

Review

Controlled Generation of Dehydroascorbic Acid: A New Mechanistic Framework for High-Dose Vitamin C Anticancer Therapy

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Abstract

This article reviews pharmacological strategies targeting key metabolic pathways in cancer cells and highlights their inherent limitations, including metabolic plasticity and lack of selectivity. It is proposed that these vulnerabilities can be addressed through a global redox-based approach using high-dose vitamin C. Evidence suggests that the anticancer activity of vitamin C is mediated by its oxidation to dehydroascorbic acid (DHA). Although DHA cannot be administered directly due to its instability, it can be generated in situ within the circulatory system. Once taken up by cancer cells, DHA perturbs multiple redox-sensitive processes, leading to depletion of NADPH and collapse of cellular redox homeostasis. We present a mechanistic framework outlining how controlled generation of DHA may enable a more robust and clinically effective anticancer strategy.

Keywords: cancer; vitamin C; dehydroascorbic acid; hydrogen peroxide; thiols; NADPH

“What is now proved was once only imagined”

William Blake (The Marriage of Heaven and Hell)

1. Introduction

A recurring limitation of many metabolic anticancer strategies is that they focus on a single enzyme, pathway, or nutrient dependency. Although such targets are often essential under experimental conditions, tumour cells possess extensive metabolic flexibility and can compensate through alternative pathways, altered nutrient utilisation, or activation of stress-response mechanisms [1–3]. In addition, inhibition of a single target rarely occurs in isolation and is frequently limited by toxicity to normal tissues, preventing complete pathway suppression in patients. These considerations suggest that a more effective strategy may be to impose simultaneous pressure on multiple metabolic processes that collectively support tumour survival. Rather than targeting a single pathway, disruption of the cellular reducing environment has the potential to affect several interconnected systems, including glucose metabolism, thiol homeostasis, DNA synthesis, and methionine metabolism.

This paper reviews several metabolic strategies explored to date and proposes an alternative concept: controlled oxidation of vitamin C to dehydroascorbic acid (DHA) as a means of simultaneously perturbing multiple redox-sensitive metabolic pathways, thereby promoting collapse of tumour redox homeostasis through depletion of intracellular reducing capacity.



Academic Editor: Dooil Jeoung

Received: 22 June 2026

Revised: 26 June 2026

Accepted: 26 June 2026

Published: 3 July 2026

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2. Glucose Metabolism

The first identified metabolic difference in cancer cells was their dependence on glucose, even in the presence of oxygen, as the main energy source, coupled with lactate production [4,5]. This phenomenon, known as the Warburg effect, has been consistently observed in cancer cells of various tissue origins [6].

Inhibition of increased glycolysis in tumours has been considered and targeted for anticancer treatment. Extensive reviews on research on inhibitors of pathways related to glucose metabolism and using the knowledge for patient treatment are available [7–11]. Here we discuss some of the most promising treatments as examples to estimate how progress in this field could lead to health benefits.

2.1. 2-Deoxyglucose

2-Deoxyglucose (2-DG) is a competitive inhibitor of glucose metabolism [12]. After uptake by cells, 2-DG is phosphorylated by hexokinase and inhibits glycolysis because unlike phosphorylated glucose it cannot be processed by phosphoglucose isomerase. Therefore, no conversion of phosphorylated glucose to phosphorylated fructose occurs, and ATP production downstream of this pathway is blocked. While 2-DG shows high efficacy in cell-based studies [13], clinical studies have not demonstrated comparable benefits. Although patient tolerance is generally good, anticancer efficacy is limited, even in combination therapies [14–16]. This discrepancy is largely attributed to metabolic plasticity, which enables tumour cells to bypass inhibited pathways [17,18].

2.2. Lonidamine

Lonidamine is a derivative of indazole-3-carboxylic acid and an inhibitor of hexokinase 2 [19], which is highly overexpressed in cancer cells [20].

It exhibits cytotoxicity to cultured cancer cells in combination with other drugs [21]. In addition to its metabolic role, hexokinase 2 may protect cells from apoptosis through interactions with other proteins and may contribute to metastasis [22]. However, clinical trials have not demonstrated improved patient survival [23]. Modified derivatives show increased cytotoxicity, possibly due to effects beyond hexokinase 2 inhibition [24].

2.3. 3-Bromopyruvate

3-Bromopyruvate (3-BP) is a pyruvate mimetic with promising anticancer activity [25]. In animal models, it can completely inhibit hexokinase 2 and significantly inhibit tumour growth [26].

However, its mechanism likely involves non-specific alkylation of thiol groups in glycolytic enzymes and other proteins [27,28]. As a highly reactive electrophile, 3-BP may also affect thiol-containing proteins in normal cells, limiting its clinical applicability.

3. Thiols

Thiol metabolism is widely considered a target for anticancer therapy due to the reliance of cancer cells on elevated antioxidant defences [29]. This vulnerability has historically been exploited by traditional medicine long ago by using arsenic for treatment [30]. Arsenic (As^{3+}) binds strongly to sulfhydryl (-SH) groups. Although toxic and carcinogenic, it has shown therapeutic benefit at controlled doses.

Here we review some topics of thiol metabolism considered as the most promising for anticancer treatment.

3.1. GAPDH

GAPDH is an oxidant-sensitive thiol protein [31]. Although primarily involved in glycolysis, it also performs other functions [32]. A selective inhibitor koniginic acid (KA) has been identified; it is a sesquiterpene lactone isolated from fungi and it directly binds to the active site of human GAPDH [33]. So far, no information on using KA in clinical trials is available. Interestingly thiol oxidation of GAPDH may act as redox switch to stimulate the oxidative pentose phosphate pathway by rerouting glucose [34]. This study highlighted that aiming at a single target even if it looks very promising may not be a winning strategy in anticancer action.

3.2. The Thioredoxin–Thioredoxin Reductase System

The thioredoxin–thioredoxin reductase system is recognized as a central for controlling cellular redox state via thiol-disulfide exchange and considered as a target for anticancer treatment [35,36]. Thioredoxin (Trx) is a small thiol protein, it can reduce disulfides by a thiol exchange mechanism, oxidising Trx to form an internal disulfide. Oxidised Trx is recycled to its reduced form by thioredoxin reductase (TrxR) which uses NADPH as a source of reducing equivalents. While Trx and TrxR participate in various processes like transcription, proliferation, and apoptosis, we would like to specifically highlight that synthesis of deoxyribonucleotides depends on Trx, which makes the system vital for DNA synthesis [37]. Trx and TrxR inhibitors are cytotoxic for cancer cells in culture or in mouse models and the search for inhibitors that destabilize Trx and/or TrxR specifically in cancer cells with limited toxicity for patients is ongoing [38–40].

3.3. Peroxiredoxin

Peroxiredoxins (Prdxs) are thiol-containing proteins that cycle between oxidised and reduced forms [41]. They react with hydrogen peroxide exceptionally rapidly [42] and play critical roles in cell signalling [43,44]. Reduction of oxidised Prdxs depends mostly on Trx and in some cases on Grx [41,45]. There is a growing body of evidence that Prdxs promote tumour survival, progression, and metastasis, and are upregulated in cancers [46–50]. It has been reported that adenanthin, a diterpenoid isolated from plants that directly targets the conserved resolving cysteines of Prdxs, promotes differentiation of leukemic cells in culture [51]. Subsequent studies showed that the reaction of adenanthin with Prdxs lacks specificity, as it also reacts with other thiols, where selenoproteins appear to be even more favourable targets [52]. Thus, the remarkable biological effects of adenanthin may be attributed to a broader disruption of thiol metabolism in leukemic cells rather than to specific inhibition of Prdxs.

3.4. Glutathione

The importance of glutathione, GSH, for cancer cells' progression, metastases, and resistance to treatment is widely appreciated [53–56]. The problem is that GSH is pivotal for normal cells [57] and selective targeting remains difficult.

4. Methionine

Methionine depletion has been shown to induce cell cycle arrest and apoptosis in cancer cells [58]. This phenomenon, known as methionine auxotrophy—where cancer cells are unable to proliferate in the absence of methionine while normal cells remain relatively unaffected—has been observed in many, although not all, human cancer cell lines [59,60].

Methionine dependence has also been explored therapeutically in vivo. Methionine-restricted diets have been investigated, and to further reduce plasma methionine levels recombinant methionine- γ -lyase (MGL) has been employed [61–64]. MGL catalyses the

oxidative deamination of L-methionine to α -ketobutyrate, ammonia, and methanethiol. Although MGL demonstrated promising anticancer activity, clinical studies revealed significant adverse effects, including immunogenic reactions, gastrointestinal disturbances, and hyperammonaemia, which is harmful to the kidneys and liver [65,66].

One of the major biological functions of methionine is its involvement in DNA methylation. Although global hypomethylation is common in cancer cells, methionine depletion, particularly in combination with other anticancer agents, may produce undesirable epigenetic alterations that reprogram gene expression toward a more aggressive phenotype [67].

