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Progress in the design of ascorbic acid derivative-mediated drug delivery

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Antioxidant-based pharmaceutical products are currently experiencing a surge in popularity and satisfaction, demonstrating promising preclinical and clinical prospects. These products exert their beneficial effects by displaying protection against mischievous free radicals. One potent antioxidant is ascorbic acid (AA), which plays numerous crucial biochemical roles and is typically distinguished as a primary hydrophilic, non-enzymatic antioxidant in tissues. AA is a water-soluble essential antioxidant vitamin that can only be obtained from the diet. However, AA's instability, coupled with challenges related to its delivery, has presented formulation challenges for chemists. As a result, various stable hydrophilic and lipophilic derivatizations of AA have been devised. Capitalizing on their potential, delivery platforms, particularly nano-sized ones utilizing ascorbic acid derivatives, have been extensively investigated in recent years. Two such derivatives, namely, ascorbyl-6-palmitate (AP; a lipophilic derivative) and ascorbyl-2-glucoside (AA-2G; a hydrophilic derivative), have been extensively studied in previous works. Herein, the scientific data related to their utilization, either as a drug or as an integral component in delivery vehicles, and their pharmaceutical applications are evaluated.

1. Introduction

The term "antioxidant" is widely used and can be broadly depicted as an agent that considerably decreases or prevents the oxidation of oxidizable substrates; it is usually administered at a low concentration relative to that of the substrates.[1,2] Generally, antioxidants exert their protective effects employing the following mechanisms: (i) scavenging of free radicals to neutralize and remove them, preventing oxidative damage; (ii) inactivation of peroxides and other reactive oxygen species, inhibiting their formation or neutralizing their reactivity; (iii) metal chelation, rendering pro-oxidant metal ions unavailable for harmful Fenton-type reactions; and (iv) quenching of subsequent lipid oxidation products, interrupting the chain reaction of lipid peroxidation. Through these diverse mechanisms, antioxidants play a pivotal part in defending biological systems from the deleterious effects of oxidative stress, preserving cellular integrity and function.[3–6] Oxidative stress stems from an imbalance between the output of reactive free radicals and the body's ability to neutralize them, leading to potential cellular damage (Scheme 1).[7–9]

The antioxidant defense against oxidative stress can be done enzymatically and non-enzymatically. The primary enzymatic repairing systems include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase.[10,11] Conversely, the non-enzymatic systems include compounds that are able to scavenge the free radicals, such as vitamin C, carotenes, vitamin E, ferritin, selenium, melatonin, zinc, flavonoids, and cysteine.[12–14] Current biomedicine theories suggest that oxidative stress is a key pathophysiological factor contributing to significant diseases related to stress and aging, such as cancer, lung disorders, and cardiovascular conditions.[9,15–19]

Vitamin C or L-ascorbic acid (L-AA) is a water-soluble, non-enzymatic antioxidant. It appears as a white or pale-yellow powder or powdery crystal with a slightly acidic taste. AA is freely soluble in water, slightly soluble in alcohol, and insoluble in chloroform and ether. The term "vitamin C" is used to refer AA in chemistry, which has a molecular weight of 176.13 Da and empirical formula of $C_6H_8O_6$ (Fig. 1A). AA is a highly effective free radical scavenger in aqueous media, but it exhibits a relatively low antioxidant effect in hydrophobic phases.[20] It has been identified as a potent skincare agent with considerable whitening and anti-wrinkle effects.[21,22]

Interestingly, AA is utilized as a drug or functional material in the pharmaceutical scene.[23–27] However, the exploitation of AA as a drug is highly challenging due to its instability.[24,28–32] Several strategies have been developed to overcome such challenges, including its incorporation in an assortment of delivery platforms. Instead, the synthesis of more stable AA derivatives with different chemical characteristics has been attempted,

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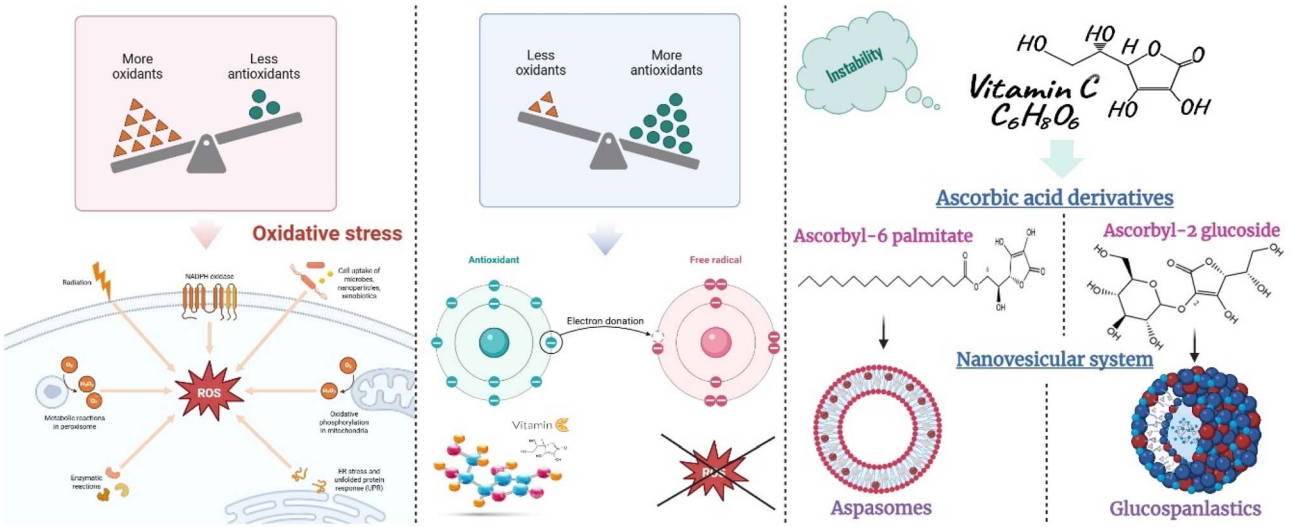

Scheme 1 Balance between oxidative stress and antioxidant activity, highlighting the crucial role of AA and its derivatives. The left panel depicts the impact of oxidative stress, marked by an imbalance between the levels of reactive oxygen species (ROS) and antioxidants within the body. The central panel emphasizes the antioxidant properties of AA, explaining how it works to neutralize free radicals and mitigate oxidative damage. The right panel showcases various AA derivatives, including ascorbyl-6-palmitate and ascorbyl-2-glucoside, alongside innovative nano vesicular systems, such as aspasomes and glucospanlastics. Collectively, this figure underscores the importance of AA and its derivatives in combating oxidative stress and enhancing therapeutic efficacy through advanced delivery systems.

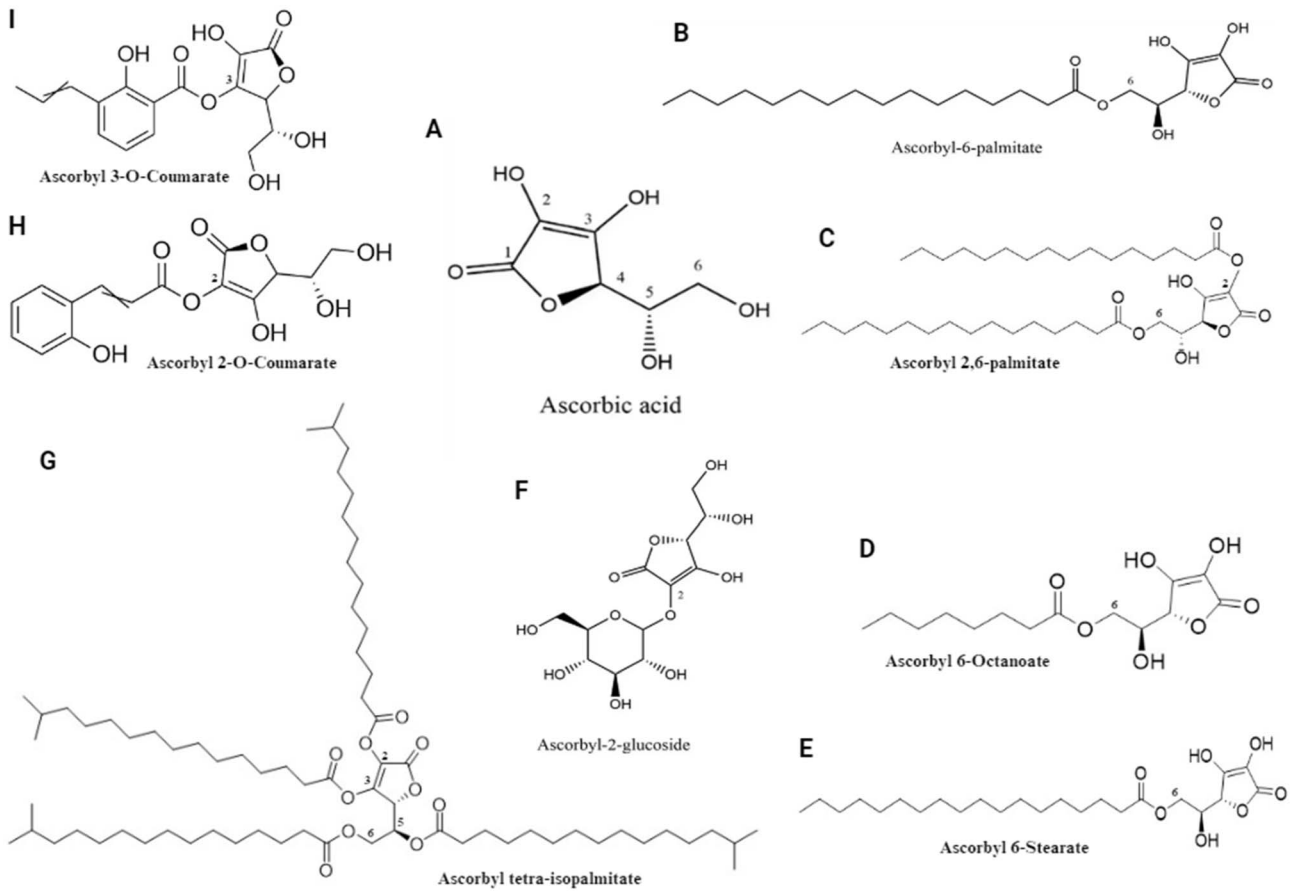

Fig. 1 The structure of some representative derivatives of ascorbic acid. (A) Ascorbic acid, (B) ascorbyl 6-palmitate, (C) ascorbyl 2,6-palmitate, (D) ascorbyl 6-octanoate, (E) ascorbyl 6-stearate, (F) ascorbyl 2-glucoside, (G) ascorbyl tetra-isopalmitate, (H) ascorbyl 2-O coumarate, and (I) ascorbyl 3-O coumarate.

outperforming AA and showing better beneficial biological prospects.[33–35] Beyond their non-derivatized types, both hydrophilic and lipophilic AA derivatives have been employed for the integration of novel multi-functional formulations in diverse pharmaceuticals. Clinically, such a perspective could highlight the relevance of such derivatives as therapeutics and as competent carriers, supporting nanotechnology and drug delivery in general.

