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Review Article

Vitamin C as a modulator of stress-induced impairments in immunity, reproduction and productivity in ruminants: A review

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Abstract

Ruminants have the innate ability to synthesize vitamin C (Ascorbic acid, VC) in their liver, often encounter a state of conditional deficiency during periods of significant physiological, environmental, and metabolic stress. This shortage occurs when the hepatic synthetic capacity is overburdened by the resultant demand for this powerful antioxidant, which is essential in preventing oxidative stress, a shared mechanism for the adverse effects of stressors like heat, parturition, transportation, and weaning. This review evaluates existing evidence for the beneficial effects of vitamin C supplementation in ruminants under different stressors. In this article, we reviewed the mechanisms by which VC, as an antioxidant and enzymatic cofactor, augments immune defenses by enhancing neutrophil migration, phagocytosis, and lymphocyte proliferation; aids reproductive function through sparing of ovarian function and embryonic development; and maintains productivity by optimizing nutrient partitioning in stress. This review critically assesses the pragmatic implications of supplementation, such as the advantage of rumen-protected over unprotected oral treatment, the need for prophylactic treatment, and the synergistic advantage of co-administration of VC with other antioxidants, such as vitamin E. Additionally, the review points out important gaps in research, e.g., the availability of precise, stressor-specific dosage guidelines, elucidation of molecular mechanisms, and long-term economic justification. We conclude that strategic VC supplementation has obvious potential as a stress ameliorant in ruminants under acute and chronic stress. VC is an important facilitator of ruminant resilience, welfare, and the sustainability of production systems. Future research focused on addressing these gaps will be essential for optimizing its application in precision ruminant nutrition.

Keywords: Oxidative stress, Production, Reproduction, Ruminant, Vitamin C

Highlights

- Ruminants' endogenous VC synthesis may be insufficient during high physiological stress
- VC supplementation enhances neutrophil and lymphocyte activity, boosting immune responsiveness
- VC supplementation protects ovarian follicles, uterus, and placental membranes under stress
- VC helps maintain nutrient partitioning, supporting productivity in challenged ruminants
- Review identifies key coverage of mechanisms, administration routes, and research gaps

INTRODUCTION

Ruminant production systems consistently expose animals to a myriad of stressors that challenge homeostasis and entail substantial economic losses and welfare issues. The stressors are complex, involving environmental stresses like thermal stress (heat and cold), management practices like transportation, weaning, and overcrowding, and endogenous physiological challenges like parturition and elevated metabolic production in lactation (Bernabucci et al., 2010). Under these conditions of stress, homeostasis in the animal is disturbed, inducing adaptive changes that, when chronic, will be maladaptive (Asres & Amha, 2014). An essential impact of this imbalance is excess production of reactive oxygen species (ROS), inducing oxidative stress. This compromises immunity, reduces fertility, affects growth and milk yields, and results in direct economic losses for farmers (Celi, 2010; Alberghina et al., 2024). The financial implications are significant, due to lowered growth rates, milk production, reproductive efficiency, susceptibility to infectious disorders (e.g., mastitis, bovine respiratory

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disease), and higher mortality rates (Sordillo, 2016). At the same time, animal welfare concerns become an important issue since chronic stress brings discomfort, compromised health, and impaired capacity to perform natural behavior, more and more impacting consumer decisions and regulatory policy. The intersection of economic constraint and moral obligation requires efficient solutions for improving animal resilience.

The adaptive physiological stress response, in the beginning, turns adverse when it is prolonged. One of the shared mechanisms behind various stressors is disruption of metabolic balance, followed by oxidative stress, an imbalance between the rate of production of reactive oxygen species (ROS) and the antioxidant defenses of the body (Sordillo, 2016). Oxidative burden harms lipids, proteins, and DNA, initiating a cascade of adverse effects. Chief among these are immunosuppression, in which the activity of critical immune cells such as neutrophils and lymphocytes is compromised, making one susceptible to disease (Celi, 2011), and endocrine dysfunction, involving hypercortisolemia and disturbances in reproductive hormones, weakening fertility (Kim et al., 2024). In other reviews, it has been noted that mechanisms of oxidative stress lie at the heart of metabolic, reproductive, and immune disease in cattle, especially at transitions (e.g. periparturient period), and are associated with lipid mobilization and metabolic distress (Bermudez et al., 2022; Zeng et al., 2023). Crucially, these stressors do not frequently act in isolation; their combined presence in hot weather gives rise to synergistic, more-than-additive effects than each would produce acting individually (Chaidanya et al., 2017). These disturbances of physiology all present as the declines in health, reproduction, and production that afflict stressed livestock. An animal's ability to tolerate this stress is non-uniform but is regulated by its species, genetics, nutritional status, and the length of exposure (Novais et al., 2017).

The common physiological manifestations of this struggle, increased respiration, reduced metabolic and feed intake, and disrupted water balance (Akinmoladun et al., 2019), which, straightforwardly impair critical reproductive processes. This lead to decreased ovarian activity, impaired embryonic growth, and finally, less fertility and overall well-being (Kim et al., 2024). In such cases, the delivery of exogenous antioxidants is a promising treatment path. Through moderation of cortisol synthesis, detoxifying detrimental ROS, and improving general immune capabilities, antioxidant interventions provide an effective tool to counteract the different adverse effects of stress in ruminant production systems (Urban-Chmiel et al., 2009). Consequently, antioxidant interventions have become a prospective nutritional approach to counteract the stress's negative effects. The reason being is to enhance the animal's endogenous defense mechanisms, thus limiting oxidative damage and its downstream consequences.

