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Multidisciplinary consensus on the benefits of topical vitamin C

Consenso multidisciplinar sobre os benefícios da vitamina C tópica

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ABSTRACT

Vitamin C, or L-ascorbic acid, is the most abundant antioxidant in human skin and its topical replacement has proven relevant, since this reservoir is consumed by external aggression, and it is used in the prevention and treatment of skin aging. This review was based on bibliographic research in the PubMed and LILACS databases and two consensus meetings between the authors to analyze the evidence for its topical use. The highest level of evidence of skin activity has been found in the pure and stabilized form of ascorbic acid. Derivatives, carriers, and nanoformulas are being developed, however further clinical and comparative studies are needed.

Keywords: Ascorbic Acid; Antioxidants; Skin Aging; Hyperpigmentation; Cosmeceuticals.

RESUMO

A vitamina C, ou ácido L-ascórbico (AA), é o antioxidante mais abundante na pele humana, e sua reposição tópica mostrou-se relevante, pois seu estoque é consumido diante de agressões externas, e por atuar na prevenção e tratamento do envelhecimento cutâneo. Essa revisão baseou-se em pesquisa bibliográfica nas bases PubMed e LILACS e em duas reuniões de consenso entre os autores para análise das evidências sobre seu uso tópico. O AA puro e estabilizado é a forma que apresenta maior nível de evidências de atividade na pele. Derivados, carreadores e nanofórmulas estão sendo desenvolvidos, entretanto mais estudos clínicos e comparativos são necessários.

Palavras-chave: *Ácido Ascórbico; Antioxidantes; Envelhecimento da Pele; Hiperpigmentação; Cosmecêuticos.*

Review article

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INTRODUCTION

Given that the skin is the organ most exposed to external factors that accelerate the skin aging process, such as ultraviolet radiation, smoking, pollution, poor diet and stress,[1] the skin care market is the leading segment of the cosmetics industry, accounting for approximately 36% of the global market.Vitamin C, or L-ascorbic acid (AA), is an important ingredient in dermocosmetic products due to its multifunctionality.[2,3] AA is an essential nutrient obtained exclusively from exogenous sources, and is the most abundant antioxidant in human skin,[4] whose biochemical activity is restricted to its levorotatory (L) form, since the dextrorotatory form has no significant biological activity.[5] The first publications on the topical use of AA date back to the early 1960s, and this form is essential for increasing cutaneous bioavailability, given that the levels achievable through topical application are 20 to 40 times higher than with oral AA supplementation.[6] Moreover, when the skin becomes saturated with AA through topical application, a reservoir effect occurs in which AA tends to stabilize and remain available in the skin for 3 to 4 days.[4,6,7] This storage provides prolonged protection against environmental damage, such as UV radiation, pollution, and smoking, which induces oxidative stress in the skin.[1,7–9] Although the effectiveness of topical AA has been demonstrated,[8,10] developing formulations for topical use is still challenging due to the molecule's instability, which has stimulated research into AA derivatives and active release technologies. However, although molecular stability has been improved through these innovations, comparative studies on the clinical response and therapeutic action of these new derivatives in comparison with AA are still lacking in the literature.This review will explore the types of AA available for topical use, their proven benefits, and their applicability for clinical dermatology.

METHODS

This article is the result of two consensus meetings between the authors, dermatologists, and pharmacists held in November 2022. Prior to the meetings, a comprehensive bibliographic search was performed in the PubMed and LILACS databases, using a combination of the keywords "vitamin C" or "ascorbic acid" and "skin" and "topical", to find relevant articles involving three themes: (1) the efficacy, function, and mechanism of action of AA in its different formats; (2) advances in formulation regarding the efficacy, stability, skin penetration, and bioavailability of AA and its derivatives; and (3) the application and clinical efficacy of topical AA in different forms. A third of the selected articles involved authors affiliated with Brazilian institutions, indicating the relevance of the topic in Brazil. In the meetings, the topics were discussed based on the published literature, and while preparing the review's manuscript, other published articles and relevant technical documentation were included by mutual agreement among the authors.

RESULTS AND DISCUSSION

Biological functions of vitamin C in the skin

The most discussed functions of AA in the literature are its ability to neutralize free radicals (including reactive oxygen species) and its relevance in collagen synthesis. Table 1 summarizes the evidence of these and the other functions of AA and some of its derivatives in the skin, including anti-inflammatory action, photoprotection, its importance in the skin barrier function, antiglycation action, and brightening action.[2,8–11]

Specificities of topical vitamin C formulation

In topical formulations whose main active ingredients are antioxidants, factors such as compatibility, stability, and penetration must be prioritized, ensuring that their action is synergistic and that the active ingredients are not neutralized in the vehicle.[7,20] One of the main challenges in using AA is to ensure its chemical stability and topical bioavailability in a suitable vehicle.[23,24] Eight types of serum sold in the Brazilian market were evaluated biweekly for AA content with ultra-high performance liquid chromatography, of which only three had concentrations ≥ 5% at baseline and after 60 days. It was also observed that the cost of the AA serum may be related to the product's quality and stability, since the most expensive samples had the highest concentrations of AA throughout the study.[25] AA is a very unstable molecule that can easily oxidize, losing its antioxidant capacity, either by ionization in water at neutral or higher pH (greater stability is obtained at pH ≤ 4), or by exposure to light, high temperature, contact with air, or the occurrence of metal ions.[26] In fact, AA initially degrades to dehydro-L-ascorbic acid in a reversible manner, but can be irreversibly hydrolyzed to 2,3-diketo-L-gulonic acid (Figure 1), losing its activity and degrading into small molecules. The reversible transformation of AA into dehydro--L-ascorbic acid in the skin functions as an oxidation-reduction system that allows cellular interaction and bioactivity of the two molecules.[5] In formulations, the AA degradation process is generally accompanied by a gradual change in color,[24] However, the isolated darkening of the formula cannot necessarily be considered as loss of dermatological efficacy, since it is also related to the concentration of free AA and bioavailability in the skin.[25] Pinnell et al.[7] studied the ideal parameters for enabling percutaneous absorption of AA and supplementing the skin's natural antioxidant reservoir. They found that pure AA (pharmaceutical grade) should be formulated cold in an acidic medium (pH ≤ 3.5) to prevent ionic charge degradation.[7] In addition to adjusting the pH, the formulation must contain an ideal concentration of AA (5 to 20%) to promote delivery of the active ingredient through the stratum corneum and hence achieve better results. When testing AA concentrations of 5 to 30% at pH 3.2, skin levels of AA increased, reaching their maximum at 20%, with decreased permeation tending to occur at higher concentrations.[2,7] In addition to standardizing the physical-chemical parameters of pure and free AA solution, such as the ideal concentration and pH to ensure stability and dermal penetration,[7,20,27] other strategies have

