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A REVIEW

PHYSIOLOGICAL AND MEDICAL EFFECTS OF PLANT FLAVONOID QUERCETIN

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ABSTRACT

Flavonoid compounds in vegetable-based diets bring a significant contribution to the role of fruits and vegetables as health-promoting foods. This review summarizes the available data concerning physiological and therapeutical effect of plan flavonoid quercetin. Quercetin has a number of beneficial influence on health because of their antioxidant, anti-inflammatory, anti-proliferative, anti-carcinogenic and anti-diabetes properties. Effects of quercetin have been explained by its interference with cellular enzymes, receptors, transporters and signal transduction systems. Despite the available data reviewed here, the targets, effects, absorption, metabolism and areas of practical application of quercetin are still poorly understood, therefore further studies in this areas are required.

Keywords: quercetin, oxidation, proliferation, inflammation, cancer, cardiovascular diseases

INTRODUCTION

Recent studies of natural substances with pharmacological activity have become an emerging trend in nutritional and pharmacologic research (**White *et al.*, 2007**). The age-old system of herbal medicine remains popular in medicine and nutrition for its long-lasting curative effect, easy availability, natural way of healing, and less side-effects, moreover due to these features, today herbal medicine is gaining more importance, popularity and expansion throughout the world (**Rai, 1994**).

In plants, flavonoids serve as protectors against a wide variety of environmental stresses, while in humans they appear to function as biological response modifiers (**Percival, 1998**). Flavonoid quercetin appears to have many beneficial effects on human health, including cardiovascular protection, anticancer activity, antioxidant, anti-diabetic, antiartherosclerotic and anti-inflammatory effects. Because of its putative beneficial effects in the prevention and treatment of disease, quercetin is used as a food supplement and a promising ingredient of so-called functional food (**Verhoeyen *et al.*, 2002**).

RESULTS AND DISCUSSION

Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) (Fig.1) is one of the most known flavonoid belonging to a group of plant-derived nonsteroidal compounds known as phytoestrogen (**Moutsatsou, 2007**). It is widely distributed in fruits and vegetables, for example in apple, blueberries, broccoli, grape, leek, lettuce, onion and tomato (**Chen and Zhou, 2010**) (see table 1). This bioflavonoid we can also find in tea, wine (**Middleton, 1998**) and healing herbs (**Yoshikawa *et al.*, 1997**).

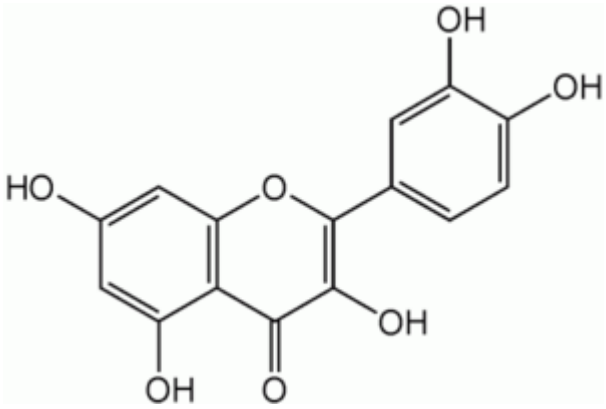


Figure 1 Molecular structure of quercetin (**Moskuag *et al.*, 2004**)

Quercetin in plants is mainly present in its glykosylated forms, such as quercitrin (3-rhamnosyl-quercetin) or rutoside (3-rhamnosy-glucosyl quercetin) (**Hertog *et al.*, 1993**). The absorption of quercetin in organism is considerably enhanced by its conjugation with a sugar group (**Boots *et al.*, 2008**). Quercetin aglycone and its glucosides are absorbed better than quercetin administred in nonglucosic forms (**Olthof *et al.*, 2000**). In plants, quercetin occurs almost exclusively bound to one or more sugar molecules, so-called quercetin-ß-glycosides. The dominant type of glykoside varies between plants. Apple, for example, contains predominantly galactosides, rhamnosides and arabinosides, while onion contains mainly glukosides (**Hollman and Arts, 2000**). Contents of quercetin in selected foods are shown in table 1.

