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Review

Nano-vitamin C: A promising candidate for therapeutic applications

Takwa Bedhiafi [a], Sourour Idoudi [b], Queenie Fernandes [a,c], Lobna Al-Zaidan [a], Shahab Uddin [d,e], Said Dermime [a,f,g], Nashiru Billa [b,*], Maysaloun Merhi [a,f,**]

[a] Translational Cancer Research Facility, Translational Research Institute, Hamad Medical Corporation, Doha, Qatar
[b] College of Pharmacy, Qatar University, Doha, Qatar
[c] College of Medicine, Qatar University, Doha, Qatar
[d] Translational Research Institute and Dermatology Institute, Academic Health System, Hamad Medical Corporation, Doha, Qatar
[e] Laboratory Animal Research Center, Qatar University, Doha, Qatar
[f] National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar
[g] College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar

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ABSTRACT

Vitamin C is an important nutrient implicated in different physiological functions in humans. Despite its important biological functions, therapeutic applications of vitamin C are rare and its use is further impacted by low chemical stability. Several nano-encapsulation techniques have been described in the literature and yet, there are only a handful of clinical investigations dedicated to unlocking the therapeutic applications of nano-encapsulated vitamin C. Clearly, further investigations are warranted in order to affirm the promising clinical potential of nano-encapsulated vitamin C. In this review, we describe the mechanisms of vitamin C activity as a modulator of crucial therapeutic uses in biological systems. We look at key factors affecting the chemical stability of vitamin C alone and in nano-encapsulated and explore pre-clinical and clinical evidence on current vitamin C nano-formulations along with their therapeutic applications. Finally, we critically appraise the gaps and opportunities prevailing in nano-vitamin C research and its potential translation towards relevant clinical outcomes.

1. Introduction

Vitamin C (L-ascorbic acid) was discovered by Albert Szent-Györgyi in 1912. Mammals are unable to synthesize vitamin C because of an L-gulono-γ-lactone oxidase gene mutation, which encodes an enzyme involved in the biosynthesis of this vitamin [1]. Citrus foods are rich in vitamin C and remain the primary source of this vitamin in humans [2]. However, synthetic version is also available as supplements.

Vitamin C reduces oxidative damage in cells and improves several physiological activities in humans [1,3,4]. In addition to its antioxidant potential, vitamin C has multiple distinct biological functions including antimicrobial, anti-aging and immunomodulatory activities [5–7]. It is also a critical co-factor for various enzymes that are implicated in epigenetic regulation and cell reprogramming [8–10]. Moreover, vitamin C induces cell apoptosis and cell cycle arrest in various tumor cells lines [11,12]. Interestingly, vitamin C exhibits hypomethylation, based on evidence that it enhances DNA hydroxymethylation and synergizes the chemotherapeutic effects of hypomethylating anti-cancer drugs [13,14].

Paradoxically, the therapeutic use of vitamin C is impeded by its poor stability. Several physical and chemical factors influence the stability of vitamin C including light, temperature, enzymatic oxidation, atmospheric oxygen, metal ions, and alkaline pH, which lead to rapid degradation into less active species [15]. Once solubilized, vitamin C

Abbreviations: 8-OHdG, 8-hydroxy-2′ -deoxyguanosine; AA, Ascorbic acid; Au-NPs, Gold nanoparticles; Bcl-Xl, B-cell lymphoma-extra large; DL, Drug loading; EE, Encapsulation efficiency; EMC, Extracellular matrix remodulation; FDA, Food and Drug Administration; HIF-1α, Hypoxia-inducible factor 1-alpha; HMP-L, High methoxyl pectin; IGF-1, Insulin-like growth factor 1; JHDM, Jumonji-C domain-containing histone demethylases; LMP-L, Low methoxyl pectin; PDI, Polydispersity index; RAIL, TNF-related apoptosis-inducing ligand; RH, Relative humidity; TET, Ten eleven translocation; URTI, Upper Respiratory Tract Infections; ZP, Zeta potential.

* Corresponding author.
** Corresponding author at: Translational Cancer Research Facility, Translational Research Institute, Hamad Medical Corporation, Doha, Qatar.
E-mail addresses: nbilla@qu.edu.qa (N. Billa), mmerhi@hamad.qa (M. Merhi).

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degrades rapidly by atmospheric oxygen, where the reaction is catalyzed by light, heat, and metal ions. Even in the dry form, vitamin C might be prone to oxidation in humid conditions [16]. During food processing, vitamin C easily decomposes into biologically inactive compounds [17–19]. The low stability of vitamin C also constrains its therapeutic applications when orally or intravenously administered [20].

