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Semi-Review Article

Zinc(Ⅱ) Ions Can Modulate Prostate Cancer Suppressive Progression

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Abstract

Zinc(II) induced prostate cancer (PCa) suppressive progression with PCa Stage 1, Stage 2, and Stage 3 is investigated, subsequently, the zinc-ions binding prostate anti-cancer molecular mechanism is clarified.

At PCa Stage 1, zinc regulates proliferation and growth, apoptogenesis in prostate cancer cells that zinc suppresses the growth of tumor xenografts and the development of normal prostate cancer tumors can be diminished. At PCa Stage 2, zinc suppresses the progression of PCa by proliferation, migration, and invasiveness that zinc is confirmed to function as a tumor suppressor in PCa cells, in which zinc, zinc transporters, and zinc and ZRT- and Irt-like proteins1 (ZIP1) can suppress tumor growth, invasive and migratory tumor malignant cell, and regional lymph nodes in PCa cancer. At PCa Stage 3, metastatic prostate cancer is composed of proliferation, neovascularization, extravasation, and bone or bone marrow metastasis that MAZ regulates PCa bone metastasis, intercellular zinc levels inhibit metastatic and angiogenic malignant cells, and ZMYND8 inhibits tumor angiogenesis.

Zinc induced ROS generation in PCa cell is involved that ROS-mediated oxidative stress on prostate cancer can be modulated by rich antioxidants and accumulated zinc, resulting paclitaxed (PTX) to mitochondrial dysfunction, leading to apoptotic tumor cells.

Zinc coordinated molecular apoptosis mechanism in PCa cells is involved that Zn2+ ions having Zn2+ ions-centered tetrahedral geometric coordination pattern bind with each PCa stage tumor proteins, causing Zn2+ ions-several protein complex formation and apoptosis of PCa cells, leading to molecular apoptosis of prostate cancer tumor cells.

Keywords: Zinc(II), PCa proliferation and growth, Invasive and migratory malignant cell, Regional lymph nodes, Bone and bone marrow metastasis, Tumor angiogenesis, ROS and oxidative stress.

Introduction

Prostate cancer (PCa) is most common among men that PCa is an aged-related malignancy and has a cellular senescence in man that androgen receptor (AR) target agnonist and androgen deprivation therapy (ADT) induced cellular senescence are carried out, the therapy induced senescence-associated secretory phenotype (SASP) of regulation and reduction of tumor growth is performed by tumor microenvironment **[1].** PCa procedure is composed of PCa primary malignant tumor formation and growth within the prostate, malignant tumor proliferation outside the prostate, migration and invasion, and metastasis. Specially, prostatic cancer carcinogenesis occurs in prostatic malignancy, anti-proliferative effect, apoptogenic effect, and invasive and migratory effect **[2].** While, zinc(II) ions have important anti-cancer effects for cancer tumor cells of malignant proliferation, local invasion, and metastasis **[3].** Zinc acts

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as the maintenance of prostate health that zinc suppresses tumor progression and protects DNA integrity in prostate cells, and zinc transporter functions as tumor suppressor **[4].** Furthermore, zinc regulates cell proliferation and growth, apoptotic characteristics appearance in prostate tumor cells that zinc has apoptotic effects on the regulation of normal and malignant cell growth and proliferation under physiological of cellular zinc distribution and concentration **[5].**

In PCa patients, plasma zinc level is mild-moderate disease 10.49 ± 2.89**μ**mol/L, severe disease 7.64 ± 2.33**μ**mol/L, advancd disease 6.98 ± 1.97**μ**mol/L in PCa patients that zinc status in PCa disease is inversely associated with disease grades which to define the disease stage, in which low zinc status influences the severity and progression of PCa disease **[6].**

The role of angiogenesis in PCa growth and progression is important in angiogenic growth factors in prostate cancer that angiogenesis in PCa tumor growth progression plays an important role of vascular endothelial growth factor A (VEGF-A) in angiogenic prostate cancer and this prostate cancer angiogenesis mechanism should be clarified in order to be elucidated that anti-angiogenesis therapy may be effective in the treatment of PCa **[7].**

In this semi-review article, zinc(II) induced prostate cancer suppressive development with prostate cancer Stage 1, Stage 2, and Stage 3 are investigated, subsequent, the zinc-ions coordinated binding PCa protein molecular apoptosis mechanism is clarified.

