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What are the Mechanisms by which Vitamin C Can Relieve Stress?

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Abstract **Review Article**

Vitamin C (ascorbic acid) is a vitamin that can dissolve in water, important in acting against oxidative stress, and acts as co-mediator for biosynthesis carnitine and collagenous fibers, and the anabolism and catabolism of catecholamine, and in addition to its impact on the gut absorption of iron. Human has no ability of manufacturing ascorbic acid. Green leafy vegetables, potatoes, tomatoes, berries, and citrus fruits are major suppliers for vitamin C. It was found that ascorbic acid plays a major role in relieving stress and many disorders related to it like anxiety and depression. Three major mechanisms have been used to explain the anti-stress impact of vitamin C, they include: antioxidative effects, anti-inflammatory effects, and direct effect on hypothalamus-pituitary-adrenal (HPA). This article tries to answer the questions about the mechanisms by which vitamin C can relieve stress and enhance disorders related to stress.

Keywords: vitamin C, ascorbic acid, stress, oxidative stress, anxiety, depression.

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INTRODUCTION

Ascorbic acid is the familiar name of vitamin C, an vitamin that can dissolve in water, important in acting against oxidative stress. Vitamin C can be found in Turnip, citrus fruits and Brussels sprouts among many other sources. Tomato, strawberry, red pepper, green pepper, Indian gooseberry and various green vegetables are rich in Vitamin C. Animal sources typically have low levels of Vitamin C which range between 30 to 40 milligrams per 100 grams; thus, plant sources gain importance owing to their high content that can go up to 5 grams per 100 grams. Absorption takes place in oral cavity by simple diffusion but in the stomach and intestine it occurs through active transport using transporters that depend Na to transport ascorbic acid (Chambial *et al*., 2013).

Vitamin C is essential to humans and many other mammals. While astonishingly, global intake of ascorbic acid declines annually, leading to an increase in number of diseases caused by ascorbic acid deficiency within the population. The active form of the anion-based ascorbic acid acts as a free radical cleaners known for reacting with free radicals— such as hydrogen peroxide— to protect macromolecules from oxidative impact by helping maintain an indirect antioxidant action along with participation in plasma membrane oxidant/antioxidant homeostasis; this is done through generation of vitamin E (AL-Ma'atheedi and Hassan, 2012: Gospe *et al*., 2018).

The majority of animals and almost all plants use glucose to produce ascorbic acid, while humans and other primates, in addition to a few species of bats, guinea pigs, and teleost fish are unable to produce ascorbic acid. It is worth mentioning that certain mammals carry a gene that does not function properly for L -gulono - γ -lactone oxidase (GULO), which is an enzyme essential in the final stage of ascorbic acid production which means their only source of ascorbic acid is through their diet (Luibil *et al*., 2023).

The stress response is an ancient evolutionary feature: its primary role is to boost the survival prospects of the species. Among mammals, this response entails triggering the HPA axis and SAS in addition to ramping up production as well as release of vitamin C. These three components— vitamin C, catecholamines and cortisol— work hand in hand by boosting hemodynamic reserve (which helps in maintaining blood pressure), ensuring optimal immune function while also protecting the host

from damage resulting from excessive oxidants. It is only humans (together with other anthropoid apes) that have lost this capability to produce their own ascorbic acid; thus, leading to what can be described as having a flawed stress response system. This flaw becomes critically important among septic humans. However, there has been some success reported where treatment involving administration of vitamin C led to restoration of normal stress responses which in turn translated into improved outcomes on survival for those humans under stressors (Carr *et al*., 2022).

Several studies have shown the impacts of ascorbic acid intake in relieving stress; Al-fahham (2019) investigated the impact of vitamin C intake on public speaking stress, and found that subjects supplemented with vitamin C have exhibited less stress indicators and decreased blood pressure and heart rate; Ghafel (2021) observed that vitamin C perform as effective immunomodulator and antioxidant action to decrease psoriasis severity; Aburahma and Hasan (2023) found that there is a deficiency in vitamin C in patients with rheumatoid arithritis.

Three major mechanisms have been used to explain the anti-stress impact of vitamin C, they include: antioxidative effects, anti-inflammatory effects, and direct effect on hypothalamus-pituitary-adrenal (HPA).

Mechanisms of Vitamin C in relieving stress antioxidative effects

Recent research has indicated that oxidative stress could be the cause behind some neuropsychological disorders. Antioxidants could be of considerable help in containing the damage caused by oxidative stress— especially for individuals who fall prey to anxiety. Hence it was proposed, within this framework, that oral intake of vitamin C would lower anxiety as it is a good antioxidant among other things. The acidity works well with neutralizing free radicals while its penetration into aqueous compartments helps protect molecules from oxidations; these combined effects result in prevention of oxidation to major biological molecules like lipid or protein (de Oliveira *et al*., 2015; Alani *et al.*, 2021).

