Research Article

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Vitamin A

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Abstract

Fredrick Hopkins discovered Vitamin A, a fat-soluble 20 carbon unit molecule acquired through natural sources like carrots and synthetic options like gelatin capsules or supplements. It has a vital role in developing the human eye, early stages of lung formation, and immune system. Deficiency of vitamin A causes Xerophthalmia, can lead to night blindness, and severe conditions advance to permanent blindness. On the other side, toxicity results in skin irritation and teratogenicity in newborn babies. The action of Retinoic acid as a neurotransmitter and the effect of different doses of Vitamin A on morbidity are essential topics that make scientists curious. This paper describes Vitamin A history, deficiency accompanied by toxicity, role, and importance for the eye and the treatment of SARS-CoV-2.

Keywords: Retinol, β-carotene, xerophthalmia hypercarotenemia, SARS-CoV-2

Introduction

Vitamin A, a fat-soluble 20 carbon unit molecule, was discovered a century ago as a compound essential for growth and nutrition in our food. These are the number of compounds with activity similar to retinol, a cyclohexene derivative containing primary allylic alcohol.[1] Its good sources include milk and liver. These are present in retinyl esters of fatty acids and are primarily stored in the liver. Retinol in our body is synthesized with the help of Beta-Carotene, a compound with 40 carbon units.[2] Vitamin A is responsible for the eye's proper functioning, and its deficiency may lead to blindness. It also has a crucial role in immunity, RBC production, anti-inflammatory action.[3.] Hence, it is a vital area to study and research. Figure 1. depicts the chemical structure of Vitamin A.

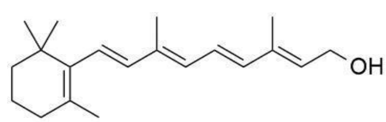

Figure 1. Vitamin A (Retinol)

History

It all started with Frederick Hopkins winning the 1929 Nobel Prize to discover Vitamin A.[4] Paul Karrer won Nobel Prize in 1937 for finding the chemical structure of the vitamin. In the same year, Harry Homes & Ruth Corbet Crystallized Vitamin A. Decade later, Hoffman la Roche developed the most efficient synthesis of Vitamin A.[5] George Wald found out the relation of Vitamin A and its association with rhodopsin in the retina, which rewarded him with Nobel Prize in Physiology or Medicine in 1967 Testing.[6]

Sources

One of the significant natural sources of Vitamin A is the carrot containing β-carotene, a Pro-Vitamin that gets converted to retinol in the body. Others are spinach mangoes.[7] Dietary sources are liver, oily fish, egg yolks, milk, and cheese. The liver is the richest of Vitamin A.[8] It comes as a supplement in Pro-Vitamin forms like retinyl acetate or retinyl palmitate. 2,500-10,000 IU Vitamin A is present in Multivitamin in form of B-Carotene and Retinol. The conventional way of consuming it is in chewable tablets and capsule form, with 50000IU.[9,10]

Deficiency

Vitamin A deficiency gives rise to Xerophthalmia, which causes dryness in the conjunctiva and cornea. Symptoms start from night blindness and can progress till the critical stages of necrosis, advancing to permanent blindness.[11] Pregnant women with deficiency of vitamin A can affect the newborn's congenital function.[12] Vitamin A is considered an Anti-Infective factor; lack of Vitamin A gives rise to a risk of bronchopulmonary dysplasia (BPD) and is followed by severe lung infections diseases.[13] If the body does not get an adequate amount of retinoic acid, its deficiency can contribute to the liver tumour.[14]

Vitamin A Fortification

Alone, vitamin A deficiency is accountable for the death of almost 6 in 100 children under the age of 6 years in the African continent and nearly 8% of child deaths in the south-eastern part of Asia. Food materials can be fortified with vitamin A to tackle vitamin A deficiency effectively. Fortification of food is when essential nutrients are added to the food to increase its nutritional value. This process costs not more than 3% of the cost of the food unfortified. Food products fortified with retinol are delivered to a massive population, indirectly providing vitamin A in small doses.[15,16]

Oils (vegetable oil, other hydrogenated oils, margarine, etc.) fortified with retinol are available globally. Vitamin A is a fat-soluble vitamin; hence oil acts as a suitable carrier. It is a straightforward and accessible process to implement at a meagre cost. As per the food aid program in the US, it is recommended to add about 20mg of retinol to one kilogram of vegetable oil. The cost for fortifying vitamin A with oil is about 2 USD per metric tonne of oil.[16]

