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A Review of Clinical Efficacy of Topical Vitamin C and Its Derivatives

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Abstract: The last two decades have seen an increase in active-led skin care products in over the counter and retail market places. Consumers have become more knowledgeable about ingredients used in topical products resulting in formulations with vitamins and other active ingredients gaining popularity. Further, the need for instantaneous and short-term benefits, consumers are moving towards high doses of active products. This poses a challenge for formulation scientists to stabilize high active doses and ensure potency over shelf life. Vitamin C or ascorbic acid is one such ubiquitous active commonly found in topical products claiming brightening, skin firming and toning benefits. As humans lack the enzyme required for synthesis of Vitamin C, we obtain it through diet or topical application. Vitamin C consumption results in insignificant benefits due to limited bioavailability, making topical application the major route of delivery. Ascorbic acid is an antioxidant; when applied topically it protects the skin from damaging free radicals produced due to exposure to UV-rays and other environmental stressors. However, ascorbic acid has been reported to be unstable in aqueous systems and readily undergoes oxidation making it inactive. This has led to the generation of multiple pro-drugs and derivatives which dissociate to release free ascorbic acid or its ionic form in the skin. In this review, we have focused on the clinical efficacy of vitamin C and its derivatives, suitable for various applications. This will serve as a ready reckoner for formulators creating vitamin C based products.

Keywords: Ascorbic Acid, Vitamin C, Antioxidant, Depigmentation, Ethyl Ascorbic Acid, Ascorbyl Glucoside

1. Introduction

Vitamin C, also known as Ascorbic acid (AA) is one of the powerful natural antioxidants obtained from citrus fruits and other plants such as broccoli and strawberry. D and L-Ascorbic acid are the isomers of AA among which L-AA is biologically active (Figure 1). It is also found in both reduced and oxidized forms; AA and dehydroascorbic acid (DHA) respectively. [1] The human body cannot synthesize AA due to the lack of enzyme L-glucono-gamma lactone oxidase hence obtains it through diet. Even when consumed adequately, the amount of AA is too small to have a significant result on the skin, hence topical application becomes the only route to provide vitamin C [2].

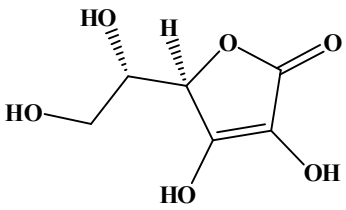


Figure 1. *L-Ascorbic Acid.*

L-AA is a water soluble, non-enzymatic antioxidant (which interrupts free radical chain reaction) that can be used alone or in combination with other ingredients in a cosmetic formula. Figure 2 summarizes the functions of AA as an antiaging agent, helps in depigmentation, anti-inflammation, and boosts collagen synthesis for healthier skin. Antioxidants present in skin protect against the oxidative stress caused by free radicals.

[2] AA modulates photoaging by donating electrons to neutralize the free radicals that are accumulated in our skin. A more stable ascorbate free radical is formed on the donation of first electron; donation of second electron results in formation of DHA which is non-reactive and can be converted back to AA by the enzyme DHA reductase in presence of glutathione [3]. AA also acts as a cofactor for the enzymes prolyl hydroxylase and lysyl hydroxylase which catalyze hydroxylation of proline and lysine. The triple helical structure of collagen formed by three collagen α-chain is stabilized by the presence of hydroxylated proline and hydroxylation of lysine influences fibrillogenesis and crosslinking of collagen. The procollagen mRNA which regulates type I and type III collagen synthesis are stabilized and transcription factors are activated by vitamin c thereby imparting anti-aging effect. [2] Vitamin C acts as a depigmenting agent by interrupting the step of melanogenesis by interacting with copper ions present in the active site of tyrosinase enzyme. Tyrosinase enzyme helps in the conversion of tyrosine to melanin [4]. Vitamin C also shows anti-inflammatory properties [2]. The activation of NF-kB transcription factor is suppressed by L-AA, which is responsible for pro-inflammatory cytokines production.

