Vitamin C -Ascorbic Acid : Cancer

Locally available:

https://choicenutrition.ca/services/intravenous-therapy/

This is a therapy frequently used in the support of patients affected by cancer and infections. At very high doses, Vitamin C actually has a selective oxidative/destructive effect on some cancer cell lines in vitro, and is compatible with MOST conventional treatments. Vitamin C also supports immune function via interferon and interleukin, which is why it is useful for overcoming infections. Vitamin C can help with increased production of hydrogen peroxide (pro-oxidant). It is anti-angiogenesis (stop the blood supply that feeds cancer), and anti-inflammatory.

https://truepotentialhealth.com/intravenous-iv-therapy-saskatoon/
https://www.saskatoonnaturopathic.com/nutritional-iv-therapy

https://www.cancer.gov/about-cancer/treatment/cam/hp/vitamin-c-pdq

Intravenous Vitamin C (PDQ®)–Health Professional Version

Two studies that used IV vitamin C in cancer patients reported improved quality of life and decreases in cancer-related toxicities

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7996511/

High-Dose Vitamin C in Advanced-Stage Cancer Patients 2021

In this narrative review, we decided to deal with this issue, trying to answer the question whether there is any scientific evidence supporting the rationale for application of high-dose IVC therapy in advanced-stage cancer patients. Although results obtained from preclinical studies demonstrated that millimolar ascorbate plasma concentrations achievable only after IVC administration were cytotoxic to fast-growing malignant cells and inhibited tumor growth as well as prolonged the survival of laboratory animals, such positive effects were not found in human studies with advanced-stage cancer patients. We also have not found the rationale for the use of IVC to increase the effectiveness of chemotherapy and to reduce the chemotherapy-induced toxicity in the above mentioned group. Nevertheless, in palliative care, high-dose IVC might be considered as a therapy improving the quality of life and reducing cancer-related symptoms, such as fatigue and bone pain. However, because of the absence of placebo-controlled randomized trials on IVC efficacy in advanced-stage cancer patients, the placebo effect cannot be excluded.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9030840/

The Result of Vitamin C Treatment of Patients with Cancer: Conditions Influencing the Effectiveness 2022

Vitamin C (ascorbic acid, AA) is a weak sugar acid structurally related to glucose. All known physiological and biochemical functions of AA are due to its **action as an electron donor**. Ascorbate readily undergoes pH-dependent autoxidation creating hydrogen peroxide (H_2O_2). In vitro evidence suggests that vitamin C functions at low concentrations as an antioxidant while high concentration is pro-oxidant.

The analyzed results indicate that HAAT might be a useful cancer-treating tool in certain circumstances. The AA's cytotoxic effect is hypoxia-induced factor dependent. It impacts only the anoxic cells, using the Warburg metabolism. It prevents tumor growth. Accordingly, discontinuation of treatment leads to repeated expansion of the tumor. We believe that the clinical use of HAAT in cancer treatment should be reassessed. The accumulation of more study results on HAAT is desperately needed.

The study by Levine M et al. [7] showed that when vitamin C is ingested by mouth, plasma and tissue concentrations are tightly controlled by at least three mechanisms in healthy humans: absorption, tissue accumulation, and renal reabsorption. With ingested amounts found in foods, vitamin C plasma concentrations usually do not exceed 100 µmol/L. Even with supplementation approaching maximally tolerated doses, ascorbate plasma concentrations are always <250 µmol/L and frequently <150 µmol/L. By contrast, when AA is i.v. injected, tight control is bypassed until excess ascorbate is eliminated by glomerular filtration and renal excretion. With i.v. infusion, pharmacologic ascorbate concentrations of 25–30 mmol/L are safely achieved. Pharmacologic AA can act as a pro-drug for H_2O_2 formation, leading to an extracellular fluid at levels as high as 200 µmol/L. In addition, pharmacologic ascorbate can elicit cytotoxicity toward cancer cells and slow tumor growth in experimental murine models

Tumor cells use 200 times more glucose than healthy ones [17]. Malignant tumor cells perform glycolysis at a ten times faster rate than their healthy tissue counterparts [18]. While rapidly growing tumor cells do not have adequate vessels during their genesis, the limited capillary support often results in hypoxia within the tumor. In addition, some tumor cells overexpress specific glycolytic enzymes, resulting in higher glycolysis rates, referred to as the **Warburg** effect [19].

Short-term fasting (STF) 48 to 72 h before chemotherapy appears to be more effective than intermittent fasting. Preliminary data show that STF is safe but challenging in cancer patients receiving chemotherapy. Ongoing clinical trials need to unravel if STF can also diminish the toxicity and increase chemotherapeutic regimens' efficacy in daily practice [33].

7.3. Glutathione and Catalase Result Resistance of Cancer Cells against AA Mediated Cytotoxicity

Hardaway et al. [55] showed that H_2O_2-produced cell death was partly mediated by losing total glutathione levels in the cells. Glutathione reduced cytotoxicity by 10–95% by attenuating AA-induced H_2O_2 production. Co-treatment with glutathione inhibits the cytotoxic responses [54]. One study analyzed the impact of catalase on cancer cells' resistance to ascorbic acid-mediated oxidative stress. The tested human cancer cell lines demonstrated apparent differences in their opposition to AA-mediated oxidative cell stress [56].

9.1. **Glucose Dependency**

It is known that pharmacologic AA can induce some cancer cell death in vitro and inhibit several types of tumor growth in animal models through the production of H_2O_2. It is also known that glucose deprivation as well as i.v. AA might result in benefits for cancer patients. Limited case reports indicate that a ketogenic diet combined with i.v. AA improves the effectiveness of HAAT [78]. Based on these results, it is predictable that the patient's serum glucose level might influence the effectiveness of i.v. AA therapy. Consumption of carbohydrate-containing food or drink when the serum level of AA is in the toxic range (300 min after finishing the infusion) might prevent the realization of the poisonous effect. Unfortunately, most publications do not contain data relating to the nature of carrier infusion (NaCl, Ringer, Ringer's lactate, or 5% dextrose). We assume that dextrose might terminate the cytotoxic effect of vitamin C if AA is dissolved in a 5% dextrose infusion [66,67].

10.1. The **Glucose Deprivation and Vitamin C Therapy's Way of Action**

During energy transfer in cells, O_2e^- is continuously produced in the presence of glucose and AA. During energy transformation, ribose will be

cut from the glucose molecule, forming adenosine. If glucose is not available, the O2e− produced by Fe-S clusters destroys the tumor cell. The situation might be formed by a glucose deficit or a high intracellular concentration of AA [8].
The cell's ability to protect against free radicals in the presence of O2 is significantly higher than that in a low-oxygenated environment due to the intensive mitochondrial defense against ROS action. However, the normoxic tumor cells survive. Therefore, i.v. AA therapy and glucose deprivation should be long lasting and used in combination with conventional anticancer treatments.

https://pubmed.ncbi.nlm.nih.gov/30174242/
Ascorbic Acid in Cancer Treatment: Let the Phoenix Fly 2018
Vitamin C (ascorbic acid, ascorbate), despite controversy, has re-emerged as a promising anti-cancer agent. Recent knowledge of intravenous ascorbate pharmacokinetics and discovery of unexpected mechanisms of ascorbate action have spawned many investigations. Two mechanisms of anti-cancer activity with ascorbate have gained prominence: **hydrogen peroxide-induced oxidative stress** and DNA demethylation mediated by ten-eleven translocation enzyme activation. Here, we highlight salient aspects of the evolution of ascorbate in cancer treatment, provide insights into the pharmacokinetics of ascorbate, describe mechanisms of its anti-cancer activity in relation to the pharmacokinetics, outline promising preclinical and clinical evidence, and recommend future directions.