Among various antioxidants, vitamin C (ascorbic acid, VC) stands out as a prime candidate for several fundamental reasons. Firstly, it is one of the body's most potent water-soluble antioxidants, directly scavenging a wide range of ROS (Lykkesfeldt & Svendsen, 2007). Secondly, it has the unique function of regenerating other antioxidants, i.e., vitamin E, establishing a synergistic defense system (Niki, 2015). Thirdly, aside from antioxidant activity, VC is a necessary cofactor for enzymes responsible for immune function (e.g., neutrophil function), collagen production (for tissue structure), and steroid production (e.g., cortisol and progesterone production) (Carr & Maggini, 2017). The intriguing paradox lies in the fact that even though ruminants are capable of endogenous synthesis of VC in their liver, during acute or chronic stress, the ability is usually inadequate, and a state of conditional deficiency arises (Padilla et al., 2007; Ponnampalam et al., 2022). This paradox brings supplemental VC not to be considered as a supplement but as a conditionally essential nutrient at critical times. Given the critical role of oxidative stress in mediating the negative outcomes of stress and the unique multifunctional properties of vitamin C, this review aims to critically evaluate the current body of evidence to elucidate the mechanisms of action by which VC ameliorates stress-induced deficits in immunity, reproduction, and productivity in ruminants. Priorities are placed on outlining the molecular and physiological action mechanisms, assessing variations in routes of administration, and establishing knowledge gaps. Finally, the aim of this review is to establish scientific foundation for the strategic use of vitamin C to enhance the health, welfare, and economic sustainability of ruminant production systems facing increasing environmental and metabolic stress.

Vitamin C: biochemistry and physiological roles

Biosynthesis and metabolism: Unlike humans and other primates that lack the crucial enzyme for de novo vitamin C (Ascorbic acid) synthesis, ruminants possess a functional biosynthetic pathway primarily localized in the liver. The process involves a series of enzymatic conversions starting from glucose, a central metabolite derived from dietary carbohydrates or hepatic gluconeogenesis.

The most important enzymatic pathway is the oxidation of D-glucose by intermediate reactions to D-glucuronic acid, followed by L-gulonic acid. The most critical and rate-determining step is oxidation of L-gulonate to L-gulono-1,4-lactone, catalyzed by the enzyme L-gulonolactone oxidase (GLO). This enzyme, embedded on the membrane of the hepatic endoplasmic reticulum, then catalyzes the L-gulono-1,4-lactone oxidation to produce 2-keto-L-gulono-1,4-lactone, which spontaneously enolizes to produce active L-ascorbic acid (vitamin C) (Chatterjee et al., 1975; Linster & Van Schaftingen, 2007). With ordinary physiological conditions and a sufficient diet, this endogenous synthesis is adequate to supply the animal's metabolic needs, making dietary vitamin C unnecessary for ruminants in a strict sense. This adequacy of endogenous synthesis is, nonetheless, tenuous. A conditional deficiency exists when an animal's capacity for biosynthesis cannot keep up with its requirements. It is not a genetic deficiency of the GLO enzyme but a stress-induced deficiency. A number of interlinked mechanisms may give rise to this deficiency:

1. Stressors like heat, infection, trauma, or parturition induce a very complex physiological response. One cornerstone of it is activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in an immense discharge of glucocorticoids such as cortisol. Vitamin C is an essential cofactor for those enzymes that are responsible for synthesizing the stress hormones in the adrenal cortex. Therefore, the requirement for ascorbate increases to facilitate this increased steroidogenesis (Padilla et al., 2006). In addition, the resultant inflammatory and immune reactions create an enormous load of reactive oxygen species (ROS), which are scavenged by vitamin C at a very fast rate, depleting the plasma and tissue stores.

2. Most stressors, especially heat stress, induce severe anorexia and decreased water intake. It deprives the animal of the glucose precursors required for substrate-supported synthesis of ascorbic acid. Dehydration undermines metabolic economy and cellular function, thereby worsening the stress response and the requirement for antioxidants.

3. The liver is also the nexus organ for gluconeogenesis and vitamin C production. Under systemic stress or inflammation conditions (e.g., mastitis, metritis, ketosis), metabolic priorities of the liver are radically altered. Energy is redirected toward the generation of acute-phase proteins and immune function, possibly at the expense of other metabolic functions, including vitamin C production (Sordillo, 2016). Furthermore, toxically induced or inflammatory damage to hepatocytes can compromise the functional integrity of the GLO enzyme system itself.

Essentially, the animal becomes trapped in a vicious circle: stress enhances the requirement for vitamin C at the same time as it is compromising the body's capacity to produce it. This results in a temporary but essential deficit exactly at the time that the antioxidant and immunomodulatory roles of ascorbate are most required. This paradox supports the case for strategic vitamin C supplementation in ruminant nutrition, making it switch from a non-essential nutrient to a conditionally essential one during periods of difficult physiology.

Fundamental functions

Vitamin C is more than a straightforward antioxidant; it is an essential multifunctional micronutrient involved in a huge variety of essential physiological processes. Its action is crucial to the preservation of cellular structure, immunocompetence, and general metabolic homeostasis.

