Analysis of the effect of resveratrol and quercetin separately and together on Wnt Signaling path regulators, tumor differentiation, dietary intake and weight changes in rat's empirical colon cancer

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Abstract

Cancer is one of the most common diseases in the world. 1 out of 8 deaths in the world happen as a result of cancer. Cancer is the third cause of mortality in Iran. Colon cancer is the fourth cause of mortality at the world and annually 1.2 million people with the disease are being diagnosed. About 8% of overall mortality rate is associated with colon cancer. Colon cancer has considerably increased in Iran over the last 3 decades and it is the second most common cancer in Iran according to the annual report of National Cancer Institute of Iran. Spread of colon cancer in Iran can be estimated to be 8 out of 100,000 people. 3,641 new cases of cancer are reported annually in Iran and 2,262 people die in Iran every year as a result of colon cancer. Spread of the disease in the Iranian population is equal to 22% and accordingly and because of conflicting reports on effectiveness of resveratrol and quercetin in different steps of cancer, and lack of existence of study on simultaneous effect of the two compounds on colon cancer in vivo, this study intends to evaluate their effect together, so that positive results obtained from this study can be generalized to human studies.

Key words: resveratrol and quercetin, Wnt signaling path regulators, empirical colon cancer

Introduction

Colon cancer is the fourth cause of mortality in the world and the second most common cancer in the Europe (1). About 8% of the overall mortality rate caused by cancer is due to colon cancer. The highest increase rate is reported in Asia and Eastern Europe (2). According to the statistics of the World Health Organization (WHO), 1 million people with colon cancer are being annually diagnosed across the world (3). Colon cancer has significantly increased in Iran over the past 3 decades and is the second most common cancer in Iran according to the annual report of the National Cancer Institute of Iran (3). Spread of colon cancer in Iran is estimated at 8 out of 100,000 people (4). 3,641 new cases of cancer are reported annually in Iran and 2,262 people die in Iran every year as a result of colon cancer (5). Spread of the disease in the Iranian population is equal to 22% (3). According to the relevant studies in Iran on colon cancer age distribution, this cancer is happening in a younger population compared to western countries (6).

Early diagnosis of colon cancer over the years has played a key role in survival, since chemotherapy drugs can prevent excessive proliferation of cells in special body organs and apoptosis induction in tumor cells (7). However, one of the most important problems is that the recent medical methods for advanced colon cancer steps have imposed damaging effects on the health system and on the patients (8).

Common Cancer treatments

While this paper concentrates on chemotherapy, Radiotherapy and Surgery are other common medical treatments and choice of method of approach depeneds on the type of the cancer and the location of the cancer.

Chemotherapy

The common chemotherapy approach is as follows: the effective chemotherapy agent is taken orally or infused into the body by IV route and the agent affects some other cells and tissues in addition to cancerous cells and more importantly, it can damage the adjacent tissues and the entire bodily system (7). Effectiveness of treatment is not satisfying even with development of new anti-cancer drugs and the American Society of Clinical Oncology (ASCO) emphasizes necessity of finding a new approach to treat cancer. The main objective of colon cancer treatment is purposeful use of cancer chemoprevention materials (9).
Sliddique et al (10) analyzed the effectiveness in cancer through prescription of one or more natural or synthetic substances preventing cancer relapse or slowing down cancer progress as a chemoprevention mechanism.
The main objective of chemoprevention is identification of natural components of edible plants, or molecules which can prevent cancer cell growth or metastasis through interference with intercellular paths of cancer cells (9).
The main mechanism for chemoprevention can be natural components of certain plants including modulation in expression of genes regulating cell proliferation, modulation in differentiation, modulation in apoptosis, and stopping angiogenesis and metastasis (1).

The most effective compounds of cancer treatment monitoring

The components and contents of natural components of different ingestable materials are the most reliable compounds to monitor cancer treatment, since their effects have been studied in the field of accidents related to cell process and Pleiotropic nature of target tissue and non-toxicity for normal cells, over the years. Food materials can be considered as environmental factors responsible for 20-30% of cases of colon cancer, since food materials can determine the microenvironment of colon cancer cells and the interaction of cancer cells and the microenvironment around the cell can also affect tumor growth (2).

Among chemoprevention factors reducing cancer risk, phytochemicals can be the most effective factor (12-15). The majority of studies conducted over the past 3 decades have introduced the extracts of plants as suppressing factors or as a factor causing delay of spread in types of cancer. These results are consistent with the results of epidemiologic studies showing that using fresh green and yellow fruits and vegetables can decrease cancer and mortality in colon, breast, prostate, esophagus and bladder cancers (14, 16, 17). Phytochemicals are herbal non-nutritious compounds with disease prevention properties with anti-cancer effects (18).