2. Prostate cancer progressing and development in PCa Stage 1, Stage 2, and Stage 3

Prostate cancer (PCa) process on PCa Stage 1, 2, 3 is considered that Staging of PCa is composed of primary malignant tumor, neovascularisation, local invasion and the migration, regional lymph node, and metastases **[8].**

The Staging is as Follows;

PCa Stage 1 (Malignant tumor formation and proliferation); Cancer tumor is in half or less half and in more than half of the prostate, without spread outside of the prostate.

PCa Stage 2 (Local invasion, regional lymph node); Cancer tumors spread beyond the outer layer of the prostate, but not to lymph nodes.

PCa Stage 3 (Metastasis, bone metastasis, angiognesis); The tumor has spread to nearby tissues, lymph nodes or other organs of the body, beyond the outer layer.

Thus, PCa Stages are thought to be composed of PCa Stage 1 with malignant tumor formation and growth, PCa Stage 2 with local invasion and regional lymph node, and PCa Stage 3 with bone and bone marrow metastasis.

3. Zinc Induced Prostate Cancer Initial Stage 1 with Tumor Malignant Cell

At PCa Stage 1, zinc can inhibit proliferation of PCa cell that zinc suppresses the expression androgen receptor (AR) and prostate specific antigen (PSA), AR-mediated transaction in androgen receptor-sufficient (AR(+)) PCa cells, and then $ZnCl_2$ （0～300 μM) functions as a negative growth regular for (AR(+)) PCa cells **[9].** Zinc concentration (100～1000 ng/mL) can inhibit PCa cell growth and prevent the PCa progressing **[10].**

Zinc suppresses the growth of tumor xenografts and the development of normal prostate that the androgen receptor (AR), the proliferating cell nuclear antigen (PCNA), and proliferation index can be diminished by 10, 20 mg/kg $ZnCl_2$-treated prostate cancer tumors can be diminished **[11].** Zinc regulates proliferation and growth, apoptogenesis in prostate cancer cells that Zinc (**15 μM**) increases the Bax-associated mitochondrial pore forming process and cellular production, and the Bax/Bcl-2 ratio, leading to apoptotic effect **[12].** Zinc exist a state of $\mathbf{Zn^{2+}}$ dyshomeostasis in prostate cell that 10 μM $\mathbf{Zn^{2+}}$ reduces PC3 cell proliferation and induces HIF1α in normal HK-2 renal tubular cells and PC3 cell survival under oxidative stress **[13].**

Zn^{2+} induced coordinations can gain intrinsic stability effects for black phosphorus nanosheets (BPNSs) through chemo-photo thermal therapy **[14].**

Thus, at PCa Stage 1, zinc can inhibit proliferation PCa cell growth, proliferation, and can prevent PCa progressing.

4. Zinc Induced PCa Moderate Stage, Local Invasion and Migration, and Regional Lymph Node

At PCa Stage 2, Zinc has anti-proliferative effects of prostatic malignancy and tumor suppressor, apoptogenic effects, invasive and migratory effects that zinc uptake transporter function as tumor suppressor, and invasive and migratory effects **[2].** The significant heterogeneity of lymph node metastasis (LNM) in PCa luminal and interstitial cells contributes to tumor progression and results in tumor microenvironment (TMA) immunosuppression. Malignant cells in LNM were already present in the initial stage of PCa, and the cells with metastatic ability were a specific population in PCa cells, indicating that these luminal cells may have characteristics of strong tumor growth, metastasis, and immune evasion, the heterogeneity of luminal cells, tumor infiltrating immune cells, and fibroblasts contributed to the special TME in metastasis of PCa, which was characterized by high cell growth capacity, high levels of immune suppression **[15].**

Zinc such as **50-150μM zinc acetate** and zinc transporters such as ZIP1 protein can suppress the proliferation, migration and invasion of PCa cells that zinc and zinc transporters can inhibit the PSA and uPA activities, the proliferation, the invasion of LNCaP cells and overexpression of ZIP1 reduced cell growth and invasion by Inhibition of NF-κB activity, in which the intake of Zinc 15 mg/day may be beneficial for advanced PCa **[16].** Zinc has an anti-tumor growth and a cytotoxic effect in prostate malignant cells that the malignant cells evolved with condition that silence ZRT- and Irt-like proteins1 (ZIPs1) expression, and zinc intake (**Zn Ligands** containing **20 μM Zn**) increases accumulation of zinc and its cytotoxic effects in PCa regional lymph nodes **[17].** Zinc may inhibit

