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# Potential Chemotherapeutic Effects of Quercetin in Neuroblastoma

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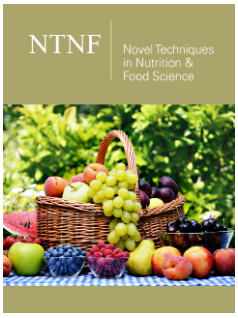


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## Abstract

Neuroblastoma is a cancer common to pediatric populations and are categorized as neoplastic growths inside the central and peripheral nervous systems. Neuroblastomas can dissipate early in life or can grow become deadly tumors by metastasizing. For low-risk neuroblastomas, surgery and essential treatments are sufficient for good outcomes. Conversely, high-risk tumors, isolated by specific genetic markers, are being studied in the hopes of one day generating better treatments and patient prognoses. Quercetin (Qu), a flavonoid in plants, has become popular in medical research for its various chemical (antioxidant and anti-inflammatory) and cancer treatment (metabolic regulatory) properties. Qu's mechanism of action depends on its concentration and the type of cancer. Extensive research using many cancer lines has identified numerous pathways that mediate Qu-induced loss of cell viability. Limited research has been done on neuroblastoma cell lines and quercetin. Future research is needed to identify specific mechanisms of action with concentrations of Qu needed to modify the growth of neuroblastoma cells.

**Keywords:** Neuroblastoma; MDM2; C-Myc; Apoptosis; Pro-Oxidant; Antioxidant

**Abbreviations:** MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; Qu: Quercetin; ROS: Reactive Oxygen Species; TRAIL: Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand

## Quercetin (Qu) Overview

### General properties

Qu is an abundant flavonoid found in high concentrations in many foods (e.g., apples, berries, kale, nuts, onions, soybeans, and tomatoes), drinks (e.g., beer, black tea, and red wine), and herbs (e.g., Ginkgo biloba and Hypericum perforatum [St. John's wort]) [1-3]. The health-protective effects of diets rich in fruits and vegetables are thought to be mediated, at least in part, by Qu's antioxidant, anti-inflammatory, and anti-carcinogenic effects. Although Qu is relatively easily obtained in a balanced diet (a typical Western diet is estimated to have 4-40mg Qu daily), it has been developed as an over-the-counter nutritional supplement (500-1,000mg daily). Side effects associated with Qu are few: abdominal discomfort, nausea, and headache. Notably, liver injury resulting from Qu supplementation has not been reported [1]. Indeed, Qu prevents liver damage in a mouse model of excessive alcohol intake [4].

### Chemical properties and bioavailability

Qu, whose IUPAC name is 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one, is a pentahydroxyflavone and 7-hydroxyflavonol with five hydroxy groups at the 3-, 3′-, 4′-, 5-, and 7- positions. It also has numerous phenol functional groups, giving the flavanol unique biochemical properties. Various sugars (glucose, xylose, or rutinose) can conjugate to one of the hydroxyl groups, forming Qu glycosides [2]. Qu is reportedly more bioavailable than other phytochemicals [2]. However, although it has 12 hydrogen bond donors or acceptors, it has a

formal charge of 0 and is far more soluble in alcohol (~3.45mg/mL) than in water (<1mg/mL) [5]. Qu is unstable in the physiological medium of the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism, resulting in a short biological half-life. These factors, alongside the previously mentioned poor aqueous solubility, limit the therapeutic potential of Qu. However, the use of nanoparticles to deliver Qu is proposed as a promising method to enhance Qu bioavailability (reviewed in [2]).

The bioavailability of Qu and its conjugates have been closely analyzed in both animal and human studies. In one study involving rats, it was determined that 93.3% of the Qu was absorbed in the gut, whereas 3.1% was absorbed in the liver [6]. The remaining 5.3% was deemed note bioavailable. In contrast, it was revealed in a human study that the majority of Qu is lost in the intestine (93%), whereas 6.7% is absorbed in the portal vein [7]. Although quercetin may not have robust bioavailability, its conjugates seem to fare better in absorption by the body. One study suggests that is quercetin (a Qu conjugate) is the most optimal in terms of absorption in the body [8]. Other studies indicate that absorption is increased when Qu is combined with vitamin C, folate, or bromelain.