Working on such considerations, the current review explores the exploitation and recent advances of AA derivatives in the pharmaceutical arena. Information was collected about the employed AA derivatives regarding their chemical nature and related features. Of note, two lipophilic and hydrophilic derivatives, namely ascorbyl 6-palmitate (AP) and ascorbyl 2-glucoside (AA-2G), were prioritized in the present review, due to their extensive utilization in drug-delivery systems. Specifically, an example of a greatly exploited nanoplatform: aspasomes (ASP) based on AP, was fully addressed, covering their delivery target and indication, composition, and efficacy.

2. Beneficial effects and roles of ascorbic acid in the body

AA is a crucial nutrient that performs an assortment of physiological tasks. It participates in the repair and maintenance of diverse tissues throughout the body. Additionally, AA is involved in the enzymatic production of certain neurotransmitters, highlighting its importance in supporting neurological function.[36–41] As a potent antioxidant, mitigating oxidative

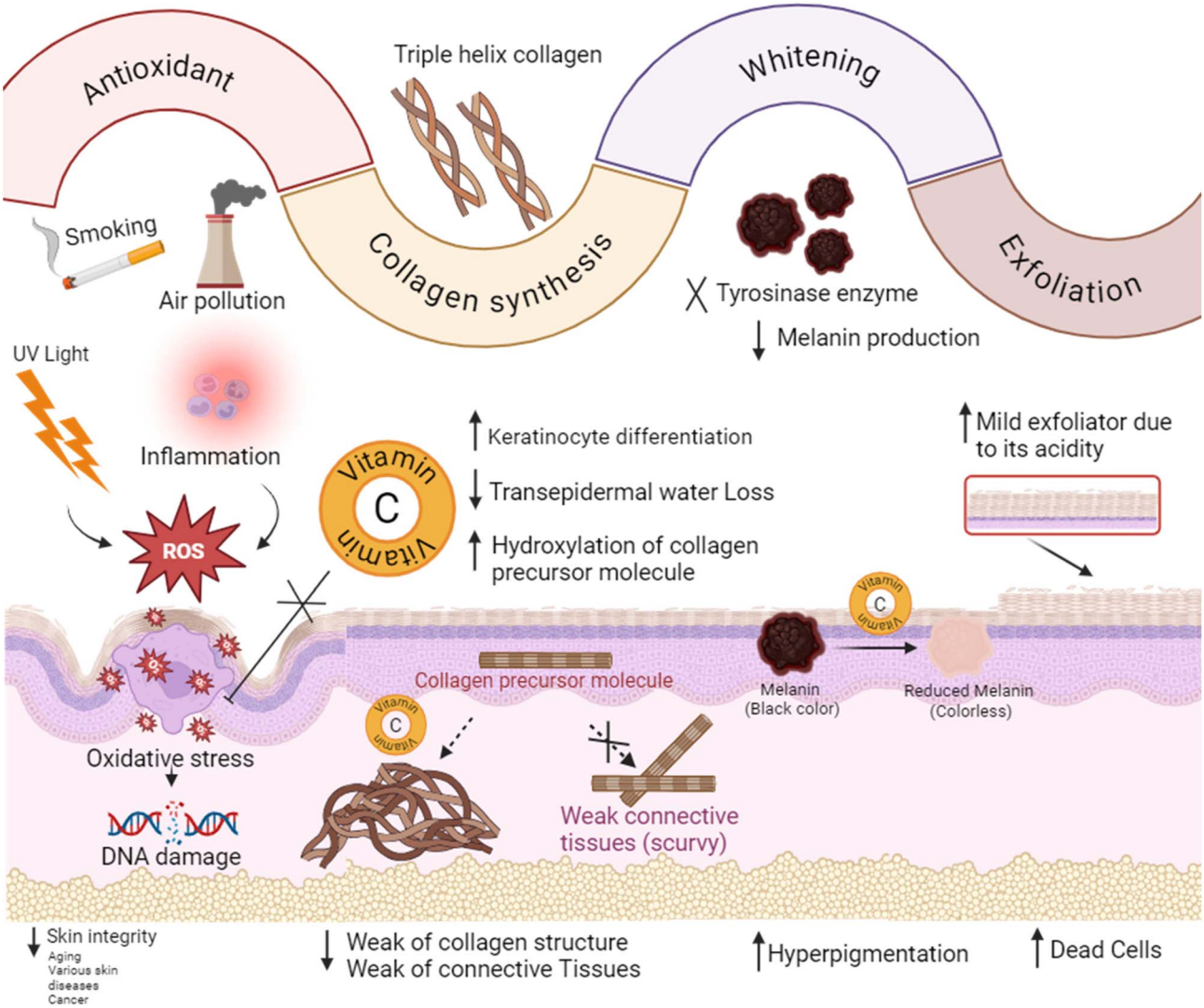

Fig. 2 Diagram representing the role of ascorbic acid in the skin. In the context of cutaneous physiology, AA is substantial for the following roles: (i) biosynthesis of collagen, supporting dermal structure and elasticity, (ii) suppression of melanogenesis, benefiting skin lightening, whitening and depigmentation applications, (iii) exfoliation, acting as mild exfoliator due to its acidity (iv) photoprotection, shielding the skin from the deleterious influences of UVA and UVB radiation upon sun exposure, (v) anti-inflammatory potential, possessing curative competence in the management and control of various inflammatory skin ailments, and (vi) countering skin cancer and aging *via* mitigating oxidative stress. This figure was created with BioRender.

stress, which is the key driver of inflammation, AA exhibits strong anti-inflammatory properties through several mechanisms.[42–47] Recently, it has been identified that AA may be a beneficial adjunct therapy for inflammatory bowel diseases due to its anti-inflammatory properties, immune support, and potential to promote gut health.[48,49]

In the context of cutaneous physiology, AA is valuable for the biosynthesis and retention of collagen, a critical structural protein that provides strength, elasticity, and integrity to the dermal layer of the skin. Beyond its structural and antioxidant functions, AA also exhibits profound modulatory effects on key cellular signaling pathways governing skin cell growth and differentiation. Intriguingly, emerging research has pinpointed the potential of AA in the context of skin cancer, demonstrating its ability to reduce the viability and invasive potential of certain cutaneous malignant cells.[50–52] Several dermatological clinical trials have investigated the role of AA in the remediation of skin diseases, such as atopic dermatitis,[53] herpes zoster,[54] malignant melanoma,[55] as adjuvant therapy in acne,[56] allergic contact dermatitis,[57] and psoriasis.[58] AA offers a multitude of additional benefits for cutaneous health and function. As a photoprotective agent, it can shield the skin from the deleterious influences of UVA and UVB radiation, mitigating the harmful impacts of sun exposure.[59,60] The vitamin also promotes neocollagenesis, stimulating the synthesis of new collagen fibers to support dermal structure and elasticity.[61,62] Moreover, AA exhibits the power to suppress melanogenesis, making it a valuable ingredient in skin lightening and depigmentation applications.[63–65] It has also been studied for its curative competence in the management and control of various inflammatory skin ailments[46,66] (Fig. 2).

AA has been demonstrated to have direct anti-tumor potentials, with the ability to induce apoptosis (programmed cell death) and suppress the proliferation of an assortment of cancer cell types.[67–71] AA can also exert indirect anti-cancer impacts by enhancing the mission of the immune system, promoting the differentiation, proliferation, and activation of various immune cell types.[72,73] AA can increase the cytotoxicity and cytokine production of natural killer (NK) cells, being crucial for the immune-mediated termination of cancerous cells.[74–76]

Collectively, the multifaceted benefits of AA, ranging from photoprotection and collagen synthesis to melanogenesis suppression and potential anti-cancer applications, solidify its status as a versatile and indispensable nutrient for maintaining optimal body health and function.

3. Ascorbic acid utilization in delivery systems

Importantly, benefiting from its anti-oxidant potential, AA has been exploited as a drug and incorporated in delivery systems to tackle its instability. Indeed, AA is highly susceptible to degradation in aqueous environments, particularly at elevated pH levels, in the presence of oxygen, and when exposed to metal ions, often leading to a noticeable color change in AA-containing formulations.[28,77–79]

To overcome these stability challenges and harness the benefits of AA, researchers have incorporated it into various delivery approaches aimed at protecting the vitamin from the factors that contribute to its degradation.[80–82] As a consequence, AA is formulated in an assortment of delivery modes for various administration routes, specifically the topical route.[83–88] Interestingly, the incorporation of AA along with various drugs and bioactive compounds such as oxaliplatin and olaparib into nanoplatforms has emerged as a promising strategy to boost their therapeutic performance across different applications.[89–91]

On the other hand, lately, AA has been utilized as a functional component in delivery systems. It is exploited as a reducing agent in the synthesis of metallic nanoparticles, including silver, gold, selenium, iron oxide and copper ones.[26,92–96] AA is also employed to modify the surfaces of different NPs, imparting desirable merits to the surface-modified ones, such as titanium dioxide NPs.[26] In cosmetic-directed research, for modulating skin hyperpigmentation and whitening, AA has been incorporated in various nanoplatforms, such as nanoemulsions,[97] and liposomes[98] and ethyl cellulose NPs in hydroxypropyl methyl gels.[99]

4. Exploitation of ascorbic acid derivatives in the pharmaceutical arena

As aforementioned, one of the greatest challenges in the exploitation of AA is maintaining its stability. The high aqueous solubility and inherent instability of AA, particularly in the presence of factors, such as oxygen, pH changes, and metal ions, can limit its effective administration and formulation. To address this challenge, lately, researchers have developed striking strategies to limit the degradation processes that affect AA, including the use of stable derivatives, which exhibit enhanced stability compared to the parent compound.[100–102] To address the stability challenges of AA, researchers have synthesized a wide range of stable hydrophilic and lipophilic derivatives of the vitamin. The preponderance of these derivatives over AA has been verified, concerning their stability and functionality (Fig. 3).