Table 1: Evidence of the main biological actions of L-ascorbic acid and some of its derivatives in the skin

Biological action	Study design	Active ingredients/ concentrations	Main results and mechanisms	Reference
Antioxidant effect	*In vitro* (chemiluminescence)	AA 0.000125% to 0.002%; MAP 0.0021% to 0.0337%; ATIP 0.0082% to 0.1316%	Antioxidant activity proven by inhibiting the formation of free radicals even at low concentrations; AA showed a better antioxidant effect than the derivatives.	Maia Campos *et al.*[12]
	In vitro (lipid peroxidation)	AA 0.6% and 1.5%; MAP 0.45% and 0.9%; and ATIP 0.45% and 0.9%.		
Moisturizing effect	*In vivo* (daily application for 4 weeks on the forearm of healthy individuals)	AA 2% at pH 3.5; MAP 2% at pH 7.0; ATIP 2% at pH 5.5	All formulas increased hydration of the stratum corneum; AA increased transepidermal water loss, indicating increased epidermal cell renewal; MAP, despite penetrating less than AA, increased hydration in the deep epidermis; ATIP had no effect.	Maia Campos *et al.*[12]
	In vitro (keratinocyte culture)	AA 50 µg/ml and 1.2 mM calcium ions	Significant increase in ceramide content, helping in the proliferation and differentiation of keratinocytes in the epidermis and improving hydration	Kim *et al.*[13]
Effect on skin barrier integrity	*In vitro* (keratinocyte culture, reconstructed human epidermis and bilayer skin equivalent)	AA	Increased content of glucosylceramide and ceramide 6 and 7; improved lipid profile and architecture of the stratum corneum.	Ponec *et al.*[14]
	In vitro (keratinocyte culture)	MAP	Increased keratinocyte differentiation through activation of the protein kinase C-dependent transcription factor activating protein-1.	Savini *et al.*[15]
Effect on collagenesis	*In vivo* (biopsy, postmenopausal women)	AA 5% at pH 6.0	Increased mRNA levels for procollagens I and III	Nusgens *et al.*[16]
	In vitro (culture of human skin fibroblasts exposed to UV radiation and hydrogen peroxide);	AA	Cofactor of lysyl and prolyl hydroxylase enzymes that crosslink and stabilize collagen fibers (adequate structure)	Gegotek *et al.*[17]
	In vitro	AA	Protective effect on degenerative changes that reduce collagen due to decreased superoxide dismutase in the skin	Addor[18]
Anti-inflammatory effect	*In vitro* (keratinocyte and fibroblast cultures)	AA	Inhibition of nuclear transcription factor kappa B. Oxidative stress activates nuclear transcription factor kappa B, which is responsible for inducing the production of several pro-inflammatory cytokines, such as TNF-alpha, IL-1, IL-6 and IL-8, which contribute to inflammation and skin aging.	Farris[2]
Antiglycation effect	*In vitro*	AA	Inhibition of glycation and subsequent end-products.	Gkogkolou & Böhm[19]
Photoprotective effect	*In vivo* (topical application to porcine skin for 4 days prior to UV irradiation)	AA 15% + vitamin E 1% at pH 3.2; comparison with isolated actives at the same concentration	AA 15% and vitamin E 1% alone protected the skin from UV-induced erythema 2 times more than the vehicle; AA 15% + vitamin E 1% and ferulic acid 0.5% alone protected the skin 4 times more. AA 15% + vitamin E 1% + ferulic acid provided 8 times more protection against UV, which was confirmed by colorimetry of the erythema and sunburn cell count with significant decrease.	Lin *et al.*[20]
		AA 15% + vitamin E 1% + ferulic acid 0.5%; comparison with isolated active ingredients in the same concentration		
Whitening effect	*In vitro* (culture of UVA-irradiated keratinocytes)	3-O-ethyl ascorbic acid	3-O-ethyl ascorbic acid had antimelanogenic effects via Nrf2-mediated α-MSH inhibition and autophagy induction	Chen *et al.*[21]
	In vivo (clinical examination, women 23 to 43 years of age)	AA 5%	AA inhibited tyrosinase through interaction with copper ions at the beginning of the melanin synthesis pathway	Espinal-Perez *et al.*[22]

AA: L-ascorbic acid; ATIP: ascorbyl tetraisopalmitate; MAP: magnesium ascorbyl phosphate.

