Role Of Different Natural Compounds For Potential Treatment For Their Ability 3To Be Used As Potential Adjuncts In Treating Prostate Cancer

Gunjan Choudhary*, Komal kaushik†, Vandana*, Akanksha*, Runjhun Mathur* , and Abhimanyu Kumar Jha**

Faculty Of Life Sciences, Department Of Biotechnology, Institute Of Applied Medicine And Research, Ghaziabad, Uttar Pradesh, India.

Keywords:
Prostate cancer
natural compounds
phytochemicals
chemoprevention
novel therapeutic strategies
nutraceuticals.
through the work of Sporn and colleagues, it re-entered the cancer research mainstream in the 1970s [Sporn et al., 1976]. Till now, natural products have been played an most important role in the discovery of compounds that is used in development of drug for the treatment of multiple human diseases [Koehn et al., 2005]. Medical use of natural compounds and related drugs, including antibacterial, anticancer, antiparasitic, immune suppressant agents and anticoagulants, are being used to treat 87% of all known human diseases [Cragg et al., 2005]. Till the 1970s, drug discovery was based on screening of a great number of natural and synthetic compounds, until with the introduction of computer and other molecular biology techniques, which resulted in the modern and rational drug discovery [Patwardhan et al., 2005]. Many natural products and compounds have provided a rich source of drugs for cancer treatment [Amin et al., 2009]. While different approaches are available for discovery of novel and potential curative agents, natural products from medicinal plants are good source for novel agents with advanced medicinal activities. So, identification of natural compounds has ability not only to block but also inhibit the initiation of carcinogenesis, and also to reverse the initial stages by inducing apoptosis and development in cancer cells without cytotoxic effects in normal cells [Lekphrom et al., 2009].

### Apoptotic signalling pathways

Apoptosis plays a significant role in embryonic development and tissue homeostasis of multicellular organisms. It is carried out in a regulated way, which is linked with typical morphologic features like cell shrinkage, cytoplasmic membrane blabbing and chromatin condensation. A variety of diseases has been implicated by unregulated apoptosis, which involves tumor formation or development of cancer cells [Johnstone et al., 2002]. In mammalian cells, apoptosis is activated through two well-characterized pathways. The first is extrinsic pathway, which depends on activation of death receptors (e.g., TNF), transmembrane proteins expressed on the cell surface, and the second is intrinsic pathway, which is mediated by molecules released from the mitochondria [e.g., Bcl-2 protein family; Green et al., 2000].

The extrinsic apoptosis pathway is initiated through the binding of ligand to death receptors that consist an intracellular death domain [death-inducing signaling complexes; Ashkenazi et al., 1998 and Block et al., 1992]. So, intrinsic pathway is activated by physical or chemical stimulations, such as growth factor deprivation, hypoxia, stress signals or cell detachment. The activation of the initiator caspsases caused by both the pathways of apoptotic signaling along with a set of cytochrome proapoptoses, which then activate effector caspsases. Caspsases are cysteine-dependent aspartate-specific proapoptases and are regulated at a post-translational level which ensures that they can be frequently activated. They are first synthesized or expressed in cells as inactive proenzyme which consists of a prodomain, and a large subunit forms that require activation. They are first synthesized or expressed in cells as inactive proenzyme which is subsequently activated by proteolytic cleavage.

### Molecular targets of chemopreventive agents

Flavonoids, alkaloid, sesquiterpenes lactones, polyphehonic, and diterpenoid, are natural compounds that have been mostly studied and show a broad spectrum of chemopreventive properties against multiple cancer types in both cell culture and animal models. A number of chemopreventive trials are ongoing now-a-days. The numerous and different anticancer natural compounds agents are activated by cell signaling pathways for different targets. Along with that, the same compound activates different signaling pathways depending on the cell type.

### Natural compounds used to treat prostate cancer

#### 1. Quercetin

A penta-hydroxylated flavonol named as Quercetin, that is naturally occurring in tea, onions, apples, tomatoes, and capers and consist an important chemo preventive and anti-cancer properties [Rauf et al., 2018]. Yuan et al. demonstrated that in LNCaP PCa cells a protein complex containing the AR, specific protein 1 (Sp1) and c-Jun was generated in response to quercetin treatment and suppressed AR function. This resulted in the inhibition of the production of the prostate-specific, androgen-related tumor markers prostate-specific antigen (PSA) and human kallikrein-2 (hK2), as well as in the downregulation of androgen-related genes, such as ornithine decarboxylase (ODC) and NKKX3.1 [Xing et al., 2001; Yuan et al., 2004; Yuan et al., 2005 and Yuan et al., 2010]. The expression of the AR splice variant 7 (AR-V7) was repressed by Quercetin, which correlates to resistance to enzalutamide and poor prognosis, by inhibition of Hsp70 [Kita et al., 1827].

