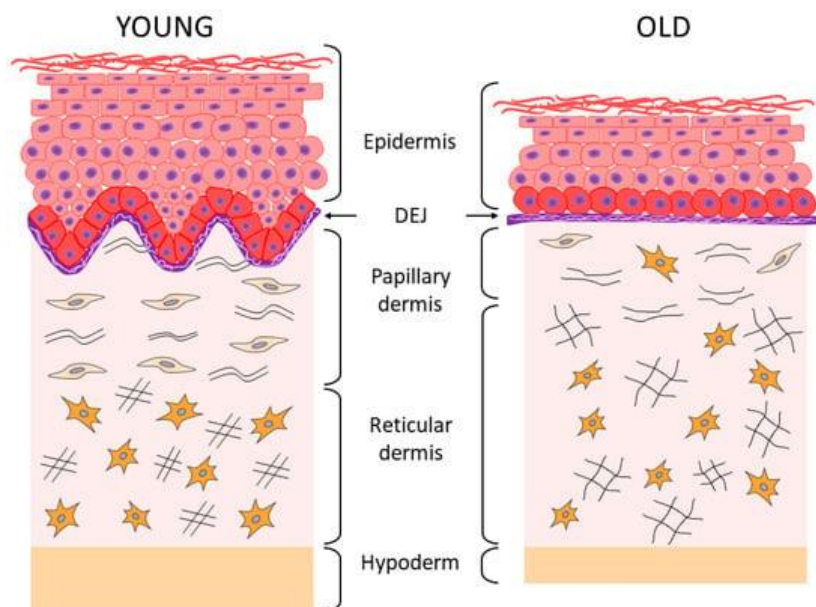


Figure 1. Representation of cellular level of aging skin (4).

During aging, the epidermis thins, also the dermo-epidermal junction (DEJ) weakens and flattens, resulting in the dermis and hypodermis losing thickness as the skin ages.

Each skin layer has its characteristics that determine the aging process (4). Atrophy of the epidermis and flattening of the DEJ are examples of age-related loss of functions and structures indicative of intrinsic aging (5). In aging skin, the number of cells decreases. The basal cell layer of the epidermis shows the greatest histological changes. One of the factors leading to the cell decrease is a process called senescence. It describes the decreased growth of fibroblasts, keratinocytes, and melanocytes. Due to the DEJ weakening with age, the epidermis and dermis shift, resulting in a poorer nutrient supply (1).

Figure 1 shows a visualization of the aging process of the skin. Between the ages of 30 and 80, the epidermis thins by 10-50%, primarily because basal keratinocytes migrate to the spinous layer after losing their proliferative capacity. Age-related changes in the basal layer of the epidermis, including marked differences in the size of keratinocytes, have been demonstrated in skin biopsy samples taken from older people. Collagen type XVII, which connects keratinocytes to the basement membrane, is one of the main causes of homeostasis being disturbed in the basal keratinocyte group (4).

β -Galactosidase, a senescence marker that can be measured in dermal fibroblasts and epidermal keratinocytes, increases with age (1). The presence of the biomarker can typically distinguish senescent cells from quiescent cells and is unrelated to deoxyribonucleic acid (DNA) synthesis. The most common type of detection is the use of near-infrared fluorescent probes (6, 7). Transforming growth factor (TGF)- β 1 plays an important role in the synthesis of collagen. When the activity of the TGF- β /Smad pathway decreases, less type 1 procollagen, the precursor of type I collagen, is produced. This type is the most abundant collagen type in the body (1).

Melanocytes also change with age: their functional activity decreases, their number decreases (20% per decade), and their diversity increases. This leads to irregular pigmentation of the skin. As mentioned above, the skin becomes dry with time, due to a decrease in epidermal hyaluronic acid and glycosaminoglycan, which have the largest molecular weight and function to bind water, thus maintaining tissue hydration (4).

The most damaging long-term consequences of modifiable extrinsic variables are caused by UV radiation, which leads to photoaging in addition to natural chemical aging. Depending on the phototype of the skin, the extent and degree of age-related pigmentation changes may vary (8).

Extended sun exposure leads to the continuous deterioration of essential proteins in the skin's dermis, namely collagen, and elastin. Fibroblasts, responsible for their production, struggle to keep up with the destructive effects. Despite representing a small fraction of the skin's protein composition (2%-4%), elastin plays a crucial role in maintaining elasticity and resilience. Photoaging, primarily caused by UVA (wavelength 320-400nm) radiation, poses the greatest threat due to its ability to penetrate deeper into the dermis compared to UVB (wavelength 290-320nm) radiation. UVA exposure triggers apoptosis in dermal fibroblasts and increases levels of matrix metalloproteinases (MMPs), enzymes that contribute to the breakdown of collagen and other components of the extracellular matrix (9, 10).

