

REVIEWING THE THERAPEUTIC ACTIVITY OF VITAMIN D WITH ASTAXANTHIN

Prerna P. Singh¹, Sneha Basu², Sreelakshmi M P.³

¹Jain (Deemed-to-be-University), Bangalore

²St. Joseph College of Arts & Sciences, Bangalore

³Union Christian College, Aluva (MG University), Kerala.

Article Info: Received 08 August 2021; Accepted 17 September 2021

DOI: <https://doi.org/10.32553/ijmbs.v5i9.2221>

Corresponding author: Prerna P. Singh

Conflict of interest: No conflict of interest.

Abstract

This article is an examination of the Rar The scientific development and subsequent “vitamin D and astaxanthin” continues to influence the researchers all over the globe today. This article examines the research done and published by researchers and scientists. Consideration of current trends and data in scientific queries and demonstrates further aspects of Therapeutic activity of vitamin D with astaxanthin. Additionally, this article explores options for vitamin D with asthaxanthin in orthopaedic. The combination of both results in enhanced endurance and walking distance in senior adults, as well as increased muscular strength and size (sarcopenia). Thus, in elderly adults, mobility, endurance, and strength were all increased using a single training strategy. Vitamin D with astaxanthin in ENT. The vitamin D and astaxanthin has been proven to possess effective activity against reactive oxygen species, cell apoptosis, inflammatory and auto immune disorders. Vitamin D with astaxanthin in gynecology. Antioxidants and vitamin D have been found to play an important role in reducing the causes of diseases linked with female infertility.

Keywords: Infertility, antioxidant, otolaryngological diseases, musculoskeletal system, cartilage homeostasis

1. INTRODUCTION:

Vitamin D is an essential micronutrient which is known for bone mineralization. Its deficiency can present varying degree of clinical manifestation. It is present in several forms in the human body. Naturally, it can be produced in our skin through UV light exposure or can be ingested through dietary supplements. Vitamin D is an endocrine system comprises of 3 forms: cholecalciferol, calcidiol and calcitriol. Cholecalciferol is the only natural form of vitamin D which is produced in the skin on exposure to sunlight or can be supplemented externally. Calcidiol and calcitriol are by-products of cholecalciferol converted in the liver and kidneys. Calcitriol increases absorption of calcium and phosphorus; which further promotes bone resorption along with parathyroid hormones. Earlier studies have shown prevalence of vitamin D deficiency observed in patients with otolaryngological diseases as reported by different studies. Insufficiency of vitamin D may result in autoimmune conditions such as rheumatoid arthritis, type I diabetes and some late life cancers, 13 chronic diseases such as high blood pressure, 14 multiple sclerosis 15, chronic pain, depression, peripheral artery disease 16 and many others.

Astaxanthin is a red colour carotenoid pigment which has effective antioxidant, anti-inflammatory and anti-apoptic properties. It can be extracted from a marine microalga *Haematococcus pluvialis*, a freshwater Chlorophyta species. Astaxanthin can also be consumed through marine fishes

such as shrimp, krill, salmon and trout which are also rich in the pigment. It has been approved as a nutraceutical by the FDA of the United States in 1999. These pigments can prevent lipid peroxidation in cell membranes, due to its chemical structure which consists of ionic polar rings and non-polar conjugated carbon bonds. Astaxanthin consists of polar ionic rings and non-polar conjugated double bonds. These conjugated double bonds in its polyene backbone possess the ability to quench singlet oxygen species through the transfer of excitation energy. Astaxanthin shows 10 times more antioxidant property compared to other carotenoids such as lutein, β -carotene and canthaxanthin. The high lipophilic in thermolabile nature of astaxanthin increases its functioning in lipid membranes and lipid-rich regions. The chemical nature of astaxanthin also provides protection against UV radiation damages, phospholipid peroxidation, age-related diseases. It promotes immune reactions in the liver, kidney, eyes and joints; also plays important roles in inflammatory and related responses.

The basic studies of vitamin D and astaxanthin metabolism, the epidemiology of vitamin D levels were done along with that a large number of pre-clinical and clinical research on vitamin D, possible health beneficial characteristics have been published in recent decades. While some studies have found that vitamin D has beneficial impacts on a range of human bodily systems, others have failed to find that it has

health-promoting properties. Furthermore, numerous studies have been published that show the incidence of vitamin D shortage and insufficiency in healthy people as well as subgroups of patients with various disorders. This narrative reviews goal is to provide an overview of vitamin D levels with orthopaedic, ENT, gynaecology. In addition, we would like to provide an overview of vitamin D and its relevance in orthopaedics, ENT and gynaecology as the role of astaxanthin in each of them. This review goal or motive is to look into the effects of vitamin D and astaxanthin in these area. A growing corpus of research shows both the positive and harmful effects of vitamin D and astaxanthin. The underlying science of vitamin D metabolism, the epidemiology of vitamin D levels, the role of vitamin D within the musculoskeletal system, and the link of vitamin D with injuries. This review study which was done on the basis of earlier findings and experimental studies sums up the therapeutic effects of Vitamin D and astaxanthin in orthopaedic, ENT, gynaecology.

2. MATERIAL AND METHODS:

The study was conducted using four databases Google Scholars SAGE, DOAJ and PubMed. Selection of papers were done based on keywords and theme relevant to this review. Further the published papers from these databases were arranged in systematic order with respect to year of publication.

3. RESULT:

- Vitamin D with astaxanthin in gynaecology.
- Vitamin D with astaxanthin in ENT.
- Vitamin D with astaxanthin in orthopaedic.

