Quercetin

high Qu concentration, causes a reduction in GSH (which is a Hallmark of Cancer) content, which causes it to act as pro-oxidant. (Which raises ROS killing cancer cells)

https://www.nature.com/articles/s41598-023-39279-z
The effect of resveratrol, curcumin and quercetin combination on immuno-suppression of tumor microenvironment for breast tumor-bearing mice 2023
Quercetin supplementation for 8 weeks at 500 mg day^{-1} significantly reduced inflammation, morning pain, and post-activity pain in women with rheumatoid arthritis[65].
Therefore, the recommended dose for humans is 0.3–4 mg day^{-1}.
400-500 mg orally three times daily
Prostatitis: 500 mg orally twice daily
420-1400 mg/m2 intravenous (IV) bolus once/week
https://onedaymd.aestheticsadvisor.com/2021/12/quercetin-101-heres-what-you-need-to.html
Most quercetin studies use a dosage of around 500mg per day, although some studies use a dosage of 500mg taken twice per day.
Most supplements have a similar dosage, offering 500mg to 1,200mg of quercetin per serving.
In some studies, researchers have given participants up to 5,000mg of quercetin per day with no reported side effects.
Quercetin has poor bioavailability. You might take a 1,200mg quercetin supplement, but your body only absorbs a small percentage of it. That's why many quercetin supplements contain vitamin C or bromelain, as some evidence suggests they boost absorption.

https://pubmed.ncbi.nlm.nih.gov/9890646/
Quercetin may act as a cytotoxic prooxidant after its metabolic activation to semiquinone and quinoidal product 1999
In the last ten years, there has been an important increase in interest in quercetin action as a unique antioxidant, but its putative role in numerous prooxidant effects is also being continually updated. The mechanism underlying this undesirable ability seems to involve its metabolic oxidoreductive activation. Based on the structural properties of quercetin, we have investigated whether its catechol moiety may be the potential tool for revealed toxicity. We demonstrated, with an ESR spin-stabilization technique coupled to conventional spectrophotometry, that o-semiquinone and o-quinone are indeed the products of enzymatically catalyzed oxidative degradation of quercetin. The former radical might serve to facilitate the formation of superoxide and depletion of GSH, which could confer a specificity of its prooxidative action in situ. The observed one-electron reduction of o-quinone may enrich the semiquinone pool, thereby magnifying its effect. The two-electron reduction of quinone can result in constant resupply of quercetin in situ, thereby also modulating another pathway of its known biological activities. We have also tried to see whether the intracellular oxidative degradation of quercetin can be confirmed under the controlled conditions of model monolayer cell cultures. The results are indicative of the intracellular metabolic activation of quercetin to o-quinone, the process which can be partially associated with the observed concentration-dependent cytotoxic effect of quercetin.