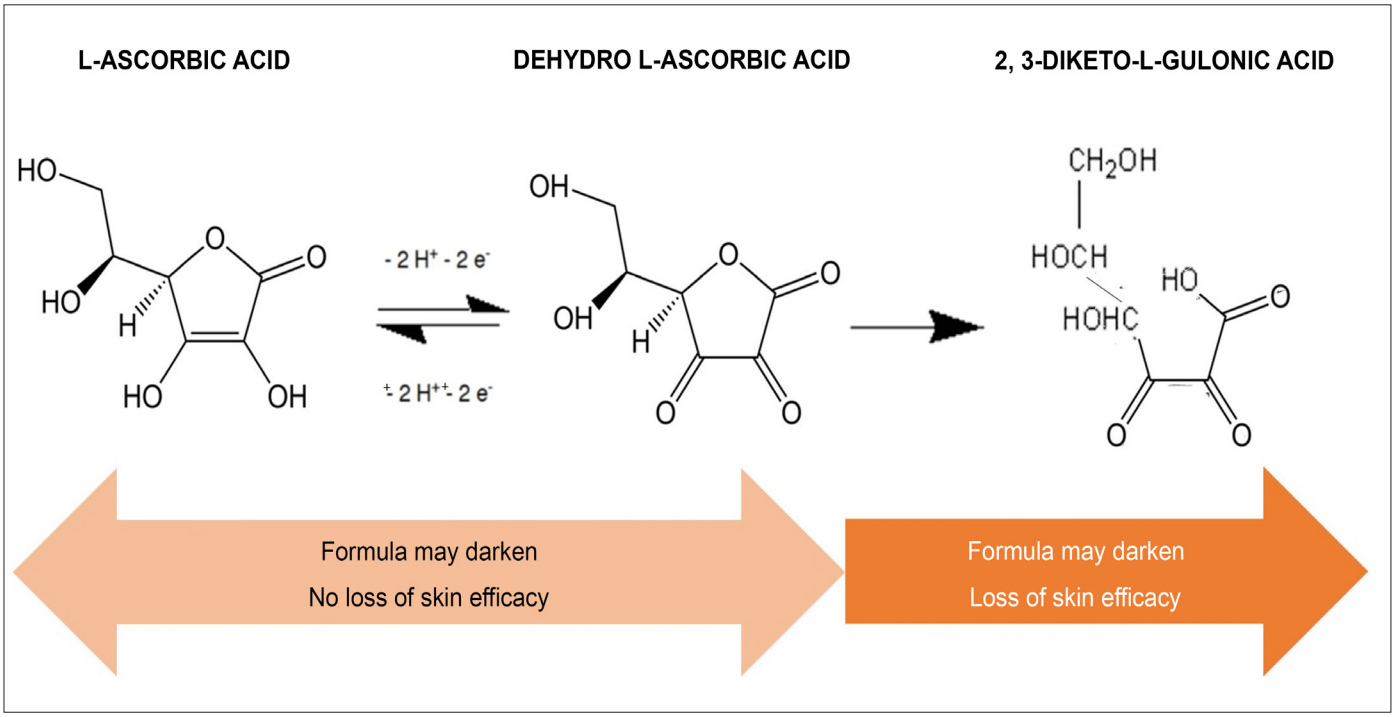

FIGURE 1: Oxidation of L-ascorbic acid

been developed to overcome the limitations of topical administration (Figure 2). Efforts to make the topical administration of AA viable are only clinically important when the strategy not only stabilizes AA but ensures its safe penetration into the skin and that it remains free and stable long enough to perform its activity. Adding preservatives and co-antioxidants prevents the degradation of AA. Vitamin E, ferulic acid, and sodium metabisulfite have shown good results, although use of the latter is limited due to its odor.[24,28] In addition to ferulic acid, other active plant-based ingredients can be used in synergistic antioxidant systems to stabilize AA.[24,29] The flavonoid phloretin stabilizes and increases the cutaneous availability of topically applied AA and ferulic acid.[29,30] The lipophilicity of phloretin, which indicates high solubility in skin lipids, can explain its use as a permeation enhancer for other active ingredients.[29] Silymarin 0.5%, obtained from the Silybum marianum thistle, synergizes with AA 15% and ferulic acid 0.5% in an aqueous formulation with an acidic pH to reduce lipid peroxidation caused by exposure to UV radiation.[31]

Degradation of topical AA can also be avoided by using polyol-type humectants and solvents, such as glycerin, propylene glycol, and butylene glycol for non-aqueous vehicles with low oxygen permeability.[24] Humectants, such as palmitic acid, propanediol, and glycerin, have also positively influenced the stability of AA in anhydrous vehicles or emulsions.[24] Based on these results, polyols have been used in water-in-silicone emulsions, with a formulation prepared in a nitrogen atmosphere, to associate pure AA in concentrations of 5 to 10% with glycerin and other polyols that, in addition to preventing contact between AA and the water in the emulsion, facilitate penetration and action directly in the dermis, where collagen fibers are formed.[16,32] A number of AA derivatives have been proposed, and some are already being used in dermatology, to facilitate the permeation, stability, and bioavailability of AA. Generally, AA derivatives must be enzymatically converted to AA in keratinocytes and fibroblasts to have an effect.[28,33] To date, however, no information could be found on the impact of AA derivatives on the skin's AA reservoir. However, the possibility of numerous combinations of AA derivatives with similar or different solubilities, and even with AA itself in the same formulation, could be advantageous.[24] The main AA derivatives used in Brazil, both in industry and in compounding pharmacies, are magnesium ascorbyl phosphate,[12,24,26,28] sodium L-ascorbyl-2-phosphate,[24,28] ascorbyl tetraisopalmitate,[12,24,28,34] ascorbyl methylsilanol pectinate,[25,35] ascorbic acid 2-glucoside[24,28,36–38] and 3-O-ethyl ascorbic acid[21,28,39], which may be known by different trade names. However, the level of scientific evidence for the efficacy of AA is superior to that of derivatives (Table 2). Nanotechnology vectorization and encapsulation have been used to improve topical delivery of the active ingredient and protect AA from degradation.[24] These systems include microvectors and nanovectors, liposomes (double lipid membrane with hydrophilic content), microemulsions, and micelles, which can dynamically increase the stability of AA in search of more durable products. However, it is challenging to define the ideal concentration of AA or derivatives and the permeation of AA into the skin.[24,28] In general, articles that address