3.1 Astaxanthin for reproductive health

It was found that astaxanthin and vitamin both are responsible and has potential properties that would help reduce the causes of infertility in couples and are applicative in reducing the signs of underlying diseases linked with reproductive health. Astaxanthin is a potent antioxidant and is known to have better antioxidant properties than other carotenoid. It is known to have 10 time better antioxidant properties than other carotenoids, such as, - carotene, lycopene, zeaxanthin and 100 times more than α -tocopher. It has been found that astaxanthin have unique properties linked with antiperoxidation activity. Astaxanthin is found to inhibit lipid peroxide formation and enhance the anti-oxidant enzyme status in the glycated protein/iron chelate-exposed endothelial cells by suppressing ROS generation. In an evaluated study by Comhaire et.al, the effects of astaxanthin as a complementary treatment to improve the outcome of World Health Organization (WHO) male fertility guidelines. Semen levels were observed for the patients supplemented with astaxanthin which showed an improved semen quality and sperm parameter. Antioxidant oral therapies are found to be beneficial in infertile man and women, idiopathic fertility and PCOS. It is found to improve the functions of cells in the body by reducing the oxidative stress. Recommended dose

of 5mg astaxanthin per day (250mg of algal meal) can help improve the reproductive health and promote efficient fertilization rates. Astaxanthin (C 40 H 52 O 4) which showed anti-oxidant properties and reduces the effect of free radicals and reactive oxygen species. Also, no adverse effects have been observed when humans were supplemented with dosages ranging from 2.38 to 40 mg/day. Also, it helps in decreasing the risk of endometrial cancer. Studies have proved that in physiological conditions, carotenoid concentration was predominantly higher in the follicular phase endometrium. Various drug supplements are taken by couples in order to attain effective results and improve the conceiving patterns and fertility rates resulting in the improvement of their reproductive ability. Antioxidants are sufficiently helpful in benefiting males found to be suffering with idiopathic OAT which is a condition that includes oligozoospermia, asthenozoospermia and teratozoospermia. Also, antioxidants have found to be of help in women suffering from PCOS, underlying reproductive disorders and infertility. Astaxanthin is one such antioxidant which has been found to increase the pregnancy rates. However, excessive ROS production and its accumulation is said to have negative impacts on the placenta foundation and could affect the overall growth and development of embryo. Moderate levels of ROS can be beneficial in reducing inflammation, wound healing and tissue repair process. There are many ROS targeting pathways in embryo including exogenous non-enzymatic antioxidants like hypotaurine and endogenous like superoxide dismutase but these are inefficient in maintaining an embryo. Thus, to sustain an efficient placental and embryo growth it is important to limit the oxidative stress in embryo culture for successful embryo implantation. It was estimated that astaxanthin was sufficiently efficient in increasing cell viability with 10 μ M concentration and it was found that the antioxidative effects of astaxanthin against the damaged trophoblast cells varied with the dose provided and 10 μ M of Astaxanthin was found an efficient optimal dosage for reducing or limiting the amount of ROS. Astaxanthin is proved very effective against oxidative stress as it reduces the inflammation and provides protective environment against ROS. Astaxanthin is also found to decrease DNA damage in women affected with ovarian cancer and improves the immune response after 8 weeks of intake. Astaxanthin has successfully been found to elicit a strong immune response by its uptake and found to inhibit tumour growth and formation by showing anti-cancer properties. Serum concentrations were measured using HPLC of the bioactive compounds, which were found to be lower in ovarian cancer patients suffering with early stage cancer as compared to healthy individuals. The patients with advanced stage ovarian cancers had significantly lower level of mean concentrations of carotenoids like astaxanthin. Thus, proper and increased uptake of vitamin D and carotenoids such as astaxanthin has shown to reduce and lower the risk of ovarian cancers in women.

3.2 Vitamin D for reproductive health

Vitamin D deficiency in women increases the risk of certain symptoms of low fertility and adverse pregnancy complications. Since, lower levels of Vitamin D have been observed in women with symptoms of PCOS, endometriosis, preeclampsia and impaired infertility during clinical trials. It has been found efficient to use oral administration of Vitamin D supplementation in order to suffice the levels of vitamin D in female body. An optimal level of vitamin D may help women to achieve protection against preeclampsia and other adverse effects. A study conducted by Garland *et al.* considered 30 studies linked with vitamin D and colon cancer, out of 30 such studies 20 findings were statistically significant with the importance of vitamin D its beneficiary metabolites or sunlight exposure. Also 13 studies involving breast cancer were taken into account out of which 9 relevant studies showed favourable association of vitamin D markers with decreased in the risk of cancer development. Also 7 studies concerned with ovarian cancer were taken into account 5 of which showed an increase in mortality with lower vitamin D intake. Such relevant studies show that supplement with vitamin D are an important potential factors in reducing the risk of such diseases and improves the prevention from the diseases. Also, supplements rich in vitamin D improve the functions of the cells and aids in improving the fertility in males and females. In women with low level of vitamin D there has been a low fertility rate with obesity and signs of PCO. Also low levels of vitamin D affects the rate of pregnancy in women and might also lead to severe malignancies. PCOS affects 5–10% of women of reproductive age. It is also known to affects the endocrine hormonal system by affecting insulin activity, lipid profile and menstrual cycle. various clinical trials were conducted in women with either the supplementation or administration of vitamin D3 which was found successful and showed positive results on insulin secretion, lipid profile, follicular development and proper menstrual cycle. Obesity is the main factor observed in PCOS that has been known to have an association with Vitamin D as observed. Also, endometriosis and preeclampsia (PE) are the most commonly observed reproductive health problems that are linked with the status of vitamin D in the body. HTR8/SVneo cells exposed to hypoxia/reoxygenation (H/R) revealed that oxidative stress from the trophoblasts is one of the possible pathological mechanisms of Preeclampsia. Vitamin D treatment induced a reduction in endometriosis cyst cross-sectional area by 49% and produced fibrosis as well as apoptosis in the stroma, suggesting that vitamin D administration may have a beneficial effect in the treatment of endometriosis. Preeclampsia is one of the most commonly occurring reproductive health problems in women linked with the presence of low level or deficiency of Vitamin D in the body. PE has been found to show a distinction in the level of Vitamin D as women with such conditions are known to implicate lower levels of Vitamin D in the body but it has also been found that an optimal level of Vitamin D in the body could help reduces the complications associated with

