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Plant derived secondary metabolites in cancer therapy: actions, applications, and future prospective of dietaryflavonol (quercetin)

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ABSTRACT

Higher plants are prominent sources for several bioactive chemical constituents (secondary metabolites) who include photochemical, flavoring agents, fragrant molecules, and food additives. According to WHO estimates, it has been reported that more than 80% of population in developing countries prefer these natural bioactive active compounds for their primary health requirement. At present, conventional chemotherapy is constrained due to the nonselective toxicity to human organs and their usage is limited now a days. In a recent survey, more than 60% of cancer patients have been preferring adjuvant phototherapy along with chemotherapy. Thus, photochemical are being widely used as anticancer agents to target specific pathological pathways underlying cancer with low toxic profiles and side effects. These photochemical are cost-effective and easily accessible to the public to treat cancer diseases. These bioactive photochemical are meticulously belongs to secondary metabolites such as alkaloids, flavonoids, polyphenols. Among them, the flavonoids are polyphenolic substances, which are found in all parts of the plant such as flowers, fruits, leaves, roots, seeds, and bark. They possess high medicinal properties like being anti-cancer, anti-hypertensive, anti-inflammatory, anti-obesity, anti-malarial, antioxidant agents. Quercetin is major flavones associated with a profound antioxidant and medicinal property to prevent the oxidation of lipids in vitro and in vivo, and also exhibits direct proapoptotic effects on tumor cells. This compound has proven efficacy in targeting several cancer cells of breast, colon, prostate, ovarian, and lung tumor in vitro. The present review focuses on the effect of quercetin in cancer therapy.

Keywords: Quercetin, cancer, antioxidant, anticancer activity.

1. INTRODUCTION

Cancer is a rigorous metabolic syndrome, which also causes death [1-2]. In 2017, USA alone reported around 600920 cancer deaths [3]. A normal cell can turn malignant due to genetic instabilities and alterations within cells and tissues. These genetic instabilities comprise mutations in DNA repair genes (p21, p22, p27, p51, p53 and toolbox for DNA), tumor suppressor genes (p53, NF1, NF2, RB and biological breaks), ontogenesis [MYC, RAF, Bcl-2, RAS (biological accelerators)] and genes involved in cell growth metabolism. Both external factors and internal factors can cause cancer 4].

Chemotherapy is one of the widely used treatments for cancer [5]. Most of the chemotherapeutic agents can destroy cancer cells via the production of reactive oxygen species and the induction of either apoptosis or necrosis of tumorouscells[6-9].The purpose of chemotherapy is to eradicate the tumor cells, but along with this, diverse ranges of normal cell types are also affected leading to many adverse side effects in multiple organ systems and also leads to major clinical problems, whereas the toxicity often restricts the effectiveness of anticancer agents. Fatigue, nausea, vomiting, malaise, diarrhoea, mucositis, pain, rashes, infections, and headaches are most common acute problems (side effects) in cancer patients who have undergonecytotoxic therapy [9-12], and also these cytotoxic agents destroys the haematopoietic cells, intestinal epithelial cells, and hair matrix keratinocytes [10]. At present, conventional chemotherapy is constrained due to the no selective toxicity to human organs and their usage is limited now a days. In a recent survey, more than 60% of cancer patients have been preferring adjuvant phototherapy along with chemotherapy.

Higher plants are prominent sources for several bioactive chemical constituents (secondary metabolites) who include photochemical, flavouring agents, fragrant molecules, and food additives. In that, photochemical are predominant dietary agents that influence various aspects of chemotherapy treatment and their involvement in the cure of cancer patients is enormously indicated and needful. Different kinds of photochemical constituents can improve efficiency of chemotherapeutic agents, decreases the resistance of chemotherapeutic drugs, lower and alleviate the adverse side effects of chemotherapy. According to WHO estimates, it has been reported that more than 80% of population in developing countries prefer these natural bioactive active compounds for their primary health requirement. Thus, photochemical are being widely used as anticancer agents to target specific pathological pathways underlying cancer with low toxic profiles and side effects. These photochemical are cost-effective and easily accessible to the public to treat cancer. These bioactive photochemical meticulously belong to secondary metabolites such as alkaloids, flavonoids, polyphones.