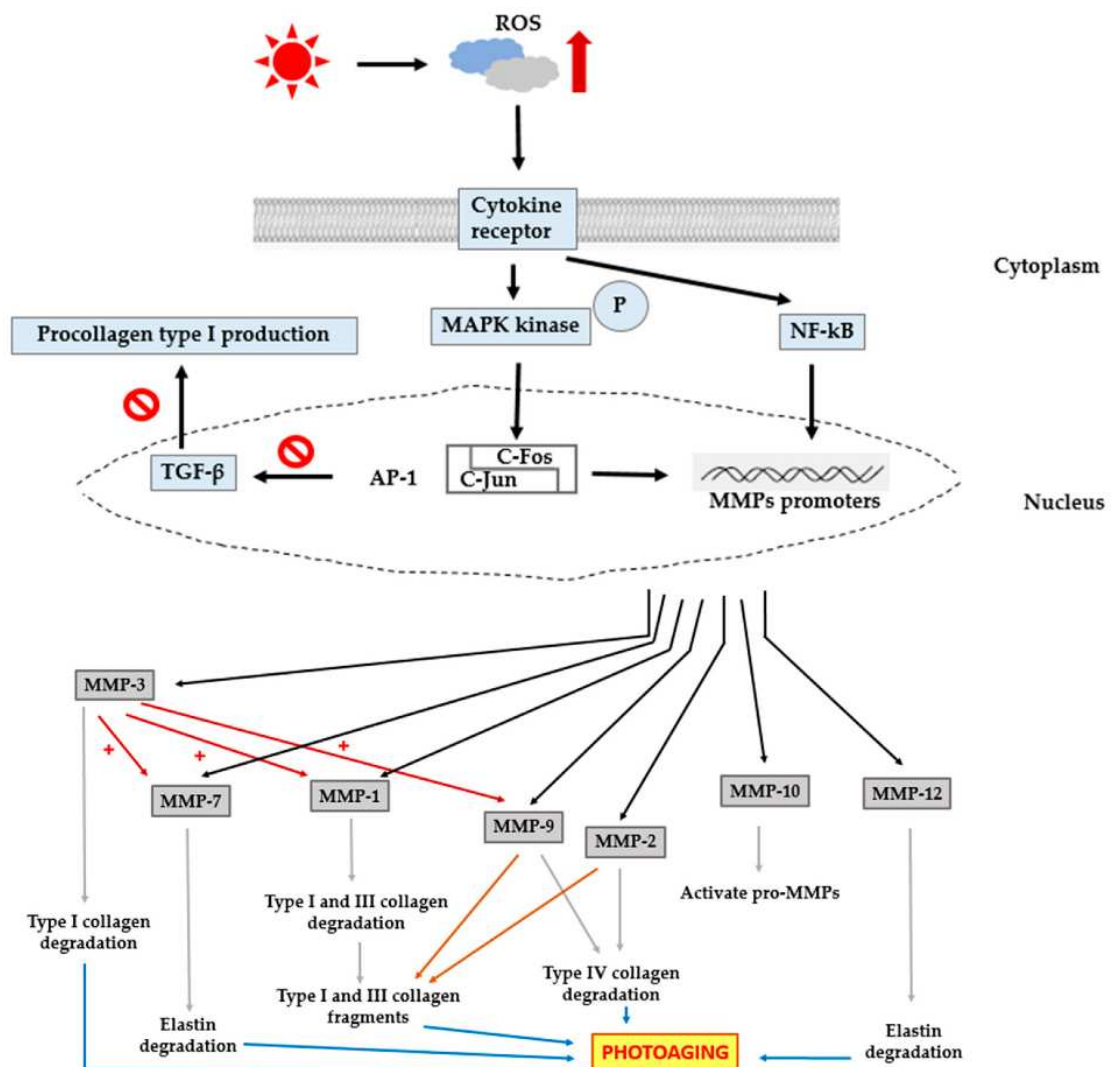


Figure 2. Schematic diagram showing the role of MMPs in photoaging (9).

These MMPs are released not only by fibroblasts but also by keratinocytes in response to a variety of triggers, including oxidative stress, UV radiation, and cytokines (9).

Certain MMPs target the degradation of specific proteins. An example is MMP-12, which focuses on elastin, or MMP-1, which belongs to a group that functions as a collagenase and targets the degradation of fibrillar collagens type I and III. This process is illustrated in Figure 2 (9). Prolonged exposure to UVA also increases the levels of photoaging indicators such as ferritin and lysozyme, which are associated with the oxidative stress response and elastin degradation, respectively, on human skin exposed to UVA *in vivo* (10).

The angiogenic and antiangiogenic factors, e.g. thrombospondin-1 (TSP -1) and vascular endothelial growth factor (VEGF) are also altered by exposure to UV light. Normally, VEGF is expressed in a relatively small amount in the normal epidermis of human skin, TSP -1 is produced by epidermal keratinocytes and is persistently expressed in the normal epidermis, especially in the higher layers. VEGF (angiogenic) is increased by UV exposure, whereas TSP -1, which is anti-angiogenic, is decreased. The resulting changes in the TSP -1/VEGF ratio lead to angiogenesis in the papillary dermis and increased migration of leukocytes that are elastase positive, which eventually damages the elastic fibers of the skin. The initial stage of cutaneous photoaging, which involves matrix degradation, may be a consequence of this pro-angiogenic state (5).

1.2. Pathophysiology of hyperpigmentation

The darkening of the natural skin tone is called hyperpigmentation. The main cause is hypermelanosis, which is an increased accumulation of melanin in the dermis and epidermis (11). Other causes worth mentioning are iron deposition, also known as hemosiderosis, and carotenderma, which is the deposition of excess cutaneous carotene. Hyperpigmentation can also be classified according to the type of spread. In the diffuse type, it is probably not a primary condition but a secondary sign of a systemic problem, such as a general metabolic or endocrine disease and drug therapy, also known as drug-induced hyperpigmentation (12).