### Pharmacological effects overview

Providing an exhaustive listing of the totality of Qu's pharmacological effects is beyond the scope of this review. Briefly, Qu and other polyphenolic compounds protect against Reactive Oxygen Species (ROS)-induced cellular oxidative stress, thereby inhibiting the development of oxidative stress-related disorders and diseases. Examples include neurodegenerative disease, cardiovascular disease, diabetes, infectious disease, and (see more below) cancer [9]. Six quercetin derivatives were shown to be anti-inflammatory in human platelets, as determined by the inhibition of cyclooxygenase-1 and 12-lipoxygenase [10]. The COVID-19 pandemic ushered in a new era of basic and clinical research. SARS-CoV-2 infection elicits a cytokine storm and subsequent inflammatory state that ultimately causes acute lung injury, respiratory distress syndrome, and multiple organ dysfunction syndromes, sometimes resulting in death. Qu was shown to suppress the inflammasome called NLRP3 (nucleotide-binding oligomerization domain, leucine-rich repeat-containing protein 3), an effect the authors suggested could be exploited therapeutically to reduce the life-threatening inflammation seen in patients with COVID-19 [11]. Qu also may have direct antiviral activity against SARS-CoV-2: it binds robustly to the receptor-binding domain of SARS-CoV2 [12]. This antiviral activity extends to influenza A, inhibiting the entry of the H5N1 virus using a pseudovirus-based screening system [13]. The anti-carcinogenic properties of Qu are numerous. Briefly, Qu-mediated chelation of metal ions maintains the function of DNA repair pathways in lung cells, an effect that may inhibit carcinogenesis. Higher doses of Qu induce apoptosis of cancer cells through a wide variety of ways; Qu also inhibits the canonical phosphatidylinositol-3 kinase (PI3K)/Akt/Wnt and signal transducer and activator of transcription 3 (STAT3) pathways in cancer cells [14] (see more below). The adage credited to Paracelsus that "all things are poison, and nothing is without poison, the dosage alone makes it, so a thing is not a poison [15]" perfectly describes Qu. At typical concentrations, Qu serves in a protective role as an antioxidant. However, Qu transforms into a pro-oxidant at higher concentrations in a mechanism involving the glutathione pathway [16] (see more below).

### Significance statement

This short review describes Qu's therapeutic effects and potential mechanisms related to the prevention and chemotherapy of cancers in general. The therapeutic effects of Qu on neuroblastoma, with a focus on its interaction with cell growth and apoptotic pathways, are explored in more detail.

## Anti-Carcinogenic Effects of Qu

Neuroblastoma is a relatively common pediatric neoplasm that can develop into peripheral and central nervous systems tumors. Neural crest maturation or relocation errors can lead to neuroblastoma during fetal development [17]. Although cases of children born with neuroblastoma that degenerates in infancy have been reported, some neuroblastoma tumors can metastasize and results in poor patient prognoses. [17,18]. A genetic aberration seen in 80% of high-risk neuroblastoma cases is the deletion of a portion of the short distal arm in chromosome 1, specifically around 1p36 [18,19]. The omission led researchers to investigate what deleted gene in this chromosome is responsible for this finding [18,19]. A crucial tumor suppressor gene, perhaps Chromodomain Helicase DNA binding protein 5 (CHD5), is thought to be deleted from the 1p36 region to initiate neuroblastoma development [19]. The heterogeneity of patients with neuroblastoma complicates the determination of treatment options, prognoses, or risks. One genetic factor is the amplification of the MYCN oncogene on chromosome 2 [17,18,20,21]. Although many treatment options exist for the varying types of neuroblastomas present in pediatric patient populations, surgery seems to be the most beneficial for low-risk neuroblastomas without MYCN gene amplification [20,21]. Conversely, there are few treatment options that produce optimal survival rates in patients with high-risk neuroblastoma. Thus, there is a definite need to understand the mechanisms underlying neuroblastoma development and to develop treatments exploiting those mechanisms for high-risk neuroblastoma [22-37].

