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Quercetin induces human colon cancer cells apoptosis by inhibiting the nuclear factor-kappa B Pathway

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ABSTRACT

Quercetin can inhibit the growth of cancer cells with the ability to act as chemopreventers. Its cancer-preventive effect has been attributed to various mechanisms, including the induction of cell-cycle arrest and/or apoptosis as well as the antioxidant functions. Nuclear factor kappa-B (NF-κB) is a signaling pathway that controls transcriptional activation of genes important for tight regulation of many cellular processes and is aberrantly expressed in many types of cancer. Inhibitors of NF-κB pathway have shown potential anti-tumor activities. However, it is not fully elucidated in colon cancer. In this study, we demonstrate that quercetin induces apoptosis in human colon cancer CACO-2 and SW-620 cells through inhibiting NF-κB pathway, as well as down-regulation of B-cell lymphoma 2 and up-regulation of Bax, thus providing basis for clinical application of quercetin in colon cancer cases.

Key words: Apoptosis, colon cancer, nuclear factor-kappa B, quercetin

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INTRODUCTION

Colon cancer is one of the most prevalent cancers throughout the world and especially in the Western countries. Many epidemiological studies indicated that western style diet such as consumption of red meats is possibly associated with a high colon cancer incidence.[1] Despite earlier detection and dropping death rates in colon cancer, 112,340 new cases were estimated for 2007.[2] The most common treatment for colon and rectal cancer is surgical resection, followed by adjuvant therapy with 5-fluorouracil, oxaliplatin, and leucovorin. Early detection can provide a 5-year survival rate of up to 90%, and surgery is most often curative. However, if patients present with distant metastasis at the time of diagnosis, the 5-year survival rate drops to only 10%.[2] Despite recent improvements in surgical techniques and chemotherapy, advanced colon cancer continues to have poor clinical outcomes. Molecules intimately related to cancer cell survival, proliferation, invasion, and metastasis have been studied as candidates for molecular targeted agents.[3]

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Dietary polyphenolic compounds have showed various pharmacological activities including anti-cancer activity.[4-10] Quercetin (3,3',4',5,7-pentahydroxyflavone) [Figure 1a], an important dietary polyphenol present in red onions, apples, berries, citrus fruits, tea, and red wine,[11] exhibits anti-oxidant, anti-inflammatory, anti-obesity and anti-cancer properties.[12] Quercetin has received increasing attention as a pro-apoptotic flavonoid with specific and almost exclusive activity on tumor cells rather than normal, nontransformed cells.[13,14] However, the mechanisms by which quercetin exerts its anti-cancer activity remain unclear.

The nuclear factor-kappa B (NF-κB) pathway is thought to play an important role in the process leading from inflammation to carcinogenesis and thus may be a candidate for targeted intervention.[15-17] Multiple pro-inflammatory stimuli activate NF-κB, primarily through inhibitor of κB kinase (IKK)-dependent phosphorylation and ubiquitin-mediated degradation of IκB proteins. Once activated, NF-κB stimulates the transcription of genes encoding cytokines, growth factors, chemokines, and anti-apoptotic factors.[18,19] Moreover, NF-κB pathway has also been implicated in tumor initiation, progression, metastasis, and resistance to chemotherapy.[17,20] In colon cancer, NF-κB is constitutively activated.[21,22] Aberrant NF-κB activation results in enhanced proliferation,[23] evasion of apoptosis,[23-25] genomic instability,[26] increased rate of glycolysis[27] and drug resistance[28] in colon cancer cells.

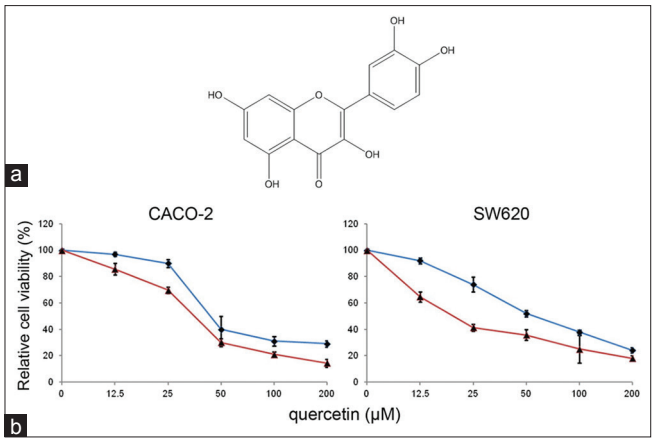

Figure 1: Inhibitory effect of quercetin on cell viability of human colon cancer cells. (a) Chemical structure of quercetin; (b) human colon cancer CACO-2 and SW-620 cells were treated with quercetin with designated concentrations, and cells viability were detected using Cell Counting Kit-8 assay at 6 h (diamond) and 24 h (triangle)