Two forms of melanin, eumelanin, and pheomelanin, are mainly responsible for human skin color. The number of blood capillaries, the presence of chromophores such as carotenoids or lycopene, and the collagen content of the skin are other important factors influencing skin color (11).

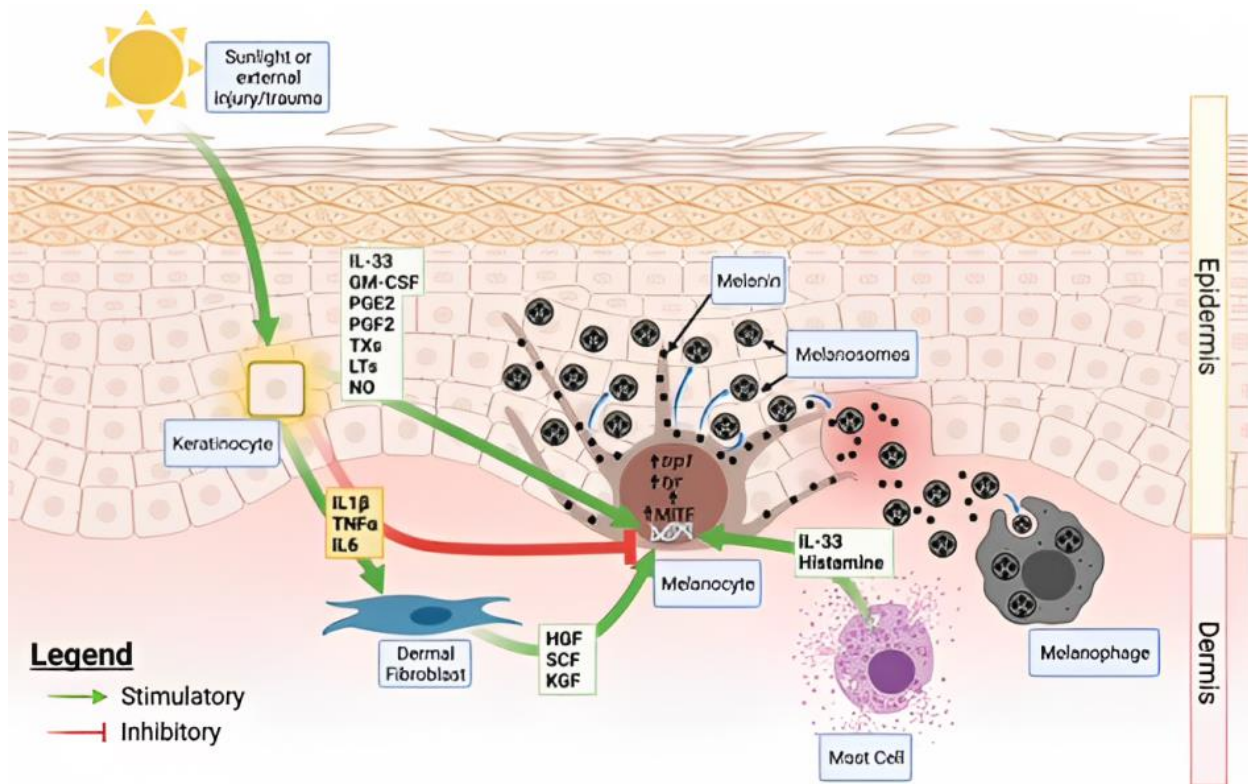


Figure 3. Mechanism of post-inflammatory hyperpigmentation (PIH) (13).

Figure 3 illustrates the complex pathogenesis of post-inflammatory hyperpigmentation mediated by many cytokines, growth factors, and various cellular cross-links. After an external trigger, such as trauma, keratinocytes release their inflammatory cytokines, which stimulate the production of growth factors by dermal fibroblasts. These growth factors in turn stimulate melanocytes. Through small openings in the basal lamina, melanin can either be deposited directly into the dermis or it can be captured in the epidermis by macrophages, which then migrate into the dermis and contribute to skin pigmentation (13).

Another common hyperpigmentation disorder of the face, with usually bilateral and symmetrical hyperpigmented blemishes and patches, is melasma. Since UV radiation is the main risk factor along with oral contraceptive use and pregnancy, irregularly framed spots usually occur in sun-exposed areas (14).

1.3. Treatment of skin conditions

Topical corticosteroid therapy may be a treatment option for inflammatory or chronic conditions such as *lichen sclerosis*. These corticosteroids can be classified based on their efficacy and treatment area. Due to known adverse effects, e.g., atrophy, *striae*, rosacea, telangiectasia, purpura, and similar cutaneous or systemic adverse effects, the duration and frequency of therapy should be monitored carefully. Prolonged use and higher potency increase the risk of such adverse reactions occurring (15).

A multimodal approach is the therapy of choice for many other dermatologic conditions. The therapy of vitiligo is a good example. The most effective vitiligo treatments include many methods to achieve both reductions in levels of oxidative stress in the skin and also a treatment that causes immunosuppression (16).

