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Multifactorial role of flavonoids in prevention and treatment of various cancers

Title in Spanish: *Papel multifactorial de los flavonoides en la prevención y tratamiento de algunos cánceres*

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ABSTRACT: Bioactive compounds isolated from plants have gained a lot of attention in recent years. Among them flavonoids, which consist of a large group of polyphenolic compounds, are at the forefront in the treatment of various diseases including cancer. Flavonoids possess anti-cancer properties and they exert their curative effect by modulating different cell-signalling pathways like the Nf-kB pathway, PI3K/AKT/mTOR pathway and the JAK/STAT pathway. Flavonoids also possess anti-oxidant activity and they regulate the redox status and prevent damage caused by oxidative stress. Chemokines and cytokines play a key role in mediating the inflammatory response in a cell. Consequently, more inflammatory markers are recruited to the site of inflammation that leads to increased ROS and cause damage at the site of accumulation. The present review covers the recent studies, *in vitro* and *in vivo*, that highlight the promising potential of flavonoids in treating cancer.

RESUMEN: Los compuestos bioactivos aislados de las plantas han ganado mucha atención en los últimos años. Entre ellos los flavonoides, que consisten en un gran grupo de compuestos polifenólicos, están en la vanguardia del tratamiento de diversas enfermedades incluyendo el cáncer. Los flavonoides poseen propiedades anticancerígenas y ejercen su efecto curativo mediante la modulación de diferentes vías de señalización intracelular como la vía Nf-kB, PI3K / AKT / mTOR y la vía JAK / STAT. Los flavonoides también poseen actividad antioxidante regulando el estado redox y previniendo los daños causados por el estrés oxidativo. Las quimiocinas y citocinas juegan un papel clave en la mediación de la respuesta inflamatoria en las células. Por lo tanto, el aumento de los marcadores inflamatorios que son reclutados en el sitio de inflamación conduce a un aumento de las especies reactivas del oxígeno causando daños en el lugar de su acumulación. La presente revisión abarca los estudios más recientes, tanto in vitro como in vivo, en donde se destaca el potencial que presentan los flavonoides en el tratamiento del cáncer.

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1. INTRODUCTION

The beneficial effects of food have been known from ancient times and have been applied in treating various human diseases. Various phytochemical substances in the functional food have antioxidant properties. Phytochemicals can modulate different signal transduction pathways and play a key role in treatment of cancer. The phytochemicals studies about citrus fruits have shown to contain most of the flavonoids (1, 2). These flavonoids mediate important physiological functions and are commercially very important in nutrients and pharmacy companies owing to broad therapeutic applications (3, 4). The equilibrium between cell growth and death is very important for the development and maintenance of normal body functions in multicellular organisms (5). The process of cell death helps repair damaged tissue and eliminate harmful cells (6). Altered signaling can lead to an imbalance in cellular functions which may lead to pathological disorders such as embryogenesis, neurological diseases and cancer.

Normal cells are stimulated by carcinogen and leads to mutation. Subsequently inhibit the function of tumor suppressor gene and stimulate oncogene. This cause uncontrolled growth of the cell known as carcinogenesis (5). In carcinogenesis, formation of new blood vessels is a key step to provide nutrients and oxygen supply to cancer cells. Tumor cells can invade and spread throughout the body through blood and lymph vessels (6).

Flavonoids are polyphenolic compounds with powerful and strong antioxidant, anti-inflammatory and anti-cancer activity. Citrus flavonoids mainly influence blood and microvascular endothelial cells by blocking regulatory enzymes, which mediate cell division and activation (7). The polyphenolic content of citrus fruit was reported to consist 81-97 % flavanones, while the remaining accounted for flavones, flavonols, hydroxycinnamic acids and coumarins (8). Despite being under investigation for long time, the mechanisms underlying the biological action of these compounds are not yet completely understood (9).