PE and also help increase the outcomes of pregnancy and improve the rate of fertilization in women in the clinical trials. Since, lower levels of Vitamin D have been observed in women with symptoms of PCOS, endometriosis, preeclampsia and impaired infertility during clinical trials. It has been found efficient to use oral administration of Vitamin D supplementation in order to suffice the levels of vitamin D in female body. An optimal level of vitamin D may help women to achieve protection against preeclampsia and other adverse effects. 600IU of vitamin D was found useful and safe for consumption in pregnant women.

3.3 Role of Astaxanthin as an antioxidant

Reactive oxygen species are a product of cellular metabolism occurring during signalling pathways and intercellular homeostasis. These reactive species have several roles in the body such as host-defence system and in stimulating adaptive immunity. The complications arise when these reactive species levels get augmented due to environmental stress that results in cell apoptosis, leading to oxidative stress. The imbalance caused by the oxidative stress can have deleterious impacts. This plays important role in various chronic illnesses such as atherosclerosis, renal failure, inflammatory bowel disease, Parkinson's disease, preeclampsia and many others. Astaxanthin is a lipophilic molecule that plays crucial role in light filtering, quenching singlet oxygen and excited molecule (triple state), and antioxidant pathways. The lipid soluble nature of astaxanthin helps in efficient distribution of the molecules in lipophilic cell compartments and cell membranes. The pharmacological activities of astaxanthin includes antioxidant and anti-inflammatory properties, as a skin protectant from UV light, and from chronic inflammatory diseases such as rheumatoid arthritis, Parkinson's disease and many others. The chemical structure of astaxanthin consists of hydroxyl and keto groups, which is the assumptive reason for its radical scavenging activities. Hence, it might be a possible non-toxic therapeutic lead of natural origin. It is found to be effective even at lower dose administration, which optimizes the absorption of the drug in the body. Earlier study in a mouse model shows astaxanthin against oxidative stress, inhibits p38 MAPK marker that protects the oxidative stress in neurological issues. Thus, astaxanthin proves itself to be a powerful antioxidant. The power of astaxanthin to remain in its natural form even after metabolism helps it to stay longer in the body and due to its negligible side effects, it sounds to be a potential drug candidate.

3.4 Astaxanthin in Cancer Treatment

Cisplatin a well-known antineoplastic agent, used in the treatment of various cancers in spite of its therapeutic activities it shows adverse side effects. Among these ototoxic effects are observed that leads to hearing loss although, mechanism of cisplatin in its contribution are yet to be understood. The emergence of ROS may occur in maintenance of cochlear function. High metabolic activity leads to leakage of electrons, which react with oxygen to

produce ROS. Cisplatin promotes reactive oxygen species by deactivating anti-oxidant systems. Regardless of its anti-tumour effects it shows damaging side effects causing structural damage to the submandibular gland of the salivary gland, as seen in an earlier study. Morphological changes and decreased secretions found in acinar cells and ductal system due to damaged protein pathways. Here, Astaxanthin as a cytoprotective agent shows therapeutic activity against the effect of Cisplatin induced salivary gland damage. A histopathological and histochemical study performed on albino rats showed the protective effects against cisplatin-induced cellular damage. The seromucous acinus area and ducts showed negligible neutrophil infiltration in astaxanthin administered cisplatin-induced group when compared to the cisplatin group. In another study, astaxanthin showed protection against incidence of oral cancer in rats. The incidence of neoplasm lesions in the tongue in the form of squamous papilloma observed in histological studies in the control group treated with 4-NQO (17%). Whereas astaxanthin with 4-NQO did not show any lesions. The control group (100%, $p < 0.05$ and $p < 0.005$) showed higher levels of hyperplasia compared to the other 2 groups treated with Astaxanthin (75% and 78%). Frequency of dysplasia were also lower in groups treated with Astaxanthin (0% and 5%) when compared to the control group (58%). In a comparative study of cisplatin ototoxicity and astaxanthin against its protection that showed the control group and astaxanthin with cisplatin group gave similar results compared to the cisplatin induced group, which suffered cellular damage and decreased total antioxidant capacity. These data sums up the activity of astaxanthin against Cisplatin which can be used in treating the side effects of cancer.