Sugar proves to be an appropriate vehicle for vitamin A and can be used to tackle vitamin A deficiency as it is consumed every day by everyone, with an annual consumption of 27 million metric tonnes in India. The technology used to fortify vitamin A with sugar was developed by INCAP (Institute of Nutrition of Central America and Panama), which created a technology where the retinol compound binds to a sugar crystal with the help of vegetable oil does not get separated. This caused a drastic reduction in VAD (Vitamin A deficiency) occurrence rates as sugars in the household contained almost 0.01 gram of vitamin A per kilogram of sugar. The cost for this is about 0.2 USD per year per person.[16]

Noodles, yogurt, cereal flours, tea, etc., are other food materials fortified with vitamin A. Many experiments were also carried out to make MSG (monosodium glutamate) a source of retinol.[17]

Recommend Dietary Allowances[1,18]

Table 1. contains the recommended dietary allowances of retinol for male and female

Age	Weight	Male	Female
0-6 months	5.8 kg	350 mcg RAE	350 mcg RAE
7-12 months	8.5kg	500 mcg RAE	500 mcg RAE
1-3 years	13kg	390 mcg RAE	390 mcg RAE
4-6 years	18 kg	510 mcg RAE	510 mcg RAE
7-9 years	25.3	630 mcg RAE	630 mcg RAE
10-12 years	35 kg	770 mcg RAE	790 mcg RAE
19-50 years	65kg	1000 mcg RAE	900 mcg RAE

Table 1. Recommend Dietary Allowances

RAE = Retinol activity equivalents

IU = International Units

One mcg RAE is equal to 1 mcg retinol

One IU Retinol = 0.3 mcg RAE[19]

Toxicity of Vitamin A

Toxicity caused by vitamin A consumption is observed only in a few cases. A higher intake of vitamin A leads to skin irritation and hypercarotenaemia, yellowish discolouration of the skin. It may also lead to nausea, headaches, dizziness, pain in bones and joints, etc.[20,21] Teratogenicity, the ability to cause defects in the foetus, is the severe side effect of higher retinol consumption. According to a study, women who consumed more than 10000 IU of preformed vitamin A had a probability of 0.017, that the foetus will have certain defects.[22]. Excess intake of retinol may also lead to the reduced mineral density of the bone, further leading to fractures.[23]

Tolerable upper intake levels of preformed vitamin A [1,18]

Table 2 contains the tolerable intakes of vitamin A for males and females with respect to age.

Table 2. Tolerable Intake of Vitamin A wrt age

Age	Male	Female
0-12 months	600 mcg	600 mcg
1-3 years	600 mcg	600 mcg
4-8	900 mcg	900 mcg
9-13	1700 mcg	1700 mcg
14-18	2800 mcg	2800 mcg
19+	3000 mcg	3000 mcg

Biological Role

1. Immune System- It regulates the homeostasis of bone marrow by preventing apoptosis of bone marrow cells and promoting the development and function of T-Cells.[24]

2. Light Sensor and Eye- 11-*cis* retinal chromophore is for vision in multicellular organisms.[25] It keeps the Cornea wet; otherwise, it can cause severe dryness leading to Corneal Xerosis, Corneal Ulcer.[26]

3. Tooth- Teeth are made from a protein matrix mineralized with collagen, calcium, and phosphorus which consists of minerals like Vitamin A and Vitamin D. The synthesis of glycoprotein such as mucin is also one of the functions of Vitamin A. [27]

4. Lung Development- Retinoic Acid helps in the development of lungs and alveolar formation developing while it is in the early stage.[28]

Vitamin A interactions with other nutrients

Vitamin A interacts with other micronutrients, which helps in the proper functioning of the body. Interaction of retinol with iron results in increased hemoglobin concentration in pregnant women. Further studies concluded that this resulted from improved iron utilization due to the presence of retinol[17]. It can also be consumed to treat anaemia; vitamin A supplemented with vitamin B9 and iron showed an improved response for teenage girls suffering from anaemia. [29]