With pharmacokinetics as a foundation, it was shown that only ascorbic acid at pharmacologic concentrations from intravenous dosing, and that would not occur from oral dosing, acted as pro-drug for hydrogen peroxide (H2O2) formation in the extracellular space (Chen et al., 2005; Chen et al., 2007). Pharmacologic, but not physiologic, ascorbic acid was selectively toxic to cancer cells in-vitro and in vivo (Chen et al., 2005; Chen et al., 2008; Verrax and Calderon, 2009).
Conversely, there are no data showing that pharmacologic ascorbate interferes with chemotherapy. Early phase clinical trials indicate that IV ascorbate at 1g/kg over 90–120 minutes two to three times weekly is well tolerated and may enhance chemosensitivity as well as decrease chemotherapy related side effects. (Carr et al., 2014; Hoffer et al., 2015; Ma et al., 2014; Monti et al., 2012; Schoenfeld et al., 2017; Shim et al., 2014; Stephenson et al., 2013; Welsh et al., 2013).
Supportive evidence that H2O2 is generated by pharmacologic ascorbate in humans is provided by reports of oxidative hemolysis in patients with glucose 6-phosphate dehydrogenase deficiency who received intravenous ascorbate (Huang et al., 2014; Rees et al., 1993). Indeed, it is for this very reason that patients who receive intravenous ascorbate must be prescreened for glucose 6 phosphate dehydrogenase deficiency. Taken as a whole, Cameron's reported cases hint that there could be other H2O2-independent potential actions of pharmacologic ascorbate, because intravenous doses at those used are predicted to have relatively small effects on extracellular H2O2 formation.
The rationale for the use of high dose intravenous ascorbate in cancer treatment is not to correct plasma deficiency, but rather to induce an **oxidative stress** on cancer cells (Chen et al., 2005; Chen et al., 2007; Chen et al., 2008) and to ensure adequate delivery of ascorbate within tumors for optimal cofactor function (Kuiper et al., 2014).
Dosing information is limited, including dosing amount, dosing frequency, ascorbate administration timing with conventional agents, and treatment duration. Clinical evidence is that at a minimum 1 g/kg should be administered intravenously over 2 hours twice weekly, with more frequent administration perhaps better (Hoffer et al., 2008; Ma et al., 2014; Monti et al., 2012; Polireddy et al., 2017; Schoenfeld et al., 2017; Welsh et al., 2013).
The implications are substantial of a therapeutic agent that is universally available and accessible, with the potential of anti-cancer activity across multiple tumor types as well as reducing chemotherapy toxicity. Should the oncology research community invest in the necessary randomized trials to test whether there is benefit of IV ascorbate? We firmly recommend yes, utilizing well-designed randomized (and where possible, placebo-controlled) trials. Establishing biomarkers for selection of patients who benefit from IV ascorbate would enable us to tailor treatment more effectively and efficiently. Mechanism bases should be explored, with caveats. However, despite intentions to pursue well-defined biomarkers of response, it may be difficult to zero in on a single, highly predictive biomarker. This is because pharmacologic ascorbate can be considered a promiscuous agent mechanistically with respect to generation of extracellular H2O2 as well as its varied cofactor functions (Levine and Violet, 2017). Once extracellular H2O2 is present, myriad mechanisms can mediate cancer cell death. While these aspects may not be in keeping with the "targeted therapy" era in oncology, they should not deter exploration of ascorbate's potential as a therapeutic agent. Primary endpoints may be tumor response rate or survival. Secondary endpoints include adverse effect profiles and quality of life. We strongly encourage the field to explore ascorbate's potential, but also send a cautionary note that new studies need to be done properly. Let's not shoot down the re-rising ascorbate treatment phoenix.

https://pubmed.ncbi.nlm.nih.gov/38927877/
Generation of Hydrogen Peroxide in Cancer Cells: Advancing Therapeutic Approaches for Cancer Treatment 2024
4.3. **Vitamin C**
Vitamin C (also known as ascorbic acid or ascorbate) is an essential vitamin in the body's daily function. It allows for the biosynthesis of collagen and various neurotransmitters, is involved in protein metabolism, and strengthens the body's immune system. In recent years, ascorbic acid has been shown to have selective anticancer properties at millimolar (mM) concentrations, with such an anticancer effect demonstrated both in vitro and in vivo [123 –126]. The main mechanism through which vitamin C kills tumor cells is by formation of H2O2 [124 , 127].
At the beginning of this process, the ionized vitamin C is transformed into ascorbate radical by losing one electron (Figure 22). This electron then reduces a protein-centered metal, such as Fe3+ to Fe2+. The created Fe 2+ then donates an electron to O2, forming O2●− that is subsequently dismutated to form H 2O2 and O2. The created H 2O2 can cause damage to DNA, lipids, and proteins, inducing cancer cell death. Notably, these concentrations of Vitamin C are not enough to kill healthy, non-cancerous cells due to the high level of plasma catalase and/or GSH peroxidase that inhibit the redox reaction or destroy any formed H2O2 molecules, thus making cancer treatment via vitamin C even more appealing due to its selective nature
Another possible avenue that could be taken with vitamin C cancer treatment is using it in conjunction with other therapeutics, such as vitamin K3, triethylenetetramine, or other H2O2-responsive chemotherapeutic drugs (i.e., camptothecin) to achieve synergistic anticancer effect while minimizing unwanted side effects [133–135

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7063061/

Therapeutic Use of Vitamin C in Cancer: Physiological Considerations 2020

Humans, unlike most mammalian species, are unable to synthesize vitamin C, hence it is an essential dietary component and humans need to acquire this vitamin from external sources, such as vegetables and fruits (Rivas et al., 2008). The recommended dose for an adult is around 100 mg per day, which has shown to maintain plasmatic concentration of 50 μM. However, when intracellular content is measured, differential concentrations of vitamin C are found depending on the tissue. Circulating leucocytes, pituitary gland, adrenal glands and **brain**, among others, accumulate largely higher concentrations than plasma reaching millimolar range (Rose, 1988).

The mechanism of cytotoxicity is linked to the production of extracellular H_2O_2 and involves intracellular transition metals (Chen et al., 2008; Verrax and Calderon, 2009). In the same line, several reports support the induction of ROS achieved by high concentrations of vitamin C in cancer cells as a mechanism for cancer cell death induction: in human pancreatic tumor (Du et al., 2010), in human mesothelioma (Takemura et al., 2010), in human breast cancer (Hong et al., 2013), among others.

A study considering 125 breast cancer patients showed that IV ascorbate reduces chemotherapy-related side effects, such as nausea, fatigue and dizziness (Vollbracht et al., 2011). Similar results were obtained in a study with 60 patients with different types of cancer, where IV ascorbate improved their quality of life (Takahashi et al., 2012). In addition, vitamin C administrated alone also improved quality of life in a study including 17 patients with different solid tumors, although no patient showed an objective antitumor response (Stephenson et al., 2013).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8392841/

Understanding the Therapeutic Potential of Ascorbic Acid in the Battle to Overcome Cancer 2021

In anticancer drug development, ascorbic acid has played an important role by inhibiting the development of cancer through various mechanisms, including scavenging reactive oxygen species (ROS), selectively producing ROS and encouraging their cytotoxicity against tumour cells, preventing glucose metabolism, serving as an epigenetic regulator, and regulating the expression of HIF in tumour cells. Several ascorbic acid analogues have been produced to date for their anticancer and antioxidant activity. The current review summarizes the mechanisms behind ascorbic acid's antitumor activity, presents a compilation of its derivatives and their biological activity as anticancer agents, and discusses delivery systems such as liposomes, nanoparticles against cancer, and patents on ascorbic acid as anticancer agents.

Cancer becomes highly fatal and incurable after spreading beyond the primary tumour site [21]. In in vitro study, it was observed that ascorbic acid at high concentration curbed cell migration and capillary-like tube formation [24]. Accordingly, ascorbic acid can be useful to prevent the further growth and spread of tumour cells. Moreover, ascorbic acid not only protects our body from free radicals as an antioxidant and damages cancerous cells as a pro-oxidant, but it is also involved in many important physiological functions such as the formation of collagen, wound healing, repair of body tissues, and nurturing of bones, cartilage, and teeth [25].

In the early 1900s, Otto Warburg and co-workers observed that a higher amount of glucose was consumed for glycolysis by tumour cells in the absence of abundant oxygen; this is known as the **Warburg Effect** [44]. It is a crucial characteristic of tumour survival and proliferation in hypoxic environments [45]. This change in glycolytic character allows tumour cells to undergo 200 times faster rates of glycolysis than normal cells [46]. The Warburg Effect is a vital metabolic trait of cancer cells [47].

Ascorbic acid at micromolar (μM) concentrations functions as an anti-oxidant agent, but at higher, millimolar (mM) concentrations, also functions as a pro-oxidant. Intravenous administrations of vitamin C induce cytotoxicity to tumour cells [75], as it can produce 70-fold greater plasma concentration than its oral counterpart [76]. It was observed that the antitumor potential of high-dose ascorbic acid is rooted in its ability to generate hydrogen peroxide (H_2O_2) [77]. In animals, ascorbate at millimolar concentrations donates an electron to copper and iron metals, resulting in the production of superoxide, a hydrogen peroxide-like ROS [20]. The ROS induces damage to DNA, ultimately causing cytotoxicity to cancer cells [55]. Upon intravenous administration, ascorbate ($AscH^-$) reacts with protein-centred transition metal ions, i.e., ferric (Fe^{3+}) and cupric (Cu^{2+}) ions. In practice, there is a fairly low level of conversion metals, and thus greater concentrations of vitamin C are necessitated. Ascorbate reduces Fe^{3+}/Cu^{2+} to ferrous (Fe^{2+})/cuprous (Cu^+) ions, oxidizing itself into ascorbate free radical (Asc^-). The reduced Fe^{2+}/Cu^+ ions react with oxygen to form ROS such as superoxide radicals, which in the existence of hydrogen undergo dismutation and form hydrogen peroxide (H_2O_2). Further, the H_2O_2 may undergo a Fenton-like reaction catalysed by Fe^{2+}/Cu^+, yielding hydroxyl peroxide radical ($HO\cdot$) [30,55], which induces damage to cancer cells [78].

Several studies have reported elevated copper levels in cancer [81,82], as it is a cofactor of DNA replication enzymes for rapidly proliferating cancer cells [55]. In cancer, elevated copper concentrations with an altered systemic distribution of the element [83] made cancer cells vulnerable to the ROS-generated selective cytotoxicity of copper and ascorbic acid [84]. Additionally, in the case of iron, although it is stored by the glycoprotein ferritin in healthy individuals, under pathological conditions such as cancer inflammation, extracellular iron chelates are increased in tissue [85], making them susceptible to ascorbate-induced ROS toxicity.