The functions of vitamin C are largely dependent on its chemical structure, as it serves as a co-factor for various enzymes involved in the synthesis of important compounds in the body. Vitmain C helps in collagen production by facilitating the hydroxylation reactions during which it maintains metal ions at the enzyme's active center in their reduced states also optimizing activities of both oxygenase and hydroxylase enzymes. This makes vitamin C essential since collagen itself forms major part of body protein besides acting as structural protein and participating in many biological functions; therefore any factor affecting synthesis or maintenance would result into clinical manifestation called scurvy (May *et al*., 2005).

Vitamin C is a widely recognized reducing agent that easily undergoes one-electron acceptation to produce the ascorbyl radical. The ascorbyl radical tends to be unreactive due to molecular stabilization. When two molecules of ascorbyl radicals interact, they each produce an ascorbate molecule — one of them becomes dehydroascorbate (DHA), which is the 2-electron oxidized form of ascorbate. Extracellular DHA can enter glucose transporters and then is followed by reduction in vitamin C by cytosolic thioltransferase enzymatic systems. DHA, having been reduced back at physiological pH— if not degraded into metabolites — eliminates in urine generation thereby depleting cells of vitamin C since it is critical at normal pH and does not undergo back reduction to ascorbic acid, so that it is easily degraded (Turvey & Golden, 2012).

The data concerning vitamin C and its influence on oxidative DNA damage have been found to be conflicting. The differences can be attributed to the various methodologies used in the experiments. Evidence of data using biomarkers of oxidative damage of DNA bases in human lymphocytes in vitro does not compellingly support the conclusion that supplementation with vitamin C could lower the level of oxidative DNA damage— just as there are also no data from studies of strand breaks to be conclusive for a protective effect of ascorbic acid. The evidence appears more protective because consumption of food containing vitamin C (vegetables and fruits) has more positive effects in decreasing oxidative DNA damage to human cells recent studies indicate that Vitamin C is much more than just an antioxidant as it regulates the expression of some genes participating in apoptosis or DNA repair processes (Satterfield and Chambers, 2022; Faik and Mustafa 2023).

Anti-inflammatory Effects

Many different biochemical mechanisms have been suggested to account for the development of brain disorders, one of which is high inflammatory response. A previous meta-analysis of 107 studies found that there were higher systemic inflammatory indicators in individuals with depression than healthy subjects. The argument that inflammatory response might be involved in the pathogenesis and maintenance of prenatal depression is therefore reasonable, as indicated by the findings on systemic inflammation that may connect prenatal depression with such adverse pregnancy outcomes as gestational diabetes, preterm birth and pre-eclampsia. Hence it would be prudent to gain a more complete understanding of psychoimmunology during pregnancy so as not only to reduce the burden of mental illness at this special time but also increase chances for successful pregnancy outcome (Ravi *et al*., 2022).

Vitamin C is well-known as a co-factor possessing several anti-inflammatory characteristics; therefore, it is considered that its intake leads to decreased activity of C-reactive protein (CRP) which is

a stable downstream biomarker of inflammatory response in serum. Anyhow, an evaluation of the received findings reveals that activity of the vitamin does not have unambiguous effects — according to one group the level of CRP in human plasma is greatly decreased by ascorbic acid supplement (leading to a 4 times increase in ascorbate concentration in plasma) while according to others there is no effect on CRP by the vitamin. In addition, there is no reliable information available about the impact of ascorbate on plasma anti/pro-inflammatory cytokines. This is because it is typically used in combination with other protective molecules — such as 25-hydroxyvitamin D, β-carotene, or α-tocopherol— that greatly reduce pro-inflammatory molecules like interferon-γ (IFN-γ) or interleukin 6 (IL-6). And at the same time irregularly influence the levels of anti-inflammatory IL-4 in human serum (Gęgotek & Skrzydlewska, 2022).

Some data suggests that ascorbic acid because of its anti-inflammatory properties, it is very useful in fighting stress. Studies have shown that administration of vitamin C leads to lowering of inflammation biomarkers, which include IL-6 (interleukin-6) and CRP (C-reactive protein) — pro-inflammatory cytokines— in individuals with high levels of inflammation. The exact mechanisms are unclear but the anti-oxidentive role of vitamin C might be important because a relationship between inflammation and oxidative stress can be identified as a common feature in many diseases— among them depression (Carr *et al*., 2023).

