Review Article

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Flavonoids: Agents with Prodigy of Therapeutic Wonders in Cancers

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Abstract

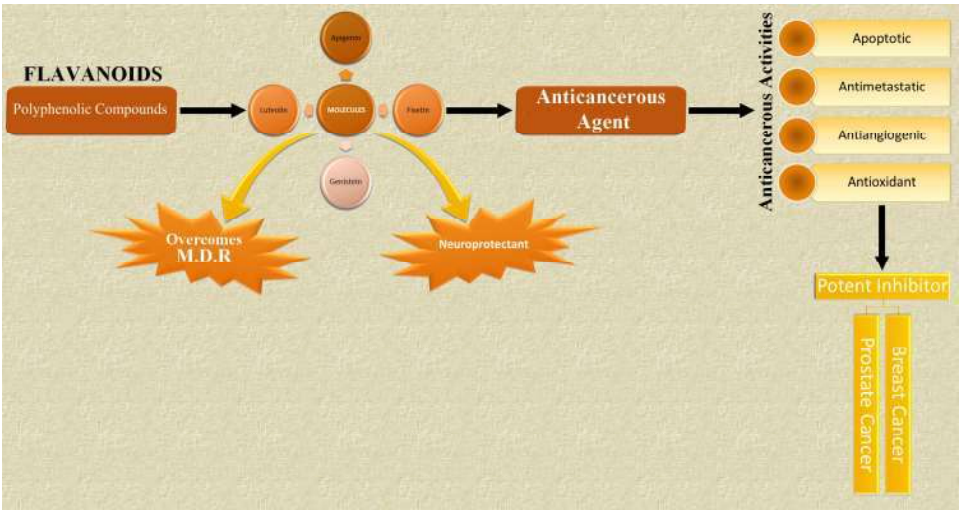
Flavonoids, naturally occurring polyphenolic compounds comprises of more than 4000 members. Being edible in nature they became an integral part of human diet. Flavonoids act as potent inhibitor of various types of cancer on virtue of their ability to induce anti-cancer activities. Flavonoids induces anti-inflammatory, anti-angiogenic, apoptotic activities and also leads to inhibition of invasion and metastasis including cell cycle arrest. Multiple drug resistance is the major principal mechanism via which one amongst the most dreadful disease named as cancer acquires resistance. Several ATP-binding cassette (ABC) transporters causes multidrug resistance in cancer cells. Flavonoids target the ABC transporters and help the cells in restoration of drug sensitivity in multiple drug resistant cancer cells. Flavonoids are capable of mediating both hormone dependent and hormone independent action against various types of cancer including breast and prostate cancer. The present review article describes the potent role of flavonoids as an anti-cancer agent as it possess a mark impact in controlling breast and prostate cancerand an efficient agent to overcome issues of multiple drug resistance. Further *in vivo* studies of these bioactive compounds become essential so that flavonoids can be used as a potent therapeutic drug of wonder to treat various types of cancers.

Keywords: Cancer; Drug Resistance; Flavonoids; Neuroprotectant.

Introduction

Flavonoids belong to naturally occurring compounds possess plant based origin. Flavonoid group comprises of more than 4000 polyphenolic compounds. The major common characteristic feature of flavonoids is their structural configuration, they possess phenyl benzopyrone structure (C6-C3-C6) and they are also classified, based upon their saturation level and the opening of their central pyran ring [1,2]. Flavonoids also known as antioxidants, exhibit 4000 type of chemically unique and varying moieties. Flavonoids comprises of different classes including flavonols, flavans, proanthocyanidins and anthocyanidins. Being edible in nature they are widely used as an integral part of human diet. Regular intake of flavonoids in U.S.A is approximately found to be 0.5 to 1 g expressed as glycosides but afterwards the figure is considerably found to be lower, approximately 200 mg. Such a small amount also proves to be pharmacologically beneficial for plasma and body tissue and the facts relating these observations are reported in numerous studies [3–6].