Another such example is the interaction of retinol and zinc. Retinol dehydrogenase (an enzyme involved in rod function) is a zinc-dependent enzyme vital in the visual cycle. Vitamin B2 and vitamin A play a significant role in retinal rod function. Zinc deficiency may affect the synthesis of retinol-binding protein. When supplemented together, zinc and Vitamin A have beneficial effects on diarrhea and other infections like respiratory tract infections. It also enhances lymphocyte responsiveness.[30]

Vitamin A also interacts with some of the medicines. Orlistat (a drug used for weight loss) results in decreased absorption of vitamin A. Synthetic forms of vitamin A are used in some of the prescribed medications like Soriatane (used to treat psoriasis) and Targretin (used in treating skin effects of T-Cell lymphoma), here care has to be taken that no other vitamin A supplement is consumed, as it can cause a highly increased level of vitamin A in the blood, which can lead to toxicity.[31]

How is Vitamin A important in maintaining proper eye health?

Vitamin A maintains the proper function of the eye. Both the forms of vitamin A (pre-vitamin A and pro-vitamin A) are metabolized and stored in the eye's retina in the form of retinyl esters or retinol.[32] Several specialized cells are present in the retina, which activate the vitamin A stored when acted upon with light. This activated vitamin A allows our brain to interpret the signals of sight and color. These specialized cells are responsible for our vision. Hence in the absence or deficiency of Vitamin A, our brain won't interpret the signals causing low vision or night blindness. It can result in permanent blindness.[33]

Synthesis of Vitamin A

- Organon Synthesis:
  It was the first industrial synthesis of vitamin A developed by Arens and Van Drop in 1949. This synthesis, starting from beta-ionone, produces retinol as its end product as depicted in Figure 2. Typically, it uses a Reformatsky reaction to increase the chain length. While developing this synthesis, they created a reply forming alkoxy ethynyl alcohol using ethoxy acetylene and a ketone named Arens-Van Drop reaction.[34]Converting the ethoxy ethynyl alcohol formed a Grignard reagent and then reacting it with the C18 ketone successfully gives a C20 aldehyde after undergoing an MPV (Meerwein Ponndorf Verley) reduction, gives us Vitamin A.[35] However, the production of alkoxy ethynyl was considered time-consuming and expensive. Hence it was not preferred industrially. Furthermore, it led to further research on Vitamin A synthesis with a newer approach.[36]