According to the book “Fundamentals of Cancer Prevention”, prevention of cancer can be classified in 3 steps: Step 1 (mainly avoiding carcinogens); Step 2 (detection and removal of benign lesions) and Step 3 (prevention of cancer relapse and tumor progress).

Phytochemicals in 3 steps can have preventive effects on cancer from the beginning of tumor creation to all factors affecting cancer (cell proliferation, apoptosis, inflammation, genome stability) (11, 18).

As 2 main hallmarks of cancer cells include misplaced cell proliferation and resistance to apoptosis, identification of natural components of edible plants can be the most reliable compound (because of non-toxicity) to monitor cancer treatment (19, 20).

The effect of resveratrol on cancer treatment

One of these compounds is resveratrol, a natural substance (3, 4 and -5 3-hydroxy trans Acetylbenzoic acid) with abundant biologic effects on prevention and treatment of cancer. Resveratrol is a phytoalexin compound or antibiotic of the plant, which is produced in the plant in large amounts in response to environmental stress and pathologic invasion and acts therefore as natural inhibitor of cell proliferation (21, 22). The compound can be produced from Cinnamon radical transplantation (23). Resveratrol has been found in more than 70 plant species including grapes, berries, plums, peanut and pines (21). Over the

decade, it has been demonstrated that resveratrol has a wide range of pharmacologic properties. It seems that additional biochemical and molecular activities of the compound can cause the effects of resveratrol in cancer and pre-cancer cells (11, 22).

The information has resulted in conducting a large number of basic animal studies to analyze potential effects of resveratrol as a cancer chemoprevention substance. Moreover, resveratrol imitates calorie restriction and improves health and interferes in the ageing process (22). It has been reported that resveratrol can inhibit accumulation of platelets and oxidation of LDL, nitric oxide synthesis and vessel expansion in vivo (19) and inhibition of smooth muscle cell proliferation through reducing Cyclin A gene expression (24). Moreover, the compound can cause suppression of cancer cells (in vitro) (1) and reduction of tumor growth in animal models (13). The anti-cell proliferation mechanism of resveratrol is well identified. Recent studies have shown that resveratrol can cause apoptosis induction in cancer cells through increasing P53 gene expression (25) and decrease in Bcl-2 gene expression (26).

Red grape contains a substance called resveratrol, which can make a kind of conventional protein called serotonin in the human body and the protein can also maintain the youth of human chromosomes. According to studies, red grape contains substances reducing the risk of cancer and physical inflammation (10). Grape prevents cancer cell proliferation. Dr. HA Taj Mirriahi, researcher in Chemistry-Biology Department of Quebec University of Canada, analyzed the molecules in red grape called resveratrol and showed that a combination of the substance can prevent excessive proliferation of cancer cells in the body. Accordingly, resveratrol is a natural substance separated from grape shell and seed and because of special interaction of the substance with DNA and with its inhibitory effects on some malignancies; it can play a key role in cancer prevention and decreased cancer lesion growth.

The effect of quercetin on cancer treatment

The structure and biogenesis: polyphenols are secondary plant metabolites and protect plants against ultraviolet radiation, oxidants and pathogens. Flavonoids are the most frequent polyphenols of human dietary intake. Flavonoids include Anthocyanins, flavonols, flavanols, flavvounes, flavones and isoflavones and 4- Pentahydroxy Flavone; Quercetin with its structure (3, 5, 7 and 43-9) is one of the most important examples in the group of flavonoids (11).

Food sources: quercetin-rich food sources include fruits and vegetables, especially red onion, apple, berry and citrus, tea, nuts and seeds. In these materials, quercetin is mostly observable in the form of glycoside quercetin with low intake ability and in the case of hydrolysis 68% glycoside (1, 9, 10, 12, 13) the intake of the substance reaches to 81. Average daily intake of quercetin in humans is not specified although complete intake of polyphenols is 1 gr per day and two thirds are in the form of flavonoids (14).

The effects and pharmacology: the main known effects of quercetin can be its antioxidant effect, prevention of accumulation, muscle relaxation, platelet LDL, prevention of smooth vein oxidation, reduction of serum fat levels, reduced systolic hypertension, weight loss in animals and reduced plasma insulin, reduced level of plasma inflammation markers and anti-cancer effects (1, 9, 12 and 14). It has been found that antioxidant effects of quercetin are at a high level under conditions of high inflammation and high oxidative stress (9). The place of quercetin accumulation can be in liver and it can be disposed of mainly by urine and through bile (9, 10). According to the studies, quercetin can inhibit cytochrome enzymes.