The structural alteration of the AA ring in position 2, 3, 5 or 6 to produce different AA derivatives not only improves its stability but also maintains its antioxidant activity. Representative examples of such AA derivatives are shown in Fig. 1. One example of a water-soluble AA derivative, ascorbyl-2-glucoside (AA-2G) or 2-*O*-glucopyranosyl-AA, with an added glucose moiety bound to AA, was synthesized and revealed to prevent AA oxidative degradation.[103,104] Other lipophilic AA derivatives have also been synthesized *via* the esterification of AA with various acids. Ascorbyl 6-octanoate is formed by the esterification of AA with the 6-carbon saturated fatty acid, octanoic acid (also known as caprylic acid). Ascorbyl-2,6-dipalmitate[105] and ascorbyl-6-palmitate are fat-soluble esters of AA and palmitic acid, possessing good skin penetration and antioxidant activities.[106,107] 3-*O*-Ethyl-L-ascorbyl-6-ferulate is formed by the esterification of AA at the C-3 position with ferulic acid (a phenolic

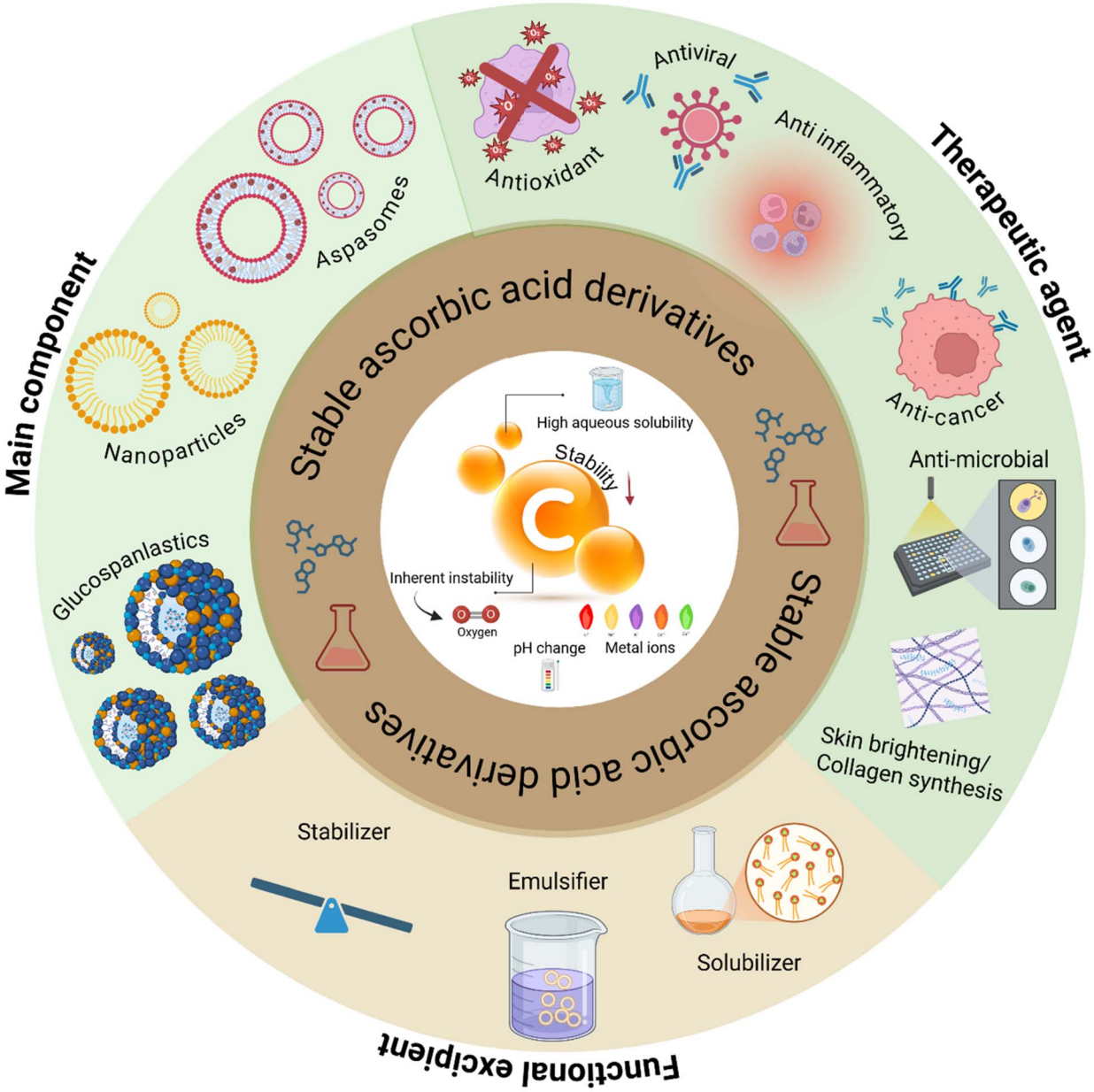

Fig. 3 Comprehensive overview highlights the significance of ascorbic acid derivatives in pharmaceutical and drug delivery applications. The central circle identifies ascorbic acid as the primary component, emphasizing its inherent instability and high aqueous solubility. Surrounding this core are AA derivatives designed to enhance the stability and efficacy of ascorbic acid. The outer ring illustrates the therapeutic potential of these derivatives, detailing their roles as antioxidants, antiviral agents, anti-inflammatory compounds, anti-cancer agents, and antimicrobial substances. Additionally, these derivatives serve as functional excipients, such as solubilizers, emulsifiers, and stabilizers, and play a crucial role in the formation of nanoparticles, including asposomes and glucospanlastics. This figure was created with BioRender.

compound in plant cell walls possessing antioxidant potential). 3-*O*-Ethyl-L-ascorbyl-6-palmitate is formed by the esterification of palmitic acid at the C-6 position, and there is an ethyl group attached at the C-3 position of the AA molecule. It was found that the encapsulation of these novel AA esters within lignin-based nanoparticles resulted in a boost to the antioxidant power and in the prevention of the degradation of AA compounds.[108]

Ascorbyl-6-stearate, in which the stearic acid is attached to the C-6 hydroxyl group of the AA molecule, was found to be similar to ascorbyl 6-palmitate and verified to have anti-tumor activity.[109] Ascorbyl 2-*O*-coumarate and ascorbyl 3-*O*-coumarate are formed *via* the esterification of the C-2 or C-3 hydroxyl group of the AA molecule and coumaric acid.[22] Ascorbyl tetra-isopalmitate is a liquid form of AA. Four isopalmitic acid molecules are attached to the AA at different hydroxyl groups

(likely the 2-, 3-, 5-, and 6-positions). The multiple esterification steps enhance the lipophilicity and stability of AA.[22]

Indeed, the newly designed AA derivatives have secured a substantial place in pharmaceutical research, breaking new ground in the pharmaceutical industry and redirecting toward integrative approaches, which necessitate collaboration among the chemical, pharmaceutical, and pharmacology fields, to elucidate their full potential. AA derivatives offer a promising therapeutic framework for enriching the drug-delivery arena.

AA derivative-based therapies could possess a wide-ranging leverage on diversified ailments affected by oxidative stress. AA derivatives can provide a therapeutic avenue for the treatment of oxidative stress comorbidities.

Earlier work has demonstrated that AA-2G can inhibit Helicobacter pylori-induced apoptosis in epithelial cells of the stomach through a mitochondrial pathway.[110,111] Similarly, in the small intestine, the derivative promotes expansion of Muribaculaceae and modulates *Paenibacillus* populations, suggesting a comprehensive approach to restoring gut ecosystem balance.[112] Beyond direct microbiota modulation, AA-2G has been shown to ameliorate high fructose-induced neuroinflammation through gut microbiota and leaky gut mechanisms, demonstrating the compound's ability to influence the gut–brain axis and prevent diet-induced metabolic dysfunction.

Additionally, the derivative 2-*O*-β-D-glucopyranosyl-L-AA has been shown to exert immunomodulatory effects and positively influence gut microbiota composition.[110,113] Studies indicate that this compound can alleviate conditions, such as colitis and neuroinflammation linked to high fructose intake, suggesting its role in maintaining gut integrity and function.

Considerably, some AA derivatives have been well-documented to exert a complex and multifaceted role in the regulation of melanogenesis, demonstrating both stimulatory and inhibitory impacts related to the specific compound and experimental conditions. The study found that various AA derivatives, such as AA-2G and 3-*O*-ethyl L-AA, were able to inhibit the autoxidation of L-DOPA *in vitro*. Additionally, magnesium L-ascorbyl 2-phosphate and L-cysteine were shown to attenuate the cytotoxicity induced by high concentrations of L-DOPA. Interestingly, while magnesium L-ascorbyl 2-phosphate and AA-2G increased the intracellular levels of melanin and the darkly pigmented cell count, the cysteine derivative L-cysteinamide exhibited the opposite effect, decreasing both the melanin levels and the count of pigmented cells.[114,115]

One of the novel AA derivatives is the 1,2,3-triazole L-AA (L-ASA) conjugate, which was synthesized and evaluated in one study.[116] This compound features a *p*-bromophenyl substituent on the 1,2,3-triazole moiety, connected to the L-ASA core *via* a hydroxyethylene linker. In the antiproliferative evaluation, compound **4e** demonstrated selective cytotoxicity against breast adenocarcinoma MCF-7 cells, exhibiting an IC_{50} value of 6.72 μM. Importantly, L-ASA did not inhibit the growth of foreskin fibroblasts, indicating its selective antiproliferative power. Such promising results highlight that the potent growth-inhibition of **4e** on the MCF-7 breast cancer cells may involve the modulation of the HIF-1 signaling pathway.

Hydrophilic AA derivatives also demonstrate improved intracellular uptake compared to AA, as the modified compounds can more readily permeate the cell membrane and accumulate within the cells.[117] Interestingly, the topical application of AA glucosides is well-documented to constantly release the active form of AA through enzymatic hydrolysis in the skin.[118] In general, developing multifunctional hybrid materials *via* the covalent combination of two substances with featured biological properties can provide additional advantages compared to the individual components.[119]

Hydrophobic derivatives excel at preventing diverse harmful effects induced by X-ray radiation. AP, demonstrating high free radical-scavenging abilities, more effectively suppressed X-ray-induced increases in intracellular ROS levels and lipid peroxidation in keratinocytes, and it significantly prevented X-ray-induced apoptosis. The studies presented here highlight the superior antioxidant and protective properties of lipophilic VC derivatives. The lipophilic AP exhibits enhanced activities compared to AA. AP has demonstrated higher free radical-scavenging abilities, more effective suppression of X-ray-induced oxidative damage, and better prevention of radiation-induced cell death in human cells, likely due to its improved lipophilicity.[120] It potently inhibits the activity of 5-lipoxygenase, an enzyme participating in inflammatory pathways, more than 15-lipoxygenase, and this inhibitory effect is stronger than those of known synthetic drugs. Correspondingly, enzyme kinetics and molecular docking analyses have revealed AP as a non-competitive, reversible 5-lipoxygenase inhibitor, highlighting the importance of its lipophilic nature.[121] The enhanced lipophilicity conferred by the palmitate moiety likely contributes to AP's improved protective effects compared to the more hydrophilic AA, suggesting that the lipophilic VC derivative could be a promising countermeasure against radiation-induced oxidative damage.