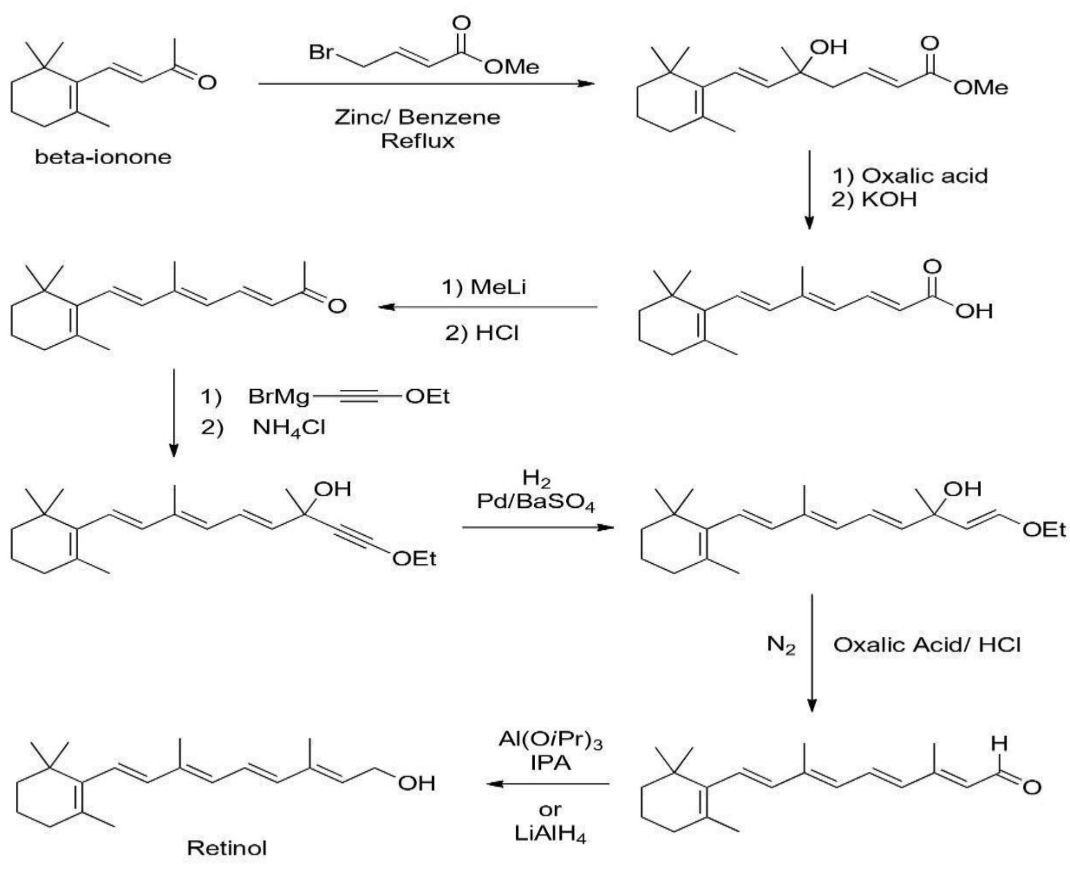

Figure 2. Organon Synthesis

- Isler synthesis:

  Patented in 1953, it is one of the most widespread industrial syntheses of Vitamin A, giving yield up to 90% in the presence of a heterogeneous catalyst. The synthesis is broken into two parts, starting with beta-ionone and forming retinol as its end product. The desired outcome is obtained by adding a 6C unit to a 14C unit. Firstly, they produced an aldehyde intermediate and condensed it with a Grignard agent, which we derive from 3-methylpent-2-en-4-en- 1-vol and ethyl magnesium bromide.[37,38] As shown in figure 3, in such a way, Retinol (Vitamin A) is formed after a series of reactions.