Flavonoids exhibit various properties by virtue of which they can be used as an anti-cancer agent. They interact with various cellular targets and produce anti-inflammatory, antiviral responses [7,8]. Epidemiological studies have revealed that hormonal replacement therapy in cancer treatment shows disastrous results in past few years. Rather than proving as a beneficial one, they are enhancing the complications. Cancer chemoprevention by virtue of natural or synthetic substances has become a need of today. Major mechanisms involved in controlling cancer includes suppression, blockage, and transformation. Suppressors prevent the formation of new cancer cell from pro-carcinogens, blockers avert the carcinogenic compounds to reach their



target site and transformation leads to conversion of carcinogenic compounds into less toxic thus inhibiting their biological action. Flavonoids also possess the ability to revert the carcinogenic process [9,10]. Following paragraphs will provide a detailed study revealing the potential of flavonoids to be used as an anti-cancerous agent, neuroprotectant agent and its potential to overcome multiple drug resistance.

Anti-Cancer activities mediated by flavonoids

Several studies have revealed the fact that naturally occurring flavonoids exhibit growth inhibitory effect on various kind of cancers on virtue of their ability to act directly upon various molecular targets through diverse molecular pathways [11–13]. Although the exact mechanistic insight of action of flavonoids is not yet clear [14,15].

Flavonoids bind to cell membrane, penetrates into *in vitro* cultured cells and disrupts various cellular metabolic activities [16,17]. They lead to inactivation of carcinogens, induces cell cycle arrest, promotes apoptosis and differentiation of cells, inhibits invasion and metastasis and also leads to inhibition of angiogenesis and thus induces anti-carcinogenic effect for which flavonoids are a point of interest in our article [18–23]. They interacts with xenobiotics metabolizing enzymes and directly induces their effect by inhibiting several protein kinases which are found to be involved in signal transduction, they also interacts with estrogen type II binding sites and alters the gene expression [24,25].

Antioxidant activity mediated by flavonoids

Continuous utilization of oxygen in human body leads to production of free radicals including a series of reactive oxygen species. These reactive oxygen species (ROS) involving super oxide anion, hydroxyl radicals, non-free radical species such as H_2O_2, singled oxygen and nitric oxide (NO) creates several pathological conditions in human body. These reactive oxygen species act as an initiator of several diseases like atherosclerosis, ischemia, central nervous system injury and cancer [26]. These phytocompounds possess ability to induce antioxidative, antimicrobial, antiviral and anti-inflammatory effect [27]. Antioxidants have the ability to neutralize the free radicals which are produced as a byproduct during the metabolic activities. Antioxidants are produced either naturally *in situ* or supplied through diet. Antioxidants prevent or repairs the damage caused by reactive oxygen species and also enhance the immune defense mechanism of body by acting as free radical scavengers hence reducing the risk of cancer. Several *in vitro* studies have elucidated the fact that flavonoids at 5 to 80 µg/mL concentration act as an antioxidant. Flavonoids exhibit dosage dependent free radical scavenging properties and hence can be used as potent inhibitor of cancer [28].

Apoptotic activity mediated by flavonoids

Expression of Heat shock factor 1 (HSF1) which is a transcription factor of heat shock proteins (HSPs) enhances the survival of cancer cells when they are exposed to different kind of stresses. In mice model it has been studied that knockout of HSF1 inhibits the carcinogen induced cancer formation. Hence HSF1 can be used as a therapeutic measure to target various type of cancers. Here in this part of article we will review the role of fisetin which is a dietary flavonoid act as a potent inhibitor of HSF1. Fisetin effectively eliminates the heat shock induced luciferase activity in HCT-116 cancer cells. Fisetin suppresses the induction of HSF1 target

proteins involving HSP70, HSP27 and BAG3 when the cells were exposed to heat shock in presence of fisetin. HSP70/BAG3 complex helps cancer cells in providing protection against apoptosis by activating anti-apoptotic Bcl-2 family proteins. Fisetin effectively suppresses the expression of HSP70/BAG3 and subsequently reduces the amount of Bcl-2, Bcl-xL, and Mcl-1 proteins. A study based on animal model revealed significant reduction in tumor growth by 35.7% when the nude mice was intraperitoneally treated with 30 mg/Kg of fisetin [29]. Therefore, fisetin can be used as a potent inhibitor of cancer on virtue of its ability to target heat shock proteins.

