

Role of Nano trace element in Prostate Cancer –an update

1. Abstract:

Recently nanomedicine has been a great impact on the drug discovery and make a huge way for the drug delivery system for the therapeutic utility. There are many Nanoscale product increasing in research field and in the medical sector .Nanoparticle modified drugs are being developed and bring into the market for treatment of cancer. The nanoparticle drug carrier can improve the stability of drug for decreasing the cancerous cell and involved the drug at disease site. Essential Trace element mostly important for the physiological and biochemical aspects in human system. Nowadays Nano trace element used for the treatment of prostate cancer. In this review the venture and exploration of application of nanomedicine and the use of nanoparticle with essential trace element will give wide range of benefits for the treatment for prostate cancer.

2. Keywords:

Prostate cancer, Nano trace elements, cancer, nanomedicine, diagnosis, chemotherapy

3. Introduction:

Prostate cancer one of common type of cancer among all types of cancer but it affect particularly in male population. Prostate cancer is the second major diagnosed cancer ,it takes the sixth place in the cause of cancer death among all men in the world .The expected growth of prostate cancer will be almost 2.3 million new cases and causes of death will be 740 000 deaths by 2040 because of increasing population [1]. The estimation by GLOBOCAN data shows 1,276,000 cases of prostate cancer worldwide in 2018, which is same as an incidence rate of 29.3/100,000 men, and consist of 7.1% prostate cancer cases when compare to all other cancer diagnoses [2].In previous study report the substantial international variations in long term prostate cancer incidence and mortality rates. These variation indicate the regional difference among the population and variation in genetic susceptibility in which African decent has higher risk than Asian population [3]. During the estimation for prostate cancer cases by the American Cancer Society's found about 191,930 new cases for prostate cancer in the United States for 2020 and also found 33,330 deaths rate for prostate cancer. In Australia/New Zealand

(104.2/100,000), contain highest rate of prostate cancer [4]. In India the incidence rates of this cancer are constantly and rapidly increasing and the cancer projection data shows that the number of cases will double by 2020. Incidence rate of prostate cancer is 26,120 and 28,079 during the period of 2010 and 2015 [5].

There lots of research is going for the therapeutic and diagnosis process of Prostate cancer. Recently LIMK2 inhibits or decrease the development of diseases and also changes the cancer phenotype .At the same PTM of PTEN act as a prognostic and diagnostic biomarkers for the Castration Resistant Prostate Cancer in in vivo and in cell [6]. Here p14ARF is a tumor suppressor inhibits the apoptosis in prostate cancer cell and prevent the androgen receptor activity [7].The Blockage of FGF/MAPK shows effects of decreasing the prostate cancer along with the Androgen receptor Null phenotype [8].Human prostate cancer shows an increased de novo synthesis of fatty acid .A new metabolic metabolic function of c-Myc (Myc) has been proposed to regulate the fatty acid synthesis [9].Here Mark Buckup fond that plectin is a regulator for prostate cancer when compare to benign prostate tissues the metastatic human prostate cancer contain high level of plectin[10]

3.2 .Prostate cancer current diagnosis:

Table 1: current diagnostic method and tools for the detection of prostate cancer:

S.no	Diagnostic method	Diagnostic tool	criteria	Author
1.	Liquid based Biomarker	Glycan	Its an multi-analyze liquid based biomarker test for prostate cancer[11]	Emma Scott., et al.,2019
2.	Serum based biomarker	4Kscore® Test	4Kscore enhanced the predictive accuracy for clinically diagnosed prostate cancer [12]	Carroll.,et al.,2016
3.	Serum based	Prostate specific	Over expressed in prostate	Auprich M.

	biomarker	antigen (PSA)	cancer [13]	,et al.,2011
4.	Serum based biomarker	PHI	It will avoid unnecessary biopsies Detect high-grade PCa [14]	Al Saidi SS., et al.,2017
5.	Serum based biomarker	TNFR1 and TNF- α and IL 8	highly significantly predictive in differentiating men with CaP[15]	Chadha KC Et al.,2014
6.	Serum Based biomarker	MicroRNAs	Different MicroRNAs are found in prostate cancer vs non cancer[16]	Rajnee Kanwal et al.,2017
7.	Urine based biomarker	Galectin-3	analyzing prostate cancer patient[17]	Cordelia Geisler et al.,2017
8.	Urine based biomarker	ExoDX Prostate IntelliScore	Improved identification of high-grade PCa[18]	McKiernan J et al.,2016
9.	Urine based biomarker	TMPRSS2:ERG (T2:ERG)	Predict the risk of PCa and csPCa[19]	Tomlins SA et al.,2016
10.	Urine Based biomarker	Sarcosine	It is metabolic profiling tools for the analysis of prostate cancer based on metabolites intermediate[20]	Lucarelli G et al.,2015
11.	Urine Based	PCA3 score	Expressed highly in	Buss makers MJ

	biomarker		Prostate cancer[21]	et al.,2019
12.	Tissue based biomarker	Secernin-1 and vinculin	Potential diagnostic biomarker candidate for prostate cancer in tissue [17]	Cordelia Geisler et al.,2015
13.	Tissue based biomarker	ConfirmMDx (MDxHealth, Irvine, CA, USA)	is a prostate tissue biopsy based, DNA methylation assay[22]	Paul Yonover et al.,2019
14.	Tissue based biomarker	Long non-coding RNAs	LncRNAs are overexpressed in tumors tissue and cancer cells [23].	Xu, Y.-H., Deng et al.,2019
15.	Tissue based biomarker	Oncotype DX	Detect the recurrence PCa death and adverse pathology at RP[24]	Klein EA et al.,2014
16.	Tissue based biomarker	Prolaris	evaluates the expression of 31 cell-cycle progression genes[25]	Cooperberg. MR et al.,2013
17.	PET/CT imaging	PSMA ligand PET/CT	Detection of sites of recurrence and nodal or distant metastases that are often occult on standard-of-care imaging [26].	Sarah M et al.,2016

