Review Article

Flavonoids used in the treatment of malignancy – A review

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ABSTRACT

The aim of the review is to give an insight into the role of flavonoids in the treatment of malignancy. Flavonoids (or bioflavonoids) are a class of plant and fungus secondary metabolites. Chemically, flavonoids have the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and heterocyclic ring (C). This carbon structure can be abbreviated C6-C3-C6. Other promising anticancer agents include flavopiridol, roscovitine, combretastatin A-4, betulinic acid, and silvestrol. From this list, one can well imagine the predominance of polyphenols, flavonoids and their synthetic analogs in the treatment of ovarian, breast, cervical, pancreatic, and prostate cancer. The role of flavonoids also includes the inhibition of activation of pro-carcinogens, inhibition of proliferation of cancer cells, selective death of cancer cells by apoptosis, inhibition of metastasis and angiogenesis, activation of the immune response against cancer cells, and modulation of the inflammatory cascade.

KEY WORDS: Cancer, Flavonoids, Malignancy, Proliferation and Treatment

INTRODUCTION

Cancer is one of the two leading human fatal diseases. Drug development for cancer intervention has progressed well in past decades, yet existing drugs face many limitations in applications and effectiveness and are often associated with serious of side effects, which can further deteriorate the patient's quality of life.[1] The recent development of natural product based and therapeutically sound anticancer agents have gained popularity in the field of functional foods, in which a few have demonstrated efficacy and minimal toxicity toward the prevention and treatment of carcinogenesis.[2]

Flavonoids are a group of >4000 polyphenolic compounds that occur naturally in foods of plant origin. These compounds possess a common phenyl benzopyrone structure (C6-C3-C6) and they are categorized according to the saturation level and opening of the central pyrone ring, mainly into flavones, flavanols, isoflavones, flavonols, flavanones, and flavanonols. Flavonoids have probably existed in the plant kingdom for over 1 billion years.[3] They are present in practically all-dietary plants, such as fruits and vegetables [Table 1].

Therefore, they are consumed in considerable amounts and are also heat stable. It is estimated that the human intake of all flavonoids is a few hundreds of milligrams per day.[4] Polyphenolic compounds display a remarkable spectrum of biological activities including those that might be able to influence processes that are not regulated during cancer development. These include, for example, anti-allergic, anti-inflammatory, antioxidant, antimutagenic, anticarcinogenic, and modulation of enzymatic activities.[5]

The use of flavonoids for both cancer prevention and treatment has also increased dramatically over the past decade, in general, due to the belief that such treatments are effective and much safer than alternative pharmaceutical treatments. Both of these assumptions must be considered with care.[1] Clearly, preclinical and clinical data demonstrate the potential for some botanicals and flavonoids to be beneficial against cancers.[6] Possible chemopreventive or therapeutic agents against cancer. This review article will focus on the use of flavonoids in the treatment of malignant anticancer activity of flavonoids as well as their molecular mechanisms since they are among the most promising anticancer agents.

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Table 1: Subclasses and dietary sources of flavonoids

Flavonoid sub-group	Representative flavonoids	Major food sources
Flavonols	Kaempferol, Myricetin, Quercetin, Rutin	Onions, Cherries, Apples, Broccoli, kale, tomato, Berries, Tea, Red wine, Tartary buckwheat
Flavones	Apigenin, Chrysin, Luteolin	Parsley, Thyme
Isoflavones	Daidzein, Genistein, Glycitein, Formononetin	Soya beans, Legumes
Flavonols	Catechin, Gallocatechin	Apples, Tea
Flavanones	Eriodictyol, Hesperidin, Naringenin	Oranges, Grapefruit
Flavonols	Taxifolin	Limon, Aurantium

MECHANISM OF ACTION

Flavonoids *In Vitro* Studies

Many researchers have conducted *in vitro* studies on the potential anticancer activity of flavonoids in diverse cell systems.[7] Dietary flavonoids critically influence several cellular and immune processes associated with the development and progression of cancer. It is clear that these food components possess the propensity to modulate a variety of biological events associated with cancer progression and development, such as cell proliferation, apoptosis, cell differentiation, and neovascularization.[3] *In vitro* studies have established an association between flavonoid-induced modulation of protein kinase and matrix metalloproteinase (MMP) activities with apoptosis, cellular proliferation, and tumor cell invasive behavior. Certain dietary flavonoids display *in vivo* antitumor activity and depress *in vivo* angiogenesis. It is important to understand how the flavonoids enter the cells and accumulate in certain cellular organelles and tissues.[8]