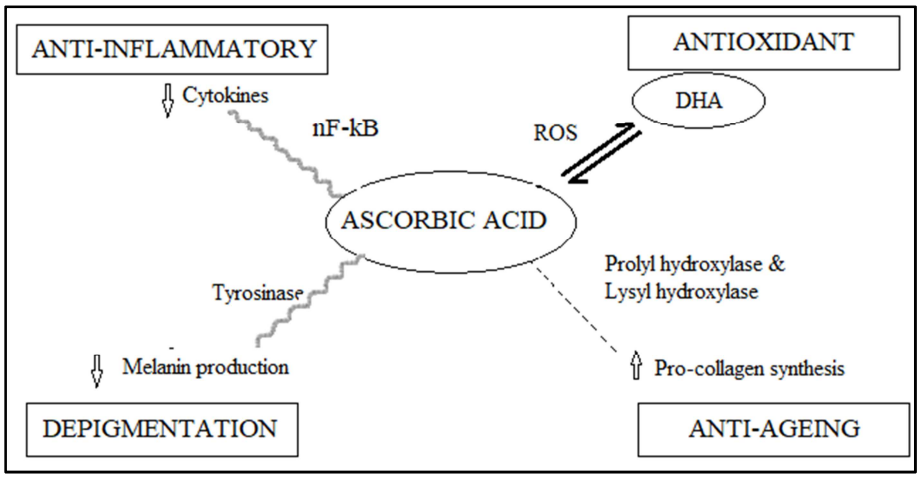


Figure 2. *Mechanisms of action of Ascorbic acid. Ascorbic acid acts as an antioxidant by readily converting to Dehydro ascorbic acid upon reaction with nascent oxygen generated from various stressors. It plays multiple roles in collagen synthesis, skin pigmentation and inflammatory pathways.*

Due to its multifunctional activity, AA is the go-to molecule in every formulator's armory. However, formulating AA is an intricate process. Vitamin C readily undergoes oxidation which is triggered by ionization in aqueous solution resulting in inactivation of the molecule while imparting a yellowish color to the formulation. The rate of degradation of AA depends on pH, temperature, and dissolved oxygen. Apart from these factors, packaging, storage condition and other formulation ingredients can also add to discoloration. Due to this highly unstable nature of AA, raw material manufacturers have developed various derivatives with enhanced stability. In this review, we have studied the physicochemical properties and pharmacological effects of AA and its derivatives.

2. Derivatives

2.1. L-Ascorbic Acid

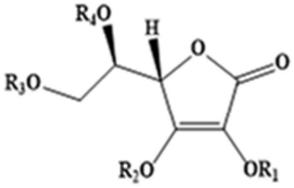
L-Ascorbic acid (AA) is a water-soluble pH sensitive antioxidant. For its penetration into the epidermis, the pH must be less than pKa value of 3.2. It is highly unstable and quickly oxidizes in aqueous solution thereby limiting its usage. In a study by Pinnel et al 2001, application of 15% L-AA for 3 days resulted in 20x saturation in the tissue levels at pH 3.2. pH-dependant absorption of L-AA was also reported; the percutaneous absorption of L-AA increased only when the pH was less than 3.5 [5]. In another clinical study, 10 women applied 5% AA cream on the dorsal side of upper forearm and placebo on other side for 6 months. The study concluded that the mRNA levels of collagen type I and III were increased by 25% and 21% respectively [6]. Another trial on 19 women with 5% AA applied on chest and forearm for 6 months showed increased skin density, improved skin ultrastructure, and reduced deep furrows [6]. Lintner et al 2020, studied the effect of 15% L-AA serum on photoaged skin in combination with tocopheryl acetate and palmitoyl tripeptides-38. Decrease in skin roughness parameter by 8% (mean) and an increase in skin isotropy by 4% (mean) was obtained on day 28, photographic analysis showed 9% decrease in skin redness and 8% increase in homogeneity [7]. Hwang et al, 2009 studied efficiency of 25% L-AA as a treatment for melasma. The study used a combination of L-AA with penetration enhancers like N-methyl-2-pyrrolidone and dimethyl isosorbide applied on the entire face. After 16 weeks of application Melasma Area and Severity Index values decreased from 15.60 to 12.03 indicating effectiveness of the treatment and mexameter scores confirmed a significant decrease in degree of pigmentation from 215.01 to 198.75 [8].

