

# Quercetin: A Phytochemical with Pro-Apoptotic Effects in Colon Cancer Cells

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## Abstract

The anti-carcinogenic effects of polyphenols have been demonstrated over the years. Polyphenols can show anti-carcinogenic effects by providing signal transduction related to cancerous cell growth, suppression of oncogene expression, arachidonic acid metabolism, inhibition of pro-inflammatory pathways, triggering apoptotic cell death, and inhibition of angiogenesis. The capacity of phenolic compounds due to their effects on many signaling pathways in cells might indicate the potential use of polyphenols as anti-carcinogenic agents. An important and well-studied polyphenol, quercetin, has been shown to have anti-inflammatory and anti-carcinogenic effects. Apoptosis is activated by many intracellular and extracellular signals through two main signaling pathways; the extrinsic pathway and the intrinsic pathway, and regulated by many proteins. In addition to the anti-inflammatory effect of quercetin, its anti-carcinogenic effect is a topic of interest. Quercetin has the potential to induce apoptosis via the mitochondrial apoptotic pathway by causing changes in the mitochondrial membrane potential. In addition, quercetin also induces apoptosis through the activation of p53, increasing the expression of pro-apoptotic molecules such as Bax, caspase-3, caspase-9, and inhibition of anti-apoptotic proteins such as Bcl-2. In conclusion, given the pro-apoptotic and anti-cancer effects of quercetin, its potential for use as a component of cancer therapy might be suggested as an alternative to other colon cancer treatments.

**Key words:** Quercetin, colon cancer, polyphenols, apoptosis, anti-carcinogenic, cell death

## INTRODUCTION

In recent years, foods and nutritional components with high therapeutic properties have gained importance when the side effects of drugs used in cancer treatment are considered.<sup>1</sup> The anti-carcinogenic effects of polyphenols have been demonstrated over the years.<sup>1</sup> Many polyphenols including catechin, isoflavone, lignan, flavones, ellagic acid, red wine polyphenols, resveratrol and curcumin have been shown to have anti-carcinogenic and chemo-preventive effects with different mechanisms depending on their dose.<sup>2</sup> Polyphenols can show anti-carcinogenic effects by providing signal transduction related to cancerous cell growth, suppression of oncogene expression, arachidonic acid metabolism, inhibition of COX-2 activity, triggering apoptotic

cell death, inhibition of angiogenesis, and inhibition of the NF- $\kappa$ B pathway. The capacity of phenolic compounds due to their effect on many signaling pathways in cells might constitute the potential use of polyphenols as anti-carcinogenic agents. An important and well-studied polyphenol, quercetin, has been shown to have anti-inflammatory and anti-carcinogenic effects.<sup>3</sup>

Quercetin is a phytochemical in the flavonol group of phytochemicals commonly found in many vegetables and fruits, such as onions, apples, grapes and blueberries and they are believed to induce apoptosis.<sup>3</sup> Apoptosis is activated by many intracellular and extracellular signals through two main signaling pathways and is regulated by many proteins. The extrinsic pathway is characterized by the activation of death receptors

**To cite this article:** Özsoy S, Soykut G, Becer E. Quercetin: A Phytochemical with Pro-Apoptotic Effects in Colon Cancer Cells. Cyprus J Med Sci 2022;7(5):587-592

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**Received:** 28.05.2021

**Accepted:** 20.11.2021



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in the cell membrane, and the intrinsic pathway is characterized by the activation of the mitochondria-apoptosome system.<sup>4</sup> Quercetin might exert anti-inflammatory properties by suppressing NF-κB translocation and the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β.<sup>2</sup> In addition to the anti-inflammatory effect of quercetin, its anti-carcinogenic effect is a topic of interest. Quercetin has the potential to exert anti-carcinogenic effects by inducing intrinsic and extrinsic apoptotic pathways and suppressing cell migration and growth. In addition, quercetin has the potential to suppress proliferation by inhibiting important signaling pathways in carcinogenesis such as MAPK, JAK-STAT, and PI3K-Akt.<sup>5</sup> Quercetin has the potential to induce apoptosis via the mitochondrial apoptotic pathway by causing changes in the mitochondrial membrane potential. In addition, quercetin also induces apoptosis through activation of p53, increasing the expression of pro-apoptotic molecules such as Bax, caspase-3, caspase-9, and the inhibition of anti-apoptotic proteins such as Bcl-2.<sup>6</sup>

In this review, we aimed to examine and briefly summarize the pro-apoptotic effects of quercetin in colorectal cancer (CRC).

