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RESEARCH ARTICLE

VITAMIN D- SAFEGUARD AGAINST CANCER.

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Abstract

Earlier, Vitamin D was implicated in bone health as it promotes the intestinal absorption of calcium and phosphates. Vitamin D is considered important for bone and mineral metabolism. Various guidelines suggest a daily intake of 5-15 µg of vitamin D. Approximately 90 % of vitamin D is generated in our body and the remaining 10 % comes from dietary intake. The deficiency of Vitamin d has been found to be linked with distinct biological processes in recent years. The improper vitamin D metabolism is responsible for various health problems including cancer. In the present review, the role of vitamin D in cancer and its prevention has been discussed. The anti-cancer effects of vitamin D involving several mechanisms such as apoptosis, anti-inflammatory, anti-angiogenesis, anti-proliferative, inhibiting invasive and metastasis, etc. are also investigated in this review.

Introduction:-

Vitamin D, a fat-soluble neurosteroid plays a key role in enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. The body makes vitamin D when skin is exposed to sunlight that's why it is called "the sunshine vitamin". For development of strong bones, vitamin D is required as it helps the body to use calcium from the diet. Most of our vitamin D requirement is fulfilled from sunlight because very few foods are available containing natural vitamin D such as fish liver oils, egg yolks, dairy and grain. The daily intake of 5–15 μg of vitamin D is recommended, but the amount of vitamin D from UV irradiation via skin or oral intake is insufficient to meet the demand for most people nowadays (Zittermann, 2010). A lot of epidemiologic studies, prove that exposure to sunlight is important to prevent many chronic diseases as the sun's energy promotes the photosynthesis of vitamin D_3 in the skin of vertebrates that is responsible for supplementing the efficiency of intestinal calcium absorption (Wacker, 2013).

It is long-established that vitamin D deficiency leads to a disease called rickets, in which the bone tissues doesn't get enough minerals, which leads to fragile bones and skeletal abnormality. With the decreasing level of Vitamin D, an increased risk of many diseases e.g. cancer, disorders of glucose metabolism, cardiovascular diseases, neurodegenerative diseases, and death is taking place (Chu et al., 2010).

It is produced by exposure of the skin to sufficient ultraviolet B radiation and absorption from the gastrointestinal tract. After vitamin D_3 is synthesized, it is carried to the liver, where 25-hydroxyvitamin D_3 is formed via hydroxylation by 25-hydroxylase. 25-Hydroxyvitamin D_3 is further converted into the physiologically active vitamin

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D_3 (1, 25-dihydroxyvitamin D_3, $1,25(OH)_2D_3$) in the mitochondria of the proximal convoluted tubules (**Fig 1**). The active vitamin D_3 and vitamin D-binding protein are subsequently transported to different organs for further metabolism (Bikle, 2014).

Role of Vitamin-D in cancer and other diseases

Several studies have directly correlated the vitamin-D with cancer progression. The involvement of vitamin D in cancer progression was first documented by Garland and Garland who observed the high risk of colon cancer due to UV light-induced production of vitamin D in the skin (Bhatt et al., 2019). It has become evident that vitamin D deficiency can support the growth of various cancers. Evidences suggest that cancerous cells involve mechanism that reduces the cellular levels of calcitriol, which is a biologically active form of vitamin D. Cancer cells also decreases the activity of calcitriol in order to protect them from antitumorigenic effects of vitamin D. Vitamin D plays a protective role in several types of cancer, such as the prostate, breast, and colon cancer (Zittermann, 2003). Inhibition of proliferation of a variety of human leukemia cell lines and instigation of differentiation of normal and leukemic myeloid precursor by vitamin D results in increasing maturation and decreasing aggressiveness of potential leukemic cells. Therefore, vitamin D is useful in the treatment of leukemia and other myeloproliferative disorders (Cao et al., 2017).

