THE COMBINATORY STUDIES WITH OMEGA-3 FATTY ACIDS AND THEIR EFFECTIVENESS IN THETREATMENT OF PROSTATE CANCER: A REVIEW

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ABSTRACT:Males have a higher probability than women to develop prostate cancer which contributes considerably to higher death rates in men worldwide. Prostate cancer patients present with either an illness that is either isolated or progressed. Prior to this study, -3 polyunsaturated fatty acids & vitamin D were employed completely separately to evaluate the efficacy of prostate cancer treatment. However, numerous combination studies for prostate cancer have since been conducted.In comparison to individual therapy, the combinatory studies used in this review's analysis of trials in terms of -3 fatty acids for the treatment of prostate cancer are quite effective at treating the disease. Because there may be significant commonalities between this combinational research on anticancer effects. In this review, the mechanics and efficacy of that will be addressed. Lastly, we contrast the combinations, finding that Vit D with -3 fatty acids as well as easy at-home strength training, omega 3 stearidonic acid with doxorubicin, and 1,2-5 Dihydroxy vitamin-D with -3 fatty acids are greater efficiency than to several other combinatory therapies with -3 polyunsaturated fatty acids & individual therapies.

KEYWORDS: -3Polyunsaturated fatty acids, Prostate cancer**,** Combinatory therapy, Vit D, Simple home strength exercise, Doxorubicin,Stearidonicacid.

INTRODUCTION:

Day by day increasing advancements in cancer biology but still,the death rate has not changed inthe past 50 years.[1]As a result of the employment of a DNA alkylating chemical known as nitrogen mustard during World War 2, conventionalmonotherapy is utilized to treat many malignancies by utilizing hazardous medications. In order to cure cancer, almost 400 chemotherapy drugs have been discovered since then. Because of the physiological intricacy of malignancies, monotherapy has unfavorable outcomes. Recently, a lot of scientists and engineers have created combination therapies for the treatment of cancer.[2]When two or more treatments are used to selectively target cancer cells, it is referred to as a combination therapy.[3,4]The conventional monotherapeutic approach, which is most frequently used to treat multiple cancers, also exhibits toxicity if only one chemotherapeutic agent is used in it. Because of this, it is typically less efficientthan combinational treatmentdue to the fact that it does not specifically target cells that are actively proliferating, causing damage to both cancerous and non-cancerouscells.[5-7]It is located where the first double bond of the -3 fatty acidsis another name for n-3 fatty acids, which is located in themethyl end ofthemoleculeis located.In n-3 fatty acids has contains two main groups such as alpha-linolenic acid&fatty acids of a long chain. α-linolenic acid has contained 18 carbon molecules and it has 3 double bonds present in it,sources such as vegetable oil and nuts and fatty acids of long chain contained 20 carbon atoms& it has five or more double bonds present in it and atleast 2 conjugated double bonds present in cis position.One of the most important significant types of very lengthy polyunsaturated fatty acids in terms of nutrition is known as marine omega 3-S, and they have all been commonly observed in fatty fish like tuna& salmon. These fatty acids include eicosapentaenoic acid& docosahexaenoic acid. All of those are -3 fatty acid subsets.[8-10]The additional root of availability for-3 fatty acids invegetable oils, walnuts, flax seeds, flax oil, canola oil, green vegetables, and some animal fats.[10]

One of the serious cancers that affect men, prostate cancer is the sonext largest prevalent kindof cancer[11]In 2012, Prostate cancer affected approximately 1.10 million men, as per Globocan. globally.In men, 15% of malignancies are detected, and it is projected that 3,07,000 men die from them. 2015 saw the diagnosis of 2,20,800 prostate cancer cases increase in the USA. In males, 26% of malignancies and 27,540 deaths are to be estimated[12] and in 2017, 1,60,000 males received a