Studies have suggested a series of pharmacologic inhibitors of NF-κB pathway to be potential anti-cancer agents,[20,29] such as IκB or IKK inhibitors,[30] ammonium pyrrolidinedithiocarbamate,[31] as well as selective ubiquitin proteosome inhibitors.[32] However, there still has no comprehensive investigation for anti-tumor effect of NF-κB inhibitors on colon cancer.

Our present study demonstrated that quercetin presented potent anticancer effects within an inhibitory effect on NF-κB, and could induce apoptosis of colon cancer cells *in vitro*, thus providing basis for clinical application of quercetin in colon cancer cases.

MATERIALS AND METHODS

Reagents and antibodies

Quercetin, glyceraldehyde 3-phosphate dehydrogenase was purchased from Sigma Chemical Co (St. Louis, MO, USA). Antibodies including phosphorylated and nonphosphorylated forms of IκB-α and NF-κB were purchased from Cell Signaling Technology Inc. (Beverly, MA, USA). Dulbecco's modified Eagle's medium (DMEM) and fetal bovine serum were purchased from GIBCO BRL.

Cell culture

Human colon cancer CACO-2 and SW-620 cells were obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Cells were incubated in DMEM (high glucose), 10% fetal bovine calf serum, 100 U/ml penicillin-streptomycin. Cells were maintained at 37°C in a humidified atmosphere of 95% air and 5% CO_2.

Cell viability assay

Cell viability was quantified by Cell Counting Kit-8 (CCK-8) (Beyotime, China) assay according to the manufacturer's instructions. In brief, CACO-2 and SW-620 cells were seeded into 96-well plates at a density of 2×10^3 cells/well. After incubation overnight, cells were treated as indicated concentration of quercetin and assessed by CCK-8 assay at 6 and 24 h respectively. 10 μl of CCK-8 reagent was added to each well and incubated for 1 h. The difference in absorbance between 450 and 630 nm was measured by a microplate reader (BioTek, Winooski, VT, USA) as an indicator of cell viability. Independent experiments were done in triplicate. About 50% growth inhibitory concentration (IC_{50}) values were calculated as the concentration of the compound that inhibited the viability of cells by 50% as compared with control cells grown in the absence of inhibitor.

Cell lysis and immunoblotting

Cells were lysed, and proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride membrane (Immobilon; Millipore, Billerica, MA). Immunoblotting was done with different antibodies and visualized by an enhanced chemiluminescence (Amersham, Piscataway, NJ) method.

Nuclear factor kappa-B transcription factor assay

Nuclear factor kappa-B (NF-κB) p65 subunit DNA binding activity was determined by an enzyme-linked immunosorbent assay (Cayman Chemicals, Ann Arbor, MN, USA) according to the manufacturer's instructions. In brief, a specific double stranded DNA sequence containing the NF-κB (p65) response element was immobilized onto the bottom of wells of a 96-well plate. Nuclear extracts were added to the plate and incubated overnight at 4°C without agitation NF-κB (p65) was detected by addition of a specific primary antibody directed against p65. A secondary antibody conjugated to horseradish peroxidase was added to provide a sensitive colorimetric readout at 450 nm. Independent experiments were done in triplicate. Nuclear extract from cells was prepared using Nuclear Extraction Kit (Millipore, Watford, UK) according to manufacturer's instructions.

Hoechst-33258 staining

CACO-2 and SW-620 cells were seeded in 12-well culture dishes (5×10^4 cells/well). After experimental treatment, cells were washed twice with phosphate buffered solution (PBS), and stained with Hoechst-33258 (5 mg/ml) for 5 min in the dark, and then followed by extensive washes. Nuclear staining was examined under a fluorescence microscope, and images were captured using ImagePro Plus software (Media Cybernetics, Silver spring, MD).