Chen et al., have observed that ascorbic acid selectively hinders tumour growth without causing any damage to normal cells via the generation of H_2O_2 [19]. Baek et al., also observed that ascorbic acid induces toxicity to cancer cells through the generation of **ROS** [86]. In another study, a high quantity of ascorbic acid prompted the cell death of malignant cells through the generation of ROS, especially hydrogen peroxide [87]. Thus, ascorbic acid at millimolar concentrations induces toxicity to various cancer cells through the generation of ROS, which themselves damage cellular components and hamper various important cellular mechanisms.

In the last few decades, several fundamental discoveries have been transformed into intellectual property with exceptionally realistic opportunities for future utilization. Consequently, new and innovative products and technologies related to the anticancer potential of ascorbic acid and its derivatives were patented. Following are some examples of such patents (Table 1):

https://www.cmaj.ca/content/174/7/937

Intravenously administered vitamin C as cancer therapy: three cases 2006 Canada

The cases reported here do not prove that vitamin C induced the favourable outcomes observed. These patients received other alternative medicine therapies. Spontaneous remission of some tumours may occur rarely, although the 3 cancers reported here are dissimilar. Accretion of more cases meeting NCI Best Case Series guidelines may indicate whether vitamin C or other factors contribute to such remissions.

It is likely that high vitamin C intakes have low toxicity, except under certain conditions.45,46 Intravascular hemolysis was reported after massive vitamin C administration in people with glucose-6-phosphate dehydrogenase deficiency.46Administration of high-dose vitamin C to patients with systemic iron overload may increase iron absorption and represents a contraindication.46,47Ascorbic acid is metabolized to oxalate, and 2 cases of acute oxalate nephropathy were reported in patients with pre-existing renal insufficiency given massive intravenous doses of vitamin

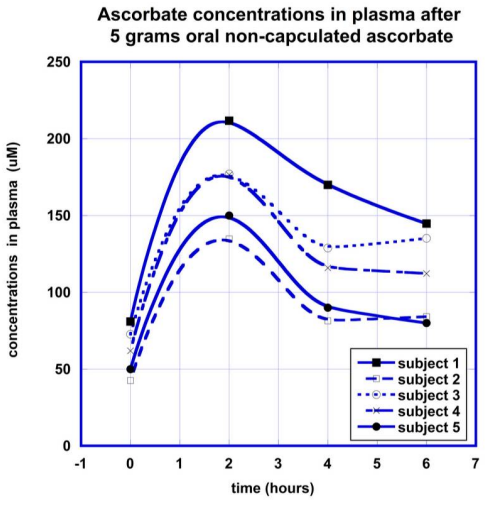
C.48,49Therefore, patients with renal insufficiency or renal failure, or who are undergoing dialysis, should not receive high doses of vitamin C.46 It is controversial whether high-dose vitamin C use is associated with oxalate kidney stones, and patients with hyperoxaluria or a prior history of oxalate kidney stones have a relative contraindication to high-dose vitamin C.46Rare cases of acute tumour hemorrhage and necrosis were reported in patients with advanced cancer within a few days of starting high-dose intravenous vitamin C therapy, although this was not independently verified by pathologic review.1,50 Although tumour hemorrhage suggests an anticancer potential for ascorbate, there is the potential for risk to some patients.
The cases reported here are of tumours confirmed by histopathologic examination to have poor prognosis but that instead had long clinical remissions. Most previous case reports lacked independent pathologic confirmation of the tumour and did not follow the NCI Best Case Series guidelines, which makes their interpretation difficult. Recent findings show that only high-dose intravenous, but not oral, vitamin C therapy results in very high plasma vitamin C concentrations (e.g., 14 000 μmol/L). At these concentrations, the vitamin is toxic to some cancer cells, possibly because at these concentrations the vitamin is a pro-drug for hydrogen peroxide formation in extracellular fluid. Accumulated data confer some degree of biological and clinical plausibility to the notion that high-dose intravenous vitamin C therapy may have anti-tumour effects in certain cancers. When all available data are considered, further clinical study as to safety and efficacy of intravenous vitamin C is warranted.

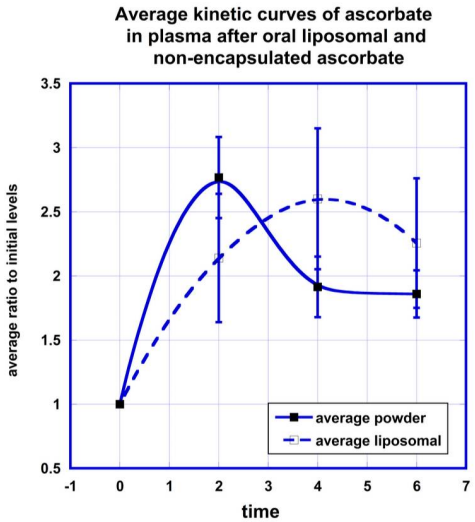
https://isom.ca/article/the-levels-of-ascorbic-acid-in-blood-and-mononuclear-blood-cells-after-oral-liposome-encapsulated-and-oral-non-encapsulated-vitamin-c-supplementation-taken-without-and-with-iv-hydrocortisone/

The Levels of Ascorbic Acid in Blood and Mononuclear Blood Cells After Oral Liposome-Encapsulated and Oral Non-Encapsulated Vitamin C Supplementation, Taken Without and with IV Hydrocortisone 2019

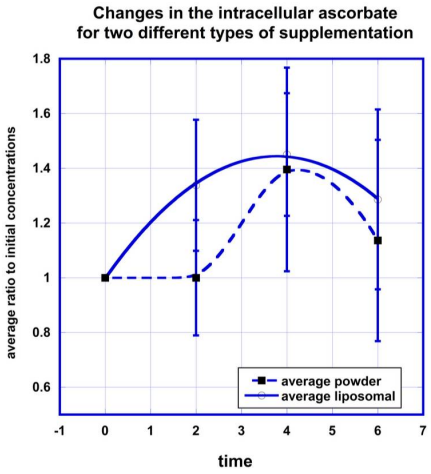
The goal of this study was to compare concentrations of ascorbate (vitamin C) in plasma and white blood cells (WBCs) after oral administration of 1) **liposomal** vitamin C versus 2) traditional vitamin C in the form of powder and to analyze the effect of hydrocortisone on the improvement of ascorbate intake by cells.
Vitamin C levels in white blood cells are higher than in plasma, which may indicate functional roles of the vitamin in these immune system cells. In particular, leukocytes have been shown to have higher levels of vitamin C than are found in the plasma (Loh et al., 1971).
The second goal of the project was to demonstrate that IV hydrocortisone when administered at the time of supplementation by the oral form of vitamin C can increase the transport of ascorbate into white blood cells, resulting in the higher intracellular ascorbic acid concentrations. Animal studies, along with human clinical studies, support the concept that vitamin C and hydrocortisone appear to be designed by nature to naturally interact with each other to optimize the antioxidant impact in diseased and infected tissues, and to directly promote the recovery of their normal functions while accelerating their healing.

Once per week on Monday	Formulations of Vitamin C	Amount (mg)	The periods of blood drawing at the day of supplementation (hours)
week 1	sodium ascorbate (powder) (NOW Foods, IL)	5000	0, 2, 4, 6
week 2	liposomal ascorbate (LivOn laboratories, INC)	5000	0, 2, 4, 6
week 3	sodium ascorbate (powder) +hydrocortisone	5000+50	0, 2, 4, 6
week 4	liposomal ascorbate + hydrocortisone	5000+50	0, 2, 4, 6





According to these data, in plasma the maximum concentration of ascorbate encapsulated in the liposomal carrier was reached 4 hours after supplementation in comparison with maximum at 2 hours for non-encapsulated form of ascorbate.
The area under the curve (AUC) calculated by trapezoidal summation equals 799 uMh for liposomal ascorbate and 773 uMh for non-encapsulated ascorbate.
In summary, no significant difference was noted in the maximum concentrations of ascorbate in plasma between liposome-encapsulated and non-encapsulated ascorbate, but a difference was found in the retention time of the ascorbate in blood with liposomal formulation retention longer than the retention of non-encapsulated ascorbate.

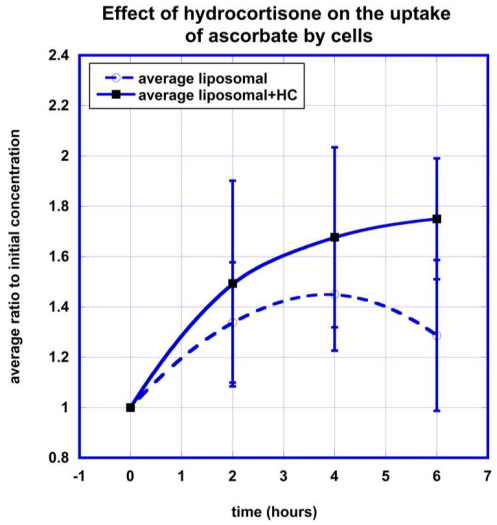


The comparison of the areas under the curve for concentrations that were higher than initial levels showed that AUC was 50% larger for liposomal formulation in comparison with non-encapsulated ascorbate.