1.3.1. Anti-aging treatments

Anti-aging therapies open a large market for many cosmetic and pharmaceutical companies with various and continuously new strategies. The anti-aging approach of dermatology is largely focused on preventing photoaging of the skin through UV protection, reduction of risk for oxidative stress, and cell-protective substances such as vitamin B3 (17). Topical formulations containing sunscreen factors are not only an important preventive measure against skin aging but also play an important role in preventing sunburn and photocarcinogenesis. Sunscreen filters can be of chemical origin such as well-established octinoxate or octocrylene. However, natural UV filters such as lignin, melanin, and silymarin are becoming more popular nowadays because of their less harmful effect on the environment (18).

When it comes to reducing surface wrinkles, over-the-counter creams containing polyphenols or amino acid peptides can be effective, while chemical peels should be administered by a dermatologist to achieve more significant results. These peels stimulate collagen production, offering a rejuvenating effect. Dermatologic peels are categorized as superficial, intermediate, or deep based on their ability to penetrate different layers of the skin, ranging from the outermost *stratum corneum* of the epidermis to the deeper *stratum reticulare*. By utilizing peeling solutions, these procedures provoke controlled damage that prompts the

growth of new skin cells. Since aging signs tend to manifest selectively across the face, diverse substances can be applied to target specific areas with the desired depth of impact. This customized approach is typically achieved through a mosaic peel technique, incorporating multiple stages of penetration (17,19).

An organic antioxidant called vitamin C is found in both plants and mammals. While most species can make it themselves, humans and some other vertebrates lack the necessary enzyme and must instead obtain it from external sources, such as fruit or vegetables. After oral ingestion the bioavailability of vitamin C in the skin is minimal. The most abundant antioxidant in human skin, vitamin C works in conjunction with other antioxidants to defend against reactive oxygen species. It can be converted back to its active state and neutralizes free radicals by donating electrons. Vitamin C levels in the skin are reduced by UV exposure (20). As mentioned above, MMPs, which can be activated by reactive oxygen species or other triggers, play an important role in collagen degradation and thus in skin aging. Studies have shown that vitamin C, as an antioxidant, can decrease MMP activation via the inhibition of AP -1, thereby reducing collagen damage (21). It also stimulates collagen gene expression and acts as a cofactor for proline and lysine hydroxylases, which strengthen the tertiary structure of the collagen molecule (22).

Retinoids, like retinol and retinoic acid, are popular ingredients in topical emulsions and creams. Inhibiting UV-induced matrix metalloproteinases and promoting collagen synthesis in photodamaged skin are two examples of retinol's anti-aging actions, with which topical retinol therapy effectively reduced fine wrinkles in clinical tests. Due to the extra step required to transform retinol into retinoic acid, it should be remembered that retinol is less effective than retinoic acid (23).

More invasive cosmetic procedures, injections of fillers or botulinum toxin, are becoming increasingly popular. The toxin is produced by *Clostridium botulinum* and was first used as a therapy for strabismus. It prevents the release of acetylcholine from the presynaptic motor neuron, causing chemodenervation and paralysis of the affected muscle (24). Dermal fillers are an alternative for contouring, correcting volume deficiencies, and scarring, and elevating certain anatomical regions such as the lips on the face. The ideal dermal filler should be non-toxic, affordable, hypoallergenic, easy to spread and store, and painless to administer. The effect must be undetectable under the skin, long-lasting, firm and predictable, and easy to remove when needed (25).

Ablative laser therapies using carbon dioxide or erbium-yttrium-aluminum-garnet (YAG) lasers are also popular options. These techniques require extensive follow-up, a long recovery period, and the possibility of sequelae such as persistent erythema, discomfort, infection, bleeding, leakage, burns, hyper- or hypopigmentation, and scarring. A new possibility is the use of a light-emitting diode (LED) as a light source for skin rejuvenation. Since it is non-ablative and non-thermal, it does not destroy the epidermis but improves wrinkling and skin sagging. Clinical research with red and near-infrared (NIR) light has shown that collagen formation increases while MMP-1 and MMP-2 decrease, improving the appearance of skin that has been exposed to light damage (26). As with other medical problems, there are preventive measures that can be easily applied in daily life and are non-invasive, such as monitoring general health, diet, stress, and physical activity, and avoiding external triggers such as smoking or pollution (17).

1.3.2. Anti-pigmentation treatment

The ability of pigmentary disorders to resist therapy, their potential for recurrence after some time, or even the risk of worsening with various treatments are important issues in the management of pigment-associated diseases (27). Since most pigmentary disorders are exacerbated by sun exposure, sun protection is one of the most important therapeutic approaches (14).

Tyrosinase, the enzyme that controls the rate of melanin formation, is the obvious target for skin hyperpigmentation therapy, and pigmentation can be lowered in several ways. The three substances that most commonly act in this way are hydroquinone, arbutin, and kojic acid (28).