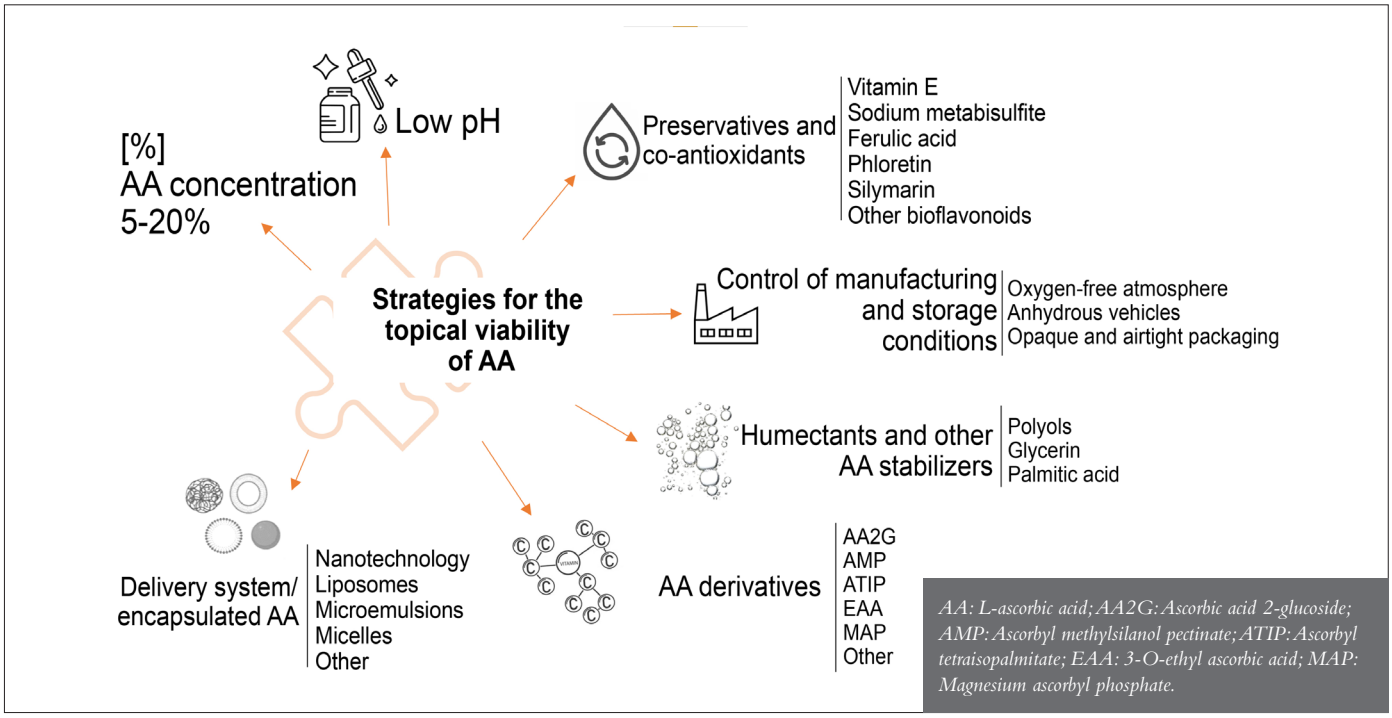

Figure 2: Main strategies for topical viability of vitamin C

the vectorization process have not reported the concentration of free AA in the vectors.[28,40]

AA: L-ascorbic acid; MAP: magnesium ascorbyl phosphate; SAP: Sodium L-ascorbyl-2-phosphate; ATIP: ascorbyl tetraisopalmitate; AMP: ascorbyl methylsilanol pectinate; AA2G: ascorbic acid 2-glucoside and EAA: 3-O-ethyl ascorbic acid.

It has been demonstrated that liposomal formulations in vesicles with different lipid compositions containing AA have increased the stability of AA and promoted greater skin retention, suggesting efficacious treatment of skin photoaging.[41] The negative liposomal charge favored retention of the active ingredient in the epidermis and dermis.[40] Nanotechnology has led to the development of several raw materials for cosmetics (nanovectors, nanocapsules, nanosomes, ethosomes, niosomes, and other nanometric systems) that improve the stability and permeation of AA in the skin, based on different types of materials. Although the supply of dermatological products and ingredients for compounding AA or nanoencapsulated AA derivatives is growing, there are still few studies, especially in vivo studies, regarding the targeting, permeation, and, most importantly, the concentration of free AA delivered to the skin through nanotechnology.[33,41,42] In Brazil, magnesium ascorbyl phosphate is available through commercial encapsulation systems in collagen and chondroitin sulfate of marine origin, in both micro- and nanospheres, which reinforce the stability of the derivative to increase skin permeation. However, even with nanotechnology, permeation appears to be limited to the epidermis, with prolonged release of the content through enzymatic degradation.[24,41] Ultradeformable elastic nanovesicles (spanlastics), formed mainly from alcohol, propylene glycol, polysorbate 80, and surfactants, which were loaded with AA and compared with AA solution at pH 2.38, have shown better permeation and cutaneous concentration at a dose sufficient to demonstrate antioxidant efficacy, lower metalloproteinase expression *in vitro*, and clinical improvement of UVB-damaged skin according to histological evaluation.[33,43] Nanotechnology requires quality control and particle size control during manufacturing. To ensure safety for topical use, vectors > 100 nm are recommended to avoid the risk of systemic permeation. Few articles have demonstrated the cutaneous bioavailability of AA in nanotechnology formulations, and limited information is available about the concentration of either AA or the derivative used in the delivery system. In general, few studies have compared AA and its nanotechnological form, despite evidence that nanoparticles can release AA for > 8 h *in vitro*.[44] Although nanotechnology is promising for cosmetics, there are regulatory and industrial issues that limit its clinical use.[24] It is difficult to determine the specificity and clinical efficacy of each nanotechnological formulation of AA and derivatives.[24,28,33] RNA or DNA structures with high affinity and specificity for targets of interest, called aptamers, were the subject of a recent study on AA delivery. The DNA and AA aptamer was proposed as a new possibility for stabilizing AA in cosmetics.[33]

Table 2: Synthesis of evidence according to the mechanism of action of AA and derivatives.[26,28,35,37,38]

