

# Research Progress of Ascorbyl Palmitate in Drug Delivery and Cancer Therapy

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**Abstract.** Cancer treatment continues to face formidable challenges, including the side effects associated with traditional treatment methods, cancer cell resistance, and the lack of specificity in existing therapeutic drugs. The anticancer properties of ascorbic acid (AA) offer new hope for cancer treatment. As a derivative of AA, ascorbyl palmitate (AP) inherits the antioxidative properties of AA and is even more stable. Additionally, AP's amphiphilic nature allows it to be utilized as a nanoliposome. This paper summarizes various modification approaches of AP within drug delivery platforms, revealing its promising role in cancer therapy. Specifically, AP can be employed to modify liposomes, enhancing the targeting and stability of existing cancer drugs while reducing their toxicity. Additionally, AP is thought to have the potential to function as a cancer vaccine platform. Despite its limitations, using AP to treat cancer offers a novel viewpoint on cutting-edge therapeutic approaches and propels the development of current therapeutic methods.

**Keywords:** Cancer, vitamin C, ascorbyl palmitate, drug delivery, nanoparticles.

## 1. Introduction

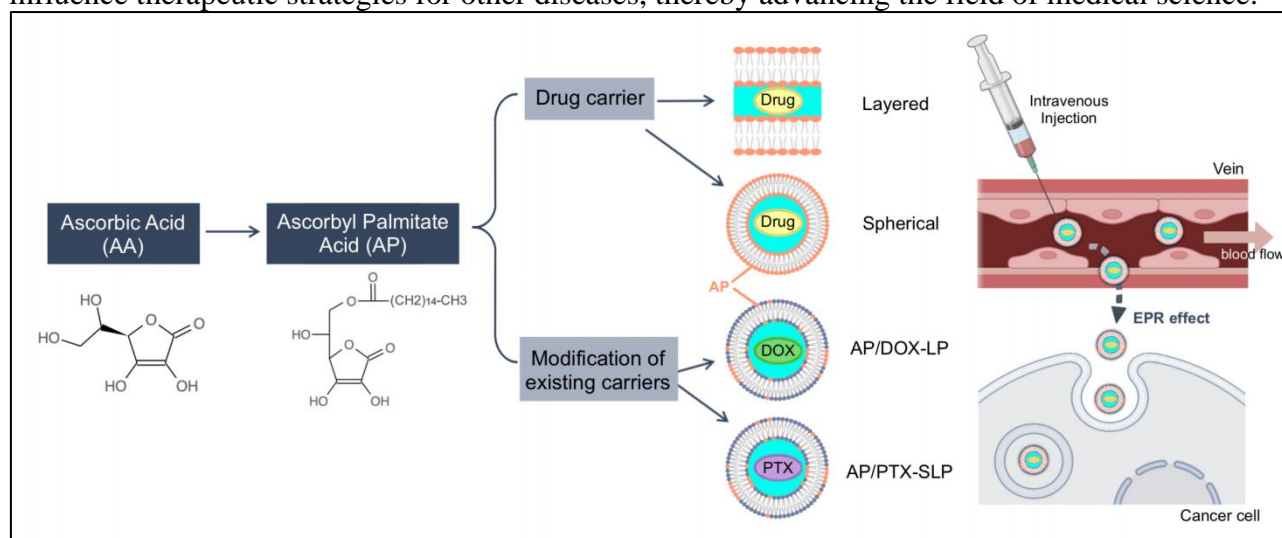
Cancer constitutes a longstanding global challenge, ranking as the second leading cause of death following cardiovascular diseases [1]. As of 2020, the number of cancer-related deaths has approached ten million, accounting for one-sixth of total global mortality [2]. Some of these cases have been exacerbated by the impact of the COVID-19 pandemic on society and the challenges posed by an aging population. However, it is undeniable that despite advancements in cancer research and highly developed technologies today, limitations persist in cancer treatment. Conventional chemotherapy and radiation therapy methods often come with severe toxicities, certain cancers display acquired resistance, and existing drugs lack specificity toward cancer cells [3]. These issues impede effective cancer treatment and inflict irreversible harm upon patients. Prolonged use of anticancer drugs may lead to permanent gastrointestinal dysfunction and reproductive system impairment [1]. Consequently, there is a growing demand for drugs with reduced side effects and enhanced therapeutic efficacy, representing a future focus in vaccine development.

