

**AN INTRODUCTION TO VITAMINS,
MINERALS AND OXIDATIVE STRESS**

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**The Role of Micronutrients and Reactive Oxygen
Species in Normal and Pathological Processes**

Stefan A. Hulea



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*An Introduction to Vitamins, Minerals and Oxidative Stress:
The Role of Micronutrients and Reactive Oxygen Species in Normal and Pathological Processes*

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PREFACE

The idea of writing this book came from the realization that in the current general biochemistry text books the information on important micronutrients such as vitamins and minerals is scattered throughout the text, which makes its retrieval time-consuming and tedious (think of how precious time is especially when preparing for an exam) so that something had to be done to alleviate the situation. In addition, oxidative stress, which has been shown to play an important role in human pathology not to mention phenomena such as programmed cell death and aging is treated sparingly despite the growing interest of biomedical researchers in the role of free radicals in the modulation of a variety of biological processes like cell growth and differentiation, the immune response, signal transduction, etc.

Readers also learn that the uptake of micronutrients is a synergistic process and that the absorption and utilization of a certain nutrient can depend on the presence and concentration of other micronutrients in the gut. For instance, the absorption of vitamin C is greatly enhanced by the presence of iron, calcium, magnesium and bioflavonoids, and that of zinc by copper, calcium, phosphorus, vitamins B1 and B6. In contrast, high daily doses of vitamin C can interfere with copper absorption while iron deficiency may impair the absorption of vitamin D.

How much of these nutrients are required on a daily basis and what advice should we give to patients? Experts are still divided over the issue. A well-balanced diet that includes five servings of fresh fruit and vegetables ensures that all the essential vitamins and minerals are supplied in physiological concentrations. However, as mentioned above, a certain vitamin or mineral taken in large doses may upset the absorption/metabolism of other micronutrients. (Patients may be overdosing on health supplements without telling their physician, of course.) Thus for certain medical conditions where supplementation is warranted, the advice of a nutritionally oriented physician should be sought. The recommended intakes of vitamins and minerals shown in this book apply to healthy individuals eating a balanced diet and wishing to maintain good health.

Part II of this book introduces the reader to the concept of oxidative stress, which is caused by free radicals whose uncontrolled action leads to disease. Reactive oxygen species (ROS) can damage DNA, proteins and cellular structures such as membranes, thus disturbing the normal functioning of cells. However, at low concentrations ROS were shown to modulate a variety of biological processes such as cell growth and differentiation, the immune response, senescence and programmed cell death. Readers will learn how free radicals are generated, what their intracellular targets are and how cells defend themselves against the deleterious action of ROS. Two very active free radical research lines deal with apoptosis and aging. The book presents the latest developments in these areas, where ROS have been shown to

PREFACE

play an important role. It also attempts to explain them in a concise and simple way so that readers do not feel overwhelmed by too many hard-to-grasp chemical concepts.

Although intended primarily for life sciences/medical university students and senior high school students with an interest in life sciences careers, this book may also prove useful to researchers in the biomedical sciences and to healthcare providers who wish to refresh their memory on essential micronutrients and their biological role or keep up to date.

The electronic format of this book, as well as sound and video files, links to the original research articles, power point presentations of selected topics, and interactive quizzes, are available through the publisher's website, where a link to the author's website is also listed. These enhancements make the reading of this book a new and exciting experience not to be missed.

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Last but not least I thank my family for support, encouragement and for patiently putting up with my long working hours and absence, at times from the family dinner table.

PART I. VITAMINS AND MINERALS

INTRODUCTION

Vitamins and minerals are essential to life. They act as cofactors or prosthetic groups for most enzymes, thus making biochemical reactions possible. Some cofactors are transiently associated with a given enzyme and in this capacity they function as co-substrates. They are also called **coenzymes**. The catalytically active protein-cofactor complex is called a **holoenzyme**. The NAD/FAD-containing enzymes for instance, are known as the oxidation-reduction enzymes. On the other hand, there are prosthetic groups that are permanently associated with the protein through hydrophobic and hydrogen bonding interactions. For instance, the tightly bound heme group (containing covalently bound Fe^{3+}) is the prosthetic group of the enzyme catalase (iron occurs as Fe^{3+}) as well as that of cytochromes of the respiratory chain (where the iron cycles between the oxidized (Fe^{3+}) and the reduced (Fe^{2+}) forms). Besides being cofactors for enzymes some vitamins such as the fat-soluble vitamins A and D have been shown to exhibit hormone-like functions. Thus, vitamin A and its metabolites retinaldehyde and retinoic acids are involved in the growth, differentiation and maintenance of epithelial tissues as well as for reproduction (1). Retinoic acids can substitute for vitamin A-deficient animals in growth promotion and epithelial differentiation. As for vitamin D is interesting to note that the skin is both the site of vitamin D_3 and 1,25-dihydroxy vitamin D_3 synthesis and a target organ for the latter. 1,25 $(\text{OH})_2$ vitamin D_3 is essential for mineral homeostasis and bone integrity as well as the regulation of growth and differentiation in normal and malignant tissues.