Hydroquinone, the longstanding gold standard since the 1960s, is a potent agent that targets the melanogenesis pathway by inhibiting tyrosinase. An alternative derivative called arbutin also possesses anti-tyrosinase activity, though with fewer melano-toxic effects. For optimal outcomes, it is recommended to combine hydroquinone with a retinoid and a corticosteroid. However, to minimize potential adverse effects such as erythema or, in severe cases, ochronosis, it is important to limit hydroquinone usage to once or twice daily for a period of three to six months. Due to concerns about its potential carcinogenicity, it was prohibited in the United States in 2006, and it has been banned in Europe since 2001 (28-30). A naturally

occurring metabolite produced by a fungus, called kojic acid, also has some anti-pigmentation properties as it inhibits the production of melanin by tyrosinase and acts as a UV protector (31).

Vitamin C is an additional therapeutic alternative. Due to its acidic pH of 3.5, L-ascorbic acid, found in a variety of formulations, is the most physiologically active but not a stable form. Additionally, the acidity of the formulation improves penetration (32). Because of its instability, combination preparations with soy and licorice are often offered on the cosmetic market to reduce pigmentation (33). Its depigmenting effect is due to the inhibition of tyrosinase activity by the action of vitamin C with copper ions in the active site of the enzyme, thus reducing melanin production. It also acts on a perifollicular pigment (33). Vitamin C is also thought to reduce ortho-quinones produced by tyrosinase, which in turn interferes with this target pathway and results in decreased melanin production (22). Vitamin C is most effective in products that contain more than 8% of it, and amounts above 20% have been shown to irritate the skin (32).

1.4. Quality of published research

Quality research reports require key elements such as clarity, structure, validity, accuracy, and simplicity to effectively communicate findings to the reader. In qualitative studies, the researcher plays a central role in data collection. Therefore, it is critical to avoid bias and errors that can affect the reliability of the data and the research findings. To ensure rigor careful preparation, continuous reflection by the researcher, and open dialog with readers about the study and its findings are essential. Authors should evaluate the data without bias and present their findings neutrally and objectively (34). They are also advised to focus on each study procedure's cultural and ethical appropriateness to ensure the highest level of research validity and reliability. The boundaries of ethical research and the promotion of quality standards can only be fostered through communication, mentorship, and co-mentorship between professional and novice researchers (35).

The key core characteristics of high-quality data itself are shown in Figure 4. When these aspects of data quality are carefully considered, errors are reduced and research is more likely to be approved by reviewers, extension specialists, and academics. Using research data quality checklists, that consider these eight components, can be helpful (36).



Figure 4. Eight components of data quality (36).

1.4.1. Consolidated Standards of Reporting Trials

One instruction created to improve the transparency and quality of reporting of randomized controlled trials is the Consolidated Standards of Reporting Trials (CONSORT) statement. Numerous research studies have examined how the statement affects the quality of reporting of published randomized trials and have found that the inclusion of the statement improves the quality of reporting (37). In terms of scientific evidence, RCTs are considered the gold standard. CONSORT the guide to assessing the quality of RCTs, which functions like a tool for reading and assessing the quality of these studies, provides pre-specified criteria that can be used to assess the quality of RCTs. It is a checklist of 25 criteria that gives us guidelines for how the study was organized, examined, and interpreted, thus helping medical professionals to critically evaluate the quality of the evidence presented, while it can be used for both protocol writing and reporting of results (38,40).

The CONSORT statement was first published in 1996 to avoid systematic reporting errors while ensuring high standards in RCT reporting. An example of the CONSORT checklist is provided in Figure 5 below (39).

Other quality assessment instruments are responsible for different types of studies, such as the Newcastle-Ottawa Scale (NOS) for observational studies or the Preferred Reporting

Items for Systematic Reviews and Meta-analysis (PRISMA) for meta-analyses. Each of these instruments has its advantages and disadvantages. As the main advantages of CONSORT have been mentioned above, one of the disadvantages relates to its earlier form, which was not aimed at assessing the quality of RCTs (40). A report should also mention several factors that CONSORT does not specifically mention, such as details about ethical approval in the institution where the study was conducted and an example of informed consent from participants. Other possible study-related disclosures that are made should also be properly documented, for instance, disclosures regarding cost-effectiveness analyses (41).

CONSORT 2010 checklist		
Section/topic	Item number	Checklist item
Title and abstract	1a	Identification as a randomized trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions
Introduction Background and objectives	2a	Scientific background and explanation of the rationale
	2b	Specific objectives or hypotheses
Methods Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined?
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomization Sequence generation	8a	The method used to generate the random allocation sequence
	8b	Type of randomization; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	The mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned received intended treatment and were analyzed for the primary outcome
	13b	For each group, losses and exclusions after randomization, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing the baseline demographic and clinical characteristics for each group
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
Discussion Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, the multiplicity of analyses
	21	Generalizability (external validity, applicability) of the trial findings
	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information Registration	23	Registration number and name of trial registry
	24	Where the full trial protocol can be accessed, if available
	25	Sources of funding and other support (such as the supply of drugs), the role of funders

Figure 5. The CONSORT 2010 checklist (39).

2. OBJECTIVES

The aim of the presented study was to assess the reporting quality of randomized controlled trial abstracts on topical vitamin C.

The hypothesis of research :

1. The quality of abstracts of topical vitamin RCTs will be poor according to the total quantity of CONSORT elements.
2. In the observed period, there will be an increase in research in the field of topical vitamin C.
3. There will be differences in the frequency of reporting CONSORT items between studies of topical vitamin C.