Therefore, the development of effective delivery systems that could courier vitamin C to the systemic circulation is necessary for attaining therapeutic blood levels. Nano-encapsulation provides a platform for the preservation of vitamin C through shielding from external milieu with the possibility of imparting controlled release capability [21]. Indeed, incorporating vitamin C in nano-carriers was found to increase its solubility, stability, bioavailability, with improved propensity to traversing epithelia barriers [22–25]. Various nano-formulation technologies have been proposed, each aimed at improving the disposition of vitamin C in biological systems in vitro and in vivo. These include polymeric, liposomal, micellar, and gold nanoparticles [26–30]. A recent clinical study showed that the bioavailability of oral liposomal vitamin C was higher than free vitamin C administered orally [23]. Interestingly, high oral dose of liposomal vitamin C increased the overall survival in patients infected by COVID-19 [31].

Based on data from the National Centre for Biotechnology Information (NCBI), there are about 70,000 investigations probing the therapeutic uses of vitamin C, however less than 3% of these are dedicated to vitamin C in nano-formulations [29]. Moreover, only two have moved on to clinical trials [32,33], where the focus is on improving the bioavailability of vitamin C and less so on the therapeutic applications of nano-vitamin C. Therefore, further in vivo investigations are warranted in order to evaluate the fate of vitamin C nano-formulations as regards to un-met clinical applications and toxicity. This review captures relevant physicochemical and biological properties of vitamin C, recently published and related to its therapeutic applications through nano-encapsulation. A summary of relevant therapeutic data derived from nano-vitamin C clinical investigations, along with challenges and opportunities are also presented.

2. Physicochemical and biological properties of vitamin C

2.1. The synthesis and downstream pathways of vitamin C

Vitamin C is a white odorless powder, very soluble in water but insoluble in organic solvents such as chloroform and benzene [34]. Moreover, It is thermolabile and in the solubilized form, it is prone to oxidation to L-dehydro ascorbic acid (Fig. 1) [35]. The degraded product is as bioactive as vitamin C, but less prone to oxidation [36]. Some animal species are unable to synthetize vitamin C including primates, guinea pigs, fish and some species of birds [1,37]. Humans are unable to synthetize vitamin C due to L-gulonolactone oxidase gene mutation [1]. Therefore, vitamin C has to be supplemented exogenously. In plants, vitamin C is mainly synthesized via the Smirnoff–Wheeler pathway, where D-mannose and L-galactose are the starting entities. Other routes of synthesis in plants include the glucose, myoinositol and the galacturonate pathways [38,39].

2.2. The upstream pathways of vitamin C

The Pharmacokinetics of vitamin C is complex and depends on various factors, ultimately dictating the vitamin C status in the body [40]. Indeed, the variability in the levels of expression of the sodium-dependent vitamin C transporter and its substrate affinity within organs control the absorption, distribution, and retention of vitamin C. Under normal physiological conditions, these transporters modulate a complex, compartmentalized, and nonlinear pharmacokinetics of vitamin C [41,42]. However, this is modified via intravenous administration of vitamin C, as used in complementary and alternative therapy in cancer patients [43,44]. Due to its hydrophilicity and low molecular weight, vitamin C is oxidized to ascorbyl radical, which subsequently undergoes dismutation to form vitamin C and dehydroascorbic acid. It is reduced back to vitamin C intracellularly [45]. Other crucial factors contributing to variability in vitamin C pharmacokinetics includes disease states, smoking and pregnancy [40]. Therapeutically, the route of administration as well as body compartmental levels of vitamin C are primordial factors with direct implications for successfully utilizing vitamin C in complementary cancer management.

2.3. The function of vitamin C

Vitamin C regulates various physiological processes, including induction of apoptosis in hepatocellular carcinoma stem cells, which comes from the increased levels of intracellular reactive oxygen species (ROS) that promote DNA damage. Moreover, vitamin C induces apoptosis in breast cancer cell lines via increased level tumor necrosis factor-related apoptosis inducing ligand (TRAIL) expression, and subsequent activation of caspases. A decreased level of B-cell lymphoma extra-large (Bcl-xL) expression has also been implicated with the use of vitamin C [11,46]. Modulation of epigenesis by vitamin C enhances the expression of Jumonji-C domain-containing histone demethylases (JHDMs) and the ten eleven translocation (TET) proteins, both of which are epigenetic regulators of DNA demethylation, gene transcription and cell reprogramming [9,47]. Furthermore, as a hypomethylating agent, vitamin C synergizes with decitabine by increasing TET-2 expression, which upregulates 5-hydroxymethylcytosine leading to DNA hypomethylation. Co-administration of vitamin C with decitabine upregulates endogenous retroviral genes expression and improves viral mimicry responses, leading to apoptosis in various cancer cell lines [48,49]. Increased levels of p53 and p21 proteins expression is induced by vitamin C, whereby these proteins regulate the G0/G1 phase of the cell cycle [12,50].