The table below lists the most common coenzymes and their precursor vitamins as well as the type of reactions in which they take part.

Table 1: The B vitamin-derived coenzymes and the reactions they catalyze

Vitamin	Coenzyme	Reaction mediated	Binding
Thiamine (B1)	Thiamine pyrophosphate	α -keto acid decarboxylation	Tight
Riboflavin (B2)	Flavin coenzymes (FMN and FAD)	Oxidation-Reduction	Tight

Vitamin	Coenzyme	Reaction mediated	Binding
Nicotinic acid (B3)	Nicotinamide coenzymes (NAD/NADP)*	Oxidation-Reduction	Loose
Pantothenate (B5)	Coenzyme A	Acyl transfer	Tight
Pyridoxine (B6)	Pyridoxal phosphate	Amino group transfer	Tight
Cobalamin (B12)	Coenzyme B12	Rearrangements (a H atom is directly transferred between two adjacent carbon atoms; Methyl group transfer between two molecules)	Tight
Biotin (H)	Biotin	Carboxylation	Tight
Folic acid	5,6,7,8 Tetrahydrofolate**	One-carbon group transfer	Tight

* In this table the pyridine nucleotides are not referred to by their oxidation state. More on that can be found on the vitamin B3 page.

** Other active forms are: N⁵, N¹⁰-methylene THF and N¹⁰-formyl THF.

Minerals are generally tightly bound to the protein moiety and are either directly involved in the catalytic process or help the protein perform its specific biological function. Among the former are metal ions such as Cu²⁺, Zn²⁺, Mn²⁺, Se²⁺, Fe³⁺, which are part of the active site of enzymes involved in redox reactions while the latter group comprises cations that do not take part in catalytic reactions. A typical example is Zn²⁺, which can function as a non-catalytic agent in the zinc-finger motifs found in the transcriptional factors that are proteins involved in DNA replication. These are specific repetitive amino acid sequences (some 30 residues long) that have Zn²⁺ covalently linked to Cys and His residues.

Most of the higher organisms, including the humans are not able to synthesize their own essential factors, which they must, therefore, acquire through diet. The high turnover of vitamins, especially the water-soluble ones, requires that they be replenished through food on a daily basis. It is well known that food processing

causes the foodstuffs we buy at the supermarket to be depleted of most vitamins and minerals. A diet rich in fresh fruits and vegetables restores the balance of essential nutrients in the body.

In vitamin deficiency, enzyme-catalyzed reactions may slow down or not occur at all. This leads to profound changes in the cellular metabolism and if vitamin/mineral deficiency is allowed to continue for a longer period of time degenerative diseases such as cardiovascular disease, rheumatoid arthritis, cancer and others may develop.

It is important to distinguish between severe vitamin deficiency - which is very rare nowadays in the Western world - and that which affects over half of the population in the Western hemisphere and is called subclinical deficiency by many nutritional experts. This means people may get most of their daily vitamin requirements from food but not in the optimal amounts. Over time this will lead to a partial breakdown of the finely-tuned cellular metabolism with unfavorable consequences for the body as a whole. Because these subtle changes occur over an extended period people are not aware that something is going wrong.

Although most people believe that they might have an adequate supply of vitamins and minerals from various foods it has become apparent that even with a “normal” well-balanced diet it is difficult to get all the necessary micronutrients required for optimal body functions because:

- Extensive farming and the use of pest-control chemicals lead to mineral depletion in soil
- Processed foods lack most vitamins and minerals
- Absorption of nutrients decreases with age
- Un-ripened fruits and vegetables (such as they are usually transported to supermarkets) as well as hybrid crops lack certain nutrients and natural flavours.