3.5 Vitamin D insufficiency associated with ENT diseases

Prevalence in vitamin D deficiency is observed in patients with otolaryngological diseases as reported by different studies. Bartley *et al.* investigates the plasma vitamin D levels in 48 patients among which 58% showed levels below 50 nmol/L. In Taneja and Taneja, 96.51% reported vitamin D levels below 80 nmol/L. Vitamin D helps in improving immune functions and reducing inflammation. It plays a significant role in immunoregulatory functions. A systematic review of statistical study shows certain correlation in vitamin D deficiency with upper and lower respiratory tract infection comprising rhinosinusitis, bronchiolitis, acute otitis media, pneumonia and pharyngotonsillitis found especially in children. The preventive effect of vitamin D in allergic rhinitis is a contradictory issue. The role of vitamin D in enhancing the development of Th2 cells and suppression of Th1 cells plays a major role in the course of the disease. In a similar investigation includes functioning of Vitamin D in the induction of allergic rhinitis, performed on a larger population health study indicated an increased risk of allergic rhinitis in men when compared to women with low vitamin D levels in the blood serum. Obstructive sleep apnoea (OSA) which is a serious sleep disorder, current research shows

patients with low levels of vitamin D suffering from the disease. In several systematic review and meta-analytical studies had revealed patients suffering from sleep apnoea with significant decrease in vitamin D level in their blood. Although the reaction mechanism of vitamin D association with OSA is yet to be understood. Vitamin D deficiency shows a direct correlation with various otolaryngological disorder. Further studies are required to understand the underlying mechanism of action. The role of vitamin D in immunoregulatory and immunomodulatory functions need clear assessment. These studies will help us establish the pharmacokinetics of the molecule in our body.

3.6 Vitamin D in orthopaedics

Vitamin D appears to play several roles in the musculoskeletal system, according to present research. Vitamin D is important for soft tissue healing and rehabilitation, as well as altering postoperative outcomes after common orthopaedic surgeries, according to new research. Vitamin D is clearly important for musculoskeletal health, according to studies. Excess calcium in the bloodstream from too much vitamin D can harm the kidneys and heart. It can also cause bone deterioration. Muscle cramps, bone discomfort, and joint pain may be more common in people with significantly low Vitamin D blood levels.

3.7 Astaxanthin in orthopaedics

The vitality of chondrocytes was not affected by astaxanthin. In chondrocytes, astaxanthin activated the Nrf2 transcription factor. Under diseased conditions, astaxanthin protected cartilage homeostasis. Under pathological conditions, astaxanthin activated Nrf2 to maintain cartilage homeostasis. By altering redox homeostasis, astaxanthin reduced TBHP-induced chondrocyte death. In vivo, astaxanthin reduced cartilage deterioration. Astaxanthin has no effect on the viability of chondrocytes. Astaxanthin stimulated the Nrf2 transcription factor in chondrocytes. Astaxanthin protected cartilage homeostasis under pathological situations. Astaxanthin activated Nrf2 to preserve cartilage homeostasis in diseased circumstances. The findings showed that pretreatment with astaxanthin aided the recovery of hind limb motor function and reduced the pathological damage caused by SCII (spinal cord). Furthermore, astaxanthin improved the antioxidative stress response and reduced mitochondrial edoema. Astaxanthin pretreatment, on the other hand, had little effect on the levels of proinflammatory cytokines following SCII 6. Osteonecrosis, or the destruction of bone cells, is associated to alcoholism. The rate of alcohol abuse is predicted to increase by 0.6 percentage points each year. Because of the high morbidity and cost of osteonecrosis treatment, it is critical to try to prevent osteonecrosis before it develops. Astaxanthin is an antioxidant that has been shown to increase the number of osteocyte and osteoblast cells, decrease the number of adipocyte cells, and reduce the risk of osteonecrosis. In rats exposed to alcohol, astaxanthin administration reduced the incidence of osteonecrosis in the femoral head.

4. DISCUSSION:

- Vitamin D with astaxanthin in gynaecology.
- Vitamin D with astaxanthin in ENT.
- Vitamin D with astaxanthin in orthopaedic.

4.1 Astaxanthin in marine reproduction

From the studies it was found that astaxanthin is a useful carotenoid in crustaceans and fishes since it is a predominant carotenoid occurring in crustaceans also it is a potent antioxidant to have shown better antioxidant properties than other carotenoids. It has been found to have many functional uses from improving the fertilization and egg survival, sexual maturity. It has potential in relieving oxidative stress as it is very efficient antioxidant. Recommended dose is 5mg astaxanthin per day (250mg of algal meal).

4.2 Effect in reproductive health

An analytical study was carried out among 40 women, who were aged between 32-74 years and had been operated for various known tumors of uterine corpus. Isolation of obtained carotenoids was done by high performance liquid chromatography (HPLC), thin layer chromatography (TLC) and column chromatography (CC). Saponification for the carotenoids was done with 10% KOH in ethanol at 20° C for 24 hours in the dark under nitrogen. CC and TLC were significantly used so as to separate the particular carotenoids (Hoffman La Roche and Sigma Company). At last, the particular desired pigments were determined by ionpairing, reverse phase HPLC. Statistical analysis was carried out to note the analytical presence of carotenoids in normal and pathological tissues of Corpus uteri. It was found out that various carotenoids were present in tissue sample, out of which few were predominantly present in all the samples obtained. One of which is Astaxanthin, which was majorly present in all the samples collected (62.8%). Astaxanthin, which found in 63% of all the tissues examined, was found to show highest anti-oxidant activity. ROS is one among such cause which is formed as a by-product of oxygen metabolism and its present higher concentration can affect the sperm motility, its capacitive activity and acrosomal reaction. Thus to regulate such activities antioxidants can provide a suitable solution by limiting the rate of reaction of ROS. As ROS widely affect leukocytes and semen thus it shows that ROS affect the semen quality thus affecting MFI. Antioxidants can reduce the Male Factor Infertility (MFI) and decrease the rate of infertility by checking up the proper regulation of ROS. Antioxidants can also lower the sperm DNA damage which is caused by ROS. Adding supplements rich in antioxidants can increase and improve the sperm motility, sperm DNA fragmentation, fertilization capacity. Also, the oral uptake of antioxidants can improve the reproductive health in men by improving pregnancy rates and decreasing sperm DNA damage.