3. Vitamin C nano-formulations

As a means of preserving its stability and improving its biological/therapeutic activity, vitamin C has been encapsulated in various nano-delivery carriers (Table 1), including, polymeric, liposomal and micellar nano-carriers. In the next section, therapeutic applications of some of these nano-carriers are discussed.

Polymeric nanoparticles are particles within a ranged size between 1

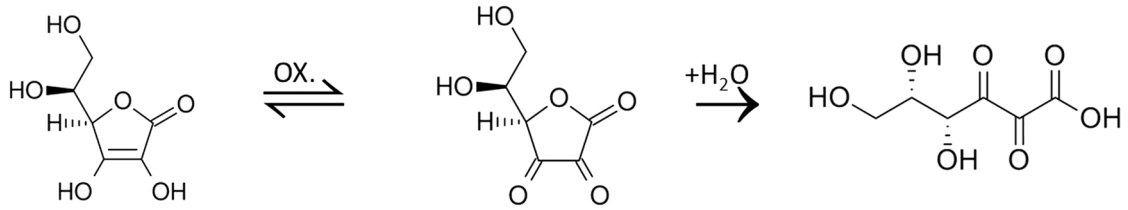

Fig. 1. Degradation of vitamin C. The degradation of vitamin C proceeds both by aerobic and anaerobic pathways and depends oxygen, temperature, light and pH.

Table 1
Recent nano-vitamin C delivery systems.

Nano-formulation	Method of preparation	Physical characteristics	Applications/biological effects	References
Nanoparticles	• Ionic gelation	• ZA: 450 ± 8 nm • ZP: − 31 mV • EE: 90.3 ± 0.42% • A constant release profile higher than 14 days	• Antibacterial function against Escherichia *coli* and *Staphylococcus aureus*.	[24]
	• double emulsion-evaporation method	• ZA: 314 nm and 303 nm • Stability over 90 days was reported • EE: 96% and 91%	• Decrease of malformations in the zebrafish. • Decrease of acetylcholinesterase activity.	[29]
Liposome	• NA	• ZA: 270.4 ± 5.2 nm • DL: content of 75.38 ± 1.03%. • ZP: − 41.7 ± 0.9 mV • PDI of 0.254 ± 0.010	• Model to predict the loading content of vitamin C liposomes	[73]
Solid dispersions	• NA	• Vitamin C was more labile when amorphous than when crystalline	Vitamin C was found to degrade in storage environments • Stability of vitamin C more than sodium ascorbate.	[61]
Micelles	• Thin-film method	• ZA: 229 nm • EE: 95%. • A biphasic drug release of about 20%	• Apoptosis induction • Inhibition of cells invasion and migration. • Protection of IκBα from degradation. • Inhibition of NF-κB p65 translocation	[74]
Gold nanoparticles	• NA	• ZA: 74.37 nm • ZP: − 0.0531 mV	• Inhibition of breast cancer cell line growth • Inhibition of colony formation.	[30]
	• NA	• ZA: 19.2 ± 2 nm • EE: 4.5 ± 0.5%	• Solubilization of vitamin C in hydrophobic media	[75]

ZA: zeta average; **ZP:** zeta potential; **EE:** encapsulation efficiency**; DL:** drug loading; **PDI:** polydispersity index, **NA**: not available.

and 1000 nm that are used to load active compounds within its polymeric core [51]. For instance, vitamin C was previously entrapped inside a double-layer zein/chitosan nanoparticle using sodium tripolyphosphate as a cross-linker [52]. The formed vitamin C nanoparticles exhibited a spherical shape with particle size between 720 and 1100 nm. After storage at room temperature for 10 days, only 5% of vitamin C was oxidized, which reflects the potential protection properties of the loaded NPs to protect vitamin C from degradation. Compared with empty NPs, vitamin C-loaded NPs revealed a sustained drug release in simulated gastric fluid (pH 1.2) and a controlled release in simulated intestinal fluid (pH 7.4). Vitamin C was also encapsulated inside PNPs through electrostatic interaction between glycidyl trimethyl ammonium chloride chitosan and phosphorylated-cellulose nanocrystals [27]. The prepared vitamin C-NPs were spherical with a diameter of 450 ± 8 nm and a zeta potential of − 31 mV. Furthermore, vitamin C encapsulation was 90.3 ± 0.42% with a sustained release profile over 14 days. Polymeric nanoparticles exhibit several advantages as drug carriers such as controlled drug release, protection of drug cargo from degradation, and enhanced therapeutic activity [53]. On the other hand, polymeric nanoparticles could possibly aggregate and only few polymeric nanoparticles are presently approved by the Food and Drug Administration (FDA) and undergoing clinical trials, which might hinder their potential activity as drug carriers [54].