Another interesting observation was that of the amount of ascorbate incorporated in the cells depended on the initial level of ascorbate in WBCs. For the lower initial intracellular level of ascorbate 50 nm/10^8 cells the increase of the ascorbate concentration in cells was higher (180%) than for higher initial concentrations 100 nm/10^8 cells (80%).

The Effect of Hydrocortisone on Ascorbate Intake in Cells

To evaluate the effect of hydrocortisone on the intake of ascorbate by cells, we compared the kinetic curves of the intracellular ascorbate concentrations after oral liposome-encapsulated vitamin C supplementation and the same dosage of the liposomal supplementation followed by 50 mg IV hydrocortisone. The data are presented in Figure 4.



The area under normalized concentration-time curve for values higher than initial levels was on 60% larger for liposomal supplementation taken after IV hydrocortisone.

Summary

Comparisons of the liposome-encapsulated and non-encapsulated (powder) ascorbate supplementations demonstrated that liposomal ascorbate intake results in longer retention of ascorbate in blood. Plasma concentrations of ascorbate remained at the level of 100% increase during 3 hours for non-encapsulated ascorbate and longer than 4.5 hours for liposomal ascorbate. The maximum percentage of ascorbate increase was the same for both formulations and reached 150%-170%.

The concentrations of ascorbate in white blood cells were changed after intake of ascorbate in the form of non-encapsulated and encapsulated liposomal ascorbate supplementations. The average maximum increase in the concentrations of ascorbate in cells was the same for both formulations (in range 40%÷50%). The data show that liposomal ascorbate resulted in faster intake by cells. The comparison of the areas under the curve for concentrations that were higher than initial levels showed that AUC was on 50% larger for liposomal formulation in comparison with non-encapsulated ascorbate.

The data support our hypothesis that hydrocortisone can have effect on the uptake of ascorbate by cells, when it is given as an adjuvant to ascorbate supplementation. The injection of hydrocortisone before intake of supplements resulted in more favorable percentage of intracellular ascorbate intake.

https://isom.ca/article/vitamin-c-cancer-use-oral-vitamin-c/

Vitamin C and Cancer: Is There A Use For Oral Vitamin C? 2013

For several decades, the role of vitamin C in the treatment of cancer has been a subject of clinical research and controversy. It has been established that ascorbate is potentially a safe and effective anti-cancer agent, able to kill cancer cells while leaving healthy cells unharmed. However, its role has been viewed in the context of existing cytotoxic chemotherapy models of medicine. Consequently, many doctors and patients have come to believe that only intravenous vitamin C administration is an effective treatment for cancer. We suggest that this view is misguided and oral intakes are preferable. .

o a first approximation, both chemotherapy and radiotherapy work by increasing local oxidation and causing free radical damage, with the aim of either killing cancer cells directly, or stimulating apoptosis (cell suicide).
One nutritional approach that a cancer cannot avoid is if it is starved of usable energy. Physically, the cancer needs energy to grow or even to continue to survive. “Starving” the cancer is a potential treatment (Robinson, Hunsberger & Westall, 1994), and is part of the reason patients should avoid carbohydrates and sugars.
We are particularly interested in **vitamin C, which acts safely as an antioxidant in healthy tissues and an oxidant in tumours**. In other words, it is the archetype for anti-cancer treatments (Benade, Howard & Burk, 1969).
So, for example, a person might tolerate well over 100 grams per day when acutely ill but have a bowel tolerance of 3 grams per day when healthy. The magnitude and easy reproducibility of this effect suggests that it is important to the mechanism of action with oral intakes.
Cathcart’s bowel tolerance observations imply that, during illness, the body responds by absorbing as much vitamin C as possible from the gut.
Firstly, the data for dynamic flow using repeated oral doses indicates that an intake of 20 g/day (20,000 mg/ day in divided doses) can maintain plasma levels at approximately 250 µM/L (Hickey, Roberts, Miller, 2008). Moreover, the massively increased Cathcart bowel tolerance in sick people, who can sometimes consume up to 200-300 g/day, reflects a greater absorptive capacity.
The availability of liposomal vitamin C has increased the plasma levels attainable with oral doses. These formulations greatly increase absorption in healthy individuals, to perhaps 90% of an oral dose. Our preliminary results indicated that a large single oral dose of liposomes could increase plasma levels of free ascorbate to a maximum of at least 400 µM/L (Hickey, Roberts, Miller, 2008).
Initial measurements suggest that liposomes and standard oral ascorbic acid are absorbed by independent mechanisms and that a combination of both can yield free molecule plasma levels at >800 µM/L.
Cameron and Pauling performed a preliminary clinical trial, on the use of vitamin C in 100 terminal cancer patients (Cameron, Pauling, 1976). Their results were remarkable, with vitamin C increasing the mean survival time more than 4.2 times, from 50 days (controls) to more than 200 days (treated). They reported that most treated patients had a lower risk of death and improved quality of life, while about 10% (13 patients) had survival times around 20 times longer than those of the control patients.
The protocol included an initial 10 day course of IV ascorbate, at a relatively low daily dose of 10 g/day, followed by continuous oral intakes of 10-30 g/day, in divided doses.
In 1982, Murata and Morishige also reported extended survival times from the use of vitamin C in cancer (Murata, Morishige & Yamaguchi, 1982). These Japanese researchers used oral doses of up to 30 g/day, supplemented with relatively low-dose 10-20 g IV infusions. Their reported survival times were 43 days for 44 low-ascorbate patients, compared to 246 days for 55 high-ascorbate patients (5.7 times longer). In another Japanese hospital, the researchers reported survival times of 48 days for 19 control patients, compared to 115 days for six treated patients. Furthermore, at the time of publication, some treated patients were still alive. In 1982 Murata and Morishige had replicated the Cameron and Pauling trial with similar encouraging results, as shown in their survival chart, reproduced in **Figure 2**.
The implication of this is that oral intakes cannot reach the levels needed to kill cancer cells, whereas injected ascorbate can reach the necessary cytotoxic levels. This interpretation is an error, which seems to have arisen through analogy with chemotherapy.
Figure 5 illustrates data calculated from Takemura et al, using mesothelioma cell lines (Takemura, Satoh, Satoh, et al. 2010). These data show a large increase in cancer toxicity when the experimental exposure time was increased from 1 hour to 24 hours. In some cases, a prolonged exposure to vitamin C at a concentration of 100 µM/L, a level easily sustained with oral supplementation, was found to be more effective than a short exposure at the much higher level of 1,000 µM/L.
Despite this, it is important to remember that vitamin C on its own is a relatively weak anticancer agent. Crucially, however, it can be used as a driver, to supply electrons to synergistic redox agents. Often, such substances combine in a Fenton style reaction, generating hydrogen peroxide which kills cancer cells. Numerous other mechanisms may also be involved, such as inhibition by the combination of vitamin C and alpha-lipoic acid of NF-kappaB, which is involved in the control of DNA copying during cell replication (Flohé, Brigelius-Flohé, Saliou, et al. 1997). When combined with **vitamin K3**, the concentration of vitamin C needed to kill cells is massively reduced – by a factor of 10-50 (Noto, Taper, Jiang, et al. 1989). Similarly, **alpha-lipoic acid** (Casciari, Riordan, Schmidt, et al. 2001), copper (Bram, Froussard, Guichard, et al. 1980), **selenium**, and other redox active supplements greatly increase the selective cytotoxicity of ascorbate (Hickey, Roberts, 2005)
Oral intakes, particularly with combined use of ascorbic acid and liposomal vitamin C, can easily achieve and maintain adequate levels for selective cytotoxicity.
Finally, the use of vitamin C as a sole anticancer agent is not recommended, as its anticancer actions are known to be greatly enhanced through use of synergistic supplements, such as **alpha-lipoic acid**.

https://www.pnas.org/doi/full/10.1073/pnas.0506390102
Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues 2005
Human pharmacokinetics data indicate that i.v. ascorbic acid (ascorbate) in pharmacologic concentrations could have an unanticipated role in cancer treatment. Our goals here were to test whether ascorbate killed cancer cells selectively, and if so, to determine mechanisms, using clinically relevant conditions. Cell death in 10 cancer and 4 normal cell types was measured by using 1-h exposures. Normal cells were unaffected by 20 mM ascorbate, whereas 5 cancer lines had EC50 values of <4 mM, a concentration easily achievable i.v.

https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1600-0609.1990.tb00340.x
Characterization of a new malignant human T-cell line (PFI-285) sensitive to ascorbic acid 1990
Concentrations down to 50 umol/l killed the cells within hours.

https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/1097-0142(19890301)63:5%3C901::AID-CNCR2820630518%3E3.0.CO;2-G/abstract;jsessionid=E9C4FE55BE79464AB9945EAFA0709A5D.f02t02
Effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K3) treatment on human tumor cell growth in vitro. I. Synergism of combined vitamin C and K3 action 1989
Combined administration of both vitamins demonstrated a synergistic inhibition of cell growth at 10 to 50 times lower concentrations.