Cell apoptosis assay

Cell apoptosis detection was performed using an Annexin-V-FITC Apoptosis Detection Kit (BD company, US) according to the manufacturer's protocol. Briefly, cells were collected after 24 h treatment with quercetin. The cells were washed twice with cold PBS then resuspended in 1 × binding buffer at a concentration of 1 × 10^6 cells/ml. Then 500 μl cell suspension was incubated with 5 μl Annexin-V-FITC and 10 μl PI for 15 min in the dark and analyzed by a FACScalibur instrument (Becton Dickinson, San Jose, US) within 1 h. Apoptotic cells were those stained with Annexin V^+/PI^- (early apoptosis) plus Annexin V+/PI+ (late apoptosis).

Statistical analysis

Results were presented as mean ± standard deviation differences between two groups were tested using Student's *t*-test; two-way analysis of variance analysis was performed where indicated. Statistical significance was determined at the level of $P < 0.05$.

RESULTS

Inhibitory effects of quercetin on viability of human colon cancer cells *in vitro*

To identify whether quercetin influence the survival of CACO-2 and SW-620 cells, cells were treated with 0–200 μM quercetin, and after that cell viability was examined by CCK-8 assay. As shown in Figure 1b, both CACO-2 and SW-620 cells viability are dramatically suppressed after treating with 200 μM quercetin, when compared to the negative control (0 μM). After 24 h, quercetin showed high inhibition of cell population growth in a dose-dependent manner with IC_{50} values of 35 μM (CACO-2 cells) and 20 μM (SW-620 cells).

Inhibitory effect of quercetin on nuclear factor kappa-B activity in colon cancer cells

We further detected the inhibitory effect of quercetin on NF-κB activity in CACO-2 and SW-620 cells. As shown in Figure 2, NF-κB DNA binding activity was dramatically decreased after quercetin treatment for 6 h. Moreover, quercetin also induced the dephosphorylation and up-regulation of IκB-α [Figure 3]. Taken together, these results suggested that quercetin displayed rapid and potent anti-tumor effects against colon cancer cell lines.

Quercetin induced CACO-2 and SW-620 cells apoptosis

The apoptotic effect of quercetin was analyzed and quantified by flow cytometry using the Annexin V-FITC Apoptosis Detection Kit. As shown in Figure 4, quercetin induced CACO-2 and SW-620 cells apoptosis in a dose-dependent manner.

Apoptotic events of Hoechst-33258 staining were also tested. After exposed to three concentrations of quercetin (0 μM, 25 μM and 50 μM) for 24 h, apoptosis of CACO-2 and SW-620 cells was demonstrated by Hoechst-33258 staining, revealed cell membrane permeability increasement and nuclear condensation [Figure 5].

In order to gain a better insight into pro-apoptotic effect of quercetin, we detected protein expression of apoptosis marker molecular. Poly (ADP-ribose) polymerase (PARP) was one of the main cleavage targets of caspase-3 and cleaved PARP always served as a marker of cells undergoing apoptosis.[33] Results demonstrated that cleaved PARP could not be detected until quercetin treated was administrated at the high dose of 30 μM, further suggesting that quercetin could induce apoptosis in a dose-dependent manner [Figure 6]. We also measured the expression of apoptosis inducing factor (AIF), which played a critical role in caspase-independent apoptosis.[34] However, results demonstrated that no increase in AIF expression was detected after quercetin treatment [Figure 6].

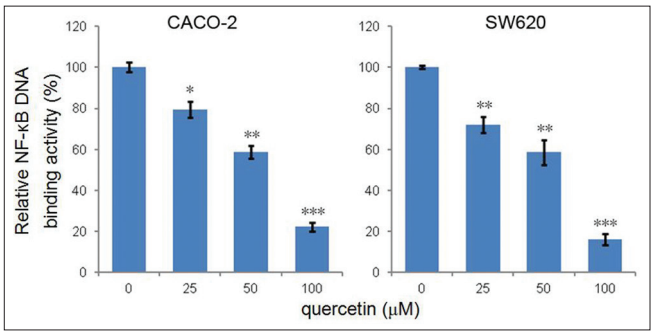

Figure 2: Nuclear factor kappa-B DNA binding activity after quercetin treatment for 6 h was determined using an enzyme-linked immunosorbent assay. Data were expressed as means ± standard deviation ($n = 3$). The experiments were repeated twice. *$P < 0.05$ significantly different from control (0 μM); **$P < 0.01$ significantly different from control (0 μM); ***$P < 0.001$ significantly different from control (0 μM)