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the tumorigenic phenotype and suppresses invasiveness and adherence in PCa cells that physiological concentration of zinc (0.12-0.5μg/ml) suppresses pro-angiogenic and pro-metastatic reduced invasiveness of highly invasive PC-3 cells **[18].**

Zinc supplementation may be an effective therapy for prostate cancer that suppressive development of malignancy leads to ZIP1 downregulation and a subsequent zinc decrease in prostate cancer and zinc show decreased expression in prostate cancer to suppress invasion and metastatic potential of prostate cancer cells by increasing telomerase activity or suppressing the anti-tumor potential of bisphosphonates **[19].**

Thus, at PCa Stage 2, zinc suppresses the progression of PCa by proliferation, migration, and invasiveness that zinc is confirmed to function as a tumor suppressor in PCa cells, in which zinc, zinc transporters, and ZIPs1 can suppress tumor growth, invasive and migratory tumor malignant cell, and regional lymph nodes in PCa cancer.

5. Zinc Induced PCa Anti-Metastasis Stage with Angiogenesis Inhibition

At PCa Stage 3, metastasis characters are migration companying interaction with host immune system, endothelium bonding, trans-migration, and metastasis formations, in which local invasion is early steps in metastasis that proliferates and **/or** coalesces with other metastasized cells to form a micro-metastasis characterization is proliferation, neovascularization and extravasation at the primary site. Then, metastatic prostate cancer in the bone or bone marrow is expressed in both primary tumors and bone metastasis of PCa **[20].** Zinc finger protein X-linked (ZFX) inhibits tumor proliferation and metastasis in PCa cells that ZFX expression, as well as the presence of lymph node metastasis and TNM stage, is negatively correlated with post-operative survival, suggesting that high ZFX expression is a risk factor **[21].** Myc-associated zinc-finger protein (MAZ) regulates PCa bone metastasis **[22].**

Intracellular zinc levels can inhibit the angiogenic and metastatic malignant cells through suppressive nuclear factor-kappa B (**NF-κB**) signaling that progressive growth and metastasis of prostate cancer is mediated by the secretion of angiogenic and metastatic factors, in which the suppressive effect of zinc on the angiogenic and metastatic potentials of PCa cells was not simply attributable to cell death but rather was mediated through the inhibition of specific pathways regulating progression of prostate cancer **[18].** Zjnc finger MYND-gene type containing 8 (ZMYND8) knockdowns suppressed angiogenesis that ZMYND8 is suitable drug target for inhibition of tumor angiogenesis **[23].** Use of zinc supplement 25-40 mg/day may be relatively safe for PCa, while use of 75 mg/day may increase risk of lethal and aggressive PCa **[24].**

Thus, at PCa Stage 3, metastatic prostate cancer is composed of proliferation, neovascularization, extravasation, and bone or bone marrow metastasis that MAZ regulates PCa bone metastasis, intercellular zinc levels inhibit metastatic and angiogenic malignant cells, and ZMYND8 inhibits tumor angiogenesis.

6. Zinc Induced ROS Generation in PCa Cell

Zinc induced NAD(P)H oxidase (NOXs) activation occurring reactive oxygen species (ROS) generation in PCa cell is involved that in role of ROS, a moderate level of ROS guaranteed by redox balance is essential for physiological activities via the activation or inactivation of metabolic enzymes that once the redox status deviates to oxidation, increased ROS can cause oxidative damage, in which zinc regulates signaling pathways, further affecting several cancer facts such as proliferation, angiogenesis, invasion, and metastasis **[25].** Zinc increases production of ROS and hydroxyl radicals, resulting in an decrease in mitochondrial aconitase (ACO2) activity, oxidative stress, and apoptosis of prostate cancer cell, and leading to ROS increase and accumulation in PCa cells, in which zinc combined with p53 can increase the antitumor effect, accumulated ROS activity leads of paclitaxel (PTX) to mitochondrial dysfunction, resulting in apoptosis tumor cells **[26].** Increased ROS enhance genetic instability, promote cell proliferation, oxidative stress, and alter somatic DNA mutations that ROS-mediated oxidative stress on prostate cancer can be modulated by dietary components rich in antioxidants **[27].**