Due to their high stability and surface characteristics, liposomes were extensively applied in developing different functionalized liposomes-based drug delivery carriers [55]. For example, the effects of different liposomal formulation prepared to encapsulate vitamin C with varied ratios of cholesterol, milk phospholipids, phytosterols powder, and varied sonication times showed that, at 40 min sonication time and the 75:25 ratio of phospholipid to phytosterol respectively, a significant decrease in particle size of nanoliposomes was noticed with an encapsulation efficiency of 35% A high stability of vitamin C was observed after 20 days at a 75:25 of phospholipid: phytosterol ratio [28]. In another study, vitamin C was encapsulated inside sesame phospholipid liposomes, where [56]. Using computational studies showed that the packing parameter of sesame liposomes was 0.64 ± 0.09, which reflects truncated cone shape of the prepared liposomes. After 8 days, the liposomal formulation showed a gradual release of encapsulated vitamin C [56]. A transdermal drug delivery system made from high methoxyl pectin (HMP-L) and low methoxyl pectin (LMP-L) containing vitamin C liposomes [57]. Both HMP-L and LMP-L formulations demonstrated an enhanced storage stability, low aggregation, low oxidation of lipid and vitamin C release from liposomes. As potential drug carriers, liposomes exhibit several advantages including their high biocompatibility, reduced cytotoxicity, cell-like membrane composition, low immunogenicity, high protection of the carried drug and active molecules, sustained drug half-life, and potential targeting of specific cells in vivo [21,55,58]. On the other hand, high production costs, fusion of entrapped drug or active molecule, their low solubility, and short half-life are some of the limitations linked to liposomal carriers [58].

Solid dispersions are simple two component systems where the drug acts as a solute and the polymer acts as solvent [59]. Vitamin C was successfully formulated in different polymer solid dispersions to investigate effects of temperature and relative humidity (RH) on the degradation of vitamin C [60]. The vitamin C-pectin and vitamin C-polyvinyl pyrrolidone solid dispersions remained amorphous during storage at low RHs, whilst crystals begin to show after 7 days at high RH. In another study, phase changes and stability of the two most common forms of vitamin C were investigated in colyophilized polyvinylpyrrolidone polymer matrices [61]. At controlled temperature ranges (20–60 ℃) and RHs (0–85% RH), prepared samples were degraded in the glassy amorphous states and degraded fast when low proportions of the polymer matrices were used. One of the main advantages related to solid dispersions is that the drug is not required to be fully solubilized inside the excipient matrix [62]. Moreover, reduced particle size, improved porosity, amorphous state, improved wettability are some of the advantages linked to solid dispersions [63]. However, applications in the market of solid dispersions is still limited as they might degrade or the drug's physicochemical properties could change during the manufacturing processes [62].

Micelles, with particle diameters between 5 and 100 nm, are amphiphilic colloids, that consist of a core formed by the hydrophobic fragments, and a micellar shell of hydrophilic fragments [64]. Vitamin C was successfully entrapped in micellar carriers where stability of vitamin C was improved. Moreover, a controlled release profile with about 14% of vitamin C was released at the first four-hour period. Controlled release of drug cargo, specific targeting, biocompatibility, high stability, and biodegradability are some of advantages associated with micelles [65,66]. On the other hand, some limitations of micelles as drug delivery carriers include their low stability [67]. Moreover, micellar delivery systems are prone to dissociate when intravenously injected [68].

Gold nanoparticles (Au-NPs), also known as colloidal gold, are small gold structured particles with a diameter that ranges between 1 and 100 nm [69]. Au-NPs were widely utilized as potential drug carriers due to their tunable chemistry that provides the capability to control and modify their size, morphology, and surface functionality [70]. Moreover, Au-NPs could be administered into the local tumor site with less non-specific distribution and are able to penetrate deeply into the targeted biological tissues [71]. On the other hand, their ability to stimulate the host's immune system, is one of the limitations linked to Au-NPs applications as a drug delivery carrier [72].