Flavonoids having various pharmacological activities are attributed by inhibiting action of enzymes in cellular stimulation. The *in vitro* elucidation shows that flavonoids alter enzymes status such as lipooxygenases, kinases, phospholipases, ATPase, cyclooxygenases, and phosphodiesterases (10, 11, 12). Furthermore, flavonoids tend to react and bind with nucleotide regulatory enzymes (7). Citrus flavonoids also actively scavenge the free radicals and, therefore, show antagonist effect on aging and degenerative events mediated by oxidative stress (13). The prime focus of this review narrates the mechanistic action of flavonoids and discusses their biological activity in regards to modulating key regulatory enzymes, signaling cascades etc. to facilitate the treatment of cancer.

2. CHEMICAL COMPOSITION OF FLAVONOIDS

A number of phytochemical compounds have been identified as flavanoids amongst which polyphenolic terpenoids have been studied most extensively. They have a characteristic structure C6-C3-C6 structure. Majority of flavonoids are formed by a combination of hydroxyl, methoxy, and O-glycoside groups that are attached to this C3-C6-C3 structure (14). Flavonoids are further divided into flavones, flavonols, flavanones, flavanols, anthocyanins and isoflavones. The different classes occur due to a difference in the C3 element of the flavonoid structure (14).

Flavonoids are considered as hydroxylated phenolic compounds that are produced as a result of a microbial infection in plants. Their characteristic 15 carbon structure (C6-C3-C6) includes two benzene rings commonly referred to as A and B rings. The A and B rings are joined together by a heterocyclic pyrane ring referred to as the C ring. The different classes of flavonoids occur because of different levels of oxidation and because of substitutions at the C ring. Different compounds within each class exist because of substitutions at the two benzene rings.

Flavonoids occur in three forms, either as aglycones (aglycosides) and glycosides or sometimes as methylated derivatives. The basic structure mentioned above (i.e C6-C3-C6) is the aglycone structure (15). Aglycosides (without sugar) or glycosides (containing sugar) are two main forms of citrus flavonoids. Glycosides contain single or multiple sugars attached to the basic flavonoid skeleton (9).

3. BIOLOGICAL ACTIVITY OF FLAVONOIDS

3.1. Anti-inflammatory effects

Inflammation is a physiological response that is brought on by different circumstances such as infection or tissue injury. Studies have revealed that an array of responses triggered by the immune system leads to inflammation (16). There is increased level of inflammatory markers, free radicals lipid peroxides whenever there is incidence of inflammation. This is due to the fact that inflammation disturbs signaling pathways. There is also evidence suggesting that inflammation plays a key role in healing wounds and fighting infections. However, if inflammation persists for longer periods of time it stimulates progression of many chronic diseases including cancer (16, 17).

The events that occur during inflammation include the recruitment of leukocytes and mast cells. This leads to what is known as a 'respiratory burst'. There is an increased level of oxygen uptake at the site of damage and hence an increase in the reactive oxygen species (18).

Inflammatory calls also produce some mediators like cytokines and chemokines. These molecules act by recruiting more inflammatory cells to the site of damage thereby increasing the number of ROS. These are the key mediators involved in inflammation and include other molecules such as metabolites of arachidonic acid. Together they are capable of activating signal cascades and inducing changes in transcription factors. The transcription factors include NF-κB, HIF1-α, AP-1, NFAT and Nrf2. Other factors apart from chemokines and cytokines mediate the inflammatory response, these include COX-2, iNOS, differential expression of certain micro RNAs. All these contribute to an increase in the oxidative stress (19). When this state of increased ROS and oxidative stress persists it leads to the disruption of healthy surrounding cells and tissue and therefore leads to the incidence of cancer (20).

