Metabolism And Deficiency Of Retinol In Ruminant: A Review

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ABSTRACT: Vitamin A (Retinol) is a vitamin that is needed by the retina of the eye in the form of a specific metabolite, the light-absorbing molecule retinal, thus is necessary for both low-light and color vision. Vitamin A also functions in a very different role, as an irreversibly oxidized form of retinol known as retinoic acid, which is an important hormone-like growth factor for epithelial and other cells. All forms of vitamin A have a beta-ionone ring to which an isoprenoid chain is attached, called a retinyl group. Both structural features are essential for vitamin activity. The orange pigment of carrots – beta-carotene – can be represented as two connected retinyl groups, which are used in the body to contribute to vitamin A levels. Alpha-carotene and gamma-carotene also have a single retinyl group, which give them some vitamin activity. None of the other carotenes have vitamin activity. The carotenoid beta-cryptoxanthin possesses an ionone group and has vitamin activity in humans. Although all vitamins are equally important in supporting animal Life, vitamin A may be considered most important vitamin from a practical standpoint. It is important as a dietary supplement for all animals, including ruminants. Deficiency occurs in endemic proportions in many developing countries and is considered to be the most common cause of blindness in youth children complete world.

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INTRODUCTION

Vitamins are defined as group of complex organic compounds present in slight amounts in natural Foodstuffs that are essential to normal mal metabolism and lack of which in the diet causes deficiency diseases.

Vitamins are required in trace amounts in the diet for health, growth, and reproduction. Omission of a single vitamin from the diet of a species that requires it will produce deficiency signs and symptoms. Many of the vitamins function as coenzymes; others haven't such role, but perform certain essential functions. Some vitamins deviate from the preceding definition in that they do not always need to be constituents of food. Certain substances that are considered to be vitamins are synthesized with intestinal tract bacteria in quantities that are often adequate for body needs. However, a clear distinction is made between vitamins and substances that are synthesized in tissues of the body. Ascorbic acid, for example, can be synthesized by most species of animals, except when they are young or under stress conditions [63, 94].

CHEMICAL STRUCTURE

Vitamin A itself doesn't occur in plant products, but its precursor, carotene occurs in several forms. These compounds are commonly referred to as pro vitamin A because the body can transform them into the active vitamin. This is how the vitamin A needs of farm animals are met, for the most part, because their rations consist mainly or entirely of foods of plant origin. The combined potency of a feed, represented by its vitamin A and carotene content, is referred to as its vitamin A value. Retinol is the alcohol form of vitamin A (Fig.1). Replacement of the alcohol group by an aldehyde group gives retinal, and replacement by an acid group gives retinoic acid. Esters of retinol are called retinyl esters. Vitamin A in animal products exists in several forms, but principally as long-chain fatty acid esters.

In addition to retinol, there is another form that is isolated from fish. It was originally distinguished on the basis of a different maximum spectral absorption and named A_2 to differentiate it from the previously from isolated. Vitamin A_2 is closely associated to vitamin A_1 but contains an additional double bond in the β–ionone ring. Liver oils of

marine fish origin usually average less than 10% vitamin A_2 of the total vitamin A content. The relative biological activity of vitamin A_2 is 40 to 50% that of A_1 [63, 93, 111].

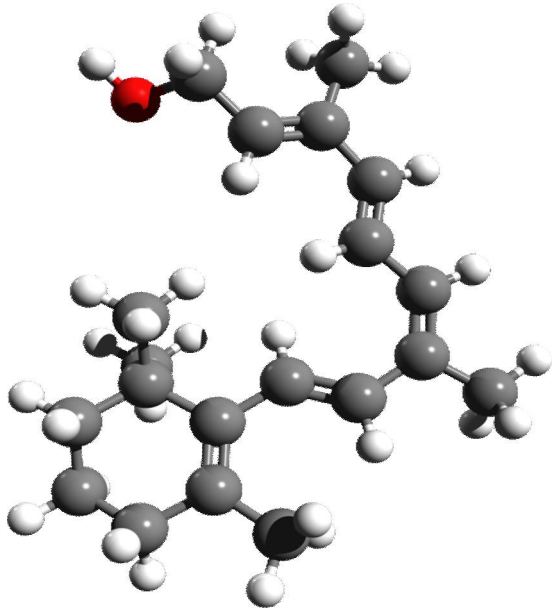

Fig.1 Chemical structure of vitamin A_1, from Www. Wikipedia.com.