AA and derivatives / Main effects	GOLD STANDARD AA	MAP	SAP	ATIP	AMP	AA2G	EAA
CONVERSION TO AA (ACTIVE FORM)	= AA	*In vitro*	*In vitro*	*Ex vivo In vitro*	No data	*In vivo In vitro*	No data
ANTIOXIDANT	**Clinical** *In vitro*	*In vitro*	Clinical	*In vitro*	**Clinical** formulated with AA+AA2G+ other antioxidants	*Ex vivo In vivo In vitro*	*In vitro* compared with AA: smaller but prolonged
NEOCOLLAGENESIS	**Clinical (biópsia)**	*In vitro*	*In vitro*	*In vitro*	No data	*In vitro*	No data
ANTIMELANOGENESIS	**Clinical**	Clinical *In vitro*	Clinical	*Ex vivo In vitro*	No data	**Clinical,** with other assets, making it difficult to evaluate the clinical effect of AA2G *In vitro*	*In vivo In vitro*
CLINICAL RESULTS	Antioxidant effect, neocollagenesis, anti-wrinkle effect, depigmenting effect	Radiance	Moisturizing and calming effect	Moisturizing effect	Brightening and reduction of wrinkles and spots in photoaged skin	Stimulation of neocollagenesis in associations	Brightening and depigmenting effect

AA: L-ascorbic acid; MAP: magnesium ascorbyl phosphate; SAP: Sodium L-ascorbyl-2-phosphate; ATIP: ascorbyl tetraisopalmitate; AMP: ascorbyl methylsilanol pectinate; AA2G: ascorbic acid 2-glucoside and EAA: 3-O-ethyl ascorbic acid.

Evidence on the relationship between the efficacy and transcutaneous penetration of vitamin C in different formulations

Both the topical application of AA and its delivery to the skin layers are intrinsically dependent on the characteristics of the formulation.[7,24,26] However, comparative studies assessing the stability and effective transdermal penetration of different forms of AA are generally limited to *in vitro* studies.[24,26] Pinnell et al.[7] tested two products commercially available in the United States that contain AA derivatives (associated with magnesium ascorbyl phosphate 12% and ascorbyl palmitate 10%) in comparison with a formulation of pure AA 15% (free and stabilized at pH 3.2). Unlike ideally parameterized AA, topical application of formulations with AA derivatives did not significantly increase the AA content in the skin.[7] Despite being more stable, these AA derivatives appear to have lower skin penetration than free AA and do not have direct antioxidant activity, requiring conversion to AA by enzymatic reaction.[24,26] Later studies indicated that esterifying AA with palmitic acid does not guarantee satisfactory stability levels in topical products, despite the lipid nature of ascorbyl palmitate, probably because it interferes with the barrier function and antioxidant action of vitamin E in the skin.[24,26,45] One study suggested using AA 2-glucoside, a derivative of AA, in cosmeceuticals, although its antioxidant activity is lower than that of AA.[36] In this derivative, a glucose molecule associated with the hydroxyl group of the second carbon atom of AA protects it from high temperatures, pH, metal ions, light, and other degradation mechanisms. In the skin, it reacts with the alpha-glucosidase enzyme to release AA.[36] Thus, AA 2-glucoside was shown to be chemically stable and completely metabolized into AA, which guaranteed antioxidant efficacy (*in vitro* and ex vivo) at concentrations lower than those recommended for pure and free AA, although in vivo it had lower antioxidant action than AA plus vitamin E.[28,37] Another study suggested that AA 2-glucoside may protect cells against ionizing radiation by acting against free radicals, reducing initial DNA damage.[38] It has been observed that 3-O-ethyl AA is more lipophilic than AA 2-glucoside, which makes it more easily absorbed by the skin than other water-soluble AA derivatives.[39] Several mechanisms have been proposed for the antimelanogenic effect of 3-O-ethyl AA: increased autophagy in melanocytes[19]; inhibition of alpha melanocyte-stimulating hormone and increase in endogenous antioxidants via Nrf2 in keratinocytes[21]; lower activity of the transcription factor that regulates melanogenesis in melanocytes[21]; and lower tyrosinase activity through melanocyte cytoplasmic acidification.[46] It was also observed that AA plus magnesium ascorbyl phosphate has lower melanin and tyrosinase activity due to cytoplasmic acidification, which could result from increased transportation of AA across the membrane by the sodium-dependent vitamin C transporter-2.[46] This mechanism is an efficient way to inhibit tyrosinase without causing cytotoxicity to melanocytes.[46] Encapsulating AA 5% in emulsions containing liquid crystals, based on a combination of cetyl alcohol and polysorbate 60, formed a complex colloidal structure at the oil-water interface that ef-

ficiently stabilized AA for 4 months. Subsequently, a controlled clinical trial evaluated the effects of topical application of this stabilized form for 30 days compared to placebo, finding dermal redensification in high-frequency ultrasound measurements.[23] Regardless of the strategy used to keep AA stable, the molecule must remain in or be converted into its free form to perform its biological activity.[24,32] It has been found that the bioavailability of free AA in the skin layers (up to the dermis) could be increased by optimizing transcutaneous penetration through the following molecule stabilization parameters: AA in pharmaceutical grade purity; concentrations ranging from 5 to 20%, formulation at a low pH (2-4) and the presence of co-antioxidants, such as bioflavonoids and/or vitamin E.[7,26] Using a non-invasive method (Raman spectroscopy), a recent study assessed AA penetration in the skin of 10 healthy individuals after topical application of a serum containing 15% pure AA, free and stabilized at a low pH in combination with other antioxidants (vitamin E 1% and ferulic acid 0.5%). There was a significant increase in total AA in the upper layers of the skin 1h and 6h after application, as well as a significant increase of AA in the dermis after 6h, which demonstrated the epidermal and dermal bioavailability of AA in this serum.[27] Raman spectroscopy has also been used in vivo to compare an emulsion containing lipophilic derivatives of vitamins A, C (ascorbyl tetraisopalmitate), and E with an emulsion containing nanoparticles of these derivatives. The nanoparticles contributed to greater penetration of ascorbyl tetraisopalmitate and vitamin E derivative in terms of speed and depth, but they did not significantly improve the penetration of the vitamin A derivative. Although, in both emulsions, the three derivatives penetrated rapidly into the stratum corneum, the nanoparticles did not contribute to deeper penetration and, after 6 h, the lipophilic derivatives had penetrated only to the upper layers of the epidermis.[47]