18.	Micro Spectroscopy	Lipid quantification by Raman micro spectroscopy	Lipogenic genes are upregulated with prostate cancer [27].	Jordan O'Malley et al.,2017
19.	PET imaging	Tetrapeptide sensor H2L	Assesment of zinc level by using Tetrapeptide sensor H2L[28]	Yong An et al., 2020
20.	Biosensor	Nanomaterial based aptasensing (PSA)	Aptasensors monitor the PSA biomarker for prostate cancer diagnosis [29].	Fatemeh Farshchi et al.,2020
21.	Fluorescence confocal microscopy	Digital Biopsy with Fluorescence Confocal Microscope	Diagnostic ability of FCM for prostate cancer and identify the grading from prostate biopsy.[30]	Rocco B et al.,2020
22.	Magnetic resonance Imaging	Targeted MRI-TRUS fusion biopsy	The MRI-targeted biopsy diagnosis with a Prostate Imaging Reporting and Data System (PI-RADS) score[31]	Benelli, Andrea et al.,2020
23.	Histopathology	Tissue based diagnosis	Diagnosis of tissue for prostate cancer by using hematoxylin and eosin stained tissue sections[32]	Humphrey PA et al 2017
24.	optical coherence elastography	TRUS Biopsy	3D data sets will be recorded by using optical	Chunhui Li et al.,2015

	(OCE)		coherence electrography for the prostate cancer occurrence [33].	
25.	PSMA-targeted radio ligands.	Prostate-Specific MembraneAntigen (PSMA)	PSMA in overexpressed in prostate cancer[34]	Haberkorn U et al.,2016
26.	Methylation assay	Methylation Marker	analysis of GSTP1, APC and RASSF1 genes [35]	Desotelle J et al.,2013
27.	Genomic driven test	The Decipher test	Measures RNA expression level of genes[36]	Karnes et al.,2013
28.	Protein based biomarker	Promark	estimate eight protein biomarker[37]	Shipitsin M et al.,2014
29.	Molecular Marker	Exosome Marker	Prostate derived exosomes shows higher in prostate cancer patients[38,39]	Duijvesz .D, Filella. X et al.,2011,2016
30.	Tissue based Test	Prostate Core Mitomic Test	identify the true negative prostate biopsies [40]	Frezza . C. et al.,2014
31.	TME associated	Tumor	Stromal AR signaling	Ricke. E.A

	biomarker	microenvironment	exhibit mediate prostate cancer metastasis[41]	et al.,2012
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Traditionally the prostate cancer is detected by using digital rectal examination, prostate-specific antigen (PSA) blood test, Transrectal ultrasound (TRUS) guided biopsy, But recently lots of biomarker has been identified for the diagnostic process in prostate cancer.

Glycans:

Glycans exhibit as a disease biomarker for prostate cancer .An alteration of glycans has been shown in the prostate cancer along with the changes in PSA glycosylation, increased sialylation and core fucosylation, increased O-GlcNacylation, the emergence of cryptic and branched N-glycans, and changes to galectins and proteoglycans [11].

Serum biomarker:

4Kscore® Test it's a serum based biomarker test detect the high grade risk in prostate cancer performed by biopsy [12]. The PCA 3 a serum based biomarker which over expressed in prostate cancer patients if level is 10 it shows the prostate cancer is positive. 4Kscore® Test is a powerful tool to perform the detection of prostate cancer in confirmatory biopsy in surveillance management. PSA is over expressed in prostate cancer patient which will indicate for the therapeutic process of prostate cancer. The rise of PSA Level also seen nonmalignant prostate disease like benign prostatic hyperplasia [13]. PHI (prostate health index) is serum based biomarker it is a strongest biomarker. When compare to other biomarker PHI has high specificity and sensitivity which use to avoid unnecessary biopsies [14]. TNF- α , sTNFR1 and IL-8 was measured in the serum sample using ELSIA kit, it gives highly significant detection of prostate cancer in men compare to PSA [15]. miRNA is a non coding RNA as regulator for gene expression at the post transcriptional level .miRNA is one of the biomarker for the detection prostate cancer .miRNA expression was predicted in prostate cancer tissue [16].

Urine biomarker:

Galectin-3 an urine based biomarker for prostate cancer patients with biochemical relapse, exhibit significant low level of Galectin-3 in prostate cancer patients [17]. Exosome gene

expression assay is an urine based biomarker, it is a noninvasive assay used to identify higher-grade prostate cancer in patients [18]. T2: ERG and PCA3 scores clinical-grade transcription-mediated amplification assays used to predict high-grade PCa on biopsy in urine sample with the development of serum prostate-specific antigen [19]. Sarcosine Metabolic profiling wonder full tool for the analysis of prostate cancer. In one of the diagnostic study PSA level in patient were analyzed in that the urinary sarcosine level was higher when compare to PSA level in patient with prostate cancer in negative control[20]. PCA3 (DD3) gene is a noncoding RNA usually mapped for 9q21–22 chromosome which is highly specific for prostate cancer tissue compare normal prostate tissue. Moreover PCA3 avoid unnessacary biopsies [21].

Tissue biomarker:

Secernin-1 and vinculin is tissue based biomarker both will be validated by using 2D-DIGE combined with MS a powerful tool for diagnostic the protein level in prostate cancer [17]. ConfirmMDx test is a tissue based biopsy it is based on the presence and absence of GSTP1, APC or RASSF1 methylation in the biopsy tissue for the diagnosis purpose of prostate cancer [22]. Long non-coding RNAs has 200 nucleotide RNS transcript used for the diagnosis of prostate cancer. It is a tissue based new biomarker which is overexpressed in prostate cancer tissue and cancer cell compare to normal tissue [23]. Oncotype DX is a commercially available test kit detect 17 genes based on genomic prostate test score. Oncotype DX test detect both high grade and high stage at surgical pathology .Oncotype DX can detect the time to biochemical recurrence at univarible analysis [24].Polaris is a commercially available test used to detect the expression of 31 cell-cycle progression genes, .It will predict the death of prostate cancer at multivariate model. In the study after the genetic study 65% treatment recommendation changed and 40% decrease in the treatment burden, But also this study shows impact on treatment targeting [25].

PET/CT imaging:

In recent years prostate-specific membrane antigen (PSMA) with ^{68}Ga -labeled and ^{18}F -labeled PET has been proposed for the detection of prostate cancer .It is clinically approved method for prostate cancer imaging based on the detection sites nodal or distant metastases that are often occult on standard-of-care imaging[21].