Flavonoids inhibit invasion and metastasis

Metastasis is a phenomenon wherein cancer cells leave their primary site, passes via circulatory system and forms a secondary tumor at a new distant site. Metastasis is a multistep process beginning with growth of cancer cells at primary site followed by decreased cell adhesion and local invasion through the basement membrane. Genistein a bioactive flavonoid exhibits the potential to inhibit invasion and metastasis. Genistein possess the ability to inhibit primary tumor growth and also influence the cell proliferation. Genistein is also known to regulate the metastasis at later stages by exerting its impact on cell adhesion, migration and invasion [30]. Therefore genistein can be used as a potent inhibitor of cancer by inhibiting invasion and metastasis.

Anti-angiogenic effects mediated by flavonoids

Epidemiological studies have revealed that flavonoids act as chemo preventive agent by inhibiting angiogenesis, proliferation of tumor cells and endothelial cells *in vitro*. Flavonoids have the potential to inhibit angiogenesis and thus referred as anti-angiogenic agents. Several studies have investigated the antiangiogenic mechanism of flavonoids including genistein, apigenin, and 3-hydroxyflavone in a human umbilical vein endothelial cell (HUVEC) model. Stimulation of serum-starved HUVECs with vascular endothelial growth factor/basic fibroblast growth factor (VEGF/bFGF) leads to the increase in MMP-1 production, activation of pro-MMP-2 and significant increase in expression of MT1-MMP. Studies have revealed that pretreatment with flavonoids before VEGF/bFGF stimulation completely abolish the VEGF/bFGF mediated action. Genistein blocks VEGF/bFGF and enhances the expression of TIMP-1 and further reduces TIMP-2 expression. VEGF and bFGF activation induces the expression of uPA and enhances the level of 33 k Dau PA and increases the expression of PA inhibitor (PAI)-1. Genistein and apigenin blocks the production of 33 kDauPA and further inhibits the expression of PAI-1. Hence here in this part of article we can concretely say that apigenin and genistein acts as a potent inhibitor of angiogenesis as they do so by suppressing VEGF/bFGF-induced MMP-1 and uPA expression [31].

Hormonal dependent and hormonal independent mediated action of flavonoids against various cancer

Several cancers are reported to be hormone dependent including breast and prostate cancer. Their growth and development is dependent upon expression of its receptors like estrogen receptors (ER) and androgen receptors (AR), respectively. Breast cancer are considered asheterogeneous in nature and possess both ER-positive and ER-negative cells. Therefore controlling breast cancer becomes a major issue due to its heterogeneous nature of growth and development. Flavonoids possess such a dual activity to inhibit both the ER-positive and ER-negative breast cancer cells and hence are a focus for research in the area of cancer biology[32]. Intake of higher flavone concentration significantly reduces the risk of breast cancer. Apigenin, baicalein, and luteolin acts as a potent inhibitor of breast cancer and extensively used in the treatment of mammary tumors [33–38]. Apigenin can target both estrogen receptor positive and estrogen receptor negative breast cancer. But the effect of apigenin against the estrogen receptor positive breast cancer is found to be more promising in comparison to estrogen receptor negative breast cancer.