Clinical evidence on the action of vitamin C

The clinical strategies and applicability of AA in dermatology are quite broad, since the skin requires a high concentration of AA to remain healthy. Topical use (Figure 3) is recommended mainly to treat skin aging, prevent photoaging, and reduce hyperpigmentation, increasing the uniformity of skin tone.[1,9]

Oxidative damage caused by the exposome

AA has been shown to be a potent topical antioxidant that neutralizes free radicals, which tend to accumulate in the skin due to exposure to exposomal factors, such as UV radiation, pollution, and smoking, which induce or aggravate dermatosis.[8,18] This activity is particularly important in the epidermis and corroborates the role of AA as a water-soluble component of the skin's antioxidant defense system, which is regulated by a complex network of enzymatic and non-enzymatic antioxidants, exogenous or endogenous, that protect the intra- and extracellular spaces from free radicals and, consequently, slow the skin aging process.[6,18]

Signs of skin aging

In addition to protecting against exposure damage, AA is essential for collagen synthesis and regulation of the collagen/elastin balance in the dermis. In a double-blind, controlled trial of 10 individuals with clinical photodamage to the face, 12 weeks of AA 10% treatment reduced photoaging scores and improved facial wrinkles and skin texture on the AA-treated side compared to the placebo side.[9,48] In addition to clinical improvement, biopsies have shown increased collagen in the dermis.[16,48] A significant improvement in skin histology and clinical appearance was observed in another double-blind, placebo-controlled trial using topical, free AA 5% stabilized in a cream applied to 20 individuals over a six-month period.[16,32] The efficacy of AA and its derivatives for skin rejuvenation can be synergistically enhanced through combination with other active ingredients,[49,50] such as amino acids, peptides, growth factors, hyaluronic acid, vitamin E, and other antioxidants.[28,33] The patient's therapeutic routine may require combination with other active ingredients, such as salicylic acid, niacinamide, or retinol.[28] Amino acids, in particular glycine, proline, and lysine or their precursors, can facilitate collagen production.[33] Reinforcing the relevance of the synergy of active ingredients in anti-aging efficacy, a gel-cream containing AA 5%, mannose 5%, and fragmented hyaluronic acid demonstrated clinical efficacy in reducing fine wrinkles and sagging, while increasing hydration, luminosity, and skin tone uniformity, which was corroborated by an *in vitro* study in an equivalent dermis model.[50] In an ex vivo study, Neves et al. assessed a serum containing AA 15% associated with neohesperidin, Pinus pinaster bark extract (trade name Pycnogenol), tocopherol, and hyaluronic acid, which, compared to the vehicle, reduced mRNA gene expression of inflammatory mediators associated with skin aging induced by air pollution.[49] The same formulation was tested for 90 days in a clinical and instrumental study (n=40), and it was found capable of reducing signs of skin aging, improving the structure of the dermoepidermal junction and reducing pigmentation of the basement membrane. Thus, it proved efficient in protecting the skin against pigmentation/skin aging induced by air pollution.[49]

Hyperchromia

In addition to its effects on signs of skin aging, AA also plays a role in the treatment and prevention of skin hyperpigmentation. Melanocytes are highly susceptible to oxidative damage, since melanogenesis is a pro-oxidative pathway. Thus, AA acts on melanogenesis by combating free radicals and inhibiting tyrosinase. In addition, AA favors the differentiation of keratinocytes and improves dermoepidermal cohesion, contributing to uniform skin tone.[8,22] Topical AA can help treat melasma and aid in skin maintenance after procedures for solar melanosis.[24,26,28] AA 5% and hydroquinone 4% in water-in--oil emulsions were compared in a for 16-week double-blind trial conducted in 16 individuals with melasma (phototypes IV