5. DNA Synthesis

Cell proliferation is a hallmark of tumours, and targeting processes related to DNA metabolism has been widely explored in cancer research. In attempts to eliminate cancer cells, several strategies have been pursued: (i) inhibition of DNA replication by targeting various stages and components of the replication machinery; (ii) suppression of DNA repair pathways, which are essential for maintaining genome stability and supporting survival of genetically unstable cancer cells, as well as resistance to DNA-damaging therapies; and (iii) interference with the supply of precursors required for DNA synthesis [68–71].

Many of these approaches have led to clinically effective anticancer drugs. Nevertheless, important limitations remain. Due to the genetic heterogeneity of tumours, some drugs are effective only in cancers carrying specific mutations. In addition, metabolic plasticity enables cancer cells to bypass biochemical blocks induced by therapy. Selectivity also remains a major challenge, and these therapies are often associated with toxic side effects. Furthermore, some highly effective anticancer agents may increase the risk of secondary malignancies. These limitations illustrate the need for therapeutic approaches that do not target a single component of DNA metabolism but instead simultaneously disrupt multiple metabolic pathways required for tumour proliferation, as proposed for DHA-mediated vitamin C therapy.

6. Vitamin C

Interest in using vitamin C for cancer patients' treatment was inspired by Linus Pauling's work [72]. Since then, there has been great progress in understanding vitamin C's role in cell metabolism, deciphering pathways it is involved in and how it affects human health. Ultimately, the data obtained resulted in understanding of the necessity to consume a significant amount of vitamin C daily [73]. The current Recommended Dietary Allowance for vitamin C, which reaches up to 100 mg/day, appears increasingly at odds with the classical definition of a vitamin. Regarding the effect of vitamin C on cancer cells, numerous reports clearly showed toxicity [74–76]. To see anticancer vitamin C must be in high doses, 10 mM or more, which in patients cannot be achieved by oral consumption and needs injection into the blood. Nevertheless, effective treatment of cancer patients with vitamin C failed to materialize, as no clinical trials came with a positive recommendation [77–79].

6.1. What Is the Mechanism of Vitamin C Toxicity for Cancer Cells?

To display toxicity, vitamin C needs to be at high concentration. Vitamin C, ascorbic acid is a strong reducing agent. At neutral pH, ascorbic acid, AH_2 , presents mostly as the ascorbate monoanion (AH^-) as the first dissociation constant is 4.1. In the presence of oxygen, AH^- donates an electron to produce an ascorbate radical, $\text{A}^{\bullet-}$ and superoxide, $\text{O}_2^{\bullet-}$. Ascorbate radicals disproportionate to form oxidised vitamin C and dehydroascorbic acid (DHA), and superoxides disproportionate to form hydrogen peroxide, H_2O_2 . The presence of metals of the transition group, like ferric, Fe^{3+} , or copper, Cu^{2+} , ions greatly facilitate the reaction. These ions are reduced by vitamin C very fast and then pass the

electron onto oxygen. So, it is not surprising to see significant formation of hydrogen peroxide in cell culture medium in the presence of high concentrations of vitamin C [80–83].

Ultimately, experiments showing that catalase abolished vitamin C-induced cytotoxicity led to the widely accepted conclusion that hydrogen peroxide is the principal mediator of the anticancer effects of high-dose vitamin C [75,84–86]. However, several physiological factors make it difficult to reconcile this mechanism with the limited success of clinical trials. In cell culture medium, hydrogen peroxide can accumulate because its removal is relatively slow. In contrast, blood contains highly efficient antioxidant systems. Erythrocytes, which constitute nearly half of the circulating blood volume, are densely packed with peroxide-removing enzymes and rapidly eliminate hydrogen peroxide from the circulation [87,88]. In addition, transferrin restricts the availability of free iron ions required for metal-catalysed oxidation of vitamin C and subsequent hydrogen peroxide generation [83]. Finally, high-dose vitamin C is cleared from the bloodstream within hours after intravenous administration [89]. Collectively, these factors make it unlikely that vitamin C-derived hydrogen peroxide could accumulate in vivo at concentrations sufficient to exert direct cytotoxic effects on tumours.

This creates a paradox for the hydrogen peroxide hypothesis, a catch-22 situation. Generation of hydrogen peroxide appears necessary for cancer cell killing by vitamin C in vitro, yet physiological conditions make sustained exposure of tumours to cytotoxic concentrations of hydrogen peroxide highly improbable in vivo. It is therefore unsurprising that vitamin C-based anticancer therapy reached a conceptual impasse and that interest in this mechanism gradually waned. Nevertheless, occasional positive outcomes reported in clinical trials [77] suggest that an important aspect of the treatment mechanism may have been overlooked.

6.2. Is Vitamin C-Derived Hydrogen Peroxide Ultimately Responsible for Its Anticancer Effect?

Well-founded doubts have been raised as to whether H_2O_2 generated by high doses of vitamin C can fully account for its anticancer effects [90,91]. Thorough and carefully conducted studies addressing this question have not been published in peer-reviewed journal, likely because no alternative mechanism capable of explaining the observed toxicity had been proposed at the time [90]. However, another mechanism that warrants consideration is the involvement of dehydroascorbic acid (DHA), the product of two electron oxidation of vitamin C or dismutation of ascorbic radicals. H_2O_2 generated in medium for cultured cells in reaction of ascorbate with oxygen can itself react with ascorbate [92,93]. By removing H_2O_2 , catalase prevents the formation of DHA and thus inhibits the toxic effect. The toxicity of high doses of ascorbate in cell culture could therefore be explained by generation of H_2O_2 , followed by the formation of oxidized ascorbate. As explained in Section 6.1, in patients high-dose IV ascorbate on its own would not be able generate H_2O_2 and DHA in the blood in concentrations high enough for an anticancer effect. DHA has been shown to be toxic to cancer cells [94–99]. Within cells, DHA can be reduced back to ascorbic acid by a variety of reducing agents [100–104]. In solution, however, DHA is highly unstable and, in the absence of reductants, undergoes rapid decomposition [105–107]. Consequently, the direct clinical administration of DHA would present substantial technical challenges, as even freshly prepared DHA solutions intended for intravenous infusion would be expected to undergo significant hydrolysis.

DHA degradation generates reactive carbonyl compounds, including 3-deoxythreosone, which can induce extensive protein modification through mechanisms such as lysine crosslinking and adduct formation [108,109]. Nevertheless, as discussed below, consideration of the mechanisms and selectivity of DHA toxicity, together with the potential for DHA

generation in the bloodstream, suggests that these limitations do not necessarily preclude the therapeutic exploitation of DHA-mediated toxicity in cancer treatment.

6.3. Mechanism of DHA Toxicity for Cancer Cells

DHA enters cells via glucose transporters (GLUTs), particularly GLUT1 and GLUT3. Expression of these transporters is increased in many, although not all, tumour types. [110]. Within a cell DHA can react with GSH, thioredoxin, glutaredoxin, and other thiols leading to their oxidation; recycling of oxidised vitamin C also can be performed by reductases of thioredoxin or cytochrome b₅ [100–104,111]. These are all ultimately dependent on a supply reducing equivalents from NADPH. DHA can oxidise and inactivate thiol proteins to disulfide form unable to react with their substrates, as observed for GAPDH and Prdx2 [112].

We can propose a complex picture of how a high concentration of DHA could exert toxicity for cancer cells (Figure 1, modified from [112]). During the uptake by a cell, high doses of DHA would compete with glucose and therefore diminish ATP production by glycolysis and NADPH when glycolysis switches to the pentose phosphate pathway. Reactions with thiols, resulting in oxidation of thioredoxin, GSH, glutaredoxin, and Prdx would put a pressure on the corresponding enzymes involved in their regeneration. These enzymes need NADPH to perform the reduction. Formation of deoxyribonucleotides needs thioredoxin and NADPH. Therefore, a deficit of precursors inflicted by DHA treatment will inevitably inhibit DNA synthesis.

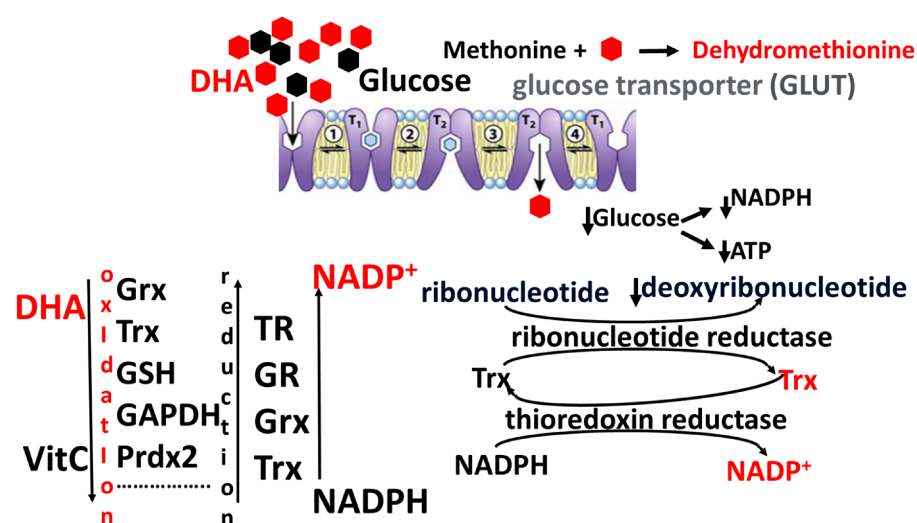


Figure 1. Interaction of dehydroascorbic acid (DHA) with cellular metabolism.