2.2. Ethyl Ascorbic Acid

3-O-Ethyl Ascorbic acid (EAA) is one of the stable derivatives of L-Ascorbic acid. The greater stability of EAA is due to the substitution of ethyl group at the third carbon

position in L-AA which protects the 3-OH group from ionization and thus prevents oxidation of the molecule [9]. Unlike AA, it is both water and oil soluble with low rate of degradation. Skin permeation ability of EAA was studied with solvents; 1,2 hexanediol (HEX), 1,2 pentanediol (1-2P), 1,3 pentanediol (1-3P), isopropyl alcohol (IPA), isopropyl myristate (IPM), transcutol (TC), propylene glycol monocaprylate (PGMC), propylene glycol monolaurate (PGML), tripropylene glycol (Tri-PG), dipropylene glycol (Di-PG), propylene glycol (PG) and glycerine (Gly). For hydrophilic solvents, skin permeability order is PG>Gly>HEX and for lypophilic solvents PGML>PGMC (9). In spectrophotometric studies conducted at 25-55°C on aqueous solution, EAA showed the same absorbance value for 3 hours indicating greater thermal stability whereas absorbance for AA decreased with time. Furthermore, pH studies concluded the AA and EAA are stable over the pH range of 7.2-8.8 and 3.0-5.0 respectively. The team also conducted a Diphenyl picryl hydrazyl (DPPH) assay to evaluate their antioxidant properties where AA gave faster reaction compared to EAA. It was found that a higher concentration of EAA is required for reaction with DPPH to show its antioxidant activity [10].

Safety and biological activity of a serum containing 30% EAA and 1% lactic acid (pH 3.82) was conducted. The UV induced damage to keratinocytes (epidermal cells) was less in case of recipients using the test serum compared to the untreated control. There was also a decrease in melanin content of 15.52% after application for 4 days [11].



Derivative	R_1	R_2	R_3	R_4
Ascorbic Acid	H	H	H	H
Ethyl Ascorbic Acid	H	H_3C–CH_2	H	H
Sodium Ascorbyl Phosphate	O, O^-Na^+, O^-Na^+	Na^+	H	H
Magnesium Ascorbyl Phosphate	O, O^-, O^-Mg^{2+}	H	H	H
Ascorbyl Glucoside	OH, HO, OH, OH	H	H	H
Ascorbyl Palmitate	H	H	O–$(CH_2)_{14}$–CH_3	H
Tetrahexyldecyl Ascorbate	O–$(CH_2)_{14}$–CH_3	O–$(CH_2)_{14}$–CH_3	O–$(CH_2)_{14}$–CH_3	O–$(CH_2)_{14}$–CH_3
Ascorbyl Tetra-isopalmitate	O, $(CH_2)_5$–CH_3, $(CH_2)_7$–CH_3	O, $(CH_2)_5$–CH_3, $(CH_2)_7$–CH_3	O, $(CH_2)_5$–CH_3, $(CH_2)_7$–CH_3	O, $(CH_2)_5$–CH_3, $(CH_2)_7$–CH_3
Sodium Ascorbate	H	Na^+	H	H

Figure 3. *Ascorbic acid and its derivatives.*

2.3. Sodium Ascorbyl Phosphate (SAP)

Another effective hydrophilic derivative of vitamin C is Sodium Ascorbyl Phosphate (SAP). SAP has no direct antioxidant activity, but it is cleaved by the enzymes present in the skin to release active L-AA [12]. In SAP, the cyclic ring contains a phosphate group at second position which protects the enediol structure from oxidation, making SAP more stable than AA [13].

A study by Dong et al 2020, on 0.9% SAP in water-glycerol system showed temperature dependent degradation [13]. Sample at 60°C was degraded within 5 days, caused by the hydrolysis of SAP in presence of water to DHA by the removal of phosphate group. Mohammadi et al 2020, studied stability under three conditions; room temperature protected from light and exposed to light, and refrigerator temperature. Room temperature formulations developed yellow color while refrigerated formulation showed no color change for up to 2 months. The color change was due to loss of drug in accordance with HPLC data. They also concluded that SAP formulations are more stable than AA formulations at same temperature (room temperature and refrigerator temperature) and concentration (5%) based on drug loss data [14].

A study on antioxidant effect of topically applied AA

formulations measured squalene hydroperoxide to determine oxidative stress on skin. Three samples with 1% & 3% SAP and 1% SAP with 1% vitamin E acetate were applied on 20 subjects for a period of 7 days. 1% SAP showed a 30% reduction in squalene hydroperoxide formation, followed by 40% by 3% SAP or a combination of 1% SAP and tocopheryl acetate. 5% SAP was also found to be more efficient in treatment of acne than 5% benzoyl peroxide lotion through a clinical study with 49 patients [15]. Another study on application of multiple emulsions on 33 volunteers showed that there is a decrease in melanin content from 12-19.64% when combination of ascorbyl palmitate and SAP were used in internal or external phases [16].