3. MATERIALS & METHODS

For this study, a cross-sectional analysis of publicly available abstracts of randomized controlled trials (RCT) of topical vitamin C was performed. All RCTs on topical vitamin C were searched in PubMed. The search strategy used the terms "vitamin C skin" and "randomized controlled trial" as the selected article type. The search engine detected 109 public article titles in English, and all of them were accessible for further analysis. The abstract analysis was conducted in December 2022.

The CONSORT checklist for abstracts was used to assess the quality of coverage in the abstracts studied, and it includes 17 items which translates to a possible total score of 17. The higher the score the higher the quality of the presented abstract, and *vice versa* (39). Data from the abstracts were first recorded in a Microsoft Office Excel 2016 spreadsheet. Subsequently, statistical analysis was performed using MedCalc software for Windows (v.11.5.1.0, MedCalc Software, Ostend, Belgium). Data are presented as the median, interquartile range (IQR), total number, and proportion. Statistical significance was set at $P < 0.05$. To check the statistical significance chi-square test was used.

The complete checklist with all its features can be found in Figure 5 of the introductory section. The first three characteristics, which were collected, were basic data like the title of the article, published journal, and year of publication. Another feature of the checklist was to determine if the title of the abstract already indicates that it is an RCT.

The country of the research and the author code, i.e., if there is a mail, the contact of the researcher, and the number of authors were also three additional features. Some characteristics of the checklist depended on the participants. These characteristics determined whether there were more or less than 100 participants in the study, whether they were blinded, whether it was mentioned in the abstract how they were randomized, whether there was a placebo group, and if the intervention had better results than the placebo, how many participants were in each group. Another important checklist item that makes the article far more reliable is the mention of adverse effects.

On the structure of the abstracts, it was asked if they have any structure or if they are written clearly, what the aim of the study is the result and the conclusion. The last items on the list were about the registration and funding of the study.

4. RESULTS

An increase in the overall number of studies on the topic of topical vitamin C use was not observed in this study, as the number of published studies was evenly distributed each year. For instance, in the year 2010, 6 articles on this matter were published in journals indexed on MEDLINE, while in the year 2020, there were 7 articles published and abstracts available for further analysis. The proportion of articles in each year is 5.5% and 6.4%, respectively. The earliest publication was from 1979 and the newest was from 2022. Most of those articles were published in the last couple of years. The publishing journals were mostly dermatological based. The lowest CONSORT total score was 0, and the highest was 13 (out of the possible 17 items).

The median value for analyzed vitamin C abstracts was 7, IQR 5-9. Figure 6 presents the median value of CONSORT's total score in the period from 2019 to 2022.

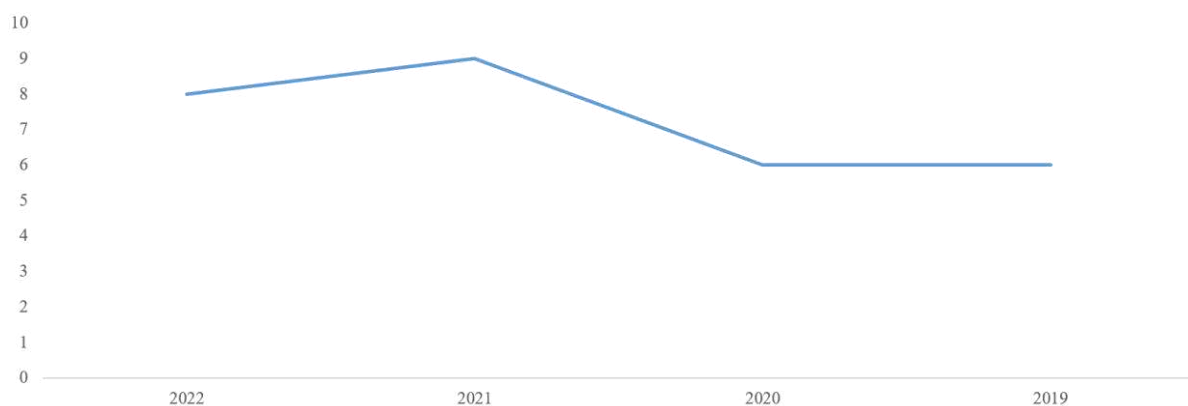


Figure 6. CONSORT median score in years 2019-2022

Only 3 studies (2.8%) were conducted as multicenter setting research. Significant results for primary outcomes were reported in 70 (64.2%) abstracts. Table 1 shows the proportion of reported CONSORT checklist items in vitamin C abstracts. The most frequently reported CONSORT items were primary outcome (95.4%), aim of the study (81.5%), and conclusion of the study (75.9%). The least frequently reported was information on how the studies were funded (2.8%) and under what criteria the randomization took place (4.6%).

Table 1. Proportion of reported CONSORT items

	N (%) N=109
Identification as RCT in the title	28 (25.7)
Authors contact details	41 (38.7)
Trial design	8 (7.4)
Participants	7 (6.5)
Interventions	70 (64.8)
Objective	88 (81.5)
Outcomes	103 (95.4)
Randomization type	5 (4.6)
Blinding (masking)	50 (46.3)
Numbers randomized	31 (28.7)
Recruitment	79 (73.1)
Numbers analyzed	24 (22.2)
Trial outcome	76 (70.4)
Reported harms	34 (31.5)
Conclusion	82 (75.9)
Trial registration	7 (6.5)
Funding	3 (2.8)

Data are presented as whole number (%)

In total, 59 (53.7%) of abstracts were structured compared to 50 (46.3%) articles not showing a structure in their abstracts. A statistically significant difference was observed between structured and unstructured abstracts in the reporting of several CONSORT items, as shown in Table 2. RCT was more frequently included in the title of structured abstracts, compared to unstructured abstracts (67.9% vs. 32.1%, $P=0.012$).