Vitamin A is a nearly colorless, fat-soluble, long-chain, unsaturated alcohol by 5 double bonds. The vitamin is made up of isoprene units with alternate double bonds, starting with one in the β−ionone ring that is in conjugation with those in the side chain. Since it contains double bonds, vitamin A can exist in different isomeric forms. The most active vitamin A form and that most commonly found in mammalian tissues is the all-*trans*-vitamin A. *cis*-Forms can arise from the all-*trans*-forms, and a marked loss of vitamin A potency results. These structural changes in the molecule are promoted by moisture, heat, light, and catalysts. Thus, conditions present during hay making and ensiling, dehydrating, and storage of crops are detrimental to the biological activity of any carotenoids present.

Vitamin A activity of β−carotene is substantially greater than that of other carotenoids. Lycopene is an important carotenoid for its antioxidant function but does not possess the β−ionone ring structure, and therefore is not a precursor of vitamin A. In humans, β−carotene and lycopene are the main carotenoids in tissue [17, 63, 87, and 90].

Theoretically, 1 mol of β−carotene could be converted to yield 2 mol of retinal. However, biological tests have consistently shown that pure vitamin A has twice the potency of β−carotene on a weight-to-weight basis. Thus, only one molecule of vitamin A is formed from one molecule of β−carotene. Loss of potential activity results from inefficient cleavage and intestinal absorption.

Vitamin A activity is expressed in international units or, less frequently, in United States Pharmacopeia Units, both of which are of equal value. An IU is defined as the biological activity of 0.300µg of vitamin A alcohol or 0.550µg of vitamin A palmitate. One IU of pro vitamin A activity is equal in activity to 0.6µg of β−carotene, the reference compound. Vitamin A may be expressed as retinol equivalents (RE) instead of IU. By definition, 1 retinol equivalent is equal to 1µg of retinol, 6µg of β−carotene, or 12µg of other pro vitamin A carotenoids.

In terms of international units, 1 RE is equal to 3.33 IU of retinol or 10 IU of β−carotene [64, 69, 77, 89, and 106].

METABOLISM

Digestion

Vitamin A in animal products and carotenoids are released from proteins by the action of pepsin in the stomach and proteolytic enzymes in the small intestine [51, 16, 63, 99, and 113].

In the duodenum, bile salts break up fatty globules of carotenoids and retinyl esters to smaller lipid congregates, which can be more easily digested by pancreatic lipase, retinyl ester hydrolase, and cholesteryl ester hydrolase.

A number of factors influence digestibility of carotene and vitamin A. Working with lambs, Donoghue et al. (1983) reported that dietary levels of vitamin A ranging from mildly deficient to toxic levels affect digestion and uptake. Percentage transfer from the digestive tract from supplemental dietary levels of 0, 100, and 12,000µg of retinol per kilogram were 91, 58, and 14%, respectively. Wing [109, 63] reported that the apparent digestibility of carotene in various forages fed to dairy cattle averaged about 78%.Variables that influenced carotene digestibility included month of forage harvest, type of forage (hay, silage, green-chop, or pasture), species of plant, and plant dry matter. In general, carotene digestibility was higher than average during warmer months and lower than average during winter.

Several reports indicate that appreciable amounts of carotene or vitamin A may be degraded in the rumen. Various studies with different diets have result in preintestinal vitamin A disappearance values ranging from 40 to 70% [63, 104].

Rode et al. [63, 88] compared microbial degradation of vitamin A from steers fed

concentrate, hay, or straw diets. Estimated effective rumen degradation of biologically active vitamin A was 67% for cattle fed concentrates compared to 16 and 19% for animals fed hay and straw diets, respectively.

Storage

Liver normally contains about 90% of total-body vitamin A. The remainder is stored in the kidneys, lungs, adrenals, and blood, with small amounts also found in other organs and tissues. A large quantity of vitamin A is stored in the kidney as well as the liver in cats and dogs. This high level of vitamin A in the kidney is unique to cats and dogs, and the reasons for the storage are not fully understood [114, 10, 17, 63, 82 and 84].

Vitamin A is highly concentrated in stomach oils of certain seabirds and in the intestinal wall of some fish [29, 77]. The entire vitamin A reserve of certain shrimp is in the eyes. Carotenoids are more evenly distributed in species that have the ability to absorb and store these precursors. Grass-fed cattle have large stores of carotene in their body fat, which is evidenced by a deep yellow color.

