Available online at www.ijpab.com

DOI: http://dx.doi.org/10.18782/2320-7051.5835

ISSN: 2320 – 7051

Int. J. Pure App. Biosci. **5 (6):** 208-214 (2017)

International Journal of Pure & Applied Bioscience

Review Article

OPEN ACCESS

Interrelationship of Micronutrients: Antagonism and Synergism

Tripathy S.[1], Dhaduk J. J.[2] and Kapadiya S.[3]

[1]Research Scholar, [2]Professor, [3]Senior Research Assistant

Department of Food Science and Nutrition,

ASPEE College of Home Science and Nutrition

Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar-385506

*Corresponding Author E-mail: sucharitatripathy1994@gmail.com

Received: 5.10.2017 | Revised: 13.11.2017 | Accepted: 16.11.2017

ABSTRACT

Vitamins and minerals are considered as micronutrients for body but they play vital role in different body functions. These minerals and vitamins interact with each other's either synergistically to increase each other's activity or antagonistically to decrease their effectiveness in body. Major vitamin antagonisms include antagonism between vitamin A and D, vitamin C and vitamin K, vitamin K and some antibiotics, vitamin C and vitamin B_{12}, Fe, Co etc. Some of the important synergism between micronutrients includes thiamine, riboflavin, pantothenic acid, vitamin D, B_{12}, E. So during diet formulation these factors should be taken care to avoid any disorder.

Key words: *Antagonism, mineral, synergism, vitamin*

INTRODUCTION

In human body system, every nutrient has a specific role either directly on the body or through interfering with the function of other nutrients. These interrelationships among different nutrients either may be advantageous or may lead to deficiency of each other. A loss of this vital balance, particularly among different trace vitamins may lead to subclinical deficiencies or decreased bioavailability leading to different deficiency diseases.

Chemically vitamins are amines which are very much essential for maintenance of vital body function. They are present in small amounts in food. They are involved in the absorption and utilization of the major nutrients like proteins; fats and carbohydrates. Vitamins also have synergistic and antagonistic relationships. Vitamins are involved in several body functions such as they act as coenzymes and are involved synergistically in many enzymatic reactions. They can also protect against deficiencies of other vitamins.

Vitamin Antagonisms

An anti-vitamin is a substance which makes the vitamin unavailable or ineffective within the body. Specifically these substances block the action of some vitamins. Sometimes, the antagonism may not be direct but indirectly they may increase the requirements of target vitamins because of their excessive intake.

Cite this article: Tripathy, S., Dhaduk, J.J. and Kapadiya, S., Interrelationship of Micronutrients: Antagonism and Synergism, *Int. J. Pure App. Biosci.* **5(6):** 208-214 (2017). doi: http://dx.doi.org/10.18782/2320-7051.5835

Vitamin A and D are mutually antagonistic to each other. Vitamin A reduces the toxic effects of vitamin D[9]. Vitamin A enhances the absorption or retention potassium and phosphorus. It has been reported that vitamin B_1 can have an antagonistic action against vitamin B_{12}[1]. The antagonistic relationship between vitamin C and vitamin B_{12} is an indirect one. Vitamin C neither directly affects B_{12}, nor destroys this vitamin. Vitamin C enhances iron absorption. Increased amount of iron in body leads to deficiency of cobalt, which is an integral part of vitamin B_{12}[26]. This is however a rare occurrence and may affect only a small segment of the population who may suffer from iron overload disorders[37].

Vitamin A antagonists

Blood-thinning medications and other drugs, including aspirin, phenobarbital, arsenicals and dicumarol (a drug used medically to retard blood clotting) destroy vitamin A in the body. Vitamin A is also depleted when nitrosamines are formed in the stomach from the union of nitrites with secondary amines and when the mucous membranes of our respiratory passages are exposed to air pollutants such as carbon monoxide, ozone, sulphur dioxide, nitrogen dioxide, lead, hydrocarbons, *etc*.

Vitamin K antagonists

The amount of vitamin K needed by humans is very small and a deficiency is highly unlikely because this vitamin is in a wide variety of commonly available plant foods and again it is synthesized by bacteria in the intestinal tract. However, antibiotic therapy (penicillin, streptomycin, tetracycline, chloromycin, terramycin, *etc*) suppresses bacterial growth and consequently, the synthesis of vitamin K. Other vitamin K antagonists include the drugs dicumarol and hydrocoumarol, which are used by medical people to relieve thrombosis (abnormal formation of blood clots in the blood vessels). As the chemical structure of these antihistamines is similar to that of vitamin K, they act as anticoagulants by interfering with the synthesis of pro-thrombin and the other natural clotting factors. Large doses of vitamin A can also inhibit the absorption of vitamin K.