3.1.1. In vitro studies

Daphne genkwa also known as D.genkwa is a medicinal plant that has a large number of flavonoids associated with anti-inflammatory response. In a study conducted on HT-29 and SW-480 human colorectal cancer cells, it was concluded that flavonoids found in D.genkwa have an ability to regulate the immune system by inhibiting the production of inflammatory cytokines (21).

in vitro studies have determined that flavonoids are capable of inhibiting the synthesis and activity of a variety of pro-inflammatory mediators such as cytokines, adhesion molecules, eicosanoids etc. Molecular mechanism includes the inhibition of various transcription factors such as the NF-kappaB, AP-1 and stimulation of Nrf2 (nuclear factor-erythroid 2-related factor 2 (22). In a study conducted by Zhang et al (2014), it was determined that apigenin, which is a non-toxic natural flavonoid has the potential to inhibit lipopolysaccharide induced inflammation through multiple mechanisms. Macrophages were utilized and it was seen that apigenin inhibited LPS induced production of

cytokines such as IL-6, IL-1B and TNF-a. The production of IL-1B was inhibited by inhibition of caspase-1 through disruption of NLRP3 inflammasome assembly. mRNA stability was also reduced due to inhibition of ERK ½ activivation (23). The phosphatidylinositol-3 kinase (PI3K) family of signaling enzymes likely plays a key role in inflammation. The PI3k signaling cascade is involved in leukocyte recruitment and activation and is therefore thought to be involved in inflammation. Apigenin has also been reported to hinder the PI3k/Akt pathway in cancer cell lines. The data from a recent study conducted on breast cancer cell lines concluded that flavones such as apigenin and luteolin induced apoptosis and cell cycle arrest. Hs578T, MDA-MB-231 and MCF-7 breast cancer cells were used. The underlying mechanism was determined to be the induction of forkhead box O3 (FOXO3a) expression. This subsequently elevated the expression of FOXO3a target genes, including the Cyclin-dependent kinase inhibitors p21(Cip1) (p21) and p27(kip1) (p27), which increased the levels of activated poly(ADP) polymerase (PARP) and cytochrome c (24). Kadioglu et al (2015) reported anti-inflammatory effect of the flavonoid kaempferol against Nf-kB pathway proteins. Nf-kB is an important factor in the proliferation, inflammation and carcinogenesis. Kaempferol belongs to the flavonol class of flavonoids and its major sources include onions, cherries, broccoli, kale etc (25).

A lot of flavonoids have been studied for their anti-inflammatory effects in *in vitro* studies but there is still lack of evidence with regards to *in vivo* studies. *in vitro* studies focus only on pure doses of flavonoids administered therefore we cannot be completely sure about their effects in humans. This is because humans intake flavonoids indirectly from plant foods and not in pure doses.

3.1.2. In vivo studies

A number of studies have been conducted in animal models. In a recent experiment conducted by Tao et al (2015), Lewis-bearing C57BL/6 mice model was established and tumor growth was induced. Immunomodulatory factors were detected that confirmed the therapeutic effect of flavonoids present in Scutellaria barbata D. Don (SB). It was established that SB could inhibit tumor growth *in vivo* by regulating the immune system (26). Many flavonoids are used in combination with other molecules and exert a synergistic effect by enhancing or modulating the activity of the molecule being used. Quercitin, a well known flavonoid has been used along with B-carotene in order to modulate the activity of B-carotene against NF-kB induced inflammation in Mongolian gerbils (27). In another study, tricin, a flavonoid extracted from rice prevented the activation of the NF-kB and the JAK/STAT pathway *in vivo*. Activation of both STAT1 and STAT3 was inhibited via downregulation of JAK1 and JAK2 (28).

3.2. Anti-cancer effects

Prevention of cancer has been linked with the intake of a variety of plant foods. Wine drinkers are also considered at a lower risk of developing cancer than other people.