DHA can oxidise methionine, potentially disrupting intracellular pathways that depend on methionine availability. DHA enters cells via glucose transporters (GLUTs) in competition with glucose. Reduced glucose uptake may diminish ATP production through glycolysis and decrease NADPH generation via the pentose phosphate pathway. Within the cell, DHA can oxidise multiple thiol groups, resulting in inhibition of thiol-dependent enzymes and increased consumption of NADPH by systems responsible for the reduction of oxidised thiols. Synthesis of deoxyribonucleotides, the precursors required for DNA replication, depends on an adequate supply of reduced thioredoxin and NADPH. Sustained intracellular accumulation of DHA may therefore impair DNA synthesis by depleting these reducing equivalents.

With prolonged DHA uptake and decreasing rate of DHA reduction in cells there is increased possibility for oxidation of thiol proteins and formation of protein adducts with DHA [103,113,114]; DHA could also interfere with S-thiolation of proteins [115].

In neuroblastoma cells, an adduct formed between DHA and homocysteine has been detected [116]. Notably, homocysteine levels are elevated in cancer patients and have been associated with tumour progression and metastasis [117].

Hydrolysis of the DHA would also result in the formation of reactive secondary products [109,110].

Additional pressure on cancer cells, which are dependent on methionine [59], can be achieved through a methionine deficit resulting from oxidation of methionine into dehydromethionine by DHA [112].

6.4. Selectivity of the Anticancer Effect of DHA

Could DHA bring about oxidative stress into a normal cell? Cancer cells uptake DHA preferentially whereas normal cells in culture do not show selectivity between DHA and ascorbic acid [118,119]. Therefore, in a normal cell, oxidation by DHA would be balanced by reductive power of ascorbic acid.

Reactivity of thiols with an oxidant depends on the thiol pKa, as well as the microenvironment [120,121]. While DHA effectively reacted with Prdx2 and GAPDH, it did not oxidise the thiol in p16^{INK4A} [112]. Protein p16^{INK4a} is a negative regulator of cell division, inhibiting the cyclin dependent kinases 4 and 6 and preventing progression of the cell cycle. Thiol oxidation of p16^{INK4a} leads to the formation of disulfide-bridged dimers that subsequently form amyloid fibrils. The loss of p16^{INK4a} activity is widely believed to be a common and important event in the development of cancer [122]. It is tempting to suggest that DHA may lack pro-carcinogenic action which is quite often observed for anti-cancer agents.

The DHA effect on DNA synthesis would be reversible and restricted to proliferating cells and those where NADPH is mainly provided by glucose metabolism. Notably, even with dividing cells in culture, DHA was dramatically more toxic for cancer cells than for normal ones [99].

Data on DHA toxicity available so far are restricted mostly to cells in culture. Its anticancer efficacy and lack of side effects remain to be proved in clinical trials. Thus far, no reasonable pitfalls can be seen to argue against such trials.

The mechanism of cancer cell death arising from DHA toxicity has not yet been established. Recently, a new form of programmed cell death termed disulfidptosis was described. Disulfidptosis is triggered by disulfide stress under conditions of impaired glucose metabolism and NADPH depletion, resulting in excessive S-thiolation of cytoskeletal proteins and collapse of the actin network [123,124]. Several features of DHA toxicity appear consistent with this mechanism. DHA competes with glucose for cellular uptake, oxidises intracellular thiols, and increases demand for the NADPH required for regeneration of reduced glutathione and thioredoxin. Sustained DHA exposure could therefore create conditions favouring disulfide stress. Whether DHA-induced cell death is accompanied by cytoskeletal protein S-thiolation and other hallmarks of disulfidptosis remains to be determined experimentally. If confirmed, disulfidptosis could provide a unifying mechanistic explanation linking DHA-induced oxidation of thiols, depletion of NADPH, and selective cancer cell death.

6.5. Does High-Dose Vitamin C Treatment Have a Future for Anti-Cancer Treatment?

High-dose vitamin C may serve as a precursor for in situ generation of DHA within the circulation, thereby exposing tumours to DHA via their blood supply. This proposal is mechanistic and exploratory rather than a defined therapeutic protocol, as the conditions required for controlled DHA generation in vivo remain to be established experimentally.

Ascorbic acid reacts efficiently with myeloperoxidase (MPO) [125], an enzyme abundant in neutrophils and monocytes that is released and activated during innate immune responses [126]. Upon activation, MPO rapidly reacts with hydrogen peroxide generated by activated leukocytes to form Compound I, which in turn oxidises ascorbic acid with a second-order rate constant of approximately $10^6 \text{ M}^{-1} \text{ s}^{-1}$ [125].

The major physiological product of MPO is hypochlorous acid (HOCl), a potent oxidant generated by oxidation of chloride ions using hydrogen peroxide. HOCl oxidises ascorbic acid very rapidly ($k = 6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) [127]. Although HOCl is an important component of the innate immune response [126], excessive HOCl production has been implicated in carcinogenesis and numerous pathological conditions [128,129]. We have recently found that millimolar concentrations of ascorbic acid, comparable to those achieved during high-dose intravenous vitamin C therapy, inhibit HOCl production by purified MPO through competition with chloride ions [112]. Under these conditions, ascorbic acid undergoes preferential oxidation by MPO, effectively shifting MPO activity away from HOCl production towards ascorbate oxidation [115]. Whether this can be achieved without compromising host defence or producing unintended side effects will require careful experimental validation.

MPO activity is most pronounced during innate immune responses to microbial stimuli [126]. Among clinically available options, Bacillus Calmette–Guérin (BCG), an attenuated strain of *Mycobacterium bovis* used worldwide as a vaccine and immunotherapy, represents a potential means of inducing controlled leukocyte activation and MPO release; however, its suitability, safety, and controllability in this context are entirely untested. Figure 2 depicts a hypothetical mechanism of MPO-dependent vitamin C oxidation in blood during high-dose intravenous vitamin C administration.

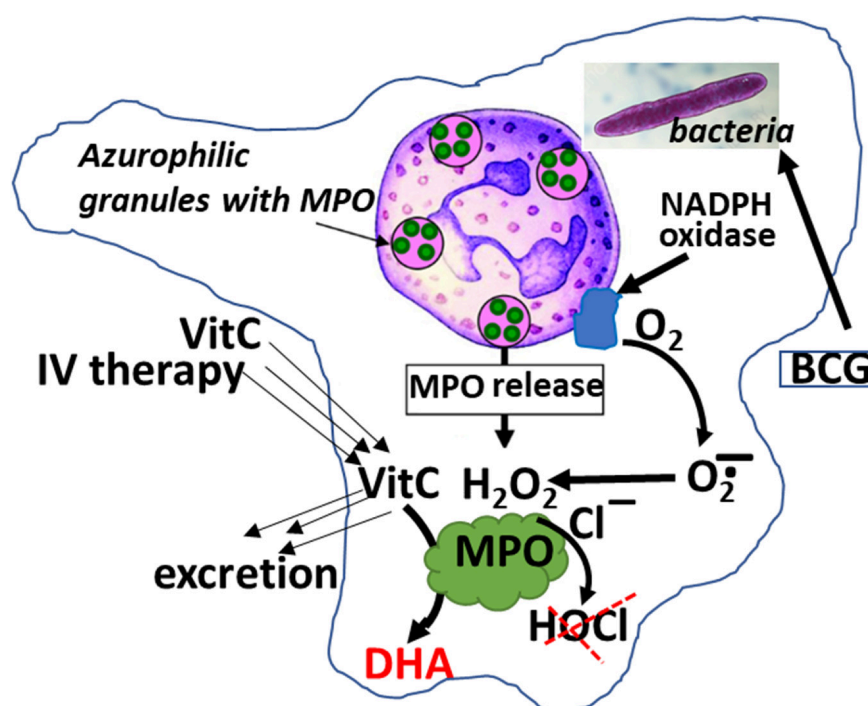


Figure 2. Proposed mechanism of vitamin C oxidation in blood.

BCG-induced activation of neutrophils may promote hydrogen peroxide generation and MPO release. Under such conditions, elevated plasma ascorbate concentrations could potentially compete with chloride as a substrate for MPO, shifting enzymatic activity from HOCl production toward oxidation of ascorbate to dehydroascorbic acid (DHA), as

observed in vitro [112]. Whether this mechanism can be reproduced in vivo in a controlled and safe manner remains unknown.