Currently, various types of drug carriers have been designed and developed for cancer therapy. These include nanoparticles, liposomes, polymer microspheres, and more [4]. These carriers can be adjusted and modified according to the nature of the drug and treatment requirements, aiming to achieve improved drug delivery effects [5]. The development of medicine delivery methods based on nanotechnology has given cancer patients new hope. Drugs encapsulated within nanoscale carriers are less prone to degradation, leading to extended circulation times in the bloodstream. The stability and controlled release kinetics of these carriers reduce the required dosages and injection frequencies for therapy. Certain lipid-based carriers enhance the solubility of hydrophobic drugs, enabling them to traverse biological barriers. Additionally, the synergistic effect between novel materials and traditional drug carriers results in heightened tumour targeting at the cancer site. Consequently, this approach minimizes damage to normal cells and reduces toxicity [3]. Notably, the utilization of ascorbic acid and its derivatives holds significant promise as a prominent avenue of research in the field of anticancer drug development.

Ascorbic acid (AA), commonly known as vitamin C, is an essential micronutrient in the human body that cannot be synthesized directly and is typically obtained through daily dietary intake [1]. Due to its antioxidant properties, AA has previously been widely used in antioxidant food additives,

cosmetics, and health supplements [6]. Studies have demonstrated that AA possesses anticancer functions. By producing reactive oxygen species (ROS) in the extracellular fluid of tumours, free AA causes apoptosis in tumour cells, boosting the anticancer effects of many chemotherapy drugs. However, AA is susceptible to oxidation and degradation and requires extremely high doses to exert anticancer effects. Consequently, the synthesis of stable derivatives of AA has emerged as a new research direction, including its lipophilic derivative: Ascorbyl Palmitate (AP) [5,7].

This paper aims to comprehensively summarize various modification approaches of AP in existing drug delivery platforms. Through detailed investigations into its structure and mechanisms, it sheds light on the enhanced performance of AP as a drug carrier and its positive impact on cancer therapy. Additionally, this paper will focus on exploring the potential of AP as a novel cancer vaccine carrier, offering new perspectives for future research in drug delivery and cancer vaccine development. Research in this field is poised not only to spur innovations in cancer treatment but also to potentially influence therapeutic strategies for other diseases, thereby advancing the field of medical science.



