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A REVIEW OF QUERCETIN: ANTIOXIDANT AND ANTICANCER PROPERTIES

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ABSTRACT

Quercetin is found in various food products and plants, including fruits, seeds, vegetables, tea, coffee, bracken fern, and natural dyes. Quercetin is one of the natural antioxidant; its anticancer properties have been proved by *in vivo* and *in vitro* experiments. A number of its actions make it a potential anti-cancer agent. Several studies demonstrated that quercetin has a significant role in inhibition of breast, colon, prostate, ovary, endometrium, and lung tumor cancer cells. Present review is covering brief description of chemical and physical properties, ADME, Antioxidant and anti-cancer activity with mechanisms of action of quercetin.

KEYWORDS

Quercetin, ADME of quercetin, Antioxidant, Anticancer.

INTRODUCTION

Quercetin (3,3',4',5,7-pentahydroxyflavone) belongs to an extensive class of polyphenolic flavonoid compounds almost ubiquitous in plants and plant food sources. Frequently quercetin occurs as glycosides (sugar derivatives); e.g., rutin in which the hydrogen of the R-4 hydroxyl group is replaced by a disaccharide. Quercetin is termed the aglycone, or sugarless form of rutin. Two extensive volumes, the proceedings of major meetings on plant

flavonoids, presented much of the biological and medical data about quercetin in 1985 and 1987.[1,2]

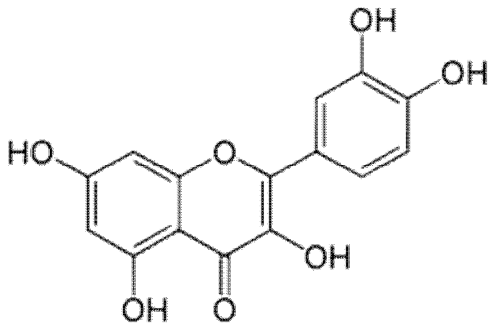

Fig-1: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one

PROPERTIES, STRUCTURE, PRODUCTION AND OCCURRENCE

Quercetin is a yellow, crystalline solid with a bitter taste, which is insoluble in water, slightly soluble in alcohol, and soluble in glacial acetic acid and aqueous alkaline solutions.[3,4] Quercetin is a member of a group of naturally occurring compounds, the flavonoids, which have a common flavone nucleus composed of two benzene rings linked through a heterocyclic pyrone ring (fig. 1). Animals are unable to synthesize the flavones nucleus; thus, flavonoids are found exclusively in the plant kingdom. Quercetin and more than 2,000 other flavonoids occur as condensation products of p-glycosides.[5,6,7,8]. Quercetin is found in various food products and plants, including fruits, seeds, vegetables, tea, coffee, bracken fern, and natural dyes. Quercetin is usually obtained from the hydrolysis of rutin (quercetin-3-rutinoside), a naturally occurring flavonoid glycoside[9] although it can also be synthesized.[10]

Table 1. Quercetin Content in Selected Foods

Food Source	Quercetin Content (mg/100g)
Apple with skin	4.42
Broccoli, Raw	3.21
Raw Onions	13.27
Spinach, raw	4.28
Black Tea Leaves, dry	204.66
Green Tea Leaves, dry	255.55
Red Wine	0.84

BIOSYNTHESIS OF QUERCETIN

The biosynthesis of phytochemicals, like flavonoids, is a defensive response of plants to their environment. Flavonoids often function as protection from ultraviolet sunlight and lipid peroxidation.[11] Mohle *et al*. (1985) demonstrated that when dill cell cultures were subjected to UV-B radiation, the predominant flavonoid synthesized was quercetin-3-O-β-glucuronide. They proposed that the biosynthesis of flavonoids is regulated by ultraviolet light and their accumulation acts as a defense.[12]

ABSORPTION, METABOLISM, DISTRIBUTION AND EXCRETION

Quercetin glycosides are relatively poorly absorbed by the small intestine. Micro flora of the lower bowel hydrolyze the flavonide-glycoside to quercetin and the sugar, and quercetin is then absorbed into the enterohepatic system.[7,13,14] After oral administration of quercetin to rabbits[15] or rats[16] **,** three metabolites of quercetin were identified in the urine: 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxy phenylacetic acid (homovanillic acid), and m-hydroxyphenylacetic acid. These metabolites are thought to be formed in the liver after fusion of the ring. When Brown and Griffiths (1983) administered quercetin to rats by intraperitoneal injection, they identified the 3'o-methyl-ether of quercetin (isorhamnetin) as a metabolite in bile.[17].