prostate cancer diagnosis this year.[13]As the male population of the world ages,it was anticipated that there would be 4,99,000 deaths and 1.7 million new cases will occur worldwide in 2030.[12]In mechanistic studies vitamin D3 is used for cancer prevention and regulates several genes by inhibiting the growth of cancer cells it is responsible for cell proliferation and differentiation.[14]The additional interactions between stearidonic □-3 fatty acids (SDA). Due to its cardioprotective qualities, it is combined with doxorubicin to stimulate the expansion of human prostate cancer cell lines LNCaP, PC3, and DU145[15]In cancer treatments, □-3 fatty acids improve the effectiveness of different cancer medications. Omega 3 fatty acids increaseseefficacy of doxorubicin[16], mitomycin[17], epirubicin[18], arabinosylcytosine[19], and CPT11.[20]Randomized controlled clinical research found that VitD, □-3 fatty acids& straightforward home exercise regimen are in concert with the direction of prostate cancer treatment,the risk of cancer is reduced for active persons aged 70 and older.[21]This study examined various medication regimens that include □-3 fatty acids in order to address prostate cancer.

PROSTATE CANCER:

History:

For men, the most typical cause of death is prostate cancer. During the previous seasons, scientists from various disciplines have begun to comprehend prostate cancer's typical course of development.Before the widespread application of prostate-specific antigen testing study was conducted.From the mid-1980s,when prostate-specific antigen analyses were introduced, there wherethe rate of prostate cancer would also have increased considerably although the death rate decreased. However, no long-term data on prostate-specific antigens were reported.[22]Many scientists have begun to learn more about the natural course for state cancer. In 1969 Barnes has started an investigation on localized prostate cancer patients for long-term survival it is treated as confidentially. Between 1930 and 1958 patients were treated confidentially. Of that 50% of patients survived in 10 years and 30% of patients survived in 15 years.Barnes noted that 2/3 of these men passed away from medical complications rather than prostate cancer, and he noted that the tumour stage is just as relevant as competing medical risks. Being a chronic condition, prostate cancer's curative therapy took up to 10 years to develop. He came to the conclusion that conservative therapy would result in patient survival rates of 10 years or less.[23]The urological cooperative of the veteran administration completed a number of controlled randomized studies between 1960 and 1974 and is currently evaluating various treatment options formales who haverecently been diagnosed with prostate cancer.A total of 2911 adult males signed up for the trial to compare the effectiveness of radiation therapy with radical proctectomy. While carrying out the study[24]Every patient's biopsy and histology who's already signed up for the Urological research cooperative of the veteran administration has been subjected to an evaluation by Dr. Donald Gleason. 9 different forms of aberrant glandular development, he observed. These nine patterns are connected to sufferers' clinical results.[25]After that from 1989 to 1997 Johansson finalized that men who are in the early diseased stage were not getting any benefits from aggressive intervention in most of the cases.[26]

In 1994 chodak conducted non-randomized trials for 868 patients in six different countries, these results which are similar to Johansson and Gleason's results.[26] The retrospective cohort study was conducted for local prostate cancer in Sweden and he died between 1988 to 1990.[27] In 1997 patients were treated with radiation, surgery, and conservative management.[28]

PATHOPHYSIOLOGY:

Genetics:

A significant risk aspect for Prostate cancer is caused by the deposition of somatotype changes inside thegenetic sequence of the prostate epithelial cell the curriculum ofa person's life.Those certain deviationscould impact oncogenes orcancer-suppressing gene expressionand alter the transcription or translation of genes as well as operative shortcomings that disturb the homeostasis of cells.[29]Mutations often impact genes and regulate cell development, cell proliferation& cell death.Since most genetic changes linked to the disease are copy number changes or genomic building rearrangements, prostate cancer is classified as a C-class cancerous cell with a modest mutational load.[30]