Further studies should help elucidate the various mechanisms by which flavonoids can markedly and decisively impact the activities of important mammalian enzymes such as protein kinase C (PKC), tyrosine and focal adhesion kinases, and MMPs, relevant to cancer cell proliferation and metastasis. It is necessary to perform both *in vitro* and *in vivo* assessments employing concentrations of flavonoids approximating to those in the diets and also at subpharmacological concentrations. Knowledge garnered from these studies may help in designing a potent, non-toxic, chemotherapeutic strategy against cancer. Most of the plant flavonoids occur as conjugates in the diet, with the possible exception of flavans, flavanols, and proanthocyanidins. However, typical flavonoids generally employed in cancer-related studies are the unconjugated (parent) moieties.[4] It is imperative to investigate the conjugated derivatives to assess the anticancer activity of dietary flavonoids. The introduction of certain functional groups such as glucose or sulfate to the unsubstituted flavonoids would increase their solubility during *in vitro* evaluation. Appreciation of the role of these substituents may greatly aid in the selection of potent flavonoid moieties in the chemotherapeutic evaluation, and anticancer drug design and development.[9]

Flavonoids *In Vivo* Studies

In vivo studies using animal models have suggested the protective effect of flavonoids against initiation as well as tumor progression. Animal model studies have provided the initial experimental evidence that soy can prevent breast cancer.[10] Catechins, a group of flavonoid molecules, inhibit invasion of mouse MO4 cells into embryonic chick heart fragments *in vitro*.[1] A polymethoxy flavonoid, nobiletin, from *Citrus depressa* inhibited the tumor-invasive activity of human fibrosarcoma HT-1080 cells in the Matrigel model, which was likely through suppressing the expression of MMPs and augmenting of tissue inhibitors of metalloproteinases production in tumor cells.

Human Clinical Trials with Flavonoids

Flavopiridol is a novel semisynthetic flavone analog of rohitukine, a leading anticancer compound from an Indian tree. Flavopiridol inhibits most cyclin-dependent kinases (CDKs) and displays unique anticancer properties. It is the first CDKs inhibitor to be tested in human clinical trials by Aventis Pharma (formerly Hoechst Marion Roussel) and the National Cancer Institute for the potential treatment of cancer and proliferative disorders. Initial human clinical trials with infusional flavopiridol demonstrated activity in some patients with non-Hodgkin's lymphoma, renal, prostate, colon, and gastric carcinomas.[5]

Molecular Mechanism

One important mechanism by which flavonoids may exert their effects is through their interaction with phase I metabolizing enzymes (e.g., cytochrome P450), which metabolically activate a large number of procarcinogens to reactive intermediates that can interact with cellular nucleophiles and ultimately trigger carcinogenesis.[6] Flavonoids are demonstrated to inhibit the activities of certain P450. Isozymes include CYP1A1 and CYP1A2. Thus, they are likely to have a protective role against the induction of cellular damage by the activation of carcinogens.

Anti-proliferation

Cancer prevention is generally associated with inhibition, reversion, or retardation of cellular hyperproliferation. Most flavonoids have been demonstrated to inhibit proliferation in many kinds of cultured human cancer cell lines, whereas less or no toxic to human normal cells. The molecular mechanism of anti-proliferation may involve the inhibition of the pro-oxidant process that causes tumor promotion.[3] It is generally believed that the formation of growth promoting oxidants (reactive oxygen species) is a major "catalyst" of the tumor promotion and progression stages, which follow the initiation stage (carcinogen metabolic activation to mutagens).