Thus, a higher level of ROS in PCa causes inflammation, proliferation, oxidative damage of proteins, lipids, DNA, and RNA, accumulation of DNA damage disrupting genome stability, involving tumorigenesis and tumor progression. ROS-relevant alternation in these cells contributes to inflammation, proliferation, angiogenesis, and metastasis. ROS, as a direct DNA mutagen, activate several oncogenes and inactivate several tumor suppressor genes. ROS, as a common proliferative and apoptotic convergent point, regulate the biological behaviors subtly in terms of different cellular environments.

Accordingly, as mentioned above, zinc(II) induced PCa suppressive progressing with Stage 1 (Malignant formation and proliferation), Stage 2 (Local invasion and regional lymph nodes), and Stage 3 (Bone and bone marrow metastasis with angiogenesis) can be summarized in **Table 1.**

Table 1: Zinc(Ⅱ) Induced PCa Suppressive Progression with PCa Stages 1～3

Zn^{2+} ions	PCa Stage 1 ・Malignant tumor growth suppression ・Tumor proliferation reduction	PCa Stage 2 ・Suppression of local invasion, regional lymph nodes	PCa Stage 3 ・Anti-metastasis ・Bone and bone marrow metastasis ・Anti-angiogenesis
Zn^{2+} ➡	➡ Zn^{2+}, ROS ・$ZnCl_2$ (0～300 μM); suppresses growth tumor cell ・Zn (100～1000 ng/mL); PCa cell growth inhibition, preventive PCa progressing ・Zn^{2+}10 M reduces PCa cell proliferation, oxidative stress ・Zn^{2+} concentration (1000 ng/mL);highest PCa growth inhibition	➡ Zn^{2+}, ROS ・Zn induced invasive and migratory effects ・Zn ligands containing **20 μM Zn** increases accumulation of zinc and cytotoxic effect in regional lymph nodes ・Zinc, zinc transporters, and ZIPs1 can suppress tumor growth, invasive and migratory tumor	➡ Zn^{2+}, ROS ・ZEX knockdown inhibits PCa cell growth and metastasis ・MAZ regulates PCa bone metastasis ・Intracellular zinc levels can inhibit metastatic malignant cells through suppressive NF-κB ・ZMYND8 promotes tumor anti-angiogenesis

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		malignant cell, and regional lymph nodes	

7. Zinc Coordinated Molecular Apoptosis Mechanism in PCa cells

Zinc has apoptogenic effects for inflammation, proliferation, invasiveness and migration, metastasis, angiogenesis, and oxidative damage of proteins in PCa cells. These zinc coordinated molecular apoptosis mechanism is involved that Zn^{2+} ions is liable to bind with each cancer proteins, in which Zn^{2+} ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern bind with each PCa stage cancer tumor proteins, causing Zn^{2+} ions-several protein complex formation, oxidative stress, and apoptosis of PCa cells, leading to molecular apoptosis of prostate cancer tumor cells.

Conclusions

Zinc(II) induced prostate cancer suppressive development with prostate cancer Stage 1, Stage 2, and Stage 3 are investigated, subsequent, the zinc-ions binding prostate anti-cancer molecular mechanism is clarified.

At PCa Stage 1, zinc can inhibit proliferation of PCa cell that zinc suppresses the expression androgen receptor (AR) and prostate specific antigen (PSA), AR-mediated transaction in androgen receptor-sufficient (AR(+)) PCa cells.

At PCa Stage 2, zinc suppresses the progression of PCa by proliferation, migration, and invasiveness that zinc is confirmed to function as a tumor suppressor in PCa cells, in which zinc, zinc transporters, and zinc and ZIP1 can suppress tumor growth, invasive and migratory tumor malignant cell, and regional lymph nodes in PCa cancer.