5. Characteristic methodologies of ascorbic acid derivatives as functional components of delivery systems

As therapeutic entities, a series of structural derivatives of AA bearing different moieties have been synthesized using diverse chemical approaches, offering strikingly advanced scaffolds mostly for the design of antioxidant, anti-inflammatory and anticancer molecules. Indeed, continued characterization and evaluation seem necessary to investigate their benefits *via* an assortment of preliminary and screening tests.

In order to demonstrate their stability and hence supremacy over AA, the stability of the fabricated derivatives in aqueous solution was tested by dissolving them in a suitable buffer and storing at 37 °C for a specified period, followed by measuring the three obtained concentrations and comparing them with the initial concentration.[122–125]

Importantly, the structural and conformational properties of the synthesized derivatives were elucidated to identify their chemical entities using ^{1}H and ^{13}C NMR.[126,127] Other solid-state depiction tests, such as DSC, FTIR and X-ray diffraction, were

also carried out. Considerably, structure–activity relationship analysis was performed to demonstrate the impact of derivatization and substitution on their bioactive potencies.

In vitro screening of proliferation across different cancer cell lines, employing the MTT test, was carried out to demonstrate the anticancer activity of some promising derivatives. For example, the anticancer potential of the 2,3-di-*O*-aryl/alkyl sulfonate derivatives of L-AA on breast and lung cancer cells was investigated, showing noticeable cytotoxicity and selectivity for cancer cells.[128]

Another instance involves evaluating the antiproliferative effectiveness of 1,2,3-triazolyl-L-AA derivatives on various malignant tumor cell lines, including cervical carcinoma (HeLa), breast adenocarcinoma (MCF-7), colorectal carcinoma (HCT-116), lung adenocarcinoma (A549), ductal pancreatic adenocarcinoma (CFPAC-1), hepatocellular carcinoma (HepG2), colorectal adenocarcinoma, and metastatic cells (SW620). The findings indicated that some synthesized derivatives exhibited selective antiproliferative activity against HeLa, HCT-116, and MCF-7 cells, as well as A549 cells, which appeared to be associated with the nature of their substitutions. Additionally, an Annexin V assay was done to assess the type of cell death, particularly apoptosis, associated with the antiproliferative effects. The study measured the percentages of apoptotic cells, along with necrosis, to emphasize the significant inhibition of cell growth.[116]

An antioxidant potential test was also done using the commonly employed reagent, DPPH, involving incubating the tested compounds with this reagent and monitoring its reduction through measuring the resultant absorbance as well as that of DPPH alone.[116] The values of IC_{50} (concentration causing 50% of the absorbance) and the antiradical efficiency (1000-fold inverse of IC_{50}) were determined as indicators of the free radical-scavenging activity and compared with those for AA.[129] Interestingly, the results attained in earlier studies pinpointed the formation of AA derivatives that can act as potent radical scavengers based on the substitution pattern relative to AA.[130,131] It is to be noted that other radicals, such as ABTS and galvinoxyl, were also utilized in assays of the radical-scavenging activity.[132]

Specifically, the investigation of the binding interactions with different targets to demonstrate their mechanism of action and specificity and the prediction of their pharmacokinetic features were done utilizing *in silico* molecular docking simulations and ADME profiling, respectively. Investigating the binding interactions between non-pancreatic secretory phospholipase A2 and the halo 6-fatty acid esters of L-AA, as well as the 6-fatty acid esters of L-AA, which demonstrate significant interactions with secretory phospholipase A2.[133] A high binding affinity of 6-amino-6-deoxy-L-AA (D1) and *N*-methyl-6-amino-6-deoxy-L-AA with human peroxiredoxin was also verified, and the docking score was found to be comparable to that for AA.[131] Interestingly, when assessing its binding with polymorphonuclear lymphocyte 5-LOX and soybean 15-LOX, the lipophilic derivative, AA 6-palmitate, showed greater MolDock and Rerank scores than AA yet comparable scores to the reference inhibitors, pinpointing its capability to inhibit lipid peroxidation (sLOX).[121]

Other tests have also been conducted to verify that they fulfill the intended purpose for their manufacture, such as testing the effect of alkylglyceryl-L-AA derivatives on the melanogenesis of B16 melanoma 4A5 cells and normal melanocytes.[125] The antiviral potential of some AA derivatives against various viruses, including Herpes simplex virus and Influenza viruses, was also tested.[134,135]

6. Selected examples of lipophilic and hydrophilic ascorbic acid derivatives

Based on their relevance in the pharmaceutical field, two AA derivatives of different natures will be discussed in this review: ascorbyl 6-palmitate (AP) as a hydrophobic derivative and ascorbyl 2-glucoside (AA-2G) as a hydrophilic derivative.

6.1. Ascorbyl 6-palmitate "AP"

Ascorbyl palmitate (AP) is a lipophilic, stable ester derivative of AA. It is an odorless white-to-yellowish powder with a slight citrus-like aroma. AP has a molecular weight of 414.53 Da.[121,136] As shown in Fig. 1B, the hydroxyl group in position 6 is combined with the alkyl chain of palmitic acid to produce ascorbyl-6-palmitate.

AP is a well-recognized skin-whitening agent that enhances skin elasticity by facilitating collagen production. As a lipophilic compound, it also assists in skin penetration.[137,138] Its antioxidant property stems from the formation of hydrogen peroxide, and it presents an effect on the apoptotic pathways by inducing pro-oxidant damage, which cannot be that cancerous cells cannot adapt to or resist.[139] From skin-delivery perspectives, AP is added to topical preparations to safeguard against oxidative changes in dermal components and as an anti-inflammatory agent.[140,141] The augmented antioxidant activity may be due to the hydrophobic palmitate chain of the AP, which has the ability to more easily penetrate cells and better preserve lipids and other cellular components from peroxidation induced by free radicals.[142,143]

Given the excellent preservation of AA's antioxidant properties, AP has shown effectiveness in reducing cellular reactive oxygen species levels after exposure to ultraviolet light, as stated earlier by Meves *et al.*[136] This makes AP a valuable active oxygen scavenger that can protect the skin against oxidative damage.[144] Owing to its lipophilic nature, AP has exhibited remarkable *in vitro* skin retention and penetration, particularly in the epidermis, as verified by *in vivo* skin-delivery investigations.[145]

Interestingly, AP has been thoroughly reported to preserve the anti-cancer properties of AA, functioning as an inhibitor of DNA replication and cell growth in different cancer cells, including skin cancer.[146,147] D'Souza *et al.* investigated AP anticancer activity, incorporating AP in liposome nanoparticles and evaluating its toxicity against various cell lines (Human ovarian carcinoma A2780, renal adenocarcinoma ACHN, breast tumor cells MCF7 and BT20 and mouse renal carcinoma line RAG). It was revealed that the cell death process was due to the generation of oxygen reactive species.[148]

Abdel-hady *et al.* explored a new application of AP in tissue engineering due to its osteogenic (bone-forming) effect. The combination of AP and strontium polyphosphate nanoparticles within the fiber mats exhibited synergistic effects, further enhancing the osteogenic potential of the biomaterial. The presence of AP was found to enhance the osteogenic differentiation of human mesenchymal stem cells that were seeded on the fiber mats. This is a novel observation highlighting the ability of AP to stimulate bone-forming cell behavior.[149]

AP has been revealed as a potent antimicrobial agent with superior antibacterial activity against *Helicobacter pylori* compared to AA. In contrast to AA, which paradoxically increased *H. pylori* survival under aerobic conditions, AP exhibited strong inhibitory effects on the bacteria under both aerobic and microaerophilic conditions.[150]

Furthermore, AP forms lamellar vesicles in water (called ASP), in addition to cholesterol and diacetyl phosphate, to strengthen the bilayer and stabilize the formulation.[151] ASP vesicles are considered a new generation of antioxidant nanovesicles having a hydrophilic core and lipophilic shell that can incorporate both hydrophilic and lipophilic drugs. Additionally, studies have shown that ASP vesicles have greater bilayer stability than liposomes, owing to their content of AP that achieves better skin penetrability than AA.[138,152] Table 1 displays earlier works highlighting different applications of AP in the pharmaceutical and medical fields, including as a therapeutic agent, an auxiliary amphiphilic molecule in delivery platforms, and the main component of newly developed aspasomal vesicles.

Another derivative of AP that can form micelles in aqueous media is trisodium L-ascorbyl 2-phosphate 6-palmitate. The conjugation of trisodium salt having a phosphate group with palmitate can enhance the hydrophilicity and the chemical stability of the compound. Inoue *et al.* were the first to explore this derivative of AA. Their study highlighted the benefits of incorporating the trisodium L-ascorbyl 2-phosphate 6-palmitate AA derivative into a nanocarrier-based drug-delivery system for skincare applications.[164]

Considerably, a crucial point is that different alkyl chains can be used to form ester bonds with AA, and modifying the alkyl chain component can be used as a way to improve the surface activity of the resulting AA ester compound. For example, ascorbyl dipalmitate (ADP) is a modified AA compound that contains two palmitate chains: one at the 6 position and another at the 2 position, differentiating it from the simpler ascorbyl 6-palmitate derivative. In 2010, Moribe *et al.* combined the AA derivative, ascorbyl dipalmitate (ADP), with the surfactant distearoyl phosphatidyl ethanolamine–polyethylene glycol 2000 (DSPE–PEG) in molar ratios of 1 : 1 and 2 : 1 to formulate stable nanoparticles capable of encapsulating hydrophobic drugs (amphotericin B). The inclusion of ascorbyl dipalmitate was believed to contribute to the stabilization of the nanoparticle structure and provide antioxidant properties to the overall drug-delivery system.[165]