Lipid quantification vibrational Raman Micro spectroscopy:

Lipid quantification used by Raman micro spectroscopy act as a capable biomarker for the diagnosis of prostate cancer. Lipogenic genes such as sterol regulatory element-binding protein-1 (SREBP-1) and its downstream effector fatty acid synthase (FASN), and rate-limiting enzyme acetyl CoA carboxylase (ACACA) were increased with prostate cancer [22].

Tetrapeptide sensor H2L:

H2L is a powerful tool for the diagnostic of prostate cancer. Based on photo-induced electron transfer principle (PET) the Tetrapeptide sensor H2L (Dansyl-Gly-Pro-Trp-Gly-NH₂) used to imaging the zinc in prostate cancer cell lines .The zinc concentration level is lower with prostate cancer than normal prostate epithelial cells[23].

Aptasensing of prostate specific antigen (PSA) with nanomaterial:

Aptamers has been termed as a tool for the detection of prostate cancer .Nowadays nanotechnology in bio sensing has become an advanced technology in the medical field for the detection of cancer. Nanomaterials improve the signal amplification in the biosensors which will reduce the time for diagnosis. Here Nanomaterial based aptasensors is more accurate and sensitive for identifying the PSA biomarker for prostate cancer diagnosis [24].

Digital Biopsy with Fluorescence Confocal Microscope:

Tissue analysis with microscopic by Hematoxylin-eosin (HE) for prostate biopsy is a conventional method for the diagnosis of prostate cancer Whereas Fluorescence Confocal Microscope specifically and reliably used for the diagnosis of prostate cancer in which the real time digital image is used without conventional method. This digitalized real time remote access developed on the basis of artificial intelligence and machine learning [25].

Targeted MRI-TRUS fusion biopsy:

Targeted MRI-TRUS fusion biopsy is used to diagnosis the prostate cancer patients in which the magnetic resonance imaging/transrectal ultrasound (MRI/TRUS) fusion-guided biopsy for

clinically significant prostate cancers (Cs PCas). It is more accurate and cost-effective than visual registration and in-bore biopsy [26].

Histopathology:

Diagnosis of the tissue of adenocarcinoma is important for development of the diagnosis of prostate cancer. Using light microscope tissue sections stained with hematoxylin and eosin for the detection of prostate cancer Histopathological difference shows the carcinoma of prostate cancer are essential for the recognition prostate cancer in tissue[27].

Optical coherence elastography (OCE):

When compare to histopathology ,Optical coherence elastography (OCE) has more specificity and sensitivity which will predict the positive and negative values to calculated for Optical coherence elastography (OCE).3D data set was recorded and imaged by using Optical coherence elastography (OCE) for the detection of prostate cancer in suspected patients[28].

Prostate-specific membrane antigen (PSMA):

Prostate-specific membrane antigen (PSMA) used for diagnosis and therapeutic process of prostate cancer .Because the Prostate-specific membrane antigen (PSMA) is overexpressed in prostate cancer and Prostate-specific membrane antigen molecules are established to diagnosis and for the treatment of metastatic castration-resistant prostate cancer. ^{68}Ga -PSMA-11 PET/CT, nowadays spreading fast technique for the detection of recurrent prostate cancer.It will diagnosis patient with tumor lesions of high percentage with recurrent prostate cancer. Comparison between ^{18}F -fluciclovine PET-CT and ^{68}Ga -PSMA-11 PET-CT the diagnosis range was lower than the ^{68}Ga -PSMA-11 PET-CT for patients with early biochemical recurrence after prostatectomy [29].

Methylation Assay:

DNA methylation related with Tumorigenesis along with hyper methylation which involves in specific gene promotors generate hypo methylation this cause silencing of tumor suppressor genes. Genes such as FILIP1L isoform 2 a known senescence the pi-class glutathione S-transferase gene (GSTP1) marker are hyper methylated in prostate cancer. Biopsies were analyzed for GSTP1, APC and RASSF1 associated with the ACTB gene by using quantitative

methylation-specific PCR. In the epigenetic assay 88% of negative value were predicated. This assay shows that it is useful to decrease unnecessary re-biopsy.

Decipher:

Decipher is genomic driven based biomarker for the diagnosis of prostate cancer will evaluate the expression of RNA of 22 different genes. These genes are selected because it exhibit different expression in 192 early metastasis cases of prostate cancer. It is Basically involved in biological pathways, including cell cycle progression, cell proliferation, differentiation, adhesion, immune response regulating signaling pathways. The decipher show high risk in RP for pathologic grade upgrading And 5 year development of metastasis. Based on the decipher score timing of postoperative radiotherapy has been involved. It was also the only independent predictor of clinical metastasis in patients with prostate cancer after surgery [35].

ProMark:

ProMark is a protein Based biomarker estimate eight protein biomarker using an automated, quantitative, and multiplex immunofluorescence assay on FFPE tissues. It will detect which cancer aggressiveness in patients based on biopsy Gleason scores of 3 + 3 and 3 + 4. The protein marker panel exhibit score 0 to 1 which will detect adverse pathology in patients. This risk score was defined in 381 patients biopsies with matched prostatectomy [36].

Exosomal Biomarkers:

Exosomes is a double lipid membrane bound extracellular vesicles consists of proteins, lipids, and nucleic acid. Exosomes designed as biomarker to diagnosis for prostate cancer. Exosomes are a rich source of molecular markers such as protein, RNA, miRNA for prostate cancer detection. This prostate derived exosomes shows higher in prostate cancer patients with high Gleason score [38-39].

Prostate Core Mitomic Test:

Prostate core Mitomic test is the tissue based test with the link of mitochondrial function with regulation by oncogenes and tumor suppressors. It mainly detect the true negative prostate biopsies [40].

Tumor Micro-Environment (TME) Associated Biomarkers:

Tumorigenesis is involved with the interaction of cancer cells with tumor microenvironment. ECM, fibroblasts and myofibroblasts, mesenchymal stem cells, neuroendocrine cells (NE), adipose cells, immune and inflammatory cells, and the blood and lymphatic vascular networks are essential tumor microenvironment. The extracellular matrix and stromal cells link determine the primary tumor is eradicated or metastasizes. At the same time Stromal AR signaling exhibit mediate prostate cancer metastasis [41].