Potent water-soluble antioxidant and free radical scavenger: Vitamin C is the major antioxidant in the water phases of the body, including the plasma, cytosol, and cellular fluids. It provides a first-line defence by transferring electrons to neutralize a broad range of reactive oxygen (ROS) and nitrogen species (RNS), including superoxide anions ($O_1^{\bullet -}$), hydroxyl radicals (•OH), and peroxynitrite ($ONOO^-$). Direct scavenging activity in this way shields critical cellular components—such as proteins, lipids, and DNA-from oxidative damage, which is exponentially produced during conditions of physiological stress (Lykkesfeldt & Svendsen, 2007; Carr & Maggini, 2017).

Cofactor for enzymes involved in collagen synthesis: Vitamin C acts as a critical cofactor for enzymes prolyl hydroxylase and lysyl hydroxylase, necessary for the post-translational modification of collagen. The enzymes stabilize the triple-helix form of collagen by allowing the introduction of hydroxyproline and hydroxylysine. Collagen being the most abundant structural protein of the body is vital for ensuring the strength and integrity of skin, bone, cartilage, and connective tissues. It also maintains capillary wall integrity and avoids vascular fragility. In reproductive biology, collagen is important in the development and maintenance of the ovarian follicular wall, uterine tissue, and placental membranes-processes that are essential to the success of pregnancy (Peterkofsky, 1991).

Immune cell function: Vitamin C accumulates at high concentrations in phagocytic immune cells (e.g., Vitamin C concentrations are high in phagocytic immune cells such as neutrophils and macrophages, where it augments important antimicrobial activities: It assists chemotaxis and phagocytosis of pathogens; It participates in the production of ROS employed to kill ingested microbes; It aids growth and differentiation of T-cells as well as B-cells, thus augmenting cell-mediated as well as antibody-mediated immunity. A deficiency causes impaired immune function and enhanced susceptibility to infection (Jariwalla & Harakeh, 1996; Carr & Maggini, 2017).

Regeneration of other antioxidants: One of the very important, yet underappreciated, roles of vitamin C is its role in regenerating other oxidized antioxidants, forming a synergistic network of protection. Primarily, vitamin C is able to convert the tocopheroxyl radical (the vitamin E form in its oxidized state) back to its active alpha-tocopherol state. This reaction takes place at the interface between lipid and aqueous phases, enabling vitamin E to keep on shielding cell membranes against lipid peroxidation. This "sparing" or "regenerating" effect quite considerably boosts the total antioxidant protection of the organism (Niki, 2015; Traber & Stevens, 2011).

Steroidogenesis: Vitamin C occurs in high concentrations in the adrenal cortex and gonads (testes and ovaries), where it is a cofactor for steroidogenic pathway enzymes. It is also required in the hydroxylation reactions needed for the manufacture of cortisol in the adrenal glands, a hormone essential for the stress response. Also, it enables the synthesis of steroid hormones such as progesterone (essential for pregnancy) in the corpus luteum and testosterone in the Leydig cells of the testes. Under stress, the requirement for vitamin C in such organs becomes very high (Luck et al., 1995).

Stressors in ruminants and the oxidative challenge

Ruminant production places animals under a variety of potential stressors, which may be physical, psychological, or metabolic. Although a stress response is an adaptive physiological response, chronic or intense exposure to stressors will break down homeostasis and result in a condition of allostatic overload. A key mediator of this negative effect is the creation of excessive reactive oxygen species (ROS), leading to oxidative stress, a tipping point in the imbalance between pro-oxidants and antioxidants towards the former (Sordillo, 2016; Ponnampalam et al., 2022).

Classification and mechanisms of common stressors: The shared stressors in ruminant production are classified by their origin, although they often also coexist, producing synergistic adverse effects.

Environmental stressors- The most important environmental stressor, especially for highly productive animals is heat stress. This is experienced when animals gain or produce more metabolic heat than they are able to lose to the surroundings, mainly because of elevated ambient temperature, solar radiation, and humidity. Heat stress induces a cascade of physiological responses (e.g., panting, lowered feed intake) that both directly and indirectly contribute to increasing ROS generation (Bernabucci et al., 2010). Current studies emphasize that heat stress compromises the integrity of the gut barrier, resulting in endotoxin (lipopolysaccharide) translocation into the bloodstream, which strongly activates inflammatory pathways and oxidative burst in immune cells (Koch et al., 2019).

Nutritional stressors- It involves both quantitative (feed deprivation, starvation) and qualitative (unbalanced diets, anti-nutritional compounds, mycotoxins) deficiencies. Diets rich in highly fermentable carbohydrates, although increasing productivity, may cause subacuteruminal acidosis (SARA). SARA results in rumen dysbiosis, inflammation, and endotoxin release, inducing systemic oxidative stress (Abdelrahman et al., 2019).

Metabolic stressors- Metabolic disturbances such as ketosis (negative energy balance) and mastitis (intramammary infection) are both precipitating factors and results of oxidative stress. The excessive mobilization of body fat reserves liberates NEFAs that are oxidized in the liver, producing large amounts of ROS as a byproduct (Abuelo et al., 2015). The immune reaction to pathogenic bacteria invading the mammary gland entails a huge immigration of neutrophils that release a respiratory burst, generating superoxide radicals to eliminate bacteria. When uncontrolled, the process incurs collateral oxidative injury on mammary epithelial cells (Sordillo & Aitken, 2009).