In another study, semen levels were compared when male partners of 20 infertile couples were administered. 20 milligrams of astaxanthin, whose semen characteristics were

found to be below the WHO recommended reference value. The observed results were quite significant which showed improved sperm parameters, semen quality and increased fertility. In a study carried out by Tripathi and Jena, it was found out that the treatments involving astaxanthin significantly improved the testes weight, sperm count and sperm head morphology. Astaxanthin is a potent antioxidant with a better antioxidant properties than other carotenoids, is very well functional in reducing the free radicals and ROS by preventing oxidative damage and apoptosis induced by oxidative stress. Astaxanthin has also been very successful in prevention of cancers like breast cancer and prostate cancer. It has known to increase fertility rates among infertile couples with proper supplementation of astaxanthin on regular basis. Astaxanthin with proper and balanced diet is ought to improve body's enzymatic activity against ROS as astaxanthin improves the cell's antioxidative capacity. It was also found out that Astaxanthin significantly decreased reactive oxygen species and also promote sertoli cells for the the secretion of inhibin B which indicates a positive effect of astaxanthin on sperm parameters and fertility.

4.3 Effect in IVF or Embryo transfer

A study conducted in 10 women showed that women undergoing IVF and embryo transfer found an enormously raised concentration of estradiol levels during gonadotropin-induced ovarian stimulation and a significant increase in the serum levels of 1,25(OH)2D3. Also, when the vitamin D levels were higher than usual a decrease in the pregnancy rates and embryo quality was observed. While conducting clinical trials in women with PCOS it was noted that vitamin D supplementation or administration of vitamin D3 shows a positive effect on insulin secretion, lipid profile and menstrual cycle. Vitamin D3 might play an important role in modulating ovarian activity. A lower serum level of vitamin D was observed in women patients suffering from PCOS and having signs of obesity (31.9 ± 9.4 nmol/l) than in non-obese women (73.1 ± 20.2 nmol/l) as analysed in a study. Vitamin D deficiency in pregnancy was found to be less than 50nmol/l that was linked with 4 fold risk of severe preeclampsia and Vitamin D with less than 37.5nmol/l was associated with 5 fold risk of developing preeclampsia. Although vitaminD is naturally acquired through the most patent source i.e. sunlight but certain foods and supplements such as dietary substitutes are advised to balance or improve the level of vitamin D in female body. Level of 25(OH)D3 of 75-110nmol/l provided suitable benefits for such conditions and can be obtained by daily uptake of 1,800-4000 IU dosage composition. Toxic levels of Vitamin D are defined as a supplementation above 150nmol/l. Also, there have been reported cases of women with low level of vitamin D that were also seen to be associated with adverse pregnancy outcomes. A higher increased rate of preeclampsia, preterm birth, smaller gestational age infants, bacterial vaginosis and gestational diabetes were observed. In order to aid such discrepancies various vitamin D supplements are supposed to be included in diet. Naturally occurring vitamin D rich foods such as fatty ocean fish,

irradiated mushrooms and cod liver oil are a great source of supplementation providing vitamin D. Foods and drinks such as milk, yogurt, orange juice, cereals and infant formula are sometimes also forfeited with vitamin D. Oral supplements are also available in the form of vitamin D2 and D3 in varying doses. Apart from such dietary supplements, acquiring vitamin D naturally through sunlight is very beneficial especially between 10 AM and 3PM is considered sufficiently efficient.

4.4 Role of Astaxanthin and vitamin D

This review study has established therapeutic roles of Astaxanthin and Vitamin D in various immunoregulatory disorders in the body. The study suggests that there is a close relationship between the deficiency of vitamin D in the blood serum level which can be measured by calculating the Serum 25-hydroxyvitamin D level in the blood. Numerous studies have shown low serum 25 O[HD] levels in the blood associated with an otolaryngological disorders. Vitamin D deficiency has been a common issue among all age group, around the world. Rickets is a resultant disorder of this deficiency that has still not been eradicated. Insufficiency of vitamin D may result in numerous autoimmune conditions such as rheumatoid arthritis, type I diabetes and some late life cancers. An earlier study had shown 48% of the patients who were detected with multiple sclerosis had vitamin D deficiency. Astaxanthin is a red coloured pigment often marine in origin with immunomodulatory responses in the body. Earlier studies had shown synergistic antioxidant activity of astaxanthin when administered with low doses of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in HepG2-C8-ARE luciferase cell lines. Thus, further studies are required to establish powerful synergistic effects with this molecule. It also helps in reducing side effects of cancer such as ototoxicity, salivary gland damage, and hearing loss. Its chemical nature and structure have an added advantage for its high efficacy and therapeutic activity in the body. Thus, it is crucial for the medical professionals to study these nutrients which may be important leads in treatment of various disorders.

4.5 Vitamin D in the musculoskeletal system

Much of the study has previously focused on vitamin D's role in fracture healing, but more recent studies have revealed the importance of vitamin D in the context of soft tissue healing and recovery, as well as its impact on postoperative outcomes following common orthopaedic surgeries. Despite this, conflicting evidence exists, and more prospective randomised trials are needed to fully understand the role of vitamin D in the musculoskeletal system. Low levels of vitamin D have been seen in a wide range of people, including young adults, the elderly, and postmenopausal women, according to numerous studies. According to study, elderly persons who take Vitamin D have fewer falls, which is likely related to improved muscle function. Vitamin D is necessary for human health in several ways. All of the prospective trials, on the other hand, looked at healthy people. To the best of our knowledge, no study focusing

exclusively on vitamin D status among orthopaedic surgery patients has been published from India. The frequency of vitamin D inadequacy and insufficiency among orthopaedic patients is frighteningly high, affecting patients of all ages. Vitamin D deficiency has both beneficial and detrimental effects on the musculoskeletal system, according to a growing body of studies. As a result, it is advised that the orthopaedic surgeon be involved in the diagnosis and treatment of vitamin D insufficiency patients. Regrettably, current research is insufficient to identify optimal vitamin D levels in patients and establish evidence-based treatment guidelines.