Furthermore, the aim of the study was more often written down in the group with structured abstracts compared to those without (64.8% vs. 35.2%, $P < 0.001$). Another statistically significant difference between these two groups was found in the recruitment category, which indicates whether the study has ended or is still ongoing (60.8% vs. 39.2%, $P=0.027$). The item of the checklist that takes into account the reporting of adverse effects in

the studies also shows an important difference on behalf of the group with structured abstracts (67.6% vs. 32.4%, P=0.023). In addition, in the category dealing with the general interpretation of results in the form of a conclusion, the group with structured abstracts performs again better (67.1% vs. 32.9%, P<0.001). The last item on the CONSORT checklist, where we found a statistically significant difference, was in the trial registration, whether the registration number was clearly written down as well as the name of the trial registry. Again, we had superior results for the structured abstract group compared to the unstructured abstract group (100.0% vs. 0%, P=0.032).

Table 2. Comparison of CONSORT items in structured and unstructured abstracts

	N (%) N=59	N (%) N=50	P value*
	Structured abstracts	Unstructured abstracts	
Identification as RCT in the title	19 (67.9)	9 (32.1)	0.012
Authors contact details	21 (51.2)	20 (48.8)	0.836
Trial design	5 (62.5)	3 (37.5)	0.887
Participants	6 (85.7)	1 (14.3)	0.172
Intervention	41 (58.6)	29 (41.4)	0.240
Objective	57 (64.8)	31 (35.2)	<0.001
Outcomes	56 (54.4)	47 (45.6)	0.865
Randomization type	3 (40.0)	2 (60.0)	0.683
Blinding (masking)	28 (56.0)	22 (44.0)	0.802
Numbers randomized	17 (54.8)	14 (45.2)	0.949
Recruitment	48 (60.8)	31 (39.2)	0.027
Numbers analyzed	14 (58.3)	10 (41.7)	0.777
Trial outcomes	43 (56.6)	33 (43.4)	0.476
Reported harms	23 (67.6)	11 (32.4)	0.023
Conclusion	55 (67.1)	27 (32.9)	<0.001
Trial registration	7 (100.0)	0 (0)	0.032
Funding	1 (33.3)	2 (66.7)	0.896

Data are presented as whole number (%)

*chi-squared test

5. DISCUSSION

Topical vitamin C has been widely used because of its proposed effect on skin aging and pigmentation disorders. Unfortunately, most of the RCT abstracts examined in this study scored poorly on the CONSORT checklist. This may be because there are generally not many studies on topical vitamin C compared with other substances that show effects on the skin. Moreover, some of the included studies were published before the CONSORT checklist was published and endorsed by scientific journals. Thus another explanation for the low score could be that the quality of reporting RCTs in the dermatological literature has not been given much attention since the late 2000s (42). It is worth mentioning that none of the included abstracts achieved a full score (17 points).

On the other hand, our results can be interpreted with caution from another point of view. According to the low number of published data on this subject in the MEDLINE database, it could be assumed that the cosmetic industry invests more effort in marketing anti-aging products, or vitamin C than the products analyzed in our study, but the money is not invested in efficacy testing and conduction of high-quality scientific studies and publication of high-quality articles.

As can be seen in Table 1, only 25.7% of the articles stated in the title that it was an RCT. If this point was considered more when writing an article, it could be more attractive to professionals in the first moment, as they would know the high quality of RCTs in research. Another point of transparency is the mentioning of adverse effects because these can also occur in studies. After all, everybody reacts differently and this should be taken into account. Of course, these adverse effects, even if they are mild, can also scare a reader away from a product, which might be a reason why they are not mentioned so often when you want to market a product.

One of the lowest-scoring items is the funding or disclosure of the source of funding. One reason for this could be a conflict of interest. If the funding for a study comes from an organization that has an interest in the results of the study, there is a possibility of a conflict of interest. In these cases, researchers may want to avoid having their results questioned because of these conflicts of interest. Sometimes, however, it may be because researchers have limited resources to conduct their studies. In such cases, they may not be able to provide full details of their funding, as this could affect their ability to obtain additional funding.

Moreover, the beneficial impacts of reporting sponsorship might include openness and credibility. Disclosing funding assists other scientists and the general public to identify

potential conflicts of interest and better evaluating study results. This improves the research's transparency and reliability. Furthermore, it may have a good influence on reproducibility. When the funding for a study is made public, other researchers can repeat it or undertake additional research to validate or extend the findings. This improves scientific research in general. Research confidence would suffer as well. The disclosure of funding contributes to public trust in research and the scientific community. Overall, it helps to alleviate worries about potential bias or influence by donors.