Table 1 Amount of quercetin in selected food (**Mangels et al., 1993**).

Plant	Quercetin concentration (mg/100g)
Broccoli, Raw	2.8
Carrots, Raw	0,4
Celery, Raw	3,5
Cocoa powder	20,1
Cranberries, Raw	14,0
Lettuce, Raw	2,0
Kale, Raw	5,1
Lingonberries, Raw	11,3
Onion, Raw	22,6
Tomatoes, Red ripe	0,5

Quercetin effects

It has a broad range of activities within cells (**Bjeldanes and Chang, 1997**). Mechanism of quercetin effects on some physiological processes and dysfunctions is in **scheme 1**. Quercetin is one of the most prominent dietary antioxidant with radical scavenging and chelating activity (**Boots *et al.*, 2008**). Within the flavonoid family, it is the most potent scavenger of ROS (reactive oxygen species), including O_2 (**Nickel *et al.*, 2011**) and RNS (reactive nitrogen species) like NO (**Haenen and Bast, 1999**) and $ONOO^-$ (**Heijnen *et al.*,**

2001). Quercetin is also a protector of low-density lipoprotein (LDL) from oxidation (**Leckey *et al.,* 2010**), lipid peroxidation (**Kleemann *et al.,* 2011**) and it prevents redox imbalance in cells (**Kostyuk *et al.,* 2011**).

These anti-oxidative capacities of quercetin are attributed to the presence of two pharmacophores within the molecule that have the optimal configuration for free radical scavenging: the catechol group and the -OH group (**Heijnen *et al.,* 2002**).

The mechanisms responsible for the cancer-preventive effects of quercetin are mediated by its anti-oxidative activity by removing free radicals (**Bors and Saran, 1987**), inhibition of enzymes that activate carcinogenes, modification of signal transduction pathways, and ineractions with estrogen receptors (**Choi *et al.,* 2001**), transcription factors (**Chen *et al.,* 2005**) and other proteins (**Murakami *et al.,* 2008**). Anti-cancer activity of quercetin including the induction of apoptosis (**Shen *et al.,* 1999**), inhibition of proliferation (**Zhong *et al.,* 2006; Daker *et al.,* 2012**), fatty acid synthase (FAS) (**Brusselmans *et al.,* 2005**), decreasing metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9) expression (**Vijayababu *et al.,* 2006**) was previously studied.

Quercetin has been shown to exert growth inhibitory activity on human breast (**Scambia *et al.,* 1993; Singhal *et al.,* 1995**), ovarian (**Scambia *et al.,* 1990**), leukaemic (**Larocca *et al.,* 1990**), colon (**Shiu-Ming Kuo, 1996**) and nasopharyngeal carcinoma cells cancer cells (**Zhong *et al.,* 2008**).

Via regulation releasing NO, cytokines- IL-6 (interleukin-6), tumor necroting factor (TNF) (**Kim *et al.,* 2007**), (IL)-1ß and IL-8 quercetin has anti-inflammatory effect. TNF-α, IL-1ß and IL-6 participate in the initiation of inflammation and acute phase reactions, while IL-8 is a potent neutrophil chemotactic molecule involved in inflammation. Quercetin decreased the gene expression and production IL-1ß, IL-6 and IL-8 and has inhibitory effect on cytokine expression nuclear factor (NF)-κB and p38 mitogen-activated protein kinase (MAPK) dependent pathways (**Min *et al.,* 2007**).