Vitamin C and vitamin E interactions

Vitamin C and vitamin E are both antioxidants and protect against reactive oxygen species. These substances are of parallel interest as water-soluble vitamin C regenerates lipid soluble vitamin E in an outside the cell of the organism[36]. There is much evidence indicating that vitamins C and vitamin E may also have a physiologically relevant interaction.

In guinea pigs, vitamin C deficiency led to reduced levels of vitamin E[2] and administration of oxidized frying oil, large doses of vitamin C increased the level of vitamin E in the liver, kidney, spleen, and lungs[17]. In inherently scorbutic rats, vitamin C deficiency led to reduced vitamin E levels in the liver, kidney, and heart. In normal rats, vitamin C supplementation increased plasma vitamin E level[8]. Contradicting to this Hruba *et al.*[14] reported that vitamin C deficiency did not affect the plasma vitamin E level in guinea pigs. The excessive doses of vitamin C may reduce plasma vitamin E levels[8].

The estrogen in oral contraceptives is also an antagonist of vitamin E. Vitamin C reacts with several alien substances in the bloodstream. All drugs and pollutants can be considered as vitamin C antagonists. Some of the foremost vitamin C antagonists include ammonium chloride, stribesterol, thiouracil, atropine, barbiturates and antihistamines. All stresses (surgery, emotional outbursts and upsets, acute pressures, extremes of heat and cold and all drugs) as well as alcoholic beverages are vitamin C antagonists.

Anemia is often observed in vitamin C deficient patients. A normocytic or macrocytic anemia is generally observed, though megaloblastic has been reported sometimes in same patients. The presence of megaloblastic anemia in some scorbutic patients has given rise to the consideration that either a dietary deficiency of folic acid existed or that folate metabolism was impaired in vitamin C deficiency. In some instances the megaloblastic anemia was effectively treated with ascorbic acid alone, while in other reports, additional amounts of folic acid supplementation were required[31].

Vitamin E supports a healthy immune system and may help to protect against cardiovascular disease by decreasing atherosclerosis and helping the blood circulation. Because of these effects on the blood, taking vitamin E supplements may increase the risk of bleeding, especially in patients taking anticoagulant medications such as warfarin or patients of vitamin K deficiency[25].

Vitamin K is necessary for blood to coagulate effectively. Patients with a vitamin K deficiency have an increased risk of uncontrolled bleeding. There are some postulations which suggest that vitamin E inhibit the vitamin K dependent carboboxylase activity and subsequently inhibit the coagulation cascade[32]. Therefore, high amount of vitamin E decrease the activity of vitamin K in coagulation. α-tocopheryl hydroquinone is an oxidized product of α- tocopherol and an efficient antioxidant. Vitamin E quinine is a potent anticoagulant as inhibitor of vitamin K dependent carboxylase that controls blood clotting[15].

B vitamin Antagonists

Cortisone is an antagonist of vitamin B_6 (pyridoxine). Since the body needs B vitamins to metabolize sugars, B vitamins are depleted when refined sugar or flour is consumed as refined sugar and flour are devoid of B vitamins that existed in the beet, cane or grain before refining. Specifically, the body's supply of vitamin B_1, vitamin B_2, biotin, choline, niacin and the mineral magnesium are depleted when refined sugar and flour are consumed. Alcoholic beverages are antagonists of thiamin and the other B-complex vitamins. Coffee is another popular beverage that is a B vitamin antagonist, because it contains caffeine and other noxious substances like chlorogenic acid. Inositol deficiency may occur among coffee drinkers along with deficiency of biotin and thiamin. Raw fish and raw shellfish, including oysters, are also B-complex antagonists as raw fish contains the enzyme thiaminase which destroys thiamine. This is one of many reasons not to eat the Japanese dish, sashimi (raw fish) or any other raw seafood.

The urinary excretion of 4-pyridoxic acid (the major metabolite of vitamin B_6) was elevated with an increased intake of ascorbic acid[31].