So, what amounts of each vitamin and mineral should our body receive on a daily basis? Although a wide consensus on the exact daily intake of vitamins and minerals has not yet been reached, most experts in nutrition suggested that the Recommended Daily Allowance (RDA) issued some 60 years ago must be amended. In 1989 the National Research Council of U.S.A. issued new RDAs (2) that took into account the developments in the nutritional sciences since the late 1940s. However, as argued in a recent article (3) most of the nutrient requirements were still based on old methods of calculating the RDA, i.e. on balance or factorial analysis (see the Daily Requirements section for a brief discussion on the balance and factorial analysis methods for determining nutrient requirements) rather than on biomarkers. Since many enzymes that require vitamins and minerals as cofactors are regulated by

gene expression it is obvious that the analysis of that expression could form a better foundation on which to build a sound dietary allowances program for human nutrition. Since 1989 the new Dietary Reference Intakes guideline, which replaced the old RDA, has been further amended (1998-2001) (4,5), but there is still a lot to do in the direction of setting the basis of daily nutrient requirements solely on good biochemical markers.

It has also become apparent in the last 15 years or so that there is a close relationship between diet and health/disease. A healthy diet should include five servings of fresh fruits and vegetables a day. This will ensure an adequate supply of vitamins and minerals that will keep the body working optimally and together with an appropriate lifestyle help prevent degenerative diseases and premature aging. Numerous epidemiologic studies have indicated that people who consume plenty of fresh fruits and vegetables have a lower risk of developing cancer than those who eat very little fruit and vegetables. Several experimental models have demonstrated that cellular metabolism is greatly disrupted when antioxidants and other factors are in short supply as so eloquently argued in an essay by the distinguished biochemist Bruce N. Ames (6). In a series of brilliant papers Ames and his associates showed that oxidants produced by the normal endogenous metabolism can damage DNA in both bacteria and higher organisms. The oxidative damage to DNA was determined by measuring the markers of DNA oxidation i.e. thymine glycol, thymidine glycol and hydroxymethyluracil in human and rat urine (7). A low intake of antioxidant vitamins and minerals such as selenium increases the risk of DNA mutations that may eventually lead to cancer. In fact, in a recent paper Ames and Wakimoto raised the question whether vitamin and mineral deficiencies, at subclinical levels as they so commonly are in North America may be a cancer risk (8). That is why it is important to remember that we are under constant attack from both endogenously and exogenously produced free radicals and we should have an adequate supply of antioxidants from diet at all times.

DNA can also be damaged by low folate levels. It was shown that chromosome breaks occur more often at low folate concentration through a mechanism that involves a block in the methylation of dUMP to dTMP. As a result there is a misincorporation of dUTP into DNA instead of dTMP (9). Here again, the damage to DNA can disrupt cellular metabolism, which in turn may lead to disease.

From the Ames' group came also an interesting concept based on the finding that the activity of defective vitamin B-dependent enzymes in human genetic disorders could be partially restored by the administration of high doses of the corresponding B vitamins (10). These defective enzymes apparently have a decreased binding affinity (increased K_m for the coenzyme) due to mutations in their genes. The so-called K_m concept may lead to important changes in our perception on how to tune up the metabolism in cases of subclinical vitamin deficiencies. Many people fail to realize that vitamin/mineral deficiency does not kill you on the spot, it only

wears you down to the point where there is a high risk of developing degenerative diseases or experience an early aging.

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CHAPTER 1.

VITAMINS

The information on vitamins and minerals in the next chapters is by no means exhaustive. It is intended to be a quick reference study guide on the basics of these micronutrients. Readers are encouraged to find out more about the world of micronutrients by turning to articles and reviews in science journals and to what is available on the subject on the internet.

Vitamin A

Vitamin A is synthesized in the liver of vertebrates from β -carotene. Retinol derivatives, i.e. *retinal* (carbon 15 becomes an aldehyde group) and *retinoic acid* (carbon 15 becomes a carboxylic group) act as visual pigment and hormone, respectively. Retinoic acid binds to receptor proteins in the nucleus, which then interact with transcription factors thus modulating gene expression in the development of epithelial tissue, including skin (1). Most of the biological activity of vitamin A is carried out by the above derivatives although in many research articles mention is made of vitamin A when describing the action of this vitamin.