The mechanism proposed for anti-cancer effects of resveratrol include cell death induction through regulating Fas level in cell membrane producing extracellular apoptosis (27-29), prevention of caspase activity (30, 31), reduced inflammation through suppression of products of gen es regulated by NFKB (31), reduced production of relevant proteins of cell cycle (expression of kinases associated with cyclin E, Cdk4 and D1 cyclin) (32, 33), increased expression of SIRT1 (a gene relevant to reduced Survivin expression), cell lifetime and slowing down he ageing process (34) and inhibition of Wnt path (35).

Quercetin is the second flavonoid in plant species, which is available in fruits and the majority of vegetables (36) and can be considered as an anti-cancer compound. Cancer prevention effects of the compound can be attributed to antioxidant activity of quercetin and inhibition of enzymes activating carcinogens, regulation of intracellular signal transfer path and interaction of quercetin with receptors and other types of proteins (37).

Among the molecular anti-cancer mechanisms proposed for quercetin, one can refer to direct effect of quercetin on reduced activity of Cyp1A7 in colon cancer (plays a role in activation of carcinogens) (37), effect on estrogen-dependent receptors and inhibitory effects on expression and function of androgenic receptors (similar activity of phytoestrogens) (38), apoptosis induction through Mitochondrial path (caspase activation) (3, 9); reduced Bcl-xs/Bcl-2 ratio and increased Bax (39), affecting DNA failure, failure of Poly (ADP-ribose) Polymerase (PARP) and increased Bax and affecting Bcl-2 level (anti-apoptosis) (39), reduction of synthesis of inflammatory cytokines and iNOS (Inducible nitric oxide synthase) expression (40).

Quercetin and resveratrol are both the polyphenols in red grape. It has been demonstrated that simultaneous intake of quercetin and resveratrol can reduce restenosis level (probably through inhibition of smooth vein cell proliferation). Therefore, using a combination of quercetin and resveratrol has high potential to control cancer (41).

Moreover, quercetin can inhibit sulfate of resveratrol and hence, it may increase biofeedback and as a result, medical quality of resveratrol through a sulfate process. However, further studies are needed in this field (22).

Discussion

It seems that among all mentioned mechanisms, apoptosis induction and cell proliferation inhibition are the most common underlying mechanisms affecting anti-cancer activity of phytochemicals, since effective drugs for cancer treatment can cause apoptosis induction (42). Stop of cell cycle is a hopeful strategy in cancer prevention. Cell cycle includes 4 steps respectively including G1, S, G2 and M (43). Abundant factors and proteins in positive or negative functions on various controlling points regulate control the cycle carefully. In the case of existence of ideal factors (quercetin and resveratrol), cancer cells fall in apoptosis in step G1; otherwise, phase S is begun with increased time of treatment of the cancer cell. With the continuity of presence of ideal factors (quercetin and resveratrol), with increased treatment time of the cancer cell, apoptosis is induced. Cell proliferation plays a key role in multiple steps of cancer creation with multiple genetic variations. Therefore, cell proliferation control is important for cancer prevention (44). Quercetin and other flavonoids can inhibit colon cancer cell proliferation (1) and stomach cancer cells (45). This can be achieved mainly through blocking cell passage from step G1 to step S.

The best path in cell proliferation in colon cancerous cells is the Wnt path. Exploration of the first Wnt gene was done in vertebrates (Wnt1 gene in rats). The term “Wnt” is a combination of Wing Less and Int for integration of Retrovirus in rats. Wnt path activation can control important evolutional events such as brain evolution, hand and feet pattern and organogenesis. Moreover, Wnt messaging is underlying in controlling stem cells and in many other aspects of evolution. Dysfunction in messaging through Wnt is associated with various cancers such as colon cancer. Wnt can be activated through two protein receptors of cell level (Frizzledz), which is directly connected to Wnt and an aid receptor, which seems that it is connected to Frizzledz in the path of Wnt messaging. According to the proposed model of Wnt path, the original and the central factor in Wnt intracellular message transfer is Beta-catenin in vertebrates and is Armadillo Vinegar in flies. The multipurpose protein acts in both functions of transcription activator and a connector protein of cell skeleton to membrane (45). In absence of Wnt message, beta-catenin is phosphorylated by a complex containing glycogen kinase 3, APC protein (tumor inhibitor) and oxyn (a cell skeleton protein). Then, phosphorylated beta-catenin is Ubiquitinized and is decomposed in proteasome. In presence of Wnt, oxyn is connected to Cytosolic duct recipient. The connection complex contains GSK3 and can decompose beta-catenin and prevents phosphorylation of beta-catenin by GSK3 and stabilization of beta-catenin in cytoplasm. Stabilization of beta-catenin induced by Wnt is also required for Dishevelled protein. The protein is connected to fz Cytosolic duct. Beta-catenin has been released and has been moved inside the core and acts there along with transcription factor (T cell factor) Tcf to control expression of target genes. The importance of stability and placement of beta-catenin is for this purpose that Wnt messages can affect beta-catenin in cell (cell skeleton, cytosol and core) (45, 46 and 47). Quercetin (44) and resveratrol (46) can reduce expression of cyclin d1 and D2, which play a direct role in progress of cell cycle. Moreover, it has been demonstrated that resveratrol has anti-cell proliferation effects and can cause pause in cell cycle in vitro (20).