**Fig. 1** Different applications of AP in anticancer drugs [1,3]

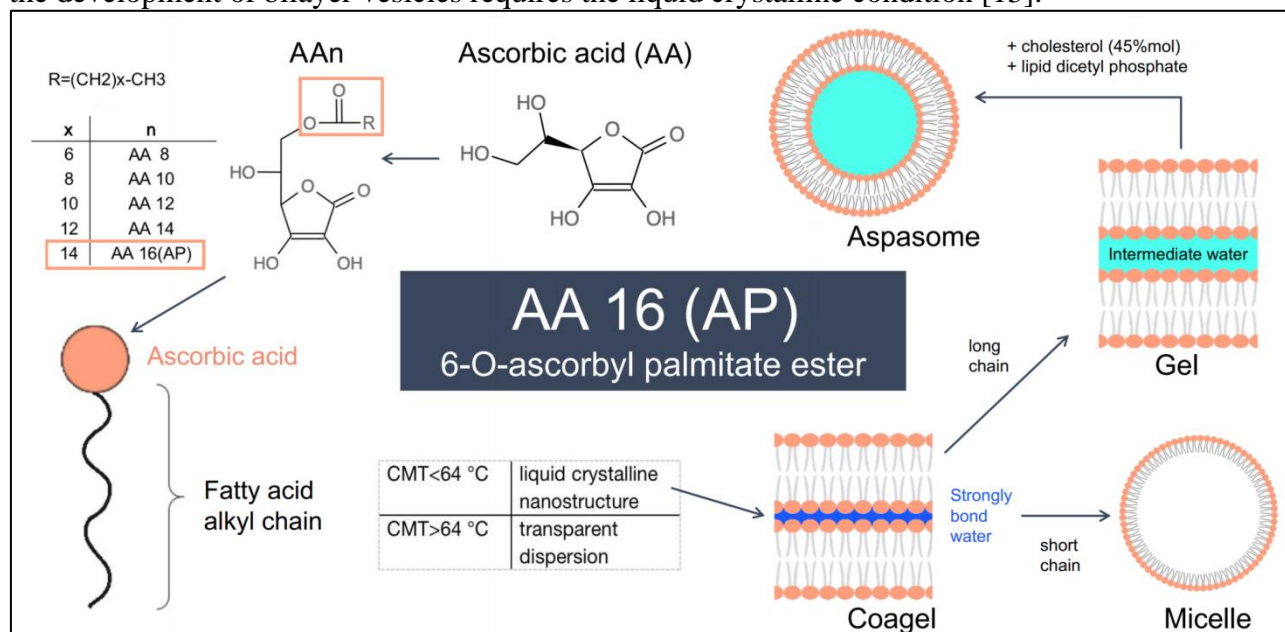
## 2. Ascorbyl Palmitate

### 2.1. Structure and Properties of Ascorbyl Palmitate

6-O-ascorbyl palmitate ester (AP) is a lipid derivative of L-ascorbic acid. It is synthesized through a covalent bond formation between the sixth hydroxyl group of vitamin C and the hydrocarbon chain of a fatty acid, resulting in the formation of AAn. This synthetic route is achieved through acylation reaction. The melting point of AAn is directly proportional to the length of the alkyl chain [8]. When the number of CH<sub>2</sub> groups in the hydrocarbon chain reaches 14, the fatty acid contains a total of 16 carbons. At this point, the fatty acid chain at the 6-O-position of acylated AA is palmitic acid, resulting in the compound known as AP [9,10]. The amphiphilic property of AP, which allows it to serve as a surfactant, enables it to create supramolecular aggregates that are ideal for both hydrophilic and hydrophobic molecules to dissolve [11]. The presence of the hydrophobic moiety (alkyl chain) enables AP to dissolve effectively in hydrophobic environments like cell membranes or lipid vesicles, while the polar head group (ascorbic acid) retains the distinctive antioxidant activity of AA [8].

The critical micelle temperature (CMT) of ascorbyl palmitate (AP) is approximately 64 °C [11]. Below the CMT, AP spontaneously assembles in water to form a liquid crystalline nanostructure known as a coagel [12]. The coagel exhibits a layered structure characterized by three types of water: the first hydration layer, the second hydration layer, and bulk water. When the temperature surpasses the CMT, AP transforms into a transparent dispersion [11]. In the presence of cholesterol at concentrations ranging from 18 to 72 mol% and negatively charged lipid dicetyl phosphate, stable bilayer vesicles are formed, constituting a specific lipid vesicle structure termed Aspasome.

Aspasome possesses a higher CMT and greater antioxidant potency than pure ascorbic acid [10]. While the cholesterol content has a non-linear relationship with the drug release rate of Aspasome, research suggests that a cholesterol content of 45 mol% provides the slowest release rate. Notably, the development of bilayer vesicles requires the liquid crystalline condition [13].



**Fig. 2** Structural changes of AP [10].

## 2.2. Anti-cancer Properties of Ascorbyl Palmitate

The anti-cancer ability of AP stems from AA (Vitamin C). As early as 1969, the intravenous injection of high concentrations of vitamin C was found to induce oxidative stress in cancer cells [14]. Based on the discovery that cancer patients lacked AA, Cameron and colleagues carried out a clinical experiment in 1976 where 100 patients with advanced cancer received AA. The trial demonstrated that subjects receiving a daily dose of 10 g of AA exhibited an average survival time that was 4.2 times longer compared to the control group [15].

