Original article

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

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ABSTRACT

In developed countries, Prostate cancer (PCa) is a major cause of cancer mortality among humans mainly in men. Tumor cells adapt the capability to escape cell death and develop resistance to existing therapies. There are many new curative approaches for the management of prostate cancer which involves cell death induction, tumor growth suppression, & inhibition of metastasis and angiogenesis in which the natural products have been commonly used for their anti-prostate cancer activities. A number of studies have been shown that the phytochemicals can particularly target the androgen receptor (AR) signaling ,as well as the prostate cancer stem cells (PCSCs). A number of clinical trials have been done to test the efficiency of nutraceuticals in human subjects, and they have partially confirmed the promising results obtained in vitro and in preclinical models. This review discusses about the anti-cancer mechanisms and curative capabilities of many different natural compounds in the prevention and treatment of prostate cancer in humans.

Introduction

Cancer is a very harmful disease found all over the world and it is the second most important cause of death around the world, mainly in Europe and the United States with an occurrence rate of about 2.6 million cases per year [Siegel et al.,2008 and Jemal et al.,2012] The unregulated and uncontrolled cellular propagation in the spectrum of cell is the main cause of cancer. The Cancer occurs in developing countries that has been known by tumor types that are related to bacterial contamination , viral and genetic mutations [Siegel et al.,2010]. Cancer has a high impact and a long period of latency on its growth and in the succession of the sickness. There are many types among humans of cancers namely prostate cancer, cervical cancer, renal cancer ,breast cancer ,etc. In all of these types of cancers ,Prostate cancer (PCa) is the most commonly diagnosed tumor that mainly occurs in men ,that is being particularly common in Western countries [Fitzmaurice et al.,2015]. In about 90% of cases, Local radiotherapy or prostratectomy proves to be useful to treat organ restricted prostate cancer. However, 30–40% of patients generally experience development of disease [Stephenson et al.,2006]; at this stage, where tumor growth depends on androgens ,the androgen –deprivation therapy proves to be most useful for the treatment , which aims at blocking hormone secretion. There are many natural products that can selectively target numerous molecules and signaling pathways which involves in tumor growth and development. Many of them have been tested in, in vitro and in vivo studies, while some clinical trials have been conducted and some are going on [Salehi et al.,2019 ; Kallifatidis et al.,2016 ; Taylor et al.,2017]. The naturally occurring molecules like, quercetin, fisetin , luteolin , resveratrol, genistein, silibinin, kaempferol, epigallocatechin-3-gallate (EGCG), tocotrienols, circumin, cellophane ,apigenin , ginsenosides , berberine, honokiol, xanthoumol, oridonin ,ursolic acid and tannic acid have shown great potential in the treatment of prostate cancer as anti-Prostate cancer agent in in vitro and preclinical experiments.

Role of natural compounds in cancer prevention

Natural products obtained from plant is a vast reservoir which shows important structural diversity, and they suggest a wide variety of novel & exciting chemical entities that have been used for a long time for curing numerous diseases. The importance of natural products in health care is supported by a report that 80% of the population even now depend on plant-derived medicines to take care of their health [Fulda et al.,2010]. It is also reported that 50% of all drugs in clinical use are natural products, their derivatives [Hsu et al.,2010], and 74% of the most important drugs consist of plant-derived active ingredients [Jaganathan et al.,2009]. More than 3,000 plant species have been reported to be used in treatment of cancer in modern medicine [Amin et al.,2009 ; Cragg et al.,2005 ; Elmore et al.,2007 ; Koehn et al.,2005]. There is a continued interest in the investigation of extracts of microorganisms, marine life forms, and terrestrial plants to search for anticancer compounds [Cragg et al.,2005]. Since 1920s along with Berren blum, chemopreventive began [Amin et al.,2009],

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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 many 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 cell drug resistance [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 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 caspases caused by both the pathways of apoptotic signaling along with a set of cysteine proteases, which then activate effector caspases. Caspases are cysteine-dependent aspartate-specific proteases 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 cleavage for activation. However, caspase-independent apoptosis is also reported [Anichini et al.,2006].It is characterized by chromatin condensation and DNA fragmentation, and it is mediated by caspases [Hengartner et al.,2000]. There are many apoptotic signals that are mediated to cell death machinery through p53 with other proteins such as TNF, FAS, and TRAIL receptors which are highly specific physiologic mediators of the extrinsic signaling pathway of apoptosis. Mitochondria is also involved in a number of key events, i.e., release of caspases activators, loss of mitochondrial membrane potential (MMP), changes in electron transport and participation of both pro-and antiapoptotic Bcl-2 family proteins [Heinrich et al.,1998 and Kreuger et al.,2012]. This breakthrough leads an important implication for targeted cancer therapy and modern application of natural compounds.

Molecular targets of chemopreventive agents

Flavonoids, alkaloid, sesquiterpenes lactones, polyphenolic, and diterpenoid, are natural compounds that have been mostly studied and show a broad spectrum of chemo preventive properties against multiple cancer types in both cell culture and animal models. A number of preventive 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 types.

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 NKX3.1 [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 reduce 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 CWR22υ1 PCa cell-bearing 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 cell lines. 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 fashion. 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, Saiko 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-I, 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 apoptotsis [Gupta et al.,2011 and Zikaki et al.,2014] or In caspase-independent cell death mechanisms, like autophagy [Sullivan 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 (20⍰μM for 24⍰h) 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 antiautophagic 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-dihyroxy-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.

Aknowledgement

Conflict of Interest

The authors declare that there is no conflict of interest.

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