4. Therapeutic applications of nano-vitamin C

Preserving the stability of vitamin C via nano-encapsulation has prompted its reemergence for use in several therapeutic conditions. Fig. 2 captures key therapeutic applications of nano-vitamin C, with a detailed review of each in the following sections.

4.1. Antioxidant and antiaging effects from nano-vitamin C

It has been shown that nano-formulations of vitamin C possess higher antioxidant activity compared to free vitamin C [76,77]. For instance, Chae and Park reported that an emulsion of nano-vitamin C exhibited antioxidant properties in gingival [76]. Moreover, encapsulation of vitamin C in pro-liposome powder demonstrated greater *ex vivo* antioxidant activity compared to free vitamin C in brain and liver cells [77]. Much of the anti-aging properties of nano-vitamin C is derived from its antioxidant properties, discussed above, and cellular regeneration and wound healing properties [78]. In this regard, Choi et al. has shown that low concentrations of nano-vitamin C accelerates collagen synthesis with significantly lower toxicity compared to free vitamin C in gingival fibroblasts [79]. In concert with this finding, vitamin C and propolis nanogel formulation showed potent wound healing properties in oral mucosa of human subjects compared to placebo [80]. A recent study also showed that human serum albumin nanoparticles loaded with vitamin C decreased the expression of the miR-133 gene, which led to collagen I and III gene overexpression in 3T3 mouse fibroblasts, with a faster wound healing rate compared to untreated group [78]. Additionally, the antioxidant activity of nano-vitamin C could be used as a skin youth activator [62]. Indeed, researchers have developed a highly functional nanoparticle carrier of vitamin C that benefit from its antioxidant activity in cosmetic and skin care products [81,82].

4.2. Anticancer effects from nano-vitamin C

Research on the anti-cancer effects of nano-formulations of vitamin C has intensified in the last decade [26,83–85]. The antioxidant activity of nano-vitamin C may be beneficial in unraveling the downregulation of anti-oxidant systems in cancer cells [76]. Synergism was observed in nano-vitamin C and paclitaxel, leading to cell-overgrowth inhibition [86]. Similarly, synergism was observed between nano-vitamin C and cisplatin in the management of chemotherapy-related fatigue [87]. The study showed that vitamin C–cisplatin-loaded chitosan nanoparticles provided anti-proliferative and anti-angiogenic activity without compromising the anti-cancer properties of cisplatin [87]. Vitamin C modulates the genetic reprogramming of immune cellular activity and cytokines secretion in tumor microenvironment (TME) [88,89]. Vitamin C has epigenetic modulatory effects with a potential to reverse the effects imposed by environmental pollutants, which trigger the cascade of events leading to the manifestation of cancer [90]. At high concentrations, vitamin C exhibits remarkable pro-oxidant activities, which holds significant potential in targeted and cell therapy applications. Interestingly, pro-oxidant and anticancer activities coud be achieved at low concentrations of vitamin C when nano-encapsulated [91]. For example, low concentrations of palmitoyl ester of ascorbic acid encapsulated in liposomal delivery systems induced ROS generation, apoptosis in vitro, and reduced tumor growth in female Balb/C mice compared to controls [92]. The nano-size dimension enables easy permeation in tumor cells