https://ar.iiarjournals.org/content/29/3/809.long
High-dose Vitamin C (Ascorbic Acid) Therapy in the Treatment of Patients with Advanced Cancer 2009
In this review, high-dose vitamin C therapy in cancer treatment is re-evaluated.
Moreover, vitamin C accumulates in solid tumors to concentrations higher than in surrounding normal tissue (20-22). This phenomenon favors the positive outcome of high-dose intravenous vitamin C therapy in cancer patients.
Laboratory data show that ascorbate is toxic to a variety of cancer cell lines (25-27). Extracellular concentrations as low 100-200 μM are toxic to some cell lines, but many types of malignant cells are killed only at concentrations approaching the mM range (19) (Figure 1).

https://www.acpjournals.org/doi/10.7326/0003-4819-140-7-200404060-00010
Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use 2004
Vitamin C at a dose of 1.25 g administered orally produced mean (±sd) peak plasma concentrations of 134.8 ± 20.6 μmol/L compared with 885 ± 201.2 μmol/L for intravenous administration. For the maximum tolerated oral dose of 3 g every 4 hours, pharmacokinetic modeling predicted peak plasma vitamin C concentrations of 220 μmol/L and 13 400 μmol/L for a 50-g intravenous dose. Peak predicted urine concentrations of vitamin C from intravenous administration were 140-fold higher than those from maximum oral doses.

https://isom.ca/article/high-dose-iv-vitamin-c-metastatic-breast-cancer-case-report/
High Dose IV Vitamin C and Metastatic Breast Cancer: A Case Report 2017/2024
This is a case of a 52-year-old patient with a diagnosis of metastatic breast adenocarcinoma. The patient arrived in our clinic after having difficulty with her chemotherapeutic regime. Positive outcomes were obtained after three months of treatment with high doses of intravenous vitamin C infusions. Studies with high dose vitamin C have shown cytotoxic and anti-metastatic activity on various cancer types mainly by its action as a pro-oxidant agent. Based on the outcomes obtained in this clinical case, we recommend continuing studying the role of intravenous infusion of high dose vitamin C, as an adjuvant treatment for breast cancer. .
The first dose was 25 g of vitamin C (sodium ascorbate) in 250cc Ringer's lactated solution during one hour infusion. The second infusion was 50 g of vitamin C in 500 cc of Ringer's lactated solution over a period of 1.5 hr. The third infusion was 75 g of vitamin C in 1,000 mL of Ringer's lactated solution over a period of 2 hrs. A maximum of 75 g of vitamin C in 1,000 mL Ringer's lactated solution was given three times a week over a period of 6 months. No other treatment was given during intravenous (IV) vitamin C therapy

https://isom.ca/article/high-dose-vitamin-c-helps-prevent-recurrence-stage-iv-ovarian-cancer-case-report/
High-Dose Vitamin C Helps Prevent Recurrence of Stage IV Ovarian Cancer: A Case Report 2018/2024
Stage IV ovarian cancer has a high recurrence rate of 90%-95%. High-dose intravenous vitamin C (IVC) therapy administered with nutritional supplements helps prevent recurrence of cancer. Case Description: The stage IV ovarian cancer patient began IVC therapy soon after completion of conventional treatments. The patient started with a consecutive 28-day program at a dosage of 25g/day, increasing gradually to 75g/day. Following this, the frequency declined gradually from twice a week over twelve months and slowly reduced to once every three to four weeks at 75g/day.
Despite the initial poor prognosis and high relapse rate of late-stage ovarian cancers, this patient is cancer-free five years after diagnosis and enjoys a good quality of life. High-dose IVC is documented to enhance the cancer patient's recovery and prolonged survival.
However, at high concentrations (350- 450 mg/dL), vitamin C dissociates in the extracellular fluid to become an ascorbate radical (AscH−), causing iron to be reduced to the ferrous form (AscH− + Fe3+ → _Fe2+ + AscH− + H+). The ferrous iron then reacts with oxygen, producing a superoxide anion (O2−), which reacts with hydrogen to form H2O2 (Riordan Clinic Research Institute, 2015). As the concentration of H2O2 increases in these tumour cells, they are vulnerable to the cytotoxic effects of H2O2, and hence inducing apoptosis and tumour cells are killed (Chen et al., 2005; Fritz et al., 2014; Putchala et al., 2010).

https://www.researchgate.net/publication/324771538_Suppression_of_alkaline_phosphatase_in_prostate_cancer_patients_by_high_dose_intravenous_Vitamin_C_Treatment_Three_cases
Suppression of alkaline phosphatase in prostate cancer patients by high dose intravenous Vitamin C Treatment: Three cases 2017
Results: Tracking the changes in PSA and ALP in patients for whom data was available indicated that the level of ALP correlated with the presence of metastasis in our patient group. In the few cases where we found both PSA and ALP measurements, these variables tended to track each other and decrease during IVC therapy. The reductions in PSA and/or ALP concentrations (or their stabilization) were reversed once treatment stopped.

https://isom.ca/wp-content/uploads/2020/01/JOM_2004_19_4_02_The_Use_of_Vitamin_C_with_Chemotherapy_in_Cancer-.pdf
The Use of Vitamin C with Chemotherapy in Cancer Treatment: An Annotated Bibliography 2004
In conclusion, this annotated bibliography of literature on the effectiveness of vitamin C alone, or with other vitamins, during chemotherapy confirms the conclusions of Prasad and coworkers (1999): "... antioxidants [including vitamin C] do not protect cancer cells against free radical and growth-inhibitory effects of standard therapy. On the contrary, they enhance its growth-inhibitory effects on tumor cells, but protect normal cells against its adverse effects."

https://www.sciencedirect.com/science/article/pii/S2215016120303678
Preparation of magnetic nanoparticle integrated nanostructured lipid carriers for controlled delivery of ascorbyl palmitate 2020
Most cancer treatments can cause vital side effects on healthy tissues. Ascorbic acid (AA) is a water-soluble antioxidant molecule and possesses a variety of functions such as prevention of tumor proliferation and treatment of cancer. However, AA, is very sensitive to air, heat and light. Its high hydrophilicity also makes the controlled delivery difficult. To overcome these problems, AA can be chemically-modified and made more hydrophobic by the esterification. Palmitic acid is one of the most common long-chain fatty acids that can be used for this purpose. It is known that Ascorbyl palmitate (AP) which is a lipopihilic derivative of AA, can inhibit cell proliferation and DNA synthesis in many types of cancer. Although AP has higher stability, its bioavailability and therapeutic effect is low due to its lipophilicity and low release capacity.
In this study, nanostructured lipid carriers (NLC) which are colloidal nanoparticles with high biocompatibility, low crystallinity and high

hydrophobic-drug encapsulation capacity was prepared to increase the bioavailability of AP.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5106370/

Tumor cells have decreased ability to metabolize H2O2: Implications for pharmacological ascorbate in cancer therapy 2016

Ascorbate (AscH−) functions as a versatile reducing agent. At pharmacological doses (P-AscH−; [plasma AscH−] ≥≈20 mM), achievable through intravenous delivery, oxidation of P-AscH− can produce a high flux of H2O2 in tumors. Catalase is the major enzyme for detoxifying high concentrations of H2O2. We hypothesize that sensitivity of tumor cells to P-AscH− compared to normal cells is due to their lower capacity to metabolize H2O2. Rate constants for removal of H2O2 (kcell) and catalase activities were determined for 15 tumor and 10 normal cell lines of various tissue types. A differential in the capacity of cells to remove H2O2 was revealed, with the average kcell for normal cells being twice that of tumor cells. The ED50 (50% clonogenic survival) of P-AscH− correlated directly with kcell and catalase activity. Catalase activity could present a promising indicator of which tumors may respond to P-AscH−.

Studies have shown that all but one human cancer cell type, a human renal adenocarcinoma, have low levels of both catalase and GPx [29]. This suggests that the vast majority of cancer cells may lack the biochemical machinery needed to detoxify higher fluxes of H_2O_2 efficiently. While in general, the levels of catalase are low in cancer cells, catalase activity appears to vary greatly across different cancer cell lines [28]. This may correspond to a differential capacity to remove H_2O_2 and differential sensitivity to H_2O_2 -producing agents (*i.e.* P-AscH$^-$). We hypothesize that the sensitivity of tumor cells to P-AscH$^-$ compared to normal cells is due to their lower capacity to remove extracellular H_2O_2; across different tumor cell types there will also be a differential sensitivity to P-AscH$^-$ that is correlated with their individual capacities to remove extracellular H_2O_2, as reflected by k_{cell} of H_2O_2 removal and catalase activity.

When catalase was inhibited using 3-amino-1,2,4-triazole (3-AT) in HepG2 cells, which have a high basal level of catalase activity, there was a 4.6-fold decrease in the rate constant at which these cells remove extracellular H_2O_2 (Fig. 3A). These results both suggest and support the important role of catalase in the removal of high concentrations of extracellular H_2O_2.

We observed that both increasing and decreasing the catalase activity had a significant effect on the rate constant of H2O2 removal and further investigated whether similar manipulation of basal catalase activity would affect the cells' sensitivity to P-AscH−.

