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Review

Ascorbic acid and its pro-oxidant activity as a therapy for tumours of oral cavity – A systematic review

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ABSTRACT

Background: Ascorbic acid or Vitamin C is a potent dietary antioxidant with a double faced character, in that it exhibits a pro-oxidant activity arising from its routine antioxidant property that generates reactive free radicals, which induce cytotoxic effects at pharmacologic concentrations. A systematic review of this effect of ascorbic acid in the oral tumours and normal oral tissues would clearly elucidate the merits or demerits of employing vitamin C in treating the same.

Objective: The aim of our systematic review is to critically review the studies reported in literature that have studied the pro-oxidant activity of ascorbic acid as a therapeutic option for treatment of oral neoplasms and its effects on normal oral cells.

Methods: Articles were searched in PUBMED, MEDLINE using appropriate key words like ''ascorbic acid'', ''pro-oxidant activity'', ''treatment'', ''oral neoplasms''. Hand search of Journals was also performed. Articles were reviewed and analysed.

Results: The search strategy included 17 potentially relevant articles for review of which, 12 were in vitro studies; 3 were in vivo animal studies; 1 was in vivo human study and 1 was ex vivo human study. The optimum concentration of ascorbic acid used to produce potential pro-oxidant associated cytotoxic effects was found to be 3–5 mM in vitro, 0.88–5 mM in vivo animals, 0.5–2 mM ex vivo in humans, and the corresponding effects are induction of apoptosis (caspase activation), necrosis, free radical formation, H_2O_2 generation, and DNA fragmentation. In contrast, the same pro-oxidant concentrations had no effect on the normal cells.

Conclusion: The results of our systematic review show that the pro-oxidant activity of pharmacologic ascorbic acid is a part of its dose-dependent bimodal activity and is a result of the proposed Fenton mechanism. In vitro, animal and ex vivo studies of pharmacologic ascorbic acid (AA) have yielded meritorious results proving vitamin C as an effective cytotoxic agent against oral neoplastic cells with potentially no harming effects on normal cells. However, a shortage of clinical trials and in vivo human studies pertaining to evaluation of anti-tumour activity of vitamin C in tumours of oral cavity remains a lacuna in concluding ascorbic acid as a beneficial therapeutic option in treatment of oral neoplasms.

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Contents

1. Background

Ascorbic acid or Vitamin C is a water soluble vitamin that has gained importance over years by distinguishing itself from the rest by exhibiting a spectrum of biological functional properties. Vitamin C is a dietary antioxidant, classified under the group of primary or natural antioxidants.[1] While lower vertebrates having the ability to self-synthesize the vitamin, apes and humans cannot synthesize Ascorbic acid due to the lack of an enzyme gulonolactone oxidase that catalyzes the terminal step in the synthesis of L-ascorbic acid from the substrates, D-glucose or D-galactose.[2]

The chemical name of ascorbic acid is 2-oxo-L-threo-hexono-1,4-lactone-2,3-enediol and it exists in two major dietary forms: L-ascorbic acid, a reduced form and dehydroascorbic acid (DHA), an oxidised form. Ascorbic acid is readily absorbed by active transport in the intestine. A body pool of 1.2–2.0 g of ascorbic acid is maintained by intake of 75 mg/day. Its average half life in adult human is about 10–20 days. The main route of elimination is through urine and the major metabolites are DHA, 2,3-ketogulonic acid and oxalic acid.[2]

1.1. *Antioxidant ascorbic acid*

Ascorbic acid is a potent antioxidant or reducing agent that is capable of scavenging free radicals of reactive oxygen and nitrogen species (ROS and RNS) that have potential to damage nucleic acids and promote carcinogenesis.[3,4] The physiological functions are largely dependent on its oxido-reductive properties. The ascorbate reacts with ROS, quenches them and gets converted into poorly reactive semi-hydroascorbate radical. Therefore ascorbate efficiently decreases in vivo damage to proto-oncogenes and tumour suppressor genes, thereby reducing the risk of cancer by suppressing the oxidative stress induced by reactive free radicals.[3]

1.2. *Pro-oxidant ascorbic acid*

Ascorbic acid presents a double faced character in that it exhibits a pro-oxidant activity arising from its routine antioxidant property. Apart from reducing oxidising sources like H_2O_2, ascorbate also reduces metal ions like Fe^{3+} and Cu^{3+}, the process during which free radicals are generated. This reaction in which ascorbate generates highly reactive free radicals in presence of transition metal ions is called Fenton reaction.[2,5]

$$2Fe^{3+} + \text{Ascorbate} \rightarrow 2Fe^{2+} + \text{DHA}$$

$$2Fe^{2+} + 2H_2O_2 \rightarrow 2Fe^{3+} + 2OH^- + 2OH*$$

These hydroxyl radicals are reported to interact with DNA inducing its damage by causing breaks in phosphodiester backbone and modification of DNA bases.[3] This property of pro-oxidant activity inducing cytotoxicity has been employed in many studies in the prevention and treatment of cancers and is proposed to be dose-dependent. On the other hand, there are existing controversies questioning the activity of ascorbic acid whether, it is beneficial in the treatment of tumours or antagonizes the oxidative stress induced by traditional therapeutics by providing antioxidant protection to tumour cells.

1.3. *Review of literature*

Mamede et al.[4] and Naidu[2] stated that the ROS generated in response to high concentration of vitamin C can catalyze lipid peroxidation and are cytotoxic to cancer cells; the concept that was also advocated by Verrax and Calderon.[6] Koch and Baiglow[7] also reported this activity results in damage to cell membranes and DNA, unless neutralized by catalase. Benade et al.[8] suggested that tumour cells are often catalase deficient, thereby being more sensitive to H_2O_2 than normal cells. Augus et al.[9] and Langemann et al.[10] reported accumulation of vitamin C at high concentrations in solid tumours than in normal surrounding cells.