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Prospected epigenetic moderators from natural sources and drug of class NSAIDS as effective treatment options to Prostate cancer

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ABSTRACT

Prostate cancer (PC) is one of the most common and leading cancer amongst the males all around the world. Depending upon it long latency and cost involved in its management and treatment, there is extensive need for more personalized and economical therapeutic approach for its effective therapy. The current review here discusses agents from natural dietary sources and drug class Non-Steroidal Antinflammatory (NSAIDS) that bears chemopreventive potential to regulate PC progression & tumour development and therefore could be devised into effective future treatment strategy against PC along with its metastatic castration-resistant form. Based on the literature search the therapeutic scope of selected agents are delineated, sighting their previous activity and prospects as epigenetic moderators in specific to particular PC causing biomarkers like over expression of AKR1C3, lost intracellular glutathione/glutathione-s-tranferases(GSH/GST) expression, DNA hypermethylation, aberrant cell proliferation and other related factors that are thought to potentiate and aggravate the onset of PC like smoking and use of other narcotics products.

1. Background

Prostate cancer (PC) is the fourth most common and second most prevalent cancer amongst males worldwide. In estimation to its mortality rates it is the 8th most consistent cause of cancer deaths around the world. It was estimated in year 2012 that around 1 111 000 new cases were diagnosed with PC out of which 307 000 were dead. While, New Zealand/Australia toped the chart with highest diagnosed cases, Caribbean islands and sub-Saharan African countries had witnessed to have maximum PC related mortality rates[1,2].

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There has been number of prominent biomarkers that have been associated at certain stages leading to onset and progression of PC. Some to be seriously considered includes over expression of AKR1C3 enzyme leading to castrate resistant PC. AKR1C3 originally functions via reducing 4-androstene-3, 17-dione (△ (4)-Adione) to the androgen receptor (AR) ligand testosterone i.e. fostering conversion of ketones and aldehyde to respected alcohols using NADH/NADPH as cofactors[3-5]. It also bear critical role catalyzing reduction of steroids, prostaglandins,PGH2, D2, phenantherenequinone, oxidation 9-alpha,11-beta-PGF2 to PGD2 and pathogenesis of certain diseases like diabetic complications, steroid hormone dependent malignancies including PC via regulating/controlling cell proliferation/differentiation etc[6-8]. Aberrant up regulation in normal AKR1C3 enzyme and its related gene functionality in PC is mainly due to intracellular synthesis

of AR ligands which further leads to stimulation of proliferation through AR signalling and later promoting PC progression to castrate resistant state[3,9].

DNA promoter Hypermethylation in GST (Glutathione-S-Tranferases) enzyme is another biomarker designated to cause prostate cancer which results in the silencing of tumour suppressor gene (GSTP1)[10,11]. -This gene originally act by protecting normal cells from toxic and carcinogenic agents via promoting their conjugation with Glutathione (GSH) substrates further transforming them to less toxic and easily excreted metabolites. It also protect DNA from oxidative damage through intrinsic pathway activity by conversion of toxic peroxides to non-active alcohol and reducing lipid hydroperoxides via glutathione peroxidases activity which is Se-independent to detoxifying end products like 4-hydroxynonenal (4-HNE) by lipid peroxidation. Abruption/inactivation/low expression of this enzyme leads the normal prostate cells for direct exposure to toxins, mutagens and carcinogenic agents later transforming them to cancerous form[12].

There are chances that these selected androgen and estrogens biomarkers might work synergistically upon the onset or at certain stages to cause PC and its progression, making it more resistant and tough to treat. There are studies focussing on treating and regulating these biomarkers individually at certain extent through both conventional (Chemo and Hormonal therapy) and nonconventional (Via Natural agents) therapeutic methods but none showed targeting both enzymatic biomarkers simultaneously. PC is considered to be immensely dependent upon the age with individuals mostly over 50 years[13]. However, It might not just the age which bears impact on initiation of these biomarkers causing PC, but there may be other factors like life style, diet, genetic variability, cancer history in family, Hormone imbalance etc which are also needed to be addressed and could potentiate the risk by encouraging both enzyme based biomarker working simultaneously for onset, aggravation and progression of PC. In some of the latest study it was elucidated that individuals smoking tobacco has vast chances to be diagnosed with prostate cancer with increase of biochemical recurrence, distant metastasis etc[14-16].