Increasing the catalase activity within the same cell line (MIA PaCa-2) increased resistance to P-AscH− (Fig. 5B).

https://medicine.uiowa.edu/content/why-high-dose-vitamin-c-kills-cancer-cells

Why high-dose vitamin C kills cancer cells 2017

"Our results suggest that cancers with low levels of catalase are likely to be the most responsive to high-dose vitamin C therapy, whereas cancers with relatively high levels of catalase may be the least responsive," he explains.

A future goal of the research is to develop methods to measure catalase levels in tumors.

https://bmccomplementmedtherapies.biomedcentral.com/articles/10.1186/1472-6882-12-61

Natural resistance to ascorbic acid induced oxidative stress is mainly mediated by catalase activity in human cancer cells and catalase-silencing sensitizes to oxidative stress 2012

Ascorbic acid demonstrates a cytotoxic effect by generating hydrogen peroxide, a reactive oxygen species (ROS) involved in oxidative cell stress. A panel of eleven human cancer cell lines, glioblastoma and carcinoma, were exposed to serial dilutions of ascorbic acid (5-100 mmol/L). The purpose of this study was to analyse the impact of catalase, an important hydrogen peroxide-detoxifying enzyme, on the resistance of cancer cells to ascorbic acid mediated oxidative stress.

Results

The tested human cancer cell lines demonstrated obvious differences in their resistance to ascorbic acid mediated oxidative cell stress. Forty-five percent of the cell lines had an EC50 > 20 mmol/L and fifty-five percent had an EC50 < 20 mmol/L. With an EC50 of 2.6–5.5 mmol/L, glioblastoma cells were the most susceptible cancer cell lines analysed in this study. A correlation between catalase activity and the susceptibility to ascorbic acid was observed. To study the possible protective role of catalase on the resistance of cancer cells to oxidative cell stress, the expression of catalase in the breast carcinoma cell line BT-20, which cells were highly resistant to the exposure to ascorbic acid (EC50: 94,9 mmol/L), was silenced with specific sh-RNA. The effect was that catalase-silenced BT-20 cells (BT-20 KD-CAT) became more susceptible to high concentrations of ascorbic acid (50 and 100 mmol/L).

Conclusions

Fifty-five percent of the human cancer cell lines tested were unable to protect themselves against oxidative stress mediated by ascorbic acid induced hydrogen peroxide production. The antioxidative enzyme catalase is important to protect cancer cells against cytotoxic hydrogen peroxide. Silenced catalase expression increased the susceptibility of the formerly resistant cancer cell line BT-20 to oxidative stress.

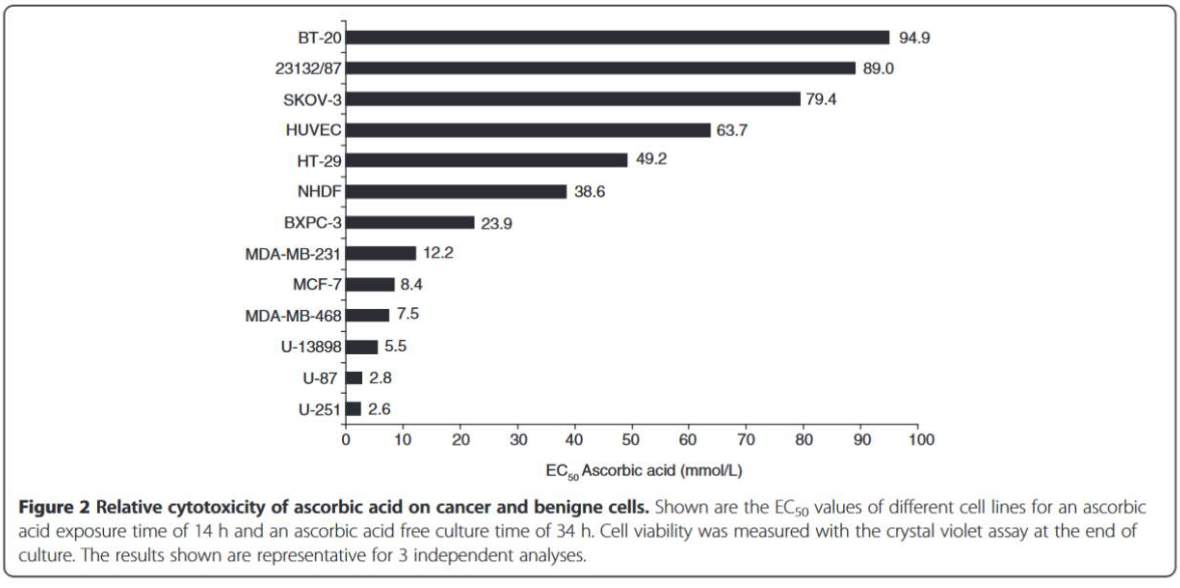


Figure 2 Relative cytotoxicity of ascorbic acid on cancer and benigne cells. Shown are the EC_{50} values of different cell lines for an ascorbic acid exposure time of 14 h and an ascorbic acid free culture time of 34 h. Cell viability was measured with the crystal violet assay at the end of culture. The results shown are representative for 3 independent analyses.

https://isom.ca/article/case-study-high-dose-intravenous-vitamin-c-in-the-treatment-of-a-patient-with-adenocarcinoma-of-the-kidney/

Case Study: High-Dose Intravenous Vitamin C in the Treatment of a Patient with Adenocarcinoma of the Kidney 1990

He was followed by an oncologist at another clinic. About three months after surgery, the patient's x-rays and CT. scan studies showed "multiple pulmonary lesions and lesions in several areas of his liver which were abnormal and periaortic lymphadenopathy". None of the lesions were biopsied. The patient decided not to undergo chemotherapy, hormone therapy or cytotoxic treatment of any kind. He requested and was started on vitamin C intravenous treatment. He was started on 30 grams of vitamin C (Ascorbic Acid Injection, Sodium Ascorbate equivalent to 250 mg/mL, Steris Laboratories, Inc. Phoenix, Arizona 85043) in 250 mL of Ringer's Lactate given by intravenous injection (60 drops per minute) twice a week.

To date, after 3'/2 years the patient remains cancer free. He will continue to be followed both at our center and by the oncologist. The patient's vitamin C treatment protocol was 30 grams of vitamin C in 250 mL of Ringer's Lactate given by intravenous injection (60 drops per minute) twice a week for seven months. The treatments were then reduced to one per week and 1 mL of magnesium was added to the vitamin C and Ringer's Lactate. This treatment lasted for eight months, then for six months he received 15 grams of vitamin C weekly in 250 mL of Ringer's Lactate with 1.0 mL of magnesium. Today, he returns at irregular intervals for a 30 gram vitamin C intravenous treatment.

https://riordanclinic.org/wp-content/uploads/2014/12/89023765_jom.pdf

Sixteen-Year History with High Dose Intravenous Vitamin C Treatment for Various Types of Cancer and Other Diseases 2002

Our experience over the past 16 years has shown vitamin C to be a safe and effective treatment for many diseases. We continue to use it today and will continue to do so in the future.

https://pubmed.ncbi.nlm.nih.gov/26201606/

Treatment of Pancreatic Cancer with Pharmacological Ascorbate 2015

The prognosis for patients diagnosed with pancreatic cancer remains dismal, with less than 3% survival at 5 years. Recent studies have demonstrated that high-dose, intravenous pharmacological ascorbate (ascorbic acid, vitamin C) induces cytotoxicity and oxidative stress selectively in pancreatic cancer cells vs. normal cells, suggesting a promising new role of ascorbate as a therapeutic agent. At physiologic concentrations, ascorbate functions as a reducing agent and antioxidant. However, when pharmacological ascorbate is given intravenously, it is possible to achieve millimolar plasma concentration. At these pharmacological levels, and in the presence of catalytic metal ions, ascorbate can induce oxidative stress through the generation of hydrogen peroxide (H_2O_2). Recent in vitro and in vivo studies have demonstrated ascorbate oxidation occurs extracellularly, generating H_2O_2 flux into cells resulting in oxidative stress. Pharmacologic ascorbate also inhibits the growth of pancreatic tumor xenografts and displays synergistic cytotoxic effects when combined with gemcitabine in pancreatic cancer. Phase I trials of pharmacological ascorbate in pancreatic cancer patients have demonstrated safety and potential efficacy. In this chapter, we will review the mechanism of ascorbate-induced cytotoxicity, examine the use of pharmacological ascorbate in treatment and assess the current data supporting its potential as an adjuvant in pancreatic cancer.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8750500/

The Role of Vitamin C in Cancer Prevention and Therapy: A Literature Review 2021

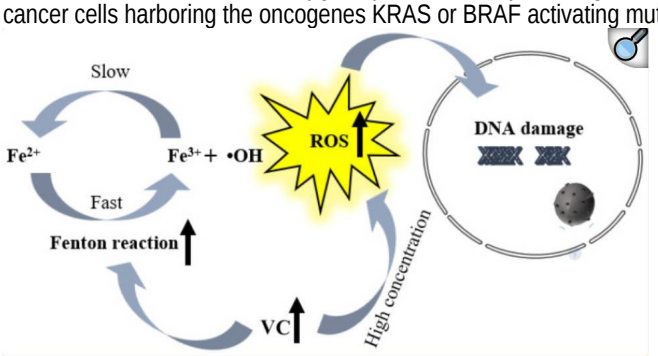
In cancer, vitamin C is associated with prevention, progression, and treatment, due to its general properties or its role as a pro-oxidant at high concentration.

https://pmc.ncbi.nlm.nih.gov/articles/PMC11123810/

The Involvement of Ascorbic Acid in Cancer Treatment 2024

Observational studies suggest that higher intakes of VC, whether through diet or supplements, may correlate with a lower risk of gastrointestinal cancers [12]. Laboratory studies further reveal VC's capabilities to induce apoptosis and inhibit proliferation in cancer cells, affecting key cellular signaling pathways that regulate growth and division [13]. VC has been observed to boost the effectiveness of some chemotherapy drugs and radiation therapy, enhancing their impact on cancer treatment [14].