2.4. Magnesium Ascorbyl Phosphate (MAP)

Magnesium Ascorbyl Phosphate (MAP) is another water-soluble derivative of AA. It is stable at pH 7. Like SAP, its effectiveness depends on the in vivo conversion to AA.

Studies comparing the stability of MAP, ascorbyl palmitate (AP) and AA attributed highest stability to MAP followed by AP [17]. In another study, stability of MAP, SAP and AP in an o/w emulsion formula for a period of 18 months concluded that SAP and MAP maintained its stability up to 65% of time when stored in dark at ambient temperature however AP was unstable in the same time period. The study also concluded that addition of butylhydroxytoluene in the formula favors long-term stability of vitamin C derivatives [18]. Maia Campos et al, 2008 compared the effect of MAP and AA on human skin. Both MAP and AA affected the Trans Epidermal Water Loss (TEWL) values with MAP treatment showing increased hydration in the deeper layers of epidermis compared to AA. MAP also caused an increase in viscoelastic-to-elastic ratio suggesting improvement in skin elasticity [19]. The effect of MAP on hyperpigmentation was studied by Kameyama et al in 1996, 1% MAP inhibited melanin formation by 48% (mean) and 0.5% MAP by 25% (mean) [20].

2.5. Ascorbyl Glucoside (AG)

The condensation of ascorbic acid with glucose yields Ascorbyl Glucoside (AG), another important derivative of Ascorbic acid. The presence of a conjugated glucose functional group at the 2nd position protects AA from degradation due to pH, temperature, and metal ions. The highest stability of AG was shown at 55.3 0C and pH 6.4 [21]. When topically applied, the glucosidase enzyme present in skin reacts with AG to release active AA.

A study by Huang et al, 2013 with 5% AG at pH 6.5 on the DPPH radical scavenging activity reported that AG was 50% active compared to AA. They also found that pH influences the DPPH activity and AG has better DPPH scavenging ability at pH 4 [21]. A study by Takebayashi in 2006 on DPPH and ABTS (2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) radical scavenging ability of AG, AA-2 Phosphate (AA-2P) and AA-2 Sulphate (AA-2S) showed the following order AG>AA-2P=AA-2S for DPPH and against ABTS as AA-2P>AG>AA-2S [22]. Another study by Kumano et al in 1998 regarding the effect of AG on melanogenesis showed that AG inhibited synthesis of melanin for a period of 2 days compared to AA-2P or AA [23]. Similar observation was also noted in another study when B16 melanoma cells were cultured with AG for 48 hrs. Cultured human skin fibroblasts were used for evaluation of collagen synthesis in presence of AG. Concentration of 0.1-0.5 mM showed effective collagen synthesis and cell growth was enhanced 3x when culture medium in continuously supplied with AG for 24 days [24, 25]. In a report by Starr et al 2019, supramolecular hydrogel formulation containing AA and AG at 5%, enhanced skin absorption was found for AG compared to AA [26].

2.6. Ascorbyl Palmitate (AP)

Ascorbyl Palmitate (AP), an amphiphilic derivative of vitamin C is formed by the alteration at the 6th position thereby offering no protection against oxidative degradation and making it less stable than other derivatives. On the other hand, AP is capable of directly generating an ascorbyl radical and is biologically active [27]. When applied to skin, AP molecules orient themselves in the lipid bilayer of skin such that the palmitic group is in the lipophilic phase and lactone ring in the lipid-water interphase. As only 3-hydroxyl group of lactone ring reacts with free radical, scavenging occurs only at hydrophilic part [28].

A study on AP and its effect on human keratinocytes under UV-B irradiation by Meves et al 2002, showed that despite the antioxidant property of AP it tends to intensify skin damage after irradiation. Even though AP could scavenge hydrogen peroxide, promote glutathione depletion (that helps in inhibition of epidermal growth) and inhibit kinases 1 and 2, it promotes lipid peroxidation that leads to formation of 4-hydroxy-2-nonenal which is toxic to cell causing cytotoxicity [29]. A study on hydration values of different concentration of AP concluded that the highest hydration value was found for w/o emulsion with 5% AP followed by 2% AP and 5% AP in anhydrous cream, 2% AP in w/o emulsion and finally 2% and 5% AP in gel formulations [30]. Khan et al in 2016 studied the antioxidant and acne reduction properties of a formula containing combination of SAP and AP. A split face study with formula ME1 (combination of SAP and AP) and a control was applied on 11 female volunteers. The sebum secretion and antioxidant activity were measured. The combination was found to have 89% antioxidant activity and AP and SAP individually with 88% and 21% activity by DPPH method. ME1 treatment reduced secretion of facial sebum by 17.19% by 12th week [16].