The distribution, metabolism and excretion of 4-[^{14}C] quercetin in male ACI rats were studied by autoradiography and quantitation of radioactivity.[18] After oral administration, 20% of the dose was absorbed from the digestive tract and then excreted into the bile and urine within 48 hours as glucuronide or sulfate conjugates. Autoradiographic analysis of a rat 3 hours after receiving a single 2.3 mg/kg oral dose of quercetin showed that most of the radioactivity remained in the digestive tract with low levels seen in the blood liver, kidney, lung, and rib. In five human volunteers, no quercetin was detected in the plasma or urine after oral administration of 4g quercetin.[19]

ANTIOXIDANT PROPERTIES

Quercetin is considered to be a strong antioxidant due to its ability to scavenge free radicals and bind transition metal ions. These properties of quercetin allow it to inhibit lipid peroxidation[20,21] Lipid peroxidation is the process by which unsaturated fatty acids are converted to free radicals via the abstraction of hydrogen.[22] Lipid peroxidation can create deleterious effects throughout the body, such as cardiovascular and neurodegenerative

diseases; however, it can be terminated by antioxidants, like quercetin, which interfere by reacting with the radicals formed.[20, 23, 24] Quercetin can also reduce inflammation by scavenging free radicals. Free radicals can activate transcription factors that generate pro-inflammatory cytokines, which are often found, elevated in patients that suffer from chronic inflammatory diseases.[25]

MECHANISM OF ACTION

Anti-oxidative action

Living organisms have developed antioxidant line of defense systems include enzymatic and non-enzymatic antioxidants that keep in check ROS/RNS level and repair oxidative cellular damage. The major enzymes, constituting the first line of defence, directly involved in the neutralization of ROS/RNS are: superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). The second line of defence is represented by radical scavenging antioxidants such as vitamin C, vitamin A and plant phytochemicals including quercetin that inhibit the oxidation chain initiation and prevent chain propagation .This may also include the termination of a chain by the reaction of two radicals.[26]

Direct radical scavenging action

Quercetin acting as free radical scavengers was shown to exert a protective effect in reperfusion ischemic tissue damage.[27] Quercetin prevents free radical induced tissue injury by various ways. One way is the direct scavenging of free radicals. By scavenging free radicals, Flavonoid; particularly Quercetin can inhibit LDL oxidation in vitro.[28] This action protects against atherosclerosis.

Inducible nitric oxide synthase Inhibitory action

Quercetin results in a reduction in ischemia-reperfusion injury by interfering with inducible nitric oxide synthase activity.[29] The higher concentration of nitric oxide produced by inducible nitric oxide synthase in macrophages can result in oxidative damage. In these circumstances the activated macrophages greatly increase their simultaneous production of both nitric oxide and superoxide anions. Nitric oxide reacts with free radicals, thereby producing high damaging peroxynitrite. Peroxynitrite can directly oxidize LDLs resulting in irreversible damage to cell membranes. Quercetin causes scavenging of free radicals; therefore can no longer react with nitric oxide, resulting in less damage.[30] Nitric oxide interestingly can be viewed as radical itself and can directly be scavenged by Flavonoids.[31]

Xanthine oxidase inhibitory action

The xanthine oxidase pathway has been implicated as an important route in the oxidative injury to the tissues especially after ischemia-reperfusion.[32] Both xanthine dehydrogenase and xanthine oxidase are involved in the metabolism of xanthine to uric acid. Quercetin seems to inhibit xanthine oxidase activity thereby resulting in decreased oxidative injury.[33]

Modulation of gene expression

Tumor necrosis factor alpha (TNF-α) is one of the major proinflammatory cytokines involved in the pathogenesis of chronic inflammatory diseases and is modulated by oxidative stress.[34] Quercetin significantly inhibited TNF-α production and gene expression in a dose-dependent manner. A decrease in endogenous TNF-α production in the presence of quercetin indicates that flavonoids have the capacity to modulate the immune response and have potential anti-inflammatory activity.[35] Quercetin-induced suppression of TNF-α can result in the stimulation of anti-inflammatory cytokines via inhibiting the activation of NF-κβ, and therefore, one can anticipate that quercetin could be widely used as an anti-TNF-α therapy.