Low mood and depression are the result of Vitamin C deficiency, but in our cohort no associations were found between the several mood scores and vitamin C status during baseline. This can be explained by a low presence of hypovitaminosis C and an absence of deficiency altogether due to the fact that most participants were from middle to high income groups. Therefore, further research looking into the association between Vitamin C and prenatal depression or anxiety has to be done with populations at risk of Vitamin C deficiency— for example those from low socioeconomic strata or those having higher body weight at baseline (Carr *et al*., 2022).

Direct Effects on HPA

The production of gucocorticoid (GC) is controlled through physiologic negative feedback: the GC-mediated negative feedback is thought to be affected in many pathological conditions. The failure of negative feedback at the level of the hypothalamus-pituitary-adrenal (HPA) axis in many disorders results from excessive production of reactive oxygen species (ROS)— but while this does imply effects on HPA functionality under normal conditions, little else is known about ROS effects during homeostasis! This work looked at puttingatively modulating antioxidants to see their impact on HPA activity along with how they modulate GC-mediated negative feedback upon HPA cascade (Prevatto *et al.*, 2017).

The HPA axis is a part of the neuroendocrine system, controlled by stress and circadian cycle. Neurons in the paraventricular nucleus of the hypothalamus are stimulated to secrete corticotropin-releasing hormone (CRH) through hypothalamic-pituitary portal circulation after POMC is cleaved from ACTH upon CRH stimulation at pituitary corticotrophic cells. ACTH then acts on MC2R located in adrenals which later results into production glucocorticoids (Papadimitriou & Priftis, 2009).

Stress response is mainly controlled by two systems: the HPA axis and the sympathoadrenal system (SAS). While not widely acknowledged, high release of vitamin C from the liver and adrenal likely have significant contributions towards coordinating the stress response. HPA axis activation leads to ACTH release by the anterior pituitary along with cortisol synthesis and subsequent release. SAS trigger results in epinephrine and norepinephrine secretion from adrenal medulla and sympathetic nerves. The elevated levels of cortisol and catecholamines act through different mechanisms— enhancing cardiovascular reserve plus providing glucose/lactate fuel — to ensure proper functioning of skeletal muscles, heart and brain, which enable organism take appropriate action (flight or fight). Vitamin C has various biological functions (Marik, 2020).

The capacity of an animal to synthesize vitamin C endogenously is inversely related to its cortisol response when stressed. This hints at the importance of heightened synthesis and release of vitamin C as part of the stress response— where ascorbic mutants try to make up for their inability to produce the vitamin by elevating cortisol levels. The lack of vitamin C synthesis during stress situations puts mutant humans at a higher risk for negative outcomes during all types of stresses— psychological and physiological alike. In a experimental study, Brody *et al*., showed that oral vitamin C reduced cortisol, blood pressure, and subjective responsivity to psychological stress in human subjects (Brody *et al*., 2002).

This essential vitamin for glucocorticoid synthesis is ascorbic acid, which acts as a cofactor for enzymes located in the cortex of the adrenal gland and involved in the pathway glucocorticoid synthesis. As an instance, ascorbic acid serves as a cofactor for 11β - hydroxilase, which helps in enhancing the transformation of 11 - deoxycortisol to cortisol by moderate degree hence keeping cortisol tone at physiological conditions. The high levels of ascorbic acid in adrenal gland — and its secretion upon ACTH stimulation — point to the possible involvement of ascorbic acid in stress response (Bo *et al*., 2024).

Supplementation of vitamin C is effective in easing behavioral dysfunctions resulting from stress. Moreover, excessive release of cortisol was reported in guinea pigs made shortage in ascorbic acid. Interestingly rats which can manufacture ascorbic acid had lower levels of vitamin C both in the CNS (cerebral cortex) and adrenal glands during a chronic stress protocol (hypercortisolemia condition) when compared to animals with no stress (Afifi & Embaby, 2016).

CONCLUSIONS

Vitamin C (ascorbic acid) is a vitamin that can dissolve in water, important in acting against oxidative stress, and acts as co-mediator for biosynthesis carnitine and collagenous fibers, and the anabolism and catabolism of catecholamine, and in addition to its impact on the gut absorption of iron. Human has no ability of manufacturing ascorbic acid. Green leafy vegetables, potatoes, tomatoes, berries, and citrus fruits are major suppliers for vitamin C. It was found that ascorbic acid plays a major role in relieving stress and many disorders related to it like anxiety and depression. Three major mechanisms have been used to explain the anti-stress impact of vitamin C, they include: antioxidative effects, anti-inflammatory effects, and direct effect on hypothalamus-pituitary-adrenal (HPA).

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