https://pubmed.ncbi.nlm.nih.gov/37656383/
The multifaceted role of quercetin derived from its mitochondrial mechanism 2024
Quercetin is a flavonoid with promising therapeutic applications; nonetheless, the phenotype exerted in some diseases is contradictory. For instance, anticancer properties may be explained by a cytotoxic mechanism, whereas antioxidant-related neuroprotection is a pro-survival process. According to the available literature, quercetin exerts a redox interaction with the electron transport chain (ETC) in the mitochondrion, affecting its membrane potential. It also affects ATP generation by oxidative phosphorylation, where ATP deprivation could partly explain its cytotoxic effect. Moreover, quercetin may support the generation of free radicals through redox reactions, causing a prooxidant effect. The nutrimental stress and prooxidant effect induced by quercetin might promote pro-survival properties such as antioxidant processes. Thus, in this review, we discuss the evidence supporting that quercetin redox interaction with the ETC could explain its beneficial and toxic properties.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7314298/
PROOXIDANT ACTIVITIES OF ANTIOXIDANTS AND THEIR IMPACT ON HEALTH 2019
The most abundant flavonol is quercetin; it prevents oxidative stress and cell death by scavenging ROS, chelating metal ions and quenching singlet oxygen (*24*).
Prooxidant Activities of Antioxidants
Surprisingly, some popular antioxidants have been reported to have prooxidant behavior. At least three factors can influence the function of an antioxidant transforming it to a prooxidant; these factors include the presence of metal ions, the concentration of the antioxidant in matrix environments and its redox potential (35-37).
Vitamin C is a potent antioxidant but it can intervene as a prooxidant depending on the dose. It can have an antioxidant effect in case of low dose (30-100 mg/kg body weight) and prooxidant effect in case of high dose (1000 mg/kg body weight) (38-40). The prooxidant effect of vitamin C also occurs when it combines with iron, reducing Fe3+ to Fe2+ or with copper reducing it from Cu2+ to Cu+39,40. The reduced transition metals in turn reduce hydrogen peroxide to hydroxyl radicals through Fenton reaction (41, 42). The supplementation of vitamin C and trolox (water-soluble analog of vitamin E) may result in lower normal biological response to free radicals and create an environment that is more sensitive to oxidation. These antioxidants might provoke mild oxidative stress due to their prooxidative properties (43).
Alpha-tocopherol is also known as a potent antioxidant and harmful prooxidant in high concentrations. When reacting with ROS, it becomes a radical itself, and if there is not enough vitamin C for its regeneration, it remains in the reactive state (8, 9).
The prooxidant activity of **beta-carotene** depends on its interaction with biological membranes and the presence of co-antioxidants such as vitamin C. At higher oxygen tension, beta-carotene loses its effectiveness as antioxidant. A systematic review and meta-analysis revealed increased mortality rates after prolonged use of supplements with beta-carotene, vitamin A and vitamin E (44).
Even **flavonoids** have been reported to act as prooxidants in the systems that contain transition metals (7). Flavonoids, such as quercetin and kaempferol, induce DNA damage and lipid peroxidation in the presence of the transition metal.
Phenolics can also display prooxidant effects, especially in a system containing redox-active metals. The presence of iron or copper catalyzes their redox cycling and may lead to the formation of phenolic radicals which damage lipids and DNA (45, 46).

https://www.sciencedirect.com/science/article/abs/pii/B978044464056700009X
Chapter 9 - Quercetin: Prooxidant Effect and Apoptosis in Cancer 2009
Quercetin is the main flavonoid present in the human diet, being the most characteristic representative of the subclass flavonols. Although the beneficial health effects of quercetin are usually linked to its antioxidant properties, there is substantial evidence that its prooxidant features are also relevant regarding its tumoricidal effects. Here we aim to demonstrate that the generation of reactive oxygen species (ROS) by quercetin could also be a desired biological property. The oxygen paradox and its relationship with the mechanisms of intracellular generation of ROS and autoxidation of polyphenols are described herein. The chemical properties, susceptibility to autoxidation, and the role of quercetin as a cocatalyst in peroxidase-mediated reactions are also discussed. The signaling pathways related to apoptosis and their relationship with intracellular redox imbalance are presented. Oxidation therapy, a strategy to treat cancer, and its relationship with ROS and apoptosis are also discussed in the chapter. Finally, we present several experimental findings that support the proposal that the capacity of quercetin as a phytochemical that is able to trigger apoptosis in several tumor cell lineages might be related to its prooxidant features. In conclusion, we propose that quercetin should be considered as a redox-active compound, that, by altering the cellular redox status, through anti- or prooxidant action, is able to promote tumoricidal effects.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/vjch.201900085

Antioxidant vs. pro-oxidant activities of quercetin in aqueous phase: A Density Functional Theory study 2019

The antioxidant potential of quercetin (Quer) has been investigated for its radical scavenging activity and Cu(II) ion chelating one. Two intrinsic reactivities including bond dissociation enthalpy (BDE) and proton affinity (PA) were systematically calculated in water at the M05-2X/6-311++G(d,p) level of theory. All possible hydrated Quer–Cu(II) complexes were also performed to consider its indirect antioxidant activity via the meal ion chelation capacity. Furthermore, reaction enthalpies as well as Gibbs free energies of reactions between Quer-Cu(II) complexes with O2- and ascorbate anion (Asc-) in forming corresponding Quer-Cu(I) ones have also been investigated to draw the larger picture on reduction potential of Cu(II)to Cu(I) ions which may involve in Fenton-like reactions leading to HO radical formation.