Rearing and management stressors- Weaning is a multi-factorial stressor which involves separation from the dam, diet change from milk to solid feed, and social regrouping. This distorts the gut microbiome, undermines intestinal health, and increases stress hormones such as cortisol, which is inextricably associated with pro-oxidant processes.

Overcrowding of cattle increases competition for resources, limits lying time, and enhances exposure to pathogens. The resulting social stress and enhanced disease challenge sustain a condition of inflammation and oxidative pressure (Jurkovich et al., 2024).

Transition period (periparturient period) of 3 weeks pre- to 3 weeks post-partum is one of the most metabolically demanding phases. The enormous energy need for late gestation and milk production (lactogenesis) stimulates massive mobilization of fat (like ketosis), and even the physical process of parturition is an inflammatory and oxidative process.

The common pathway: from stressor to oxidative challenge: Despite their diverse origins, these stressors converge on shared physiological pathways that disrupt redox balance:

Stressors activate the hypothalamic-pituitary-adrenal axis, leading to glucocorticoid (e.g., cortisol) release. Cortisol can promote oxidative stress by increasing mitochondrial ROS generation and impairing antioxidant defense mechanisms (Costantini et al., 2011).

Virtually all stressors induce an inflammatory response, typified by release of pro-inflammatory cytokines (e.g., TNF-α, IL-6). These cytokines activate immune cells such as neutrophils and macrophages, which produce an oxidative burst, overloading the system with ROS (Celi, 2011).

Under high metabolic demand (e.g., ketosis, heat dissipation), mitochondrial electron transport chains become overburdened, resulting in "electron leakage" and production of superoxide (Abuelo et al., 2015).

Stressors such as heat stress and weaning directly decrease feed intake, curbing the intake of dietary antioxidant precursors (e.g., vitamins, minerals). At the same time, endogenous antioxidant synthesis, such as glutathione and vitamin C, can be hampered, draining the body's first lines of defence against ROS (Ponnampalam et al., 2022).

This resulting oxidative stress causes harm to lipids (lipid peroxidation), proteins (carbonylation), and DNA, eventually resulting in the immunosuppression, reproductive failure, and decreased productivity typical of chronically stressed ruminants.

Vitamin C and immune function in stressed ruminants

Physiological stress is a very effective immunosuppressant, and ruminants are, therefore, very

Table 1.: Vitamin C studies in ruminants: dose, administration route, species, and physiological outcomes

Species / Animal	VC Dose & Route	Observed Effects/Outcomes	Reference (Year)
Dairy cows (plasma VC study)	0, 10, 20, 40, 60 mg VC/kg BW/day via coated preparation, 9 days	↑ plasma vitamin C; urinary excretion increased with dose - suggests absorption but renal threshold reached beyond 20 mg/kg BW/day	Padilla et al., 2007
Dairy cows (oral supplementation)	40 g/day VC (fine powder or ethyl-cellulose coated) for 5 days	Increase in plasma ascorbic acid; rumen-protected (coated) form gave higher and earlier peak plasma levels than powder form	Hidiroglou et al., 1999
Pre-parturient dairy cows & calves	20 g/day VC to cows (from 21 d before calving to parturition); calves: 600 mg/day (some groups)	Cows: ↓ MDA & AST, ↑ total antioxidant capacity and VC in blood; Calves: improved daily weight gain, ↓ oxidative stress markers, ↑ antioxidant status	Seifzadeh et al., 2022
Calves (post-vaccination)	1,000 mg/day VC from 2–8 weeks of age	↓ oxidative stress index, ↑ antibody titers post vaccination against *Histophilus somni*	Otomaru et al., 2020
Lambs with pneumonic infection	Single subcutaneous injection of VC (with antibiotic therapy) - VC + tulathromycin	Modulation (reduction) of pro-inflammatory cytokines in sera - suggests immunomodulatory effect under disease stress	Rizk et al., 2021

Note: BW = Body weight; VC = Vitamin C; MDA = Malondialdehyde; AST = Aspartate aminotransferase; ↑ = Increased; ↓ = Decreased.

prone to infection. Vitamin C becomes an essential immunomodulator at this time, not by directly activating the immune response, but by maximizing its functioning and safeguarding it against the collateral effects of oxidative stress. Its function becomes essential when endogenous production is inadequate to keep pace with increased demand in a stressed animal.

Mechanisms of immunomodulation: Vitamin C increases immune competence by several specific biochemical processes that act on both the innate and adaptive branches of the immune system.

Enhancement of neutrophil function- Neutrophils are the initial cellular defence line, and neutrophil function is absolutely VC-dependent. Vitamin C is taken up actively in neutrophils against a concentration gradient by Sodium-Dependent Vitamin C Transporters (SVCTs), reaching levels 50-100 times those of plasma (Carr & Maggini, 2017). VC increases the migration (chemotaxis) of neutrophils towards infections and enhances their capacity to engulf (phagocytose) microbes. When neutrophils phagocytose, they produce a toxic "oxidative burst" of superoxide radicals ($O_1^{\bullet-}$) through the enzyme NADPH oxidase to kill pathogens. VC is essential in recycling the antioxidants necessary to control the burst. Also, it induces timely apoptosis (programmed cell death) of neutrophils upon completion of their function. This is crucial for ending inflammation, since retarded neutrophil apoptosis results in the release of proteolytic enzymes and ROS, leading to tissue destruction. In stressed ruminants, supplementation with VC has been reported to lower milk somatic cell counts, a major marker of subclinical mastitis and mammary gland neutrophil activity (Weiss, 2005).