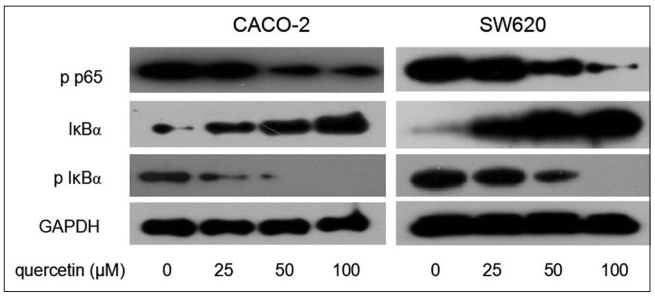

Figure 3: The inhibitory effect of quercetin on IκBa phosphorylation and nucleus translocation of Nuclear factor kappa-B p65 subunit in CACO-2 and SW-620 cells was detected using western blot at 6 h. Glyceraldehyde 3-phosphate dehydrogenase as controls for loading of total cell lysates and nuclear extracts respectively

B-cell lymphoma 2 family proteins were involved with quercetin induced apoptosis

We next investigated the expression of B-cell lymphoma 2 (Bcl-2) families, which regulated mitochondrial apoptosis and could be separated into pro-survival members (such as Bcl-2, Bcl-extra large (Bcl-xL), and myeloid cell leukemia-1), as well as pro-apoptotic proteins (such as Bax).[35,36] As shown in Figure 7, after quercetin treatment, Bcl-2 is down-regulated significantly, and Bax is up-regulated on the contrary. These results are consisted with the general notion that Bcl-2 and Bax play a pivotal role in regulating mitochondrial apoptosis pathway.[37]

DISCUSSION

Dietary phytochemicals consist of a wide variety of biologically active compounds that are ubiquitous in plants, many of which have been reported to have anti-tumor properties. Epidemiological studies have shown that the consumption of vegetable, fruits, and tea is associated with a decreased risk of cancer and cardiovascular diseases, and polyphenols are believed to play an important role in preventing these diseases.[38,39] Among them, quercetin has been reported to have therapeutic potential for treating many human cancers.[11-14]

An enormous amount of data strongly implicate that the inhibition of NF-κB signaling could be potentially effective in suppressing inflammation or tumor progression, and development of new small molecule inhibitors of this pathway is needed.[40,41] Recently, studies have been made in the design of potent orally active NF-κB pathway inhibitors for anti-inflammation or anti-tumor purposes.[42-45] Compounds that inhibited the NF-κB pathway could lead to the decreased expression of endothelial cell adhesion molecules.[46] Further studies searching for alternative therapeutic strategies against malignancies have shown that it is a potent inducer of apoptosis in a number of malignant cells such as in colorectal cancer,[47] breast cancer,[48] and

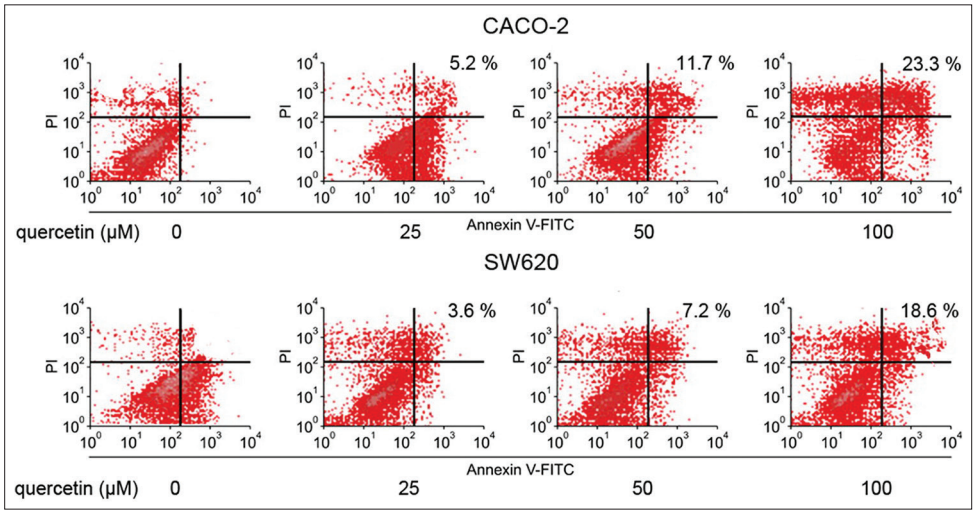

Figure 4: Quercetin induces apoptosis in a dose-dependent manner. The apoptotic fraction of CACO-2 and SW-620 cells was detected by Annexin V-PE and PI double staining