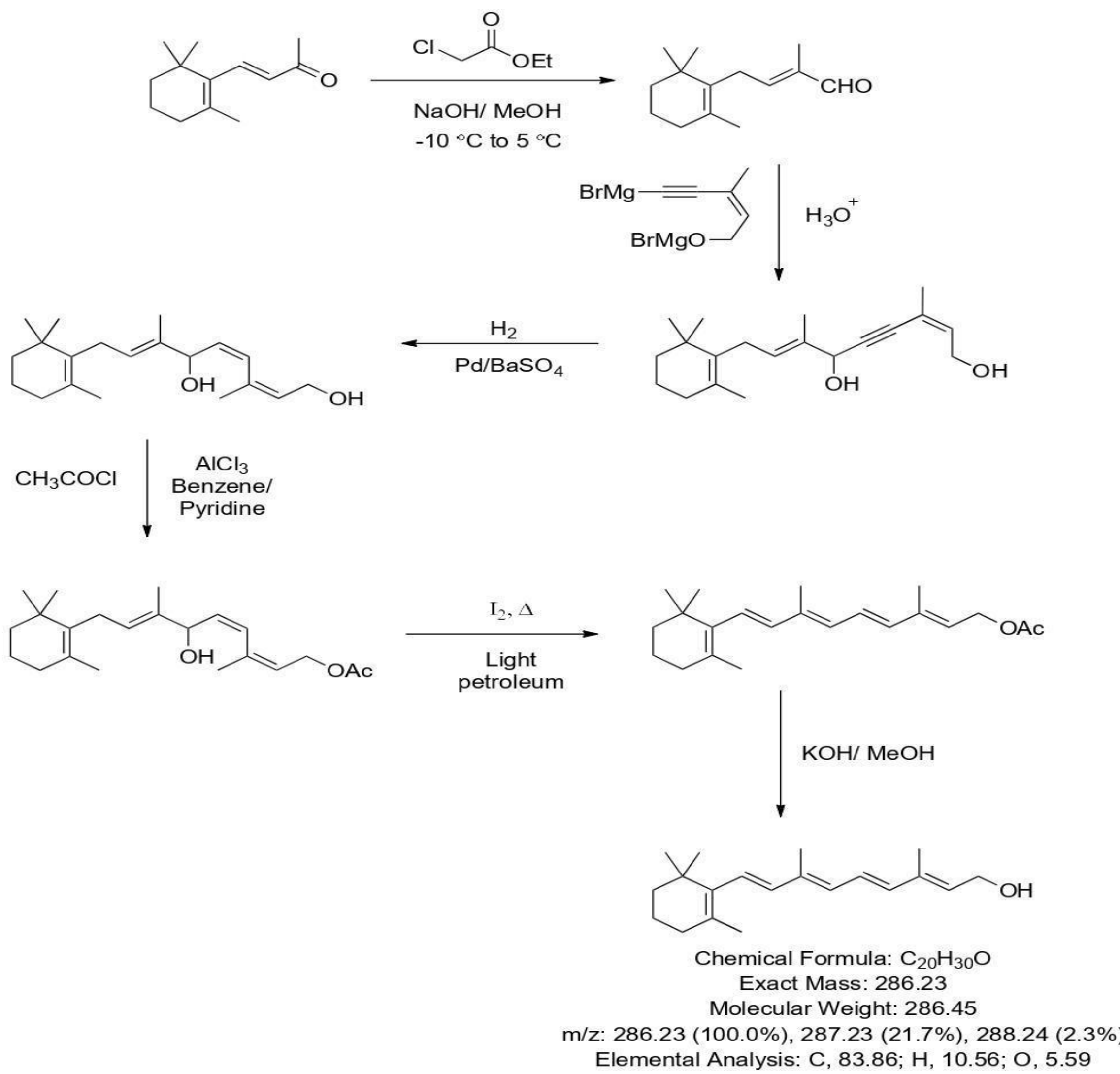

Figure 3. Isler Synthesis

- BASF Synthesis:
  BASF synthesis was patented in 1957, primarily focusing on the Wittig reaction. This synthesis starts with beta-ionone undergoing a Reformatsky reaction with propargyl bromide, undergoing several such reactions; it finally gives Retinol as the end product. In this synthesis, they produce C15 phosphonium ylide and combine it with C5 aldehyde, which yields Vitamin Acetate, which after saponification, yields Vitamin A as shown in figure 4.[39,40]

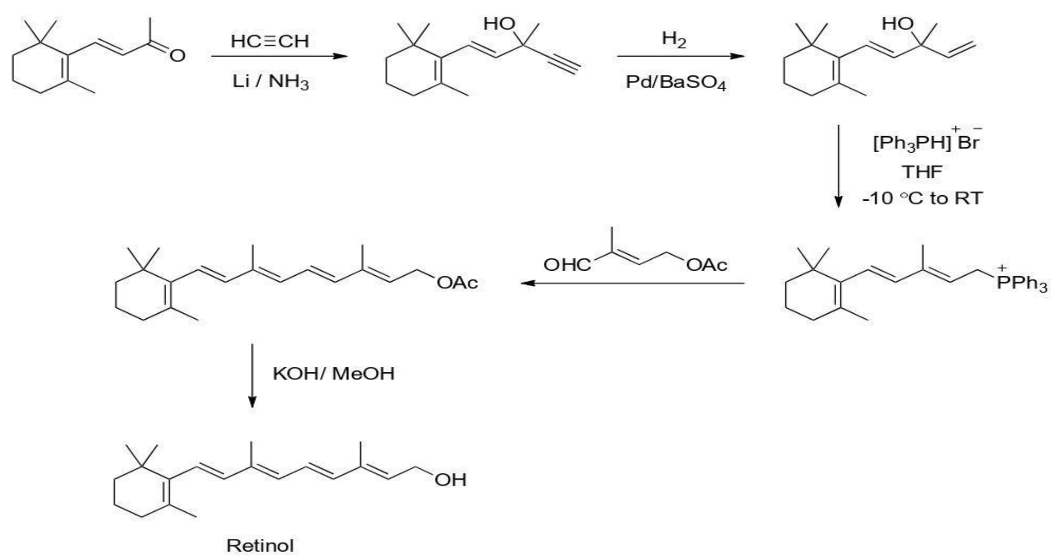

Figure 4. BASF Synthesis

The therapeutic effect of Vitamin A on Covid 19 patients

Humanity has been suffering for the past two years due to the SARS-CoV-2 (COVID-19) outbreak. A lot of research has been done to tackle this. One of this research was regarding the therapeutic effect of Vitamin A on COVID-19. Initially, patients with severe COVID-19 were divided into two groups. One of these groups was treated with two doses of vitamin A and three doses of salbutamol. Data regarding SPO_2 and respiratory rate were collected two days after the treatment. The results proved that patients treated with Vitamin A significantly improved their respiratory rate and SPO_2 levels. It may be a result of the anti-inflammatory properties of vitamin A. Also, Vitamin A plays an essential role in T-cell differentiation which improves our immune system.[41]