Hoffer et al. conducted a Phase I-II clinical trial, where high-dose IVC was combined with cytotoxic chemotherapy in patients with advanced cancer. The study aimed to evaluate the safety, tolerability, pharmacokinetics, and efficacy of IVC. Doses ranged up to 1.5 g per kilogram of body weight per infusion. This study confirmed that these dosages were well tolerated and safe under clinical conditions, showing only transient adverse effects, which were manageable [38]. VC demonstrates antioxidative effects at physiological plasma concentrations but exhibits pro-oxidative effects at high concentrations [39]. Elevated levels of VC can elevate the levels of reactive oxygen species, thereby exerting anti-tumor effects. Moreover, high-dose VC has been shown to selectively eliminate colorectal cancer cells harboring the oncogenes KRAS or BRAF activating mutations [40].



7. **VC Enhances the Efficacy of Starvation Therapy**

Cancer starvation therapy, a strategy that entails obstructing blood supply and depriving tumors of glucose and essential nutrients, has garnered considerable attention as a promising cancer treatment approach. Glucose acts as the primary fuel for tumor cells, with the oxidized form of VC, DHA, being transported via the glucose transporter protein GLUT1. Tumor cells undergo a metabolic shift from oxidative phosphorylation to glycolysis to meet their energy demands. Consequently, an excess of VC may impede glucose transport and adenosine triphosphate (ATP) production, triggering an energy crisis and eventual cell death (Figure 3) [65].

https://pmc.ncbi.nlm.nih.gov/articles/PMC6164730/

Ascorbic Acid in Colon Cancer: From the Basic to the Clinical Applications 2018

This shift also allows AA to enter which leads to a disruption in the Warburg effect and a shutdown of the downstream *KRAS* pathway in mutated *KRAS* colon cancer cells. At the clinical level, AA is associated with tumour regression in advanced disease and improved tolerability and side effects of standard therapy. A case report of a 68-year-old newly diagnosed metastatic pancreatic cancer patient who refused to receive the conventional chemotherapy regimen and was treated with AA showed no disease progression at his 6-month follow up after surgery [47]. Another example is a case report of a 42-year-old man who was newly

diagnosed with widely disseminated reticulum cell sarcoma. There was a delay in this patient receiving his conventional treatment and he was maintained on high dose intravenous AA as a "holding operation. Surprisingly, on the 10th day, the patient had symptoms improved and on the 22nd day, his chest X-ray was almost clear [48]. Seven months later, after a reduction in ascorbic acid intravenous dose, it is noteworthy that the disease was reactivated; therefore, a re-initiation of high-dose AA was used to re-induce a second complete remission [49].
In a phase I dose-escalating trial, the administration of ascorbic acid 1.5 g/kg three times weekly was reported to be essentially free of risk. A case report on advanced ovarian cancer showed that adding intravenous AA adjunctively to first-line chemotherapy, might improve the efficacy of chemotherapy [19]. There appears to be a growing number of studies showing improvement in the quality of life and an increase in the survival times of terminal cancer patients [52].
Two case reports on metastatic renal cell carcinoma described in the late 1990s showed the resolution of metastatic lesions after the initiation of intravenous AA as a sole therapy; one of the patients remained cancer-free for 14 years and died from congestive heart failure [56].
A recent case report discussed a newly-diagnosed stage IV poorly-differentiated pancreatic ductal adenocarcinoma. This 68-year-old male patient electively chose to be treated with escalating doses of intravenous AA as his sole treatment as an exclusive regimen, declining the conventional standard of care. The doses of AA ranged from 75 to 125 g per infusion and were administered 2–3 times per week (after being screened for G6PD deficiency or abnormal renal function). The results were outstanding; the patient achieved objective regression of his disease and he survived nearly 4 years after diagnosis. He died from a bowel perforation event leading to sepsis and organ failure [58].
A phase I clinical trial was conducted in the USA in which biopsy-proven metastatic pancreatic adenocarcinoma patients were given AA intravenously in addition to gemcitabine. The results revealed that the average survival time was 13 ± 2 months, compared to survival times of 5.65 months for patients in similar cases [45,59].
A case report in 2004 described a stage IV poorly-differentiated colon adenocarcinoma with stomach wall and liver metastatic lesions. The patient was determined to have very poor prognosis. He started intravenous administration of 15 grams of AA per hour combined with second line adjuvant chemotherapy. The intravenous AA administration doses were gradually increased during bi-weekly infusions until they reached 100 grams twice weekly. On his one-year follow up, the patient was found to be disease free.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6566697/
The Effect of Vitamin C (Ascorbic Acid) in the Treatment of Patients with Cancer: A Systematic Review 2019
In only 4 trials randomization was used to determine if patients received vitamin C or a placebo. The result of this review does not prove that there is a clinically relevant positive effect of vitamin C supplementation in cancer patients in general on the overall survival, clinical status, quality of life (QOL) and performance status (PS), since the quality of the studies published is low. Interventions and patient groups are very diverse, hence an effect in some patient groups is possible. There seems to be a better effect with intravenous than oral administration. Nevertheless, treatment with vitamin C is safe with minimal side effects.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6071214/
Systematic Review of Intravenous Ascorbate in Cancer Clinical Trials 2018
Results: A total of 23 trials involving 385 patients met the inclusion criteria. Only one trial, in ovarian cancer, randomized patients to receive vitamin C or standard of care (chemotherapy). That trial reported an 8.75 month increase in progression-free survival (PFS) and an improved trend in overall survival (OS) in the vitamin C treated arm. Conclusion: Overall, vitamin C has been shown to be safe in nearly all patient populations, alone and in combination with chemotherapies.