It has been confirmed that AA can selectively inhibit or kill cancer cells. The mechanisms underlying AA's anticancer effects are diverse, including epigenetic regulation, downregulation of hypoxia-inducible factors, and impairment of cancer cell glucose metabolism. In animal models subjected to AA therapy, the average growth rate of tumours was reduced to 60%. This effect was achieved by intravenously administering high levels of free AA, which generated reactive oxygen species (ROS) within tumour cells, leading to damage in glucose metabolism [7]. To support their rapid growth and metabolic activities, cancer cells experience heightened oxidative stress and require substantial glucose. Consequently, cancer cells tend to upregulate the glucose transporter protein (GLUT1) gene to acquire more energy. Upon entry into the body, AA is locally oxidized to dehydroascorbic acid (DHAA). Due to its structural similarity to glucose, DHAA readily enters tumour cells through mutant glucose transporter (GLUT) binding [1]. Once inside the cell, DHAA is reduced back to AA by nicotinamide adenine dinucleotide phosphate and glutathione. While GLUT can transport DHAA, it cannot transport AA. As a result, the concentration of AA within cancer cells accumulates. The reduction of DHAA yields a substantial generation of ROS, consuming nicotinamide adenine dinucleotide and inactivating glyceraldehyde-3-phosphate dehydrogenase rendering cancer cells unable to produce ATP and eventually leading to cell death [1,16]. Simultaneously, the oxidative nature of AA is a pivotal factor in cancer treatment. Micromolar ( $\mu\text{M}$ ) concentrations of AA possess antioxidant properties. This is attributed to ROS, a byproduct of cellular metabolism, which, when accumulated at high concentrations, can induce carcinogenesis. AA can donate electrons to ROS, thereby reducing the likelihood of genomic damage. Higher millimolar (mM)

concentrations of AA can function as pro-oxidants. Elevated AA concentrations produce hydrogen peroxide, inducing damage to cancer cells [1, 14].

However, it cannot be ignored that suppressing tumours requires a significantly high plasma concentration of ascorbic acid (AA) within the body. A study from 2004 indicated that high doses of AA exhibit anticancer effects only through intravenous injection (approximately 40-400 mg/kg). Large oral doses merely elevate plasma concentration from 0.07 mM to a maximum of 0.22 mM. Additionally, AA's chemical nature is unstable as it readily dissolves in aqueous media and is challenging to store [17,18]. Consequently, interest has emerged in chemically modified stable derivatives of AA, such as Ascorbyl Palmitate (AP), as potential new anticancer agents. AP inherits the anticancer properties of AA and offers enhanced stability, being less susceptible to oxidation in the presence of air [1]. Upon entering the body, AP selectively binds to cancer cells, inducing production of ROS similar to AA but at higher concentrations, thereby promoting cancer cell death [16]. Liposomes encapsulating AP can inhibit tumour growth at lower doses [5]. Benefitting from its lipophilic tail, AP can traverse cell membranes with ease [17]. When co-transported synergistically with other anticancer drugs, AP can augment the antitumour efficacy of these agents [14]. Thus, AP serves as both a delivery carrier for drugs and as a modifier for the surface of liposomes when combined with other agents for enhanced effect [17].

### 2.3. Ascorbyl Palmitate as a Drug Carrier

The stability and immunogenicity of ascorbyl palmitate (AP) make it a potential platform for cancer vaccine delivery. Currently, various vaccine platforms have been developed and applied, including liposomes, nanoparticles, microspheres, and protein nanoparticles. Nanomaterials are a prominent direction in drug carrier development, offering enhanced drug solubility and reduced dosages, similar to liposomes. Moreover, nanomaterials excel in controlled release and targeted drug delivery [19].