The pro-oxidant enzymes induced or activated by various tumor promoters, for example, phorbol, esters, include the arachidonate metabolizing enzymes, cyclooxygenases (COX), and lipoxygenases (LOX). Flavonoids are particularly effective at inhibiting xanthine oxidase, COX or LOX and therefore inhibit tumor cell proliferation. Furthermore, flavonoids are also effective at inhibiting signal transduction enzymes, for example, protein tyrosine kinase, PKC, and phosphoinositide 3-kinases, which are involved in the regulation of cell proliferation.[11]

Cell Cycle Arrest and Apoptosis

CDKs have been recognized as key regulators of cell cycle progression. Alteration and deregulation of CDK activity are pathogenic hallmarks of neoplasia. A number of cancers are associated with hyperactivation of CDKs as a result of mutation of the CDK genes or CDK inhibitor genes.[8] Therefore, inhibitors or modulators would be of interest to explore as novel therapeutic agents in cancer. Flavonoids have been shown to induce apoptosis in some cancer cell lines while sparing normal cells. The molecular mechanisms by which flavonoids induce apoptosis have not yet been clarified. Preliminary evidence from our laboratory that apoptosis induced by tartary buckwheat flavonoid in HL-60 cells may be associated with early activation of caspase-3, likely mediated through Fas and cytochrome c pathways, as well as regulated through the inactivation of nuclear factor-Kappa.

Promotion of Differentiation

Cancers arise from cells harboring mutations that relinquish the need for exogenous growth factors. Deregulation of growth control ultimately leads to the selection of clonal lines of cells that replicate at embryonic pace and yet fail to respond to differentiation and maturation signals.[5]

Inducers of terminal differentiation have been used as novel therapies for the prevention and therapy of cancer. Induction of terminal differentiation by flavonoids may lead to the eventual elimination of tumorigenic cells and rebalance of normal cellular homeostasis. Thus, these compounds could be developed into promising anticancer agents.[2]

Antioxidative Activity

Dietary flavonoids are natural antioxidants. They may be against cancer through the limit of damaging oxidative reactions in cells, which may predispose to the development of cancer. Oxygen-derived free radicals appear to possess the propensity to initiate as well as to promote carcinogenesis.[1] Lipid peroxidation products originating from dying cells could also exert a cancer promotional effect. Oxidation of DNA is likely to be an important cause of mutation that potentially can be reduced by antioxidants.[12-14]

Inhibition of Angiogenic Process

Flavonoids are known as angiogenesis inhibitors derived from natural sources. The abilities of particular flavonoids to block solid tumor growth may be due to their inhibition of the neoangiogenic process.[15] Angiogenesis is a strictly controlled process in the healthy adult human body, which is regulated by a variety of endogenous angiogenic and angiostatic factors. However, pathological angiogenesis can occur in cancer. When deprived of proper vascularization, the high proliferation rate in the tumor would be balanced by cell death due to the lack of diffusion of nutrients and oxygen.[3] Angiogenesis inhibitors such ass flavonoids are able to interfere with various steps of angiogenesis such as basement destruction of blood vessels, proliferation, and migration of endothelial cells, or the lumen formation. Therefore, these compounds may have potential for the treatment of solid tumors.[16,17]

Modulation of Multidrug Resistance

Multidrug resistance due to P-glycoprotein or multidrug resistance-associated protein is a serious impediment to successful chemotherapy of cancer.[5] Much effort has been spent to modulate multidrug resistance in the different species using specific inhibitors, but generally with little success due to additional cellular targets and/or extrusion of the potential inhibitors.

CONCLUSION

Flavonoids greatly influence the cascade of immunological events associated with the development and progression of cancer. One has to understand the mechanism of how these flavonoids get accumulated in cellular organelles and tissues once they enter inside.[5] Flavonoids have the potential of modulating many biological events in cancer such as apoptosis, vascularization, cell differentiation,

and cell proliferation. A strong correlation persists between flavonoid-induced modulations of kinases with apoptosis, cell proliferation, and tumor cell invasive behavior *in vitro*.[3] Furthermore, some of the dietary flavonoids have been known to display *in vivo* antitumor activity and repress *in vivo* angiogenesis. The cross talk between flavonoids and the key enzymes related to neoplastic cells and metastasis has to be understood *in vitro* and *in vivo* as well, providing new insights for fighting against cancer.

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