Quercetin by abolishing the NF-κB signal transduction pathway may block the production of early diabetes tissue injury and in the evolution of late complications. Treatment with quercetin has protective effect in diabetes by decreasing oxidative stress, NF-κB activation, and iNOS overexpression in liver (**Dias *et al.,* 2005**). Quercetin significantly inhibited basal and oxidized LDL (oxd-LDL)-stimulated MMP-1 expression contributes to plaque destabilization by blocking the extracellular signal-regulated kinase (ERK) (**Song *et al.,* 2001**). Via inhibiting inflammation-producing enzymes and subsequent inhibition of

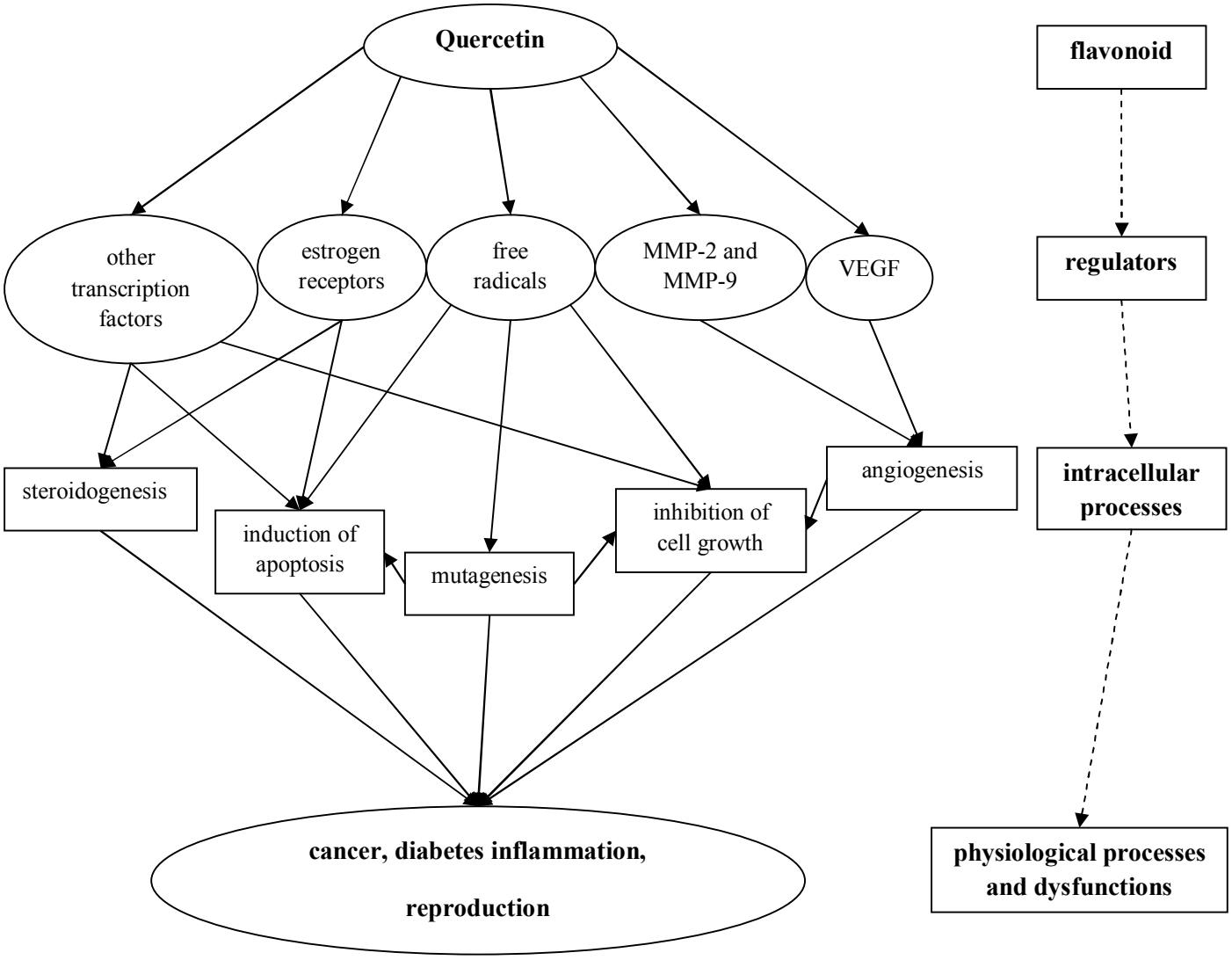
inflammatory mediators quercetin protects pancreatic ß-cells from type 2 diabetes (**Kim *et al.*, 1998**). These results suggest that quercetin exert beneficial antidiabetic effects.