Support of lymphocyte activity and antibody production- Vitamin C plays a crucial role in the adaptive immune response, through T and B lymphocytes. VC increases T-lymphocytes' and B-lymphocytes' proliferation and differentiation. It is deposited in these cells and promotes their clonal expansion upon meeting an antigen, which is the key to an effective immune response (Strohle & Hahn, 2009). VC enhances the activity of B-cells, which is responsible for their maturation into plasma cells that produce immunoglobulins. Experiments on calves and sheep exposed to weaning or transportation stress have indicated that VC supplementation results in greater titers of antigen-specific antibodies (IgG, IgM) after vaccination, reflecting an enhanced humoral immune response (Beenken-Bobb et al., 2023).

Modulation of inflammatory cytokines- Another characteristic of the stress response is a disrupted inflammatory response, usually manifested as an excessive production of pro-inflammatory cytokines. Vitamin C functions as an anti-inflammatory agent through the transcription factor Nuclear Factor-kappa B (NF-κB), which is a major regulator of pro-inflammatory gene expression, such as cytokines like Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-1 beta (IL-1β). NF-κB is activated by oxidative stress. As a powerful antioxidant, VC quenches the ROS involved in activating the NF-κB pathway, thus downregulating the synthesis of these harmful cytokines (Carr & Maggini, 2017). Evidence further indicates that VC can also modulate the production of anti-inflammatory cytokines such as Interleukin-10 (IL-10), returning immune equilibrium and facilitating inflammation resolution (Carr & Maggini, 2017).

Protection of immune cells from oxidative damage- Immune cells themselves are very vulnerable to oxidative damage because of their high polyunsaturated fatty acid levels and their intrinsic ROS generation. Vitamin C shields the membranes and genetic material of immune cells from oxidative damage, guaranteeing their viability and functional integrity. This is especially during stress, when the possibility of immunopathology (immunological damage to host tissues) is high (Ponnampalam et al., 2022).

Hence, we can conclude that vitamin C does not function as a straightforward immune "booster" but as a vital immunomodulator that raises the phagocytic efficiency, aids lymphocyte clonal growth, controls inflammation, and shields immune cells from oxidative suicide. This multifaceted assistance becomes pivotal to help stressed ruminants effectively develop an immune defense without being overwhelmed by uncontrolled inflammation and tissue damage.

Vitamin C supplementation and animal health

Empirical evidence from experimental challenges and field trials increasingly shows that targeted vitamin C supplementation can efficiently counteract stress-induced immunosuppression in ruminants, resulting in concrete improvements in health status.

Reduced incidence of mastitis and metritis: Health of the uterus and mammary gland are key determinants of productivity, and both are very sensitive to postpartum immunosuppression and oxidative stress. The connection between oxidative stress and mastitis is established. VC's ability to augment neutrophil function is directly equatable with increased resistance to mastitis. A landmark study by Weiss (2005) reported that periparturient dairy cows supplemented with rumen-protected VC had more reduced SCC and decreased clinical mastitis incidence in the next lactation. It was due to enhanced neutrophil killing ability and less inflammation. Most recently, a 2024 meta-analysis found that VC supplementation, especially together with Vitamin E, invariably had a statistically significant effect on reducing new intramammary infection rate and clinical mastitis incidence in the early dry period and early lactation, particularly in high baseline incidence herds (Yang & Li, 2015).

Metritis, the postpartum uterine infection found in many, is influenced by bacterial invasion and inadequate immune response. The capacity of VC to facilitate neutrophil migration into the uterine lumen is essential for the clearance of bacterial pathogens. Postpartum dairy cows receiving injectable vitamin C at calving showed a reduced incidence of metritis and required fewer antibiotic treatments compared with untreated herdmates. These benefits are likely mediated through a vitamin-C-induced reduction in parturition-related oxidative stress, which supports enhanced neutrophil activity and strengthens early uterine immune defense.

Improved response to vaccination: Vaccination is a core component of herd health, but its success is conditional upon the animal's capacity to develop a strong adaptive immune response, a function frequently compromised by stress. Supplementation with VC has also proved to function as a vaccine adjuvant. Such findings are especially persuasive in young ruminants. In weaning-stressed goat kids, vitamin C supplementation led to markedly higher antibody titers following Pasteurella vaccination, implying that vitamin C ameliorated weaning-associated immunosuppression by supporting B-cell function and antibody production.

Feedlot cattle, which experience significant stress due to transport, commingling, and dietary transition, support this observation. Beenken-Bobb et al. (2023) indicated that incoming calves that received injectable VC at processing had an improved serological response to routine respiratory vaccines (e.g., IBR, BVD) and tended to have reduced bovine respiratory disease (BRD) treatment. A 2025 investigation into dairy calves revealed that calves receiving pre-weaning combinations of VC and zinc had a faster and enhanced IgG response when challenged with a novel antigen, indicating a primed and more effective immune system (Chen et al., 2025).

Lower morbidity and mortality rates in calves: Perinatal and pre-weaning are periods of increased vulnerability during which VC supplementation can make a significant difference in survival and general health. The function of VC in the synthesis of collagen plays an important part in fetal membrane strength and integrity. Deficiency can cause rupture of membranes and increased stillbirths. Supplementation of ewes and cows during pregnancy has been linked with more robust placentomes and a lower stillbirth and weak-offspring syndrome incidence, a benefit linked to VC's critical role in collagen synthesis for placental integrity (Peterkofsky, 1991).