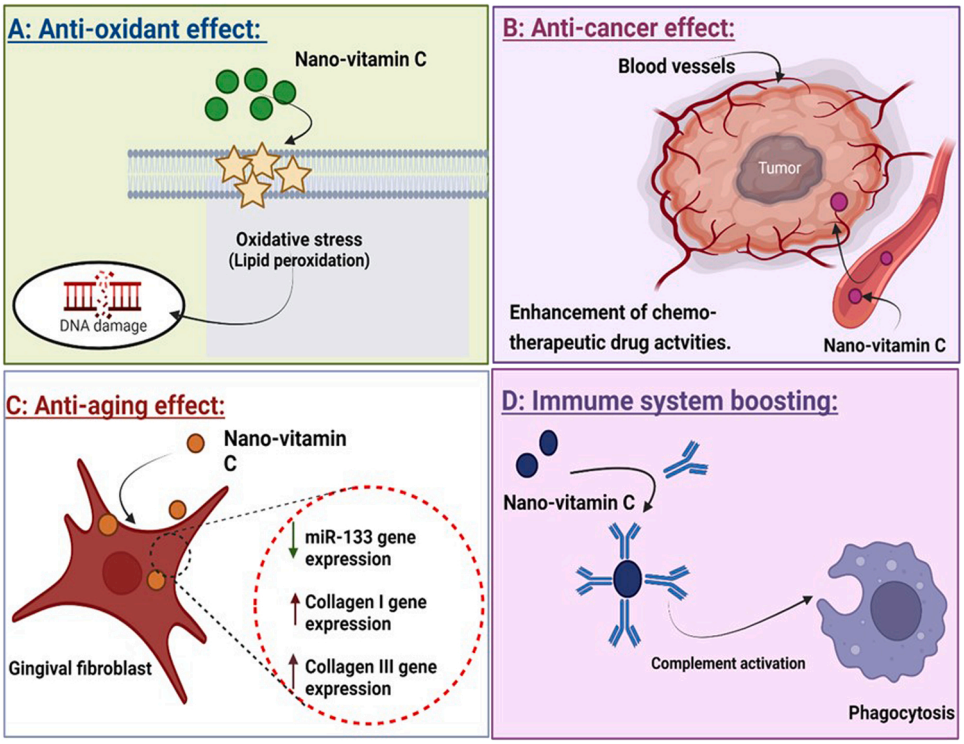

Fig. 2. Nano-vitamin C therapeutic applications. Overview that highlights the various therapeutic applications of nano-vitamin C: **A)** Oxidative effect by increasing lipid peroxidation, **B)** Anti-cancer activity by enhancing chemotherapy effect, **C)** Anti-aging activity by increasing the collagen genes expression, and **D)** Immune boosting properties by increasing complement contents and promoting phagocytosis.

and access to the TME. Thus, targeting of TME with nano-vitamin C provides a further frontier for enhancing the anticancer effects of nano-vitamin C with reduced toxicity (Fig. 3) [93–95].

4.3. Immune boosting properties of nano-vitamin C

Vitamin C exhibits immunomodulatory effects through enhancement of innate and adaptive immune responses [96]. Indeed, vitamin C enhances the differentiation and proliferation of B and T lymphocyte. As an antioxidant, it is able to improve the phagocytosis, modulate cytokine production and decrease histamine levels [97]. Unsurprisingly, vitamin C can be utilized as a powerful adjunct for cancer immunotherapy [88, 98,99]. For example, nano-nutraceutical vitamin C has been shown to enhance the immune system in vivo [100]. It is important to note that the immunomodulatory effects of vitamin C is enhanced when combined with other vitamins, notably, vitamin D and with essential nutrients such as zinc [101–103]. Indeed, supplementation of diet with vitamin C nanoparticles and zinc oxide improved the immune function of broiler chickens exposed to heat stress conditions [104]. A boost in immune responses was also observed in *Nile tilapia* following treatment with 400 mg/kg chitosan vitamin C nanocomposites [70], prompted by increased levels of lysozyme activity and nitric oxide release compared to controls [103]. Similarly, chitosan vitamin C nanoparticles increased the lysozyme levels in rainbow trout [105]. These findings suggest that chitosan nanoparticle formulation of vitamin C presents a promising approach to boosting the immune system.

4.4. Others biological effects of vitamin C nanoparticles

High-fat high-fructose diet induces an insulin-resistant state in the brain, whereby the level of insulin-like growth factor 1 (IGF-1) is reduced and acetylcholine esterase activity is increased [74]. Moreover, 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels increases, all of which signal cellular DNA fragmentation. This degenerative effect imposed by consumption of high-fat high-fuctose diet is reversible by vitamin C chitosan nanoparticles at a 10 fold lower dose than free vitamin C [106]. Vitamin C upregulates the concentration of catalase and improves spermatogenesis, sperm concentration, motility, and viability [107]. In concert with the preceding findings, vitamin C in nanoparticles reversed impaired fertility in male [75]. At low concentration, liposomal vitamin C caused a lowering of the systolic blood pressure in contrast to the free compound. This effect is mediated by the production of nitric oxide [108]. Chitosan nanoparticles loaded with vitamins C and E protected plasma testosterone levels in rats and improved the deposition of seminiferous tubules caused by cisplatin administration [109]. This vitamin combination in chitosan nanoparticles may be a useful strategy for use in circumventing reproductive toxicities induced by cisplatin in patients receiving chemotherapy.

In summary, growing evidence demonstrates the therapeutic effects of nano-vitamin C in various diseases. Toxicity arising from use of high concentration of vitamin C is negated when nano-encapsulated and yet, therapeutically meaningful concentrations are achievable in nano-carriers. Notwithstanding, further studies aimed at understanding and harnessing the full therapeutic activities of nano-vitamin C are warranted. Studies should also be aimed to deciphering the mode of action of nano-vitamin C and how it could be translated to the clinical applications.