Another item that only a small proportion of studies included is the multicenter study setting. It would be of interest to a broader population, from different climate areas or different race/ethnicity, if studies would include several centers. Other than generalizability, multicenter studies would also include experts from different centers, which could hypothetically lead to an improvement of study quality and consequently to a better article and abstract.

However, the CONSORT checklist should be seen as an opportunity for future scientists to use it as a certain standard to achieve more transparency and reliability in their RCTs. Especially in the cosmetics industry, where a lot of money is earned with anti-aging products and skin care in general. With a certain amount of transparency, more patients can find the right product with the desired effect. And expensive, supposedly promising products, which don't work lose their value.

A systematic review from 2009 of two dermatological journals, namely the Journal of the American Academy of Dermatology and the British Journal of Dermatology, using the CONSORT principles showed similar results. They revealed that the quality of RCTs in dermatology is poor and needs to be improved (43). After adjustment for variables, studies with central randomization published in the British Journal of Dermatology, which now requires registration of studies and full publication in accordance with the reporting guidelines of CONSORT, were essentially associated with optimal reporting quality (42, 44).

A 2017 study on alopecia, written according to the CONSORT guidelines, is a good example of how to achieve a high score on the checklist. Reading this article, one can see the positive effects of the guidelines. The article is easy to read due to its structure and shows high reliability and transparency (45).

Our study has one large limitation, as we have only included the MEDLINE database. Future studies should include abstracts available on Scopus and Google Scholar.

6. CONCLUSIONS

In conclusion, after analyzing the 109 publicly available articles on PubMed, we can say that the quality of research on topical vitamin C is generally low. This fact also implies the general field of dermatology as seen in previous studies. The CONSORT checklist provides a helpful tool to make an article more readable, but also more transparent and trustworthy for readers. As the first journals have recently adopted CONSORT as a standard for publishing articles, there is hope that this checklist will become more widely used, thereby increasing quality and reducing bias.

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8. SUMMARY

Objectives: The aim of this study was to assess the reporting quality of randomized controlled trial abstracts on topical vitamin C.

Materials and Methods: We conducted a comprehensive analysis of randomized controlled trials focused on local vitamin C. The quality of abstracts was assessed using the CONSORT checklist, which consists of 17 items.

Results: During the observation period, there was no significant increase in the number of studies on the topical use of vitamin C products over the years. The proportion of articles in each year was 5.5%. The total CONSORT score ranged from 0 to 13 out of a possible 17 points, with a median score of 7 and an interquartile range of 5-9. The least frequently reported items were information on funding sources (2.8%) and randomization criteria (4.6%). There were significant differences between structured and unstructured abstracts in the reporting of several CONSORT items. Structured abstracts were more likely to include the term "RCT" in the title (67.9% vs. 32.1%, $P=0.012$). The last item for which a significant difference was observed was trial registration, with structured abstracts more likely to report the trial registration number and the name of the trial registry (100.0% vs 0%, $P=0.032$).

Conclusion: Analysis of abstracts on the use of topical vitamin C indicates that the quality of abstracts in this area is generally low. The CONSORT checklist has proven to be a valuable tool for improving the readability, transparency, and reliability of articles. As more journals adopt CONSORT as their publication standard, it is desirable that it be used in the field of cosmetology.

9. CROATIAN SUMMARY

Naslov: Kvaliteta sažetaka randomiziranih kontroliranih ispitivanja topikalnog vitamina C.

Ciljevi: Cilj ovog istraživanja je bio procijeniti kvalitetu sažetaka randomiziranih kontroliranih ispitivanja pokusa koji su ispitivali učinak topikalno korištenog vitamina C.

Metode: Proveli smo presječnu analizu randomiziranih kontroliranih ispitivanja koja su se usredotočila na lokalni vitamin C. Kvaliteta sažetaka procijenjena je CONSORT kontrolnom listom koja se sastoji od 17 stavki.

Rezultati: U promatranom periodu nije uočeno značajno povećanja broja istraživanja o lokalnoj uporabi proizvoda s vitaminom C tijekom godina. Udio članaka u svakoj godini bio je 5,5%. Ukupni rezultat CONSORT-a kretao se od 0 do 13 od 17 mogućih bodova, s medijanom rezultata od 7 i interkvartilnim rasponom od 5-9. Najrjeđe prijavljene stavke bile su informacije o izvorima financiranja (2,8%) i kriterijima randomizacije (4,6%). Postojale su značajne razlike između strukturiranih i nestrukturiranih sažetaka u izvješćivanju nekoliko CONSORT stavki. Strukturirani sažeci češće uključuju izraz "RCT" u naslovu (67,9% u odnosu na 32,1%, $P=0,012$). Posljednja stavka u kojoj je uočena značajna razlika bila je registracija ispitivanja, sa strukturiranim sažecima koji pokazuju jasniji registracijski broj i naziv registra ispitivanja u usporedbi s nestrukturiranim sažecima (100,0% naspram 0%, $P=0,032$).

Zaključak: Analiza sažetaka o korištenju lokalnog vitamina C pokazuje da je kvaliteta sažetaka u ovom području općenito niska. Kontrolni popis CONSORT pokazao se kao vrijedan alat za poboljšanje čitljivosti, transparentnosti i pouzdanosti članaka. Kako sve više časopisa usvaja CONSORT kao svoj standard objavljivanja, poželjno je da se koristi i u području kozmetologije.