2.7. Tetrahexyldecyl Ascorbate (THDA)

Tetra-hexyldecyl ascorbate (THDA) is a pro vitamin C in the lipid form. It has increased ability to permeate into the dermis and convert to vitamin C enzymatically. Studies by Fitzpatrick, 2002 on 10 patients with photodamaged skin involved applying cream with 10% AA and 7% THDA, to evaluate their combined effect. It was hypothesized that water soluble AA would act only as an antioxidant protecting

the skin and penetrates stratum corneum slowly whereas THDA would penetrate the deeper layers acting as both antioxidant and collagen synthesis promoter. The penetrating power of THDA was confirmed by Barnet Product Corporation, where they found that even when concentration of AA is 25-times THDA, the penetrating power of THDA is exceptionally high. At same concentrations THDA is 3 times more penetrating than AA. An experiment on human melanoma cell culture with THDA showed a reduction in melanogenesis by 80% [31]. Swindell et al, 2021 studied stability of THDA under oxidative stress and found that THDA undergoes prompt degradation due to less oxygen radical absorbance. A combination of THDA and acetyl zingerone was found to be more stable and protective. This combination caused considerable increase in COL IV and VI protein resulting in greater structural support [32].

2.8. Ascorbyl Tetra-Isopalmitate (ATIP)

Ascorbyl tetra-isopalmitate (ATIP) is a liquid derivative of AA. Xiao et al, 2009 studied ATIP and found that it provides protection against UV-A, increased collagen synthesis and suppressed activities of MMP2 and MMP9 in human fibroblasts. Another double blind, placebo-controlled, split faced study evaluated the anti-wrinkle effect of ATIP at concentration of 1%, 2%and 3% for 8 weeks in 23 female subjects. It was found that dosage did not have much effect on wrinkling effect, all the samples gave significant reduction in wrinkles [33].

2.9. Sodium Ascorbate (SA) / Calcium Ascorbate (CA)

Sodium Ascorbate is the sodium salt of AA. It is used at a concentration of 0.003-0.03%. In a study Hinek et al 2014, found that concentrations of 50 mM - 200 mM of SA increased elastin production. AA gets slowly absorbed into the cells via sodium-dependent Vitamin C transporters (SVCTs), but for SA due to Na+ ions it gets absorbed via SVCTs at maximum kinetics thereby increasing elastin production. They also found a decrease in ROS levels for fibroblasts treated with SA for 1h, concluding that the non-oxidised ascorbate anion was responsible for ROS scavenging [34]. Another study was done by Pielesz et al, 2019 on the effect of SA in burn wound healing. Non-healing wounds have high concentration of Fe which undergoes Fentons and Heber-Weiss reaction to produce reactive hydroxyl radical and hydrogen peroxide. This hydrogen peroxide is converted to free radicals which cause damage of membrane proteins and lipids thereby increasing the oxidative stress on the body. SA was used due to its antioxidant property in treating burned skin thereby decreasing oxidative stress in the wound [35].

Calcium Ascorbate, another salt of ascorbic acid functions as an antioxidant and a skin conditioning agent. A comparative study conducted by Gonullu et al 2006, on hydration levels of formulations with CA, AA and vitamin E found that in short term (6h) evaluation vitamin E formula gave higher moisturization than CA and AA [36]. In case of combinations, CA-vitamin E combination was more effective than AA-vit E. Long term studies also gave similar results for the combination, while CA and vitamin E alone showed equivalent hydration. In another comparative study CA formulations gave lower hydration values when compared to AP both in short term and long-term basis [30]. The increase in elastin and collagen production contributes to the hydration effect.

3. Conclusion

While ascorbic acid has been a common topic of discussion for years due to a plethora of skin benefits, its highly unstable and hydrophilic nature limited its usage. Discovery of more derivatives has enabled enhancing the stability of AA in formulations and exploiting the benefits of vitamin C. In the absence of a single study that compares the properties of all derivatives of AA, we have tried to draw some conclusions from the data available. Studies showed that storage of AA formulations in refrigerated and dark condition can help in increasing the shelf life of the formulation.

Both SAP and MAP are more stable than AA; MAP has higher stability compared to AP. We also found that the penetrating power of THDA is exceptionally high making it effective in lower doses. Overall, combinations of hydrophilic and lipophilic grades are expected to give improved stability and activity compared to individual materials.

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