### Development of Colorectal Cancer

CRC is the 3<sup>rd</sup> most common type of cancer in men and the 2<sup>nd</sup> most common in women. The World Health Organization reported that the incidence of CRC in men was 10.2%, and 9.5% in women.<sup>7</sup> Colon cancer is a disease of the large intestine which starts with the cecum and ends with the anus.<sup>8</sup> The intestinal wall from outside to inside consists of serosa, muscularis peopia, submucosa and mucosa.<sup>8</sup> Typically, CRC develops from precancerous polyps which are localized growths of abnormal cells within the intestinal mucosa. Molecular changes such as genetic and epigenetic mutations, and also histological changes may begin to accumulate within polyp cells; these changes start stepwise progressions from premalignant polyps to invasive carcinoma. In CRC, chromosomal instabilities (CIN), genetic and epigenetic mutations can create growth and proliferation advantages for cells.<sup>9</sup> Deficiency in the expression of tumor suppressor genes such as adenomatous polyposis coli (APC), p53, MCC, DPC-4 (pancreatic corsynomal deletion-4), and mutations in oncogenes such as RAS, Src (cytoplasmic tyrosine kinase) are genetic changes in colon cancer which contribute to colon cancer development (Figure 1).<sup>8</sup>

The APC gene is responsible for encoding-catenin, which is involved in many cellular processes such as cell adhesion, migration, signal transduction, microtubule assembly and chromosome separation.<sup>10</sup> The tumor suppressor capacity of the APC gene is related to its effect

on β-catenin.<sup>10</sup> The Wnt/β-catenin pathway is an intracellular signaling pathway in which growth signals may be effective in tissue homeostasis and morphogenesis and are associated with the development of many cancers, including CRC as a result of its mutation.<sup>9</sup> In addition, the APC gene mutation is closely related to the development of familial adenomatous polyposis (FAP).<sup>11</sup> FAP is an autosomal dominant hereditary disease characterized by the development of adenoma or polyp in the colon or rectum.<sup>12</sup> APC mutation contributes to carcinogenesis by affecting the cell cycle and different cellular events in addition to the FAP and Wnt/β-catenin pathway.<sup>13</sup> Mutations in genes such as p53, p21, or pRb (retinoblastoma protein) cause a decrease in the restrictions on cell division and tumor formation. It enables the activation of the E2F transcription factor, which stimulates the synthesis of proteins required for phosphorylated pRb DNA synthesis, and the synthesis of proteins required for cell division. Cell cycle and division are regulated by cyclin-dependent kinases. pRb phosphorylation is regulated by cyclin dependent kinase-2 and cyclin E complex. As a result of DNA damage activating the p53 gene, cyclin stimulates the synthesis of p21, which is an inhibitor of cyclin-dependent kinase-2 complex, and thus, the damaged cell cycle with DNA damage is inhibited.<sup>14</sup> The p53 gene affects cancer cell apoptosis, cell cycle escape, cellular aging or DNA repair, and it is thought to be mutated in 50% of human malignancies.<sup>15</sup> Ras pathway activation affects the differentiation, movement, survival and proliferation of cells. The binding of epidermal growth factor to the epidermal growth factor receptor, which is its receptor, causes a series of autophosphorylation within the cell, stimulating Raf-MEK-ERK and PI3K-Akt signaling, such as Ets, Elk-1 (ETS-like protein 1), and Myc. It causes the stimulation and proliferation of transcription factors. In 90% of SRMs (SRMS Src-related kinase lacking C-terminal regulatory tyrosine and N-terminal myristoylation sites), the *Kristen rat sarcome virus (KRAS)* gene is mutated.<sup>16</sup>

### Risk Factors for Colorectal Cancer Development

Obesity, physical inactivity, Western dietary habits, alcohol consumption, smoking, age, history of inflammatory bowel disease, family history of CRC, genetic predisposition, Lynch syndrome (hereditary non-polyposis CRC), familial adenomatous polyposis, ethnicity and type 2 diabetes are risk factors which contribute to the development of CRC.<sup>17</sup> It is suggested that 25% of CRC cases have familial CRC history and 5-6% of them are caused by mutations in the genes related to CRC.<sup>18</sup> Mutations in genes such as APC, MUTYH, MLH1, MSH2, STK11, SMAD4, BMPR1A and PTEN contribute to the development of CRC.<sup>18</sup> The genetic basis of CRC development is associated with two mechanisms: chromosomal and microsatellite instability.<sup>19</sup> Changes which affect processes such as chromosome number deletion, duplication, rearrangement, and