A central unanswered question is whether MPO-mediated oxidation can generate DHA at concentrations sufficient to overwhelm the reducing capacity of cancer cells. This will depend on multiple interdependent variables, including leukocyte number and activation state, MPO release kinetics, plasma ascorbate concentration, tumour perfusion, and intracellular DHA reduction and decomposition rates. At present, these parameters are not known with sufficient precision to define a dosing or timing strategy. Therefore, quantitative modelling combined with ex vivo human blood experiments will be required before any translational protocol can be considered.

6.6. Requirements for Successful DHA-Mediated Vitamin C Therapy

Three conditions may be necessary for successful anticancer activity:

1. Sustained millimolar concentrations of vitamin C in the circulatory system.
2. Efficient oxidation of vitamin C in blood to generate therapeutically relevant DHA concentrations.
3. Maintenance of DHA exposure for a sufficient duration to exhaust the reducing capacity of cancer cells.

High doses of vitamin C were used in clinical trials, and patient tolerance was generally good [78,79]. However, no attempts were made to induce oxidation of vitamin C in the circulation during treatment in order to ensure tumour exposure to DHA. It is possible that successful outcomes observed in some patients [79] occurred in the presence of inflammatory conditions associated with activated WBCs, resulting in MPO-mediated oxidation of vitamin C. Retrospective analysis of clinical trial data in this context may therefore be of interest, for example the blood markers of inflammation as C-reactive protein and erythrocyte sedimentation rate, which are absent in the published data.

Another limitation of vitamin C therapy was the methodology used for intravenous administration. Vitamin C is cleared from the circulation relatively rapidly, with plasma concentrations declining from millimolar to micromolar levels within a few hours after intravenous infusion [89]. Maintenance intravenous administration may therefore be required to sustain prolonged DHA generation at levels sufficient to exhaust the reducing capacity of cancer cells and achieve tumour elimination. In this regard, an analogy may be drawn with prolonged antibiotic treatment protocols.

7. Conclusions

High-dose vitamin C treatment may have therapeutic potential in patients with well-vascularised tumours. For successful anticancer action to occur vitamin C would need efficient oxidation in the blood. As it was discussed above, DHA can affect many targets considered attractive for anti-cancer treatment. Intracellular influx of DHA occurs in cancer cells preferentially and competes with glucose. In blood DHA can oxidise methionine and prevent cancer cells from obtaining methionine, which for them is the essential amino acid. Inside cells DHA can oxidise thiol groups resulting in overspending NADPH and over a certain period of time may result in drop of NADPH to unsustainable level. It has been suggested that maintenance of NADPH levels is often more limiting for tumour growth than are energy levels or biosynthetic precursors [130].

As there are many targets for DHA, one may suggest that metabolic plasticity of cancer cells would not be able to cover all of them. Notably, some modes of action, such as competition with glucose for cellular uptake could not be lethal on their own. Glucose concentration in blood is approximately 5 mM and therefore it would not be possible for DHA totally outcompete glucose. However, maintenance of IV vitamin C to ensure

millimolar DHA levels, along with fasting regime for patients during treatment, which could bring glucose down by 20%, would contribute to the overall DHA effect by decreasing glucose influx. The therapeutic potential of methionine depletion, particularly for brain tumours where drug delivery is hindered by the blood–brain barrier, has been limited by significant adverse effects of methods used [65–67]. In this context, oxidation of methionine by DHA appears to be an especially attractive therapeutic strategy.

The principal strength of a DHA-based therapeutic strategy may lie in its ability to simultaneously perturb multiple metabolic processes rather than targeting a single vulnerability. Such a multifaceted mechanism could reduce the ability of cancer cells to compensate through metabolic plasticity. If efficient and controlled DHA generation in the circulatory system can be achieved safely, high-dose vitamin C may evolve from a largely empirical treatment into a rationally designed metabolic therapy. Experimental validation of this concept now represents the critical next step.

Apart from efficiency of anti-cancer treatment itself, one needs to keep in mind that patients tend to report poorer functioning and quality of life in the long term. Survivors of childhood cancer frequently develop cognitive and functional deficits that impair their ability to complete education successfully and obtain employment, ultimately reducing psychological well-being, financial security, and overall quality of life [131,132]. Currently, we are investigating how high-dose vitamin C, which is well tolerated can be effectively oxidised in human blood without side effects.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: No new data were created or analysed in this study.

Acknowledgments: The author expresses gratitude to Christine Winterbourn, Armino Salvador, and ChatGPT, GPT-5.5 for valuable improvements to the manuscript.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Lavi, O. Redundancy: A critical obstacle to improving cancer therapy. *Cancer Res.* **2015**, *75*, 808–812. [[CrossRef](#)] [[PubMed](#)]
2. Fendt, S.M.; Frezza, C.; Erez, A. Targeting Metabolic Plasticity and Flexibility Dynamics for Cancer Therapy. *Cancer Discov.* **2020**, *10*, 1797–1807. [[CrossRef](#)] [[PubMed](#)]
3. Luo, Z.; Eichinger, K.M.; Zhang, A.; Li, S. Targeting cancer metabolic pathways for improving chemotherapy and immunotherapy. *Cancer Lett.* **2023**, *575*, 216396. [[CrossRef](#)] [[PubMed](#)]
4. Warburg, O.; Wind, F.; Negelein, E. The metabolism of tumors in the body. *J. Gen. Physiol.* **1927**, *8*, 519–530. [[CrossRef](#)] [[PubMed](#)]
5. Warburg, O. On the Origin of Cancer Cells. *Science* **1956**, *123*, 309–314. [[CrossRef](#)] [[PubMed](#)]
6. Gatenby, R.A.; Gillies, R.J. Why do cancers have high aerobic glycolysis? *Nat. Rev. Cancer* **2004**, *4*, 891–899. [[CrossRef](#)] [[PubMed](#)]
7. Pelicano, H.; Martin, D.S.; Xu, R.H.; Huang, P. Glycolysis inhibition for anticancer treatment. *Oncogene* **2006**, *25*, 4633–4646. [[CrossRef](#)] [[PubMed](#)]
8. Floberg, J.M.; Schwarz, J.K. Manipulation of Glucose and Hydroperoxide Metabolism to Improve Radiation Response. *Semin. Radiat. Oncol.* **2019**, *29*, 33–41. [[CrossRef](#)] [[PubMed](#)]
9. Zhou, Y.; Guo, Y.; Tam, K.Y. Targeting glucose metabolism to develop anticancer treatments and therapeutic patents. *Expert Opin. Ther. Pat.* **2022**, *32*, 441–453. [[CrossRef](#)] [[PubMed](#)]
10. Stine, Z.E.; Schug, Z.T.; Salvino, J.M.; Dang, C.V. Targeting cancer metabolism in the era of precision oncology. *Nat. Rev. Drug Discov.* **2022**, *21*, 141–162. [[PubMed](#)]
11. Li, S.; Gong, J.; Kang, B.; Wang, Z.; Ma, Y.; Xia, X.; Yan, H. Targeting Glycolytic Metabolism in Cancer Therapy: Current Approaches and Future Perspectives. *Cells* **2026**, *15*, 362. [[CrossRef](#)] [[PubMed](#)]
12. Brown, J.J. Effects of 2-deoxyglucose on carbohydrate metabolism: Review of the literature and studies in the rat. *Metab. Clin. Exp.* **1962**, *11*, 1098–1112. [[PubMed](#)]
13. Christensen, N.V.; Knudsen, J.H.; Laustsen, C.; Bertelsen, L.B. The effect of 2-Deoxy-D-glucose on glycolytic metabolism in acute myeloblastic leukemic ML-1 cells. *Sci. Rep.* **2025**, *15*, 17685. [[CrossRef](#)] [[PubMed](#)]