As a type of nanolipid, AP presents advantages due to its inherent properties. AP has a critical micelle temperature (CMT) of 64 degrees Celsius. When injected into the body at 37 degrees Celsius, it forms an insoluble colloid, extending drug release time. Furthermore, AP possesses adjuvant characteristics that can induce inflammation, enhancing the body's immune response against cancer cells compared to other lipid carriers [12]. AP's amphiphilic nature provides accommodation for various insoluble or unstable drugs [10]. Its internal aqueous environment includes three different states of water: the first and second hydration layers are tightly connected by hydrogen bonds, stabilizing the ASC16 structure. The intermediate Bulk water contains numerous water molecules and serves as the main site for dissolving hydrophilic drugs. These factors contribute to the local depot effect, enabling a slow and sustained drug release [11]. AP's lipophilic head retains the antioxidant properties of ascorbic acid (AA) and exhibits targeting capabilities for transformed cells. Its lipophilic structure facilitates easy passage through cell membranes, making it more accessible to tumour cells [10]. Additionally, AP consists of biodegradable ascorbic acid and palmitic acid ester molecules, which have negligible negative impact on human health [12]. These attributes position AP as a promising carrier for anticancer drugs.

Based on the conformational changes of AP, both its layered liquid crystal nanostructures and spherical liposome structures can be used as vaccine platforms. Sánchez et al. attempted to use layered AP (i.e., AP in its hydrogel form) to deliver protein subunit vaccines in a study from 2015. While subunit vaccines are relatively safe, they suffer from poor immunogenicity. Few adjuvants that can enhance human immune responses are available and establishing long-lasting T-cell immunity is challenging [12]. Thus, the safe, stable, and inherently immunogenic nature of AP makes it an appealing choice. In this study, AP was employed as a vaccine platform, conjugated with model protein antigen ovalbumin (OVA) and Toll-like receptor (TLR) 9 agonist CpG synthetic oligodeoxynucleotide (CpG-ODN). Results demonstrated robust IgG1 and IgG2a antibody production in mice injected with OVA/CpG-ODN/AP (hydrogel) combination. Additionally, Th1/Th17 cell responses were observed. Compared to the combination without AP, this formulation

elicited an immune response lasting nearly 6.5 months in mice. Experimental results suggest that this immune response primarily relies on AP's stimulation of MyD88 protein and the inflammatory factor IL-6, though the exact mechanisms remain unclear. It can be inferred that AP enhances the immunogenicity of the original CpG-ODN/OVA combination, addressing issues such as the short half-life of CpG-ODN and its lack of specificity [12].

In the presence of 18-72 mol% cholesterol and 10% negatively charged lipid dicetyl phosphate, layered AP forms stable bilayer vesicles called aspasomes [10]. Aspasomes exhibit stronger antioxidant activity and enhanced skin penetration compared to ascorbic acid. The presence of cholesterol stabilizes the bilayer structure of aspasomes without compromising their permeability. Because aspasomes are amphiphilic, they can infiltrate hydrophobic areas of blood cell membranes and prevent lipid peroxidation. They also eliminate free radicals in the aqueous blood cell suspension environment. Additionally, because of their smaller size and stronger adherence to blood cell membranes, aspasome vesicles can localise to specific cell regions [13].

However, research on hydrogel-based AP as a carrier is not yet comprehensive. The main reason is that its inflammation mechanisms are not well understood, and only a limited range of cell lines, including breast cancer, ovarian cancer, renal cell carcinoma, Ehrlich ascites carcinoma, skin cancer, and leukemia (totaling 7 types), have been utilized for studies. When AP is used as an aspasome, the addition of excipients leads to AP accounting for 34.6% of the total mass [20]. This proportion results in an encapsulation rate of only 20-30% for the final drug [10]. Therefore, in most cases, AP tends to be used in synergy with other anticancer drugs. Drug carriers modified with AP can offer increased stability, improved tumour targeting, and reduced toxicity [20].