Recently, several groups have motivated on the oxidative stress, or pro-oxidant activity, caused by flavonoids or amine based-compounds. And this activity is influenced by concentration, pH of environment and the presence of redox metal.[11] The pro-oxidant activity of the flavonoids is directly proportional to the total phenolic group. When the phenolic group becomes more abundant, significantly increases the production of hydroxyl HO radical in the Fenton reaction.[12] Castaneda-Arriaga et al. reported that purines'anions are capable to reduce Cu(II) to Cu(I) and making the Cu(I) ion available to be involved in Fenton-like reactions which yield HO radicals.[13] The pro-oxidant potential of quercetin has been evaluated via the reduction reaction of the [QuerCu(H2O)2]2+ complexes to [Quer-Cu(H2O)2]+ ones (Fig. 4). In this reaction, Cu(II) ion will be reduced to Cu(I) one which is involved in the Fenton-like reaction producing HO radical.

However, the Cu(II) complex obtained from this O3H/O4 chelation site has high potential to be reduced to Cu(I) complex in both the reactions with the O2- and Asc- reductants. This observation indicates that quercetin may show a dual antioxidant/ pro-oxidant activities in some reactive conditions.

https://www.researchgate.net/publication/326802723_Quercetin_Prooxidant_Effect_and_Apoptosis_in_Cancer

Quercetin: Prooxidant Effect and Apoptosis in Cancer 2018

Quercetin is the main flavonoid present in the human diet, being the most characteristic representative of the subclass flavonols. Although the beneficial health effects of quercetin are usually linked to its antioxidant properties, there is substantial evidence that its prooxidant features are also relevant regarding its tumoricidal effects. Here we aim to demonstrate that the generation of reactive oxygen species (ROS) by quercetin could also be a desired biological property. The oxygen paradox and its relationship with the mechanisms of intracellular generation of ROS and autoxidation of polyphenols are described herein. The chemical properties, susceptibility to autoxidation, and the role of quercetin as a cocatalyst in peroxidase-mediated reactions are also discussed. The signaling pathways related to apoptosis and their relationship with intracellular redox imbalance are presented. Oxidation therapy, a strategy to treat cancer, and its relationship with ROS and apoptosis are also discussed in the chapter. Finally, we present several experimental findings that support the proposal that the capacity of quercetin as a phytochemical that is able to trigger apoptosis in several tumor cell lineages might be related to its prooxidant features. In conclusion, we propose that quercetin should be considered as a redox-active compound, that, by altering the cellular redox status, through anti- or prooxidant action, is able to promote tumoricidal effects.

https://pubmed.ncbi.nlm.nih.gov/14644160/

The antioxidant, rather than prooxidant, activities of quercetin on normal cells: quercetin protects mouse thymocytes from glucose oxidase-mediated apoptosis 2003

The bioflavonoid quercetin is a dietary anticancer chemical that is capable of inducing apoptosis in tumor cells. Although the activity of quercetin is believed to be due to its antioxidative properties, it has recently been suggested that quercetin also has prooxidant activities, which might effect cytotoxicity directly. In this study, we used mouse thymocytes to investigate whether quercetin behaved as a protector against oxidative stress or as a cytotoxic agent. Quercetin treatment did not induce oxidative damage, but protected mouse thymocytes from glucose oxidase (GO)-mediated apoptosis in a dose-dependent manner. Furthermore, electrophoretic mobility shift assays revealed that quercetin (50 microM) treatment suppressed the GO-mediated DNA binding activity of redox state-sensitive transcription factors, such as NF-kappaB, AP-1, and p53. This result suggests that quercetin has antioxidative effects on thymocytes. More interestingly, quercetin treatment alone (50 microM) increased the DNA-binding activity of AP-1, which consisted of heterodimer of c-Jun and Fra-2. Finally, the antioxidant activity of quercetin was confirmed using a cell-free system of radical generation. Our findings suggest that quercetin protects mouse thymocytes from oxidative stress-mediated apoptosis and modulates the intracellular redox state through its antioxidant activity.

