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Review Article

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Resveratrol and Quercetin:- Novel Polyphenolic Chemopreventive Agents

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Abstract

Cancer continues to be a major public health concern worldwide and the main modalities for treatment include chemo and/or radiotherapy and surgery which are often commonly used in conjuction to control and treat cancer. Recent advances in the area of cancer prevention have opened new avenues for research and several medicinal plants are being used to prevent and cure a variety of diseases, including oncological ailments. Herbal drugs have been in use for several thousands of years in various traditional systems of medicine existing in different parts of the world. In recent years, there has been a paradigm shift in the way we look at herbals which today are being viewed as potential agents for tackling various diseases, particularly for which there is no effective cure available in modern system of medicine or when the side effects of synthetic drugs are too many. It has been estimated by the World Health Organization (WHO) that currently 80% of the world's population is still dependent on herbal drugs for solving their health needs in one or the other way. They are less toxic alternatives to modern medicine, offer much scope for prevention of diseases, are easily available, cheaper costs, effective nature and promise to cure the so far incurable diseases like cancer, AIDS, hepatitis C, Alzheimer's and Parkinson's disease, diabetes makes them much sought for. Chemoprevention offers a promising approach to primary cancer prevention for a variety of organs. A plethora of compounds, including several promising plant derived compounds are being evaluated in the laboratories and two phytocompounds which hold a lot of promise include resveratrol and quercetin – as novel chemopreventive agents.

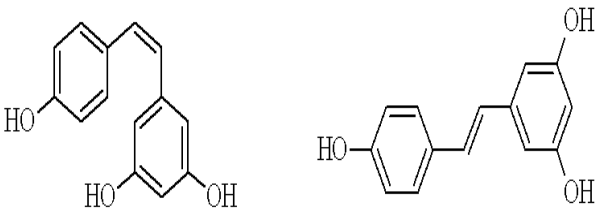
Keywords: Resveratrol; Quercetin; Cancer; Polyphenolic; Chemopreventive Agents

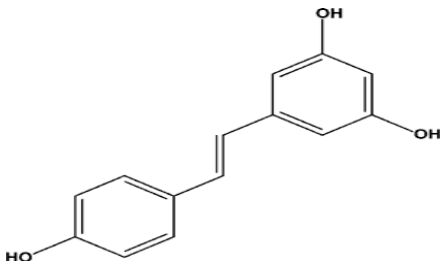
Introduction

Cancer chemoprevention was first defined as "a strategy of cancer control by administration of synthetic or natural compounds to reverse or suppress the process of carcinogenesis." The term chemoprevention was first coined by Dr. Michael Sporn for the first time referring to the activity of natural forms of vitamin A in preventing the development and progression of epithelial cancer and was first defined as "a strategy of cancer control by administration of synthetic or natural compounds to reverse or suppress the process of carcinogenesis"[1]. Chemopreventive agents usually act at the initiation stage by enhancing DNA repair, detoxification, scavenging of free radicals and carcinogen metabolism and at the promotion and progression stage by free radical scavenging, suppression of proliferation, induction of differentiation, enhancement of immunity, reduction of inflammation, increased apoptosis, altered gene expression and decreased angiogenesis [2,3,4,5,6]. Chemoprevention forms one of the important biomedical facet for prevention and treatment and involves evaluation of effectiveness of novel biological or molecular markers as intermediate end points [7]. Chemoprevention inhibits cancer basically by blocking the DNA damage that initiate carcinogenesis or by arresting and reversing the progression of premalignant cells in which such damage has already taken place [8].

A variety of naturally occurring agents were found to possess chemopreventive potential, including retinoic acid derivatives, phenolic antioxidants, coumarins, aromatic isothiocyanates, thiocarbamates, indoles, flavones, tannines, terpenes etc.[9]. Medicinal plants are used in prenatal care, in obstetrics, in gynaecology, in respiratory disorders, in skin disorders, in cardiac diseases, in nervous and muscular disorders, and in mental health, etc.[10,11]. Polyphenols are proposed to inhibit carcinogenesis by affecting molecular event at various stages including initiation, promotion and progression. The biochemical properties and bioavailability of many polyphenolic compounds have been reviewed recently [12]. All plant phenolic compounds arise from the common intermediate, phenylalanine, or its precursor, shikimic acid and can be divided into at least 10 different classes, based on their chemical structures [13]. Over 5000 flavonoids, the largest class of phenolics, have been described which are structurally related to the parent compound, flavones (2-phenylbenzopyrone) and most important of them are resveratrol and quercetin.

