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Vitamin A, Action on the Human Body: A Review Study

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Abstract: Vitamin A and its associated compounds - *the retinoids* - are implicated in a lot of useful and necessary biological functions of the human body. The retinoids are considered as an essential element in the mechanism of image formation on the retina and as an indispensable element that intervenes in the cell cycle (growth, differentiation and proliferation). The potential effects of retinoids on other organ systems of the human body has only encouraged the researchers to include the vitamin A on their research list in order to identify all its benefits and applications. The importance of these findings implies that they could play a major role in medicine as do their relatives - *the steroids*. The goal of this research paper consists in investigating the influence of the vitamin A on the human organism, as well as determining its procedures of identification, dosage and extraction. Theoretical and practical importance of this work is confirmed by the main analysis and conclusions made at the end of the research which can contribute in the development of other researches on the impact of vitamin A to the human body and on the procedures of its identification, dosing and extraction.

Keywords: Vitamin A, Identification, Action, Dosage, Extraction, Human Body

1. Introduction

Vitamins are a group of organic compounds, which are essential for normal growth and are required in small quantities in daily nutrition because they cannot be synthesized by the body. While vitamins do not directly serve as a source of energy, they do help the enzymes to generate energy from nutrients. There are two types of vitamins: fat-soluble and water-soluble.

a) *Fat-soluble vitamins* (A, D, E, K) are stored in the adipose tissue of the human body for long periods of time and generally pose a greater risk for toxicity when consumed in excess than water-soluble vitamins, consequently they require fat substances in order to be absorbed.

b) *Water-soluble vitamins* (complex B, C) are not stored in the human body and they are easily absorbed into the body. If you consume more of a water-soluble vitamin than you need, the excess will be excreted, not stored. Therefore, they need to be replenished daily. [1]

The naturally occurring compounds having Vitamin A activity and the synthetic analogues of *retinol* (with or without Vitamin A activity) are included in the term "retinoids". [3] Interest in the research of retinoids has amplified in relation to their antioxidant protective effect against the free radicals ($OH^{\bullet}$, O_2^{-}, H_2O_2, RO^{-}, ROO^{-}, $ONOO^{-}$, HOCl etc.). Free radicals are a highly reactive specie, capable of damaging biologically relevant molecules such as DNA, proteins, carbohydrates, and lipids; also, they are responsible for aging, initiation of the cancer and cardiovascular diseases. Furthermore, Vitamin A is involved in the biosynthesis processes of carbohydrates (glycoproteins and proteoglycans). Vitamin A is a mediator in production and activity of leucocytes; also, it helps to maintain the health of endothelial cells. [5]

The fact that vitamin A helps protect the surface of the eye *(cornea)*; it plays an enormous role in a good vision. In fact, one study published by the National Eye Institute found that over-the-counter lubricating eye drops containing vitamin A were effective for the treatment of dry eye syndrome. Another study published in the journal of *WHO,* found that a synthetic, altered form of vitamin A might be able to slow the progression of *Stargardt's disease*, an inherited eye disease that causes severe vision loss in young people. Also, it is well known that vitamin A is a precursor of *rhodopsin* (pigment found in rods) within the retina of our eye that helps us to see at night. [9]

2. Methods and Materials

2.1. Methods of Research

In this research, I have used a series of methods such as analysis and synthesis, comparison, induction and deduction, observation, tabular method and others.

Vitamin A is a fat-soluble vitamin, a group of unsaturated nutritional organic compounds that includes retinol, retinal, retinoic acid, and several provitamin A carotenoids, and beta-carotene. Vitamin A has multiple functions: it is important for growth and development, for the maintenance of the immune system and good vision. Vitamin A is needed by the retina of the eye in the form of retinal, which combines with the protein opsin to form rhodopsin, the light-absorbing molecule necessary for both low-light (scotopic vision) and color vision. Vitamin A also functions in a very different role as retinoic acid (an irreversibly oxidized form of retinol), which is an important hormone-like growth factor for epithelial and other cells.