The most potent folacin (folic acid) antagonist is aminopterin, a substance that has been used in the medical treatment of leukemia, a disease in which there is a marked increase in the production of leucocytes (white blood cells). Some research indicates that large doses of vitamin C block the absorption of vitamin B_{12}[31].

Vitamin Synergisms

Synergy is defined as the combined interaction of several system elements which produces an entirely different or greater effect compared to what they produce by their separate effects. In many cases, a synergistic relationship between certain elements can produce long-term benefits[4].

Vitamins are involved in many reactions and also have beneficial effect or synergistic effect. They act as coenzymes and are involved synergistically in many enzymatic reactions. They can also protect against deficiencies of other vitamins.

Table: 1 Different vitamin and their synergistic vitamins[35]

Vitamins	Synergist Vitamins
A	B_2-C-E-B_3-B_1-B_6
D	B_{12}-E
E	A-B_6-C-B_{12}-B_1-B_5-B_3-D
B_1	E-C-B_6-B_{12}-B_3-B_5-A-B_2
B_2	A-B_3-B10
B_6	E-A-B_6-B_3-B_5
B_{12}	B_1-B_3-B_6-E-B_5-C--D
C	A-E-B_6-B_3-B_5
B_3	B_1-B_2-B_6-A-B_5-E
B_5	C-E-A-B_1-B_3-B_6

Antioxidant vitamin supplementations may reduce the severity of trypanosome infection by offering protection against possible oxidative injuries associated with the disease[33] and thus, beneficial in pregnancy related infections (malaria) and complication (hyperlipidemia). In the last 20 years, some clinical and epidemiological researches have suggested a potential protective effect of antioxidant nutrients such as beta-carotene, vitamin C, and vitamin E on the risk of cancer and cardiovascular diseases. Vitamin C can also regenerate oxidized Vitamin E by

reducing it back to its active form. The key step is the reaction between the tocopheroxyl radical and vitamin C[5]. Vitamin C regenerates active vitamin E and increases cholesterol excretion[3]. Plasma tocopherol levels also improved upon supplementation of vitamins E and C, this improvement suggests synergism of vitamin C with glutathione peroxides to revitalize vitamin E[19].

Vitamin K_2 (menaquinone) is responsible for activating certain proteins by adding CO_2 (carbon dioxide) to them. Vitamins A and D help body to absorb zinc which in turn enables body to absorb fat-soluble vitamins. Vitamins A, D, and K_2 work together to build strong bones and teeth, promote growth, protect against calcification of the soft tissues, and support immune system[20].

Vitamin B synergism

Vitamin B_{12} supports the formation of healthy red blood cells. Taking folic acid (vitamin B_9) can mask the effects of megaloblastic anemia. The interaction between folic acid and vitamin B_{12} can increase the effects of the anemia and lead to permanent neurological damage.

For the conversion of folic to folinic acid, vitamin B_{12} is essential. Folic acid therapy of patients, suffering from sprue, causes an increase in plasma vitamin B_{12} content. Vitamin B_{12} deficiency causes a rise in unconjugated folates and depletion of intracellular conjugated folates.

Vitamin B_6, a member of the B family of vitamins along with B_{12}, promotes the production of hormones and neurotransmitters, the chemicals that carry signals between the nerves. Vitamin B_6 is also important for the production of healthy red blood cells because the presence of B_6 enhances the absorption of B_{12}[31].

Administration of thiamine, riboflavin and pantothenic acid offered partial protection from spontaneous seizures, which may be due to vitamin B_6 deficiency[31]. A deficiency in vitamin B_6 can lead to a deficiency in B_{12}. In addition, vitamins B_6, B_{12} and folic acid all work together to control the level of homocysteine, an amino acid associated with an increased risk for heart disease[31]. Thiamine deficiency is often accompanied by disturbance of riboflavin metabolism, causing considerable excretion of riboflavin in urine. In another interaction, deficiency of pantothenic acid affects adversely the mobilization of riboflavin from the liver. Administration of pantothenic acid of deficient animals increases the mobilization of riboflavin from liver and raises the levels of riboflavin in blood[31].

The liver of rats fed on thiamine deficient or riboflavin deficient diets contained smaller amount of niacin than normal controls[31]. Treatment of pellagra with niacin precipitates symptoms of thiamine and riboflavin deficiencies indicating that niacin deficiency is accompanied by secondary deficiency of thiamine and riboflavin.