At PCa Stage 3, metastatic prostate cancer is composed of proliferation, neovascularization, extravasation, and bone or bone marrow metastasis that MAZ regulates PCa bone metastasis, intercellular zinc levels inhibit metastatic and angiogenic malignant cells, and ZMYND8 inhibits tumor angiogenesis.

Zinc induced ROS generation in PCa tumor cells is causes inflammation, proliferation and growth, and oxidative stress.

Zinc coordinated molecular apoptosis mechanism is involved that Zn^{2+} ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern bind with each PCa stage cancer tumor proteins, causing Zn^{2+} ions-several protein complex formation, oxidative stress, and apoptosis of PCa cells, leading to molecular apoptosis of prostate cancer tumor cells.

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References

1. Julia Kallenbach, Golnaz Atri Roozbahani, Mehdi Heidari Horestani and Aria Baniahmad; Distinct mechanisms mediating therapy-induced cellular senescence in prostate cancer Cell and Bioscience 2022; 12(200): 1-17.
2. Vladimir Kolenko, Ervin Teper, Alexander Kutikov, and Robert Uzzo; Zinc and zinc transporters in prostate carcinogenesis Nat Rev Urol 2013; 10(4): 219-226.
3. T. Ishida; Anti-Cancer Effects of Zinc(II) Ion in Tumor Formation and Growth, Proliferation, Metastasis and DNA Damage Degenerative Intellectual & Developmental Disabilities 2017; 1(1): 1-8.
4. Yang Song and Emily Ho；Zinc and prostatic cancer Curr Opin Nutr 2009; 12(6): 649-645.
5. Renty B. Franklin and Leslie C. Costello; The Important Role of the Apoptotic Effects of Zinc in the Development of Cancers J Cell Biochem. 2009; 106(5): 750–757. doi:10.1002/jcb.22049.
6. Victor C. Wakwe, Ehimen. P. Odum, Collins Amadi; The impact of plasma zinc status on the severity of prostate cancer disease Investigative and Clinical Urology 2019: 60: 162-168.
7. Zsombor Melegh and Sebastian Oltean; Targeting Angiogenesis in Prostate Cancer International Journl of Molecular Sciences 2019; 20: 1-16.
8. Nigel Borley, Mark R. Feneley; Prostate cancer: diagnosis and staging Asian Journal Andrology 2009; 11: 74-80.
9. Phuong Kim To, Manh-Hung Do, Young-Suk Cho, Se-Young Kwon, Min Soo Kim and Chaeyong Jun; Zinc Inhibits Expression of Androgen Receptor to Suppress Growth of Prostate Cancer Cells International Journal of Molecular Science 2018; 19: 1-13.
10. Ji-Yong Liang, Yi-Yan Liu, Jing Zou, Renty B. Franklin, Leslie C. Costello, and Pei Feng Inhibitory Effect of Zinc on Human Prostatic Carcinoma Cell Growth Prostate 1999; 40(3): 200-207.
11. Phuong Kim To, Manh-Hung Do, Young-Suk Cho, Se-Young Kwon, Min Soo Kim and Chaeyong Jung; Zinc Inhibits Expression of Androgen Receptor to Suppress Growth of Prostate Cancer Cells International Journal of Molecular Sciences 2018; 19 : 1-13.
12. Pei Feng, Tieluo Li, Zhixin Guan, Renty, Franklin and Leslie C Costello; The Involvement of Bax in Zinc-Induced Mitochondrial Apoptogenesis in Malignant Prostate Cells Molecular Cancer 2008;7:25: 1-6. doi:10.1186/1476-4598-7-25
13. David Wetherel, Graham S. Baldwin, Arthur Shulkes, Damien Bolton, Joseph Ischia, and Oneel Patel; Zinc ion dyshomeostasis increases resistance of prostate cancer cells to oxidative stress via upregulation of HIF1α Oncotarget 2018; 9, No.9: 8463-8477.
14. Li Gao, Ruobing Teng, Sen Zhang, Yun Zhou, Miaomiao Luo, Youqiang Fang, Lei Lei and Bo Ge; Zinc Ion-Stabilized Aptamer-Targeted Black Phosphorus Nanosheets for Enhanced Photothermal/Chemotherapy Against Prostate Cancer Frontiers in Bioengineering and Biotechnology, 2020; 8, Article 769: 1-13.
15. Shiyong Xin, Xiang Liu, Ziyao Li, Xianchao Sun, Rong Wang, Zhenhua Zhang, Xinwei Feng, Liang Jin, Weiyi Li, Chaozhi Tang, Wangli Mei, et al; ScRNA-seq revealed an immunosuppression state and tumor microenvironment heterogeneity related to lymph node metastasis in prostate cancer Experimental Hematology & Oncology 2023;12(49):1-21. https://doi.org/10.1186/s40164-023-00407-0.
16. Phuong Kim To, Manh Hung Do, Jin-Hyoung Cho and