Interaction with other enzyme systems

Calmodulin transports calcium ion across cellular membranes, initiating numerous cellular process. Quercetin appears to act as calmodulin antagonist. Through this mechanism, Quercetin functions at cell membrane level with a membrane stabilizing action.[36] Quercetin inhibits calmodulin dependent enzyme present at cell membrane such as ATPases and phospholipases thereby influencing membrane permeability.[37] A number of investigations have demonstrated the ability of Quercetin, to reduce histamine secretion from mast cells in various tissues and also from basophils.[38] The enzyme inhibitory action of Quercetin extends to phospholipases which catalyses the release of arachidonic acid from phospholipids stored in cell membranes. Arachidonic acid serves as a key substrate for substances such as thromboxane, inflammatory prostaglandins and leukotrienes. In addition, Quercetin also inhibits the enzymes cyclooxygenase and Lipooxygenase which catalyses the conversion of arachidonic acid to its metabolites.[39] Quercetin also chelates ions of transition metals such as iron which can initiate the formation of oxygen free radicals.[40] Direct inhibition of lipid peroxidation is another protective measures.[41]

ANTI-CANCER EFFECTS OF QUERCETIN

Oxidative DNA damage is a known risk factor of cancer. Antioxidants, such as quercetin, are thought to play an important role in protecting cells from oxidative stress induced by reactive oxygen species. It is increasingly proposed that reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a key role in human cancer development, especially as evidence is growing that antioxidants may prevent or delay the onset of some types of cancer. ROS is a collective term often used by biologists to include oxygen radicals, superoxide, hydroxyl, peroxyl and alkoxyl and certain nonradicals that are either oxidizing agents.[42]

ROS\RNS can have the following effects.