In 2021, the same research group investigated the high loading capacity of ascorbyl 2,6-dipalmitate in newly developed nanoparticles. They successfully obtained ADP nanoparticles when the molar ratio of ADP to DSPE–PEG (a lipid-based stabilizer) was between 5 : 1 and 20 : 1, opposing earlier works stating that molar ratios greater than 3 : 1 fail to form nanoparticles. Interestingly, the proposed nanoparticles were morphologically rod-shaped, possessing a size around 100 nm. According to the accomplished work, the critical ADP to DSPE–PEG molar ratio was determined to be less than 33 : 1. Based on previous studies, these rod-shaped ADP nanoparticles could serve as an efficient administration vehicle enclosing high-dose AA for optimal tumor-targeting in cancer therapy, showing their superior *in vitro* and *in vivo* behavior compared to spherical particles.[166]

Concerning the combination of palmitate-based AA esters, Plaza-Oliver *et al.* investigated the use of both ascorbyl 2-palmitate and ascorbyl 2,6-dipalmitate in the development of nanoemulsions containing α-tocopherol for oral delivery. The study examined the effect of the intestinal protein corona on the mucodiffusion of these types of drug-delivery systems under simulated intestinal conditions.[167] When the nanoemulsions were incubated in simulated intestinal fluid, an "intestinal protein corona" (I-PC) was generated on the colloidal surface. The researchers found that the formation of this I-PC influenced the possible interaction between the proposed nanoemulsions and the intestinal mucus barrier, displacing the nanoemulsions from an "immobile-hindered" population to a mobile "diffusive" population. The study highlighted the critical impact of this I-PC on the substantial mucodiffusion properties of the formed nanoemulsions within the intestinal mucus layer, which is an important consideration for the design of promising oral nano-platforms.[105]

In a study published in 2021, Sonkaew *et al.* utilized the environmentally friendly supercritical CO_2 technique to produce ascorbyl 2,6-dipalmitate (ADP) nanoparticles. The researchers found that the resulting nanoparticles containing ADP exhibited potent antioxidant activities, and these beneficial properties were maintained even after the nanoparticles were incorporated into cellulose-based packaging films.[168]

6.1.1. Aspasomes: an example of AP-based nanocarriers. Nano-dermatological solutions utilizing lipid-based nanocarriers, particularly safe and biocompatible nano-sized vesicular ones, could offer promising merits in dermal-oriented applications.[169–172] These advantages include the facile consistency of a protective topical film on the surface of dermal layers, enhancement of skin hydration and occlusion to improve barrier function, boosting of the penetrability and deposition of payloads within the various dermal strata, and enhancement of solubilization and bioavailability of hydrophobic drugs to enable more effective delivery to the target site.[169,173–176] Compared to non-lipid nanocarriers, these lipid-based systems exhibit superior performance in terms of topical formulation development, skin delivery, and optimization of the pharmacokinetic profiles of lipophilic compounds for dermatological applications.[177]

Of these, ASP vesicles represent a novel class of multilayered nanovesicles, with AP serving as the primary and extensively studied component of the vesicle bilayer. AP, a hydrophobic derivative of AA, has obtained FDA approval and is commonly

Table 1 Different applications of AP in the pharmaceutical and medical fields, highlighting the versatile uses of AP in enhancing delivery, providing stability, and offering therapeutic benefits across various medical fields

Role/function of AP	Delivery system/dosage form	Status of investigation	Application of AP	Reference
Active constituent	—	*In vitro* (assessed the recovery of the ascorbate radical from neural tissues susceptible to the hypoxic stimulus "cerebral cortex and carotid body", following the administration of AP by gavage)	Carrier delivery of ascorbates into "bio-membranes" neural tissues due to its lipophilicity	153
	Microemulsion	*In vitro* (determination of the effective concentrations of AP for inhibiting free radicals that were formed in porcine skin, using electron paramagnetic resonance (ESR) spectroscopy and the spin trapping approach)	Skin protection against UVB irradiation using microemulsion as a carrier system	154
	Cream, gel, and oil/water emulsion (O/W)	*In vitro* (determination of skin hydrating effect in comparison to vitamin E)	Skin moisturizing potential effect	155
	Solid lipid nanoparticles and nanostructured lipidic carriers in hydrogels	*In vitro* (PS, PDI determination, DSC), *ex vivo* (determination of penetration ability using excised human skin), *in vivo* (moisturizing effect testing on female Caucasian volunteers)	Skin moisturizing and penetration abilities of AP have been evaluated when the compound is entrapped within solid lipid nanoparticles and when incorporated into a nanostructured lipid carrier hydrogel formulation	156
	Semisolid nanostructured lipid carrier	*In vitro* (physicochemical evaluation and release study)	Antioxidant potential and permeation enhancement	157
	Polyethylene glycol phosphatidyl ethanolamine micelles	*In vitro* (physicochemical profiling and cytotoxicity assay) and *in vivo* (female Balb/c mice "induction of murine mammary carcinoma)"	AP has demonstrated anti-cancer effectiveness against cancer cell lines, as verified by the assigned *in vitro* and *in vivo* studies	158
	Liposomes	*In vitro* (physicochemical characterization, cytotoxicity, antioxidant and antimicrobial activity)	AP exhibits enhanced stability and safety, as well as antimicrobial and antioxidant activities	159
Excipient (negatively charged lipid)	Lipid nanoparticles (composed of phosphatidylcholine and AP)	*In vitro* (physical, morphological characterization and cytotoxicity assay) and *in vivo* (Balb/c female mice *via* the induction of orthotopic breast cancer models)	Surface-charge modifier to enhance targeting in the induced tumor and exhibit superior tumor inhibitory potentials	160
Main component of bilayer vesicle formation	ASP	*In vitro* (physical characterization, DSC, release study, transdermal permeation, DPPH assay) and *ex vivo* (transdermal permeation)	Ability to form a bilayer vesicular system called (ASP)	140
	Hydrogel	*In vitro* (evaluation of gel properties, including rheology, drug loading, cytotoxicity, and drug release, using an intestinal model)	Hydrogel formation for rectal delivery (local, intestinal delivery of macromolecules)	161
	Glossypol incorporated in AP coagel for topical formulation	*In vitro* (evaluation of the immobilization effect of coagels on sperm motility)	Coagel formation that was able to immobilize gossypol	162
Auxiliary amphiphilic molecule	AP in chondroitin sulfate/chitosan nanoparticles	*In vitro* (physical characterization, DSC, FTIR, release study, DPPH assay) *In vivo* (male rats weighing 180–225 g)	Suspension for arthritis treatment *via* the intra-articular route	163

utilized as an inactive ingredient in numerous skincare formulations.[178] In the fabrication of ASP, AP is consolidated with cholesterol and charged lipids for optimal drug association and entrapment, as demonstrated in several studies.[140,151,179] ASP vesicles were initially proposed in 2004 by Gopinath *et al.*, who explored the potential of the amphiphilic AP to form bilayered vesicles using cholesterol as a stabilizing agent and dicetyl phosphate to induce charge, aiming to encapsulate the hydrophilic drug azidothymidine.[140] Fig. 4 demonstrates the schematic diagram of the assembly of the main components of ASP vesicles.

ASP vesicles have demonstrated several advantageous features for topical drug delivery. These include enhanced permeation through the stratum corneum, safety, and biocompatibility, as well as the use of low drug amounts while achieving therapeutically relevant concentrations in the targeted skin areas, thereby reducing the potential for systemic side effects.[180,181] AP serves a dual function in ASP, performing as both a lipid bilayer-producing agent and a stabilizer, all while exhibiting its inherent antioxidant activity. The role of oxidative stress and imbalance in the antioxidant–oxidant equilibrium is well-recognized in the pathogenesis of assorted skin ailments.[182] The antioxidant capacity of ASP can play a crucial part in mitigating the excessive inflammation associated with worsened skin conditions by neutralizing the involved ROS.[183]

Interestingly, ASP vesicles have been verified to possess superb antioxidant and dermal permeation enhancement attributes, which have enabled their use in the treatment of conditions affecting the skin, such as androgenic alopecia, acne, and psoriasis.[137,179,184] Owing to the capacity of ASP vesicles to be dermally retained, the payload persistence in the target region can be anticipated and potentiated, as stated earlier.[137,138] Assortments of scientific studies were conducted to incorporate various hydrophilic and lipophilic drugs in these vesicles, as demonstrated in Table 2.

Expanding on previous research, aspasomal dispersions were effectively created using the rotary-evaporation–sonication approach. This method has been noted for its ability to produce vesicles with outstanding drug-incorporation efficiency.[179] This technique involves creating a thin film that promotes thorough and effective hydration of the vesicles, allowing for the encapsulation of substantial quantities of drugs, as illustrated in Fig. 5.

Specifically, for lipid-based vesicles generated using thin-film hydration technique, formulation and processing parameters have been well documented to greatly affect the physical characteristics of the produced nanosystems. Formulation design and optimization are crucial steps for boosting the therapeutic competence of vesicles.

Of note, referring to literature, ASP-based topical products (creams or gels) enclosing diverse drugs were evaluated clinically as a competent remedy for androgenic alopecia, melasma, fungal infections (candidiasis and tinea), acne and skin aging.[180,188–192]

6.2. Ascorbyl 2-glucoside "AA-2G"

Ascorbyl-2-glucoside (AA-2G) has emerged as one of the most investigated vitamin C derivatives and has garnered significant

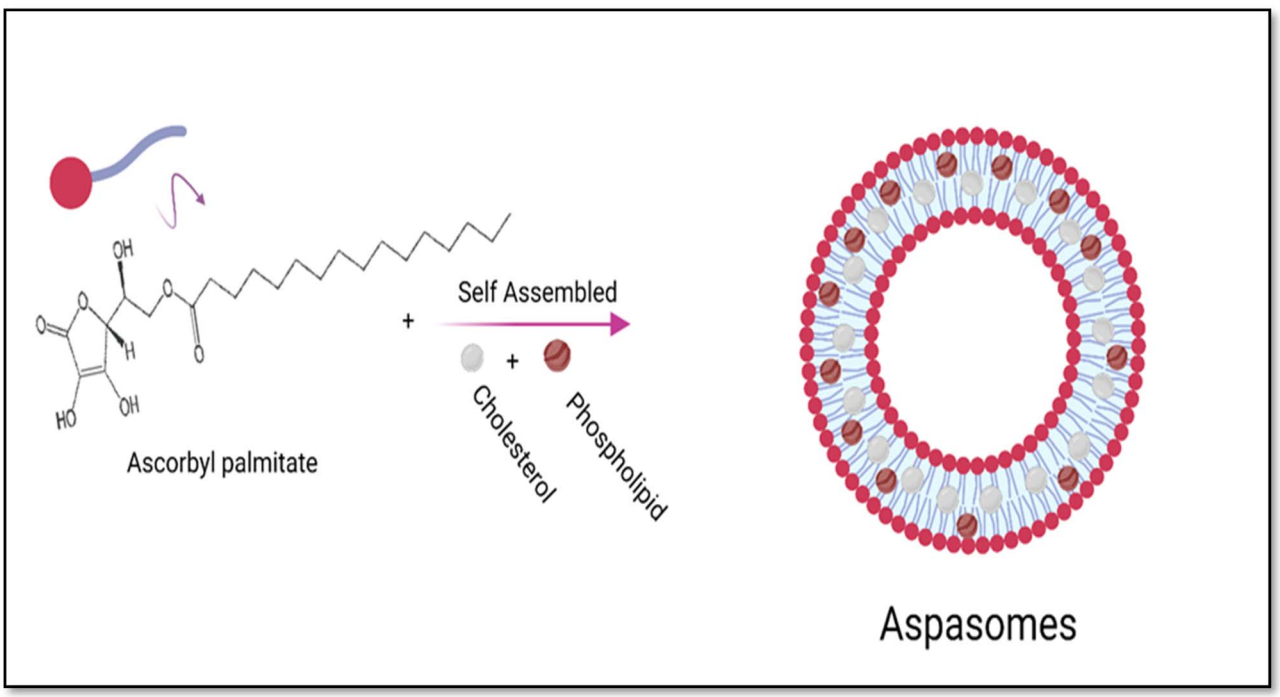

Fig. 4 Schematic diagram of the assembly of the main components of aspasomes vesicles. For the formation of aspasomes, the amphiphilic ascorbyl palmitate (AP) is consolidated with phospholipid to form bilayered vesicles. Cholesterol is added as a stabilizing agent. This figure was created with BioRender.