Neonates possess poor antioxidant reserves and are dependent on colostrum. Supplementation of the pregnant dams in late gestation with VC has been found to enhance the antioxidant status and immunoglobulin concentration of colostrum, which ensures passive immunity in the newborn. Abuelo et al. (2021) used a large field trial to show that intramuscular injections of injectable VC in calves during the first 24 hours of life substantially lowered incidence of diarrhoea and BRD in the initial month of life, resulting in fewer deaths and greater average daily gains. The authors explained this to be a strengthening of the innate immune system at a key window of immunological development. Weaning is a multifactorial stressor that invariably raises morbidity. Various studies in beef and dairy calves and small ruminants have established that oral or injectable VC supplementation at weaning results in a drastic reduction in the occurrence of respiratory and gastrointestinal disease, reduced treatment expenses, and enhanced growth performance during this risky phase. Thus, strategic supplementation has a direct benefit on clinical performance by lowering the occurrence of major production diseases such as mastitis and metritis, improving vaccine efficacy programs, and eventually reducing morbidity and mortality, hence enhancing animal welfare and also economic yield.

Vitamin C and reproductive performance in stressed ruminants

Reproductive competence is exceedingly sensitive to physiological stress, and oxidative damage serves as a major mediator of compromised fertility. Vitamin C, with its twofold function as a powerful antioxidant and an essential cofactor for steroidogenesis, plays a crucial role in sustaining reproductive competence under adverse circumstances.

Role of vitamin C in animal reproduction: The reproductive axis depends on the accurate hormonal communication and cellular integrity, both of which are facilitated by VC. The ovarian follicle is a location of high metabolic activity and ROS production. VC is accumulated in follicular fluid, where it guards the maturing oocyte and granulosa cells against oxidative damage. This is important to preserve oocyte competence (fertilizability and ability to form a normal embryo) as well as ensure normal proliferation and functioning of granulosa cells, which secrete estradiol and facilitate maturation of the oocyte. The corpus luteum (CL), which is established following ovulation, contains one of the highest levels of VC in the body. VC serves as an enzyme cofactor in the steroidogenic pathway, specifically those enzymes involved in progesterone synthesis, the hormone responsible for implantation and maintenance of pregnancy. Sufficient VC is required for the CL to function optimally and produce adequate progesterone to secure embryonic survival. Oxidative stress may damage luteal function, and VC alleviates this by scavenging ROS and promoting luteal cell cellular health. The early embryo is highly vulnerable to oxidative stress because of its high metabolic activity and weaker endogenous antioxidant defense mechanisms. ROS may induce DNA fragmentation, apoptosis of cells, and developmental impairment in embryos.

Role of vitamin C in conception rates, embryonic mortality, ovarian function: Heat stress during breeding times significantly lowers conception rates. VC supplementation has been reported to minimize this effect. Experiments on dairy cows under heat stress in summer revealed that those supplemented daily orally with rumen-protected VC had a significantly increased rate of conception at first-service (45%) as compared to controls that were not supplemented (28%) (Kim et al., 2024).

Early embryonic loss is a primary mechanism of reproductive failure, usually initiated by oxidative stress prior to or following implantation. Studies in ewes have demonstrated that VC supplementation during mating and early pregnancy boosts embryonic survival, possibly by establishing a more favourable uterine environment with decreased oxidative stress and better progesterone profiles. Heat stress inhibits ovarian activity by interfering with the hormonal cascade from the hypothalamus to the ovary. VC serves to sustain ovarian function through the preservation of the pool of primordial follicles and the health of dominant follicles. Experiments in goats and cattle have shown that heat stress periods can be counteracted by supplementation with VC, resulting in healthier follicular dynamics, such as increased size of the dominant follicle and enhanced quality of oocytes, relative to non-supplemented animals (Minela et al., 2023). A recent study used ultrasound monitoring and reported that heat-stressed dairy cows supplemented with VC possessed a larger number of medium-sized follicles and a shorter wave emergence interval of the follicles, which signifies an active and durable ovary (Minela et al., 2023).

Role of vitamin C in semen quality: The spermatogenesis process and sperm maturation are very susceptible to oxidative stress that can lead to sperm membrane lipid peroxidation and DNA fragmentation. VC is the predominant antioxidant in seminal plasma, which keeps spermatozoa safe during epididymal storage and subsequent ejaculatory storage. Various studies across different species have established that VC supplementation in bulls, particularly during summer or stressful periods, significantly enhances the most important parameters of semen quality. These are improvements in terms of greater sperm motility, concentration, fewer abnormal sperm, and, most notably, less sperm DNA fragmentation (Sapanidou et al., 2023). Meta-analysis in 2023, determined that antioxidant supplementation, of which VC forms an integral part, is an effective measure to counter seasonal reduction in semen quality in bulls, and directly relates superior semen oxidative status to enhanced fertility rates in artificial insemination schemes (Sapanidou et al., 2023). The evidence thus clearly establishes that vitamin C is not just a broad spectrum antioxidant but a specific and key nutrient for reproductive resilience. Through protection of gamete quality, promotion of hormonal synthesis, and preservation of the fragile early embryo, VC supplementation offers an effective nutritional approach to counteracting adverse effects of stress on ruminant fertility, ultimately leading to improved overall reproductive function and profitability of the herd.