There are multiple conventional treatments options currently available in form of Hormonal and chemotherapy, drugs like Docetaxel, goserelin, entazalutamide, Degarelix, Mitoxantrone, Epirubicin, Estrmustine, Abiraterone Acetate etc[17] are widely in use for treating these biomarkers causing PC separately. However, these drug treatment options are limited to efficiency with the negative feature of high toxicity and adverse effects with chronic impact as in case of some like abiraterone acetate and docetaxel[18]. Therefore, a method using bioactive agents from natural dietary sources[19] and drugs belonging to class of NSAIDs(OTC) which has not been researched effectively to their potentials in reducing risk to Prostate Cancer and its cell survival in recent times[20], may be considered one of the novel ways for chemoprevention in healthy tissue and therapeutic option for treating PC. The screening and selection of the potential natural agents[21] and NSAIDS class of drugs[22,23] could be based on their potential to cause reversal of over expressed AKR1C3 enzyme and inducing poorly expressed GST/GSH activity in PC cell lines (LNCaP and PC-3). Natural agents like epigallocatechin-3gallate[24-28], curcumin[29-33], resveratrol[34-38], quercetin[39,40], genistein[41,42] and drugs like Aspirin[43,44], meclofenamic acid[45] atorvastatin[46,47], celecoxib[48,49], Indomethacin[3,50-52],diclofenac and naproxen[53-56] belonging to class NSAIDS shown immense potential to be anti cancerous agents and therefore could be prospected to work efficiently regulating both the androgen and estrogens biomarkers as potential human prostate cancer treatment options.

Based on this fact the current review focuses on to give a insight on prospected naturally occurring dietary sources along with agents belonging to class of NSAIDS that could be devised to potential treatment strategy against prostate cancer acting as epigenetic moderators and had shown abilities to down regulate overexpression of AKR1C3 enzyme caused by intracellular synthesis of AR ligands, induce intracellular GSH/GST level lost due to hypermethylation i.e. phase II detoxification activity as being an potent DNA methylation inhibitors(DMI'S), apoptosis resulting to prostate cancer cell death, inhibition of cell proliferation and lastly eliminating the negative impact of factors which might synergistically aggravate or act to be a prominent initiator for these biomarkers causing PC such as Tobacco smoking.

2. Natural dietary agents

Owing to the multifactorial applications of agents from natural sources in the field of medicine therefore, developing plant based bioactive compounds as drugs could be a novel method devising a therapeutically effective and cheaper treatment options for PC and a possibility to target biomarker based therapy.

There are numbers of evidences suggesting that plant based treatments could be common approaches to treat and prevent PC. Research evidences shows potential extracts from plants such as Carica papaya[57], Papaver somniferum[58], Dimocarpus Longan Lour[59] etc. carry's healthy insight to be developed into effective treatment option for PC. However, in spite decades of research on variety of such plants based agents, steadfast and economical solutions still needed to be addressed immensely. Considering the fact the agents described here are amongst the most desirable and ideal to be developed as biomarker based anti cancer agents.

2.1. Epigallocatechin-3-gallate (EGCG)

The major polyphenolic constituent present in green tea. It has shown its marked potential for further development as a perfect dietary agent in treatment and prevention of cancer especially Prostate Cancer (PC). Based on the latest studies, regular intake of green tea might reduce the chances of developing PC in males[27,28,60,61]. EGCG has already been proven to have potential

anticancerous effects with the major ability to induce apoptosis in both androgen sensitive and insensitive PC cell lines with cell cycle arrest and dysfunction, delaying DNA oxidative damage etc in both *in vivo* and *in vitro* studies[62-66]. Moreover EGCG has also demonstrated their ability to down regulate AR acetylation in androgen dependent PC via modulation in histone acetyl tansferases activity resulting into PC cancer cell death, AR regulated gene transcription and suppressed agonist-depenedent AR activation. It also led to suppression in histone methylation preventing cell survival/proliferation in skin cancer cells by inducing apoptosis[67]. In studies[68,69] EGCG has potentially reactivated hypermethylated-silenced genes via inhibition of DNA methyltranferses (DNMT) in cancer cell lines including PC-3 and therefore could be prospected to restore GST/GSH activity lost in other PC cell lines[70]. The efficient anticancer potential of EGCG has gained it lot of popularity in recent times encouraging its utilization in treating and preventing castrate resistant PC likely to be caused due to overexpressed AKR1C3 enzyme, as suggested by[71] EGCG bears the ability to regulate this abrupt expression of AKR1C3 enzyme in hormone dependent malignancies including PC with the vital ability to minimise potential risk factors to the disease like blocking Nicotine/tobacco induced cancer proliferation via alfa 9-nicotinic acetylcholine receptor in breast cancer cells and inducing marked dose dependent decrease in nicotine-DNA adducts[72-74].