3.3 Prostate cancer current therapy:

Radiation therapy for prostate cancer:

Many advance radiation therapy has been emerged for the treatment of prostate cancer. External-beam radiotherapy (EBRT), and brachytherapy are mostly used radiation therapy for prostate cancer, in high risk diseases both External-beam radiotherapy (EBRT), and brachytherapy will control the disease. Image-Guided Intensity Modulated Radiation Therapy (IG-IMRT) used for rapidly increasing dose response radiation therapy. IG-IMRT treated for men with prostate cancer will decrease the treatment failure rate compare to low dose of radiation therapy [42]. Stereotypic radiation therapy is mainly used for the therapy for localized prostate cancer. Ultra-hypo fractionated radiation therapy with high dosage per fraction has been used for the prostate cancer therapy by stereotactic body radiation therapy (SBRT) technique [43]. Radiomics mainly involved in the characteristics at cellular and genetic level imaging. It has the capacity to genetic alteration and imaging in the prostate features for disease therapy [44]. proton beam radiation therapy used for the indication of prostate cancer in which the proton energy with charges particles travel to the tissue till the depth then the radiation dose is distributed to the sharp Bragg peak with accurate point[45].

Hormonal Therapy:

Androgen deprivation therapy (ADT) is mainly used for the treatment of prostate cancer. It will suppress the hormone in prostate cancer cells to grow, because prostate cancer cells need androgen hormones like as testosterone to grow decrease this hormones will protect the patient from the prostate cancer [46]. Abiraterone and Enzalutamide recently found hormonal therapies for prostate cancer .It have been tested and mainly designed for castration resistant prostatic

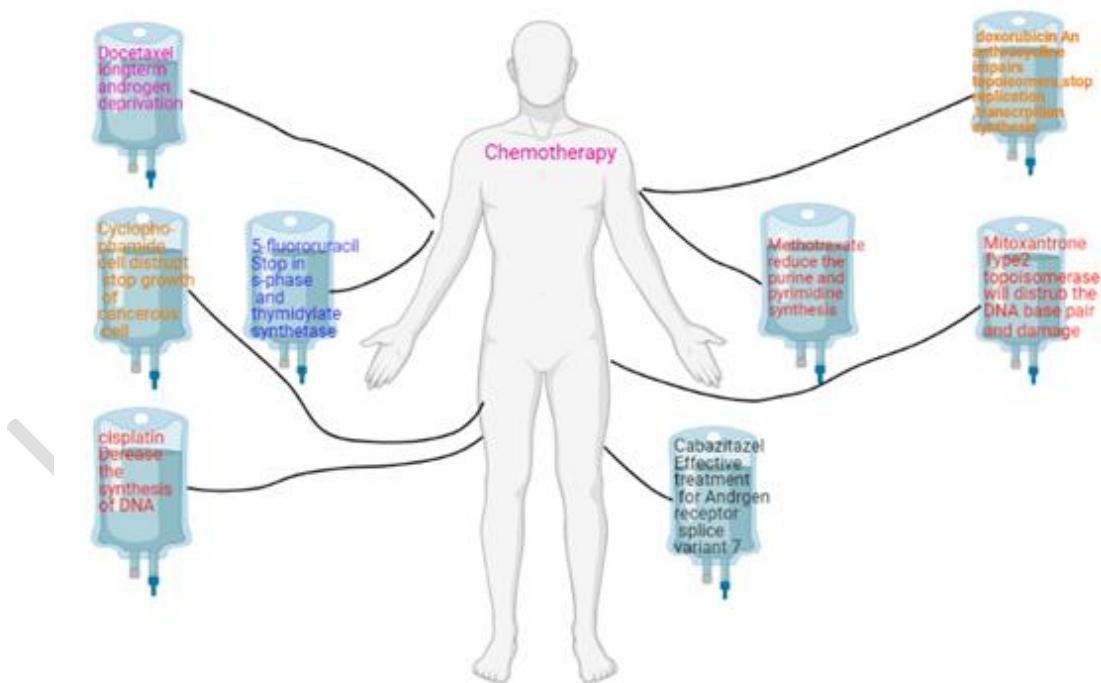
cancer patients .Some studies are going to use this two drugs for prostate cancer [47]. Using testosterone therapy in men with prostate cancer has been restricted previously .But now there are data will challenge this statement and recent changes has been evaluate for testosterone therapy regarded as visible opinion for prostate cancer from testosterone deficiency[48].

Immunotherapy for Prostate cancer:

Recently Immunotherapy is an essential cancer treatment modality. Sipuleucel-T and Ipilimumab became a new process for immune oncology which was approved by FDA. Immunotherapeutic alone cannot reduce the prostate cancer in patients, but combination of immunotherapy may workout to reduce prostate cancer .Many different ongoing studies exhibit the combination of cancer vaccine with different immunotherapeutic agents hormonal therapy (enzalutamide), radiation therapy (radium 223), DNA-damaging agents (olaparib), or chemotherapy (docetaxel) can increase the immune response without any significant toxicity[49].

Chemotherapy:

Fig:1 :Chemotherapy for prostate cancer



Chemotherapy process has been elevated in recent year for the treatment of prostate cancer. In earlier years chemotherapy treatment will become highly palliative rather than curative and tolerable response in patients.

Docetaxel:

Docetaxel was the first chemotherapy agent which shows improvement in the treatment of metastatic castration-resistant prostate cancer. But the combination with docetaxel drug has failed to show the improvement and survival rate in prostate cancer patients. However there are varying chemotherapy agent have been used for the treatment of prostate cancer [50].The upfront docetaxel increase the survival rate for metastatic hormone naïve prostate cancer patients with long term androgen deprivation therapy and mainly the metastatic burden for M1 patients was arranged for the long term outcomes[51].

Cyclophosphamide:

Cyclophosphamide is a chemotherapy medication, it is an alkylating agent which disrupt the cell division and cross linking the DNA strand, stop the DNA synthesis and growth of cancerous cell. It usually works by suppressing the immune system in the body. Before it was used to deliver suboptimal responses in urologic tumors [52]. Later it is used in angiogenesis inhibition through metronomic cycling [53].A study was conducted to quantify the immunologic effects in GM-CSF-secreting allogeneic cellular vaccine with the cyclophosphamide for prostate cancer survival studies, it shows complex immune response along with androgen deprivation therapy [54].