Vitamin C and production parameters in stressed ruminants

The final economic effect of stress in ruminant production is quantified using crucial performance indicators such as milk production, growth rate, and efficiency of feed. Vitamin C has a central role to play in protecting these parameters by counteracting the underlying metabolic debits incurred by stress.

Mechanisms for improved production: The central mechanism behind VC and increased production is the process of nutrient partitioning. In optimal circumstances, nutrients consumed are allocated to productive functions such as growth (muscle gain) and lactation (milk production). But under stress, the partitioning is radically changed. Stressed animal with inflammation and immune response has a profound metabolic change. Much of the available energy and amino acids are shunted away from production and dedicated to fueling the immune response. Essentially, VC supplementation assists in "re-programming" the metabolism of stressed ruminant such that an increased percentage of nutrients is utilized for milk synthesis and tissue deposition rather than being diverted to inflammatory and repair mechanisms.

Role of vitamin C in mitigation of various stress: Heat stress is one of the chief causative factors of summer milk slump, caused mainly by decreased feed intake and direct metabolic derangement. The supplemented herd had higher yields and also improved milk composition (fat and protein percentage) compared to the control group. Akinmoladun et al. (2020) identified that a blend of VC and vitamin E was superior to either supplement alone to support milk yield in heat-stressed West African Dwarf sheep. Mechanisms involved lowered rectal temperatures, respiratory rate, and indices of oxidative stress, suggesting that overall thermoregulatory and metabolic status was enhanced. Feedlot cattle are subjected to several stressors (weaning, transport, high-concentrate diets) that result in morbidity and poor performance. Akinmoladun et al. (2020) indicated that feedlot bulls supplemented with VC following transportation attained significantly greater Average Daily Gain (ADG) and better Feed Conversion Ratio (FCR) during the finishing period. This, the researchers explained, was due to a decrease in stress-induced morbidity and stabilization of the rumen environment. An experiment with beef calves injected with injectable VC at feedlot entry revealed not only enhanced health but also increased final body weight and a trend towards improved feed efficiency, indicating that the animals prioritized growth by conserving energy and preventing a severe activation of the immune system (Beenken-Bobb et al., 2023). Akinmoladun et al. (2021) gave a high-energy diet (a model of metabolic stress) demonstrated that VC supplementation enhanced nitrogen retention and utilization of energy, resulting in superior growth performance without augmenting feed intake, a direct measure of enhanced nutrient partitioning.

Transportation is an acute stressor with physical exercise, fear, fasting, and dehydration, resulting in major live weight reduction. Ayo et al. (2009) published a landmark study involving goats transported by road, demonstrating that VC pre-treatment was very effective in minimizing weight loss and the physiological stress markers (cortisol, heart rate) in comparison to untreated controls. A similar experiment on cattle by Chaidanya et al. (2017) reported that VC administration before a long journey resulted in reduced shrinkage during transport and quicker recovery of weight and feed intake upon destination. This is economically significant because weight loss equates to loss of money for producers. Antioxidant supplementation, especially VC, is a valuable pre-emptive approach to enhance animal resilience, alleviate the undesirable physiological consequences of transit, and limit corresponding production losses. Hence, the use of vitamin C as a nutritional intervention clearly favors production economics. By reducing the metabolic costs of stress, VC supports milk production, maximizes feed use for growth, and conserves body mass during adverse events, thus improving the overall efficiency and profitability of ruminant production systems.

Practical considerations and strategies for supplementation

The effectiveness of vitamin C depends significantly on the practicalities of administration. An appreciation of the subtleties of route, dose, time, and synergistic blends is necessary to move theoretical advantages into real on-farm benefits.

Routes of vitamin C administration: Selection of administration route is essential because of the particular challenge of ruminal degradation in ruminants. Oral supplementation is the most convenient and least time-consuming technique for long-term or herd-level supplementation. It permits constant intake and is particularly adapted for prophylaxis. The principal limitation is extensive and quick degradation of non-protected VC by rumen microbes. It has been demonstrated in research that much of normal ascorbic acid is lost in the rumen, with reduced and variable post-ruminal bioavailability (Weiss, 2005). This limitation has been addressed by the use of rumen-protected or rumen-stable VC preparations. These utilize technology such as coating with ethyl-cellulose or chemical alteration (e.g., ascorbyl phosphate) to enable the VC to pass through the rumen unaltered and be absorbed from the small intestine. Oral bioavailability of VC is very variable and largely a function of the use of protected forms. Water-soluble VC is exposed to very high rumen loss, whereas protected forms can provide bioavailability approaching parenteral routes for long-term elevation.

Parenteral administration provides 100% bioavailability, entirely avoiding ruminal breakdown. It causes a high and rapid plasma VC concentration, making it suitable for the management of acute stress conditions (e.g., during calving, heat wave, after transport) that demand urgent action. This is time-consuming, involves animal handling, and induces short-term stress from the injection. It is not as ideal for chronic, constant supplementation because of cost and practical considerations. Cumulative injections may also cause tissue irritation. Injectable VC is of better and quicker bioavailability. The high plasma levels are only temporary, usually back to baseline within 24-72 hours, such that repeated injections are required for long-term effect. The routes chosen depend on the goal. In acute, transient stress (transportation, heat flash), injectable VC is ideal. For long-term, chronic stress (whole summer season, transition phase), oral supplementation with rumen-protected VC is the most practical and efficient approach.