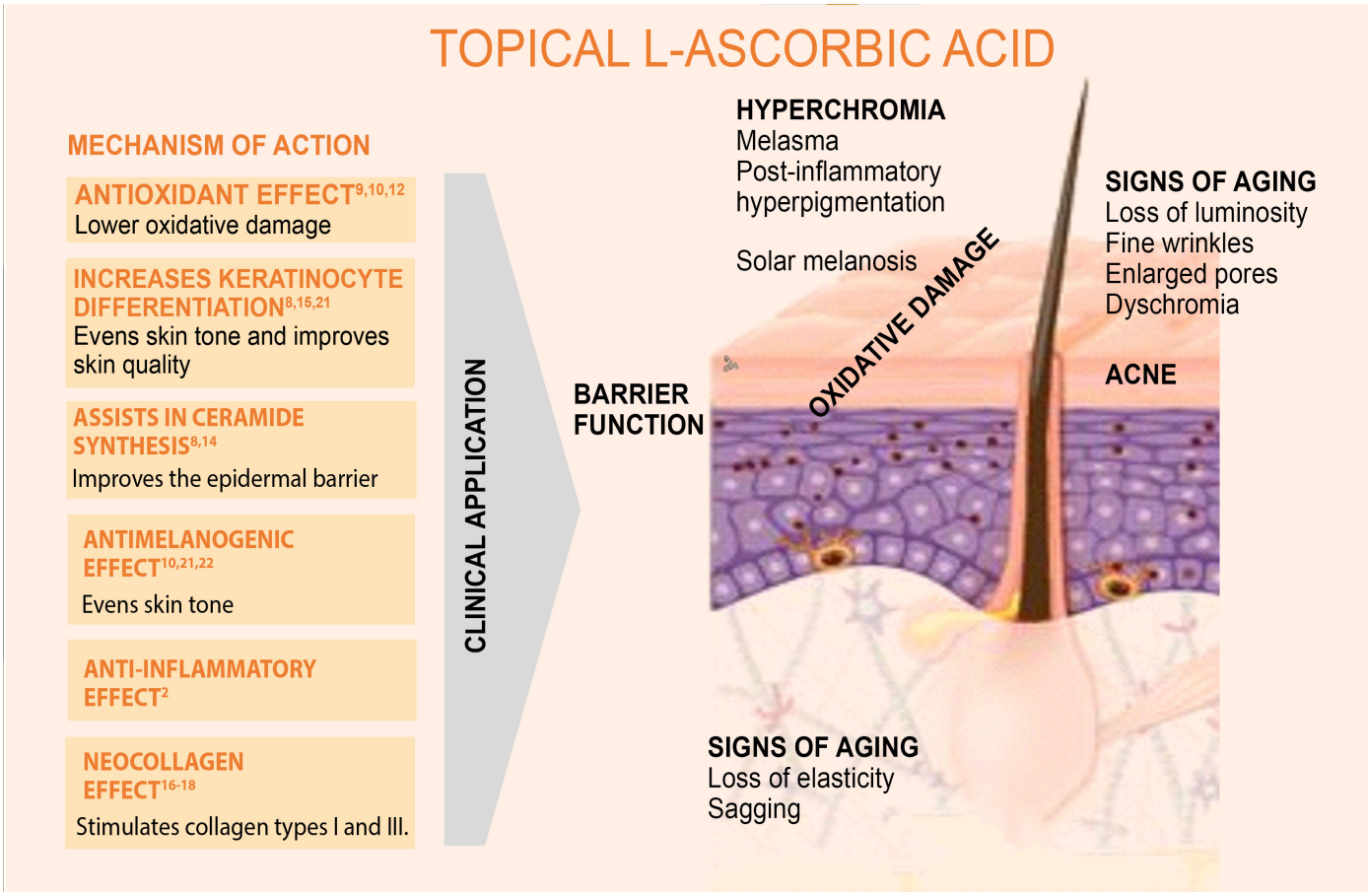

Figure 3: Actions and indications of topical vitamin C

and V). Although there was a faster and much better clinical response with hydroquinone (93.75% showed good to excellent improvement), adverse effects occurred in 68.75% of the patients, while on the side treated with AA they occurred in only 6.25% of the patients, which showed positive results (good to excellent improvement) in 62.5% of cases.[22]

Dermatological procedures and technologies

Topical application of AA and derivatives has been combined with procedures such as ultrasound, iontophoresis, ablative laser, microneedling, and microdermabrasion to increase the penetration and effects of AA.[33,51] The use of iontophoresis after topical application of AA increases the percutaneous absorption of the active ingredient in comparison with simple topical application. A controlled trial investigated 24 individuals treated with a serum containing AA 10% to the entire face and, on only one side, used a portable iontophoresis device at home twice a week for 8 weeks. Standardized images and corneometer measurements were made every 2 weeks, showing significant improvement in hydration and pore closure, although the device had less power than the model developed for medical use.[52] Previous studies have shown that iontophoresis following topical application of AA increases collagen production.[33] Fractional lasers have been used by dermatologists to treat signs of skin aging, and these procedures can substantially consume skin antioxidants. Combining the procedure with topical AA may reduce inflammation and help restore the skin.[51] A study demonstrated that after a fractional laser procedure, 7 daily applications of a serum containing AA 15% (stabilized at acidic pH) in association with ferulic acid and vitamin E reduced edema and erythema more rapidly than the vehicle (hemifacial; n=15). Overall, the serum was well tolerated immediately after fractional laser treatment, and the acidic pH helped inhibit infection. Furthermore, compared to the vehicle, the AA serum prevented a reduction of basic fibroblast growth factor. This marker is important not only in the proliferation of fibroblasts, but also in the synthesis of extracellular matrix macromolecules (glycosaminoglycans and hyaluronic acid) and inhibition of matrix metalloproteinase-1.[51] More recently, an article proposed topical application of a serum with AA 15% stabilized at acidic pH and associated with vitamin E and ferulic acid as an adjuvant treatment with Q-Switched Nd:YAG laser therapy. A comparative controlled trial included 18 men and women with melasma or solar melanosis, who applied the serum twice a day for 2 weeks after the laser

procedure. On the treated side, they presented a significant reduction in melanin index, but not in post-procedure erythema.[53] This laser therapy's brightening potential also enhances the penetration of active topical brightening and antioxidant ingredients for a synergistic effect. A case study on melasma treatment assessed the effect of a topical antioxidant serum containing AA 10% stabilized with phloretin and ferulic acid that was, for 120 days, applied daily and immediately after each biweekly Q-Switched laser session as an adjuvant treatment, due to the role of oxidative stress in this type of dermatosis.[54] These practices are consistent with integrated skin care that combines in-office treatments with at-home products to achieve complementary clinical benefits and reduce unwanted side effects. These studies support the efficacy of topical AA application immediately after deliberate barrier-breaking procedures, but the use of cosmetics for post-procedure AA delivery is under investigation by regulatory authorities.[33,51]