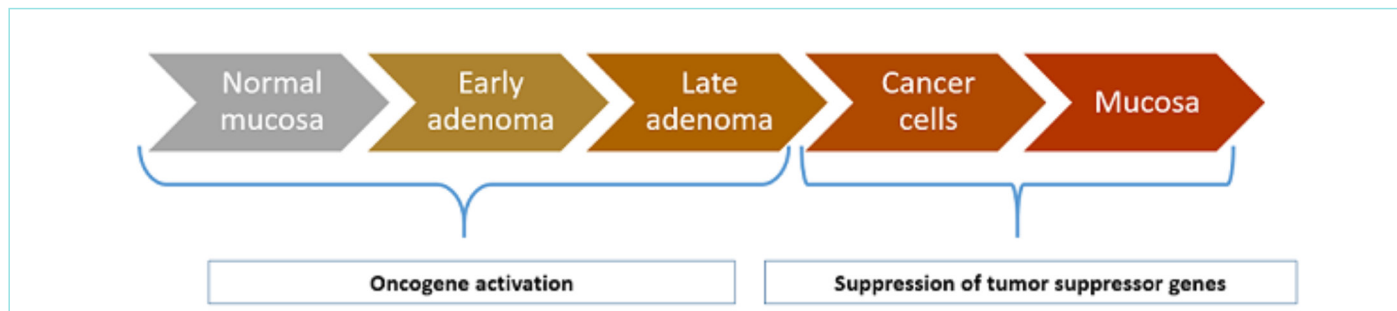


Figure 1. Colorectal cancer development.<sup>4</sup>

translocation are associated with CIN. Microsatellite instability is associated with incompatible DNA repair (MMR) and the silencing of tumor suppressor genes such as *p53* and *MLH1* as a result of hyper-methylation.<sup>19</sup>

### Molecular Mechanisms Contributing to the Development of Colorectal Cancer

There are three main mechanisms for CRC carcinogenesis. The first of these is the suppressor pathway or CIN pathway put forward by Fearon and Vogelstein<sup>20</sup> in 1990. Activation of *KRAS*, an oncogene, and the suppression of tumor suppressor genes *APC*, *SMAD4*, and *p53* are observed in this pathway. These molecular changes cause neoplastic transformations.<sup>20,21</sup> The second mechanism is also known as the mutator pathway or the micro-satellite instability pathway. The formation of CRC is due to errors which occur during DNA replication and mutations in repair genes (mismatch repair genes). These anomalies occurring in repetitive DNA fragments (micro-satellite) cause mutations in many genes involved in many cancer prognosis and accelerate tumor formation.<sup>21</sup> Another mechanism which plays a role in CRC formation is known as the epigenetic pathway involving aberrant hyper-methylation. In this pathway, changes or silencing of gene functions is observed as a result of hyper-methylation. Methylation pathway tumors mostly affect women and the elderly. These tumors are often poorly differentiated and more likely to have *BRAF* mutations. If the methylation pathway is active in the person, it is known not to respond to 5-fluorouracil, which is one of the most important chemotherapy treatment methods in CRC.<sup>21</sup>