## **2.4. Ascorbyl Palmitate Modification of Existing Carriers**

AP can be utilized to modify the surface of nanoliposomes encapsulating drugs, enabling synergistic cancer treatment with other drugs. Liposomes enter cells through endocytosis. The application of nanocarriers in cancer therapy is primarily based on the Enhanced Permeability and Retention (EPR) effect. As tumour cells multiply quickly and require nutrients, they stimulate the formation of more blood vessels via growth factors, relying on the newly established vascular supply for continued growth. As these newly formed blood vessels exhibit structural anomalies and lack smooth muscle layers, drug-loaded nanoparticles more easily permeate through the blood vessel walls to access the tumour tissue. Moreover, the absence of lymphatic vessels surrounding these vessels hampers the filtration and elimination of fluids and their contents, leading to prolonged retention of drugs in the vicinity of the tumour tissue [21]. These phenomena enable nanocarriers to effectively target cancerous regions. The EPR effect is currently widely employed in anticancer drug delivery, exemplified by liposomes encapsulating doxorubicin (DOX) and paclitaxel (PTX).

### **2.4.1 Liposomes of ascorbyl palmitate and doxorubicin (DOX)**

Doxorubicin (DOX), an anthracycline antibiotic, is extensively employed as a chemotherapy agent in cancer treatment. By interacting with DNA, DOX disrupts DNA replication and repair, consequently retarding cancer cell division and proliferation. Furthermore, DOX induces programmed cell death in cancer cells, facilitating the elimination of damaged cells. DOX also interferes with tumour angiogenesis, limiting the blood supply to tumours, thereby reducing the provision of nutrients and oxygen. However, it is noteworthy that DOX is associated with severe side effects. Prolonged high-dose DOX usage can result in cardiotoxicity, damaging myocardial cells. Additionally, DOX suppresses bone marrow production, leading to increased risk of anemia and infection [5].

Shimpo et al. demonstrated in 1991 that AP can mitigate chronic cardiac toxicity induced by DOX by scavenging myocardial lipid peroxidation products through its antioxidant function. Importantly, AP does not compromise the anticancer activity of DOX [22]. This finding has since been experimentally validated. Mice injected with DOX: AP=1:20 co-loaded liposomes exhibited larger tumour cell necrotic areas compared to the control group injected with saline. Administration of AP-DOX resulted in a 2.4-fold reduction in tumour weight and a 4-fold decrease in tumour size. AP

extended the plasma half-life, thereby prolonging drug retention time. Mice receiving DOX/AP liposomes (LPs) did not exhibit significant histopathological changes in their hearts, livers, or kidneys, and their body weight remained stable, indicating no substantial toxicity from the combined use of DOX and AP. Confocal Laser Scanning Microscopy (CLSM) fluorescence staining images suggested that DOX, when combined with AP, accumulated more intensely in the nuclei of cancer cells. This accumulation could be attributed to AP's tumour-targeting capability [5]. Therefore, the co-administration of AP with DOX enhances the anticancer properties of the drug while mitigating its toxicity, overcoming the clinical limitations associated with DOX.

#### **2.4.1 Solid lipid liposomes of ascorbyl palmitate and paclitaxel (PTX)**

Paclitaxel (PTX) is another widely used drug in cancer therapy. Microtubule polymerization is prevented by PTX because it lowers the threshold concentration of pure tubulin subunits required for microtubule assembly. By disrupting the process of mitosis and destabilizing microtubules, it impedes the proliferation and division of tumour cells. PTX also inhibits tumour growth and metastasis through pathways such as tumour angiogenesis. However, PTX has limitations, including but not limited to neurotoxicity, myelosuppression, and gastrointestinal reactions. Drug resistance to PTX can also compromise the effectiveness of cancer treatment [23].

Min Zhou et al. aimed to mitigate PTX toxicity by combining it with AP in solid lipid nanoparticles (SLNs), thereby reducing PTX dosage. Simultaneously, AP's anticancer effects were intended to counteract PTX resistance. The extent of PTX-induced apoptosis was reflected by measuring the Bcl-2/Bax ratio [17]. The proteins Bcl-2 and Bax are essential to programmed cell death. Reduced Bcl-2 expression induces apoptosis, while reduced Bax expression inhibits it. Aberrant Bcl-2 expression in tumour cells can evade normal apoptotic processes. Exposure of tumour cells to PTX reactivates apoptosis, halting cancer cell growth. Thus, a decreased Bcl-2/Bax ratio signifies effective synergy in PTX combination therapy [23]. According to experimental findings, cells treated with PTX/AP-SLNs displayed lower levels of Bcl-2 expression and higher levels of Bax expression. Compared to cells treated with AP-SLNs or PTX-SLNs alone, cells treated with PTX/AP-SLNs experienced a minimum 20-fold reduction in the Bcl-2/Bax ratio. Additionally, mouse body weight remained unchanged. Examination of serum concentrations of inflammatory cytokines indicated that the PTX/AP combination did not induce significant systemic toxicity and inflammation in mice [17]. Thus, the combined treatment of PTX and AP significantly enhances the anticancer effect of PTX with minimal adverse effects on the subjects.