Parameters for prescription

A range of dermocosmetics that include AA is available to dermatologists, featuring different packaging, concentrations, and textures, mainly in serum, gel-cream, and cream forms.[3] While product availability makes it easier to adapt to the daily routine of patients, it also requires dermatologists to have in-depth knowledge of pharmacotechnical techniques to best adapt AA therapy to the clinical needs of each patient. In addition to considering the concentration, quality, and molecular form of AA, it is important to select a vehicle that presents a sensory experience adapted to the patient's skin type and profile, which facilitates treatment adherence. However, the main indication for AA in daily facial care seems to be the stimulation of collagen synthesis, which prevents and reduces signs of skin aging, smoothing fine wrinkles, and promoting perceived improvement in skin vitality, brightness, and firmness.[28] To this end, the active form of AA should reach deeper layers of the skin, ideally the dermis. Although AA does not absorb UV radiation, its undeniable ability to neutralize free radicals has justified the use of topical AA as a daily antioxidant (before applying sunscreen) to optimize protection against exposomal damage and, consequently, reduce the degradation of collagen and elastin, preventing signs of skin aging.[9] Using topical AA to maintain the skin's antioxidant reservoir at adequate levels is an adjuvant strategy to the daily use of sunscreen. These are important complementary mechanisms,[7] since UV radiation and high ozone levels due to pollution deplete vitamins C and E from the skin's surface.[1,7] Furthermore, laboratory studies have demonstrated a significant reduction in UVB-induced erythema after topical application of AA 10%.[2] AA derivatives have been added to sunscreens to prevent lipid peroxidation in oily and acne-prone skin, but the effects of each formula must be verified in vivo. For everyday use, AA has been shown to be a safe active ingredient, even with prolonged use[5] in all skin types, including sensitive skin.[8,54] However, some products may include warnings about the possibility of skin discomfort due to the high concentration of AA, suggesting a longer interval between applications.[5] For sensitive skin, formulations with very low pH should be avoided due to the possibility of irritation. Specific products have been developed for these individuals that combine soothing ingredients, such as acetyl dipeptide-1 cetyl ester (trade name Neurosensine), with 5% to 10% pure and free AA stabilized at pH 4.0 to 6.0 to reduce the possibility of sensitization. Formulations with AA derivatives (stable at pH 5 to 7) or nanoencapsulated AA promise less irritation and also seem suitable for those with sensitive skin. Dermocosmetics with AA are often indicated for use once or twice a day, and deciding about the most suitable product is influenced by several factors, such as a history of sensitive skin, the degree of oiliness, age, the individual needs of each patient, as well as the relationship between AA concentration and skin permeation.[9,27,28,40] Clinical trials of topical products containing AA are increasingly important, since different vehicles and combinations with other active ingredients can have different results. The results of AA derivatives can also differ from the free form, even when using the same vehicle. Because interactions between the ingredients can be unpredictable, dermatological studies and clinical evaluations must be performed on each formula to provide clinical confidence. *In vitro* studies, which indicate possible mechanisms of action, cannot guarantee the same efficacy in vivo. Proof of a product's efficacy must be based on clinical trials. Table 2 shows that, at present, only free AA has shown clinical efficacy and, thus, is considered the gold standard molecule in dermatology. Furthermore, it has been demonstrated that free AA, stabilized in its active form, has the best penetration in both the epidermis and the dermis, preventing and treating of signs of skin aging and skin hyperpigmentation.[7,20,30] There are still few comparative studies between AA and its derivatives or standardized clinical trials on different forms developed to provide greater topical efficacy. Thus, new studies are needed to fill this gap. This review has led to the following conclusions: increasingly higher concentrations of AA do not result in more effective products[7]; in addition to the concentration, the effectiveness of AA depends on the chemical form, vehicle, and even the packaging; pure AA, although easily oxidizable, can be stabilized at an acidic pH and through association with co-antioxidant active ingredients, as well as through specific technologies (polyols, for example); not all AA derivatives can release AA into the skin, and many only permeate the superficial epidermal layers; although some products report that nanovectors containing AA derivatives are can release AA equivalents, no clinical trials have validated this information.

FINAL CONSIDERATIONS

Numerous forms of AA are already available for topical use in dermatology, being recommended for the prevention and treatment of signs of photoaging, either as monotherapy or in combination with other active ingredients or in-office procedures. Clinical practice should be based on published evidence

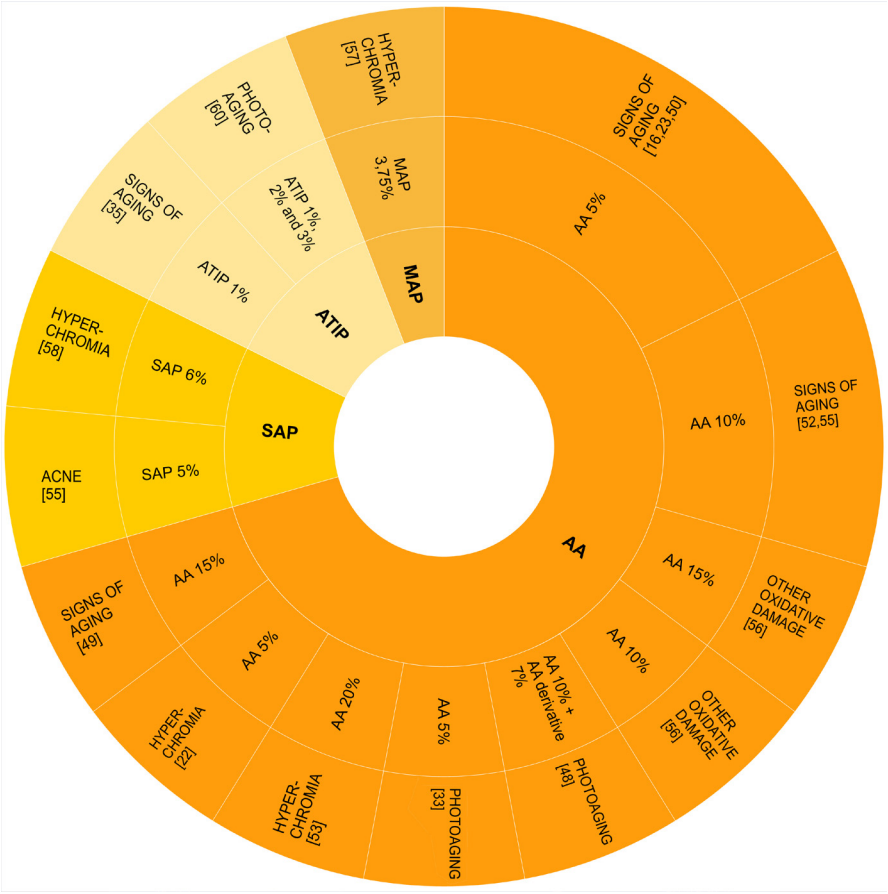

FIGURE 4: Clinical evidence of the mechanisms of action of topical vitamin C

AA: L-ascorbic acid; ATIP: ascorbyl tetraisopalmitate; MAP: magnesium ascorbyl phosphate; SAP: sodium L-ascorbyl-2-phosphate.

and should encourage research, in addition to transparency regarding technical information, efficacy and safety. For each formulation, the stability, penetration, and bioavailability of AA in the skin must be assessed, and data on clinical efficacy and patient adaptation to the product must be provided. AA is still the gold standard molecule for clinical practice (Figure 4) due to the higher level of evidence[16,22,23,32,48–50,52,53] regarding its mechanisms of action and clinical activity than other derivatives[34,55–60] and molecules available through nanotechnology. ●

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