Likewise to that of estrogen, androgen receptors are essential for prostate cancer growth and survival. Flavonoids shows anti-cancerous effects against both the androgen receptor positive and androgen receptor negative prostate cancer cell lines. Flavonol specially quercetin, fisetin, galangin, kaempferol, and myricetin exhibits strong cytotoxic activity against androgen dependent prostate cancer. Quercetin is known to decrease the expression of AR in 22rv1 human prostate cancer cells [39]. Fisetin inhibits androgen receptor signaling pathways and can be effectively used as a chemo preventive agent against prostate cancer. On the other hand naringenin exhibits higher efficacy against androgen receptor negative prostate cancer. Therefore flavonoids can be used as a promising anti-cancerous agent against both the hormone dependent and hormone independent cancers [40–42].

Flavonoids as potential neuroprotectant

Flavonoids play an extensive role in maintenance of health and prevention of several chronic diseases. Being an anti-cancer agent flavonoids exhibits potential to act as an anti-inflammatory, antioxidant agent and also inhibits invasion and metastasis. Recent studies have also highlighted an enormous role of flavonoids as a neuroprotectant. They controls the neurological functions. Flavonoids and their bioavailable metabolites are involved in cytoprotection. They acts against the oxidative stress which is independent of conventional antioxidant reducing activities. Flavonoids exerts their impact by interacting with cell signaling cascades. They also influences gene expression, causes down regulation of pathways leading to cell death [43] and hence can be potentially used as neuroprotectant to fight against neuronal injury.

Potential of flavonoids to overcome multiple drug resistance

Flavonoids have the potential to influence the pharmacokinetics involving drug absorption, penetration and elimination they do so by modulating function of ABC transporters [44,45]. Flavonoids after the ingestion gets metabolized into flavonoid conjugates and exert its impact by either acting as a stimulator or inhibitor of ABC transporters. Multiple drug resistance is the major principle mechanism by virtue of which most dreadful disease cancer acquires resistance. Flavonoids have the capability to act against the multiple drug resistance. They have potential to inhibit Pgp-, MRP1- and ABCG2-mediated efflux and helps in restoring drug sensitivity in multiple drug resistance cancer cells [46–48]. Recently *in vitro* and *in vivo* experiments were carried out using cell lines overexpressing ABC drug transporters. Knockout animals have also been designed to check the action of flavonoids on ABC transporters [49]. Biochemical and pharmacological studies have proven the fact that flavonoids modulates ABC transporters. Flavonoids competitively binds to the substrate binding site of ABC transporters and create hindrance in their mode of action. Whereas certain flavonoids affects the ATP binding or hydrolysis at nucleotide binding domains and also known to alter the expression of ABC transporters [50–57]. Therefore it can now be clearly said now that flavonoids act as an anti-cancer agent and helps the cells in restoring the drug sensitivity against drug resistance cancer cells.

Conclusion and Future Perspective

Naturally occurring flavonoids potentially acts as promising candidate for chemotherapeutic agent. On virtue of its ability to exhibit anti-cancerous activities they can be significantly used as potent inhibitor of various types of cancer. Various polyphenolic compounds like fisetin, genistein, apigenin, baicalein, luteolin, quercetin, galangin, kaempferol, and myricetin exhibits anti-cancer activities. They possess the ability to inhibit angiogenesis, oxidative stress, invasion and metastasis and also has the potential to induce apoptosis. Firstly they binds to cell membrane followed by its penetration into target cells eventually leading to disruption of several cellular metabolic activities. Flavonoids mediates its effect without showing any kind of reliance on hormones to act upon various types of cancers. In case of breast cancer they exhibit dual functioning by acting against both ER positive and ER negative breast cancer and the same with prostate cancer by acting against AR positive and AR negative prostate cancer. Flavonoids also emerges out as an effective neuroprotectant. They helps in restoring the drug sensitivity against the multiple drug resistant cancerous cells. Hormonal replacement therapy comprises of combination of drugs which is basically enhances the complications of cancer rather than rectifying them. Flavonoids can be used as effective alternative to hormonal replacement therapy. These polyphenolic compounds are valuable agents in anticancer therapies and studies of their clinical use for development of novel drugs should be continued.

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