### **3. Limitation**

As time has progressed, there has been a gradual shift in attention towards the anticancer properties of AP and its selectivity towards cancer cells. More drug delivery models and treatment approaches have been proposed, including those mentioned in this paper, which utilize AP as a drug delivery platform or involve the modification of existing carriers with AP for dual drug delivery. The anticancer properties of AP primarily stem from the antioxidant and pro-oxidant properties of AA [1]. However, to this day, the effectiveness of AA in cancer therapy remains a subject of controversy. The majority of clinical trial results tend to suggest that oral intake of AA does not significantly impact cancer treatment outcomes. In a study led by Serge Hercberg and his team, which involved a 7.5-year follow-up of 12,741 individuals aged 35-60 years of varying genders, it was found that the intervention group receiving a daily dose of 120 mg of AA along with other micronutrient supplements showed no significant difference in cancer incidence compared to the control group receiving a placebo (267 cases in the intervention group vs. 295 cases in the placebo group) [24]. Many other studies have reported similar findings. It is important to note that the results indicating the ineffectiveness of AA (including AP) in cancer therapy are likely due to studies primarily focused on oral AA supplementation and the lack of comparison of plasma AA concentrations before and after supplementation.

The anticancer effects of AA require extremely high doses [22-18]. However, the plasma concentration of orally administered vitamin C in the human body is tightly controlled. A dose of 100mg of AA is sufficient to saturate neutrophils, monocytes, and lymphocytes. A plasma concentration of 200mg of AA has reached the maximum bioavailability, and higher concentrations result in reduced bioavailability. This implies that if patients have already obtained an adequate amount of AA from their diet before the experiment, achieving near-saturation levels of AA concentration would have little impact on the measured results [25]. Even though intravenous injection can achieve higher plasma concentrations than oral administration, oral vitamin C remains the mainstream treatment. Therefore, experimental results using oral AA for cancer treatment need to be reevaluated, which is crucial for understanding the anticancer properties of its derivative, AP. Furthermore, AP does not possess direct antioxidant activity; it needs to undergo enzymatic conversion to active AA within the body to exert its antioxidant effect. Additionally, AP does not exhibit the high skin permeability observed with AA [1, 14]. The immunological mechanisms induced by the use of AP as a carrier are also not yet fully understood. Consequently, the potential of AP as an adjunctive treatment or in combination with other therapeutic strategies is still under investigation, rather than being considered a primary method for cancer treatment.

#### 4. Conclusion

This paper explores the significance of Ascorbyl Palmitate (AP) in the fields of cancer therapy and drug delivery, provides an overview of the structure, properties, and anticancer characteristics of AP. In comparison to ascorbic acid (AA), AP is demonstrated to be more stable and possesses enhanced potential for drug delivery. Furthermore, this paper delves into the potential applications of AP as a drug carrier, including its ability to synergistically transport other drugs and improve drug targeting. Despite the tremendous potential of AP in cancer treatment, challenges and controversies exist. Research relying on oral AA to ascertain its anticancer effects needs to be reevaluated. Additionally, AP lacks direct antioxidant activity and requires *in vivo* conversion to active AA (vitamin C). Therefore, the prospects of AP as a primary modality for cancer treatment remain uncertain. Notably, the potential of AP as a drug delivery platform and a carrier for cancer vaccines offers directions for future research. Studies in this field are poised to spark innovation in cancer therapy and could potentially have a positive impact on treatment strategies for other diseases, further advancing the field of medical science.

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