Baker *et al.*[24] followed whole blood ascorbic acid levels in normal adult men subjected to depletion and repletion of vitamin B_6. Whole blood level of ascorbic acid progressively fell during the vitamin B_6 depletion phase and returned to normal level upon repletion with pyridoxine. In a subsequent study on Vitamin C deficiency in adult men, the urinary excretion of free pyridoxine was measured[31].

Vitamin B_6 deficiency has been reported to cause impairment in vitamin B_{12} absorption in the rat, resulting in a lowering of vitamin B_{12} levels in the serum and in reduced vitamin B_{12} stores in the liver[31]. The riboflavin deficiency in the rat slowed the uptake of labeled pyridoxine into the liver and decreased the conversion of pyridoxine to its metabolites[31].

Interaction among vitamin C, vitamin E, and β-carotene

The effects of vitamin C (ascorbic acid), vitamin E (α-tocopherol), and β-carotene as antioxidants and their cooperative action against the oxidation of lipid in solution, membranes, and lipoproteins have been studied and reviewed by Niki and associates. Ascorbic acid and α -tocopherol act as potent and probably the most important, hydrophilic and lipophilic antioxidants, respectively. They function at their own site individually and

furthermore act synergistically. β-carotene acts as a weak antioxidant in solution and has lower reactivity toward radicals than that of α – tocopherol[23].

Some other interrelationship of vitamins:

Biotin and pantothenic acid: Biotin deficiency may be aggravated by a simultaneous pantothenic acid deficiency. The addition of biotin to the diet not only protects the animals from biotin deficiency but also reduces the severity of the symptoms of pantothenic acid deficiency[31].

Vitamin A, E and K: It has been shown that albino rats fed on a vitamin K deficient diet develop signs of vitamin K deficiency when vitamin A in diet is increased. Considerable amount of work has been carried out by different workers on the role of vitamin E in influencing storage and mobilization of vitamin A in liver. Administration of vitamin E helps to increase the storage of vitamin A in liver[31].

Ascorbic acid and other vitamins: The albino rat can synthesize ascorbic acid. This synthetic capacity, however, is diminished considerably in thiamin and riboflavin deficiencies. This indicates that both these vitamins play an important role in the biosynthesis of ascorbic acid. A depletion of the ascorbic acid content of tissues of rats occurred when the animals were fed on diets deficient in vitamin A or thiamin or riboflavin[31].

Folic acid and Vitamin B_{12}: For the conversion of folic to folinic acid, vitamin B_{12} is essential. Folic acid therapy of patients, suffering from sprue, causes an increase in plasma vitamin B_{12} content. Vitamin B_{12} deficiency causes a rise in unconjugated folates and a marked depletion of intracellular conjugated folates.

Vitamin B_{12} and Vitamin C: Vitamin B_{12} is an important nutrient that plays a role in neurological function, the synthesis of DNA and the creation of red blood cells. Vitamin B_{12} deficiencies result in numerous symptoms such as anemia and neurological problems.

Herbert and Jacob[12] reported that presence of ascorbic acid in meal destroys the vitamin B_{12}, but the same report was not replicated during further study by Newmark *et al.*[22]. Again Herbert *et al.*[13] reported that some patients having spinal cord injury found to have deficient amount of vitamin B_{12} after receiving ascorbic acid for a period of 2 years. Lucock *et al.*[18] reported that dietary vitamin C regulates red cell folate status of body either directly or indirectly protecting dietary 5-methyle-tetra hydro folate as vitamin C is an antioxidant. So it can be said that antioxidant vitamin C is critical in sparing highly labile trace levels of the natural 5-methyle- tetra hydro folate.

CONCLUSION

In human daily requirements of vitamins and minerals and very less and also considered as micronutrients. The understanding of nutrition and its important role in health is most important and intricate part of health care, particularly among today's progressive health care providers. Vitamin interrelationship with other nutrients and drugs are very important study for the nutrition science personnel to avoid unnecessary side effect of both deficiency and toxicity of micronutrients.

Vitamin synergism action is very useful for the body proper mechanism action and also effective for other nutrients absorption in the body. Nutritional therapeutics has largely been directed towards the recognition and correction of nutritional deficiencies. It is now becoming evident that a loss of homeostatic equilibrium between the nutrients can also have an adverse effect upon health. A loss of this vital balance, particularly between the trace elements, can lead to subclinical deficiencies.