The liver can store large amounts of vitamin A; in humans approximately 50 to 80% of the total body vitamin A is stored in the stellate cells in the form of retinyl esters [10, 63].

[9, 63] compared vitamin A content in liver lobes between dogs and other species. Uniformity of liver vitamin A was less for dogs than cattle and chickens. In all species, there was a low correlation between liver and blood retinol. Several studies have shown that liver can store enough vitamin A to protect the animal from long periods of dietary scarcity [61, 63].This large storage capacity must be considered in studies of vitamin requirements to ensure that intakes that appear adequate for a given function aren't being supplemented by reserves stored prior to the period of observation. Measurement of the liver store of vitamin A at slaughter or in samples obtained from a biopsy is a useful technique in the investigate of vitamin A status and requirements.

FUNCTIONS

Vitamin A is necessary for support of growth, health, and life of higher animals. In the absence of vitamin A, animals will cease to grow and eventually die. The classic biological assay method is based on measurement of growth responses of weanling rats to graded doses of vitamin A. It is of primary importance in development of young, growing animals.

The metabolic function of vitamin A, explained in biochemical terms, is only now beginning to be understood. Vitamin A deficiency causes at least four different and probably physiologically distinct lesions: loss of vision due to a failure of rhodopsin formation in the retina; defects in bone growth; defects in reproduction and defects in growth and differentiation of epithelial tissues, frequently resulting in keratinization. Keratinization of these tissues results in loss of function; this occurs in the alimentary, genital, reproductive, respiratory, and urinary tracts. Such altered characteristics make the affected tissue more susceptible to infections. Thus, diarrhea and pneumonia are typical secondary effects of vitamin A deficiency. Retinoic acid is the form of vitamin A that has been shown to perform as a hormone [63, 94].

Vitamin A-deficient rats fed retinoic acid were healthy in every respect, with normal estrus and conception, but failed to give birth and resorbed their fetuses. When retinol was given even at a late stage of pregnancy, fetuses were saved. Male rats on retinoic acid were healthy but produced no sperm, and without vitamin A, both sexes were blind [4, 63].

Although retinol is needed for normal vision and some aspects of reproduction, discoveries have revealed that most, if not all, actions of vitamin A in development, differentiation, and metabolism are mediated by nuclear receptor proteins that bind retinoic acid, the active form of vitamin A [6, 63].

A group of retinoic acid binding proteins function in the nucleus by attaching to promoter regions in a number of specific genes to stimulate their transcription and thus affect growth, development, and differentiation. Six high-affinity receptor proteins for retinoic acid have been identified. Apparently RAR nuclear receptors bind to all-*trans* retinoic acid, while RXR receptors bind with 9-*cis*-retinoic acid [52, 55 and 63].

Retinoic acid receptors in cell nuclei are structurally homologous and functionally analogous to the known receptors for steroid hormones, thyroid hormone and vitamin D [1, 25-$(OH)_2$D]. Thus, retinoic acid is now recognized to function as a hormone to regulate the transcription activity of a large number of genes [63, 90].

As an example, the well-known connection between vitamin A deficiency and hepatic glycogen depletion caused by reduced gluconeogenesis can now be explained at the molecular level by the dependence of phosphor enol pyruvate carboxy kinase gene expression on adequate vitamin A [63, 97].

Actions of vitamin A in development, differentiation, and metabolism are mediated by nuclear receptor proteins that bind retinoic acid with steroid and thyroid hormone receptors. The super

family of nuclear proteins interacts with specific genes and regulates their transcription. Retinoic acid has been found to stimulate, synergistically with thyroid hormone, the production of growth hormone in cultured pituitary cells. The RARs have been found to bind both the gene element responsive to RAR, in addition to the one responsive to triiodothyronine, suggesting that retinoic acid and the thyroid hormone control overlapping networks of genes. Many proteins appear during retinoic acid-induced cell differentiation.

Retinoids have a wide spectrum of biological activities. Retinoic acid plays an important role in growth and differentiation of embryonic tissues. It also regulates the differentiation of epithelial, connective, and hematopoietic tissues [63, 92].

The nature of the growth and differentiation response elicited by retinoic acid depends upon cell type. Retinoic acid can be an inhibitor of many cell types with a potential to reduce adipose tissues in meat-producing animals [63, 101, 108, 112].