14. Mohanti, B.K.; Rath, G.K.; Anantha, N.; Kannan, V.; Das, B.S.; Chandramouli, B.A.R.; Banerjee, A.K.; Das, S.; Jena, A.; Ravichandran, R.; et al. Improving cancer radiotherapy with 2-deoxy-d-glucose: Phase I/II clinical trials on human cerebral gliomas. *Int. J. Radiat. Oncol. Biol. Phys.* **1996**, *35*, 103–111. [[CrossRef](#)] [[PubMed](#)]
15. Stein, M.; Lin, H.; Jeyamohan, C.; Dvorzhinski, D.; Gounder, M.; Bray, K.; Eddy, S.; Goodin, S.; White, E.; Dipaola, R.S. Targeting tumor metabolism with 2-deoxyglucose in patients with castrate-resistant prostate cancer and advanced malignancies. *Prostate* **2010**, *70*, 1388–1394. [[CrossRef](#)] [[PubMed](#)]
16. Raez, L.E.; Papadopoulos, K.; Ricart, A.D.; Chiorean, E.G.; Dipaola, R.S.; Stein, M.N.; Rocha Lima, C.M.; Schlesselman, J.J.; Tolba, K.; Langmuir, V.K.; et al. A phase I dose-escalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. *Cancer Chemother. Pharmacol.* **2013**, *71*, 523–530. [[PubMed](#)]
17. Wang, X.; Chen, L.; Li, Y.; Chen, L.; Hao, C.; Yan, Q.; Yu, S.; Zhang, C.; Li, R.; Xu, B.; et al. Uridine metabolism promotes lung adenocarcinoma progression by activating FBL transcription via YBX1. *J. Transl. Med.* **2026**, *24*, 518. [[CrossRef](#)] [[PubMed](#)]
18. Wang, F.; Hu, P.; Han, S.; Zhang, Y.; Li, Y.; Zhuo, W.; Zhao, Y.; Huang, Y.; Lv, G.; Wang, H.; et al. Lactate Facilitates the Survival and Invasion of Pancreatic Cancer Cells Under Glucose Deprivation. *FASEB J.* **2026**, *40*, e71726. [[CrossRef](#)] [[PubMed](#)]
19. Floridi, A.; Paggi, M.G.; Marcante, M.L.; Silvestrini, B.; Caputo, A.; De Martino, C. Lonidamine, a selective inhibitor of aerobic glycolysis of murine tumor cells. *J. Natl. Cancer Inst.* **1981**, *66*, 497–499. [[CrossRef](#)] [[PubMed](#)]
20. Li, R.; Mei, S.; Ding, Q.; Wang, Q.; Yu, L.; Zi, F. A pan-cancer analysis of the role of hexokinase II (HK2) in human tumors. *Sci. Rep.* **2022**, *12*, 18807. [[CrossRef](#)] [[PubMed](#)]
21. Rosbe, K.W.; Brann, T.W.; Holden, S.A.; Teicher, B.A.; Frei, E., 3rd. Effect of lonidamine on the cytotoxicity of four alkylating agents in vitro. *Cancer Chemother. Pharmacol.* **1989**, *25*, 32–36. [[CrossRef](#)] [[PubMed](#)]
22. Mathupala, S.P.; Ko, Y.H.; Pedersen, P.L. Hexokinase II: Cancer's double-edged sword acting as both facilitator and gatekeeper of malignancy when bound to mitochondria. *Oncogene* **2006**, *25*, 4777–4786. [[PubMed](#)]
23. Papaldo, P.; Lopez, M.; Cortesi, E.; Cammilluzzi, E.; Antimi, M.; Terzoli, E.; Lepidini, G.; Vici, P.; Barone, C.; Ferretti, G.; et al. Addition of either lonidamine or granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose epirubicin and cyclophosphamide. *J. Clin. Oncol.* **2003**, *21*, 3462–3468. [[CrossRef](#)] [[PubMed](#)]
24. Cheng, G.; Zhang, Q.; Pan, J.; Lee, Y.; Ouari, O.; Hardy, M.; Zielonka, M.; Myers, C.R.; Zielonka, J.; Weh, K.; et al. Targeting lonidamine to mitochondria mitigates lung tumorigenesis and brain metastasis. *Nat. Commun.* **2019**, *10*, 2205. [[CrossRef](#)] [[PubMed](#)]
25. Roy, S.; Dukic, T.; Bhandary, B.; Tu, K.J.; Molitoris, J.; Ko, Y.H.; Shukla, H.D. 3-Bromopyruvate inhibits pancreatic tumor growth by stalling glycolysis, and dismantling mitochondria in a syngeneic mouse model. *Am. J. Cancer Res.* **2022**, *12*, 4977–4987. [[PubMed](#)]
26. Linke, C.; Wösl, M.; Harder, A. Anti-cancer agent 3-bromopyruvate reduces growth of MPNST and inhibits metabolic pathways in a representative in-vitro model. *BMC Cancer* **2020**, *20*, 896. [[CrossRef](#)] [[PubMed](#)]
27. Zhao, B.; Aggarwal, A.; Marshall, J.A.; Barletta, J.A.; Kijewski, M.F.; Lorch, J.H.; Nehs, M.A. Glycolytic inhibition with 3-bromopyruvate suppresses tumor growth and improves survival in a murine model of anaplastic thyroid cancer. *Surgery* **2022**, *171*, 227–234. [[CrossRef](#)] [[PubMed](#)]
28. Shoshan, M.C. 3-Bromopyruvate: Targets and outcomes. *J. Bioenerg. Biomembr.* **2012**, *44*, 7–15. [[CrossRef](#)] [[PubMed](#)]
29. Hayes, J.D.; Dinkova-Kostova, A.T.; Tew, K.D. Oxidative Stress in Cancer. *Cancer Cell* **2020**, *38*, 167–197. [[CrossRef](#)] [[PubMed](#)]
30. Hu, J.; Fang, J.; Dong, Y.; Chen, S.J.; Chen, Z. Arsenic in cancer therapy. *Anticancer Drugs* **2005**, *16*, 119–127. [[CrossRef](#)] [[PubMed](#)]
31. Winterbourn, C.C.; Peskin, A.V.; Kleffmann, T.; Radi, R.; Pace, P.E. Carbon dioxide/bicarbonate is required for sensitive inactivation of mammalian glyceraldehyde-3-phosphate dehydrogenase by hydrogen peroxide. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2221047120. [[CrossRef](#)] [[PubMed](#)]
32. Tristan, C.; Shahani, N.; Sedlak, T.W.; Sawa, A. The diverse functions of GAPDH: Views from different subcellular compartments. *Cell Signal.* **2011**, *23*, 317–323. [[CrossRef](#)] [[PubMed](#)]
33. Liberti, M.V.; Dai, Z.; Wardell, S.E.; Baccile, J.A.; Liu, X.; Gao, X.; Baldi, R.; Mehrmohamadi, M.; Johnson, M.O.; Madhukar, N.S.; et al. A Predictive Model for Selective Targeting of the Warburg Effect through GAPDH Inhibition with a Natural Product. *Cell Metab.* **2017**, *26*, 648–659.e8. [[CrossRef](#)] [[PubMed](#)]
34. Talwar, D.; Miller, C.G.; Grossmann, J.; Szyrwiel, L.; Schwecke, T.; Demichev, V.; Mikecin Drazic, A.M.; Mayakonda, A.; Lutsik, P.; Veith, C.; et al. The GAPDH redox switch safeguards reductive capacity and enables survival of stressed tumour cells. *Nat. Metab.* **2023**, *5*, 660–676. [[CrossRef](#)] [[PubMed](#)]
35. Arnér, E.S.; Holmgren, A. The thioredoxin system in cancer. *Semin. Cancer Biol.* **2006**, *16*, 420–426. [[CrossRef](#)] [[PubMed](#)]
36. Powis, G.; Kirkpatrick, D.L. Thioredoxin signaling as a target for cancer therapy. *Curr. Opin. Pharmacol.* **2007**, *7*, 392–397. [[CrossRef](#)] [[PubMed](#)]
37. Holmgren, A.; Sengupta, R. The use of thiols by ribonucleotide reductase. *Free Radic. Biol. Med.* **2010**, *49*, 1617–1628. [[CrossRef](#)] [[PubMed](#)]