REFERENCE

1. Allen, R. Abstracts, 18th Congress of the International Society of Hematology. Mont., Ca. Aug. (1980).
2. Bendich, A., D'Apolito, P., Gabriel, E. and Machlin, L. J.. Interaction of dietary vitamin C and vitamin E on guinea pig immune responses to mitogens. *Journal of nutrition*. **114(9):** 1588-1593 (1984).

3. Bisby, R.H. and Parker, A.W. Reaction of ascorbate with the "α-tocopheroxyl radical in micellar and bilayer membrane systems. *Arch. Biochem. Biophys.* **317:** 170-178 (1995).
4. Bodalier, T. The synergistic relationship between Magnesium, Zinc and Vitamins A, D and K_2**.** Accessed from: http://beautynutrition.com/vitamins/synergistic-relationship-magnesium-zinc-vitamins-d-k2 (2014).
5. Böhm, F., Edge, R., Land, E.J., McGarvey, D.J. and Truscott, T.G. Carotenoids enhance vitamin E antioxidant efficiency. *Journal of American Chemical Society*. **119(3):** 621-2 (1997).
6. Byers, T. and Perry, G. Dietary carotenes, vitamin C, and vitamin E as protective antioxidants in human cancers. *Annual Review of Nutrition*. **12:** 139-159 (1992).
7. Chen, L.H., Lee, M.S., Hsing, W.F. and Chen, S.H. Effect of vitamin C on tissue antioxidant status of vitamin E deficient rats. *International Journal of Vitamin Nutrition Research*. **50(2):** 156-162 (1980).
8. Chen, L.H., Chang, H.M. Effects of high level of vitamin C on tissue antioxidant status of guinea pigs. *International Journal of Vitamin Nutrition Research***. 49:** 87-91 (1979).
9. Clark, I. and Bassett, C.A.L. The amelioration of hypervitaminosis D in rats with vitamin A. *J. Exp. Med.* **115(1):** 147-156 (1962).
10. Corrigan, J.J. The effect of vitamine on warfarin-induced vitamin K deficiency. *Ann. N. Y. Acad. Sci.*, **393(1):** 361-368 (1982).
11. Diplock, A.T. Antioxidant nutrients and disease prevention: an overview. *American Journal of Clinical Nutrition*. **53:** 189S-193S (1991).
12. Herbert, V. and Jacob, E. Destruction of vitamin B_{12} by ascorbic acid. *JAMA*. **230:** 241-242 (1974).
13. Herbert, V., Jacob, E., Wong, K.T., Scott, J. and Pfeffer, R.D. Low serum vitamin B_{12} levels in patients receiving ascorbic acid in megadoses: studies concerning the effect of ascorbate on radioisotope vitamin B_{12} assay. *American Journal of Clinical Nutrition*. **31:** 253-258 (1978).
14. Hruba, F., Novakova, V. and Ginter, E. The effect of chronic marginal vitamin C deficiency on the α-tocopherol content of the organs and plasma of guinea-pigs. *Experientia*. **38(12):** 1454-1455 (1982).
15. Jain, P., Pareek, A., Ratan, Y., Sharma, S., Paliwal, S. Free radicals and dietary antioxidants: a potential review. *Int J Pharm Sci Rev Res*. **18(1):** 34-48 (2013).
16. Kanazawa, K., Takeuchi, S., Hasegawa, R., Okada, M., Makiyama, I., Hirose, N., Toh, T., Cho, S.H. and Kobayashi, M. Influence of ascorbic acid deficiency on the level of non-protein SH compounds and vitamin E in the blood and tissues of guinea pigs. *Nihon Univ. J. Med*. **23:** 257-263 (1981).
17. Liu, J.F. and Lee, Y.W. Vitamin C supplementation restores the impaired vitamin E status of guinea pigs fed oxidized frying oil. *Journal of Nutrition*. 128:116-22 (1998).
18. Lucock, M., Yates, Z., Boyd, L., Naylor, C., Choi, J.H., Ng, X., Skinner, V., Wai, R., Kho, J., Tang, S. and Roach, P. Vitamin C-related nutrient–nutrient and nutrient–gene interactions that modify folate status. *Europian Journal of nutrition*. **52(2):** 569-582 (2013).
19. Madhavi, M., Samudram, P., Kumar, A.H. and Victor, L. Effect of antioxidant vitamins C and E supplementation on its plasma levels and on lipid profile in pulmonary tuberculosis patients. *Am J Infect Dis*. **5(3):** 263-72 (2009).
20. Masterjohn, C. Nutritional Adjuncts to the Fat-Soluble Vitamins. The westernA. price foundation for wise traditions in food, farming and health arts. Accessed from: http://www.westonaprice.org/health-topics/abcs-of-nutrition/nutritional-adjuncts-to-the-fat-soluble-vitamins (2013).