### Molecular Mechanism of Apoptosis and the Importance of Apoptosis in Colorectal Cancer

In multicellular organisms, there is a homeostatic balance between the number of cells which increase with mitosis and the number of cells which are damaged or no longer needed. The mechanism which provides this balance is the apoptosis mechanism which comes into play with the detection of cellular abnormalities.<sup>22</sup> Apoptosis first attracted attention as a result of programmed cell death in some of the somatic cells during the normal development of a nematode *Caenorhabditis elegans*.<sup>23</sup> Apoptosis is regulated by the family of proteases known as caspase (cysteinyll, aspartate-specific proteases).<sup>17,24</sup> It is possible to categorize those caspases which manage apoptosis, also known as programmed cell death, into two groups; initiator caspases (caspase-8, -9) and terminating caspases (caspase-3, -6, -7).<sup>22</sup> Activation of terminating caspases irreversibly induces the activation of endonucleases, destruction of nuclear proteins and cytoskeleton, and the elimination of damaged cells by stimulating the expression of phagocytic ligands.<sup>4,22</sup> Apoptosis is activated on many intracellular and extracellular signaling pathways.<sup>25</sup> One of these pathways is the intrinsic pathway, also known as the mitochondrial pathway, and the other is the extrinsic pathway, also known as the death receptor pathway.<sup>25</sup> The intrinsic (mitochondrial) apoptotic pathway is stimulated in response to situations such as DNA damage, activation of oncogenes, insufficiency of growth factors or the presence of oxidants. Oligomerization of the *BAX* and *BAK* proteins causes the mitochondrial membrane to become permeable and causes leakage into the intermembrane space of the intra-membrane second mitochondria-derived caspase activator (*SMAC*), cytochrome-c. As a result of cytochrome-c release; together with cytochrome-c, apoptotic proteinase activating factor-1 (*APAF-1*), *dATP*, and pro-caspase-9, the apoptosome is formed. Conversion of the

procaspase-9 in its apoptosome to caspase-9 enables the induction of the terminating caspases (caspase-3, -6 and -7) and cell death.<sup>22,26</sup>

Ligands which are placed in the extrinsic or death ligand apoptotic pathway are Fas-ligand (*Fas-L*) and TNF-associated apoptosis-inducing ligand. The binding of the ligands to the receptor causes the death regions (*FADD*, *TRADD*) in the cytosolic part to bind to the procaspase-8 and -10 and the formation of a signal complex (*DISC*), which causes intracellular death. Formation of the *DISC* complex causes caspase-3, -6, and -7, terminating caspases activation and so triggers cell death.<sup>22,27</sup>

Apoptosis is a form of cell death necessary for tissue homeostasis, embryonic development and immune regulation.<sup>28</sup> The reduction of apoptosis or the development of resistance to apoptosis, which is important for the elimination of malignant cells and suppression of tumorigenesis, is the most important factor contributing to carcinogenesis.<sup>29</sup> In general, the impaired balance of pro-apoptotic and anti-apoptotic proteins decreased caspase function and impaired death receptor signaling are changes that can be seen in cancer cells.<sup>29</sup> The changing mechanisms associated with apoptosis which contribute to cancer development can be summarized as follows;

- Decreased death receptor expression,
- Reduced death signaling,
- *p53* mutation,
- Decreased caspase expression,
- Impaired *Bcl-2* protein family balance,
- An increase in anti-apoptotic proteins (*Bcl-2*, *Bcl-xL*, *Mcl-1*, *Bcl-w*),
- A reduction in pro-apoptotic proteins (*Bid*, *Bim*, *Puma*, *Noxa*, *Bad*, *Bax*, *Bak*),
- Increased apoptotic protein inhibitor expression.<sup>28</sup>

In the development of colon cancer, the inability or interruption of the apoptosis mechanism has molecular importance. In colon cancer, there is an imbalance between the number of cells renewed and the number of cells which die. This imbalance can be explained by increased proliferation.<sup>29</sup> Over time, the cell cannot respond to dangerous signals resulting from mutations with apoptosis, and this causes malignant transformations. While proliferation occurs more than necessary in CRC formation, apoptosis occurs less frequently.<sup>28</sup>

### PRO-Apoptotic and Anti-Cancer Effects of Quercetin

Quercetin is a polyphenolic compound in the flavonol group of flavonoids. Vegetables, fruits and beverages such as onions, apples, strawberries, broccoli, tea and red wine are considered rich sources for quercetin. Quercetin can be found in foods in free (aglycone), carbohydrate (quercetin glycoside) or alcohol forms (quercetin methyl ester).<sup>30</sup> It is thought that there is an estimated 3-40 mg of quercetin intake per day in Western diets, and this rate may increase to 250 mg in societies with high vegetable and fruit consumption.<sup>31</sup> The quercetin contents of some foods in our daily diet are given in Table 1.