4.6 Role of Astaxanthin in elderly people

It has discovered that astaxanthin pretreatment effectively enhanced motor capabilities and mitigated pathological damages in the spinal cord by reversing histological abnormalities. Furthermore, following the SCII, astaxanthin dramatically reduced oxidative stress and reduced mitochondrial edoema. More notably, the PI3K/Akt/GSK-3 signalling pathway was linked to astaxanthin's protective benefits in SCII-treated rats. Astaxanthin, a dietary supplement with no known side effects, is being studied in a variety of therapeutic settings, including cardiovascular health, acute pancreatitis, and neuropathic pain, all of which are linked to oxidative stress and inflammation in their pathogenesis. Furthermore, astaxanthin plays a therapeutic effect in the preservation of cognitive function by increasing or maintaining neuronal plasticity in elderly patients and patients with neurodegenerative illness. It has also been proven to help skeletal muscle damage patients preserve mitochondrial integrity and function while also reducing oxidative stress. Recent research has found that astaxanthin has significant antioxidant and/or anti-inflammatory capabilities in many types of ischemia and reperfusion injury, including steatotic liver, muscle, and brain tissue. The study's main findings were that astaxanthin in combination with functionally focused exercise training enhanced endurance and walking distance in senior adults, as well as increased muscular strength and size (sarcopenia). Thus, in elderly adults, mobility, endurance, and strength were all increased using.

5. CONCLUSION:

This research review's purpose is to help the reader understand different aspects posed by the research on the Therapeutic activity of vitamin D with Astaxanthin. This is significant because it gives insights about Vitamin D with Astaxanthin in gynaecology, ENT and orthopaedics . There has been much research and discussion conducted on these opinions of researcher and the Therapeutic activity of vitamin D with Astaxanthin. Most of the research found was on the about Vitamin D with Astaxanthin in gynaecology, ENT and orthopaedics, Infertility, antioxidant, otolaryngological diseases, musculoskeletal system, cartilage homeostasis More research and testing is required to gain a better understanding of the Vitamin D with Astaxanthin in gynaecology, ENT and orthopaedics.

6. ACKNOWLEDGEMENT:

We would like to thank our supervisor/guide Bharat Kwatra, from Invenzion Labs Inc. whose expertise was invaluable in formulating the research questions, methodology and drawing conclusions. His insightful feedback and guidance pushed us to sharpen our thinking and brought our work to a higher level.

7. ETHICS APPROVAL AND CONSENT TO PARTICIPATE.

Not applicable.

8. HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

9. CONSENT FOR PUBLICATION

Not applicable.

10. AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

11. FUNDING ACKNOWLEDGEMENT AND CONFLICT OF INTEREST

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

REFERENCES

- Agarwal, A., Hamada, A., & Esteves, S. C. Engaging Practicing Gynecologists in the Management of Infertile Men. In *Journal of Obstetrics and Gynecology of India* (Vol. 65, Issue 2). (2015).
- Akbar, N. A. & Zacharek, M. A. Vitamin D: Immunomodulation of asthma, allergic rhinitis, and chronic rhinosinusitis. *Current Opinion in Otolaryngology and Head and Neck Surgery*, (2011).
- Al-Amin, M. M. et al. The antioxidant effect of astaxanthin is higher in young mice than aged: a region-specific study on brain. *Metabolic Brain Disease*. (2015)
- Amano, T., Murakami, A., Murakami, T., & Chano, T. (2021). Antioxidants and therapeutic targets in ovarian clear cell carcinoma. In *Antioxidants* (Vol. 10, Issue 2). (2021).
- Anagnostis, P., G. Athyros, V., Adamidou, F., Florentin, M. & Karagiannis, A. Vitamin D and Cardiovascular Disease: A Novel Agent for Reducing Cardiovascular Risk? *Current Vascular Pharmacology*, (2010).
- Bartley, J., Reid, D. & Morton, R. P. Prevalence of vitamin D deficiency among patients attending a general otolaryngology clinic in South Auckland. *Annals of Otolaryngology, Rhinology and Laryngology*, (2009).
- Böhm, F., Edge, R. & Truscott, T. G. Interactions of dietary carotenoids with singlet oxygen (1O_2) and free radicals: Potential effects for human health. *Acta Biochimica Polonica* vol. 59 (2012).
- Bohon, T. M., & Goolsby, M. A. The Role of Vitamin D Supplements in Women's Health. *Clinical Medicine Insights: Women's Health*.(2013)
- Brotosudarmo, T. H. P., Limantara, L., Setiyono, E. & Heriyanto. Structures of Astaxanthin and Their Consequences for Therapeutic Application. *International Journal of Food Science* vol. 2020 (2020).
- Clerici, W. J. & Yang, L. Direct effects of intraperilymphatic reactive oxygen species generation. *Hearing Research*, (1996).
- Czeczuga-Semeniuk, E., & Wolczyński, S. Dietary carotenoids in normal and pathological tissues of corpus uteri. *Folia Histochemica et Cytobiologica*, 46. (2008).
- Erdoğan, C. et al. The evaluation of oxidative stress in patients with chronic renal failure. *Clinica Chimica Acta*, (2002).
- Esposito, S., Baggi, E., Bianchini, S., Marchisio, P. & Principi, N. Role of vitamin D in children with respiratory tract infection. *International Journal of Immunopathology and Pharmacology* vol. 26 (2013).
- Esposito, S. & Lelii, M. Vitamin D and respiratory tract infections in childhood. *BMC Infectious Diseases* vol. 15 (2015).
- Esteves, S. C., Hamada, A., Kondray, V., Pitchika, A., & Agarwal, A. What every gynecologist should know about male infertility: An update. *Archives of Gynecology and Obstetrics*, 286(1). X. (2012).
- Fu, J. Y., Jing, Y., Xiao, Y. P., Wang, X. H., Guo, Y. W., & Zhu, Y. J. Astaxanthin inhibiting oxidative stress damage of placental trophoblast cells in vitro. *Systems Biology in Reproductive Medicine*, 67. (2021).
- Fu, J. et al. Astaxanthin alleviates spinal cord ischemia-reperfusion injury via activation of PI3K/Akt/GSK-3 β pathway in rats. *J. Orthop. Surg. Res.* (2020).
- Gammone, M. A., Riccioni, G. & Orazio, N. D. ' marine drugs Marine Carotenoids against Oxidative Stress: Effects on Human Health. *Mar. Drugs*. (2015).
- Grundmann, M., & von Versen-Höyneck, F. Vitamin D - roles in women's reproductive health? In *Reproductive Biology and Endocrinology* (Vol. 9). (2011).
- Gu, J. et al. Astaxanthin-loaded polymer-lipid hybrid nanoparticles (ATX-LPN): Assessment of potential otoprotective effects. *Journal of Nanobiotechnology*, (2020).
- Hasan, D. et al. Vitamin D Deficiency in South Sharqiya in Oman and its Impact on ENT Patients-A Retrospective Study. *Bengal Journal of Otolaryngology and Head Neck Surgery* vol. 24 (2016).
- Higuera-Ciapara, I., Félix-Valenzuela, L., & Goycoolea, F. M.. Astaxanthin: A review of its chemistry and