https://www.frontiersin.org/journals/chemistry/articles/10.3389/fchem.2019.00818/full

Theoretical Study of the Antioxidant Activity of Quercetin Oxidation Products 2019

However, its possible role in numerous prooxidant effects in intracellular environments is also being continually updated (Laughton et al., 1989; Metodiewa et al., 1999; Choi et al., 2003; Kessler et al., 2003; Spencer et al., 2003; Ruiz et al., 2015).

https://pubmed.ncbi.nlm.nih.gov/2476132/

Antioxidant and pro-oxidant actions of the plant phenolics quercetin, gossypol and myricetin. Effects on lipid peroxidation, hydroxyl radical generation and bleomycin-dependent damage to DNA 1989

The plant-derived phenolic compounds gossypol, quercetin and myricetin are powerful inhibitors of iron-induced lipid peroxidation in rat liver microsomes, under all five experimental conditions tested and at low micromolar concentrations (IC50 less than or equal to 1.5 microM). However, they greatly accelerate the generation of hydroxyl radicals (.OH) from H2O2 in the presence of Fe3+-EDTA at pH 7.4, as measured by the deoxyribose assay. At 100 microM, the three phenolic compounds enhanced .OH formation up to eight-fold. The hydroxyl radical generation was inhibited by catalase and superoxide dismutase, suggesting a mechanism in which the phenols oxidize to produce superoxide radical, which then assists .OH generation from H2O2 in the presence of Fe3+-EDTA. At concentrations up to 75 microM, quercetin and myricetin also accelerate bleomycin-dependent DNA damage in the presence of Fe3+, possibly by reducing the Fe3+-bleomycin-DNA complex to the Fe2+ form. Hence these naturally-occurring substances can have pro-oxidant effects under some reaction conditions and cannot be classified simplistically as "antioxidants".

https://pubmed.ncbi.nlm.nih.gov/14660033/

Anti- and prooxidant effects of chronic quercetin administration in rats 2003

Quercetin treatment decreased the glutathione concentration and glutathione reductase activity (40 and 34%, respectively) in the liver significantly and to a similar extent in vitamin E-deprived and -undeprived rats. Collectively, these results suggest that quercetin may act not only as an antioxidant, but also as a prooxidant in rats.

https://pubmed.ncbi.nlm.nih.gov/12625877/

Anti- and pro-oxidant activity of rutin and quercetin derivatives 2003

Our results are consistent with the general agreement on the structural requirements for free radical scavenging activity. Moreover, we have shown that alkylation of the hydroxyl in position 7 enhanced the scavenging, and also that in a Fenton reaction system, some quercetin derivatives with free catechol moiety or free hydroxyl in position 3 (or both) were pro-oxidant, through superoxide radical and hydrogen peroxide production. Although the structural features needed for pro-oxidant activity are not entirely clear, it appears that to avoid pro-oxidant behaviour, the hydroxyl group in position 3 should be blocked to prevent its auto-oxidation. Thus, flavonoids cannot only be considered purely as antioxidants, since under certain reaction conditions they can also display pro-oxidant activity.