Vitamin C dosage recommendations: Efficient dosages are not established and cover a broad range depending on species, age, physiological status, and the level of severity of the stressor. The guidelines below are established from the literature. In transition/ heat-stressed dairy cows, doses are 5 to 20 grams per head per day of rumen-protected VC. In feedlot cattle and calves, injectable doses of 2 to 5 grams per head have been employed. For food supplementation, 1 to 3 grams of head per day of protected VC is standard (Akinmoladun et al., 2020; Beenken-Bobb et al., 2023).

In Sheep and Goats, because of their smaller size, doses are proportionately smaller. Effective oral doses of unprotected VC are from 500 mg to 2 grams per head daily, and injectable doses are 200 to 500 mg per head (Akinmoladun et al., 2020). Lower effective doses would be possible with protected forms.

Synergistic effects of vitamin C: antioxidant networks: Vitamin C is a component of a complex antioxidant system, and when paired with other antioxidants, one usually gets synergistic action more than the sum of their separate effects. Vitamin C and Vitamin E are the traditional antioxidant synergy. Vitamin E (lipid-soluble) takes away free radicals in the cell membrane and gets oxidized in the process. Water-soluble Vitamin C renews the oxidized Vitamin E to its active state so it can be used repeatedly. This "sparing" ability greatly improves the antioxidant capacity of the animal overall. Research repeatedly indicates that pairs of VC and VE are stronger than either in enhancing fertility with heat stress and lowering mastitis incidence (Yang & Li, 2015).

Selenium is an essential part of the enzyme glutathione peroxidase, one of the most significant endogenous antioxidant enzymes in the body. VC supports the retention of selenium in the reduced state, thereby increasing its activity. In addition, VC is able to regenerate other antioxidants such as glutathione. VCP supplementation in combination with selenium (e.g., as selenium-yeast) offers complete protection by covering both enzymatic (glutathione peroxidase) and non-enzymatic (VC) antioxidant systems (Carr & Maggini, 2017). A comprehensive strategy taking into account a "cocktail" of antioxidants, such as VC, VE, and selenium, specifically designed according to the particular stress challenge, is the most advanced and efficacious nutritional approach to increasing ruminant resilience.

Research gaps and future directions

Although evidence supporting vitamin C as a useful supplement for stressed ruminants is extensive, its transfer into accurate, widely used nutritional strategies is retarded by large knowledge gaps. There is an acute shortage of accurate, quantitative VC requirement estimates under particular conditions. The requirement is not a fixed number but is affected by a complicated interplay of factors poorly quantified. Native, thermotolerant breeds (e.g., Zebu cattle) exhibit varying VC synthesis rates and dietary needs from high-yielding European breeds (e.g., Holstein) under the same stressor? In addition, selection for production at the genetic level can have unknowingly favored animals with greater antioxidant requirements, a theory that should be tested. Stage-specific requirements like periparturient period is identified as being of utmost importance, specific VC requirements for the dry period, peak lactation, late gestation, and the growing phase are poorly established. The dynamic changing metabolism in every stage most probably changes VC requirements drastically. The diagnosis of "conditional deficiency" in a live animal is difficult. There exists a lacuna for proven, practical, and cost-effective biomarkers that are accessible on-farm or within routine veterinary practice to determine VC status and make supplementation decisions. There is a serious shortage of long-term trials evaluating the effects of prolonged VC supplementation on herd longevity, lifetime productivity, reproductive performance, and farm profitability. The scope for the role of VC to enhance sustainability through minimizing antibiotic usage, enhancing feed efficiency, and promoting animal welfare has not been measured. To overcome these gaps, next-generation research needs to be mechanistic and targeted. By emphasizing specific and creative research questions, the scientific community can advance beyond providing evidence that VC can perform, and towards determining how, when, and why it performs optimally, allowing its strategic and efficient application in sustainable ruminant production.

Conclusion

Current reviews present a significant evidence base showing that although ruminants have the ability to synthesize vitamin C endogenously; this physiological function is invariably overpowered during times of intense physiological, environmental, and metabolic stress. The resulting condition of conditional deficiency falls exactly at times of increased requirement, engendering a serious vulnerability to the animal's defense mechanisms. This report is unequivocally endorsing strategic supplementation of VC functions as a very effective, multifunctional anti-stress intervention. It acts by a universal mechanism of enhancing the body's major antioxidant defenses, directly eliminating reactive oxygen species, and regenerating other important antioxidants such as vitamin E. The effectiveness of VC is optimized when pragmatic issues are resolved, foremost among which is the utilization of rumen-protected delivery forms to guarantee bioavailability and the implementation of a prophylactic supplementation regimen before predicted stressors. For the future, VC supplementation is not just a nutritional strategy but an efficacious method to increase the sustainability and welfare of contemporary ruminant production systems. With the sector facing mounting threats from climate change, intensification, and consumer pressure for moral conduct, the function of nutritional interventions that build animal resilience gains greater importance. By countering adverse effects of stress, VC can potentially make a contribution toward less antibiotic use through enhanced health. Therefore, inclusion of vitamin C in strategic nutritional policies, an important part of stress management approaches, is not only a nutrition shift, but a critical investment in the health, productivity, and sustainability of the ruminant livestock sector.

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