Resveratrol: Resveratrol (trans-3, 4, 5-trihydroxystilbene), a phytoestrogen present in red grapes seeds, red wine and other fruits exhibits antioxidant, anti-inflammatory, anti-angiogenic, anti-metastatic and pro-apoptic effect [14,15] Resveratrol is the major active compound, and is synthesized by plants (mainly spermatophytes) in response to stress conditions such as ultraviolet light [16], fungal infection [17], insects [18] and exposure to ozone[19]. Resveratrol exists in both cis-and trans-isomeric form.





Structure of Resveratrol

Reseveratrol has attracted the attention of several researchers for its role as a cancer chemopreventive agent[20] and there is growing interest in the chemopreventive properties of resveratrol, in particular about prostate cancer and gliomas.

Resveratrol and Prostrate Cancer

Prostrate cancer, one of the most common malignancies in men in the United States and other western countries is showing an increasing trend [21]. Studies indicate that adrenal androgens and androgen receptor (AR) have an impact on the progression of prostrate cancer and, therefore the concept of androgen blockade was introduced in clinical practice [22]. The increasing interest in prostrate cancer prevention by dietary component is a novel approach to modulate AR activity which has been confirmed in cell cultures and preclinical models [23,24,25]. Resveratrol inhibits the expression and function of the androgen receptor in LNCaP cells [26] and also targets several cellular and molecular events involved in cancer growth [27,28,29,30,31,32]. Resvertrol is strongly linked with androgen receptor regulation and other transcription factor p300, p53 and NF-κB and is one of the promising agents for prostrate cancer prevention [27,33,34,35,36,37].

The pharmacological profling for the safety and bioavailability of resveratrol has been well documented in pre-clinical models[38]. Resveratrol pretreatment in a dose dependent manner, cooperated with various drugs including etoposide, doxorubicin, cytarabine, actinoymycin D, paclitaxel and methotrexate to induce apoptosis in SHEP neuroblastoma cells [39]. In addition, the antioxidant action of resveratrol on UVB mediated modulation of cyclo-oxygenase (COX) activity has been studied [40] and it was demonstrated that pre-application of resveratrol resulted in a significant decrease in the UVB-mediated increase in epidermal COX activity. The pro-inflammatory nuclear factor NF-κB mediated pathogenesis of human cancer and many others hyperproliferative skin conditions are prevented by resveratrol [41]. Besides, resveratrol at 30mg/ml has been shown to inhibit UVB-induced microphthalmia associated transcription factor (MITF) promoter activity in B16 murine melanoma cells [42].

Resveratrol and Gliomas

Brain tumors are one of the leading causes of death among children and adults. Glioma's which arise from neoplastic transformation of glial cells are the most, common primary tumors affecting the brain, accounting for more than 40% of all central nervous system neoplasms [43]. The properties of resveratrol which make it useful and novel remedy in glioma include inhibiting the growth of several human cancer lines in vitro, inducing S-phase or G1-phase arrest and apoptosis [44,45]. Resvertrol administration in rat C6 glioma cells elicited a concentration and time dependent inhibition of glioma cell proliferation, mediated through the activation of caspases 3[46]. In gliomas, angiogenesis has been found related to the amount of secreted VEGF and resveratrol was found to suppress VEGF in vitro in rat RT-2 glioma cells in a concentration and time dependent manner, suggesting that its anti tumors effect(s) may be mediated by inhibition of angiogenesis [47]. Another targeting site of resveratrol is gap junction which are an important means for intercellular communication during development, tissue differentiation and maintenance of cell homeostasis allowing the coordinated responses of adjacent groups of cells to external stimuli [48,49] and in glioblastoma biopsies a decreased gap junction intercellular communication (GJIC) resulted in relation to deceased expression of CX 43 and increased cellular proliferation [50]. In rat liver cells it was shown that resveratrol was able to increase GJIC and to prevent the inhibition of GJIC by tumor promoters. This may be an important mechanism by which resveratrol exerts its protection against tumor promotion [51].

During tumor invasion, extra-cellular matrix (ECM) surrounding malignant glioma undergoes remodeling, involving also Secreted Protein Acidic and Rich in Cystine (SPARC)[52] which is a matricellular protein that influences a number of biological processes including cell differentiation, migration and proliferation and due to its counter adhesive properties, SPARC mediate interactions between cells and their extra-cellular environment [53,54,55]. This protein is frequently over-expressed in gliomas and its expression correlates with glioma invasion invitro and in vivo [56,57]. Resveratrol was able to induce a dose dependent downregulation of SPARC gene and protein expression in human glioblastoma cells in vitro [58]. This possible therapeutic benefit is supported also by the anti-angiogenic effects of SPARC, which

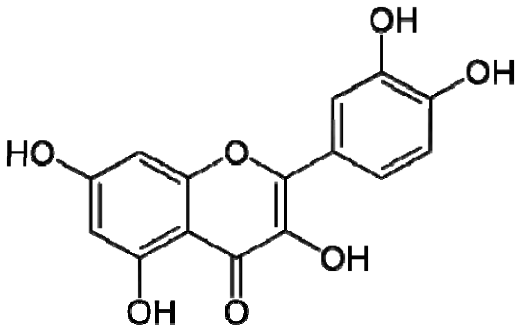
was reported also to block VEGF-induced proliferation of endothelial cells [59].