https://pubmed.ncbi.nlm.nih.gov/26106459/

Quercetin Affects Erythropoiesis and Heart Mitochondrial Function in Mice 2015

Quercetin, a dietary flavonoid used as a food supplement, showed powerful antioxidant effects in different cellular models. However, recent in vitro and in vivo studies in mammals have suggested a prooxidant effect of quercetin and described an interaction with mitochondria causing an increase in O2 (-·) production, a decrease in ATP levels, and impairment of respiratory chain in liver tissue. Therefore, because of its dual actions, we studied the effect of quercetin in vivo to analyze heart mitochondrial function and erythropoiesis. Mice were injected with 50 mg/kg of quercetin for 15 days. Treatment with quercetin decreased body weight, serum insulin, and ceruloplasmin levels as compared with untreated mice. Along with an impaired antioxidant capacity in plasma, quercetin-treated mice showed a significant delay on erythropoiesis progression. Heart mitochondrial function was also impaired displaying more protein oxidation and less activity for IV, respectively, than no-treated mice. In addition, a significant reduction in the protein expression levels of Mitofusin 2 and Voltage-Dependent Anion Carrier was observed. All these results suggest that quercetin affects erythropoiesis and mitochondrial function and then its potential use as a dietary supplement should be reexamined.

https://www.tandfonline.com/doi/full/10.3109/09637486.2013.845654

Antioxidant/prooxidant effects of α-tocopherol, quercetin and isorhamnetin on linoleic acid peroxidation induced by Cu(II) and H2O2 2013

The peroxidation of linoleic acid (LA) in the presence of copper(II) (Cu(II)) ions alone and with α-tocopherol (α-TocH) was investigated in aerated and incubated emulsions at 37 °C and pH 7.

In the absence of metal ions, quercetin becomes protective in function and prevents sulfhydryl oxidation (15,16). Therefore, the presence/ absence of metal ions modulates the biological or pharmacological behavior of flavonoids to act as an antioxidant or prooxidant (17).

https://www.sciencedirect.com/science/article/abs/pii/S0308814611012702

Prooxidant activities of quercetin, p-courmaric acid and their derivatives analysed by quantitative structure–activity relationship 2012

Recent investigations have found that phenolics with good antioxidant activity may exhibit prooxidant activity under given conditions. And this prooxidant activity can accelerate damage to molecules, such as DNA and proteins (Fukumoto & Mazza, 2000). However, it can also show some beneficial effects to human health. Hadi, Asad, Singh, and Ahmad (2000) have pointed out that prooxidant activity of phenolics is an important mechanism of anti-tumour and apoptosis induction capabilities. Though metal ion and concentration of tested phenolics are widely suggested to affect the prooxidant activity of phenolics (Vargas & Burd, 2010), the structural characteristics of phenolics should be the key responsible for their bioactivity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6390007/

Quercetin induces G2 phase arrest and apoptosis with the activation of p53 in an E6 expression-independent manner in HPV-positive human cervical cancer-derived cells 2019

Quercetin at high concentrations (>40 μM) is able to act as a prooxidant molecule causing DNA damage and resulting in cell cycle arrest and/or p53-dependent or independent mitochondrial apoptosis (12,25).

https://pubmed.ncbi.nlm.nih.gov/15735088/

Low concentrations of flavonoids are protective in rat H4IIE cells whereas high concentrations cause DNA damage and apoptosis 2005

Dietary flavonoids possess a wide spectrum of biochemical and pharmacological actions and are assumed to protect human health. These actions, however, can be antagonistic, and some health claims are mutually exclusive. The antiapoptotic actions of flavonoids may protect against neurodegenerative diseases, whereas their proapoptotic actions could be used for cancer chemotherapy. This study was undertaken to determine whether a cytoprotective dose range of flavonoids could be differentiated from a cytotoxic dose range. Seven structurally related flavonoids were tested for their ability to protect H4IIE rat hepatoma cells against H(2)O(2)-induced damage on the one hand and to induce cellular damage on their own on the other hand. All flavonoids proved to be good antioxidants in a cell-free assay. However, their pharmacologic activity did not correlate with in vitro antioxidant potential but rather with cellular uptake. For quercetin and fisetin, which were readily taken up into the cells, protective effects against H(2)O(2)-induced cytotoxicity, DNA strand breaks, and apoptosis were detected at concentrations as low as 10-25 micromol/L. On the other hand, these flavonoids induced cytotoxicity, DNA strand breaks, oligonucleosomal DNA fragmentation, and caspase activation at concentrations between 50 and 250 micromol/L. Published data on quercetin pharmacokinetics in humans suggest that a dietary supplement of 1-2 g of quercetin may result in plasma concentrations between 10 and 50 micromol/L. Our data suggest that cytoprotective concentrations of some flavonoids are lower by a factor of 5-10 than their DNA-damaging and proapoptotic concentrations.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5598249/