38. Yan, X.; Zhang, X.; Wang, L.; Zhang, R.; Pu, X.; Wu, S.; Li, L.; Tong, P.; Wang, J.; Meng, Q.H.; et al. Inhibition of Thioredoxin/Thioredoxin Reductase Induces Synthetic Lethality in Lung Cancers with Compromised Glutathione Homeostasis. *Cancer Res.* **2019**, *79*, 125–132. [[CrossRef](#)] [[PubMed](#)]
39. Chupakhin, E.; Krasavin, M. Thioredoxin reductase inhibitors: Updated patent review (2017-present). *Expert Opin. Ther. Pat.* **2021**, *31*, 745–758. [[CrossRef](#)] [[PubMed](#)]
40. Gencheva, R.; Arnér, E.S.J. Thioredoxin Reductase Inhibition for Cancer Therapy. *Annu. Rev. Pharmacol. Toxicol.* **2022**, *62*, 177–196. [[CrossRef](#)] [[PubMed](#)]
41. Rhee, S.G. Overview on Peroxiredoxin. *Mol. Cells* **2016**, *39*, 1–5. [[CrossRef](#)] [[PubMed](#)]
42. Peskin, A.V.; Low, F.M.; Paton, L.N.; Maghzal, G.J.; Hampton, M.B.; Winterbourn, C.C. The high reactivity of peroxiredoxin 2 with H₂O₂ is not reflected in its reaction with other oxidants and thiol reagents. *J. Biol. Chem.* **2007**, *282*, 11885–11892. [[PubMed](#)]
43. Stöcker, S.; Van Laer, K.; Mijuskovic, A.; Dick, T.P. The Conundrum of Hydrogen Peroxide Signaling and the Emerging Role of Peroxiredoxins as Redox Relay Hubs. *Antioxid. Redox Signal.* **2018**, *28*, 558–573. [[CrossRef](#)] [[PubMed](#)]
44. Winterbourn, C.C. Peroxiredoxins: Antioxidant Activity, Redox Relays, and Redox Signaling. *Biochemistry* **2025**, *64*, 4477–4486. [[CrossRef](#)] [[PubMed](#)]
45. Peskin, A.V.; Meotti, F.C.; Magon, N.J.; de Souza, L.F.; Salvador, A.; Winterbourn, C.C. Mechanism of glutathionylation of the active site thiols of peroxiredoxin 2. *J. Biol. Chem.* **2025**, *301*, 108503. [[CrossRef](#)] [[PubMed](#)]
46. Forshaw, T.E.; Holmila, R.; Nelson, K.J.; Lewis, J.E.; Kemp, M.L.; Tsang, A.W.; Poole, L.B.; Lowther, W.T.; Furdai, C.M. Peroxiredoxins in Cancer and Response to Radiation Therapies. *Antioxidants* **2019**, *8*, 11. [[CrossRef](#)] [[PubMed](#)]
47. Zheng, X.; Wei, J.; Li, W.; Li, X.; Wang, W.; Guo, J.; Fu, Z. PRDX2 removal inhibits the cell cycle and autophagy in colorectal cancer cells. *Aging* **2020**, *12*, 16390–16409. [[CrossRef](#)] [[PubMed](#)]
48. Goikoetxea-Usandizaga, N.; Martinez-Chantar, M.L.; Conter, C. Redox regulation meets metabolism: Targeting PRDX2 to prevent hepatocellular carcinoma. *Mol. Oncol.* **2026**, *20*, 584–587. [[PubMed](#)]
49. Szumska, K.; Sabir, F.; Szeliga, M. Peroxiredoxin 2 contributes to the malignant phenotype of glioblastoma cells. *Biochem. Biophys. Res. Commun.* **2026**, *804*, 153370. [[CrossRef](#)] [[PubMed](#)]
50. Nelson, K.J.; Smalley TL Jr; Messier, T.; Gumpena, R.; Gandhi, U.; Milczarek, S.; Habibovic, A.; Hoffman, H.; Gibson, V.; Hondal, R.J.; Lowther, W.T.; et al. Mechanism-based peroxiredoxin 3 inhibitors exploit a covalent warhead for cancer therapy. *Sci. Adv.* **2025**, *11*, eady4492. [[CrossRef](#)] [[PubMed](#)]
51. Liu, C.X.; Yin, Q.Q.; Zhou, H.C.; Wu, Y.L.; Pu, J.X.; Xia, L.; Liu, W.; Huang, X.; Jiang, T.; Wu, M.X.; et al. Adenanthin targets peroxiredoxin I and II to induce differentiation of leukemic cells. *Nat. Chem. Biol.* **2012**, *8*, 486–493. [[CrossRef](#)] [[PubMed](#)]
52. Soethoudt, M.; Peskin, A.V.; Dickerhof, N.; Paton, L.N.; Pace, P.E.; Winterbourn, C.C. Interaction of adenanthin with glutathione and thiol enzymes: Selectivity for thioredoxin reductase and inhibition of peroxiredoxin recycling. *Free. Radic. Biol. Med.* **2014**, *77*, 331–339. [[CrossRef](#)] [[PubMed](#)]
53. Locigno, R.; Castronovo, V. Reduced glutathione system: Role in cancer development, prevention and treatment (review). *Int. J. Oncol.* **2001**, *19*, 221–236. [[CrossRef](#)] [[PubMed](#)]
54. Bansal, A.; Simon, M.C. Glutathione metabolism in cancer progression and treatment resistance. *J. Cell Biol.* **2018**, *217*, 2291–2298. [[CrossRef](#)] [[PubMed](#)]
55. Kennedy, L.; Sandhu, J.K.; Harper, M.E.; Cuperlovic-Culf, M. Role of Glutathione in Cancer: From Mechanisms to Therapies. *Biomolecules* **2020**, *10*, 1429. [[CrossRef](#)] [[PubMed](#)]
56. Hecht, F.; Zocchi, M.; Tuttle, E.T.; Ward, N.P.; Alimohammadi, F.; Khan, A.A.; Gomes, V.C.; Smith, B.; Twardowski, J.J.; Mills, B.N.; et al. Catabolism of extracellular glutathione supplies cysteine to support tumours. *Nature* **2026**, *653*, 933–941. [[CrossRef](#)] [[PubMed](#)]
57. Lapenna, D. Glutathione and glutathione-dependent enzymes: From biochemistry to gerontology and successful aging. *Ageing Res. Rev.* **2023**, *92*, 102066. [[CrossRef](#)] [[PubMed](#)]
58. Mecham, J.O.; Rowitch, D.; Wallace, C.D.; Stern, P.H.; Hoffman, R.M. The metabolic defect of methionine dependence occurs frequently in human tumor cell lines. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 429–434. [[CrossRef](#)] [[PubMed](#)]
59. Cellarier, E.; Durando, X.; Vasson, M.P.; Farges, M.C.; Demiden, A.; Maurizis, J.C.; Madelmont, J.C.; Chollet, P. Methionine dependency and cancer treatment. *Cancer Treat. Rev.* **2003**, *29*, 489–499. [[CrossRef](#)] [[PubMed](#)]
60. Judde, J.G.; Frost, P. Patterns of Methionine Auxotrophy in Normal and Neoplastic Cells: The Methionine Independence of Lymphocyte Mitogenesis and Low Frequency of the Methionine-Dependent Phenotype in Human Tumors. *Cancer Res.* **1988**, *48*, 6775–6779. [[PubMed](#)]
61. Butler, M.; van der Meer, L.T.; van Leeuwen, F.N. Amino Acid Depletion Therapies: Starving Cancer Cells to Death. *Trends Endocrinol. Metab.* **2021**, *32*, 367–381. [[CrossRef](#)] [[PubMed](#)]
62. Chen, J.; Cui, L.; Lu, S.; Xu, S. Amino acid metabolism in tumor biology and therapy. *Cell Death Dis.* **2024**, *15*, 42. [[CrossRef](#)] [[PubMed](#)]