Intervention with qurecetin in animals can reduce oxidant indicator (Thiobarbituric acid reactive substances) significantly. Moreover, the supplement amount with NASH is in a nuclear group (4) and is lower than the transcription factor group interfered in factor-like defensive factors against stress-related damage. When it is activated, it can activate antioxidant activity and can increase production of proteins to reduce cell stress. Expression of this factor can be significantly increased with quercetin supplement.

Results of reviews

In the study conducted by Schneider et al (2001) (47), the effect of using 0.01% resveratrol for 7 weeks through gavage on APCmin/+ was studied and it was found that production of Small intestine and colon tumors was reduced in the group getting resveratrol. Moreover, it was demonstrated that D1 cyclin and D2 cyclin was reduced in the intervention group, which could specify the effect of resveratrol on reducing expression of genes playing a direct role in cell proliferation and cell cycle.

In the study conducted by Wan et al (2002) (51), the effect of green and white tea and Epigallocatechin on beta-catenin was analyzed in HEK293 cells and it was found that Epigallocatechin can decrease beta-catenin level.

In the study conducted by Volate et al (2005) (48) under the title of “Modulation of aberrant crypt foci and apoptosis by dietary herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin)” on F344 rats with colorectal cancer induced by Methane Azoxide, it was found that using quercetin to 1.5% in diet of rats could cause significant decrease in abnormal crypts in colon of rats (4 times reduction); although such effect was not reported for rutin independently. Moreover, it was demonstrated that using a supplement containing all mentioned compounds can reduce ACF (aberrant crypt foci) respectively to 2, 1.8, 1.5 and 1.2 times. Moreover, it was found that quercetin is stronger than other compounds to decrease ACF level and has increased apoptosis in rats more than other compounds (3 times increase). Analysis of caspase 9, Bax and Bcl-2 using Western blot method showed that quercetin can lead to apoptosis induction through Mitochondria. The effect was also reported for curcumin.

This study has proposed analysis of role of quercetin and other herbal compounds in reduction of pre-cancer lesions and apoptosis induction in colon.

In the study conducted by Sengottuvelan et al (2006) (46) on wistar rats, under intervention by Dimethylhydrazine to get colon cancer, it was found that resveratrol intake for 30 weeks in 3 time periods of 2 weeks before carcinogen

injection, 2 days after carcinogen injection and at the same time with carcinogen injection could reduce level and number of ACF in colon of rats. Moreover, it was found that the cell proliferation level could reduce Cycloxygenase 2 (COX-2) and Orentinine in carboxylase (increased at time of tumor growth) in serum of rats.

Moreover, it was demonstrated that size of ACFs was also decreased in crypts (especially in distal colon) and intake of resveratrol during the study time or before DMH (dimethylhydralazine) injection could have more effects on number of ACF and size of ACF.

In the study conducted by Dihal et al (2006) (49) under the title of "Quercetin, but not its glycosidated conjugate rutin, inhibits azoxymethane-induced colorectal carcinogenesis in F344 rats", it was found that intake of quercetin to 0.1, 1 and 10gr/kg in diet of rats for 38 weeks could reduce tumor creation and tumor size; although rutin showed no similar effect. Number of abnormal crypts in colon as a result of quercetin intake showed no significant difference. Quercetin intake was not correlated to food intake and weight of rats and their mortality.

In the study conducted by Majumdar et al (2009) (50) on HCT-116 cancerous cells of human colon, the effect of synergism of curcumin and resveratrol was studied. Cancer cells were injected from culture medium to ICR SCID female rats to make tumor. Then, curcumin was injected into rats at 500mg/kg of body weight and resveratrol was injected at 150mg/kg of rats' body weight for 3 weeks. Rats were divided into 4 groups in terms of curcumin and resveratrol intake. The first group received only resveratrol; the second group only curcumin and the third group both compounds at the same time and a group was selected as control group.