Resveratrol induces apoptosis in cultured cancer cells through mitrochondrial receptors [60] by inducing cell cycle arrest and / or by sensitizing the cells to drug induced apoptosis [61]. There are also studies showing that in certain malignant cells and other non-cancerous cell types, resveratrol may inhibit caspase activation and attenuate apoptotic cell death [62,63,64]. In addition extension of resveratrol in vitro finding to invivo animal models, using chemically induced carcinogenesis models have resulted in a few studies in which effectiveness was shown at modest oral dose of resveratrol on tumors of the colon [65], and esophagus [66] and surprisingly the mammary glands [67].

Resveratrol has been shown to synergize with both quercetin and ellagic acid in the induction of apoptosis in human leukemia cells [68] with catechin in the protection of PC12 cells from β-amyloid toxicity [69], with nucleoside analogues in the inhibition of iNoS expression[70] and with vitamin E in the prevention of lipid peroxidation [71]. These effects could help to explain how a relatively low dose of resveratrol obtained from regular daily wake of red wine or other dietary sources could produce a measurable health benefit [72].

Quercetin

Quercetin (3, 3', 4', 5, 7-pentohydroxy flavone belongs to a widespread class of polyphenolic flavonoid compounds almost omnipresent in various common foods, including red and yellow onions, apple, berries, black tea, broccoli and some nuts and seeds [73,74].



Structure of Quercetin

Much in vitro and some animal and human data indicate that quercetin inhibits tumor growth [75]. Multiple mechanisms are involved in the inhibition of carcinogenesis by quercetin including key signal transduction protein kinases, such as receptor associated tyrosine kinase [76,77], mitogen activated protein kinase (MAPK), certain cyclin dependent kinases (CDKs) and IKB. There effects can inhibit cell growth transformation and angiogenesis, and induces apoptosis. Treatment of cancer cells with quercetin results in reduced expression of the Ras oncogene and damage to DNA [78] and may be an additional anti-cancer mechanism of quercetin [79]. Inhibition of arachidonic acid metabolism which also may contribute to the inhibition of carcinogenesis by quercetin, has been reported [80,81,82,83]. Another targeting site of quercetin is heat shock proteins. Heat shock proteins form a complex with mutant p53 which allows tumor cells to bypass normal mechanisms of cell cycle arrest and permit improved cancer cells survival and different bodily stresses (poor circulation, fever, etc) and are associated with shorter disease free survival [84] and resistance to chemotherapy in breast cancer [85]. Quercetin can inhibit production of heat shock proteins in several malignant cell lines including breast cancer [86], leukemia [87], colon cancer [88] and prostate cancer [89].

Studies with animal models of carcinogenesis have yielded mixed results regarding the cancer preventing activity of quercetin. For example, it was reported that 2% dietary supplementation with quercetin inhibition azoxymethane induced hyperproliferation and focal dysplasia in mice [90]. Quercetin modulation of COX-2 transcription may also be an important anticarcinogenesis mechanism which may contribute to its prevention of lung cancer in non smoking, Taiwanese women exposed to cooking oil fumes (COF) [91]. Evidence indicate that quercetin more effectively inhibits COX than LOX [92], COX is known to be elevated in certain epithelial tumors [93] and is thought to be involved in tumor angiogenesis [94]. Therefore quercetin could be used clinically as an anticancer agent based on this observation alone.

Although preliminary, in vivo animal and human studies have confirmed that quercetin indeed has preventive and therapeutic effects on some cancers, further studies, especially carefully designed, mechanism based, in vivo investigations and effect on specific malignancies is necessary to benefit from this relatively non toxic agent. However while applying the conventional methods of controlled and randomized clinical trial on evaluation of traditional or alternative medicine especially ayurvedic medicine, its limitations come to fore. Hence there is a need for paradigm shift in the clinical research on herbal medicines. Different methodologies taking into account international guidelines should be adopted while evaluating the safety and efficacy of traditional medicine through clinical trials. Till that happens, one can hope that current chaos in clinical trial methodologies on herbal drugs would ultimately lead to more disciplined approaches which would be universally acceptable to the scientific community and regulatory authorities alike. .

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