5. Nano-vitamin C and clinical trials

Clinical studies, including pharmacokinetic, safety, and effectiveness of nano-vitamin C are rare. Indeed, only few clinical trials have

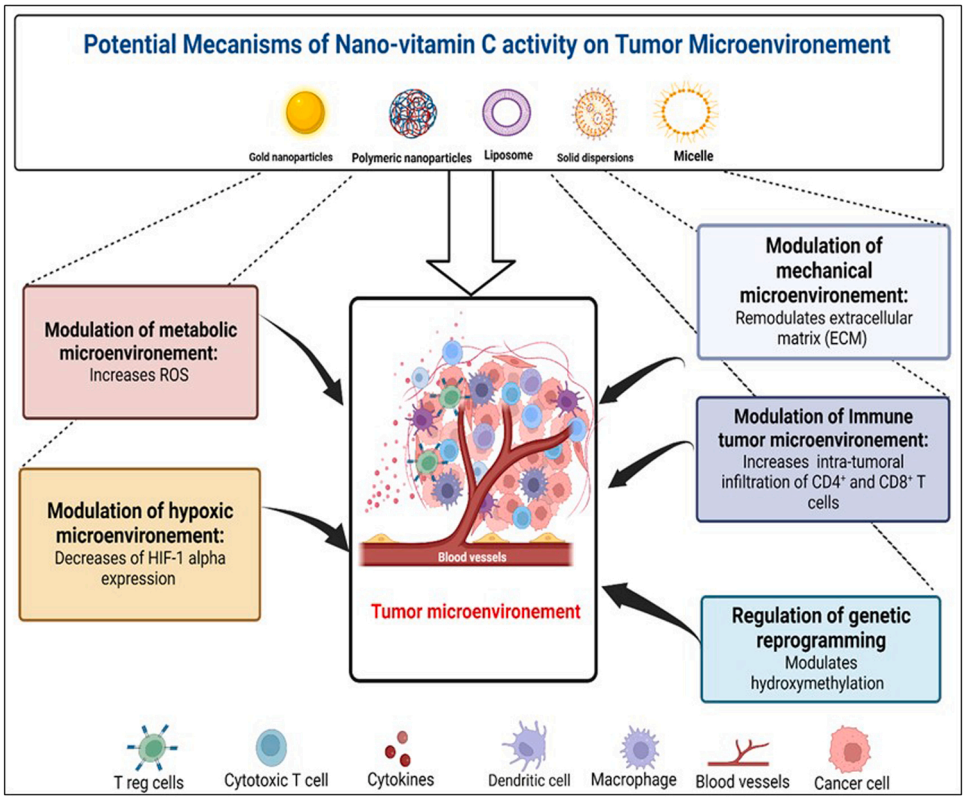

Fig. 3. The potential nano-vitamin C mechanisms of activity on targeting the TME. Nano-vitamin C might modulate the TME by regulating intra-tumoral genetic processes, immune cells infiltration (Increase intra-tumoral infiltration of $CD4^+$ and $CD8^+$ T cells), cytokines secretion (Decrease of IL-6, IL-17), ROS metabolism, and via hypoxic of (Decreases of hypoxia inducible factor- 1 alpha expression (HIF-1 α)) and mechanical properties (Extracellular matrix re-modulation (EMC)).

investigated the impact of liposomal vitamin C [32,33], with some focused on the effect of liposomal encapsulation on bioavailability (Table 2). In addition, several nano-vitamin C are available in market mainly in liposomal form [110,111]. For example, higher bioavailability and protection from ischemia was observed in patients when administered liposomal vitamin C compared to the free form [80]. The bioavailability of sodium ascorbate in liposomal formulation was higher than non-encapsulated form [112]. Furthermore, the bioavailability and blood retention of vitamin C are improved after ingestion of liposomal formulation of vitamin C compared to drug solution. Liposomal vitamin C improved the immunity in children and decreased the Wisconsin Upper Respiratory Symptom Survey scale within 4–5 days, with no relapse in 30 days [83]. Therefore, liposomal vitamin C may be used as adjuvant therapy in the treatment of URT infection in children [113]. It recently been reported that oral liposomal vitamin C at high dose decreased the mortality in patients with COVID-19. This study involved 8634 patients with COVID-19, and showed that the mortality rate was 1.9% after oral liposomal vitamin C compared to 4% mortality in the non-treated group [31]. Taken together, these data demonstrate that liposomes can be used to achieve better gastrointestinal absorption, bioavailability, precluding the need for intravenous vitamin C. However, additional clinical studies on larger samples size are required to confirm the potential therapeutic effect of liposomal vitamin C. Moreover, information is not available about the side effects of vitamin C nano-formulation administered by intravenous injection in these studies. From the forgoing, it is clear that only a handful of clinical investigations are directed towards fully understanding the therapeutic effect of nano-vitamin C. Most studies are limited to cellular laboratory investigations, some of which are very promising and hence should propell our quest to unlocking more therapeutic applications of nano-vitamin C.