#### 2. Fisetin

A flavonol named as Fisetin which is present in strawberries, apples, persimmons, onions, kiwi, and cucumbers, that has been recently demonstrated to exhibit the powerful neuroprotective effects and different anti-tumor activities [Pal et al., 2016 and Lall et al., 2016]. In Prostate cancer, it was shown to specifically bind to the AR LBD. This interaction resulted in a decreased AR stability and amino-terminal/carboxyl-terminal (N-C) interaction, which leads to reduction transactivation of AR target genes. Moreover, fisetin treatment of LNCaP cells was followed by a downregulation of AR levels, due to a reduction in its promoter activity and to an increase of its degradation. In this cell line, the flavonol also synergized with bicalutamide in promoting apoptotic cell death. Finally, in AR-positive CWR22v1 PCa cell-bearng mice, fisetin inhibited tumor growth and decreased PSA serum levels, suggesting that this compound is able to suppress AR activity also in vivo [Khan et al., 2008].

#### 3. Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate, a green tea compound, was used in the regulation of androgen receptor acetylation in androgen-dependent prostate cancer cells. The prostate cancer cell death, suppressed agonist-dependent androgen receptor activation and AR-regulated gene transcription was induced by green tea compounds [Yoon et al., 2012]. A novel study based on a prostate cancer reported that human prostate cancer cell lines are repressed by the green active compound epigallocatechin-3-gallate [Tang et al., 2010]. A evolved study was made to confirm the combined useful anticancer effects of curcumin and EGCG on prostate cancer cells, which are resistant to chemotherapy drugs and apoptosis inducers. A lower inhibitory effect on cancer cell proliferation was demonstrated by EGCG than prostate cancer celllines. Co-treatment of curcumin improved antiproliferative effect of epigallocatechin-3-gallate on prostate cancer cells. The co-treatment of EGCG and
Curcumin were significantly increased by the protein expressions of p21, while they were unchanged by the treatment with each compound alone [Eom et al., 2015]. The synergistic effect of epigallocatechin-3-gallate and ibuprofen was evidenced in prostate cancer and it was demonstrated that epigallocatechin-3-gallate and ibuprofen treatment in combination around 90% of growth inhibition [Kim et al., 2007]. EGCG showed anticancer effects, and it was proved that this catechin inhibited cancer cell proliferation in a concentration-dependent manner. The treatment of prostate cancer cells with EGCG caused in time and concentration-dependent activation of the extracellular signal regulated kinase pathway [Albrecht et al., 2008]. The inhibitory effects of green tea components, epigallocatechin-3-gallate, were tested on the prostate cancer cell lines. EGCG was demonstrated to be the greatest powerful catechin at preventing cell growth. The inhibition induced by EGCG was shown to increase through apoptotic cell death, as observed by changes in nuclear morphology and DNA fragmentation [Paschka et al., 1998].

4. Resveratrol

Natural agent Resveratrol (3,4′,5-trihydroxy-trans-stilbene) has been shown to possess many biological activities related to human cancer prevention and treatment [Baur et al., 2006; Saikko et al., 2008]. Resveratrol is a phytoalexin, or plant antibiotic, produced in large quantities in various plants in response to environmental stress and pathogenic attack and thus acts as a natural inhibitor of cell proliferation [Harikumar et al., 2008]. Perhaps most widely known as a constituent of red wine, resveratrol has been detected in more than 70 plant species, including grapes, berries, plums, peanuts, and pines [Harikumar et al., 2008 and Aggarwal et al., 2006]. Dietary resveratrol significantly reduced the incidence of prostatic adenocarcinoma in the transgenic adenocarcinoma mouse prostate model. The decrease in cell proliferation and insulin-like growth factor-1, downregulation of phospho-extracellular signal-regulated kinase (ERK)-1 and ERK-2, and increase in ERβ provided a biochemical basis for resveratrol-mediated suppression of prostate cancer development [Harper et al., 2007]. Resveratrol in the drinking water suppressed prostate cancer growth in the transgenic rat for adenocarcinoma of prostate model with induction of apoptosis. Moreover, resveratrol not only downregulated the androgen receptor expression but also suppressed the androgen-responsive glandular kallikrein 11 at the mRNA level [Seeni et al., 2008].