Quercetin is a powerful antioxidant and lipid peroxidation inhibitor, thanks to its catechol and hydroxyl group configuration, its capacity to scavenge free radicals and to bind metal ions.<sup>32,33</sup> Quercetin exerts an

anti-inflammatory effect by suppressing the NF-kB transcription factor responsible for the expression of COX-2 enzyme and pro-inflammatory cytokines. Quercetin has the potential to exert an anti-cancer effect by inhibiting important signaling pathways in carcinogenesis such as MAPK, JAK-STAT, and PI3K-Akt. In addition, it may show a potential inhibitory effect on cancer proliferation by inducing p53 activation in cancer cells (Figure 2).<sup>33</sup>

Quercetin is a lipophilic compound which can cross the cell membrane and activate multiple intracellular signaling pathways in chemoprevention.<sup>32</sup> The best known effects of quercetin are its dual function as a pro-oxidant or anti-oxidant. Oxidative stress caused by ROS species causes DNA damage and mutation development. Mutations are effective in hyperplasia and the proliferation of malignant tumor cells. Quercetin can reduce ROS by exchanging electrons and thus has the potential to prevent ROS-mediated DNA damage. In addition, quercetin can induce apoptotic pathways by showing cytotoxic and pro-oxidative effects.<sup>32,33</sup>

Quercetin has the potential to induce apoptosis via the mitochondrial apoptotic pathway by causing changes in mitochondrial membrane potential. In addition, quercetin also induces apoptosis through the activation of p53, increasing the expression of pro-apoptotic molecules such as Bax, caspase-3, and caspase-9, and also the inhibition of anti-apoptotic proteins such as Bcl-2.<sup>32,33</sup> Quercetin increases the expression of cyclin-dependent kinases and cyclin B1 inhibitors p21, p27 and the tumor suppressor gene *p53*, which are involved in the cell cycle, and induces the cell to stop its cycle in the G1 and G2/M phases, thereby inhibiting cancer proliferation.<sup>29</sup> Heat shock proteins (HSPs) are proteins known to increase under stressful conditions such as wound healing, tissue repair, and carcinogenesis. Studies have shown that overexpression of HSPs, particularly HSP27, is closely associated with poor prognosis in many types of cancer. These proteins can affect cancer cell proliferation, invasion, differentiation, metastasis, and cell death.<sup>34,35</sup> It is thought that quercetin inactivates protein chaperones by

inhibiting kinases which contribute to the induction of HSPs. Therefore, it is thought that quercetin can be applied as a supplement in cancer treatment in combination with existing chemotherapies.<sup>29</sup>

Experimental studies have demonstrated that quercetin affects the cell viability on different cell lines and colon cancer cell lines.<sup>27,36-39</sup> Özsoy et al.<sup>6</sup> conducted a study with two colon cells of different origins, primary and metastatic colon cancer cell lines, and demonstrated that the effective dose and incubation time was 25 µg/mL quercetin for 48 hours in both the Colo 320 and Colo 741 colon cancer cell lines. Their study showed that quercetin induced apoptosis which is the biological process cells use to achieve homeostasis and it plays a critical role in eliminating cancer cells. Apoptosis is governed by initiating caspases (caspases-8, -9) and terminating caspases (-3, -6, -7). Anti-apoptotic proteins such as Bcl-2, Bcl-XL, and Bcl-w and also pro-apoptotic proteins such as Bax, Bak, Bid, and Bim are proteins involved in both the intrinsic and extrinsic apoptosis pathways.<sup>22</sup> Afrin et al.<sup>40</sup> and Soykut et al.<sup>41</sup>, in their studies on different colon cancer cell lines, found the result that plant extracts rich in quercetin content trigger apoptosis in colon cancer cells. Afrin et al.<sup>40</sup> showed that while terminator caspase-3 levels increased in the LoVo metastatic colon cancer cell line after the application of manuka honey, which contains quercetin, levels of the anti-apoptotic protein Bcl-2 decreased. Becer et al.<sup>42</sup> revealed that quercetin was the dominant polyphenolic compound in the content analysis of molokhiya (*Corchorus olerius* L.), a local food in Cyprus, and reported that apoptosis was triggered after the application of *Corchorus olerius* L. extract. An *in vitro* study investigating the pro-apoptotic effects of quercetin in Colo 320 and Colo 741 colon cancer cell lines found that the effects of quercetin on apoptosis may differ depending on the cell type and it is more effective in primary (Colo-320) colon cancer cell lines.<sup>7</sup> Yang et al.<sup>43</sup>, in their study on the HT-29 colon cancer cell line, determined that after 48 hours of 81 µM quercetin administration, anti-apoptotic Bcl-2 levels decreased, pro-apoptotic Bax levels increased, and the terminator caspase-3 levels increased and apoptosis was triggered. In another study, the colorectal adenocarcinoma cell lines HCT15 and HT-29 were compared. Cell viability of HT-29 cells was found to be lower as a result of incubation with quercetin. It was found that apoptosis was induced only in HT-29 cells, and that the activation of caspase-3 and cytochrome-c increased significantly. According to the results of that study, it was noted that increased intracellular ROS production and COX2 gene expression may induce apoptosis.<sup>44</sup> In addition, in another study where the *in vivo* and *in vitro* pro-apoptotic effects of quercetin were examined in a dose and time dependent manner, the results reported that quercetin induced apoptosis in CT-29 (mouse colon cancer) cells (120 µM). In subsequent *in vivo* experiments, quercetin reduced tumor growth and increased survival rates when given in high doses (100-200 mg/kg).<sup>45</sup>