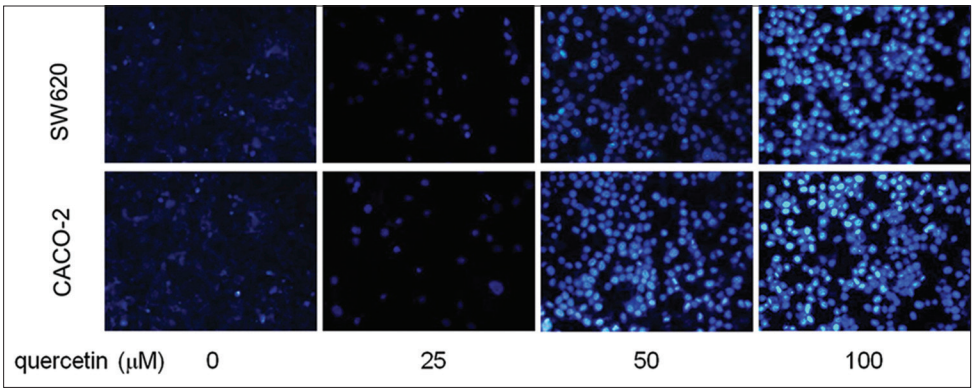

Figure 5: Hoechst 33258 staining analyzed the cell apoptosis after indicated treatments using a fluorescence microscope, ×100

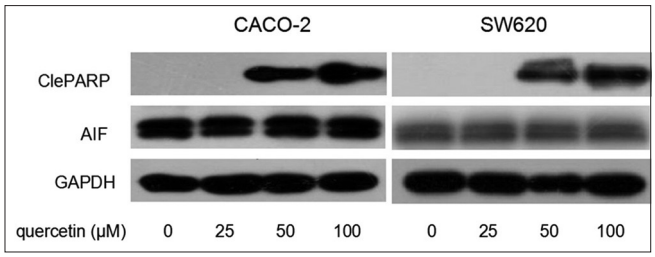

Figure 6: Protein expression of cleaved poly (ADP-ribose) polymerase and apoptosis inducing factor in CACO-2 and SW-620 cells after indicated treatments was measured by western blots. Glyceraldehyde 3-phosphate dehydrogenase served as a control for loading

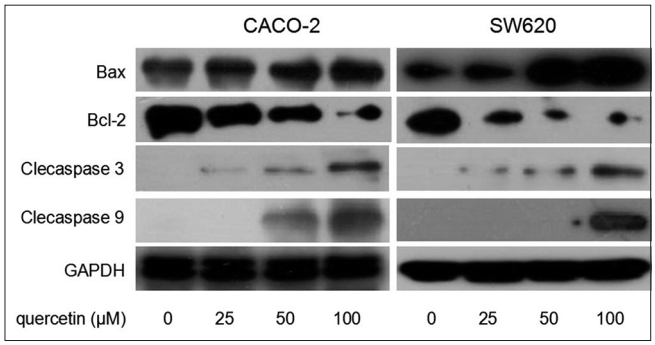

Figure 7: Mitochondrial pathway is involved in the apoptotic effects of quercetin. Protein expression of cleaved caspase 3, 9, as well as B-cell lymphoma 2, Bax in CACO-2 and SW-620 cells after indicated treatments was measured by western blots

hematological malignants.[49-51] In this study, we showed the potent anti-tumor effects of quercetin as a novel NF-κB inhibitor against human colon cancer *in vitro*.

In colon cancer cells, NF-κB is always constitutively activated,[21,22] and contributes to enhanced proliferation[23] and evasion of apoptosis.[23-25] Degradation of IκB release NF-κB proteins to the nucleus where they transactivate approximately 300 target genes, including those encoding regulators of pro-survival factors, such as Bcl-2,[52] Bcl-xL.[40] NF-κB is an important inhibitor of apoptosis and can protect cancer cells from cell death induced by tumor necrosis factors (TNFα) or TNF superfamily members, different pharmaceuticals or irradiation.[53] In this study, we found that quercetin could down-regulate Bcl-2 as well as up-regulate Bax, which may contribute to this apoptosis induction. However, the exact mechanism how quercetin induces mitochondrial dysfunction and cellular apoptosis also needs further investigation.

CONCLUSIONS

Quercetin could induce human colon cancer cells apoptosis via inhibiting NF-κB pathway. Since quercetin showed potent inhibition on the proliferation of human colon cancer cells, it had the potential to be developed into a drug candidate for treating human colon cancers.

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