Cisplatin:

It is a platinum-containing compound Decrease the synthesis of DNA and disrupt the DNA strand. Cisplatin was studied based on the weekly schedule for 6 weeks then every 3 weeks maintenance and it became partial and complete remission in 17 patients out of 54[55].The effects of cisplatin and docetaxel were studied in biomechanical and morphological characteristics of prostate cancer cells .It shows the more stiffness in cisplatin and docetaxel cells also reduce the motility [56].

5-fluorouracil:

It is an analog of pyrimidine which stop the DNA synthesis during the S Phase and stop the thymidylate synthetase. In this 124 patient under taken the 5-fluorouracil with varying doses and it exhibit 9% antineoplastic responses [57]. Prostate cancer treatment has been improved after androgen deprivation, abiraterone, and taxane therapy and it became successful. 5-fluorouracil also rapidly improved with continuous infusion in metastatic castrate-resistant prostate cancer [58].

Methotrexate:

It is a dihydrofolic acid reductase inhibitor which decrease the purine and pyrimidine acid synthesis by disrupting the DNA synthesis. Methotrexate was taken at varying doses, the PR were occurred in only one out of 63 patients and 20% the disease was stable [59]. Combination of LHRH analog [DLys6]-LHRH and chemotherapy agent Methotrexate reduce the growth of prostate cancer cells in vitro and in vivo based on the concentrations of IC50 value[60].

Doxorubicin:

It is an anthracycline inserted in the DNA base pairs which impairs the topoisomerase II function and stop replication and transcription synthesis. The NPCP results exhibit clinical benefit shows the response rate which included the stable disease reaching at 84% [61]. Costunolide with doxorubicin prompt the prostate cancer cells to apoptosis along with activated mitogen-activated protein kinases and with the reactive oxygen species production [62].

Mitoxantrone:

It is an anthracenedione drug stop or slow the growth of cancerous cells .It act as inhibitor of Type II topoisomerase will disturb with DNA base pair and damage. Patient those who are not responsible for primary androgen deprivation but, found an improvement in 30% patient with low dose prednisone and mitoxantrone and improvement in symptoms and mainly from bone pain [63].Based on the pain palliation, cabozantinib versus mitoxantrone-prednisone has been compare in men with metastatic castration-resistant prostate cancer. Cabozantinib did not show better for pain relief than mitoxantrone-prednisone in castration-resistant prostate cancer patients [64]

Cabazitaxel:

It is a third generation semisynthetic tubulin-binding taxane drug. It has the capacity to treat against cancer cells like docetaxel .It has an antitumor activity to the models which was resistant effective treatment for Androgen receptor splice variant 7 (AR-V7) in circulating tumor cells in patients with metastatic castration-resistant prostate cancer [65].

4. Trace elements in Cancer:

Trace elements are essential for all living organisms to carry out various metabolic reactions including the fundamental driving force of oxygen transport, neurotransmission and mitochondrial respiration and oxidative phosphorylation to name a few Excessive amount of trace element or deficiency of trace element may lead to cancer. Recently in the comparative study serum trace element level was analyzed in Korean Breast Cancer Patients by using ICPMS [66].There are many essential trace elements leads to be anti-cancer effects .

Copper is one of the trace element which include in mechanistic process of our body. High level copper will increase the proliferation of cancer .But a new suggestion has been increased copper became an anticancer effects. Recently copper combined with curcumin elevated the inhibitory effects in the oral cancer cells. This gives a way to mechanistic insight of copper effect in oral cancer cells [67].Combination of iodinated chlorin p6 with copper (ICp6-Cu) was a chemo toxic agent increased the cytotoxic effects in Human oral carcinoma cells NT8e, 4451 with the increase of reactive oxygen species [68]. Zinc deficiency may lead to various infection in human body system .In many studies shown the connection between zinc and cause of cancer. Zinc exhibit anticancer effect through the antioxidant properties in such a way it also influence the immune system[69].Higher level of zinc ,copper induce the mortality in lung cancer patients. This studies in patients improve to do cohort studies in patients with other cancer risk[70].Iron is an essential trace element in human body system higher level iron induce risk of diseases causes carcinogenesis and Ferroptosis .Ferroptosis is denpent on iron became an inducer to cancer therapy .FDA approved ferroptosis as a cancer resistant therapy[71].Ferroptosis plays an important role in reduce growth of the cancer cells. Different types of drugs like sulfasalazine, lanperisone, sorafenib, fenugreek (trigonelline), acetaminophen, cisplatin, artesunate, combination of siramesine and lapatinib, ferumoxytol, and salinomycin can induce the ferroptosis [72].Calcium provide an anticancer effects in hormone dependent breast cancer by Src degradation in which the phosphoinositide 3-kinase and protein kinase B were significantly

decreased the clonogenic ability of hormone-dependent breast cancer cells[73].Calcium became an antitumor effect by destabilizing epithelial growth factor receptor which proteolysis Src or α -tubulin and shows some effect in non-small cell lung carcinoma[74].Ascorbic acid contain antioxidant properties . High Sodium-dependent vitamin C transporter family-2 shows sensitive to AA than low SVCT-2 but it shows hormetic response .Supplement with magnesium ion became an anticancer effect with AA[75].Comparison between Mgcl2 and cisplatin for anticancer effect in breast cancer in that Mgcl2 shows 59% and 44% apoptosis at 24h .It exhibit Mgcl2 has cytotoxic effect in MCF7 cells[76]. Selenium increase the anticancer activity in MCF7 cells of breast cancer through the transient receptor potential vanilloid 1 (TRPV1) cation channel with or without cisplatin activity [77]. Selenium also shows anticancer effects in cisplatin-induced nasopharyngeal cancer through the activity of caspase 3 [78]. Cobalt became anticancer agent and nontoxic with combination of other anticancer agent through induction of autophagy, cell cycle arrest, and inhibition of cell invasion and P-glycoprotein (P-gp)activity [79].The cobalt (III) Schiff base complexes such as trans-[Co(salen)(DA)2](ClO4) (1) and trans-[Co(salophen)(DA)2](ClO4) (2) (where salen: N,N'-bis(salicylidene)ethylenediamine, salopen: N,N'-bis(salicylidene)-1,2-phenylenediamine, DA: dodecylamine) are accumulated and showed anticancer activity and also as a chemotherapy agent mainly active in lung cancer[80].