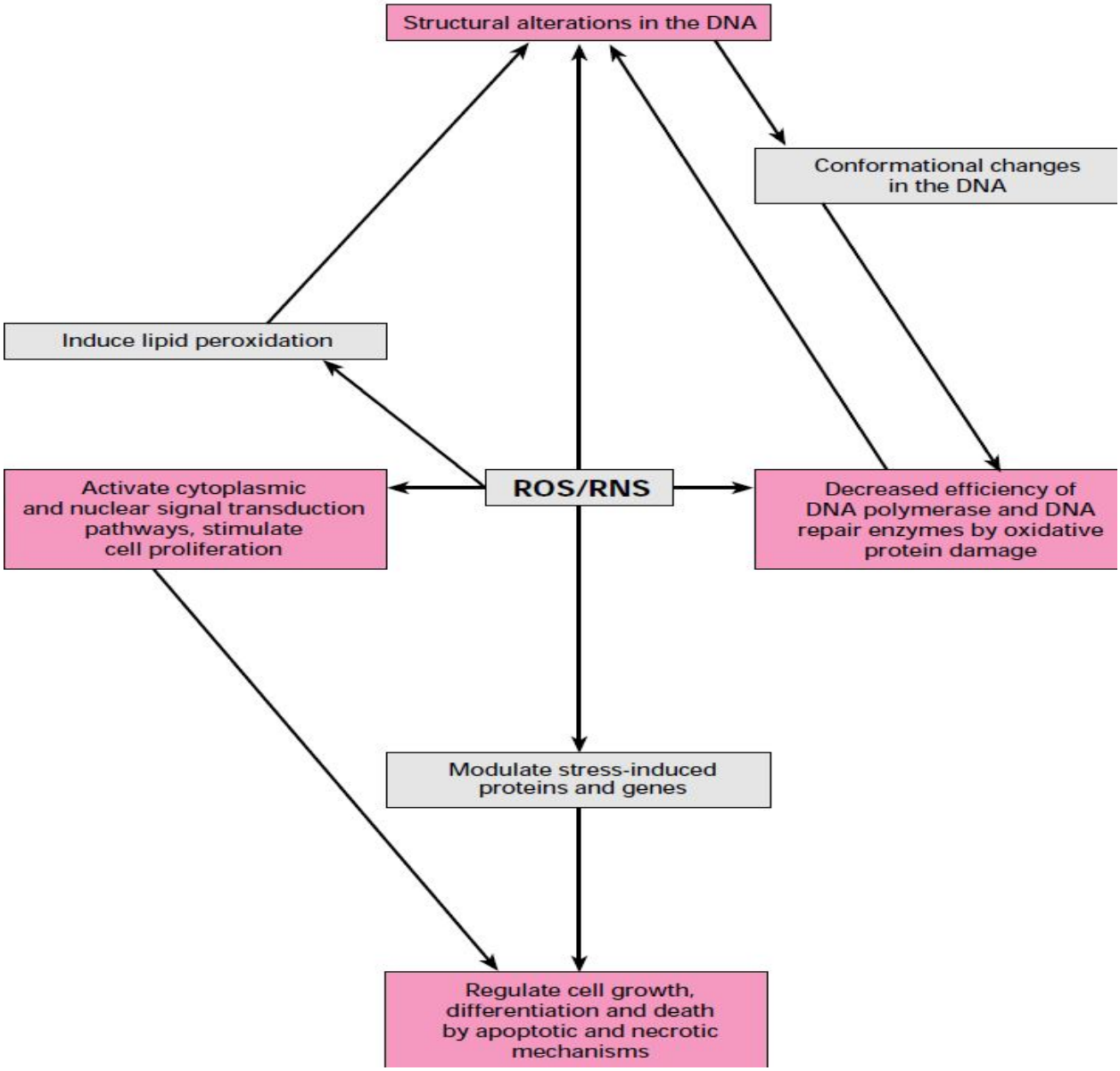

Fig. 2: Role of ROS/RNS in cancer development

Major Molecular Mechanisms of Action of Quercetin

Down regulation of mutant P53 protein

Quercetin (248 microM) was found to down regulate expression of mutant p53 protein to nearly undetectable levels in human breast cancer cell lines. Lower concentrations gave less reduction.[43]The inhibition of expression of p53 was found to arrest the cells in the G2-M phase of the cell cycle. This down regulation was found to be much less in cells with an intact p53 gene.[44] Mutations of p53 are among the most common genetic abnormalities in human cancers.[45]

G_1 phase arrest

The G_1 checkpoint controlled by the p53 gene is a major site for the control of cellular proliferation. Quercetin has been found to arrest human leukemic T-cells in the late G_1 phase of the cell cycle. At a 70 microM concentration, 64 percent of cells were in G_0 G_1 compared with 50 percent in control cultures.[46] This G_1 arrest was also seen in gastric cancer cells treated with quercetin. Concentrations of 70 microM were found to reduce DNA replication to 14 percent of control values, leading to a delay of cell division. At the 70 microM concentration, quercetin was found to reduce growth of cell cultures to 10 percent of that seen in controls.[47]

Inhibition of tyrosine kinase

Tyrosine kinases are a family of proteins located in or near the cell membrane involved in the transduction of growth factor signals to the nucleus. In patients with advanced cancers, intravenous administration of quercetin (dosages 60-1700 mg/m^2) led to inhibition of lymphocyte tyrosine kinase at one hour in nine of eleven cases.[48] *In vitro* experiments have confirmed these results, both in non-malignant cells[49]and in rat mammary tumor cells.[50] Tyrosine kinase expression is thought to be involved in oncogenesis via an ability to override normal regulatory growth control.[51]

Inhibition of heat shock proteins

Quercetin has been found to inhibit production of heat shock proteins in several malignant cell lines, including breast cancer,[52] leukemia,[53] and colon cancer.[54] Heat shock proteins form a complex with mutant p53, which allows tumor cells to bypass normal mechanisms of cell cycle arrest. Heat shock proteins also allow for improved cancer cell survival under different bodily stresses (low circulation, fever, etc.), and are associated with shorter disease free survival[55] and chemotherapy drug resistance[56] in breast cancer.

Inhibition of expression of ras proteins

Quercetin (10 microM) has been found to inhibit the expression of the p21-ras oncogene in cultured colon cancer cell lines.[57] Mutations in this important gene usually impair cellular GTP-ase, which has the effect of continual activation of the signal for DNA replication. Mutations of ras proto-oncogenes are found in over 50 percent of colon cancers, as well as many other tumor types.[58]