3.2.1. In vitro studies

Oncology reports published a study, Proanthocyanidins were investigated for their ability to stimulate programed cell death in human gastric cell line. The findings from this study suggest the use of Proanthocyanidins with autophagy inhibitors to significantly increase the rate of apoptosis and induce cytotoxicity (29). In agreement with this study, inhibition of esophageal adenocarcinoma by cranberry derived Proanthocyanidins (C-PAC) was investigated. C-PAC induced caspase-independent cell death by inducing autophagy in acid-sensitive cell lines. A number of signaling pathways were also identified in other cell lines. In-activation of the PI3K/AKT/mTOR pathway, stimulation of pro-apoptotic proteins, modulation of MAPKs and G2-M cell cycle arrest were some of the key factors of action (30). Quercitin is a widely studied flavonoid attractive for its anti-cancer and anti-proliferative activities. *in vitro* studies have acertained the anti-proliferarive outcome of quercetin against human colon adenocacinoma cells. The underlying mechanism was associated with a vital upsurge in the expression of the endocannabinoids receptor (CB1-R) following therapy with quercitin. This occurred because CB1-R is an estrogen responsive receptor and quercetin is similar in structure to estrogens so it interacts with CB1-R and regulates cell growth. To further clarify the underlying mechanism, principal molecular pathways were also investigated. Important survival signals like the PI3K/Akt/mTOR were inhibited, at the same time pro apoptotic JNK/JUN signaling pathways were induced. The metabolism of β-catenin was also modified. The interactive action of Quercitin with CB1-R was secured by means of anandamide (Met-F-AEA), a CB1-R agonist, SR141716, a CB1-R antagonist (31). A number of fruits have been considered as a valuable source of flavonoids and are recommended for the prevention of cancer. Yang S et al (2015) investigated the anticancer activities of flavonoids extracted from pink lady apples. The flavonoids were divided into two groups; peel-flavonoids and flesh-flavonoids. It was seen that the both type of flavonoids were capable of inhibiting cancer cell growth in a dose dependent manner (32).

3.2.2. In vivo studies

Many flavonoids have been subjected to studies based on animal models. *in vivo* studies reinforce the efficacy of the drug being used and its underlying mechanism of action. Toxicity studies can also be conducted on animal models before any drug is administered to human cohorts. A number of *in vivo* studies have been successfully conducted that highlight the anti-cancer activity of flavonoids. Bioactive proanthocyanidins decrease the accumulation of B-catenin and thereby inhibit growth in human melanoma cells. Dietary administration of grape seed proanthocyanidins (GSPs), suppressed the growth of nude mice melanoma tumor xenografts.. Furthermore, xenograft growth was reduced in β-catenin-activated

Mel928 mice but remained unaffected in β-catenin-inactivated Mel1011 mice (33). Swiss albino mice were utilized in one study where the anti-proliferative potential of hesperetin (HSP) was investigated against benzo(a)pyrene induced lung carcinogenesis. Pre- and post-treatment with HSP alleviated Lipid peroxidation, increased the level of antioxidants and decreased the expression of NF-κB, PCNA and CYP1A1 (34). Luteolin is a flavone that is found in a number of plant foods and is thought to possess anti-cancer activity. Cook et al (2016) demonstrated the ability of luteolin to suppress progestin-accelerated mammary tumors. Both low (1 mg/kg) and high (25 mg/kg) doses of luteolin considerably reduced progestin-dependent upsurges in tumor prevalance, while increasing tumor inactivity and decreasing the incidence of large (>300 mm3) mammary tumors. Immuno histochemical examination of tumor tissues showed that at all concentrations levels of VEGF were considerably reduced within the tumors (35). Chromatin acetylation is linked with epigenetics that play a crucial role in how people respond to drugs with relevance to gene expression in normal and diseased conditions. Luteolin, a flavonol, was found to inhibit this acetylation. The underlying mechanism was determined to be the competitive binding of luteolin to the acetyl CoA binding that inhibited p300 acetyltransferase. Effects of luteolin were seen at multiple levels i.e. at the level of gene expression as well as at the level of miRNA processing. Tumor model of head and neck squamous cell carcinoma (HNSCC) was used. This xenografted model was treated with luteolin which led to a reduction in the size of the tumor within 4 weeks along with a decrease in the acetylation of histones (36).

3.3. Anti-oxidant effects

Anti-oxidants regulate the cellular levels of reactive oxygen species thereby preventing or reducing oxidative damage. Oxidative stress is the underlying cause for a number of diseases including cancer. Irregular levels of free radicals generated inside a cell can activate a number of signaling cascades that lead to cell-proliferation, cell cycle progression, inflammation and thus cancer. Flavonoids have been known to have anti-oxidant activity whereby they exert a protective effect on cells. A number of mechanisms are employed by flavonoids by which they reduce or prevent oxidative damage.