Flavonoids are polyphenolic substances which are found in all parts of the plant such as flowers, fruits, leaves, roots, seeds, and bark. They are also richly present in foods and plant beverages, like, tea, wine and coco [13]; for this reason, they are also termed as dietary flavonoids. They are formed in plants, by phenylalanine, tyrosine and malonate (phenylproponaid pathway). Animals are unable to manufacture flavones nucleus; flavonoids are exclusively present in plant kingdom. Flavonoid participate sin several biological activities in microbes, plants and animals. Flavonoids are responsible for pigmentation and aroma of flowers, attracting pollinators to fruits, thereby resulting in fruit dispersion as well as spore germination. It also aids the growth and development of seedlings. In animals, they have huge amount of medicinal properties like being anti-cancer, anti-hypertensive, anti-inflammatory, anti-obesity, anti-malarial, hepato-protective, and antioxidant agents [14]. Flavonoids are sub grouped into several classes that includes flavones, flavonones, and flavones, is flavones, flavones and anthocyanins.

In flavonoids, flavones are an important sub class, which contains ketene group in their structure. The flavones are originator molecules of proanthocyanins. Quercetin, kaempferol, myricetin and fisting are the important flavones in flavonoid group. The rich source of flavones includes onions, kale, lettuce, tomatoes, apples, grapes and berries. These compounds have high medicinal properties such as being antioxidant, and anticancer.

QUERCETIN

Quercetin, (3, 3', 4', 5, 7-pentahydroxyl-flavone) (Fig. 1) is a major flavonol found in various fruits and vegetables (Table 1) such as onions, apples, chokeberries, cranberries, and lingonberries [15] and also associated with a profound antioxidant and medicinal property to prevent the oxidation of lipids in vitro and in vivo, and also exhibits direct proapoptotic effects on

tumor cells. This compound has proven efficacy in targeting several cancer cells of breast, colon, prostate, ovarian, and lung tumor *in vitro*[16].

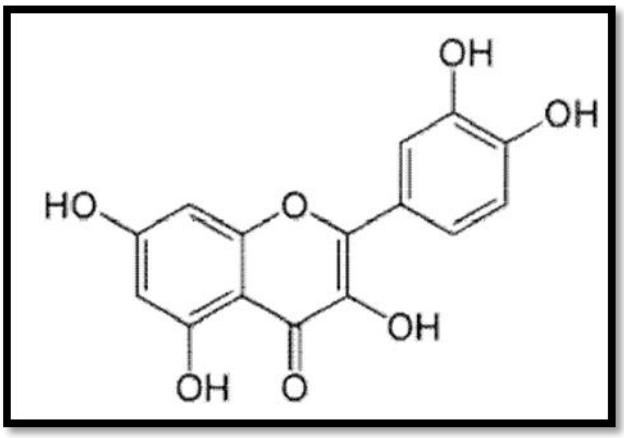

Fig-1: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one (Baghelet al., 2012)

Table 1. Quercetin Content in Selected Foods (Baghelet al., 2012)

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

QUERCETIN AND ANTI CANCER EFFECT

In Vitro Studies of Quercetin

In vitro studies shows that quercetin has anticancer activity in different cell lines and tumor cells, including glioma (U138MG, Braganhol*et al*., 2006 [17]); osteosarcoma (MTX300, Xie*et al*.,2010 [18]);cervical cancer (HeLa, VidyaPriyadarsini*et al*.,2010 [19]); prostatecancer (CWR22Rv1, Hsieh andWu,2009 [20]); breast cancer (MDA-MB-453, Choi etal., 2008 [21]); myeloid leukaemia (Duraj etal.,2005 [22]); Anti proliferative effect has also been reported at the dosage range from 3 to 50 mM*in vitro* (Lamson and Brig all, 2000; Gibellinietal., 2011[23-24). Recent report shows that nanoqurecetin enhances the apoptosis and mRNA expression levels in Michigan Cancer Foundation7 (MCF-7) breast cancer cells. Quercetin was found to sensitize MCF-7 cells to doxorubicin (Dox) and reduce cellular NAD(P)H quinone oxidoreductase 1 and multidrug resistant protein 1 gene expression levels [25-26].Quercetin has exhibited the inhibitory effect on MCF-7 and MDA-MB-231 human breast cancer cell lines through multiple mechanisms such as up-regulation of miR-146a expression, induction of apoptosis, activation of caspase-3 and mitochondrial-dependent pathways, and down-regulation of the expression of epidermal growth factor receptor (EGFR) [27]. In MCF-7 and MDA-MB-231 breast cancer cell lines, gold nano