Evidence indicates a morpho genic role for retinoic acid and one of its metabolites, 3, 4-didehydroretinoic acid [5, 63]. Morpho gens form concentration gradients or morpho genic fields through developing tissues that specify the eventual three-dimensional structure at maturity. Cell differentiation in the developing chick limb bud has been studied where vitamin A morpho gens are operative. Cells of the limb bud can differentiate into muscle, cartilage, and bone cells.

Maintenance of Normal Epithelium

Vitamin A is required for maintenance of epithelial cells, which form protective linings on many of the body's organs. The respiratory, gastrointestinal, and urogenital tracts, as well as the eye, are protected from environmental influences by mucous membranes. If, however, there is a deficiency of vitamin A, epithelial cells that make up the membrane will change their characteristic structure. It is postulated that vitamin A plays an important role in altering permeability of lipoprotein membranes of cells and of intracellular particles. Vitamin A penetrates lipoprotein membranes and, at optimum levels, may act as a cross-link-age agent between the lipid and protein, thus stabilizing the membrane [60, 63, and 100].

The normal mucus-secreting cells of epithelium in various locations throughout the body become replaced by a stratified, keratinized epithelium when vitamin A is deficient. Keratinized epithelium allows pathogen entry through the skin, lung, gastrointestinal tract, and urogenital tract surface. Vitamin A deficiency can impair regeneration of normal mucosal epithelium damaged by infection or inflammation [5, 63] and therefore could increase the severity of an infectious episode and/or prolong recovery from that episode. Adequate dietary vitamin A is necessary to help maintain normal resistance to stress and disease.

Studies have shown that the epithelial cells from vitamin A deficient animals fail to differentiate to mucus-secreting cells, and mesenchymal cells fail to differentiate beyond the blast stage. This occurs in the alimentary, genital, reproductive, respiratory, and urinary tracts. Such altered characteristics make affected tissues more susceptible to infection. Thus, colds and pneumonia are typical secondary effects of vitamin A deficiency. Adequate dietary vitamin A is necessary to help maintain normal resistance to stress and disease. However, greater than optimal intakes of vitamin A will not aid in preventing infections.

There are many non-infective problems due to keratinization of epithelium, such as diarrhea. The formation of kidney and bladder stones is favored when damaged epithelium interferes with normal secretion and elimination of urine, and sloughed keratinized cells may form foci for the formation of stones. There is a specific interference with reproduction caused by altered epithelium that is of great importance. Squamous metaplasia in the parotid gland is an early change in vitamin A-deficient calves and proves useful in diagnosing deficiency. Elevated cerebrospinal fluid pressure observed in vitamin A-deficient animals, a very sensitive measure of the onset of vitamin A deficiency, is the result of cell changes. Increased ground substance in the dura mater surrounding the arachnoid villus and altered epithelial cells cause a decreased absorption of the fluid.

There is evidence that vitamin A is necessary for the formation of large molecules containing glucosamine [44, 63].

These are the muco polysaccharides occurring in almost all tissues of mammalian organisms but principally in the mucus-secreting epithelia and in the extracellular matrix of cartilage, mainly as chondroitin sulfate. The intimate involvement of vitamin A in the biosynthesis of glycoproteins, which are constituents of membrane systems in cells, helps explain many biological effects of this vitamin.

In severe vitamin A deficiency, abnormalities in both RNA metabolism and protein synthesis have been reported. These changes in nucleic acid metabolism and protein synthesis may, however, reflect secondary effects of deficiency rather than the primary function of the vitamin.

DEFICIENCY

Effects of Deficiency

Vitamin A is necessary for normal vision in animals and humans, maintenance of healthy epithelial or surface tissues, and normal bone development. The vitamin A deficiency signs observed in ruminants vary somewhat, but most relate to these three changes in tissues. Numerous studies have also demonstrated increased frequency and severity of infection in vitamin A-deficient animals. Lack of vitamin A results in decreased antibody production and impaired cell-mediated immune processes against infective agents [36, 63].

Clinical signs may be specific for vitamin A deficiency, or only general signs may be observed, including loss of appetite, loss of weight, unthrifty appearance, thick nasal discharge, and reduced fertility. The normal epithelium in various locations throughout the body becomes replaced by a stratified, keratinized epithelium when vitamin A is deficient. This effect has been noted in the respiratory, alimentary, reproductive, and genitour - nary tract as well as in the eye.