1. Direct scavenging of ROS.
2. Inhibition of superoxide anion production by inhibiting oxidases.
3. Activation of anti-oxidant enzymes.
4. Chelation of free metals; involved in oxygen metabolism.
5. Alleviation of oxidative stress caused by nitric oxide (37).

3.3.1. In vitro studies

In a recent study published in the journal of photochemistry and photobiology, anti-oxidant activity of extracts from Galinsoga species was determined. The anti-oxidant activity was examined by determining the scavenging property of these species. ROS scavenging is one of the mechanisms by which flavanoids exert their anti-oxidant activity. This activity was determined against two radicals generated in cell-free systems; O2- and H2O2. It was seen that ethanolic extracts from the herb exerted cytotoxic effects while the aqueous extracts exerted protective effects by inhibiting ROS generation. The aqueous extracts can therefore be labeled as effective photoprotectors (38). In a similar study conducted by Sung et al (2015), free-radical scavenging assays were used to determine the anti-oxidant activity of a perennial herb, Humulus japonicas. Extracts from this herb contain a number of bioactive compounds comprising luteolin, luteolin 7-glycoside, quercetin and quercitrin which effectively caused scavenging of ROS in *in vitro* and intracellular systems. Furthermore, experiments also demonstrated the upregulation of longevity-related proteins, sirtuin 1 and AMP-activated protein kinase. Thus it is safe to conclude that these flavanoids can be used as effective anti-aging and anti-oxidant compounds (39).

Ashraf et al (2016), demonstrated the antioxidant activity of three extracts of Psidium guajava leaf; methanol, chloroform and hexane on three different cell lines (KBM5, SCC4 and U266). The hexane extract completely inhibited activation of TNF-a and Nf-kb activation in KBM5 cells and hence had antitumor and cytotoxic activity. All the extracts had different phenolic and flavonoid contents (40).

3.3.2. In vivo studies

Animal models have also been used to further determine the protective activity of different flavonoids although present *in vivo* studies are very limited. Wedelia chinensis is a traditional herb known to have hepatoprotective properties. This herb was seen to have neuroprotective effects in mice models by inhibiting oxidative stress- induced damage. Extracts from this herb contain luteolin that has been shown to have anti-cancer properties in multiple studies (41).

Drug resistance during chemotherapy is one of the many hurdles that lead to poor prognosis in cancer patients. Isorhamnetin (IH), which is a metabolite of quercitin, was evaluated for its attenuating effect against chemoresistance. IH was administered along with capecitabine to enhance its efficacy in gastric cancer. Nude mice were used as tumor models. The results showed that IH enhanced the apoptotic effects of capecitabine and inhibited activation of the transcription factor Nf-kB. Whether administered alone or together with capecitabine, it showed anti-tumor activity and negatively regulated Nf-kB and various other oncogenic biomarkers (42).

4. CONCLUSION

Many plant-derived and natural products are being tested for their anti-cancer activities. Several of these agents are in clinical trials all over the world such as taxol, vinblastine, vincristine, etoposide etc (14). Other flavonoids that show great promise include quercitin,

hesperitin, luteolin, proanthocyanidins. Flavonoids exhibit anti-oxidant, anti-inflammatory, anti-tumor, anti-angiogenesis activity. Flavonoids modulate the biological events in cancer progression by effecting different signaling cascades. They have been shown to inhibit several key transcriptional factors and are capable of inducing apoptosis and cell death. Quercitin, a well-studied flavonoid induced G2/M phase cell cycle halt and mitochondrial programed cell death through a P-53 dependent mechanism in HeLa cells (human cervical cancer cells) (43).

Further studies and biochemical tests should be carried out to validate the relationship between the structure and function of specific flavonoids. This validation is important if flavonoids are to be used commercially for the treatment of cancer. Moreover, the lack of epidemiological studies that focus on the intake of pure doses of flavonoids, is also a major area that lacks data.

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