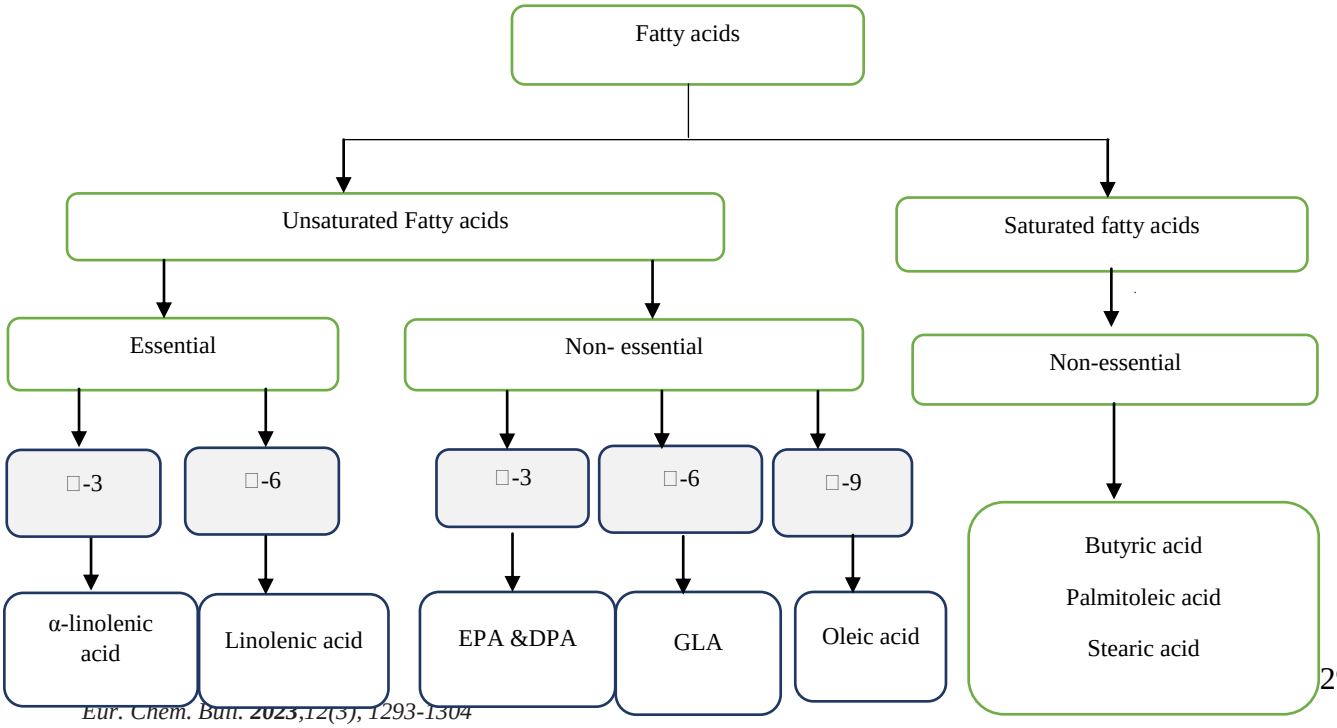
POLYUNSATURATED FATTY ACIDS:

Two primary constituents of □-3 polyunsaturated fatty acids are eicosapentaenoic acid & docosahexaenoic acid, which have several medical advantages. Epidemiological studies from the 1970s were the first to hypothesize that dietary

polyunsaturated fatty acids would be helpful in reducing disease.[31,32] □-3 polyunsaturated fatty acids are currently being studied today, but their particular working mechanisms are still not completely known. Several recent developments have increased our knowledge of how □-3 polyunsaturated fatty acids affect human disease.As an example, it has been demonstrated that the DHA-receptor GPR120 helps in the detection and regulation of obesity and metabolic syndrome.[33] □-3 mediators resolvins and protectins, two recently identified ones, have been shown to exhibit anti-inflammatory as well as pro-resolving properties.[34]The primary source of □-3 fatty acids such as fish oil, which contains a double bond upon that third carbon atom of a carbon chain, starting from the methyl end.[35]

Role of polyunsaturated fatty acids in Cancer:

During the Industrial Revolution,entire fat consumption and the □-6 to □-3 polyunsaturated fatty acidsratioschanged dramatically from Western food.[36,37]Except for □-3 polyunsaturated fatty acids, which stand out and exhibit effects that guard against colon, breast, and prostate cancers ina variety of testing platforms,There's been an increase in fat intakelinked to the formation of particular cancer types such as breast, colon, pancreaticand prostate cancers.[38-40]Investigations into the link between dietary fat and cancer conducted by epidemiologists indicate that□-3polyunsaturated fatty acids have taken steps to avert the disease while □-6 polyunsaturated fatty acids have a cancer-promoting impact. Experimental studies provide the majority of its clinical information about the influence of dietary fat on malignancies,[41]those findings are inconsistent because few of these studies show a meaningful link between □-3polyunsaturated fatty acids and decreased prostate cancer danger or tumorprogression.[42,43]Western food has a high □-6 to □-3 polyunsaturated fatty acids proportion, which indicates□-6polyunsaturated fatty acids concentrations are hugely disproportionate large and n-3 polyunsaturated fatty acids,the sum seems to be insufficient. A reduction in the risk of prostate cancer is connected to increased dietary □-6 polyunsaturated fatty acid advantages, according to different studies.[44-46]The percentages of□-3 and □-6 polyunsaturated fatty acids precursors werefound much higher in malignant tissues, according to research from Sweden that compared the polyunsaturated fatty acids composition of the same prostate specimens contained both benign and malignant prostatic tissues.According tothis research further substantiates the connection between □-6 dietary fat and prostate cancer.[44]Williams& co-workers et;al found that the large percentage of□-6 to □-3 fatty acids can also elevatethe entire prostate cancer risk in white men and probably an elevated risk of advanced prostate cancer over every man based on evaluates based on race of case-control research with 79 incidents of prostate cancer with 187 controls.[45]In their meta-analysis of fish consumption and prostate cancer, Szymanski et al. concentrated on prostate incidence rates and prostate cancer-specific mortality. However, they were unable to establish a protective connection between fish consumption& the occurrence of prostate cancer, despite their findings showing a large 63% decrease in prostate cancer-specific death.[47]