Vitamin A Market

The Global Vitamin A market is expected to grow at 4.2%CAGR during the forecast period of 2026. The driving force for this demand is due to nutritional processed food and its need in the pharmaceutical and cosmetical industry. Europe is considered the largest market of Vitamin A, and side by side, Asia-Pacific is making a move and is the fastest-growing market. This growth is caused by urbanization, leading customers to shift to a healthy diet in the sub-segmented side of Vitamin A like food grade, pharmaceutical grade, and feed grade. Feed grade dominated the market and is expected to continue that domination shortly. If we consider the basis on type of Vitamin A which are preformed Vitamin A, formed Vitamin A and combine Vitamin A. In 2020-2021 pre-formed dominated the market because healthcare staff recommended pre-formed during treatment. The powder has the upper hand over liquid as far as form is concerned because of its stability and can be easily transported. Considering the competitive landscape of Vitamin-A, Royal DSM, Zhejiang Medicine, Xiamen Kingdom way, BASF is the significant Vitamin A manufacturing player.[42,43]

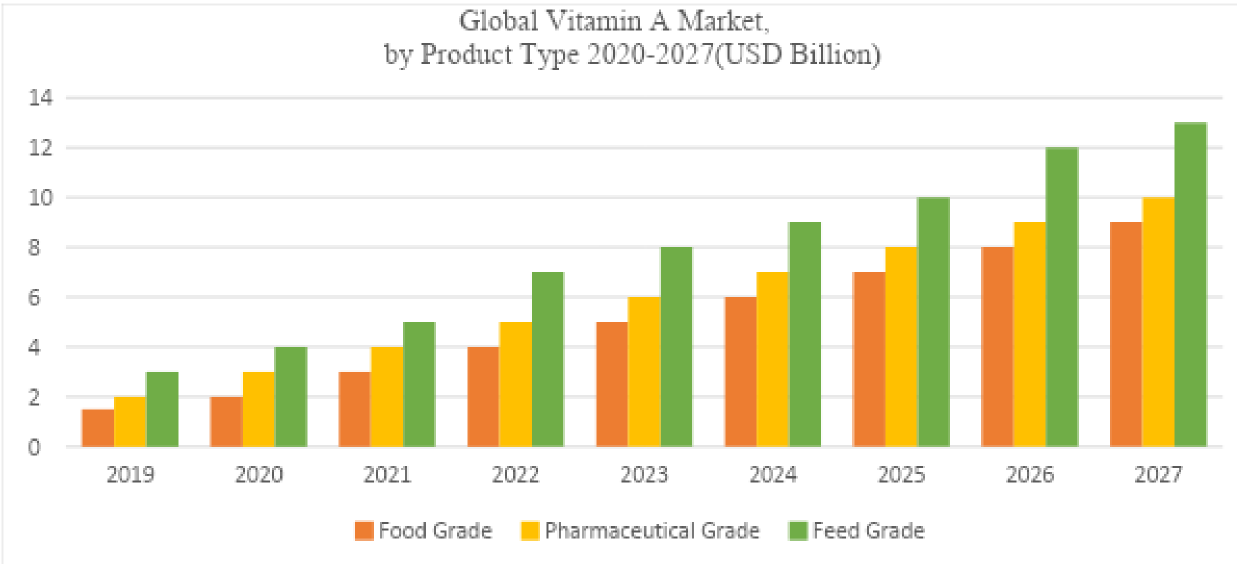

Figure 5. Global Vitamin A Market Graph

Future Scope and Research

Vitamin A supplements affect morbidity and mortality due to different doses and the identification of field-friendly clinical and biochemical indicators of vitamin A status and storage.[10] Relation between vitamin A and Iron simultaneous administration on vitamin-deficient patients showed a positive effect on their haematological and biochemical indicators of Fe status[44]. Another exciting topic is the role of 9-cis retinoic acid and its mechanism in endogenous production parallel other sources of Pro-vitamin, which will have more bioavailability.[45] Furthermore, the action of retinoic acid as a brain neuromodulator is a field of significant research. Predominantly it's regulation in neuroplasticity (capacity of neurons to change their connections and behaviour in response to new information) and neurogenesis (birth of new neurons) in the hippocampus.[46]

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