Active vitamin D regulates inborn and adaptive immune system. It is thought to be able to activate cathelicidins, antimicrobial peptides present within the lysosomes of macrophages, and polymorphonuclear leukocytes (Lai, 2013). Due to ability of vitamin D to elevate CNS dopamine levels, it has been examined as a potential neuroprotective agent in various models of Parkinson disease (Eyles et al., 2013). It is also engaged in cardiovascular diseases such as coronary artery disease, myocardial infarction, congestive heart failure, stroke, atrial fibrillation, or peripheral vascular disease. Because of abnormal insulin secretion and immune dysfunctions, deficiency of vitamin D has also been found to be associated with earlier-onset and highly severe diabetes mellitus. Vitamin D also shows some relation with neuropsychiatric rather than neurological diseases. It has been associated with depression which is one of the most common mental disorders. However, it is difficult to interpret, as the findings may simply reflect the altered behavior of depressed individuals. Vitamin D deficiency may lead to brain dysfunction of foetal as it significantly affects brain cell differentiation and proliferation during the neonatal period. Furthermore, vitamin D deficient individuals are at greater risks of having schizophreniz People born in winter/spring and those born at higher latitudes have a significantly increased risk of developing schizophrenia. Vitamin D levels are reliably reported to be lower in people with dark skin that's why they are also prone to Schizophrenia.schizophrenia is a group set of neuropsychiatric disorders characterized by symptoms like hallucinations, delusions, confused thinking, and disorganized speech. The mechanisms through which vitamin D deficiency might be associated with schizophrenia remain Unclear. It was found that vitamin D-deficient persons were 2.16 times (95 % CI 1.32, 3.56) more prone to have schizophrenia than those with vitamin D sufficiency (Valipour et al., 2014). Thus, Vitamin D supplements prove to be a low-cost population-based intervention capable of reducing utilization of more intensive physical and mental health treatments; multiple trials are underway assessing impact on a variety of physical health conditions including osteoporosis, insulin resistance, and cardiovascular risk.

Preventive role of vitamin D against cancer

Vitamin D plays an important role in the cancer prevention and treatment and several mechanisms have been proposed in order to explain its anticancer effects. Vitamin D have the ability to regulate every step in tumorigenesis, from initiation to metastasis and cell-microenvironment interactions. Numerous studies and experimental data suggest that the activation of vitamin D signaling emerges as a promising strategy for the prevention and treatment of different types of cancers (Jeon et al., 2018). Vitamin D-induced protection against cancer includes several mechanisms such as anti-inflammatory, antiproliferative effects, apoptosis, stimulation of cell dedifferentiation, angiogenesis inhibition, invasion and metastasis (**Fig 2**) (Feldman et al., 2014).

The anti-inflammatory properties of VitaminD are expressed by suppressing the activity of prostaglandin by inhibiting the cyclooxygenase 2 expression, NF-κB signaling, stress kinases and enhanced tissue inhibitor of metalloproteinases 1. Vitamin D diminishes the expression of tumor-suppressor genes such as *MYC* and retinoblastoma (*RB*), cyclin-dependent kinases, increases P21 and P27 expression, which shows its antiproliferative action. Vitamin D also induces apoptosis by suppressing the NF-κB signaling, which increases the expression of proapoptotic gene *BAX* and decreases the expression of antiapoptotic gene *Bcl-2*. It diminishes the activity of hypoxia-inducible factor α, interleukin-8, vascular endothelial growth factor (*VEGF*) gene and prostaglandin E2

levels, which exhibits the antiangiogenesis activity of Vitamin D (Umar et al., 2018; Fathi et al., 2019). Calcitriol have the potential to reduce the expression of estrogen receptors, which further decreases the estrogen signaling in cancerous cells. It also downregulates the aromatase expression, an enzyme that catalyzes the synthesis of peripheral estrogen from androgens and also in cancer tissue (Krishnan et al., 2012).

Vitamin D against aging problems

$1,25(OH)_2D_3$ also regulates α-klotho, which is a renal hormone (antiaging enzyme) that protects against skin atrophy, hyperphosphatemia, cognitive defects, osteopenia, impaired hairing and neurodegenerative disorders. This combination maintains various molecular signaling pathways assisting growth and development for normal functioning and also provides protection against degeneration and malignancies. Thus, vitamin D also plays a key role in promoting health span by slowing down the chronic diseases of aging (Gil et al., 2018).

Conclusion:-

Vitamin D becomes a necessity for human beings throughout their lifecycle in order to maintain optimum health. The deficiency of vitamin D can result into numerous preventable diseases. Various studies have suggested that vitamin D provides protection against cancer. Several new trials are still in progress to determine the optimum dosage of vitamin D for cancer prevention. Vitamin D possess different kinds of anticancer properties which further helps to better understand the mechanisms involved in the pathogenesis of cancer and other diseases.