### General anti-carcinogenic effects of qu

Outside of the flavanol's free radical scavenging and anti-inflammatory effects described above, it also affects cellular division and programmed cell death in certain cancer cell lines-suggesting the potential for Qu as a preventive supplement, cancer chemotherapy drug, or an adjunct medication combined with traditional chemotherapy. Despite quercetin's rising popularity, speculation exists regarding its effects on cancer. However, such speculation can be attributed to a lack of clinical trials because in vitro studies have shown promising results concerning the substance's antioxidant and anti-cancer effects. Various studies

have shown promising effects of highly concentrated quercetin on certain cancers, including prostate, colon, breast, and kidney. These studies revealed that Qu's mechanistic action induces cell cycle arrest, ultimately decreasing cancer cell proliferation [38]. One study showed that quercetin inhibits cervical cancer cells through reducing ubiquitin-conjugating enzyme E2S (UBE2S) expression [39,40]. Another study using Qu glucuronides to treat lung cancer cell proliferation showed G2/M arrest and apoptosis, ultimately inhibiting the proliferation of the cancer cells [41]. Despite the data indicating tangible improvement in cell cycle arrest, decreased gene expression, and decreased cancer cell proliferation with Qu, very few clinical trials have been performed. This is partly due to the various limitations that quercetin treatment presents. As discussed earlier, Qu has poor bioavailability and absorption rates. Additionally, quercetin undergoes rapid metabolism and elimination [42]. Therefore, because Qu conjugates possess an increased bioavailability and absorption compared to quercetin alone, they may be the better choice to serve as the treatment studied in clinical cancer trials.

## Antioxidant properties

Antioxidants are molecules that can reduce and neutralize ROS and free radicals that could damage the cell's necessary structures-membranes, DNA, proteins, or other biochemicals. Qu is an effective antioxidant and free radical scavenger because of its capacity to become oxidized while simultaneously remaining stable [8]. Specifically, because of its many hydroxyl groups, conjugated pi orbitals, and benzene rings, Qu donates electrons to ROS in a manner that does not damage or kill the cell in the process [8,22]. Qu's ($C_{15}H_{10}O_7$) structural makeup is unique in its ability to scavenge free radicals while simultaneously chelating metal ions, thereby producing antioxidant effects. Qu is only capable of this specialized process based on the inclusion of two antioxidant pharmacophores found within its structure [32]. Qu's influential antioxidant properties are attributed to its ability to control oxidative balance [33]. The oxidative balance is made possible through managing glutathione levels and enzymatic activity, and ROS such as peroxides [33].

As introduced earlier, Qu has dose-dependent effects with respect to its ability to serve as an antioxidant or as a pro-oxidant molecule, especially in cancer cells. Certain cancers result from DNA damage, possibly ROS-induced oxidative damage, and gene mutations; in these cases, lower concentrations of Qu prevent the development of cancer in its role as an antioxidant [23]. The switch to its pro-oxidant role involves glutathione, which is a tripeptide that scavenges free radicals. Qu reacts with hydrogen peroxide to produce the o-semiquinone radical plus Qu-quinones. The Qu-quinones, like ROS, induce cell death by damaging proteins and DNA [22,24]. If glutathione levels are sufficient, however, Qu preferentially reacts with it rather than hydrogen peroxide. Higher concentrations of Qu, especially with extended exposure, substantially reduce glutathione levels and its pro-oxidant role overshadows its antioxidant role.

Thus, high concentrations of Qu are likely to damage cancer cells. Certain cancer cells exhibit metabolic and signaling pathway hyperactivity and the overproduction hydrogen peroxide and superoxide anions [22,23]. Under these conditions, glutathione is likely to be depleted, initiating the switch to pro-oxidant Qu [16]. Therefore, it is necessary to determine whether Qu in lower or higher concentrations in specific cancer cells acts as an antioxidant or pro-oxidant before it can be recommended as a cancer preventive agent or therapeutic agent.

## Cell cycle control

From in vitro studies, Qu has been viewed to inhibit cell cycles at various points and regulate multiple molecules. In colon, breast, and ovarian cancer cell lines, Qu was observed to induce apoptosis by inhibiting the cell's G1 phase and stopping the transition of the cell's G0/G1 phase and G2/M phase [3,23]. In hepatoma cell culture lines, Qu arrested cell division at the G2/M phase by upregulating p73 and p21 genes and decreasing cyclin B concentrations required for the G2/M stage in cellular division [16]. In prostate cancer cell culture lines, Qu induced arrest at the G1 phase by increasing activity of the p21 gene [25]. Studies in cancerous hepatocytes showed that Qu is an inhibitor of DNA topoisomerase 2, an enzyme needed for replicating genetic material during cell division [16]. In contrast, other studies use Qu and doxorubicin, a potent DNA topoisomerase 2 inhibitor, to treat breast cancer to show how Qu protects non-cancerous tissues from the lytic effects of the drug [26]. Through the various views on Qu and cancer cells, it is postulated that Qu's impact on the cell cycle is dependent on cell type.