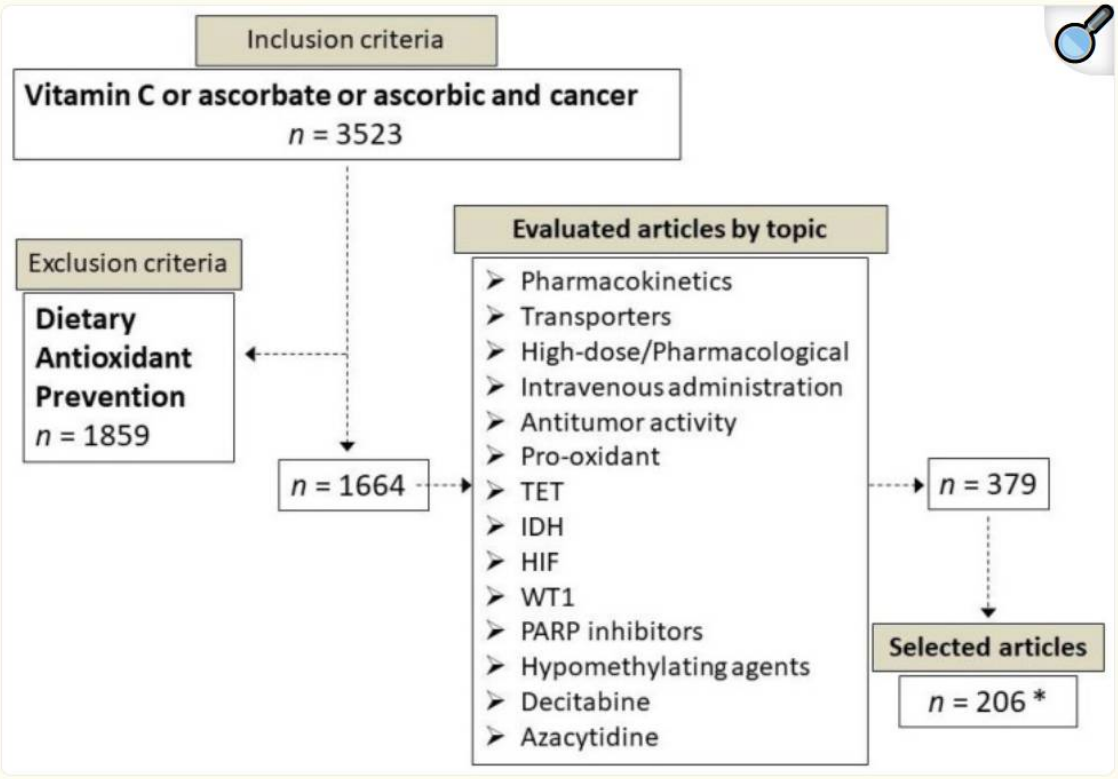
https://pmc.ncbi.nlm.nih.gov/articles/PMC9231292/
High-Dose Vitamin C for Cancer Therapy 2022
Given that Vit-C can occur in several oxidative states, interestingly, ascorbic acid is oxidized by ROS or/and free radicals, resulting in the formation of a reactive anion intermediate radical ($Asc^{\bullet-}$), which is subsequently oxidized to de-hydroascorbic (DHA) acid [41,42]. DHA, which has a relatively short half-life of just a few minutes [43], is converted to around 1–5% of the Vit-C inside the human cells [44], and it can be transferred into the cell or hydrolyzed irreversibly into 2,3-Diketo-L-gulonic (2,3-DKG) acid ($C_6H_8O_7$). When 2,3-DKG is broken down into Ethanedioic acid ($C_2H_2O_4$) and (2R,3S)-2,3,4-Trihydroxybutanoic acid ($C_4H_8O_5$), the Vit-C level is significantly decreased [45]. DHA is quickly converted to Vit-C within the cell, by interacting with reduced glutathione (GSH) [45,46,47]. NADPH then recycles the oxidized glutathione (glutathione disulfide (GSSG)) and converts it back into GSH [45].
As the therapeutic impact of high-dose Vit-C is strongly dependent on the formation of ROS, it is essential to define this term. The term "ROS" refers to a group of highly reactive chemical species formed when electrons escape from the mitochondrial electron transport chain (ETC; coenzyme Q) and interact with molecular O_2, which is converted enzymatically to superoxide ($O_2^{\bullet-}$) and dismutated to produce H_2O_2, which is then partially reduced to form hydroxide ions (OH^-), hydroxyl radicals ($HO^{\bullet}$), and water (H_2O) [53,54]. It is worth noting that the superoxide and the hydroxyl radical are together referred to as ROS free radicals [54].
First, cancer cells, owing to their defective mitochondria and increased metabolic reliance, are more sensitive to oxidative stress than normal body cells [64].
It is generally accepted that iron metabolism is altered in malignancies such as breast cancer, prostate cancer, and lymphoma via a different mechanism, involving an increase in the expression of various iron-intake pathways or the downregulation of iron exporter proteins and storage pathways [94]. For instance, the amount of Fe(II) ion in breast cancer cells is almost double that in normal breast tissues [95]. Furthermore, macrophages in the cancer microenvironment have been revealed to increase iron shedding [96,97]. Advanced breast tumor patients had substantially greater Fe(II) levels in their blood than the control groups without the disease [98]. Cancers with high amounts of iron might be more susceptible to mega-dose Vit-C than non-cancer cells, because they may produce higher amounts of H_2O_2 and $OH^{\bullet}$ via LIP.
Although reports have anticipated that DHA is Vit-C's most pharmacologically effective form, it is essential to demonstrate that Vit-C, instead of DHA, must be utilized in both preclinical and clinical anti-cancer treatments. Due to its great volatility at neutral pH [76], bolus therapy with mega-dose DHA has only transitory effects on tumor cells, both in vitro and in vivo.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6940627/
Enhanced Anticancer Effect of Adding Magnesium to Vitamin C Therapy: Inhibition of Hormetic Response by SVCT-2 Activation 2019
Cancer cells that showed high SVCT-2 expression levels were more sensitive to AA treatment than cancer cells with low SVCT-2 expression levels. Cells with low SVCT-2 expression showed a hormetic response to a low dose of AA. Magnesium ions, which are known to activate SVCT-2, could increase the V_{max} value of SVCT-2, so we investigated whether providing magnesium supplements to cancer cells with low SVCT-2 expression that had shown a hormetic response to AA would elevate the V_{max} value of SVCT-2, allowing more AA to accumulate. To evaluate the effects of magnesium on cancer cells, $MgSO_4$ and $MgCl_2$ were screened as magnesium supplements; both forms showed synergistic anticancer effects with AA. Taken together, the results of this study suggest that magnesium supplementation enhanced the anticancer effect of AA by inhibiting the hormetic response at a low dose. This study has also demonstrated that AA treatment with magnesium supplementation provided more effective anticancer therapy than AA treatment alone.

https://www.nature.com/articles/s41698-017-0044-8
Vitamin C preferentially kills cancer stem cells in hepatocellular carcinoma via SVCT-2 2018

Our data highlight that pharmacologic VC can effectively kill liver cancer cells and preferentially eradicate liver CSCs, which provide further evidence supporting VC as a novel therapeutic strategy for HCC treatment.

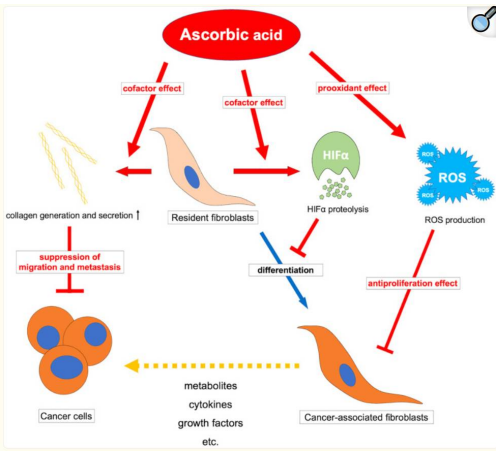
https://pmc.ncbi.nlm.nih.gov/articles/PMC8003833/
High-Dose Vitamin C: Preclinical Evidence for Tailoring Treatment in Cancer Patients 2021



The pro-oxidant properties have been attributed to the ability of ascorbate to reduce Fe^{3+} to Fe^{2+} with consequent generation of ROS through the Fenton reaction (Figure 3). In fact, tumor cells contain higher levels of labile iron (Fe^{2+}) compared to normal cells and this favors higher ROS generation [75].

Most of the reported cytotoxic effects induced by vitamin C are observed at concentrations that can only be reached after I.V. administration of high doses. However, due to the short half-life detected after I.V. injection, these concentrations cannot be maintained for a prolonged time. Indeed, weekly I.V. administration of high-dose vitamin C to prostate cancer patients did not induce tumor regression [50,64]. Thus, it has been suggested that in patients with an intact kidney function, a bolus loading dose followed by a maintenance continuous infusion is likely required to achieve a steady-state plasma concentration of vitamin C in the millimolar range [50].

https://pmc.ncbi.nlm.nih.gov/articles/PMC9531273/
Diverse antitumor effects of ascorbic acid on cancer cells and the tumor microenvironment 2022
However, high pharmacological concentrations of ascorbic acid achieved *via* intravenous administration produce H_2O_2 *in vivo* (18, 33, 34) and then hydroxyl radicals *via* the Fenton reaction (35). Intravascularly, ROS produced by high concentrations of ascorbic acid are degraded by catalase in serum, whereas extravascularly, ROS accumulate without degradation by ascorbic acid and act as a pro-oxidant. Thus, ascorbic acid is notable for its paradoxical activity, serving as an antioxidant at low doses and a pro-oxidant at high doses (28, 29). In addition, oral administration of ascorbic acid does not reach the same pharmacological concentrations as intravenous treatment (19, 20); therefore, intravenous administration of ascorbic acid is required for pro-oxidant activity to occur.



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Overview of the antitumor effects of ascorbic acid on cancer-associated fibroblasts. ROS, reactive oxygen species; HIFα, hypoxia-inducible factor-alpha.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3061919/

Intravenous ascorbic acid to prevent and treat cancer-associated sepsis? 2011

At the chronic end, low grade inflammation causes a variety of pathologies to the patient, perhaps most profound of which is cachexia [32-35], but also other effects such as poor post-surgical outcomes [36,37]. At the other end of the spectrum is the acute inflammation observed in the systemic inflammatory response syndrome (SIRS), a major cause of death of cancer patients and especially patients with hematological malignancies [38-40]. While we focus in this paper on SIRS and cancer, some of the concepts discussed are also applicable to chronic inflammatory conditions.

Several clinical studies have supported the possibility that AA mediates a beneficial effect on endothelial cells, especially in the context of chronic stress.

A closer look at the literature suggests that there are several general mechanisms by which AA may exert endothelial protective properties. The importance of basal production of NO in endothelial function comes from its role as a vasodilator, and an inhibitor of platelet aggregation [95,96]

AA administration decreases iNOS in the context of inflammation [101,102], but appears to increase eNOS [103].

Within the context of this discussion, profound reduction of AA is observed in cancer patients [140-146], SIRS patients [147], and ICU patients [134].

https://pubmed.ncbi.nlm.nih.gov/30703479/

The combination of ascorbate and menadione causes cancer cell death by oxidative stress and replicative stress 2019

The combination of ascorbate and menadione (VC:VK3 = 100:1) is an investigational treatment for cancer under clinical trials.

The mechanism of cell death induced by VC/VK3 was also elucidated. We found that VC/VK3 inhibited glutathione peroxidase activity and led to an elevated level of lipid peroxidation, which triggered apoptosis-inducing factor (AIF) mediated cell death pathway. Therefore, the combination not only induced replicative stress by inhibiting RNR, but also oxidative stress by targeting anti-oxidant systems and triggered AIF-mediated cancer cell death.