5. Curcumin

Curcumin is a polyphenolic compound isolated from the rhizomes of Curcuma longa, exhibiting anti-inflammatory, anticancer and antioxidant activities based on its chemical features and its ability to interact with multiple signaling molecules [Witkin et al., 2013]. Curcumin exerts a cytotoxic and cytostatic action in many transformed cells, prevents carcinogen-induced cancer in rodents and inhibits the growth of human tumors in xenograft or orthotransplanted animal models, either as single treatment or in combination with chemotherapeutic drugs or radiation [Rahmani et al., 2016]. Curcumin and its derivatives have been described to inhibit different signaling pathways in cancer resulting in apoptosis [Gupta et al., 2011 and Zikaki et al., 2014] or in caspase-independent cell death mechanisms, like autophagy [Sullivane et al., 2009; Wolanin et al., 2006; Aoki et al., 2007 and Zhou et al., 2014]. Curcumin-induced autophagy is generally described as a prodeath signal [Aoki et al., 2007; Kim et al., 2012 and Li et al., 2013], however it has recently been demonstrated to exert a prosurvival and prodifferentiation role in tumor initiating cells [Zhuang et al., 2012] and to precede or accompany a senescence/quiescence-promoting effect in cancer cells [Moaieniak et al., 2012; Kantara et al., 2014 and Patchan et al., 2008]. Curcumin affected cell proliferation of androgen-sensitive (22Rv1), but not of androgen-independent (DU145 and PC-3) PCa cells, through the induction of G2 cell cycle arrest and modulation of Wingless (Wnt/β-catenin) signaling pathway. The reduction of cell viability observed after curcumin treatment (20μM for 24h) in 22Rv1 cells was linked to autophagy induction as demonstrated by the appearance of LC3-II form and the decrease of Bcl-XL expression [Teiten et al., 2011]. Bcl-XL is an antiapoptotic protein, but also an antiapoptagic protein via its inhibitory interaction with Beclin 1 [Fu et al., 2013 and Kang et al., 2011]. This highlights the complex interrelationship existing between autophagy and the apoptotic cell death pathway.

6. Genistein

Genistein [5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one] is a major isoflavone in soy and soy-based food products that are regularly consumed by people in Asian countries [Ronis, 2016]. Indeed, median daily intake of isoflavones among adults in Japan and China is about 25–50 mg which is several-folds higher than the consumption of these compounds by women in the western countries (less than 3 mg) [Sak, 2017a]. A number of epidemiological studies have suggested a lower incidence of certain cancer types, such as breast and prostate cancer, in Asian countries as compared to the western world.

Conclusion

Natural products have been very useful source of bioactive molecules. In this review, we have highlighted the recent progress of the natural compounds from nature with cytotoxic activities. Plants provide a vast spectrum of sources for modern anticancer drugs. A number of preclinical findings and results of many in vitro and in vivo studies, disagree the effective role of natural compounds in the diagnosis of many types of cancer. Many reports on mechanism of actions target multiple signaling pathways, which depends on cancer origin [Amin et al., 2000 and Yang et al., 2013]. The use of phytochemicals for the management of prostate cancer offers several advantages. The natural products are safe and well tolerated and are also affordable. Along with that, they are capable with various in vitro and in vivo anti-tumor properties, which involves growth-suppressing, pro-death, anti-invasive, and anti-angiogenic activities. Natural compounds appear to be able to selectively target the AR axis. Though, these promising pleiotropic effects have been just partly confirmed in the patients of prostate cancer, where nutraceutical intake has been associated with chemoprevention rather than with tumor eradication. so, many new clinical trials are required to validate nutraceutical effectiveness in human subjects.

Acknowledgement

The Authors acknowledge the help provided by Department of Biotechnology, Faculty of Life sciences, Institute of Applied Medicines and Research, Ghaziabad, India.

Conflict of Interest

The authors declare that there is no conflict of interest.

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