21. McDowell, L.R. Vitamins in Animal Nutrition. Comparative Aspects to Human Nutrition. Vitamin A and E. London, *Academic Press*, **10(52):** 93-131 (1989).
22. Newmark, H.L., Scheiner, J.M., Marcus, M., Prabhudesai, M. Stability of vitamin B12 in the presence of ascorbic acid. *American Journal of Clinical Nutrition.* **29:** 645-649 (1976).
23. Niki, E., Noguchi, N., Tsuchihashi, H. and Gotoh, N. Interaction among vitamin C, vitamin E and beta-carotene. *American Journal of Clinical Nutrition*. **62(6):** 1322S-1326S (1995).
24. Packer, J.E., Slater, T.F. and Wilson, R.L. Direct observation of a free radical interaction between vitamin E and vitamin C. *Nature.* **278:** 737-8 (1979).
25. Pastori, D., Carnevale, R., Cangemi, R., Saliola, M., Nocella, C., Bartimoccia, S., Vicario, T., Farcomeni, A., Violi, F. and Pignatelli, P. Vitamin E serum levels and bleeding risk in patients receiving oral anticoagulant therapy: a retrospective cohort study. *Journal of the American Heart Association*. **2(6):** e000364 (2013).
26. Pollack, S., George, J.N., Reba, R.C., Kaufman, R.M. and Crosby W.H. The absorption of nonferrous metals in iron deficiency. *Journal of Clinical Investigation.* **44(9):** 1470 (1965).
27. Rumah, I.A. Effects of intraperitoneal administration of vitamins C and E or A and E combinations on the severity of Trypanosomabruceibrucei infection in rats. *African Journal of Biochemistry Research.* **2(3):** 089-091 (2008).
28. Sharma, M.K. and Buettner, G.R. Interaction of vitamin C and vitamin E during free radical stress in plasma: an ESR study. *Free Rad. Biol. Med*. 15:649-653 (1993).
29. Sies, H., Stahl, W., Sundquist, A.R. Antioxidant functions of vitamins. *Annals of the New York Academy of Sciences.* **669(1):** 7-20 (1992).
30. Simon, J.A. and Hudes, E.S. Relation of serum ascorbic acid to serum vitamin B12, serum ferritin, and kidney stones in US adults. *Arch. Intern. Med.* **159(6):** 619-624 (1999).
31. Swaminathan, M. Principles of Nutrition and dietetics. Interrelationship between nutrients. *The Bangalore printing andpublishing Co., Ltd*. 443-448 (1997).
32. Traber, M.G. Vitamin E and K interactions–a 50-year-old problem. *Nutrition reviews*. **66(11):** 624-629 (2008).
33. Umar, I.A., Ogenyi, E., Okodaso, D., Kimeng, E., Stancheva, G.I., Omage, J.J., Isah, S. and Ibrahim, M.A. Amelioration of anaemia and organ damage by combined intraperitoneal administration of vitamins A and C to Trypanosomabruceibrucei-infected rats. *African Journal of Biotechnology*. **6(18):** (2007).
34. Umar, I.A., Toh, Z.A., Igbalajobi, F.I., Igbokwe, I.O., Gidado, A. The effect of orally administered vitamin C and E on severity of aneamia in Trypanosomabrucei–infected rats. *Trop. Veterinarian*. **18:**n71-77 (2000).
35. Watts D.L. Nutrient interrelationships: minerals, vitamins, endocrines. *J. Orthomol. Med.* **5(1):** 11-19 (1990).
36. Weisburger J.H. Nutritional approach to cancer prevention with emphasis on vitamins, antioxidants, and carotenoids. *American Journal of Clinical Nutrition.* **53:** 226-237 (1991).
37. White H. S. Principles of Biochemistry, 3rd Ed. McGraw Hill, N.Y. (1964).
38. Wijesundara, M.B.J and Berger, S. The redox pair vitamin E and vitamin C, a 13-C-NMR study. Liebigs. *Ann. Chem.* **12:** 1239-1241 (1994).