63. Tan, Y.; Zavala, J.S.; Xu, M.; Zavala, J.J.; Hoffman, R.M. Serum Methionine Depletion without Side Effects by Methioninase in Metastatic Breast Cancer Patients. *Anticancer. Res.* **1996**, *16*, 3937–3942. [[PubMed](#)]
64. Gay, F.; Agüera, K.; Sénéchal, K.; Tainturier, A.; Berlier, W.; Maucourt-Boulch, D.; Honnorat, J.; Horand, F.; Godfrin, Y.; Bourgeaux, V. Methionine Tumor Starvation by Erythrocyte-Encapsulated Methionine Gamma-Lyase Activity Controlled with per Os Vitamin B6. *Cancer Med.* **2017**, *6*, 1437–1452. [[CrossRef](#)] [[PubMed](#)]
65. Yang, Z.; Wang, J.; Yoshioka, T.; Li, B.; Lu, Q.; Li, S.; Sun, X.; Tan, Y.; Yagi, S.; Frenkel, E.P.; et al. Pharmacokinetics, methionine depletion, and antigenicity of recombinant methioninase in primates. *Clin. Cancer Res.* **2004**, *10*, 2131–2138. [[CrossRef](#)] [[PubMed](#)]
66. Hendy, M.H.; Hashem, A.H.; Suleiman, W.B.; Sultan, M.H.; Abdelraof, M. Purification, Characterization and anticancer activity of L-methionine γ -lyase from thermo-tolerant *Aspergillus fumigatus*. *Microb. Cell Fact.* **2023**, *22*, 8. [[CrossRef](#)] [[PubMed](#)]
67. Sowers, M.L.; Sowers, L.C. Glioblastoma and Methionine Addiction. *Int. J. Mol. Sci.* **2022**, *23*, 7156. [[CrossRef](#)] [[PubMed](#)]
68. Galmarini, C.M.; Mackey, J.R.; Dumontet, C. Nucleoside analogues and nucleobases in cancer treatment. *Lancet Oncol.* **2002**, *3*, 415–424. [[CrossRef](#)] [[PubMed](#)]
69. Puigvert, J.C.; Sanjiv, K.; Helleday, T. Targeting DNA repair, DNA metabolism and replication stress as anti-cancer strategies. *FEBS J.* **2016**, *283*, 232–245. [[PubMed](#)]
70. Vider, B.Z. Targeting energy, nucleotide, and DNA synthesis in cancer. *Front. Oncol.* **2025**, *15*, 1736064. [[CrossRef](#)] [[PubMed](#)]
71. Gu, L.; Hickey, R.J.; Malkas, L.H. Therapeutic Targeting of DNA Replication Stress in Cancer. *Genes* **2023**, *14*, 1346. [[CrossRef](#)] [[PubMed](#)]
72. Cameron, E.; Pauling, L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 3685–3689. [[CrossRef](#)] [[PubMed](#)]
73. Young, V.R. Evidence for a recommended dietary allowance for vitamin C from pharmacokinetics: A comment and analysis. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14344–14348. [[CrossRef](#)] [[PubMed](#)]
74. Saitoh, Y.; Ishikawa, T.; Yamamoto, M.; Oki, A.; Makino, H.; Takeda, M.; Ozeki, Y. High-dose vitamin C preferentially exerts a sustained growth-inhibitory effect in human tongue carcinoma cells over dysplastic oral keratinocytes. *Biochim. Biophys. Acta Gen. Subj.* **2026**, *1870*, 130957. [[CrossRef](#)] [[PubMed](#)]
75. Chen, Q.; Espey, M.G.; Krishna, M.C.; Mitchell, J.B.; Corpe, C.P.; Buettner, G.R.; Shacter, E.; Levine, M. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13604–13609. [[CrossRef](#)] [[PubMed](#)]
76. Chen, Q.; Espey, M.G.; Sun, A.Y.; Pooput, C.; Kirk, K.L.; Krishna, M.C.; Khosh, D.B.; Drisko, J.; Levine, M. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 11105–11109. [[CrossRef](#)] [[PubMed](#)]
77. Zasowska-Nowak, A.; Nowak, P.J.; Ciałkowska-Rysz, A. High-Dose Vitamin C in Advanced-Stage Cancer Patients. *Nutrients* **2021**, *13*, 735. [[CrossRef](#)] [[PubMed](#)]
78. Wang, F.; He, M.M.; Xiao, J.; Zhang, Y.Q.; Yuan, X.L.; Fang, W.J.; Zhang, Y.; Wang, W.; Hu, X.H.; Ma, Z.G.; et al. A Randomized, Open-Label, Multicenter, Phase 3 Study of High-Dose Vitamin C Plus FOLFOX $\pm$ Bevacizumab versus FOLFOX $\pm$ Bevacizumab in Unresectable Untreated Metastatic Colorectal Cancer (VITALITY Study). *Clin. Cancer Res.* **2022**, *28*, 4232–4239. [[CrossRef](#)] [[PubMed](#)]
79. Nauman, G.; Gray, J.C.; Parkinson, R.; Levine, M.; Paller, C.J. Systematic Review of Intravenous Ascorbate in Cancer Clinical Trials. *Antioxidants* **2018**, *7*, 89. [[CrossRef](#)] [[PubMed](#)]
80. Tóth, M.; Kukor, Z.; Valent, S. Chemical stabilization of tetrahydrobiopterin by L-ascorbic acid: Contribution to placental endothelial nitric oxide synthase activity. *Mol. Hum. Reprod.* **2002**, *8*, 271–280. [[CrossRef](#)] [[PubMed](#)]
81. Kuo, S.M.; Tan, D.; Boyer, J.C. Cellular vitamin C accumulation in the presence of copper. *Biol. Trace Elem. Res.* **2004**, *100*, 125–136. [[CrossRef](#)] [[PubMed](#)]
82. Kalus, W.H.; Filby, W.G. The effect of additives on the free radical formation in aqueous solutions of ascorbic acid. *Int. J. Vitam. Nutr. Res.* **1977**, *47*, 258–264. [[PubMed](#)]
83. Løvstad, R.A. Copper catalyzed oxidation of ascorbate (vitamin C). Inhibitory effect of catalase, superoxide dismutase, serum proteins (ceruloplasmin, albumin, apotransferrin) and amino acids. *Int. J. Biochem.* **1987**, *19*, 309–313. [[CrossRef](#)] [[PubMed](#)]
84. Schoenfeld, J.D.; Sibenaller, Z.A.; Mapuskar, K.A.; Wagner, B.A.; Cramer-Morales, K.L.; Furqan, M.; Sandhu, S.; Carlisle, T.L.; Smith, M.C.; Abu Hejleh, T.; et al. $O_2^{\cdot-}$ and H_2O_2 -Mediated Disruption of Fe Metabolism Causes the Differential Susceptibility of NSCLC and GBM Cancer Cells to Pharmacological Ascorbate. *Cancer Cell* **2017**, *31*, 487–500.e8. [[CrossRef](#)] [[PubMed](#)]
85. Ma, E.; Chen, P.; Wilkins, H.M.; Wang, T.; Swerdlow, R.H.; Chen, Q. Pharmacologic ascorbate induces neuroblastoma cell death by hydrogen peroxide mediated DNA damage and reduction in cancer cell glycolysis. *Free Radic. Biol. Med.* **2017**, *113*, 36–47. [[CrossRef](#)] [[PubMed](#)]
86. Sanookpan, K.; Chantaravisoot, N.; Kalpongkul, N.; Chuenjit, C.; Wattanatham, O.; Shoaib, S.; Chanvorachote, P.; Buranasudja, V. Pharmacological Ascorbate Elicits Anti-Cancer Activities against Non-Small Cell Lung Cancer through Hydrogen-Peroxide-Induced-DNA-Damage. *Antioxidants* **2023**, *12*, 1775. [[CrossRef](#)] [[PubMed](#)]

87. Winterbourn, C.C. Redox biology from the perspective of the red blood cell. *Free Radic. Biol. Med.* **2026**, *250*, 483–491. [[CrossRef](#)] [[PubMed](#)]
88. Orrico, F.; Möller, M.N.; Cassina, A.; Denicola, A.; Thomson, L. Kinetic and stoichiometric constraints determine the pathway of H₂O₂ consumption by red blood cells. *Free Radic. Biol. Med.* **2018**, *121*, 231–239. [[CrossRef](#)] [[PubMed](#)]
89. Nielsen, T.K.; Højgaard, M.; Andersen, J.T.; Poulsen, H.E.; Lykkesfeldt, J.; Mikines, K.J. Elimination of ascorbic acid after high-dose infusion in prostate cancer patients: A pharmacokinetic evaluation. *Basic. Clin. Pharmacol. Toxicol.* **2015**, *116*, 343–348. [[PubMed](#)]
90. Chen, C. Cytotoxicity of Ascorbate to Cancer Cells: Mathematical Modelling, Mechanisms and Clinical implications. PhD Thesis, School of Medicine, The University of Queensland, Queensland, Australia, 2015. [[CrossRef](#)]
91. Vissers, M.C.M.; Das, A.B. Potential Mechanisms of Action for Vitamin C in Cancer: Reviewing the Evidence. *Front. Physiol.* **2018**, *9*, 809. [[CrossRef](#)] [[PubMed](#)]
92. Grant, N.H.; Alburn, H.E. Fast Reactions of Ascorbic Acid and Hydrogen Peroxide in Ice, a Presumptive Early Environment. *Science* **1965**, *150*, 1589–1590. [[CrossRef](#)] [[PubMed](#)]
93. Deutsch, J.C. Ascorbic acid oxidation by hydrogen peroxide. *Anal. Biochem.* **1998**, *255*, 1–7. [[CrossRef](#)] [[PubMed](#)]
94. Poydock, M.E.; Reikert, D.; Rice, J.; Aleandri, L. Inhibiting effect of dehydroascorbic acid on cell division in ascites tumors in mice. *Exp. Cell Biol.* **1982**, *50*, 34–38. [[CrossRef](#)] [[PubMed](#)]
95. Poydock, M.E. Effect of combined ascorbic acid and B-12 on survival of mice with implanted Ehrlich carcinoma and L1210 leukemia. *Am. J. Clin. Nutr.* **1991**, *54*, 1261S–1265S. [[CrossRef](#)] [[PubMed](#)]
96. Toohey, J.I. Dehydroascorbic acid as an anti-cancer agent. *Cancer Lett.* **2008**, *263*, 164–169. [[CrossRef](#)] [[PubMed](#)]
97. Ferrada, L.; Salazar, K.; Nualart, F. Metabolic control by dehydroascorbic acid: Questions and controversies in cancer cells. *J. Cell Physiol.* **2019**, *234*, 19331–19338. [[CrossRef](#)] [[PubMed](#)]
98. Yun, J.; Mullarky, E.; Lu, C.; Bosch, K.N.; Kavalier, A.; Rivera, K.; Roper, J.; Chio, I.I.; Giannopoulou, E.G.; Rago, C.; et al. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. *Science* **2015**, *350*, 1391–1396. [[CrossRef](#)] [[PubMed](#)]
99. Ledinski, M.; Caput Mihalić, K.; Šimić Jovičić, M.; Ostojić, K.; Škibola, Z.; Kolundžić, R.; Urlić, I. Dehydroascorbic Acid Induces Cell Death in Sarcoma Stem Cells Under bFGF-Mediated Stemness-Supporting Conditions. *Antioxidants* **2025**, *14*, 1376. [[CrossRef](#)] [[PubMed](#)]
100. Winkler, B.S. Unequivocal evidence in support of the nonenzymatic redox coupling between glutathione/glutathione disulfide and ascorbic acid/dehydroascorbic acid. *Biochim. Biophys. Acta* **1992**, *1117*, 287–290. [[CrossRef](#)] [[PubMed](#)]
101. May, J.M. Recycling of vitamin C by mammalian thioredoxin reductase. *Methods Enzymol.* **2002**, *347*, 327–332. [[CrossRef](#)] [[PubMed](#)]
102. Flandrin, A.; Allouche, S.; Rolland, Y.; McDuff, F.O.; Richard Wagner, J.; Klarskov, K. Characterization of dehydroascorbate-mediated modification of glutaredoxin by mass spectrometry. *J. Mass. Spectrom.* **2015**, *50*, 1358–1366. [[CrossRef](#)] [[PubMed](#)]
103. May, J.M.; Mendiratta, S.; Hill, K.E.; Burk, R.F. Reduction of dehydroascorbate to ascorbate by the selenoenzyme thioredoxin reductase. *J. Biol. Chem.* **1997**, *272*, 22607–22610. [[CrossRef](#)] [[PubMed](#)]
104. Wells, W.W.; Xu, D.P. Dehydroascorbate reduction. *J. Bioenerg. Biomembr.* **1994**, *26*, 369–377. [[CrossRef](#)] [[PubMed](#)]
105. Huelin, F.E. Investigations on the stability and determination of dehydroascorbic acid. *Aust. J. Biol. Sci.* **1949**, *2*, 346–354. [[CrossRef](#)]
106. Bode, A.M.; Cunningham, L.; Rose, R.C. Spontaneous decay of oxidized ascorbic acid (dehydro-L-ascorbic acid) evaluated by high-pressure liquid chromatography. *Clin. Chem.* **1990**, *36*, 1807–1809. [[CrossRef](#)] [[PubMed](#)]
107. Dewhirst, R.A.; Fry, S.C. The oxidation of dehydroascorbic acid and 2,3- diketogulonate by distinct reactive oxygen species. *Biochem. J.* **2018**, *475*, 3451–3470. [[CrossRef](#)] [[PubMed](#)]
108. Linetsky, M.; Shipova, E.; Cheng, R.; Ortwerth, B.J. Glycation by ascorbic acid oxidation products leads to the aggregation of lens proteins. *Biochim. Biophys. Acta* **2008**, *1782*, 22–34. [[CrossRef](#)] [[PubMed](#)]
109. Nemet, I.; Monnier, V.M. Vitamin C degradation products and pathways in the human lens. *J. Biol. Chem.* **2011**, *286*, 37128–37136. [[CrossRef](#)] [[PubMed](#)]
110. Ancy, P.-B.; Contat, C.; Meylan, E. Glucose transporters in cancer—From tumor cells to the tumor microenvironment. *FEBS J.* **2018**, *285*, 2926–2943. [[CrossRef](#)] [[PubMed](#)]
111. Kelley, P.M.; Njus, D. Cytochrome b561 spectral changes associated with electron transfer in chromaffin-vesicle ghosts. *J. Biol. Chem.* **1986**, *261*, 6429–6432. [[CrossRef](#)] [[PubMed](#)]
112. Peskin, A.V.; Magon, N.J.; Bozonet, S.M. High-dose vitamin C blocks HOCl production by Myeloperoxidase: A potential therapeutic strategy. *Biochem. Biophys. Res. Commun.* **2025**, *776*, 152213. [[CrossRef](#)] [[PubMed](#)]
113. Regulus, P.; Desilets, J.F.; Klarskov, K.; Wagner, J.R. Characterization and detection in cells of a novel adduct derived from the conjugation of glutathione and dehydroascorbate. *Free Radic. Biol. Med.* **2010**, *49*, 984–991. [[CrossRef](#)] [[PubMed](#)]
114. Larisch, B.; Pischetsrieder, M.; Severin, T. Reactions of dehydroascorbic acid with primary aliphatic amines including α -acetyllysine. *J. Agric. Food Chem.* **1996**, *44*, 1630–1634. [[CrossRef](#)]