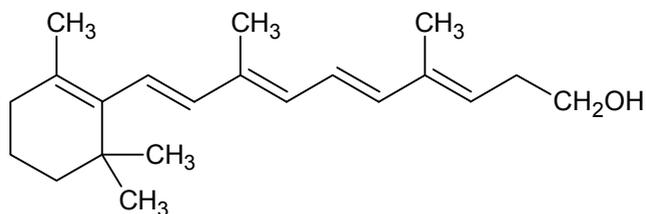


Fig.1: Chemical structure of retinol (Vitamin A1)

The most important biological functions of vitamin A are listed below:

- Involved in reproduction, growth and development, e.g. teeth and bone formation
- Essential for normal immune system maturation and function. There is evidence to suggest that vitamin A deficiency is a risk factor for low antibody production (2). In animal models it was shown that vitamin A

supplementation enhanced cytokine production and secretory immunoglobulin A response to influenza virus infection although supplementation did not alter the clinical or virologic outcome of viral pneumonia (3). Vitamin A supplementation was also found to reduce morbidity and mortality in several infectious diseases such as severe diarrhea, measles-related pneumonia and malaria. Modulation of the immune response by vitamin A varies widely depending on the type of infection and immune response involved (4).

- Stimulates antitumor activity in cancer cell lines. All-trans-retinoic acid exhibited an inhibitory effect on cell growth, cell cycle and alkaline phosphatase activity in human pancreatic cancer cells in vitro (5) while the retinoic acid derivative ABPN [4-amino-2-butylamino)phenyl(2E, 4E, 6E, 8E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoate] was shown to inhibit the growth of colon cancer cells (6).
- β -carotene (pro-vitamin A) exhibits antioxidant activity (quencher of singlet oxygen)
- Vitamin A deficiency leads to: impaired immune function, poor night vision, skin problems
- Interactions: Vitamin E and zinc are important for the proper function of vitamin A. In animal models it was shown that a low zinc intake during pregnancy may lead to teratogenic effects and vitamin A supplementation did not affect the level of zinc in plasma and liver of pregnant rats. In contrast, the concentration of vitamin A in plasma and liver of pregnant rats was affected by the concentration of dietary zinc (7). In humans, the mechanism underlying the impaired vitamin A metabolism found in zinc deficiency is far from clear. It has been suggested that a severe zinc deficiency can impair liver retinol binding protein synthesis and cause a decrease in retinene reductase activity (zinc-dependent enzyme). Zinc-deficient humans exhibit an impaired dark adaptation (8).
- Best food sources: liver, kidney, butter, whole milk, dark green leafy vegetables

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Vitamin D

The D vitamins are sterol derivatives. The natural form of the vitamin, i.e. vitamin D₃ (cholecalciferol) is formed nonenzymatically in the skin of animals through the action of UV light on 7-dehydrocholesterol (Fig.2). Vitamin D₂ is formed by the UV irradiation of the plant sterol ergosterol. It is noteworthy that both vitamins are inactive as such. They become biologically active by further processing in the liver and kidney as to yield 25-hydroxycholecalciferol and 1 α -,25-hydroxycholecalciferol [1,25(OH)₂vitamin D₃, or calcitriol], respectively. The latter, which is a vitamin D-derived hormone acts to increase serum calcium concentration by promoting the intestinal absorption of dietary calcium. As a result, there is an increased uptake of calcium by the bone tissue.