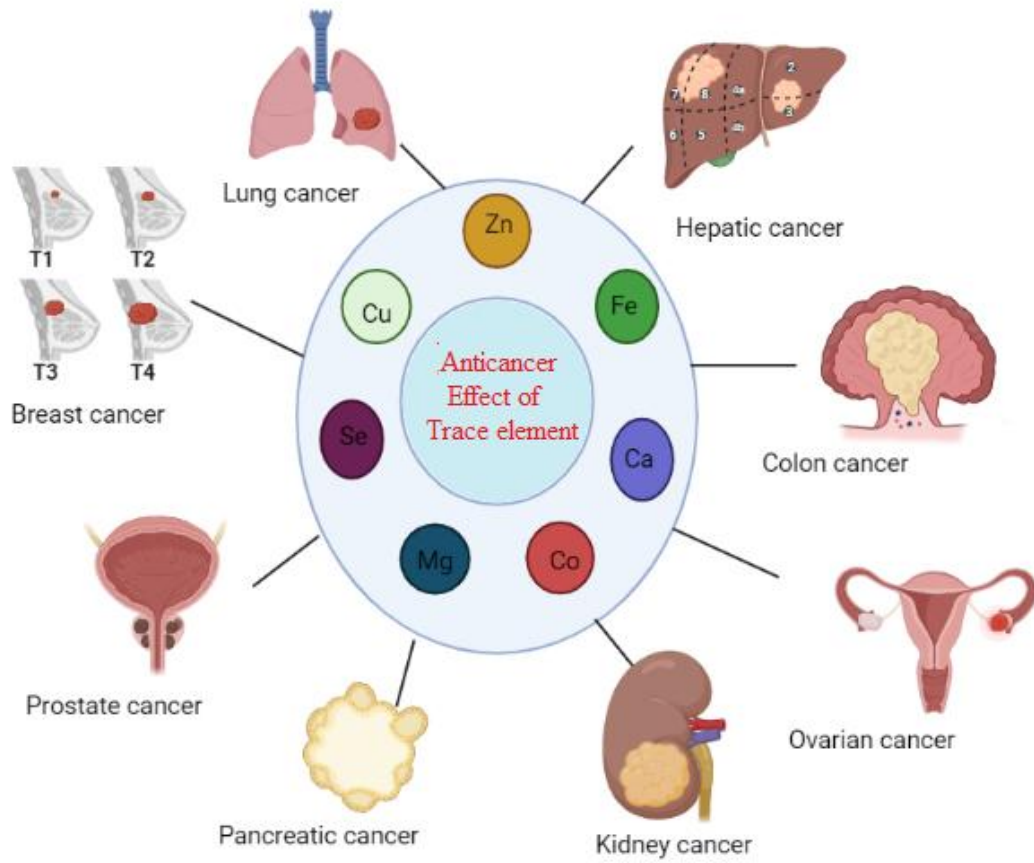
Table 2 : List of trace element and cancer types

	TRACE ELEMENT	TYPE OF CANCER	Author

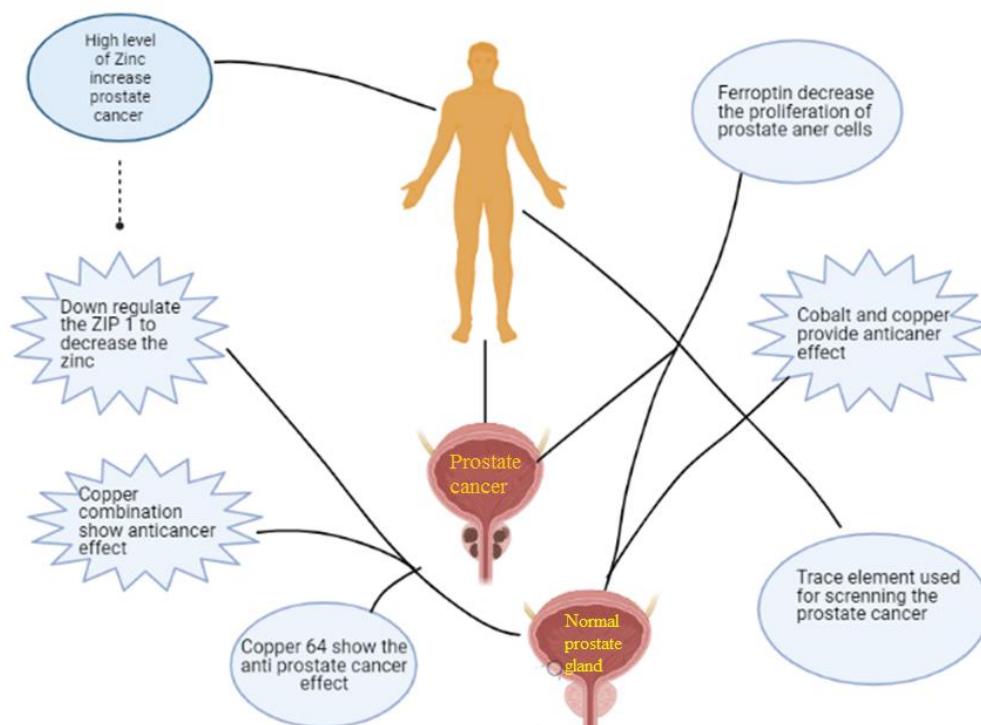
1.	Copper	Anti-cancer effect in Oral cancer	Lee HM .,et al.,(2016)
		Anti-cancer effect Human carcinoma cells	Sarbadhikary P .,et al., (2017)
2.	Zinc	Anticancer activity through the antioxidant properties	
		Higher level of zinc in lung cancer patients	Skrajnowska D.,et al.,(2019)
3.	Iron	Ferropotosis iron dependent anticancer drug	Zabłocka-Słowińska K.,et al.,(2020)
		Different types of drug induce ferropotosis	Hassannia B., et al.,(2019)
4.	Calcium	Calcium mediated Src degradation	Su Y., et al.,(2020)
		Calcium in non-small lung cancer	Park SY .,et al.,(2020)
			Kim IU ., et al .,(2018)
5.	Magnesium	Shows anticancer effect with Ascorbic acid	
		Shows cytotoxic effect than cisplatin	Cho S ., et al .,(2019)
			Mirmalek SA ., et al .,(2016)
6.	Selenium	Shows anticancer effects in MCF7 cells with or without cisplatin	Sakallı Çetin E ., et al .,(2017)
		Exihibit anticancer effect in Cisplatin-induced nasopharyngeal cancer.	Zhu K .,et al .,(2016)
7.	Cobalt	Show anticancer effect with complexes and collateral	Law BYK ., et al .,(2017)

		sensitive to multidrug resistant Cobalt complexes increase anticancer activity in lung cancer	Ambika S., et al .,(2019)
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4.1 Fig 2: Trace elements in Cancer