- applications. In *Critical Reviews in Food Science and Nutrition* (Vol. 46, Issue 2). (2006).
23. Holick, M. F. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *The American journal of clinical nutrition* vol. 80 (2004).
 24. Kaewrudee, S., Kietpeerakool, C., Pattanittum, P., & Lumbiganon, P. Vitamin or mineral supplements for premenstrual syndrome. *Cochrane Database of Systematic Reviews*, (2018).
 25. Kidd, P. Astaxanthin, cell membrane nutrient with diverse clinical benefits and anti-aging potential. *Alternative Medicine Review* vol. 16 (2011).
 26. Kimball, S., Fuleihan, G. E. H. & Vieth, R. Vitamin D: A growing perspective. *Critical Reviews in Clinical Laboratory Sciences* vol. 45 (2008).
 27. Kitashima, S. Morphological alterations of submandibular glands caused by cisplatin in the rat. *Kurume Medical Journal*, (2005).
 28. Kinal, M. E. et al. Investigation of Astaxanthin Effect on Cisplatin Ototoxicity in Rats by Using Otoacoustic Emission, Total Antioxidant Capacity, and Histopathological Methods. *Ear, Nose and Throat Journal*, (2021).
 29. Kopke, R. D. et al. Use of organotypic cultures of Corti's organ to study the protective effects of antioxidant molecules on cisplatin-induced damage of auditory hair cells. *American Journal of Otology*, (1997).
 30. Lerchbaum, E., & Rabe, T. Vitamin D and female fertility. In *Current Opinion in Obstetrics and Gynecology* (Vol. 26, Issue 3). (2014).
 31. Liu, J. et al. Memory loss in old rats is associated with brain mitochondrial decay and RNADNA oxidation: Partial reversal by feeding acetyl-L-carnitine and/or R-lipoic acid. (2001).
 32. Liu, S. Z. et al. Building strength, endurance, and mobility using an astaxanthin formulation with functional training in elderly. *J. Cachexia. Sarcopenia Muscle*, (2018).
 33. Mai, X. M., Chen, Y., Camargo, C. A. & Langhammer, A. Serum 25-hydroxyvitamin D levels and self-reported allergic rhinitis in Norwegian adults - The HUNT Study. *Allergy: European Journal of Allergy and Clinical Immunology*, (2014).
 34. Maier, G. S., Weissenberger, M., Rudert, M., Roth, K. E. & Horas, K. The role of vitamin D and vitamin D deficiency in orthopaedics and traumatology—a narrative overview of the literature. *Ann. Transl. Med.* (2021).
 35. Marchisio, P., Nazzari, E., Torretta, S., Esposito, S. & Principi, N. Medical prevention of recurrent acute otitis media: An updated overview. *Expert Review of Anti-Infective Therapy* vol. 12 (2014).
 36. Melamed, M. L. et al. Serum 25-Hydroxyvitamin D Levels and the Prevalence of Peripheral Arterial Disease Results from NHANES 2001 to 2004. (2008)
 37. Mylonas, C. & Kouretas, D. Lipid peroxidation and tissue damage. *In Vivo* vol. 13 (1999).
 38. Moon, A. S. et al. Current concepts in vitamin D and orthopaedic surgery. *Orthopaedics and Traumatology: Surgery and Research* vol. 105 (2019).
 39. Morrison, R. J. M. et al. VASO (Vitamin D and Arthroplasty Surgery Outcomes) study - supplementation of vitamin D deficiency to improve outcomes after total hip or knee replacement: Study protocol for a randomised controlled feasibility trial. *Trials*, (2017).
 40. Naguib, Y. M. A. Antioxidant activities of astaxanthin and related carotenoids. *Journal of Agricultural and Food Chemistry*, (2000).
 41. Nan, B., Gu, X. & Huang, X. The role of the reactive oxygen species scavenger agent, astaxanthin, in the protection of cisplatin-treated patients against hearing loss. *Drug Design, Development and Therapy* vol. 13 (2019).
 42. Neighbors, C. L. P. et al. Vitamin D and obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Medicine* vol. 43 (2018).
 43. Nishikawa, Y. et al. Effects of astaxanthin and vitamin C on the prevention of gastric ulcerations in stressed rats. *Journal of Nutritional Science and Vitaminology*, (2005)
 44. Osguthorpe, J. D. Pathophysiology of and potential new therapies for allergic rhinitis. *International Forum of Allergy and Rhinology* vol. 3 (2013).
 45. Palinski, W. et al. Low-density lipoprotein undergoes oxidative modification in vivo. *Proceedings of the National Academy of Sciences of the United States of America*, (1989).
 46. Patton, C. M., Powell, A. P. & Patel, A. A. Vitamin D in Orthopaedics. *J. Am. Acad. Orthop. Surg.* (2012).
 47. Punjabi, N. M. The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society* vol. 5 (2008).
 48. Rada, B. & Leto, T. Oxidative innate immune defenses by Nox/Duox Family NADPH oxidases. *Contributions to Microbiology* vol. 15 (2008).
 49. Riccioni, G. et al. Resveratrol and anti-atherogenic effects. *International Journal of Food Sciences and Nutrition* vol. 66 (2015).
 50. Santhanagopal, S., Sebastian, M., Muniswamy, M. M. & Pilar, A. A study on vitamin D status among orthopaedic patients. *Int. J. Res. Orthop.* (2020).
 51. Scragg, R., Jackson, R., Holdaway, I. M., Lim, T. & Beaglehole, R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: A community-based study. *International Journal of Epidemiology* (1990).
 52. Shimidzu, N., Goto, M. & Miki, W. Carotenoids as Singlet Oxygen Quenchers in Marine Organisms. *Fisheries Science*, (1996).
 53. Sita-Lumsden, A., Laphorn, G. & Swaminathan, R. Reactivation of tuberculosis and vitamin D deficiency: the contribution of diet and exposure to sunlight. *Thorax* 1003–1007 (2007).