Retinol activity equivalents (RAE) were developed because provitamin A carotenoids have less vitamin A activity than preformed vitamin A; 1 μg retinol = 3.33 IU. [2]

Vitamin A is required for the formation of rhodopsin, a photoreceptor pigment in the retina. Vitamin A helps maintain epithelial tissues. Normally, the liver stores 80 to 90% of the body's vitamin A. To use vitamin A, the body releases it into the circulation bound to prealbumin (transthyretin) and retinol-binding protein. B-carotene and other provitamin carotenoids, contained in green leafy and yellow vegetables and deep- or bright-coloured fruits, are converted to vitamin A. Carotenoids are absorbed better from vegetables when they are cooked or homogenized and served with some fat (e.g. oils). [12]

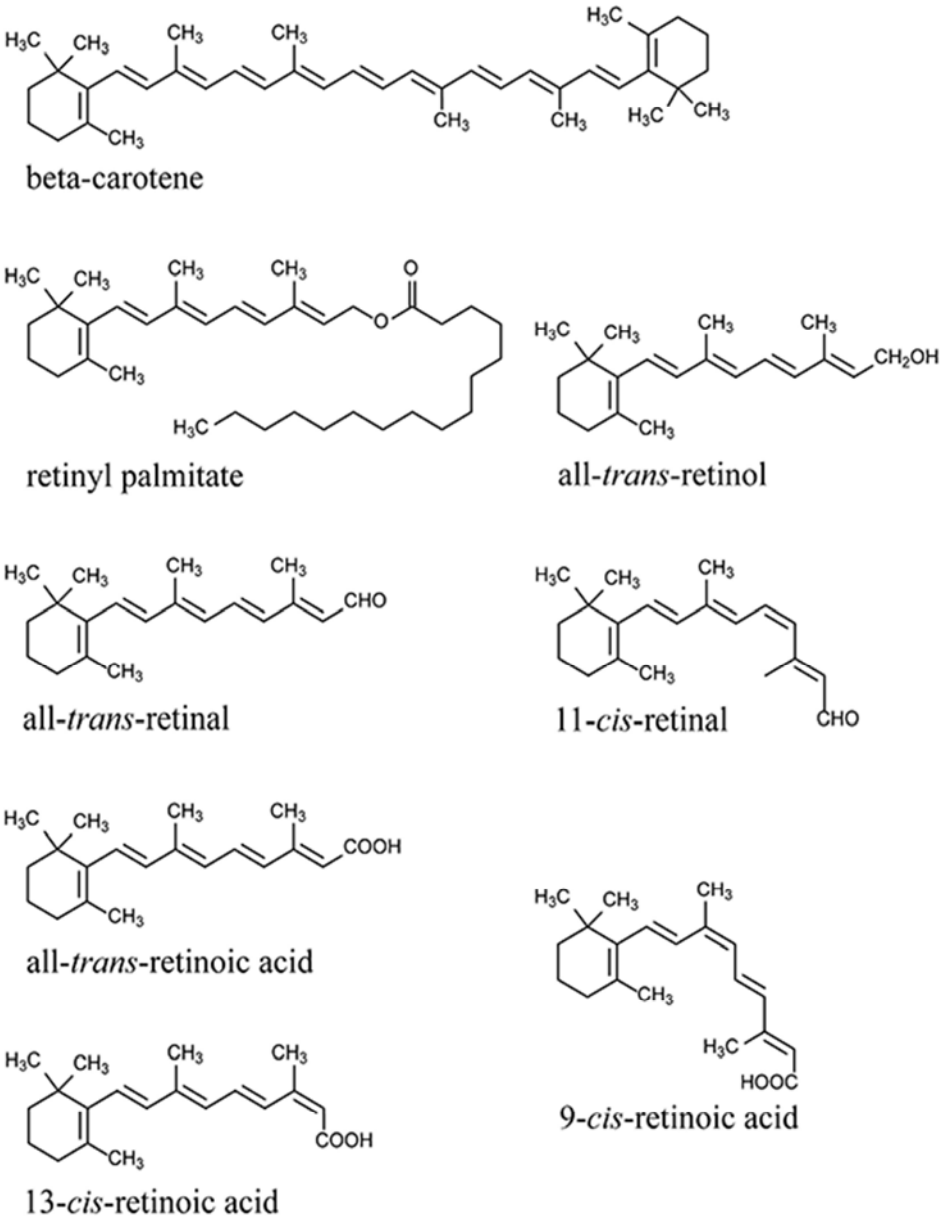

Figure 1. *Molecular structure of the vitamin A and its derivatives.*

Vitamin A comes from two sources. One group, called retinoids, comes from animal sources and includes retinol. The other group, called carotenoids, comes from plants and includes beta-carotene. The body converts beta-carotene to vitamin A. Major carotenoids, including lycopene, lutein, and zeaxanthin, have important biological properties, including antioxidant and photoprotective activities.

a) *Animal sources:* liver, eggs, fortified margarine, butter, cream, cheese, fortified milk.
b) *Plant sources:* dark orange vegetables (pumpkin, sweet potatoes, winter squash, carrots) and fruits (cantaloupe, apricots); dark green leafy vegetables.