In this study, it was observed that the effect of resveratrol and curcumin together can lead to more inhibitory effect on cancer cells in vitro and even more combined than using them separately.

Also, it was found in this study that the effect of synergism of curcumin and resveratrol in less than 20mm is very strong. Moreover, it was found that resveratrol, similar to curcumin, can inhibit EGFR and IGF-IR in colon cancer cells and using them alongside can lead to a higher rate of inhibition in said factors. Moreover, cell proliferation in tumor after simultaneous intake of curcumin (40%) and resveratrol (38%) can be stronger than their effect independently (more than 50%). Moreover, the level of apoptosis in case of simultaneous use of the two compounds was increased at 70% compared to control group and number of apoptosis cells was also increased at 21.5% compared to control group. Moreover, the adherence to DNA of factor NFk-B was decreased at 67% (resveratrol and curcumin independently caused reduction of 30-35%).

In the study conducted by Martinez et al (2010) (51), the effect of resveratrol on colon cancer was studied. 30 normal people were maintained on low-resveratrol dietary for 2 weeks. Sigmoidoscopy was done for colon tissue and the participants again got high resveratrol dietary for 2 weeks and biopsy was done. It was observed that high resveratrol can cause weight loss and reduction of fat intake. Resveratrol can decrease cell proliferation through decreased Cyclin D1. Expression of several genes in Wnt path was decreased. Moreover, people above 50 years old showed higher level of oxyn, cyclin and cmyc and this could reduce the resveratrol level to the level of young people.

In 2012, a study was conducted by Khandelwal et al (41) on analysis of the effects of quercetin and resveratrol on hyperplasia inhibition in rats with carotid dysfunction for 2 weeks. The dosage of resveratrol intake was equal to 25mg/kg of body weight and quercetin was fed to rats to 10mg/kg of body weight. Compared to control group, resveratrol could cause significant decrease in Rastnosis, which was evaluated through intima/media ratio at 76%. The effect was not observed for quercetin independently. In simultaneous use of the two compounds, intima/media ratio was significantly reduced at 94%. Both resveratrol and quercetin and a combination of them could significantly affect platelet activity and endothelial function. However, simultaneous use of the two compounds had less effect on this activity. Simultaneous use of quercetin and resveratrol could have stronger effect of inflammatory markers compared to separate use of these compounds. In general, the results obtained from the study showed that using quercetin and resveratrol together can decrease rastnosis probably through the effect of their synergism on proliferation of smooth muscle cells and inflammation.

In the study conducted by Alizadeh et al (2012) (9) under the title of "Chemoprevention of azoxymethane-initiated colon cancer in rat by using a novel polymeric nanocarrier–curcumin", 40 rats were grouped in 3 groups including control, curcumin and curcumin- Dendrozumy groups. After 22 weeks of intervention, abnormal crypts were observed in the control group. The expression of beta-catenin in the control group with curcumin- Dendrozumy was significantly decreased compared to control and curcumin groups and this showed effectiveness of the compound in prevention of colon cancer in an animal model.

In the study conducted by Cai et al (2015) (7) on APCmin rats, a type of heritance colorectal cancer created by mutation in APC 850 gene was studied and the results showed that after intake of 7mg/kg body weight of resveratrol and 14mg/kg of body weight for 14 weeks, as a result of higher dosage of resveratrol, the number of adenomas was decreased at 22%. Despite this, in the same study, in the group using high fat diet, lower dosage of resveratrol could cause decrease in number of adenomas about 40% and the disease risk was also decreased at 52%. However, higher dosage of resveratrol was also effective in decreased number of adenomas (about 25% in high fat diet). Inhibition of tumor progress as a result of using resveratrol in both dosages was associated with adenoma cell proliferation (6.5 to 9.3%); although no change was observed in the control group using HFD.

High dosage of resveratrol was correlated to weight gain in both groups (males and females) and it seems that resveratrol has protective capability against effects of tumor progress in high fat diet without body weight loss. Moreover, it was demonstrated that using a supplement containing all mentioned compounds could reduce ACF respectively to 2, 1.8, 1.5 and 1.2 times. In addition, it was found that quercetin could decrease SCF more significantly than other compounds and quercetin caused more increase in apoptosis level in rats (3 times increase) than other compounds. Caspase 9, bax and Bcl-2 analysis using western blot method showed that quercetin can cause apoptosis induction through mitochondria. The effect was also reported for curcumin. This study has proposed studying the role of quercetin and other herbal compounds in reduction of pre-cancer lesions and apoptosis induction in the colon.

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