2.2. Curcumin (diferuloylmethane)

It is a polyphenolic compound obtained from the rhizome of the plant Curcuma longa (Turmeric). It is a yellow naturally occurring spice which is widely used as food and medical agent in Indian Ayurvedic medicine and also Chinese medicine[75]. Researches utilizing curcumin confirm its ability for being one of the potential natural chemopreventive agents at different stages of prostate cancer[76]. Being the molecule of pleiotropic nature, it regulates multiple pathways involved in signalling of cells in the survival and growth of prostate cancer cell type. Curcumin has shown marked impact on both androgen sensitive and independent prostate cell lines[77,78]. Additionally, it has ability to inhibit cell viability simultaneously inducing lost GST/GSH activity in LNCaP PC cell lines and acting as a potent DNA hypermethylation inhibitor[33]. Moreover, recent studies has shown utilization of curcumin in nano formulation and microemulsified forms to increase its bioavailability and site specific action in particular to cancer cells[32,79,80].Curcumin and its related analogues has also been witnessed to induce epigenetic changes in tumour cells including PC with ability to modulate of histone acetylation by inhibiting histone acetylase[81,82], inducing apoptosis[83], Downregulation of AR and its binding ability[82], regulation of epidermal growth factor receptor(EGFR) tyrosine kinase activity[84,85],inhibition of angiogenesis/vascular endothelial growth factor(VEGF)[86,87], inhibition of cell proliferation in androgen independent and dependent PC cell lines via modulation of Wnt transcriptional activity medicated by low expression of protein in Wnt transcriptional complex[77,88-93]. However, the effect of curcumin still remain dubious specifically to intracellular synthesis of AR ligands which leads to stimulation of proliferation through AR signalling and overexpression of AKR1C3 further promoting PC to castrate resistant state. In relation to factor like smoking tobacco or nicotine which are thought to increase the risk for PC, curcumin as being one of the best prospected chemopreventive natural dietary agent is also found to be eliminating the negative impacts associated to smoking via blocking nicotine-induced activation of AKT/MTOR pathway in HNSCC retarding cell cycle, proliferation and metastasis[14,15,94,95].

2.3. Resveratrol(RSV)

A polyphenolic natural agent vastly present in fruits like grapes, blueberries and dietary products like pistachios, peanuts etc[96]. In recent studies , RSV has been found to inhibit cell growth/proliferation via cell cycle arrest and induction of apoptosis, angiogenesis in several human cancer cell lines such as A549(Lung),BT20(Breast) including PC cell lines PC-3 and DU145,LNCaP etc[37,97-99]. RSV is also associated to inhibit AR related transcriptional activity in both androgen dependent and independent prostate cancer with stimulation in expression of PTEN through AR inhibition. Additionally it inhibits epidermal growth factor (EGFR) phosphorylation by binding to EGFR directly resulting to decreased AKT phosphorylation in androgen-independent prostate cancer[36]. RSV has shown to suppress EGFR-dependent Erk1/2 activation stimulated by porbol ester and EGF in androgen independent PC-3 PC cell lines[99-101].Moreover, In past researches it has been found to restores the p53 acetylation via downregulating the overexpression of Metastatis-associated protein1(MTA1) which is linked to tumor aggressiveness and metastasis in PC cell lines[102]. As it is previously known in past researches hypermethylation in DNA results in silencing of tumor suppressor genes like GSTP1, RSV is also found to be restoring the functionality/enzymatic activity of such genes in different cancer s including PC via inhibition of DNA methyltransfereses enzyme[103-106]. Apart in Neuroblastoma solid tumor in pediatric RSV displayed ability to inhibit histone methytransferase EZH2 which is aberrantly over expressed in Neuroblastoma tumor further leading to its suppression[107]. There have been none of the studies suggesting the direct impact of RSV on overexpresssed AKR1C3 enzyme. However, RSV is found to be highly active against the risk factors causing PC like Smoking tobacco/nicotine via exerting anti-inflamtory, antioxidant and anti apoptotic effects and inhibiting nicotine based pathways[108-110].

3. OTC(Over the Counter) NSAIDS (Non–Steroidal Ant inflammatory) Agents

Anti-cancer effect of NSAIDS in animals model was first reported

in 1972[111]. Since then there has been multiple number of researches done to prove NSAIDS a relatively non-toxic drugs, to prevent cancer. Researches in past including NSAIDs and related drugs has demonstrated their significant therapeutic potency in reducing cancer mortality in meta-analysis trials in human[112,113].

