

## Ascorbic Acid, Still Controversial in Using against Cancer Resistance?

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## Abstract

Ascorbic acid is a known strong antioxidant and is evident to exert a pro-oxidative effect of high concentration/dose. Therefore, it can be used not only as a protective agent, but also as an adjuvant or direct cytotoxic agent. Resistance of cancer cells is a regular matter, stimulating scientist to search fighting tools against it. Evidences suggest that the use of ascorbic acid in cancer resistance is still controversial. This paper sketches a current scenario of ascorbic acid in cancer resistance, especially resistance occurring from chemotherapy and radiotherapy. Although, hopes are alive with the use of this vitamin in this case, but more research is needed to understand the fact clearly.

**Keywords:** Dietary Supplements, Cancer Resistance, Perspective.

## Introduction

Ascorbic acid (AA) (also known as vitamin C) is a vitamin found in many foods and used as a dietary supplement. It is well-known for its antioxidant activity and can be used as a prooxidant, chemo preventive agent as well as adjuvant in the cancer therapy [1,2]. However, the effect of AA supplementation on cancer is still controversial, although a number of earlier reports suggesting its applicability in cancer therapy, especially in radiation and chemo-resistant carcinoma [3-5]. This paper sketches a current scenario of this vitamin in cancer resistance.

## AA against cancer resistance

Cercek and Cercek suggested that tumors pre-treated with other drugs become resistant to growth inhibitory effects of ascorbate ions such as YMDR cells resistant to the antitumor drug methylenedimethanesulphonate (MDMS), HeLa cells pre-treated with colcemid, and YMDS cells pretreated with cytochalasin B [6]. In a study, liver tumor resistant to oncovin, in a separate pre-treatment with AA or vitamin K3 alone was without any effect [7]. However, the acquired vincristine resistance of the PC-9/VCR cell line was partially reversed by AA along with the reduced drug accumulation, higher efflux rate, and increased in drug uptake. In contrast, AA had no effect on drug tolerance in either PC-9 parental cells or known multidrug-resistant (MDR) cells. AA may act via P-glycoprotein-mediated MDR mechanism [8]. A similar result was also observed by Song et al. with a nontoxic concentration of L-ascorbic acid (25 µg/mL) [9]. In human neuroectodermal cells SK-N-BE (2) AA (10 nM-1 mM) showed 43% cell death resistant.

The cell death observed suggests a pro-oxidant, rather than an anti-oxidant role AA [10]. The ability of human cells to regenerate AA

from dehydroascorbate is partially dependent on the glutathione redox status of the cell and the relative activity of dehydroascorbate reductases. The antioxidant role of AA was also seen in adriamycin-resistant human breast tumor cells (MCF-7 ADRR), where normal cell viability was observed with the increased ascorbate-dehydroascorbate levels than the drug-sensitive cells [11]. As a prooxidant, AA is evident to induce cytotoxic effect through hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>)-based mechanism. For an example, U937 cells resistant to H<sub>2</sub>O<sub>2</sub> were also cross-resistant to ascorbic acid [12]. Ascorbic acid at 10<sup>2</sup>-10<sup>3</sup> µM was found to increase the cytotoxicity in complete doxorubicin-resistant, moderate-cisplatin resistant and in sensitive paclitaxel two human breast carcinoma cell lines, MCF-7 and MDA-MB-231, possibly by synergistic effect [13]. Generally, the cells with high catalase activity are resistant to pro-oxidant concentrations of ascorbate since catalase can decompose H<sub>2</sub>O<sub>2</sub> induction by the auto-oxidation of ascorbate in cells [14]. Thus, this physiological antioxidant may help the cancer cells to grow resistance to it. The melanoma cells may contribute to the intrinsic drug resistance. In this category cells, the gamma-glutamyltransferase-over expressing clone was found to exhibit a low susceptibility to As<sub>2</sub>O<sub>3</sub>-induced apoptosis, associated with low reactive oxygen species induction and increased catalase activity. AA (subtoxic concentrations) co-treated with As<sub>2</sub>O<sub>3</sub> resulted sensitization in apoptotic cell death [15]. The cancer cells are more sensitive to ascorbate/menadione than healthy cells because of their lack of antioxidant enzymes, mainly catalase. The mechanism underlying this cytotoxicity involves the oxidative cleavage of Hsp90 with a subsequent loss of its chaperone function, thus leading to degradation of wild-type and mutated Bcr-Abl protein [16].