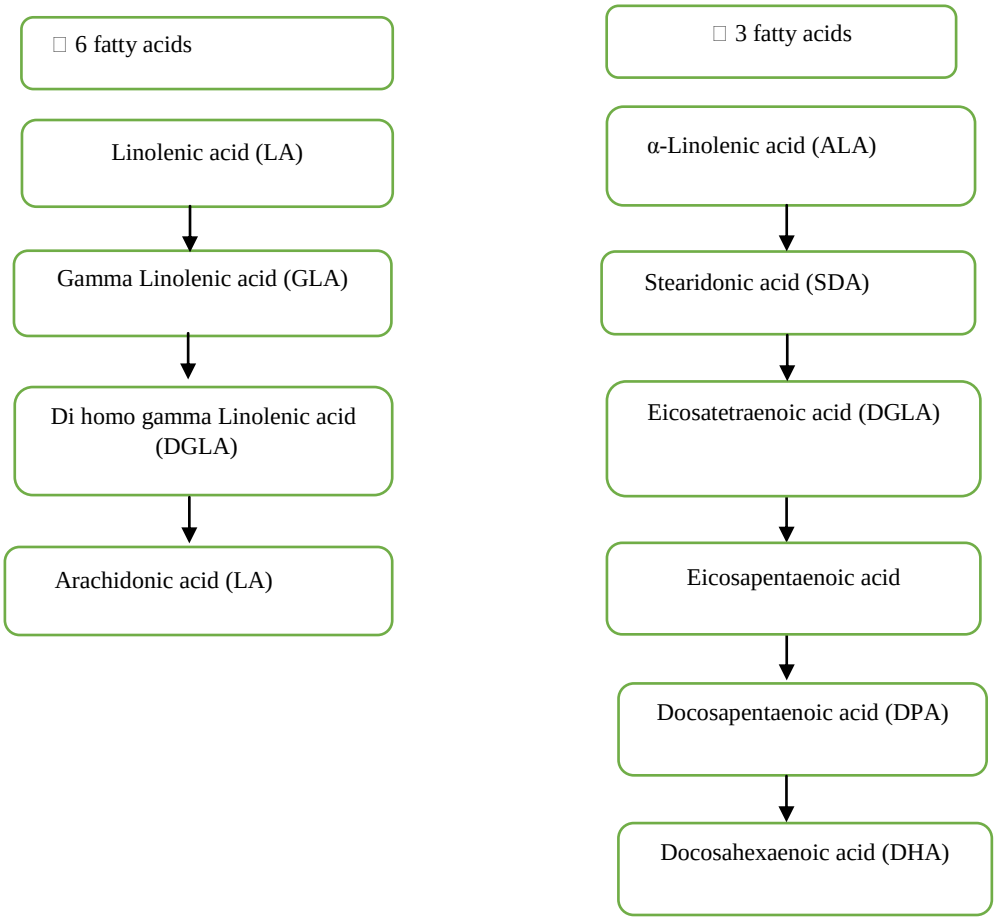


Figure1. Classification of Fatty acids

STUDIES COMBINING □-3 FATTY ACIDS:

VITAMIN D:

Anticancer benefits of Vit D&polyunsaturated □-3 fatty acidshave obtained significant consideration in recent times.A growing body ofthe study largely supports both chemical groups' anticancer properties. Breast[48-50], prostate[38,49], and colorectal cancer[38,51,52]in vitro studies looking intotheimpactof□-3 polyunsaturated fatty acids ontumour cells have yielded good results. Although less definitive, epidemiological research in human populations appears to suggest a negative correlation between an increasing □-3 polyunsaturated fatty acid diet& lower probability of cancer.[49,53]Studies

on vitamin D appear to consistently show a negative association between consumption and endangerment of the breast, prostate, colorectal, and other cancers, in contrast to epidemiological research on □-3 fatty acids.In vitro studies for vitamin D's effects on the breast[54], prostate[55], colorectal[56], and lung cancer[57] have also been consistently positive.These chemicals, although differ chemically, have some very comparable impacts on cancer.

1,25-dihydroxy vitamin D [1,25(OH)2D]:

prostate cancerous cells must have access to androgens to grow.[58]Asa result of, androgen restriction Counselling has been theprimary formof treatment for advanced prostate cancer for the previous 50 years. The average response time is only two years. As the result, cancer cells become much more aggressive, hormone-refractory, and capable of growing without androgen activation.[59]Efforts to prevent and also treat androgen-independent prostate cancer are attracting significant scientific attention. □-3 polyunsaturated fatty acids are widelyperforms preventive role of prostate cancer.[60-62]Human prostate cells have receptors for the effective type of Vit D is 1,25-dihydroxy Vit D [1,25(OH)2D]. When 1,25-dihydroxyvitaminD3was added, prostate cancer cells exhibit increased differentiation and apoptosis, a G0/G1-phase arrest, and reduced invasiveness and metastasis, if androgen suppression was unsuccessful. AstudybyIstfan et;al analysed the cytokinetic properties of androgen-dependent & androgen-independent prostate tumor cells to assessthe inhibitory activity of 1,25-dihydroxy vitamin D and three polyunsaturated fatty acids in fish oil.The transition fromthe G1/S phase has to be more suppressed when 1,25-dihydroxy vitamin D3 and fish oil were used jointly than when either medication was used alone. Interestingly, the 1,25-dihydroxyvitamin D3 and fish oil synergistic impact were observedwithinthe androgen-free LNCaP-c115 subline. These findings led us to propose that dietary elements like three polyunsaturated fatty acids and Vit D may prevent prostate cancer cells from developing into an aggressive and incurable stage. In particular, vitamin D and polyunsaturated omega-3 fatty acids can affectstrategies that make prostate cancer aggressive and challenging to cure. This research would also provide essential mechanistic information required to design the clinical and human studies in an effort to lessen prostate cancer-related Death and disease rates.[63]