4.1. Fig :3 Trace elements in Prostate Cancer



4.2. Trace element in prostate cancer

Again Serum trace element Level was analyzed with 30 patients with Prostate cancer 30 control patients by Icpms .It shows significantly increase in serum levels of Co, Cu, Mg and Pb and decrease level of Fe, Mn, and Zn levels [81]. High level of zinc contain in human prostate gland because of zinc-accumulating acinar epithelial of the peripheral zone which may affect the cell metabolism .The decrease of zinc by down regulate the ZIP 1 will stop the cytotoxicity in malignant cells and stop the tumour growth [82]. Zinc ionophore 1-hydroxypyridine-2-thione (ZnHPT) elevate the intracellular concentration of free zinc and increase the antiproliferative activity in phase A549 human lung cancer [83]. In the invitro cell the Combination of copper 8-hydroxyquinoline-2-carboxaldehyde-thiosemicarbazide complex (CuHQTS) shows an anticancer activity in metastatic prostate cancer it was shown by using fluorescent microscopic imaging [84].The three dimensional cellular model for prostate cancer exhibit a significant effect after treated with copper 64 .Copper 64 is theranostic agent mainly in PCa ,it is based on the presence of cancer stem cells DU145 shows more resistant than 22RV1, LNCaP cells[85].Ferroptin

decreased the proliferation of prostate cancer cells which is the iron exporter and essential for cellular and systemic iron metabolism. The ferropotin overexpression provide an effects in cells with multiple histological subtypes of prostate cancer[86].The ferropotin expression was determined by immunohistochemistry and western blotting analysis shows a lower level of ferropotin in prostate cancer cells than the normal prostate RWPE2 cell line[87].

The comparison studies between $[^{64}\text{Cu}]$ Cu-NOTA/NODAGA-PEG2-RM26 and $[^{57}\text{Co}]$ Co-NOTA/NODAGA-PEG2-RM26 was evaluated to see the expression of Gastrin-releasing peptide receptor (GRPR) by using PET. It shows that Co-NOTA/NODAGA-PEG2-RM26 significant changes in murine PC model than $[^{64}\text{Cu}]$ Cu-NOTA/NODAGA-PEG2-RM26[88].Trace element not only give anticancer effect but also used for the screening of prostate cancer. EDXRF is an essential data analysis to study the concentration of trace element in prostate cancer. In recent study trace element concentration was analyzed in hair sample from 22 men from Iran with prostate cancer in which aluminum, silicon, and phosphorus shows statically significant changes in patient with prostate cancer and healthy people [89]. Inversely correlated significance changes in PSA and selenium in men with median age, no smokers, men who is carrying the GPX1 rs1050450 T allele. But overall there is no significant changes in PSA and selenium level supplementation [90]

5. Nanotechnology and Cancer:

Nanotechnology the manipulation and manufacture of materials and devices on the scale of small groups of atoms. Recently Nanotechnology has become an innovative field of research is being used for the therapeutic process of diseases. Nanotechnology pays much attention in the 21 centaury for its application in nanomedicine. China and USA are two leading countries for Nanotechnology research they providing preference and funding for research [91]. Cancer is the major concern for USA and china NCI provide funds for more innovative and creative ideas for the solutions for cancer treatment assigned by researchers [92]. Nanomedicine one of the application of nanotechnology particularly in the field of research. Nanomedicine unites with engineering, physics, biology, chemistry, mathematics, and medicine. It make an efforts to improve diagnostics of diseases, imaging, and drug delivery through the use of Nano devices [93].

Nowadays scientist had a great impact on nanotechnology and creating new nanomedicine, Nano biomaterials, nanoparticles etc. There are many approaches has been taken by nanotechnology driven drug in the field of drug delivery system in which administration of drugs to eyes, skin, wound healing, via topical route is the preferred method for drug delivery .But this conventional method for drug deliver is less effective and also intravitreal is another drug delivery method which increase complication like retinal detachment, intravitreal hemorrhage, endophthalmitis, and cataracts. Nanotechnology has the capacity to develop an effective drug delivery via topical route [94].Chronic obstructive pulmonary diseases is a lung diseases .It is associated with airway obstruction, chronic inflammation and oxidative stress .There have been lot more treatment designed for COPD but nanotechnology is an advance field for the current treatment of COPD[95]. Nanoparticles are important to decrease the toxicity and bioactivity to the target for the drug delivery system for therapeutic treatment. There are different nanoparticles in such inorganics nanoparticles of metals Ag, Au, Ce, Fe, Se, Ti and Zn provide a significant contribution in drug delivery system .SeNps is an important Trace element and it has been used as nanoparticle and reduce the toxicity during drug delivery .It reduce oxidative stress and inflammation associated disorder like cancer, neuropathy , diabetes etc [96]. Molybdenum trioxide (MoO₃) Nanoparticles against skin cancer cells (melanoma and non-melanoma) This nanoparticles produce to mitochondrial-mediated apoptosis driven by the apoptotic genes such as BAX and Bcl2 [97] .Iron oxide nanoparticles has been used in many cancer treatment. The liposomal drug delivery and therapy for iron anemia with iron oxide nanoparticles is developed .The injectable iron explore between nanoparticles and innate immune system [98].Nowadays metal oxide nanoparticles such as zinc oxide nanoparticles has been used in biomedical field and in treatment of disease risk .This zinc oxide nanoparticle plays as anticancer agent[99].Zinc oxide nanoparticles treated with p53 and LC3 .Zinc oxide nanoparticle shows the upregulation in cells and upregulate the apoptosis and autophagy[100].Approach of Magnesium oxide nanoparticle has been used for the treatment cancer in which MgO NP combine with Human serum albumin(HSA) . This MgO NP increase cytotoxicity in K562 cell lines but not in peripheral blood mononucleated cells.[101].The anticancer assay shows that the Cobalt Oxide Nanoparticles with albumin reduce the K562 cell viability and reduce cell membrane damage, activation of caspase-9, -8 and -3, increase of Bax/Bcl-2 mRNA ratio, ROS production, cell cycle arrest, and apoptosis[102].Cadmium oxide nanoparticles involved in the anticancer effects