World Journal of Case Reports and Clinical Images

ISSN: 2835-1568; CODEN: USA

DOI: http://dx.doi.org/10.51521/WJCRCI.2023.220118

Chaeyong Jung; Growth Modulatory Role of Zinc in Prostate Cancer and Application to Cancer Therapeutics International Journal of Molecular Sciences 2020;21: 1-18.

17. Leslie C. Costello, and Renty B. Franklin; A comprehensive review of the role of zinc in normal prostate function and metabolism; and its implications in prostate cancer Arch Biochem Biophys 2016: 611: 100-112.
18. Robert G.Uzzo, Paul L.Crispen, Konstantin Golovine, Peter Makhov, Eric M. Horwitz and Vladimir M.Kolenko; Diverse effects of zinc on NF-kB and AP-1 transcription factors: implications for prostate cancer progression Carcinogenesis 2006; 27, No 10: 1980-1990.
19. Jie Wang, Huanhuan Zhao, Zhelong Xu, Xinxin Cheng; Zinc dysregulation in cancers and its potential as a therapeutic target Cancer Biol Med 2020; 17,No.3: 612-625. doi: 10.20892/j.issn.2095-3941.2020.0106
20. Noel W. Clarke, Claire A. Hart, Mick D. Brown; Molecular mechanisms of metastasis in prostate cancer Asian Journal of Andrology 2009; 11:57-67.
21. Xiaoling Songa, Minghui Zhue Fahong, Zhang Fei Zhanga, Yijian Zhanga, Yunping Hua, Lin Jianga, Yajuan Haoa, Shili Chena,et al; ZFX Promotes Proliferation and Metastasis of Pancreatic Cancer Cells via the MAPK Pathway Cell Physiology and Biochemistry 2018;48:274-284.
22. Qing Yang, Chuandong Lang, Zhengquan Wu et al; MAZ promotes prostate cancer bone metastasis through transcriptionally activating the KRas-dependent RalGEFs pathway Journal of Experimental & Clinical Cancer Research 2019; 38(391) 1-17.
23. Junya Kuroyanagi, Yasuhito Shimada, Beibei Zhang, Michiko Ariyoshi, Noriko Umemoto, Yuhei Nishimura, Toshio Tanaka; Zinc finger MYND-type containing 8 promotes tumor angiogenesis via induction of vascular endothelial growth factor-A expression FEBS Letters 2014; 588:03:00-409-3416.
24. Yiwen Zhang Mingyang Song, Lorelei A. Mucci, Edward L. Giovannucci; Zinc supplement use and risk of aggressive prostate cancer: a 30-year follow-up study European Journal of Epidemiology 2022; 37: 1251–1260. doi.org/10.1007/s10654-022-00922-0
25. Chenglin Han, Zilong Wang, Yingkun Xu, Shuxiao Chen, Yuqing Han, Lin Li, Muwen Wang, and Xunbo Jin; Roles of Reactive Oxygen Species in Biological Behaviors of Prostate Cancer BioMed Research International 2020; 2020, Article ID 1969624:1-19.
26. Ya-Nan Xue, Ya-Nan Liu, Jing Su, Jiu-Ling Li, Yao Wu, Rui Guo, Bing-Bing Yu, Xiao-Yu Yan, Li-Chao Zhang, Lian-Kun Sun, Yang Li; Zinc cooperates with p53 to inhibit the activity of mitochondrial aconitase through reactive oxygen species accumulation Cancer Medicine, . 2019; 8: 2462–2473.
27. Bee Ling Tan, Mohd Esa Norhaizan; Oxidative Stress, Diet and Prostate Cancer World J Mens Health 2021; 39(2):195-207. doi.org/10.5534/wjmh.200014.