6. Gaps in nano-vitamin C research

Multiple factors restrict the therapeutic use of vitamin C, such as its instability which impedes effective intestinal absorption [117]. Vitamin C is also highly excreted in urine and feces. Consequently, the rate of absorption and distribution of vitamin C are limited and vary significantly between different. This constraint cannot be overcome by increasing the dose, because higher doses, although seldom fatal, manifest side effects such as diarrhea and gastrointestinal irritations [118,119]. Fortunately, research in nano-encapsulation has provided a scope to broaden the clinical and therapeutic applications of vitamin C. In this regard, liposomal formulations remain central, with demonstrable therapeutic effects compared to free vitamin Cm and consequently, have led to the initiation of various clinical trials. However, only few liposomal nano-formulations of vitamin C have been investigated on limited number of diseases. Additionally, several other vitamin C formulations, especially the polymeric nanoparticles have also demonstrated varying levels of effectiveness in vivo but have not yet reached the clinical threshold. This review provides the reader with a scope of considerations necessary realizing the full therapeutic benefits of vitamin C.

7. Conclusions and future prospects

Growing evidence indicates that vitamin C has several clinical benefits but its use is limited due to its instability, fast degradation, and poor bioavailability in the body. Nano-encapsulation not only provides avenues to surmount these limitations, but also to broaden the therapeutic scope and biological activity of vitamin C. Several nano-formulations of vitamin C are in their primary phase of development. Additional studies must be directed to understanding the mechanisms and therapeutic effects of vitamin C in nano-formulations, since these are likely to differ from the free vitamin C activity. Furthermore, due to its high availability in nature, negligible toxicity, and its cost-effectiveness in usage, vitamin C opens the doors for therapeutic options as it has a wide range of biological applications including anticancer and antioxidant properties. It is the view of the authors that several more therapeutic benefits of nano-vitamin C are on the horizon as we delve into more potential nano-vitamin C formulations for several applications in the future. However, more conclusive answers focusing on the clinical benefits of nano-vitamin C should be evaluated.

Table 2
Published and ongoing clinical trials involving liposomal vitamin C.

Ref	Interventions	Method of preparation	Conditions	Identifier/ Status
[23]	Liposomal vitamin C	Thin-film evaporation	Bioavailability	Published 2021
[114]	Liposomal vitamin C	Empirical Labs Formula: 36 mg of mixed natural phospholipids and 284 mg of USP sodium ascorbate (NaA), in a total volume of 1 mL with ultrahigh purity water	Bioavailability	Published 2016
[115]	Liposomal vitamin C	1 g tablets of vitamin C	Bioavailability	Published 2008
[112]	Liposomal vitamin C	Glycerine containing lipids (1:1 w/w) and the aqueous solution containing sodium ascorbate	Bioavailability	Published 2020
[116]	Liposomal vitamin C	Spray drying	Bioavailability	Published 2021
[25]	Liposomal vitamin C	5 g dose of sodium ascorbate powder (NOW Foods) 5 g ascorbate dose in liposomal formulation (LivOn Lab)	Bioavailability	Published 2021
[113]	Liposomal vitamin C		Upper Respiratory Tract Infections	Published 2021
[31]	Liposomal vitamin C	4 g of oral liposomal vitamin C	COVID- 19	Published 2021
[32]	Liposomal vitamin C	Double Nutri (liposomal encapsulation)	Vitamin C Deficiency	NCT04886752 Completed
[33]	Liposomal vitamin C	500 mg capsule of liposomal vitamin C	Complex Regional Pain Syndrome I of Lower Limb	NCT04204200 Completed

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CRediT authorship contribution statement

TB, SI and QF wrote the initial draft. TB and LA prepared the figures. MM, NB and TB thoroughly revised the initial draft. SD, MM, NB and SU provided intellectual input and critical review of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflicts of interest statement

The authors declare no conflict of interest.

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