with UV irradiation in photodynamic therapy[103]. Cadmium oxide nanoparticles also contribute as an anticancer drug in human cancer cell .In the Scanning Electron Microscope (SEM) and also Transmission Electron Microscope (TEM) shows the efficiency of Cadmium oxide nanoparticles as an anticancer drug [104].Arsenic nanoparticle also used as a therapeutic process and for the treatment of cancer. In china the arsenolite has been used as a traditional medicine for more than 500 years [105].Also arsenic trioxide nanoparticles used as a drug delivery agent for solid cancer [106].Arsenic trioxide with complexes Nano drug used as a therapeutic process in solid cancer therapy [107].

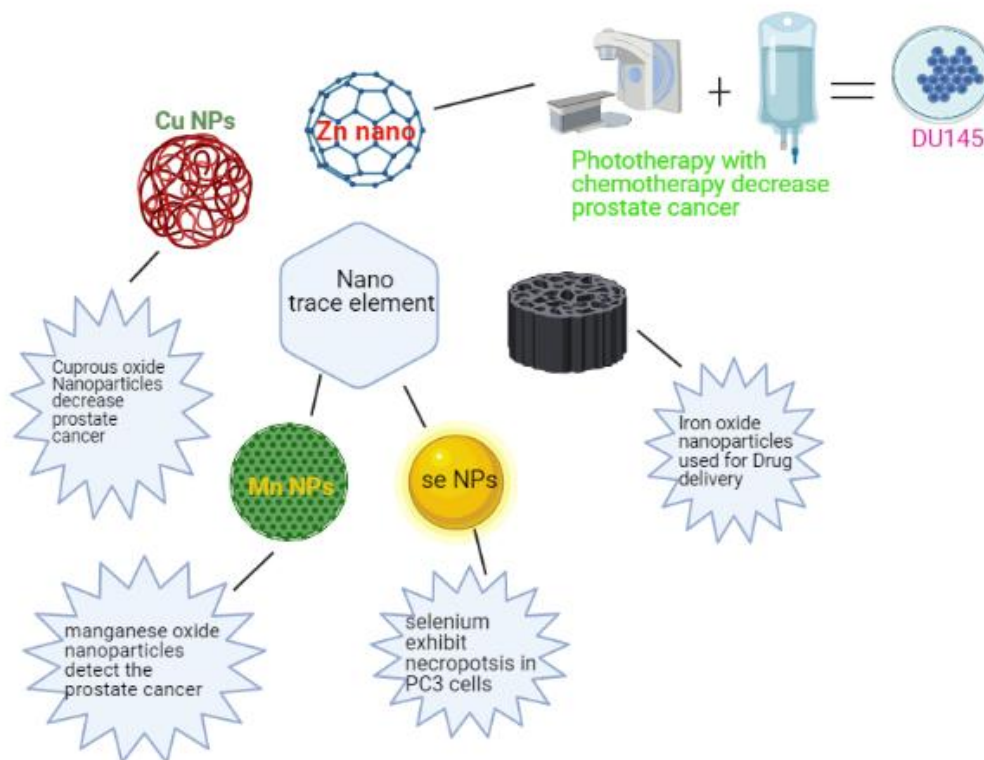
5.1. Nano trace elements in Prostate Cancer

At the Same time Nano Trace element play an essential role diagnostic or therapeutic process of cancer. Nowadays Nanotechnology become advanced technique for delivering the drug .There are many approaches has been taken in Nano trace element works for anticancer effects. Trace elements are essential for all living organisms to carry out various metabolic reactions including the fundamental driving force of oxygen transport, neurotransmission and mitochondrial respiration and oxidative phosphorylation to name a few. Here the focus on Nano trace element contribution in prostate cancer. Nowadays Nanotechnology become advanced technique for delivering the drug .There are many approaches has been taken in the nanotechnology field and many Nano trace element works for anticancer effects. ZnO NPs is used for the comparative study of cytotoxicity in PC-3 and RWPE-1 cells in which ZnO NPs decrease the cell viability in PC-3 but not in RWPE-1 cells. The apoptotic cells increased significantly in PC-3 cells in 10ug/ml concentration for 8h [108].Combination of phototherapy and chemotherapy along with zinc oxide Nano fluids has become the treatment for cancer. The UVA irradiation and zinc oxide Nano fluids grows the DOX effects in DU145 cells. It suggest the modality is a good therapeutic process for cancer [109].

Cuprous oxide nanoparticles (CONPs) Decrease prostate cancer in vitro and in vivo via decreasing the Wnt pathway signaling and induce apoptosis and Cuprous oxide nanoparticles (CONPs) also reduce the stemness of cancerous cell in vitro [110].Nano particles are also applied in the detection of cancer in patients .Here manganese oxide–mesoporous silica nanoparticles (Mn–Msn) encapsulated with prostate-specific membrane antigen (PSA) for the detection of prostate cancer[111].To eliminate side effects induce by chemotherapy for prostate

cancer a, new therapeutic process was accumulated . A multifunctional double-receptor-targeting iron oxide nanoparticles has been emerged for drug delivery system. There has two tumor-targeting peptides guided this double-receptor-targeting nanoscale drug delivery system. These peptides aims to target LHRH-R and the uPAR on PCa cells. The accumulation and binding of LHRH-AE105-IONPs in PC-3 cells compared to normal prostate epithelial cells (RC77N/E) was confirmed by Using Magnetic resonance imaging (MRI) [112]. SeNPs of 2 μg Se/ml concentration exhibit reactive oxygen species (ROS) and necroptosis in PC-3 cells. The Real-time qPCR analysis showed increased expression of necroptosis associated tumor necrotic factor (TNF) [113].

Fig 4: Nano trace element in prostate cancer:



8. Reference

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