Vitamin A versus Tetanus and Diphtheria. In two small observational studies, no relationship was found between low retinol concentrations (<0.7 μmol/liter) at the time of immunization with diphtheria and tetanus toxoids and the antibody response after 2 or 4 weeks, respectively. In a vitamin A trial from Indonesia, among children who received a placebo the anti-tetanus toxoid response of xerophthalmic children was the same as that of those who were nonxerophthalmic; in that study, both xerophthalmic and nonxerophthalmic children had low serum retinol concentrations. Low retinol concentrations have been widely used as an indicator of vitamin A deficiency; however, they may also be the result of the acute-phase response during generalized inflammatory states. [15]

The effect of vitamin A on the antibody response to tetanus or diphtheria has been examined in five clinical trials, four of which were randomized and three of which used a placebo group as a control.

It was concluded that, since both xerophthalmic and nonxerophthalmic children had low retinol concentrations at baseline and the vitamin was administered 2 weeks before the toxoid, the correction of vitamin A deficiency might be related to improved antibody responses. Vitamin A had no significant effects on the response to anti-tetanus toxoid in two subsequent clinical trials conducted among younger children (<2 months) in Bangladesh and Turkey.

The Turkish trial was a two-by-two factorial design with four arms (vitamin A alone, vitamin E alone, vitamins A and E, or placebo), with limited statistical power to make comparisons between separate arms. It is also possible that the administration of vitamin A sometime before the immunization, such as in the Indonesian study, allows for a partial correction of deficiency that may be necessary for an enhanced response to be observed. In the most recent trial from Bangladesh), vitamin A had a positive, significant effect on the antibody response to diphtheria toxoid antigen; this effect has not been examined in other randomized trials.

Hypo- / Hypervitaminosis A. Vitamin A deficiency (hypovitaminosis A) is a nutritional disorder caused by a lack of vitamin A in the body. Vitamin A deficiency can result from inadequate intake, fat malabsorption, or liver disorders. Deficiency impairs immunity and haematopoiesis and causes rashes and typical ocular effects (e.g. xerophthalmia, night blindness). Diagnosis is based on typical ocular findings and low vitamin A levels.

Interference with absorption or storage is likely in celiac disease, cystic fibrosis, pancreatic insufficiency, duodenal bypass, chronic diarrhea, bile duct obstruction, giardiasis, and cirrhosis. Vitamin A deficiency is common in prolonged protein-energy undernutrition not only because the diet is deficient but also because vitamin A storage and transport is defective. In children with complicated measles, vitamin A can shorten the duration of the disorder and reduce the severity of symptoms and risk of death.

Symptoms. Impaired dark adaptation of the eyes, which can lead to night blindness, is an early symptom. Xerophthalmia (which is nearly pathognomonic) results from keratinisation of the eyes. It involves drying (xerosis) and thickening of the conjunctivae and corneas. Superficial foamy patches composed of epithelial debris and secretions on the exposed bulbar conjunctiva (Bitot spots) develop. In advanced deficiency, the cornea becomes hazy and can develop erosions, which can lead to its destruction (keratomalacia).

Keratinisation of the skin and of the mucous membranes in the respiratory, GI, and urinary tracts can occur. Drying, scaling, and follicular thickening of the skin and respiratory infections can result. Immunity is generally impaired. The younger the patient, the more severe are the effects of vitamin A deficiency. Growth retardation and infections are common among children. The mortality rate can exceed 50% in children with severe vitamin A deficiency.

Diagnosis. Ocular findings suggest the diagnosis. Dark adaptation can be impaired in other disorders (e.g. zinc deficiency, retinitis pigmentosa, severe refractive errors, cataracts, diabetic retinopathy). Serum levels of retinol are measured. Normal range is 28 to 86 μg/dL (1 to 3 μmol/L). However, levels decrease only after the deficiency is advanced because the liver contains large stores of vitamin A. Also, decreased levels may result from acute infection, which causes retinol-binding protein and transthyretin (also called prealbumin) levels to decrease transiently. A therapeutic trial of vitamin A may help confirm the diagnosis.