Ruminants

Ruminants lacking vitamin A may be more susceptible to pinkeye or other diseases related to the mucous membranes. Keratinization lowers the resistance of the epithelial tissues to the entrance of infectious organisms. Thus respiratory diseases, such as colds and sinus infections, tend to be more severe when vitamin A is deficient.

Vitamin A deficiency could indirectly result from zinc deficiency. Zinc deficiency, interferes with the synthesis of retinol-binding protein (RBP) in liver, which carries vitamin A in plasma. Thus, in zinc deficiency, decreased liver RBP levels may cause low concentrations of plasma vitamin A. Zinc-deficient goats have been observed to have low serum vitamin A despite adequate dietary vitamin A [28, 63, 71].

In calves, serum vitamin A was significantly higher for animals supplemented with 50 mg/kg zinc [29, 57, and 68].

Cattle From tropical northern Australia showed a 12% annual mortality in part because of a slow release of liver vitamin A [46, 63]. Apparently, high calcium and low forage zinc concentrations contributed to this slow liver vitamin A release. Since tropical forages have often been shown to be low in zinc [62, 63], conditioned vitamin A deficiency may result even though liver vitamin A values indicate adequate concentrations of this vitamin.

VITAMIN A DEFICIENCY IN SHEEP

Clinical signs of vitamin A deficiency in sheep are similar to those in cattle; night blindness is the common means of determining the deficiency [23, 72, 74, and 75].

Vitamin A deficiency results in keratinization of the respiratory, alimentary, reproductive, and urinary tracts, and ocular epithelia. Keratinization causes lowered resistance to infections. The immune response is decreased in lambs with low vitamin A status [10, 63].

Additional clinical signs of vitamin A deficiency in sheep include growth retardation, bone malformation, degeneration of the reproductive organs, and elevated pressure in cerebrospinal fluid. Deficiency interferes with normal development of bone, which may relate to muscular incoordination and nervous signs. Vitamin A deficiency can also result in lambs born weak, malformed, or dead. In addition, retained placenta occurs in vitamin A-deficient ewes [63, 66, 70, 83 and 90].

Vitamin A deficiency has resulted in low semen quality in rams [57, 60]. Vitamin A deficiency has detrimental effects on wool production and characteristics, including shortened wool fibers and decreased fiber thickness, strength, and elongation [41].

β- CAROTENE FUNCTION INDEPENDENT OF VITAMIN A

Carotenoids have been shown to have biological actions independent of vitamin A [25, 63 and 76]. Some animal studies indicate that certain carotenoids with antioxidant capacities, but without vitamin A activity, can enhance many aspects of immune functions, can act directly as anti-mutagens and anti-carcinogens, can protect against radiation damage, and can block the damaging effects of photosensitizers. In animal models, β−carotene and canthaxanthin have protected against UV-induced skin cancer as well as some chemically induced tumors. In some of these models, enhancement of tumor immunity has been suggested as a possible mechanism of action of these carotenoids [12, 63].

β−Carotene can function as a chain-breaking antioxidant; it deactivates reactive chemical species such as singlet oxygen, triplet photochemical sensitizers, and free radicals, which would other-wise induce potentially harmful processes.

Cows supplemented with 300 mg of β−carotene per day had a lower incidence of intra mammary infections than cows supplemented by preformed vitamin A or the un supplemented control group. It was also demonstrated that cows supplemented by 300mg of β−carotene per day during the dry period maintained blood

concentrations of β− carotene and had a lower incidence of mastitis than those supplemented with vitamin A alone [26, 63]. β−Carotene enhances blastogenic responses of lymphocytes and increases cytotoxic activities of natural killer cells and cytokine production by macrophages [24, 63].

Poly morpho nuclear neutrophils (PMNs) are the major line of defense against bacteria in the mammary gland. β− Carotene supplementation seems to exert a stabilizing effect on PMN and lymphocyte function during the period around dry-off [63, 103].

Daniel et al. [34, 63] reported that β−carotene enhanced the bactericidal activity of blood and milk PMN against S. *auereus* but did not affect phagocytosis. Vitamin A either hadn't effect or suppressed bactericidal activity and phagocytosis. Control of free radicals is important for bactericidal activity but not for phagocytosis. The antioxidant activity of vitamin A is not important; it does not quench or remove free radicals. β−Carotene, on the other hand, has significant antioxidant properties and effectively quenches singlet oxygen free radicals [38, 63 and 115].