Vitamin D3 and Simple Home strength exercise(SHSE):

According to mechanistic research, vitamin D controls several involved in tumor division and multiplication to stop the cancer cells from expanding.[14]According to observational research, blood vitamin D levels and total cancer risk are inversely correlated.[64]But even so, inconsistent outcomes of clinical studies evaluatingvitamin D supplements suggest that the vitamin has little benefit in preventing cancer however, it might decrease the danger of deadly cancer& advanced cancer.[65-67]More recent cancer studies have postulated a separate method by which both □-3 and □-6 fatty acids influence acidic cancer cells' mortality through ferroptosis.[68]Through a variety of molecular strategies, exercise may decrease the risk of cancer, including both an improvement in the immune system's response as well as a decrease in the inflammatory process.[69-71] Increased physical activity lowers the incidence of those cancers[72] as well as improves cancer survival, according to several scientific studies.[73]Despite the fact that a recent review of randomised controlled studies failed to show that omega-3 fatty acids had a protective effect towards combatas opposed to cancer.[74]
According to investigations by Bischoff et al., the trial took place. To fill in these barriers, a study conducted for 2,157 better and healthier persons aged 70 and older examined the impact of daily maximum vitamin D3, daily □-3 fatty acid supplements, in addition, a simple home exercise program, may reduce the likelihood of developing any invasive cancer in people of that kind old group.When compared to treatments that only included vitamin D, omega 3 fatty acids, simple at-home strength training, vitamin D+simple at-home strength training, or omega 3+simple at-home strength training, adding daily maximum vitamin D3 and omega 3 fatty acid supplements with simple at-home strength training had a cumulative effect of lowering the risk of developing cancer.[21]

OMEGA-3 STEARIDONIC ACID & DOXORUBICIN:

Doxorubicin:
Antineoplastic antibiotic doxorubicin was discovered in a culture of Streptomycespeucetius.[75] In the 1950s, researchers started looking for chemotherapeutic substances in soil-based microorganisms. A novel variety ofStreptomycespeucetius

that formed a vivid red pigment and was found to have strong antitumor effects on mouse tumors was developed into an antibiotic. The brand-new drug, daunorubicin, proved effective in treating lymphoma and acute leukemia.[76,77] But by 1967, it was understood that daunorubicin causes lethal heart damage.Researchers genetically altered the Streptomyces species to generate Adriamycin, a substance that was eventually renamed doxorubicin.[78] Doxorubicin's precise action mode is complicated and also still unknown. Doxorubicin inhibits macromolecular production by interacting with DNA through intercalation.[79,80]An unfamiliar bacterial strain was used to make an antibiotic. The DNA supercoils are loosened for transcription as a matter of fact of inhibition of the topoisomerase II enzyme. A novel strain of bacteria was used to develop an antibiotic. The complex is stabilized by doxorubicin after topoisomerase II splits its DNA chain to allow for cell division, to stop the DNA dual helix from resealing, so terminating the regeneration process. Theprostate cancerous lesions, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and Hodgkin's lymphoma are most typical cancers that are treated with doxorubicin.[78]

Omega 3 stearidonic acid:

Eicosapentaenoic and docosahexaenoic acid progenitor stearidonic acid decreases the indicator of proliferation and increases apoptosis inheterograft models of prostate cancer, similarto Doxorubicin.[81,82]