115. Ahuie, G.K.; Gagnon, H.; Pace, P.E.; Peskin, A.V.; Wagner, R.J.; Naylor, S.; Klarskov, K. Investigating protein thiol chemistry associated with dehydroascorbate, homocysteine and glutathione using mass spectrometry. *Rapid Commun. Mass. Spectrom.* **2020**, *34*, e8774. [[CrossRef](#)] [[PubMed](#)]
116. Loubane, G.; Robert, G.; Firdaus, S.B.; Robidas, R.; Comeau, C.; Boudreault, P.L.; Komba, J.E.; Gagnon, H.; Wagner, J.R.; Naylor, S.; et al. Structural characterization of a L-dehydroascorbic acid-L-homocysteine thiolactone reaction product: Intracellular formation in neuronal cells. *Biochim. Biophys. Acta Gen. Subj.* **2026**, *1870*, 130882. [[CrossRef](#)] [[PubMed](#)]
117. Xie, H.; Wei, L.; Wang, Q.; Tang, S.; Gan, J. Elevated serum homocysteine levels associated with poor recurrence-free and overall survival in patients with colorectal cancer. *Sci. Rep.* **2024**, *14*, 10057. [[CrossRef](#)] [[PubMed](#)]
118. Agus, D.B.; Vera, J.C.; Golde, D.W. Stromal cell oxidation: A mechanism by which tumors obtain vitamin C. *Cancer Res.* **1999**, *59*, 4555–4558. [[PubMed](#)]
119. Lee, Y. Role of Vitamin C in Targeting Cancer Stem Cells and Cellular Plasticity. *Cancers* **2023**, *15*, 5657. [[CrossRef](#)] [[PubMed](#)]
120. Winterbourn, C.C.; Metodiewa, D. Reactivity of biologically important thiol compounds with superoxide and hydrogen peroxide. *Free Radic. Biol. Med.* **1999**, *27*, 322–328. [[CrossRef](#)] [[PubMed](#)]
121. Peskin, A.V.; Winterbourn, C.C. The Enigma of 2-Cys Peroxiredoxins: What Are Their Roles? *Biochemistry* **2021**, *86*, 84–91. [[CrossRef](#)] [[PubMed](#)]
122. Heath, S.G.; Gray, S.G.; Hamzah, E.M.; O'Connor, K.M.; Bozonet, S.M.; Botha, A.D.; de Cordovez, P.; Magon, N.J.; Naughton, J.D.; Goldsmith, D.L.W.; et al. Amyloid formation and depolymerization of tumor suppressor p16^{INK4a} are regulated by a thiol-dependent redox mechanism. *Nat. Commun.* **2024**, *15*, 5535. [[PubMed](#)]
123. Zhao, D.; Meng, Y.; Dian, Y.; Zhou, Q.; Sun, Y.; Le, J.; Zeng, F.; Chen, X.; He, Y.; Deng, G. Molecular landmarks of tumor disulfidptosis across cancer types to promote disulfidptosis-target therapy. *Redox Biol.* **2023**, *68*, 102966. [[CrossRef](#)] [[PubMed](#)]
124. Deng, X.; Zhang, C.; Xie, J.; Tang, B.; Tan, X.; Zou, Y. Disulfidptosis in cancer: From redox stress to therapeutic strategy. *Cancer Gene Ther.* **2026**, *33*, 22–25. [[PubMed](#)]
125. Hsuanyu, Y.; Dunford, H.B. Oxidation of clozapine and ascorbate by myeloperoxidase. *Arch. Biochem. Biophys.* **1999**, *368*, 413–420. [[CrossRef](#)] [[PubMed](#)]
126. Klebanoff, S.J.; Kettle, A.J.; Rosen, H.; Winterbourn, C.C.; Nauseef, W.M. Myeloperoxidase: A front-line defender against phagocytosed microorganisms. *J. Leukoc. Biol.* **2013**, *93*, 185–198. [[CrossRef](#)] [[PubMed](#)]
127. Folkes, L.K.; Candeias, L.P.; Wardman, P. Kinetics and mechanisms of hypochlorous acid reactions. *Arch. Biochem. Biophys.* **1995**, *323*, 120–126. [[CrossRef](#)] [[PubMed](#)]
128. Ohshima, H.; Tatemichi, M.; Sawa, T. Chemical basis of inflammation-induced carcinogenesis. *Arch. Biochem. Biophys.* **2003**, *417*, 3–11. [[CrossRef](#)] [[PubMed](#)]
129. Malle, E.; Furtmüller, P.G.; Sattler, W.; Obinger, C. Myeloperoxidase: A target for new drug development? *Br. J. Pharmacol.* **2007**, *152*, 838–854. [[CrossRef](#)]
130. Gruning, N.M.; Ralser, M. Cancer: Sacrifice for survival. *Nature* **2011**, *480*, 190–191. [[PubMed](#)]
131. Kent, E.E.; Ambs, A.; Mitchell, S.A.; Clauser, S.B.; Smith, A.W.; Hays, R.D. Health-related quality of life in older adult survivors of selected cancers: Data from the SEER-MHOS linkage. *Cancer* **2015**, *121*, 758–765. [[PubMed](#)]
132. Huang, I.C.; Bhakta, N.; Brinkman, T.M.; Klosky, J.L.; Krull, K.R.; Srivastava, D.; Hudson, M.M.; Robison, L.L. Determinants and Consequences of Financial Hardship Among Adult Survivors of Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study. *J. Natl. Cancer Inst.* **2019**, *111*, 189–200. [[PubMed](#)]

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