Table 2 Examples of aspasomes prepared with various drugs[a]

Drug	Drug class (indication)	Route of administration	Composition	Status of investigation	Main findings	References
Azido-thymidine (AZT)	Antiretroviral medication (HIV/AIDS)	Transdermal	-Ascorbyl-6-palmitate -Cholesterol -Dicetyl phosphate	*In vitro*	-The presence of cholesterol in ASP was found to not significantly affect the vesicular size, surface charge, and drug entrapment -The AZT release from ASP was found to undergo a substantial change upon changing the assigned cholesterol proportion -The ASP formulation containing 45 mol% cholesterol showed the highest latency or slowest release rate of the encapsulated drug compared to other cholesterol compositions tested -ASP had much higher antioxidant potency than AA and improved AZT transdermal permeation	140
Methotrexate (MTX)	Anti-rheumatic (arthritis)	Topical	-Ascorbyl 6-palmitate -Cholesterol -1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC)	*In vitro* & *in vivo*	-The optimized ASP formulation exhibited a smooth surface morphology with a particle size of 386.8 nm, appreciable drug loading of 19.41%, a negative surface charge, controlled methotrexate release over a period of 24 hours and a steady permeation rate -The increase in the cholesterol content was revealed to boost the loading capacity of the ASP -The *in vitro* drug release followed Higuchi's model and Fickian kinetics -The absence of skin irritation of the prepared hydrogel-loaded ASP formulation was confirmed -Transdermal application of a methotrexate-loaded ASP hydrogel formulation in arthritic rats for 12 days led to significant improvements in comparison to the arthritic control. Specifically, the treatment exhibited a 21.25% reduction in rat paw diameter, a 40.43% decrease in SGOT, a 54.75% decrease in SGPT, a 33.99% reduction in TNFα, a 34.79% reduction in IL-1β, an 84.41% reduction in cartilage damage, an 82.37% reduction in inflammation,	152

Table 2 (*Contd.*)

Drug	Drug class (indication)	Route of administration	Composition	Status of investigation	Main findings	References
					an 84.38% reduction in pannus formation, and an 80.52% reduction in bone resorption -ASP loaded with MTX had a beneficial dual effect against conditions related to inflammation	
Melatonin	Natural antioxidant hormone (hair growth in androgenic alopecia (AGA))	Topical	-Ascorbyl 6-palmitate -Dicetyl phosphate (DCP) -Cholesterol	*In vitro*, *ex vivo* & clinical assessment	-The PS increased with increasing AP concentration -The DPPH assay revealed the preservation of AP antioxidant potential -The *ex vivo* permeation study verified the capability of the prepared ASP to improve topical drug permeation across all skin strata, as compared to melatonin solution: a 1.34-fold greater permeation in the stratum corneum, a 2.1-fold greater permeation in the epidermis, and a 2.7-fold greater permeation in the dermis -Melatonin ASP showed clinically promising results in the treatment of AGA compared to the melatonin solution. The ASP-based treatment led to an increase in hair thickness and density and a decrease in hair loss, as evidenced by the obtained photographic observations of most of the treated patients	184
Magnesium ascorbyl phosphate (MAP)	Antioxidant derivative of AA (melasma)	Transdermal	-Ascorbyl 6-palmitate -Cholesterol -Lecithin	*In vitro*, *ex vivo* & clinical assessment	-The amounts of cholesterol and MAP were found to significantly increase the EE% -Enhanced permeation ASP over drug solution was demonstrated over the drug solution -MAP aspasomal cream performed better than the gel, exhibiting the greatest improvement in the treatment of melasma, as indicated by the hemi-MASI score. Notably, 35% of sufferers rated the ASP cream as an excellent treatment for melasma, with no observed side effects	138

Table 2 (*Contd.*)

Drug	Drug class (indication)	Route of administration	Composition	Status of investigation	Main findings	References
Tizanidine (TZN)	Skeletal muscle relaxant	Transdermal	-Ascorbyl 6-palmitate -Cholesterol -Span 60	*In vitro*, *ex vivo* & *in vivo*	-The optimized aspasomal formulations showed high TZN entrapment%, small size and high TZN release -The prepared ASP were revealed to be non-irritating and safe for topical skin application -*Ex vivo* permeation studies demonstrated that the ASP-based formulation resulted in a 4.4-fold boost in the steady-state flux compared to the free drug -The pharmacokinetic study revealed that the optimized ASP led to a 3.4-fold enhancement in the drug bioavailability relative to the oral tablets	185
Idebenone/ Naproxen	Idebenone: antioxidant Naproxen: anti-inflammatory (skin inflammatory pathologies)	Topical	-Ascorbyl 6-palmitate -Cholesterol -Negatively charged phospholipids: DMPA & DMPG	*In vitro* & *in vivo*	-The ASP formulation with the best physicochemical properties was composed of AP, cholesterol, and DMPA or DMPG at a lipid molar ratio of 35 : 55 : 10, and it was prepared by subjecting the mixture to 50% amplitude -The combination of the loaded idebenone and naproxen was found to not significantly impact the physicochemical properties of the ASP vesicles or their thermostability -The release studies revealed that the biphasic kinetic profile of the attained ASP, with a controlled release of both the loaded drugs (idebenone and naproxen) for up to 24 hours -The *in vivo* study showed that the ASP-based formulation was able to decrease chemically induced skin erythema more effectively than a commercially available naproxen gel, with the effects observed after just 1 hour of application -The ASP demonstrated a potential synergy between the loaded idebenone and naproxen and AP, self-assembled within the vesicular bilayer, when applied topically	186

Table 2 (*Contd.*)

Drug	Drug class (indication)	Route of administration	Composition	Status of investigation	Main findings	References
Mometasone furoate	Psoriasis	Topical	-AP -Cholesterol	*In vitro*, *ex vivo* & *in vivo*	-The optimized formula showed increased drug-loading capacity compared to the conventional gel formulation, and enhanced permeability and controlled drug release through the skin barrier -The *in vivo* animal model demonstrated superior therapeutic efficacy compared to the conventional gel formulation, with improved anti-inflammatory and anti-psoriatic effects, leading to a significant improvement in the clinical symptoms of psoriasis	145
Itraconazole (ITZ)	Anti-tumorigenic for skin cancer	Topical	-Dicetyl phosphate -AP-cholesterol -Epikuron® TM 200	*In vitro*, *ex vivo* & *in vivo*	-The optimized ASP exhibited desirable characteristics, including a nano-size of 67.83 ± 6.16 nm, a negative surface charge of −79.40 ± 2.23 mV, over 95% entrapment of ITZ, and high colloidal stability -The presence of AP in the formulation provided considerable antioxidant power and enhanced the cytotoxicity of ITZ against skin cancer cells "A431 cells; $IC_{50} = 5.3 \pm 0.27$ μg mL^{-1}" -The aspasomal cream formulation demonstrated improved skin penetrability and enhanced *in vivo* anticancer competence, resulting in a substantial reduction of "62.68%" in tumor weight compared to the control	187

[a] PS: particle size, PDI: polydispersity index, EE: entrapment efficiency, ZP: zeta potential, *SGOT (serum glutamic oxaloacetic transaminase), *SGPT (serum glutamic pyruvic transaminase), and *TNF-α and *IL-1β are the major serum parameters for the assessment of rheumatoid arthritis in rats; *hemi-MASI (the hemi melasma area and severity index score).

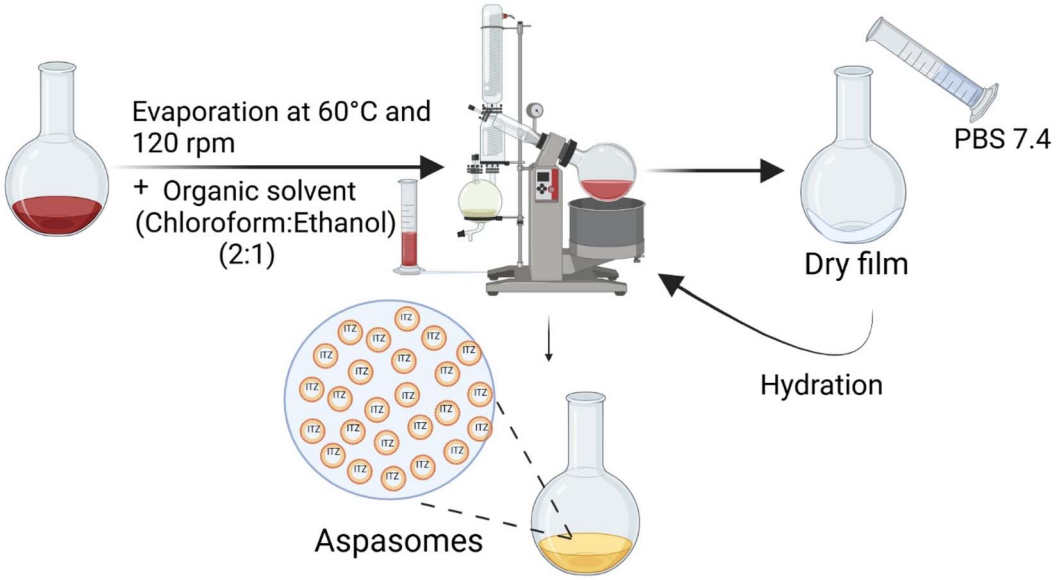

Fig. 5 Method of aspasomal dispersion preparation "thin film hydration method". In the thin film hydration method, the main components of aspasomes (ascorbyl palmitate, phospholipid and cholesterol) are dissolved in a mixture of chloroform : ethanol (2 : 1). Organic solvent evaporation is performed in a rotary evaporator at 60 °C and 120 rpm. The formed dry thin film is hydrated with phosphate buffer saline (PBS; pH 7.4). This figure was created with BioRender.