Treatment with vitamin A palmitate. Vitamin A toxicity (hypervitaminosis A) can be acute (usually due to accidental ingestion by children) or chronic. Both types usually cause headache and increased intracranial pressure. Acute toxicity causes nausea and vomiting. Chronic toxicity causes changes in skin, hair, and nails; abnormal liver test results; and, in a fetus, birth defects. Diagnosis is usually clinical. Unless birth defects are present, adjusting the dose usually leads to complete recovery. In adults, acute toxicity can occur when arctic explorers ingested polar bear or seal livers, which contain several million units of vitamin A or in other cases such as long consumption of aliments that contain a lot of vitamin A. [14]

Symptoms. Although symptoms may vary, headache and rash usually develop during acute or chronic toxicity. Acute toxicity causes increased intracranial pressure. Drowsiness,

irritability, abdominal pain, nausea, and vomiting are common. Sometimes the skin subsequently peels. Early symptoms of chronic toxicity are sparsely distributed, coarse hair; alopecia of the eyebrows; dry, rough skin; dry eyes; and cracked lips. Later, severe headache, pseudotumor cerebri, and generalized weakness develop. Cortical hyperostosis of bone and arthralgia may occur, especially in children. Fractures may occur easily, especially in the elderly. In children, toxicity can cause pruritus, anorexia, and failure to thrive. Hepatomegaly and splenomegaly may occur. In carotenosis, the skin (but not the sclera) becomes deep yellow, especially on the palms and soles. [6]

Diagnosis is clinical. Blood vitamin levels correlate poorly with toxicity. However, if clinical diagnosis is equivocal, laboratory testing may help. In vitamin A toxicity, fasting serum retinol levels may increase from normal (28 to 86 µg/dL [1 to 3 µmol/L]) to > 100 µg/dL (> 3.49 µmol/L), sometimes to > 2000 µg/dL (> 69.8 µmol/L). Hypercalcemia is common.

Differentiating vitamin A toxicity from other disorders may be difficult. Carotenosis may also occur in severe hypothyroidism and anorexia nervosa, possibly because carotene is converted to vitamin A more slowly.

Treatment. Stop consuming vitamin A or reduce to minimal consumption. [11]

2.2. Practical Methods and Materials

Types of batching.

a) The dosage of the vitamin A from the blood

10 ml of blood are poured into a mortar. Then anhydrous Na_2SO_4 is added and it is milled until it becomes powder. 40 ml of absolute ethanol are poured and the milling is continued. The solution is decanted with the vitamin extract and is washed 2-3 times with 40 ml of solvents, decanting the solution every time from the mortar. Vitamin extracts are united and the solvents are evaporated to dryness. The obtained residue is resumed in a small volume of petroleum ether.

b) The dosage of the vitamin A from the liver

We weighted 1 gram of liver tissue and milled by 5 grams of quartz sand. Anhydrous Na_2SO_4 is added and grind until it becomes dry powder. 20 ml of absolute ethanol is added. The milling is continuing. The mix is extracted with 40 ml of petroleum ether and ethyl ether, in the ratio of 1:1. The spectrophotometric emission is made in the final mixture.

The concentrates of ß-carotene from carrots.

A long time carrots were used for the obtaining of concentrates of ß-carotene. Beginning from this raw material, we were able to reach the pure substance.

The methods of extraction of the carotene from carrots vary. In general, all the procedures begin with the cutting of the raw material in small particles in order to facilitate the extraction, followed by lowering the quantity of the water by drying, pressing or by using dehydrating substances. The carotene in this form is dispersible in water. Extraction of provitamin A from carrot can be made with organic solvents typical for the fat-soluble vitamins, such as petroleum ether, hexane, petrol or others.