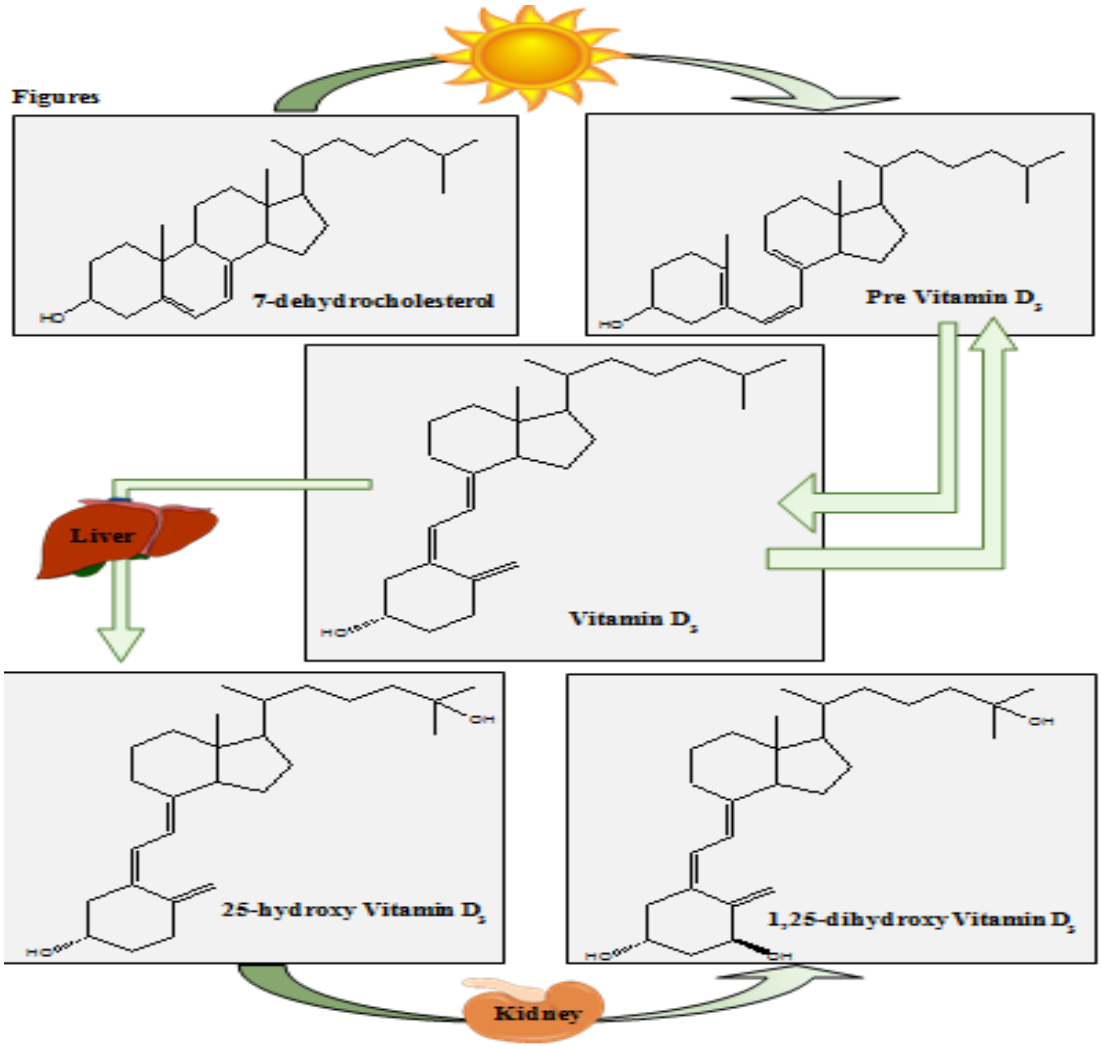

Figure 1:-Photobiosynthesis and activation of Vitamin D_3.

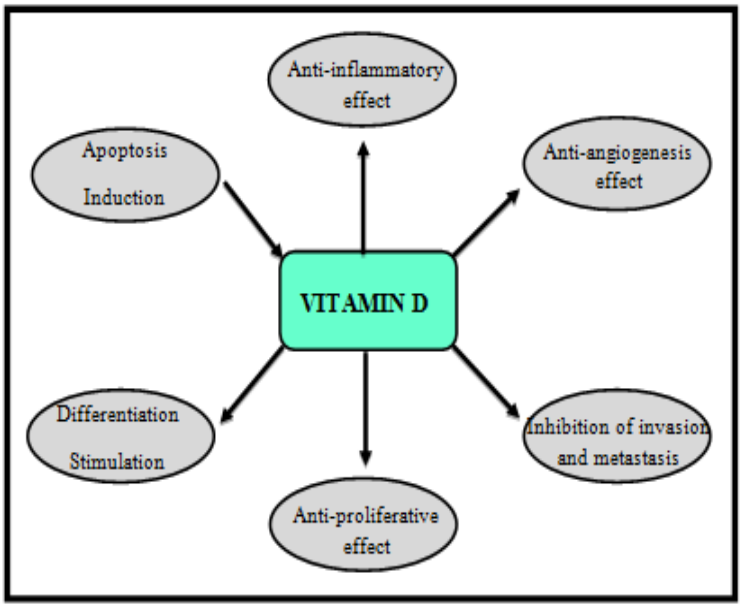

Figure 2:-Types of anti-cancer effects of Vitamin D

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