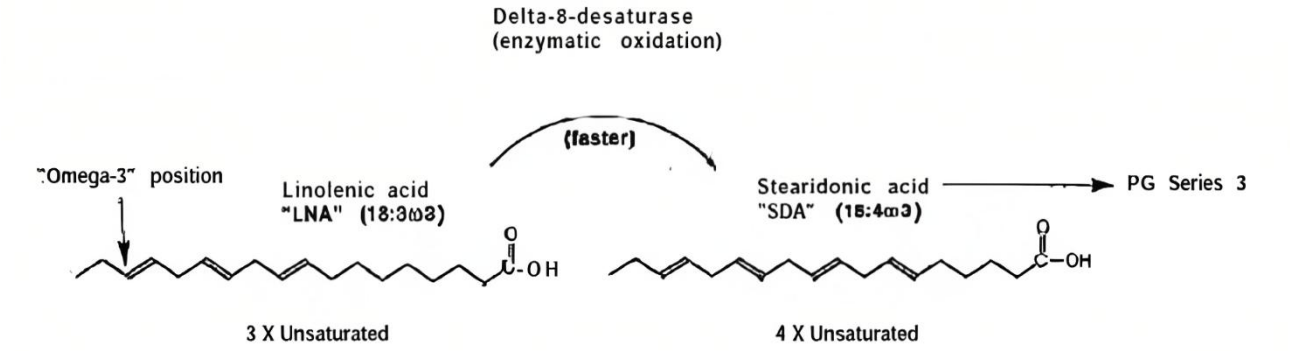


Figure 2.[83] Metabolic step for the formation of Stearidonic acid

According to the study of Mahmoud Mansour[84],the ability of the □-3 fatty acids from plantsStearidonic acid preventdevelopment of tumours & can improveDoxorubicin anticancer effects in the Cell lines LNCaP, PC3, and DU145 from prostate cancer.

Prostatecancercell line	DoxorubicinIC 50	Stearidonic acid IC 50	Combo's ratio
LNCaP	0.802 ±0.1	601±10	(1:750)
PC3	0.760±0.08	116±6	(1:150)
DU145	0.363±0.01	145±3	(1:400)

Table1[84]: Generated equipotency ratios by using IC50 values for DOX & SDA both for androgen-dependent LNCaP cells and androgen-independent PC3 and DU145 cells.

DISCUSSION

Mixed results from trials testing human treatment strategies for cancer prevention may clarify this result.[85] On the other hand, there aren't many combined interventions that take advantage of the maybe negligible cumulative advantages of various human health strategies.[86] Despite the fact that new cancer treatments combine many drugs to target various

cancer development routes.[87]For example,the Inhibition of human melanoma, oral carcinoma, lung, and breast malignancies is another usage for vitamin E. However, in both in vitro and in vivo conditions, Vit E has also inhibited thegrowth of prostate cancer by administering various chemotherapeutic dosages to rats.Accordingly, selenium combined with vitamin E is having a positive effect on prostatic cancer, according to current studies. There are numerous more combinatory therapies used for the prevention of human prostate cancer furthermore this combination with omega 3 fatty acid combinations.[88]Nowadays, a number of combination therapy based on nanoparticles are commercially available, and many more are in various phases of preclinical or clinical research.[89]Outlook for the future Combination therapies using nanoparticles has demonstrated a number of distinct advantages over conventional chemotherapy. Drug combinations cannow be given ingeniously and optimally for increased effectiveness.[90]