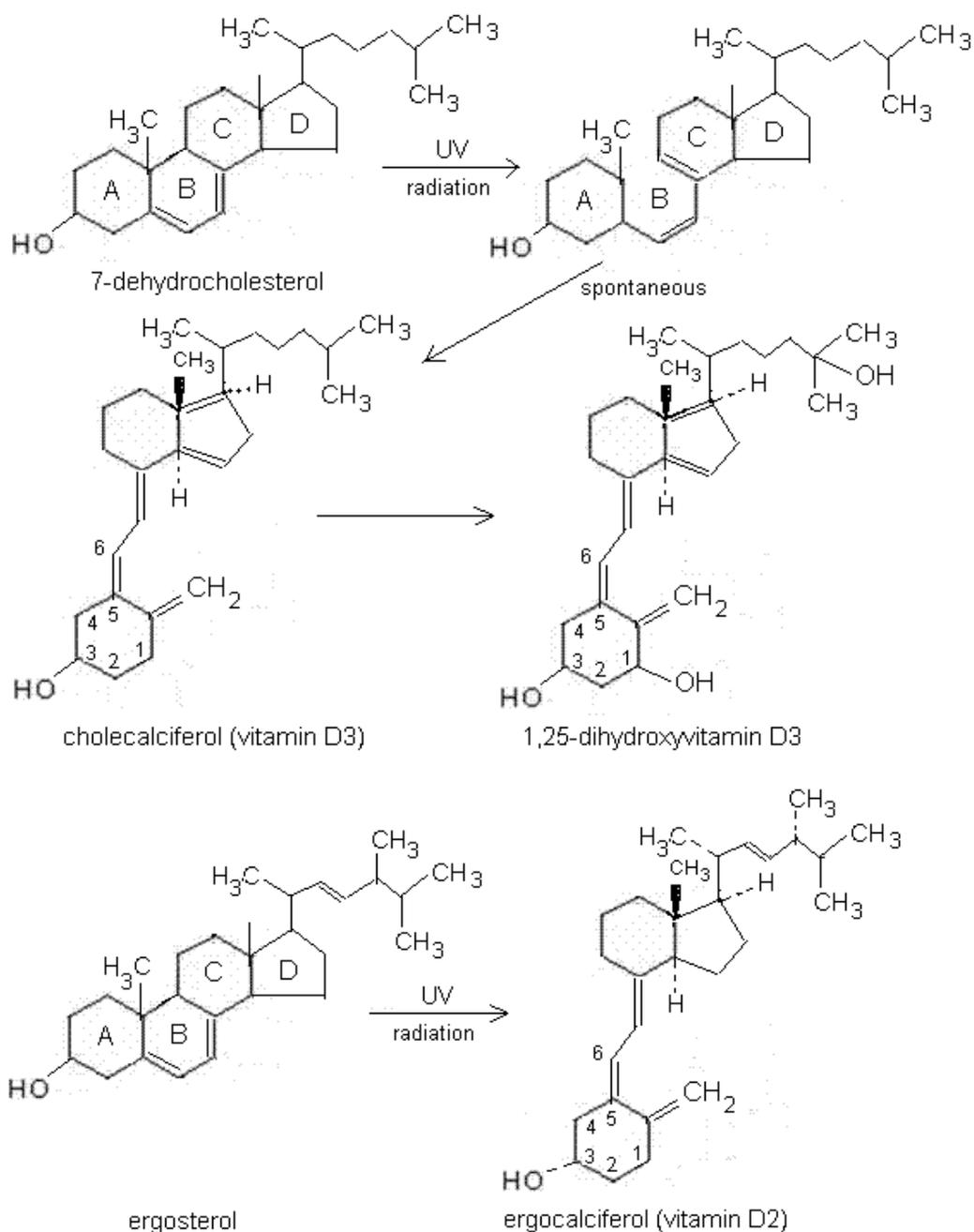


Fig.2: The conversion of two sterols, 7-dehydrocholesterol and ergosterol to 1,25-dihydroxycholecalciferol (vitamin D3) and ergocalciferol (vitamin D2), respectively.

Some of the most important functions of the biologically active D vitamins are listed below:

- Stimulates the calcification of matrix of bone and teeth.
- Promotes the absorption of calcium and phosphorus in the intestine, stimulates bone calcium mobilization and the increase of renal reabsorption of calcium in the distal tube (1).
- Stimulates calcium reabsorption in the kidney.
- Promotes a stable nervous system and heart function.
- Deficiency can lead to: tooth decay, softening of bones, muscular weakness, impaired calcium absorption.
- Best food sources: cod liver oil, fresh water fish (salmon, herring), milk, butter.

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Vitamin E

Natural vitamin E is a mixture of tocopherols and tocotrienols synthesized by plants. Chemically tocopherols consist of a chromanic ring (Fig.3) and an aliphatic side chain (saturated for tocopherols and unsaturated for tocotrienols). There is no significant difference in antioxidant power between the various tocopherols. Vitamin E does not appear to have a specific plasma carrier protein as opposed to vitamins A and D. In plasma it is found in lipoproteins where it protects cholesterol and unsaturated fatty acids against oxidative stress.

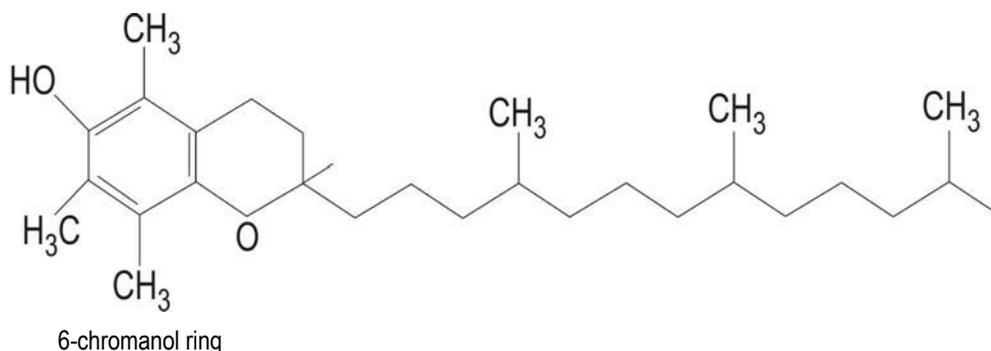


Fig.3: Chemical structure of α -tocopherol.