One classic procedure consists in the removal of the water with acetone from the pressured carrots, followed by the extraction with a suitable organic solvent (petroleum ether, hexane, petrol or others). The extract is a raw concentrated red solution containing 1-2% of beta-carotene. The method itself is not economically advantageous because are required high quantities of acetone and organic solvents. [8]

Another method resides in the heat drying of the carrots, followed by the extraction with solvent (petroleum ether or others). The obtained solution is evaporated at 40-50°C, after which the residue is retaken with carbon disulphide. The crude carotene is precipitated from this solution with ethanol, which is added in small portions until begins to precipitate the ballast substances (colorless). After filtering the residue, carotene crystals are obtained.

A simple method of the extraction of the carotene from carrots as shown in *Figure 2* is by using vegetable oil. Carrots finely minced, thermally dried are extracted with a suitable amount of vegetable oil.

The extraction is performed at warm (50-66°C) for 20-30 minutes. The ratio between the carrots and oil is 4: 1. Drained carrots are pressed to remove all the rest of the oil; oil with provitamin A is colored intensely red, but the concentration of active substance is limited to 4-5 mg carotene per 100 ml. [12]

Figure 2. *Extraction of the ß-carotene from carrots.*

Table 1 represents the main reactions used to identify vitamin A that we have extracted from carrots, blood and liver. The *Figure 3* completes this table.

Table 1. *Reactions for the identification of the vitamin A.*

Used reagent	The colour of the reagent obtained at the interaction with vitamin A
H_2SO_4 (concentrated)	Dark blue, intense
Chloroform ($CHCl_3$) and H_2SO_4 (concentrated)	Green, that turns in dark blue
Chloroform ($CHCl_3$) and fuming HNO_3	Blue, that turns in green
Formic acid 95% (HCOOH)	Insoluble, colourless
Dichloroacetic acid ($CHCl_2COOH$)	Violet
Trichloroacetic acid ($CHCl_3COOH$) and chloroform ($CHCl_3$)	Yellow, that turns in blue
Arsenic trichloride ($AsCl_3$)	Red, that turns in blue
Antimony trichloride ($SbCl_3$)	Dark blue, intense
Tin (IV) chloride ($SnCl_4$)	Blue, that turns in violet
Dichlorhydrine of glycerol (CH_2Cl-$CHCl$-CH_2-OH)	Red

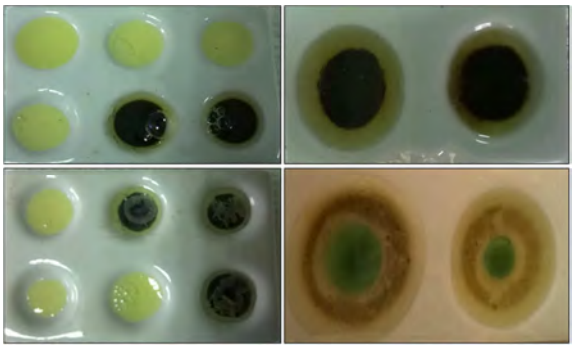

Figure 3. *Reactions for the identification of the vitamin A.*

3. Results and Discussions

The problems encountered in determination of Vitamin A in pharmaceuticals are similar to those in food. Saponification followed by solvent extraction is the most usual technique employed to prepare samples for Vitamin A analysis. Direct extraction without saponification has been also used, but to a lesser extent. Generally, the former is used for total retinol determination, whereas direct extraction allows the separation and determination of retinol and the different retinyl esters.

This paper describes also a simple and rapid procedure for determination of Vitamin A in pharmaceutical products and not only.

4. Conclusions

The studies in this work allowed the following conclusions:

a) Vitamin A is a fat-soluble vitamin, whose required quantity is inversely proportional to age and physiological condition of a person.
b) A true deficiency can cause a number of changes in the human body: follicular hyperkeratosis, twilight vision problems, abnormal ERG (electroretinogram) etc.
c) By providing a corresponding intake of foods containing vitamin A (in conjunction with other food principles), it can ensure an optimum balance of normal functioning of the whole body.
d) Performing these investigations by applying the technique of colouring with antimony chloride, sulfuric acid, nitric acid enables an excellent view of their reaction with the vitamin A. Therefore, the mentioned techniques could be proposed to be implemented in the test routine of the identification of this vitamin.
e) In the same section, the method used to extract carotene from carrots, proved to be the most accurate in obtaining it and the most advantageous economically and ecologically.

The summary of the literature in the domain and the practical results can help to complement the spectrum of knowledge on methods of identification and dosing of vitamin A, the role of vitamin A in developing the human body, respectively, can be useful in other research projects.

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