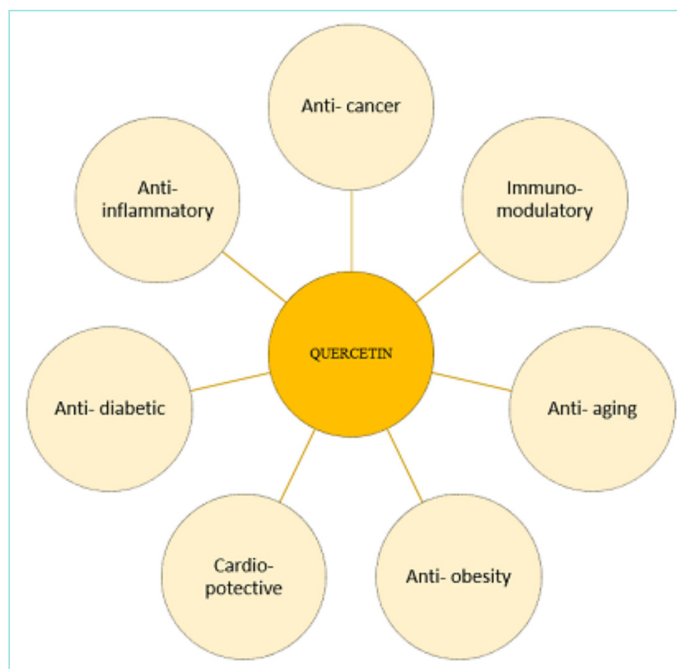


Figure 2. Health effects of quercetin.<sup>31</sup>

| Table 1. Quercetin content of some foods <sup>46</sup> |              |
|--|--------------|
| Food   | mg/100 grams |
| Onion  | 11-41.90     |
| Lettuce  | 40.27        |
| Tea  | 2            |
| Apple  | 2.0-5.0      |
| Cherry   | 1.0-3.0      |
| Tomato   | 1.6          |
| Broccoli   | 4.25         |
| Asparagus  | 7.0-20.0     |

## CONCLUSION

The studies presented suggest that quercetin has potential positive effects in CRC therapy. Various experiments have shown numerous action mechanisms which could inhibit multiple oncogenic signaling. Quercetin is a safe polyphenolic compound with no reported toxicity at cellular level in studies. Quercetin has beneficial biological effects with great potential to be used as an alternative therapy for colon cancer. However, additional clinical studies are needed for the further investigation of the mechanisms of quercetin to determine its role of suppression and intervention of cancer and possible use as an alternative colon cancer therapy.

## MAIN POINTS

- Experimental research supports that quercetin can trigger apoptosis in colorectal cancer cell lines at different doses and incubation times.
- Quercetin may be effective in integrated cancer treatment by affecting cell death.
- Quercetin may provide the future for chemo-preventive drug development.

## ETHICS

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: S.Ö., G.S., E.B., Design: S.Ö., G.S., E.B., Supervision: S.Ö., G.S., E.B., Fundings: S.Ö., G.S., E.B., Data Collection and/or Processing: S.Ö., G.S., E.B., Analysis and/or Interpretation: S.Ö., G.S., E.B., Literature Search: S.Ö., G.S., E.B., Writing: S.Ö., G.S., E.B., Critical Review: S.Ö., G.S., E.B.

## DISCLOSURES

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study had received no financial support.

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