Sakagami et al suggested that human peripheral blood lymphocytes and polymorphonuclear cells, resistant to ascorbate were found to sensitive to the *Acer nikoense* Maxim. Extract, or a combination of

them. The extracts may stimulate the degradation of ascorbates *via* ascorbyl radical production and increases the incidence of cytotoxic activity of ascorbate [17]. On the other hand, the glioblastoma multiform tumor (T98G) cells were found in more resistant to ascorbate analogs than human renal carcinoma (TC-1) and HL-60 cells, possibly due to higher intracellular glutathione concentrations. It may be due to the reduced cyclic adenosine monophosphate (cAMP) activity in the T98G cells than the others [18]. But, AA (1,000 mg/day) was found to enhance the activity of arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) (0.25 mg/kg/day) against drug-resistant multiple myeloma (MM) *in vitro* by depleting intracellular glutathione (GSH) [19]. Furthermore, co-administration of AA and vitamin K3 may increase cytotoxic effects in tumor cells and increase the lifespan of animals, while AA and vitamin D synergized with the anti-tumor effects of therapeutic genes driven by hOC increased cytotoxicity in advanced renal cell carcinoma cells [20,21].

AA in KCL22/SR cells overcome resistance to imatinib, possibly via inhibition of nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated gene expression [22]. On the other hand, ascorbate pretreatment enhanced the efflux of the multidrug resistant protein (MRP) substrate, carboxy-2',7'-dichlorofluorescein (CDF), and it prevented the 4-hydroxy-2(E)-nonenal (HNE)-induced inhibition of CDF export from THP-1 cells, suggesting that the protective effect of ascorbate against HNE cytotoxicity is through modulation of MRP-mediated transport of GSH-HNE conjugate metabolites [23].

AA was found to enhance quinone 8 (a phenylaminopyrimidoisoquinolinequinones)-mediated cytotoxicity in quinone 8 resistant human leukemia K562 cells [24]. Glioblastoma multiforme (GBM) has a very poor prognosis because of its chemo- and radiation therapy resistance. Ascorbate at 5 mM caused inhibition of G2/M arrest in GBM cells and prevented radiation-induced G2/M arrest in combined treatment [25]. The effects of AA surely depend on its concentration. In a study, the breast carcinoma cell line BT-20 highly resistant to the exposure to AA at low concentration, silenced with specific sh-RNA, become susceptible to high concentrations of AA (50 and 100 mmol/L) [26].

Labile iron (iron that is weakly bound and is relatively unrestricted in its redox activity) can be used in cancer treatment, as labile iron may contribute to their mechanism of action through pharmacological ascorbate and ionizing radiation. Generally, labile iron enhances the rate of formation of H<sub>2</sub>O<sub>2</sub> and can also react with H<sub>2</sub>O<sub>2</sub>. In a study, both pharmacological ascorbate and irradiation were found to increase the labile iron in tumor homogenates in a murine model of pancreatic cancer [27]. Moreover, the manganoporphyrins (MnPs) in combination with pharmacologic ascorbic acid was found to increase cytotoxic efficacy in pancreatic cancer [28]. AA was also evident to reduce pain and increase in survival rate when compared to the control group in radiotherapy-resistant retrospective cohorts [29]. It also exhibited strong cytotoxicity against the vemurafenib-resistance cell line A2058, however, at low concentrations it promoted cell growth, migration and cell cycle progression, and protected against mitochondrial stress [30]. However, in clinical trials phase II, an infusion with 5-60 g of AA did not induce anticancer activity against metastatic castration-resistant prostate cancer (mCRPC) in a 12 week treatment [31].

### Conclusive talks

From the above findings, it can be demonstrated that, the activity of

AA is concentration or dose dependent. At low concentration it is an antioxidant (cytoprotective) while cytotoxic at high. The cytotoxic activity of this vitamin may be due to its pro-oxidative effects in cells. However, the activity of it may be interfered with the action of physiological antioxidants (e.g. - catalase and glutathione); protein kinase (e.g. - cAMP), liable iron, or other drugs or chemicals.

Most of the anticancer drugs and radiation therapy act through induction of oxidative stress in cancer cells. In some studies, AA was found to act against radiation-resistant tumor cells. It may be the further proof of this vitamin's potent reducing capability. Although, the applications of AA in overcoming cancer resistance are still controversial, but many of the evidence suggest positive results, especially with pharmacological dose. More research is highly appreciated to confirm the applicability of ascorbic acid in the prevention and treatment of cancers and overcome of cancer resistance.

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