particles conjugated quercetin (AuNPs-Qu-5) inhibited cell proliferation through induction of apoptosis and suppresses EGFR signalling. In CT26 cells, quercetin inhibits the survival and metastatic ability [28]. Quercetin extensively prevents the proliferation of human colon cancer in CACO-2 and SW- 620 cells by suppressing the NF-κB pathway, down-regulation of Bcelllymphoma 2, and up-regulation of Bax [29]. In H460 cell lines, quercetin inhibits the cell production and enhanced sub-G1 and apoptosis despite of p53 [30].

Table2. In vitro anticancer effects of quercetin [31]

Cell lines	Effects	Mechanisms	References
MCF-7, HCC1937, SK-Br3, 4T1, MDA-MB-231	Induced apoptosis	↓Bcl-2, ↓Bax expression, ↓Her-2, inhibition of PI3K-Akt pathway	Duo *et al*., 2012
MIA PaCa-2, BxPC-3	Inhibited proliferation	↓Her-2, regulation of Wnt/β catenin	Kim *et al*., 2013
CX-1, SW480, HT-29, HCT116	Inhibited proliferation	↓HIF-1k, regulation of Wnt/-catenin	Shan *et al*., 2009
HepG2	Inhibited proliferation	↓PI3K, ↓PKC	Maurya*et al*., 2015
A549	Inhibited cell growth	↓cdk1, ↓cyclin B	Yeh*et al*., 2009

In Vivo Studies of Quercetin

Invivo study shows that oral administration of quercetin can prevent induced carcinogenesis, particularly in the colon (Murakami *et al*., 2008) [32], and also inhibit the growth, invasion, and metastatic potential (Caltagirone*et al*., 2000) [33]. In experimental animal models, quercetin that was administered through the dietinhibited the initiation and growth of tumor (Yang *etal*.,2001) [34]. In Sprague–Dawley rats, silver nanoparticle-based quercetin caused a significant reduction in the expression of various proteins including vimentin, Snail, N-cadherin, Twist, Slug, matrix metalloproteinase-2 (MMP-2), MMP-9, vascular endothelial growth factor receptor 2 (VEGFR2), p-EGFR, protein kinase B (Akt), phosphoinositide 3-kinase (PI3K), and glycogen synthase kinase 3 beta (p-GSK3β) and enhanced E-cadherin protein expression in 7, 12-dimethylbenz[a]anthracene-induced mammary carcinoma [28, 35]. Quercetin can suppress colorectal lung metastasis in the mouse model, and may be an effective therapeutic agent for the treatment of metastatic colorectal cancer [36]. Treatment with quercetin at a dose of 50 mg/kg in mice showed a protective effect on cisplatin- induced DNA damage in normal cells, without interfering with the antitumor efficacy of the combined treatment. These results suggest that quercetin can protect the blood, liver, and kidney cells of mice against HIPEC-induced injury and can increase survival of mice by improving the antitumor adaptive immunity with hyperthermia [37]. 10g quercetin/kg dose of quercetin administered to rats for 11weeks, the results show that physiological changes in rat awelessdownregulates the potential monogenic MAPK signalling *in vivo* [38].

Table 3. In vitro anticancer effects of quercetin [31]

Animal models	Effects	Mechanisms	Dose	Duration	References
FemaleCF1 mice	Retarded tumor growth	↓PCNA; ↓mmu-miR-205-5P	8 g/kg/day (diet)	42 days	Deschner*et al.*, 1991
Male F344 rats	Inhibited tumor growth	↓EphA2; ↓PI3K; ↓MMP-2; ↓MMP-9	100 mg/kg (i.p.)	18 days	Dihal*et al.*, 2006
Male F344 rats	Suppressed tumor growth	↓ACF	25 mg/kg (i.p.)	28 days	Dihal*et al.*, 2006
Male Swiss mice	Inhibited tumor nodule formation	↓AD	6 mg/kg (i.p.)	2 times/ week 21 days	Khanduja*et al.*, 1999
Female Sprague-Dawley Rats	Reduced tumor volume	↓ADC	17.5 mg/kg (i.v.)	2 times/ week for 24 days	Verma *et al.*, 1988

(i.p., intraperitoneal; i.v., intravenous)

MAJOR MOLECULAR MECHANISMS OF ACTION OF QUERCETIN

Mutant P53 Protein - Down Regulation

In humans, mutations of p53 are the most common genetic abnormalities that lead to cancer [39]. Quercetin induces p53 activation resulting in up regulation of Bax and down regulation of Bcl-2 in tumor cells (Fig.:2).