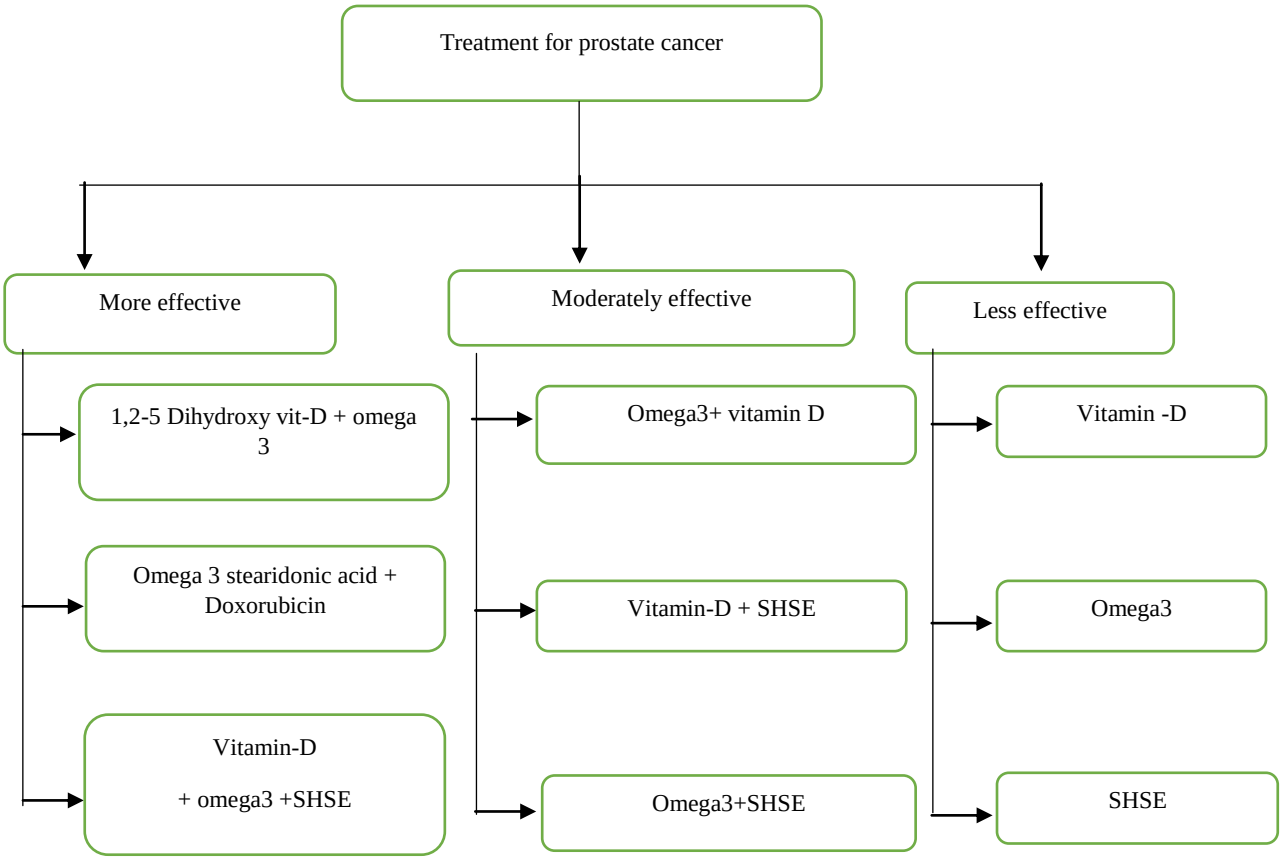


Figure 3. Combinatory effects based on Effectiveness for prostate cancer

CONCLUSION:

Treating prostate cancer combines various techniques and medications to increase effectiveness as well as decrease postoperative complications. A key factor preventing more people from using cancer drugs is their serious side effects. Besides that, cancer cells are becoming more resistant to chemo treatments, which has enhanced the need for relatively new, more affordable compounds with fewer side effects and higher cytotoxicity toward cancerous cells. In contrast to individual and only moderately effective research findings, combination studies are often more effective at treating prostate cancer.New therapeutic approaches are gaining acceptance for the aforementioned causes and for resolving these issues. The term is called "combinatory therapy".Such combinations include Vit D with □-3 fatty acids and easy at-home strength training, □-3 stearidonic acid with doxorubicin, and 1,2-5 Dihydroxy Vit-D with □-3 fatty acids.In comparison to individual pharmacological therapies, combination therapies work so well. Particularly when treating prostate cancer, combinatory chemotherapy has been revealed to have elevated favourable results.Researchers can greatly reduce prostate cancer-related fatalities by adopting these combination medicines.

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ABBREVIATIONS:

EPA: Eicosapentaenoic Acid;**DPA:**DocosapentaenoicAcid;**GLA:** Gamma Linolenic Acid

LC 50: Lethal concentration 50;**SHSE:** Simple home strength Exercise;**DOX:** Doxorubicin**SDA:** Stearidonic Acid

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