A comprehensive review of the reproductive effects of carotene and/or vitamin A in ruminants has been reported [50, 63] Since 1976, a number of researches have indicated that β−carotene has a function independent of vitamin A in dairy cattle. Dairy cattle receiving extra β−carotene have a higher intensity of estrus, increased conception rates, and reduced frequency of follicular cysts than controls. The corpus luteum of the cow has higher β−carotene concentrations than any other organ, and it has been shown that β−carotene has a specific effect on reproduction in addition to its role as a precursor of vitamin A.

Graves-Hoagland et al. [45] suggest that a positive relationship between β−carotene and luteal cell progesterone during the winter when plasma β−carotene and vitamin A are decreased. Other investigate by cattle have been reported in which pregnancy rates were lower by low dietary β−carotene but were adequate in vitamin A [18, 30 and 63]. However, other studies of cattle failed to detect differences between groups supplemented by β− carotene and control groups in the above-mentioned responses [8, 41, 63 and 109].

Aréchiga et al. [7] reported that in cows fed β−carotene the pregnancy rate at 120 days postpartum was 14.3% higher, and milk yield was 6 to 11% higher than in controls.

Injectable β−carotene has increased conception rates in swine and improved live births and live weights in pigs [24, 63]. Contradictory results were obtained from studies that investigated the effect of supplemental β−carotene on reproductive function in mares. β− Carotene supplementation had a positive effect on the pregnancy rate of mares in some studies [1, 63 and 81].

There are significant new views on the health useful of megavitamin doses, particularly the antioxidant vitamins. Because damage to mammalian tissues induced by free radicals is believed to contribute to the aging process and to the development of some degenerative diseases [21, 63], it has been proposed that dietary carotenoids serve as antioxidants in tissues [63, 102].This possibility is supported by numerous epidemiological studies that indicate an inverse association between the increased intake of carotenoid-rich fruitsand vegetables and the incidence of disease.

There has been much research regarding the potential protective effect of carotenoids against chronic diseases [92].

Studies have shown inverse relationships between serum levels of one or more carotenoids and a number of diseases, including cancer [60, 105], cardiovascular disease [43, 63 and 107], eye diseases of age-related macular degeneration [98], and nuclear sclerotic and cortical cataracts [59, 63]. In relation to cancer, *in vitro* studies have demonstrated that carotenoids can inhibit chemically induced neoplastic transformation [14, 63], induce remission of oral leukoplakia [42, 63], quench free radicals such as singlet oxygen[97, 63], and modulate immune activity [63, 65]. There is recent evidence that some of the carotenoid protection against cancer relates to gene regulation [13, 63].Several hundred carotenoid research studies have been published since 1996, when two major intervention trials showed a lack of protective effect of β-carotene supplements against lung cancer. Recent epidemiologic studies, however, continue to show an association between high dietary intake of β-carotene and lower risk of lung cancer [32, 63].

Interactive effect of β-carotene supplements against lung cancer. Recent epidemiologic studies, however, continue to show an association between high dietary intake of β-carotene and lower risk of lung cancer [31, 63].

The predominant carotenoids in human tissues are β−carotene and lycopene. Compared with other carotenoids and other antioxidant compounds, including vitamin E, lycopene has been reported to be a more efficient quencher of singlet oxygen in *vitro* [38, 63].

Lycopene disappearance precedes the disappearance of β−carotene when human low-density lipoprotein is oxidized *in vitro* [40, 63].

When skin is subjected to UV light stress, more skin lycopene is destroyed compared with

β−carotene, suggesting a role of lycopene in mitigating oxidative damage in tissues [63, 87].

One study suggests that eating tomatoes, which are rich in lycopene, can significantly reduce the risk of heart attacks and prostate cancer. The predominant carotenoids in human tissues are β−carotene and lycopene. Compared with other carotenoids and other antioxidant compounds, including vitamin E, lycopene has been reported to be a more efficient quencher of singlet oxygen *in vitro* [40, 63] disappearance precedes the disappearance of β−carotene when human low-density lipoprotein is oxidized *in vitro* [31, 63]. When skin is subjected to UV light stress, more skin lycopene is destroyed compared with β−carotene, suggesting a role of lycopene in mitigating oxidative damage in tissues [33, 63].

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