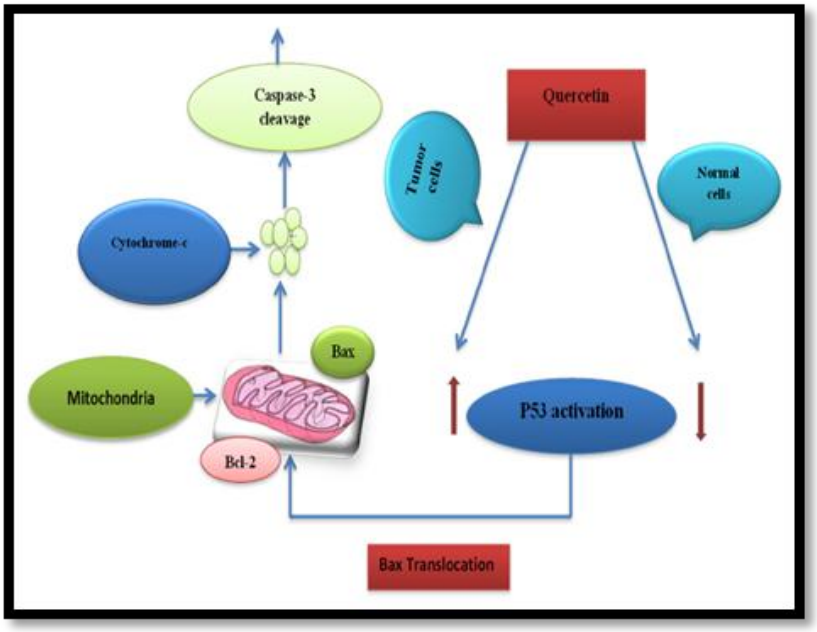

Figure 2 Anticancer role of quercetin- modulating the mitochondrial apoptotic pathways. (Ruafet al., 2018; Khan et al., 2016)

This leads to caspase activation and ultimately apoptotic cell[31, 40].Low concentrations of quercetin (248 µM) showed reduction and down regulated expression of mutant p53 protein in human breast cancer cell lines [41]. In cell cycle, G2-M phase was arrested and expression of p53 was inhibited [42].

G1 and G2 PHASE ARREST

The p53 gene is the major control point of G1 checkpoint. It is the major cellular proliferation control site. Quercetin leads to apoptosis of MCF-7 and MDA-MB-231 breast cancer cell lines and along with G1 phase arrest, which significantly suppressed the expression of Twist, CyclinD1, p21, and phospho p38 mitogen-activated protein kinases (p38MAPKs) and also effectively controlled the expression of Twist, which induces apoptosis in MCF-7 cells due to p16 and p21. These results recommend that quercetin induce apoptosis in cancer cells via suppression of twist through p38MAPK [43, 44]. In 70 µM concentration of quercetin, human leukemic T-cells were arrested at the late G1 phase whereas G1 phase of cell cycle were arrested in gastric cancer cells, thereby decrease in DNA replication [45, 46]. 8-C-(E-phenylethenyl) quercetin, a novel quercetin derivative, triggers G2 phase arrest in colon cancer cells and suppresses proliferation, and also induces autophagiccell death through ERK stimulation.

CONCLUSIONS AND FUTURE PROSPECTIVES

Quercetin (flavonol) is a major dietary flavonoid, which has ahigh quality of anticancer activity. Quercetin is safe with no reported toxicity when applied for the treatment of human cancer. Numerous *in vitro* and *in vivo*experiments shows 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.Furthermore, the production of this potent bioactive compound can be improved by tissue culture works such as hairy root culture and cell suspension culture systems. These systems can be employed in order to produce this compound in large quantities.

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