concern due to its excellent thermal stability and oxidation resistance.[193,194] AA-2G is a hydrophilic derivative of AA. It appears as a white or yellowish-white powder or crystalline powder. AA-2G is colorless and has a molecular weight of 338.265 Da, with a log *P* value of less than −2, indicating its hydrophilic nature.[195] AA-2G is produced by a reaction between glucose and AA. As illustrated in Fig. 1F, the hydroxyl group at the second position of the AA molecule interacts with glucose to form AA-2G. This connection enhances the molecule's stability, safeguarding it from possible degradation due to exposure to high temperatures and metal ions and varying pH levels. Furthermore, this specific binding site contributes to the degradation process and directly affects the antioxidant activity of AA-2G.[196]

When applied topically, ascorbyl-2-glucoside (AA-2G) is reported to undergo hydrolysis in the presence of a cellular α-glucosidase enzyme, which then converts it to L-AA within the skin.[197–200] In addition to its topical uses, AA-2G is utilized as a food additive and as a functional excipient in cosmetic preparations. AA-2G is utilized as a whitening agent due to its ability to reduce melanin production, and in the formulation of lipid-soluble vitamins.[114,195,199,201]

AA-2G can directly provide significant, concentration-dependent preservation against oxidative stress-prompted cell death in human dermal fibroblasts, without requiring conversion to AA. Experiments confirmed that the prophylactic impacts of AA-2G are inherent to the compound, rather than resulting from its hydrolysis to release AA. Hanada *et al.* suggest that AA-2G may have practical utility as a beneficial antioxidant agent even before it is converted into the active AA form.[202]

Lately, in the drug-delivery arena, AA-2G has been identified as a solubilizer for poorly soluble drugs. In light of this, Inoue *et al.* reported that co-grinding of AA-2G with the poorly water-soluble drug, clarithromycin, yielded considerable drug solubilization, and strikingly, nanoparticle formation was observed when using the drug in a molar ratio of 2 : 1.[203] This substance has been documented not only as a solubilizer but also as a promising auxiliary material in nanoparticle design.[204] On the other hand, due to its antioxidant power, it has been utilized as a drug, as reported by Lin *et al.* (2016). In their investigation, AA-2G was enclosed in a microemulsion. The findings indicated that the AA-2G microemulsion possessed higher penetrability in comparison to the commercially available emulsions.[205] Recently, AA-2G has been investigated as a prodrug derivative of AA in commercial products, demonstrating a stronger antioxidative and hence a promising protective leverage. Notably, using AA-2G at a much lower concentration, reaching 1.8%, produced comparable results to those achieved with a higher AA concentration (15%).[206]

The incorporation of AA-2G into innovative nanoparticles has emerged as an attractive strategy to potentiate the therapeutic competence of this compound. In a recent study, researchers developed solid-in-oil nanodispersions encapsulating either AA-2G or AA to improve their stability and optimize their delivery for corneal wound healing applications. The nanodispersion formulations, with an average size of 200–300 nm, exhibited high encapsulation efficiencies, good colloidal stability, and appropriate rheological properties for topical ocular administration. *In vitro* evaluation using human corneal epithelial cells demonstrated that both the AA-2G and AA nanodispersions significantly enhanced cellular proliferation, migration, and wound closure, compared to the free compounds. Importantly, the AA-2G nanodispersion showed superior performance over the AA nanodispersion in promoting

Table 3 Different applications of AA-2G in the pharmaceutical and medical fields

Role/function of AA-2G	Delivery system/dosage form	Status of investigation	Application of AA-2G	Reference
Active constituent	—	*In vitro* (DPPH assay and skin permeation)	Skin antioxidant effect and capability of skin permeation	199
	—	*In vitro* (evaluation of neurite-forming cells using neural precursor cell line "PC12 cells")	Regulation of the redox state in the neural cells. Neural differentiation and growth of neural network-forming cells	208
	—	*In vivo* (cisplatin-induced nephrotoxicity in mice)	Protection against oxidative renal damage induced by cisplatin	209
	Gel	*In vitro* (B16 melanoma cells and 3D human skin) and *in vivo* (clinical assessment)	Inhibition of melanin formation and treatment of gingival melanin pigmentation	210
	—	*In vivo* (exposure of mice to gamma radiation)	Radio protection (antioxidant potential, powerful haemopoietic stimulation and gastrointestinal protection)	211
	—	*In vitro* (sperm motility and lipid peroxidation) and *in vivo* (clinical)	Human sperm motility preservation after cryopreservation and sperm recovery	212
	—	*In vivo* (isolation of hepatocytes from rats)	Creation of DNA synthesis and proliferation of rat hepatocytes	213
	Cosmetic lotion as a drug	*In vitro* (scavenging of free radicals)	Providing stability and antioxidant power	200
	—	*In vitro* (oxidative cell death protection assay using human fibroblast cells)	Protection of the cells from free radical-induced cytotoxicity	214
	—	*In vivo* (determination of liver regeneration and function in 70% hepatectomized rats)	Powerful stimulation of normal hepatocyte proliferation and reestablishment of liver function	215
	—	*In vitro* (MTT assay on colon-26 cells) and *in vivo* (assessment of antitumor activity in colon-26 xenograft mice)	Cancer treatment (inhibitor of tumor growth for infusion therapy)	216
	—	*In vitro* (investigation of reactive oxygen species and potential of mitochondrial membrane in gastric adenocarcinoma cells)	Protection against *H. pylori* infection in epithelial cells of the stomach *via* reduction of *H. pylori*-induced apoptosis	217
	—	*In vitro* (exposure of Chinese hamster ovary cells to gamma rays and ultraviolet)	Protection of cells from radiation and UV light *via* filtration and blocking of UVC and reduced short UVB wavelengths	218
	—	*In vitro* (determination of proliferation, migration, and angiogenesis in vascular endothelial cells C166 and embryonic fibroblasts NIH-3T3) and *in vivo* (wound healing model in mice)	Promotion of wound healing of locally transplanted mesenchymal stem cells *via* boosting of proliferation and angiogenesis and collagen deposition of cells, leading to a high degree of vascularization *in vivo*	219
	—	*In vivo* (rat bladder tumor cell model)	Reduction of the intestinal damage and preservation of antitumor effectiveness of radiotherapy against bladder tumors	220
	Raw clay-based formulation emulsion	*In vitro* (release, skin permeation using human cadaver skin, skin retention study and cell viability study in HaCaT and HDF cell lines)	Appropriate delivery of AA-2G with no toxicity detected in cell lines	221

Table 3 (*Contd.*)

Role/function of AA-2G	Delivery system/dosage form	Status of investigation	Application of AA-2G	Reference
Excipient in drug delivery systems	NPs	*In vitro* (solubilization study of co-ground mixtures with drug)	Solubilization of clarithromycin, nanoparticle formation for drug AA-2G in the molar ratio of 2 : 1 (mean PS = 280 nm)	222
	NPs (cyclodextrin complex systems containing hydrophilic auxiliary substances "TPGS and AA-2G")	*In vitro* (phase solubility and saturation solubility studies and dissolution) and *in vivo* (anti-hypercholesterolemic efficacy in rats)	Enhancement of the solubility, wetting, and dispersibility of BCS class II drug "ezetimibe"	223
	Solid dispersion (containing AA-2G)	*In vitro* (dissolution study and solid-state characterization)	Improvement of dissolution of triamterene *via* complex formation	224
	Water in oil emulsion (containing zinc oxide and AA-2G)	*In vitro* (challenge test for investigation of antimicrobial potential)	Improvement of the antimicrobial activity of ZnO *via* complexing properties of AA-2G towards zinc and enhancing the solubility of the antimicrobial soluble zinc species	225
Integral part of drug-delivery systems	Gluco-spanlastics	*In vitro* (physicochemical characterization, morphological examination, differential scanning chromatography, Fourier transform infra-red spectroscopy, antioxidant activity, cytotoxicity assay) *Ex vivo* (confocal scanning microscopy) *In vivo* (Ehrlich ascites carcinoma model, histopathological study, biochemical assessment)	AA-2G is successfully integrated as a vesicle component in the formation of an innovative, powerful antioxidant vesicle called glucospanlastics, achieving a 95% loading of Itraconazole	207

corneal wound healing, which was attributed to the better stability and bioavailability of the AA-2G form in the ocular environment. Promising *in vivo* results in a rabbit corneal wound model were obtained, where the nanodispersion treatments accelerated wound closure and improved histological markers of wound healing.[193]

Recent research has developed innovative vesicles called glucospanlastics, which incorporate ascorbyl-2-glucoside (AA-2G) as an integral component to enhance their antioxidant and therapeutic properties in the delivery of itraconazole.[207] Table 3 demonstrates earlier works highlighting different applications of AA-2G in the drug delivery arena.

7. Outcomes and future directions

Currently, a renewed solicitude is growing to promote the structural modification of AA to produce functionally derived AA-preserving structures that meet pharmaceutical and medical needs. Indeed, the chemical production of AA derivatives using advanced different processing techniques can assure their high availability and give the opportunity to fabricate a series of economical and cost-effective derivatives. Interestingly, newly developed sustainable and eco-friendly AA derivatives with substituted 1,2,3-triazole moieties were fabricated utilizing both microreactor technology and ultrasonic irradiation (continuous flow process).[226] Recently, a novel eco-friendly derivative, ascorbyl-6-*O*-oleate, was synthesized with a heightened yield *via* a lipase-catalysed esterification, as well as transesterification based on the reaction between the AP substrate and oleic acid, a successful step towards its commercialization.[227] In such a way, production costs can be lowered, allowing them to replace traditional excipients and therapeutic agents while widening their applicability.