There are also strong evidences that show NSAIDs lowering risk to cancers like prostate via lowering prostate specific antigen (PSA), colorectal, breast and lung etc. However, certain meta-analysis also suggested its association with an increased risk of prostate and other cancer[114] predicting its dubious therapeutic potential which is still needed to be stated adequately in the prospects to develop and use less toxic and economically affordable treatment option for cancer[115].

3.1. Aspirin

It is one of the most common and easily available over the counter drug belonging to class of NSAIDS also known as acetylsalicylic acid sub-classed under Salicylic acid derivatives. In recent studies ,aspirin beside having anti-inflammatory, anti-pyretic effects via irreversible inactivation of both cycloxygenase(COX) 1 and 2 enzyme in multiple observational studies and controlled randomized trial has also shown promise to be effective as chemopreventive agent like in cancer of prostate, breast, pancreatic and colon either in its original or as modified form[116-121].

In specific to prostate cancer aspirin has been found to be associated with inhibiting cell proliferation in variety of its cell lines like PC-3 and DU145,LNCaP[19,122,123]. Multiple number of cohort studies suggests its ability in terms of reducing mortality and chances of recurrence of prostate cancer ultimately justifying its therapeutic potential as future treatment strategies for this deadly disease[43,124-126].

Moreover, in both *in vitro* and *in vivo* studies, aspirin has been found to be associated with reversing tumour suppressor gene hypermethylation in variety of cancer tissues[100,127-130]. At the histone level, it has also been reported to induce and inhibit of deacetylases with direct acetylation of histones[131-133]. Studies has also reported Aspirin inhibiting AR related transcriptional activity in both androgen dependent and independent prostate cancer[134] while regulating the aberrant overexpression of AKR1C3 gene in certain breast cancer cell lines[135].

Additionally, its ability to induce Phase -2 detoxification enzymes Glutathione-S Tranferases(GST) in normal cells which is under expressed in variety of cancer cell lines including Prostate cancer facilitates combating carcinogenics agents[97,136]. However the effect of aspirin against the risk factors causing PC like Smoking tobacco/ nicotine via exerting anti-inflammatory, anti apoptosis is still unclear regards to researches done in past[137].

3.2. Indomethacin

Similar to aspirin, indomethacin is also one of the most used anti-inflammatory drugs belonging to class NSAIDS sub classed under Acetic acid derivative. Multiple numbers of studies has suggested its marked potential for further development as a perfect chemopreventive agent as for treatment of cancer.

Based on the latest studies indomethacin has been found to induce apoptosis and inhibiting cell growth in the EC109 esophageal and ovarian cancer cells[138,139]. Similarly, it has also been observed to reduce breast tumor via COX-independent pathway[140]. Most of the action of indomethacin has been found to be similar to Aspirin in terms of its chemopreventive and anticancer activity.

In particular to prostate cancer Indomethacin and its subsequent analogues are witnessed to inhibit overexpression AKR1C3/ Prostaglandin F Synthase in castrate resistant-Resistant Prostate cancer[6,52,141]. Although there has been no researches predicting its role on induction of phase-2 detoxification enzymes in body cells and also its ability, to induce or to inhibit of deacetylases with direct acetylation at histonic levels. However, along with other NSAIDS indomethacin has been found to minimize the risk factors *via* its anti-inflammatory efficacy,which are thought to trigger and potentiate the initiation and progression of prostate cancer in human like smoking,tabocco/Nicotine usage[142,143].

4. Conclusion

The scope of dietary natural agents and drugs belonging to class NSAIDS as a steadfast therapeutically option for PC is very much of interest and encouraging for researchers around the world. Concerning to the limitations to the currently in place conventional PC treatment strategies there is a vital requirement to explore such out of the line agents that could potentially devised into a novel futuristic cancer therapy. PC based on its long latency, visible tumour growth which is comparatively easy to monitor as to other cancer, could be an ideal choice for agents to research both clinically as well as in the research laboratory. The Preliminary data in the review shows the immense potential for the agents and their considerable activity to individual PC causing biomarkers. However, such cancer interventions could be time taking and require rigorous multiple phases of clinical study before can be recommended as useful chemopreventive/treatment strategies for patients. Thus, a confirmational activity for agents along with their optimal doses, usage, administration profiling etc are very much desirable through a well designed clinical trials.

Conflict of interest statement

The authors report no conflict of interest.

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