Anti-atherosclerosis protection of quercetin is mediated through a combination of effects, including the inhibition of inflammation, the stimulation of NO, and the induction of heme oxygenase-1 (**Loke *et al.*, 2010**).

Quercetin was found to inhibit several important steps of angiogenesis including proliferation, migration, tube formation of human microvascular dermal endothelial cells in a dose-dependent manner (**Tan *et al.* 2003**), restraining phosphorylation of vascular endothelial growth factor receptor (VEGFR2) tyrosine kinase and supressing VEGFR2-mediated signaling pathway (**Lin *et al.*, 2012**). It has been proven that quercetin treatment significantly decreases (VEGF) secretion by myeloblastic leukemia cells NB4 in vitro (**Zhong *et al.*, 2006**).

Quercetin can modulate ovarian functions, interfering with cell steroidogenic activity and angiogenic activity. The negative effect on progesteron (P4) production could result from an inhibition of steroidogenic enzymes (**Rise *et al.*, 2006**). Quercetin has ability to promote release of P4, which has antiproliferative and proapoptotic activity. Physiological influence of curcumin on ovarian granulosa cells could be important practical viewpoint. It is not to be excluded, that quercetin may used in the regulation of reproductive function (ovarian folliculogenesis, oocyte maturation and ovulation), including fertility and treatment of reproductive disorders. As for estrogen (E2) production, quercetin has a dose-dependent biphasion activity. Follicular development is strictly dependent on the angiogenic process, driven mainly by VEGF,. Quercetin dispalyed a strong inhibitory effect on VEGF (**Hung, 2007**) and inhibit proliferation, migration, and differentiation of endothelial cells in process of angiogenesis. This finding acquires particular relevance, since it is possible to speculate a possible negative influence of quercetin on ovarian physiology. These data suggest that quercetin represents a potential modulator of ovarian functions (**Santini *et al.*, 2009**).

Via estrogen receptors quercetin induced cell cycle arrest and apoptosis in human breast cancer MCF-7 cells (**Choi *et al.*, 2001**). Antiproliferative activity of quercetin in human ovarian cancer cells is mediated by its interaction with type II oestrogen binding site (type II EBS) (**Markaverich *et al.*, 1988**). Quercetin might exert a protective effect against post-menopausal bone loss. Directly induce apoptosis of mature osteoclasts in dose-range effective for inhibiting bone resorption (**Wattel *et al.*, 2003**).



Scheme 1 Mechanism of quercetin effects on some physiological processes and dysfunctions

CONCLUSION

Given the many positive effects of flavonoids on human health, there are increasing interesting foods and beverages that contain quercetin. Nevertheless, its overall biological impact remains controversial, mostly because of limited information about its bioavailability, endogenous dynamics, and the relative contribution of different types of conjugates in humans and animals.

Quercetin is an important dietary flavonoid with putative beneficial effects, including anti-cancer, antioxidant, anti-diabetic, anti-angiogenic, anti-inflammatory activity and protective effect against post-menopausal bone loss. In the reproductive track quercetin may

mimic or antagonize the action of estrogenous actions. We suppose that quercetin is a potential modulator of ovarian functions, but further studies are needed to better define the effects of quercetin on reproductive physiology. Nevertheless, we assume quercetin can use as therapeutic agent in agriculture for higher quality of animal reproduction and for substitute synthetic substances natural in medicine. The bioactivity of quercetin depends on its bioavailability, which varies between foods widely. Although data from several studies of quercetin activity were obtained, several questions remain still unknown.

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