The most important roles played by vitamin E are:

- Major antioxidant nutrient; it slows down the aging process, which is partly caused by oxidative stress.
- Protects circulating cholesterol in LDL and membrane lipids in red blood cells against oxidative damage.
- Protects immunocompetent cells such as phagocytic cells against oxidative damage that occurs in infections (1).
- Prevents damage to informational macromolecules such as nucleic acids by scavenging free radicals (mainly oxygen reactive species) generated within cells.
- Modulates enzyme activity through specific interactions with enzymes and gene expression through interactions with regulatory proteins such as transcription factors. These actions of vitamin E involve a non-antioxidant type of mechanism that may be relevant in cardiovascular disease (2). The main effects of vitamin E at cellular and molecular level that involve a non-antioxidant mechanism are depicted in Fig.4.

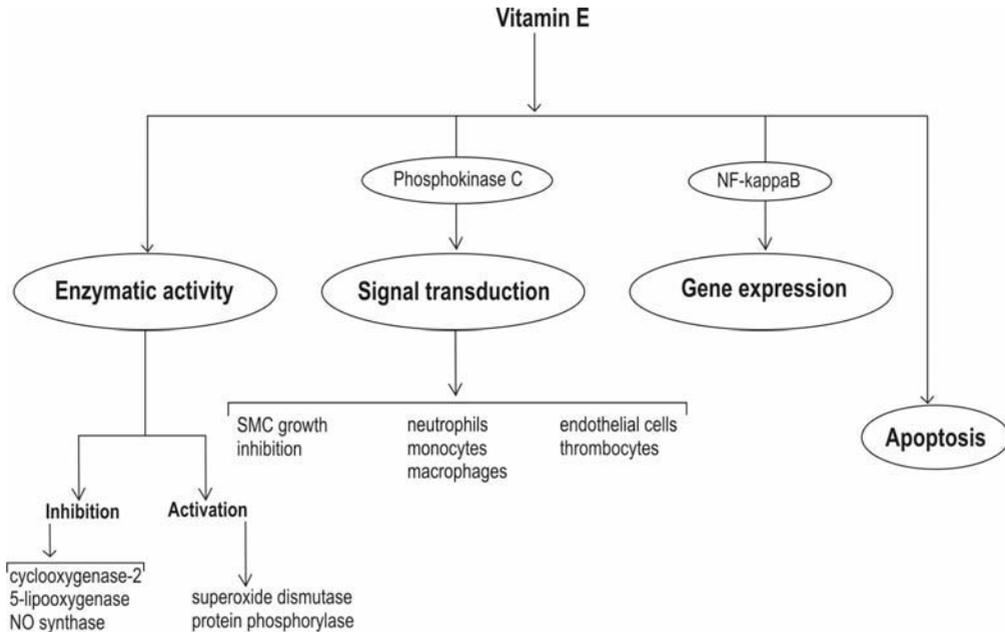


Fig.4: Non-antioxidant effects of vitamin E at molecular and cellular level.

Tocopherols, particularly α -tocopherols, were shown to influence cellular processes such as signal transduction, gene expression and apoptosis. Vitamin E is involved in the modulation of signal transduction by activating protein phosphorylase-2, which catalyzes the dephosphorylation of protein kinase C (PKC). Thus, by dephosphorylation PKC becomes inactive and this in turn triggers a host of events such as the arrest of smooth muscle cell growth, inhibition of superoxide ion production in neutrophils, monocytes, macrophages, inhibition of thrombocytes aggregation and inhibition of endothelin secretion by endothelial cells. By inhibiting cyclooxygenase-2 and 5-lipoxygenase vitamin E is involved in the modulation of the inflammatory response through decreased prostaglandin synthesis and the inhibition of interleukin-1 β (a proinflammatory cytokine), respectively. Although the involvement of vitamin E in transcription factor NF- κ B activity inhibition (NF- κ B controls the expression of various genes involved in inflammatory response and cellular proliferation) has been documented as shown by the inhibition of NF- κ B activation in human T cells culture containing α -tocopheryl acetate it is not clear whether vitamin E blocks directly some of the key steps of NF- κ B activation or acts through intracellular redox status modulation. Redox status modulation is known to be a major determinant of NF- κ B activation.