Encoded by the gene of the same name (cellular-Myc (c-Myc) on chromosome 8) c-Myc is a 62-kD oncogenic transcription factor that controls the gene expression of many genes involved in cell proliferation, cell differentiation, apoptosis, and metabolism [27]. The C-terminal domain of c-Myc contains a basic helix–loop–helix leucine zipper domain (bHLHZip) that, upon heterodimerization with another bHLHZip protein called Myc associated factor X (MAX), creates a complex that can recognize a subset of enhancer box (E box) sequences on DNA and regulates gene transcription [28]. Dysregulation of c-Myc has been linked to up to 70% of human cancers [27]. Therefore, compounds exhibiting modulating effects on c-Myc regulation are of interest in anti-tumor investigations.

Qu has been reported to reduce c-Myc by blocking the Akt/mammalian target of rapamycin (mTOR)/c-Myc signaling pathway in human skin squamous carcinoma A431-III cells [29,30] and Phosphatidylinositol-3 Kinase (PI3K)/Akt/mTOR and signal transducer and activator of transcription 3 (STAT3) signaling pathways in lymphoma cells [31,32]. In A431-III cells, downregulation of c-Myc suppresses Ribosomal Protein (RP) S19 [29] and RPS12 [30], both of which are known to contribute to the metastatic potential (e.g., invasiveness and mobility) of cancer cells. RPS19 also regulates epithelial-mesenchymal transition markers [29], whose expression has been implicated in the pathophysiology of malignancies. Moreover, Qu acts as a β-catenin

inhibitor. It blocks the Wnt/β-catenin/MYC/sex-determining region Y-box transcription factor 2 (Sox2) axis, a signaling pathway that plays a role in the formation of cancer stem-like phenotype in Anaplastic Lymphoma Kinase (ALK)-positive anaplastic large-cell lymphoma [33]. Furthermore, the binding of Qu to c-Myc promoter G-quadruplex DNA sequence Pu24T stabilizes the G-quadruplex DNA structure, thus hindering the activity of the c-Myc promoter in human cervical carcinoma cells (HeLa cell lines) [34].

Qu-induced c-Myc suppression also inhibits the proliferation of pancreatic ductal carcinoma [35] and the human gastric carcinoma cell line MGC-803 [36]. Hyperoxide, a plant-derived quercetin derivative, exhibits anti-proliferation properties against human cervical cancer (HeLa [also see above] and C-33A) cells through c-Myc gene expression reduction [37]. Qu's anti-cancer ability against colon cancer is still under investigation. A recent study studied the combination of Qu and Triphala, which is an Ayurvedic medicine comprising the fruits of three plants (Emblica officinalis, Terminalia bellerica, and Terminalia chebula) [38]: The Qu-containing methanol extract of Triphala suppresses c-Myc protein levels and inhibits the growth of human colon cancer stem cells [39]. However, when Tao et al. [40] treated colon tumors with Qu, they found that it did not affect gene expression of c-Myc [40]. In addition to hampering the cell growth of the cancer mentioned above cells, Qu-induced c-Myc suppression promotes cell differentiation in K562 human leukemia cells and apoptosis in both K562 cells [41] and Burkitt's lymphoma cells [31]. In summary, Qu and its derivatives either act alone or synergistically with other pharmaceutical chemicals to reduce the expression of c-Myc and inhibit the growth of various cancer cells through multiple pathways.

### Apoptosis regulation

Apoptosis has been proposed as a mediator of Qu's anti-cancer effects; Qu's apoptosis-inducing effects are proposed to occur through a variety of mechanisms. In a study using nine cancer cell lines (including colon carcinoma, prostate adenocarcinoma, pheocromocytoma, breast cancer, acute lymphoblastic leukemia, myeloma, lymphoid, and ovarian cancer), Qu induced cell death as measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay at doses as low as 10μM. This finding was complemented by the finding that in several of the cell lines, Qu induced apoptosis as measured by Annexin V/PI staining [42].