Estrogen receptor binding capacity

The role of the type II estrogen receptor (ER II) *in vivo* is not entirely clear. Although the ER II does bind estrogen *in vitro*, the low affinity makes it likely these sites are occupied by another ligand. One possible explanation offered is that ER II sites are intended for a flavonoid-like substance with growth inhibitory capability.[59] Quercetin has been shown to induce ER II expression in both type I estrogen receptor positive (ER+) and type I estrogen receptor negative (ER-) human breast cancer cells. The induction of ER II allows for greater growth inhibition of ER- cells with quercetin treatment.[60] In cultured human melanoma cells, quercetin was found to bind ER II sites with an affinity similar to tamoxifen and diethylstilbestrol. ER II sites are found in normal tissue and on many different human tumor types, including breast, ovarian, colorectal, meningeal, leukemic, and melanoma. ER II expression is independent of estrogen-receptor (type I) status.[61]

***IN VITRO* STUDIES OF QUERCETIN**

In vitro experiments which have studied the malignant cell culture growth inhibition of quercetin, each assay showed quercetin to significantly inhibit growth. The quercetin concentration at which tumor cell growth was inhibited by 50 percent inhibitory concentration (IC50) ranged from 7 nM to just over 100 microM.[19]. Scientists of the Henan University, China, concluded that quercetin could improve therapeutic index of doxorubicin, a drug used in cancer chemotherapy, by its opposing effects on hypoxia-inducible factor-1 alpha in tumor and normal cells. *In-vitro* test showed that quercetin reversed cell resistance to doxorubicin under hypoxia and protected spleen cells against cytotoxicity. Doxorubicin is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma and soft tissue sarcomas. However, treatment with doxorubicin has many side effects, such as a decrease in white blood cells, hair loss, cardiotoxicity and immune suppression. The scientists tested the effect of quercetin on the therapeutic index of doxorubicin in breast tumor cells and spleen cells. [62]

IN VIVO STUDIES OF QUERCETIN

Some animal studies have looked at the anti-tumor properties of quercetin. In one study, mice were inoculated with ascites tumor cells and then treated intraperitoneally with either quercetin or its glycoside, rutin. Animals treated daily with 40 mg/kg quercetin had a 20-percent increase in life span, while those treated with 160 mg/kg rutin had a 50% increase in life span. If the rutin treatment was split into two 80 mg/kg treatments per day, the increase in life span became 94%.[63]

Another animal study looked at the effect of quercetin on mice bearing abdominal tumors derived from a human pharyngeal squamous cell carcinoma line. The mice were given a daily intraperitoneal injection of quercetin. All doses tested (20, 200, 400, and 800 mg/kg) demonstrated significant inhibition of tumor growth.[64]

In-vivo tests with mouse with 4T1 breast cancer cells showed that quercetin suppressed tumor growth and prolonged survival. Quercetin enhanced therapeutic efficacy of doxorubicin and reduced toxic side effects. Another Chinese study by Shan and Wang of the Hebei Medical University, investigated the effects of quercetin on the growth of the colon carcinoma cells and the regulation effect of quercetin on the Wnt/beta-catenin signaling pathway.[65]

Quercetin may also have anti-mutagenic properties. A group of scientists lead by Gupta of the National Institute of Pharmaceutical Education and Research, Mohali,India, found that quercetin may be a potential candidate as chemoprotectant. They came to this conclusion after treating rats, which were exposed to the hepatocarcinogen diethylnitrosamine (found in tobacco smoke and processed meat) with quercetin. The hepatocarcinogen increased malondialdehyde and decreased glutathione levels in the liver, and increased plasma levels of aspartate transaminase and alanine transaminase. Treatment of the rats with quercetin restored these levels and also reduced diethylnitrosamine induced DNA damage and apoptosis.[66]

CONCLUSION

Quercetin is the subject of intense research on the basis of its antioxidant, anti-inflammatory and anti-cancer activities. Quercetin and other flavonoids, have the structure to act as powerful antioxidants1` and have often proven so *in vitro*. Quercetin, being a major constituent of the flavonoid intake, could be a key in fighting several chronic degenerative diseases. In vitro experiments show that quercetin may be effective in treatment of various types of cancer and it may be combined with other anticancer drugs to reduce their doses and

subsequently their side effects. However, the degree to which quercetin is absorbed, and thus its bioavailability, leaves some doubt as to whether quercetin can exert an antioxidant effect *in vivo*. The antioxidant activity of quercetin's metabolites and the pathways of metabolic conversion need to be identified and evaluated to accurately determine the effect quercetin has *in vivo* and its effectiveness in preventing diseases arising from oxidative damage.

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