54. Speranza, L. et al. Astaxanthin treatment reduced oxidative induced pro-inflammatory cytokines secretion in U937: SHP-1 as a novel biological target. *Marine Drugs*, (2012).
55. Stahl, W. & Sies, H. Antioxidant activity of carotenoids. *Molecular Aspects of Medicine* vol. 24 (2003).
56. Sun, K. et al. Astaxanthin protects against osteoarthritis via Nrf2: A guardian of cartilage homeostasis. *Aging (Albany, NY)*. (2019).
57. Tanaka, T. et al. Chemoprevention of Rat Oral Carcinogenesis by Naturally Occurring Xanthophylls, Astaxanthin and Canthaxanthin1. (1995).
58. Taneja, M. K. & Taneja, V. Vitamin D Deficiency in E.N.T. Patients. *Indian Journal of Otolaryngology and Head and Neck Surgery*, (2013).
59. Tavera-Mendoza, L. E. & White, J. H. Cell defenses and the sunshine vitamin. *Scientific American*, (2007).
60. Terlikowska, K. M., Dobrzycka, B., Kinalski, M., & Terlikowski, S. J. Serum Concentrations of Carotenoids and Fat-Soluble Vitamins in Relation to Nutritional Status of Patients with Ovarian Cancer. *Nutrition and Cancer*, 73. (2021)
61. Terzi, S. et al. The effects of astaxanthin on salivary gland damage caused by cisplatin in the rat. *International Journal of Research in Medical Sciences*, 1410 (2017).
62. Upala, S. & Sanguankeo, A. Association between 25-hydroxyvitamin D and obstructive sleep apnea: A systematic review and meta-analysis. *Journal of Clinical Sleep Medicine* vol. 11 (2015).
63. Urashima, M. et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *American Journal of Clinical Nutrition*, (2010).
64. Urman, B., & Oktem, O. Food and drug supplements to improve fertility outcomes. *Seminars in Reproductive Medicine*, 32. (2014).
65. Weiss, D. A., Harris, C. R., & Smith, J. F. The use of complementary and alternative fertility treatments. In *Current Opinion in Obstetrics and Gynecology* (Vol. 23, Issue 3). (2011)
66. Wiradiputra, A. E., Suyasa, I. K., Astawa, P. & Siki Kawiya, K. Astaxanthin increase osteocytes, osteoblasts, decrease adipocytes cells, and reduces osteonecrotic events in femoral head of Wistar rats exposed to alcohol. *Bali Med. J.* (2018).
67. Woźniak, M., Krajewski, R., Makuch, S., & Agrawal, S. Phytochemicals in gynecological cancer prevention. In *International Journal of Molecular Sciences* (Vol. 22, Issue 3). (2021)
68. Yang, X. et al. Astaxanthin attenuates environmental tobacco smoke-induced cognitive deficits: A critical role of p38 MAPK. *Marine Drugs*, (2019).
69. Yuan, J. P., Peng, J., Yin, K., & Wang, J. H. Potential health-promoting effects of astaxanthin: A high-value carotenoid mostly from microalgae. In *Molecular Nutrition and Food Research* (Vol. 55, Issue 1). (2011)
70. Zhang, J. et al. Astaxanthin prevents pulmonary fibrosis by promoting myofibroblast apoptosis dependent on Drp1-mediated mitochondrial fission. *Journal of Cellular and Molecular Medicine*, (2015).