Both the intrinsic and extrinsic pathways are activated by Qu. Briefly, the intrinsic pathway is activated when Bax inserts into the mitochondrial membrane (an effect that is normally inhibited by Bcl-2 and Bcl-XL). Qu targets this part of the intrinsic pathway in two ways: (1) redistributing Bcl-2 and (2) increasing the translocation of Bax to the mitochondrial membrane. At the gene level, Qu inhibits the transcription of genes like Bcl-2 and p53. Reduced Bcl-2 protein expression has the same effect as redistribution: the uninhibited Bax protein penetrates the mitochondrial membrane. The p53 protein is typically considered a tumor suppressor because it stimulates p21 and suppresses cyclin D1 and causes an arrested cell cycle. Qu, however, inhibits p53, which logically would increase cell division. Recall that the effect of Qu on cellular pro-oxidant or antioxidant status depends on the level of glutathione. Similar here is that the p53 activation has differential effects depending on the degree of redox stress: If redox stress is typical, then p53 increases antioxidant enzymes including superoxide dismutase and catalase. If redox stress is higher, p53 increases pro-oxidant and pro-apoptotic proteins (including Bax). This leads to apoptosis. Thus, in the former case the p53 protein expresses mild antioxidant properties; therefore, when Qu inhibits its expression, cancer cell has an increased chance of cytotoxicity in the presence of Qu. Conversely, in the latter case p53 induces apoptosis and its inhibition may result in unwanted cell growth [22,42]. Thus, it may be that the redox states typical of various cancer types needs to be identified before Qu can be suggested as a preventive or therapeutic supplement.

In contrast, Qu in other studies has been shown to increase the expression of p53 and activate intrinsic or mitochondrial-mediated apoptotic mechanisms [22,23,43]. In leukemia, breast cancer, ovarian, glioma, colon, and immune cancer cell lines, Qu causes a cascade as follows: increased calcium levels; reduced the mitochondrial membrane potential; increased release of cytochrome c; increased caspases (e.g., caspase 3 and 9); apoptosis [22-25,43]. Qu's other apoptosis-inducing effects in breast and prostate cancer cell lines include the following: reduced cyclin D; increased ROS production with secondary p38 and caspase activity; depolarized microtubules by binding to tubulin proteins; and Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL)-induced apoptosis by stimulating death receptors and activating extrinsic apoptosis pathways, [22]. Qu's activation of extrinsic apoptosis is observed in breast, lung, melanoma, and ovarian cancer cells by activating caspase 3 and 8 proteins from the promotion of TRAIL death receptors [22,24,44].

Cancer often produces epigenetic changes, and some studies have suggested that Qu hinders these changes through chromatin remodeling [35]. In the cancer cascade itself, murine double minute 2 (MDM2) is an oncogene considered a p53 target gene. Improper functioning of MDM2 can lead to the dysregulation of p53, which can, and most likely will, lead to tumorigenesis [36]. MDM2 is frequently overexpressed in many malignancies, such as neuroblastoma, which suggests its importance for cancer development [37]. Depending on the type of cancer, quercetin may have the ability to decrease the expression of MDM2, thus slowing the progression of cancer. However, no significant studies either confirm or deny this characteristic ability of quercetin.

## Quercetin in Neuroblastoma

The precise mechanism of Qu's effects on neuroblastoma cells is purported to be undetermined [45]. Although the action is unclear, available studies have shown decreased cell viability in neuroblastoma with different concentrations of Qu. Research in neuroblastoma cells (SK-N-SH) demonstrated adverse effects on the

neuroblastoma cell membranes and eventually cell viability when exposed to Qu, which is thought to be mediated by Qu's hydrophobic characteristics allowing it to accumulate in the insoluble portions of the cell membrane [45]. Studies in mouse neuroblastoma cells (N2a) treated with Qu showed increased activities in caspase 3 and 9 proteins, which induced apoptosis (intrinsic pathway), all while correlating Qu's effects to its dosage relative to the cell type [46]. Another hypothesized action of Qu in neuroblastoma cells was its ability to block potassium ion channels [47].

## Conclusion

Further studies into the effects of Qu with neuroblastomas would benefit the medical community when combating aggressive, high-risk tumors. Future research studies should include investigating protein concentration changes in neuroblastoma cells when treated with various concentrations of Qu. The chosen proteins would be specific to an apoptotic or cell cycle pathway that could help differentiate specific mechanisms taken by Qu to decrease the cell viability of neuroblastomas.

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## Conflict of Interest

The funders of the article processing charges had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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