Concerning pharmaceutical needs, diverse AA derivatives have been shown to be effective and promising additives in various pharmaceutical formulations, acting as solubilizers, stabilizes and emulsifiers.[228–232] From drug-delivery perspectives, if synthesized and validated, the structural derivatives of AA show promise for application as carriers, transforming the drug-delivery arena and yielding transformative implications for futuristic pharmaceutical research. In particular, the amphiphilic derivatives can be exploited as tools in the fabrication of liposomes and their newer-generation variants, as well as micelles *via* self-assembly.[227] For example, octanoyl-6-*O*-ascorbic acid, decanoyl-6-*O*-ascorbic acid and trisodium L-ascorbyl 2-phosphate 6-palmitate were employed in the production of micellar dispersions that were found to be effective as solubilization vehicles for various hydrophobic drugs.[230,233,234] Additionally, vesicular systems based on the integration of amphiphilic alkyl ester AA derivatives, such as AP, ascorbyl myristate and ascorbyl laurate, into the phospholipid bilayer were investigated in a previous study.[235]

In consideration of their bioactivity, the fabrication and evolution of such functional molecular entities could expand the pool of therapeutic alternatives with diversified bioactive attributes available to patients suffering from inflammation-

and oxidative-stress-related chronic diseases, as well as cancer.[236,237]

Considerably, shifting specific DDS is expected to potentiate and amplify therapeutic interventions that elicit antioxidant, anti-inflammatory and antiproliferative activities. Optimally, the versatility and potential of integrated delivery systems to enhance the therapeutic performance of combination therapies is substantial, spanning applications specifically in cancer treatment and oxidative-damage-related disorders, by enabling the synergistic action of such derivatives and other bioactive compounds.

Indeed, in earlier works, some AA derivative-based delivery systems have been attested to be efficacious medications. In this context, exploiting AP in the structure of the promising vesicles, *i.e.*, ASP, to enclose the repurposed anticancer drug, itraconazole, yielded tunable nano-platforms with potentiated anticancer activity, verified both *in vitro* and *in vivo*.[187] Strikingly, the aforementioned unloaded vesicles, when embedded in a cream base and tested clinically for the management of candidiasis associated with diaper dermatitis, exhibited reasonable curative consequences, owing to their role as carriers to boost skin deposition alongside their antioxidant potential and capability to neutralize reactive oxygen species at affected inflammatory sites.[188] It is worth mentioning that tolerability and safety following topical application were verified, with no reported adverse effects.

Moreover, the application scope of some AA derivatives has been explored in the field of cosmetics, being linked to the preservation of the antioxidant and melanogenesis-inhibiting features of AA. As a consequence, they can offer distinctive effects towards skin whitening, pigmentation-disorder remediation and antiaging.[189,238]

Indeed, some AA ethers and esters, including tetrahexyldecyl ascorbate, AP, ascorbyl linoleate and ascorbyl stearate, have demonstrated striking clinical outcomes in the field of cosmetics, functioning as antioxidants, skin protectants, fragrance excipients, and skin-conditioning agents.[239] Such derivatives receive regulatory approval and show widespread tolerability when applied topically.

Interestingly, several derivatives have already been marketed in cosmetic products, including serums, lotions and creams.

When exploring AA derivatives in the market, the effectiveness of several standout products has been demonstrated. For instance, Mad Hippie Vitamin C Serum[240] and TruSkin Vitamin C Facial Serum[241] utilize sodium ascorbyl phosphate, making them excellent choices for targeting brightening and acne control. Sunday Riley C.E.O. 15% Vitamin C Brightening Serum[242] and Peter Thomas Roth Potent-C Power Serum[243] feature THD ascorbate, known for its superior absorption and brightening properties. Meanwhile, products like Ole Henriksen Banana Bright 15% Vitamin C Serum[244] and Allies of Skin 20% Vitamin C Brighten + Firm Serum[245] incorporate 3-O ethyl ascorbic acid, which effectively addresses hyperpigmentation. Additionally, The Ordinary 12% AA-2G Solution[246] and Inkey List 15% Vitamin C and EGF Serum[247] leverage AA-2G for its brightening and collagen-supporting benefits. These products are suitable for diverse skin types and concerns, showcasing the versatility of AA derivatives in skincare.

Looking ahead, contemporary eco-sustainable synthetic methods for AA derivation, optimally for mass production, and great discoveries and advancements in delivery systems based on such valuable derivatives could be explored to achieve breakthroughs in various pharmaceutical and medical fields. As a consequence, tunable and scalable medicines based on AA derivatives with modulated drug release and amplified therapeutic response should be anticipated in the pharmaceutical market.

8. Limitations

Despite its striking role in the drug-delivery arena, the claim linking AA derivatives to therapeutics and functional additives and carriers has distinct limitations and challenges that must be fully addressed.

For large-scale implementation and scalability, eco-sustainable production techniques, as well as the extension of the manufacturing to the industrial scale, are still demanded. In this scenario, synthetic techniques should ensure the production of customized derivatives, establishing appropriate yields and stability. Optimizing the costs of the exploited resources and involved equipment can assist the production of cost-effective and available AA derivatives for commercial applications.

Although they are valuable therapeutic agents, their pharmacological concentration doses and tolerable levels when used as therapeutics, as well as the associated possible risks of over-supplementation, limit their application. The long-term safety profile of the majority of AA derivatives remains unclear. Accordingly, precise monitoring of dosing and the course of treatment is imperative. The setting and approval of the intake dose is considered necessary. Pharmacological evaluation and a mechanistic rationale for identifying their therapeutic utilization are necessary as well. Although *in vitro* findings and animal studies have asserted the bioactivity of individual AA derivatives and their associated delivery systems, there is presently no conclusive proof establishing their impact on human tissues. It is crucial to perform clinical investigations to validate animal models and to probe their translation to human subjects.

Another key area that needs further research is the verification of their conversion into AA following their administration, as the conversion can be affected by differences in the physiology of the intended routes. Following oral ingestion, AA derivatives have been stated to be readily available AA sources.[248] This is not the case for topical application. In light of this, the fate of the applied AA derivatives, in terms of their skin absorption or conversion into AA after dermal penetration, should be understood. Measuring the concentrations of both AA and its derivative in the skin *via* analysis of the skin after their application and comparing the AA concentration to its baseline skin level could help in this respect. Importantly, the suitability of skin-oriented delivery systems composed of AA derivatives should be

determined *via* profiling *ex vivo* skin deposition and permeation using Franz diffusion cells.[249]

Regarding their role as drug carriers and functional excipients, research into their usage, concentration levels, physicochemical properties, solid-state characterizations, and imaging, should be emphasized. More research is also needed concerning their adverse reactions, interaction with other ingredients, toxicity and tolerance. In general, empirical validation of delivery systems covering *in vitro*, *ex vivo* and *in vivo* performances should be conducted. Delivery-system-related issues must be scientifically interpreted pending powerful empirical advocacy. For example, the proposed link between nanoparticle attributes (*i.e.*, nanosize, surface charge, drug encapsulation) and *in vivo* cellular uptake in different cell cultures, cytocompatibility, distribution, pharmacokinetics and pharmacodynamics warrants further considerable exploration. Differences in the fate and behavior of different nanoplatforms inside the body are still questionable and need to be investigated.

It is worth mentioning that the suggested methodologies for administration involving new delivery systems *via* nasal, otic and pulmonary routes, as well as pharmacodynamics tests for hypertension and CNS-related diseases (such as stroke), present practical constraints due to dependence on specialized equipment and operators, invasiveness, and sometimes complexity and limited accessibility. Of note, little in vitro-in vivo correlation data were found for AA derivative-based delivery systems. From translational perspectives, their toxicological reports on animal tissues, as well as human ones, should be explored. Intense clinical experimentation should be assessed and precisely optimized in order to figure out their empirical significance and broad acceptance in the drug-delivery field.

9. Conclusions and perspectives

AA is a highly valued multifunctional antioxidant biomolecule, but its instability and delivery-related issues have resulted in the evolution of various derivatives. These derivatives have shown effectiveness in mitigating oxidative stress, potentiating antiproliferative efficacy, promoting collagen synthesis and reducing hyperpigmentation in the skin. Of these, AP is a hydrophobic derivative that exhibits good skin penetration and antioxidant activity, and a hydrophilic derivative AA-2G has been studied for its power to inhibit melanin production and improve skin brightening. However, to further enhance the delivery and performance of these AA derivatives, researchers have explored their incorporation into delivery systems either as an integral part of the system or as a drug. Modern evolutions in pharmaceutical delivery involving nanoplatforms, emulsions and gels can benefit the pharmaceutical community in this respect. The design of such innovative therapeutics can optimally offer better and potentiated curative efficacy with improved life quality.

However, adequate design and rigorous monitoring are required for modulation of their physicochemical, bioactive and toxicological features. The recognition of different biological barriers, transport pathways and complexity of various encountered permeation and targeting challenges will assist in the formulation of tailored platforms with respect to their localization in the affected site of action, distribution, targeting and prolonged intended action. In this context, a focus on the technological features is needed, encompassing a proper choice of other components as well as the formulation of delivery systems and industrial techniques for the design and subsequent technology transfer. Importantly, continued research in this area is warranted to further elucidate the structure–activity relationships and degradability while developing even more efficacious and stable AA derivative-based delivery systems for pharmaceutical and medical fields. In light of this, their stability for prolonged periods, assuring the maintenance of their physicochemical, bioactive and AA-preserving benefits over time, degradability and in-depth awareness of their link with the composition of the delivery vehicle should be taken into consideration. Besides, experimental studies using *in vivo* animal models and imaging tools to probe the *in vivo* behavior and fate are considered mandatory. Increased research into the profiles of the molecular expression of different genes of signaling pathways can provide an opportunity to demonstrate their linked mechanistic leverage and, hence, their fit-for-purpose biological performance. Moreover, the utilization of computer simulations and pharmacokinetic profiling studies and their advancements can assist in this respect. Yet, the assessments of their related toxicity and cogent *in vivo* animal and clinical studies are still limited and require further studies.

Overall, AA derivatives, particularly when incorporated in nanoparticle delivery systems and scrutinized against all the aforementioned aspects, could represent a promising approach to harness the power of AA for improved biological impacts in various therapeutic modalities. The attested achievement in the realm of cosmetics could set the substantial impetus to design various delivery platforms, based on such functional additives, with prevalent clinical utility in the management of systemic disorders. As a consequence, such functional entities in marketed delivery platforms would soon provide an efficient cure for a wide range of oxidative stress and inflammation-related ailments.

Author contributions

Caroline Lamie: formal analysis, and writing – original draft. Enas Elmowafy, formal analysis, supervision, and review & editing. Dalia A. Attia, formal analysis, supervision and review & editing. Nahed D. Mortada, formal analysis, supervision and review & editing.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Data availability

In this review article, no primary research findings, software, or code was included and no new data were generated or analyzed.

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