Potential toxicity of quercetin: The repression of mitochondrial copy number via decreased POLG expression and excessive TFAM expression in irradiated murine bone marrow 2014

Whether quercetin exerts antioxidant and prooxidant effects largely relates to its dose in a given biological system [26] and can be revealed by determining changes in the level of oxidative stress in the system when quercetin is added at different doses.

https://pubmed.ncbi.nlm.nih.gov/17559999/

Antioxidant and prooxidant effects of quercetin on glyceraldehyde-3-phosphate dehydrogenase 2007

Anti- and prooxidant properties of quercetin under different conditions were investigated using glyceraldehyde-3-phosphate dehydrogenase, a glycolytic enzyme containing essential cysteine residues. Quercetin was shown to produce hydrogen peroxide in aqueous solutions at pH 7.5, this resulting in the oxidation of the cysteine residues of the enzyme. Quercetin significantly increased oxidation of GAPDH observed in the presence of ferrous ions, particularly when FeSO(4) was added to the solution containing GAPDH and quercetin. The results suggest the formation of hydroxyl radical in the case of the addition of FeSO(4) to a quercetin solution. At the same time, quercetin protects GAPDH from oxidation in the presence of ascorbate and Fe(3+). In the absence of metals, quercetin protects SH-groups of GAPDH from oxidation by the superoxide anion generated by the system containing xanthine/xanthine oxidase.

https://pubmed.ncbi.nlm.nih.gov/15128308/

Anti- and pro-oxidant effects of quercetin in copper-induced low density lipoprotein oxidation. Quercetin as an effective antioxidant against pro-oxidant effects of urate 2004

We recently reported that, depending on its concentration, urate is either a pro- or an antioxidant in Cu(2+)-induced low-density lipoprotein (LDL) oxidation. We also previously demonstrated an antioxidant synergy between urate and some flavonoids in the Cu(2+)-induced oxidation of diluted serum. As a result, the effect of the flavonoid quercetin on the Cu(2+)-induced oxidation of isolated LDL has been studied either in the presence or absence of urate. We demonstrate that, like urate, quercetin alone, at low concentration, exhibits a pro-oxidant activity. The pro-oxidant behavior depends on the Cu(2+) concentration but it is not observed at high Cu(2+) concentration. When compared with urate, the switch between the pro- and the antioxidant activities occurs at much lower quercetin concentrations. As for urate, the pro-oxidant character of quercetin is related to its ability to reduce Cu(2+) with the formation of semioxidized quercetin and Cu(+) with an expected yield larger than that obtained with urate owing to a more favorable redox potential. It is also shown that the pro-oxidant activity of urate can be inhibited by quercetin. An electron transfer between quercetin and semioxidized urate leading to the repair of urate could account for this observation as suggested by recently published pulse radiolysis data. It is anticipated that the interactions between quercetin-Cu(2+)-LDL and urate, which are tightly controlled by their respective concentration, determine the balance between the pro- and antioxidant behaviors. Moreover, as already observed with other antioxidants, it is demonstrated that quercetin alone behaves as a pro-oxidant towards preoxidized LDL.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8799102/

The interplay between reactive oxygen species and antioxidants in cancer progression and therapy: a narrative review 2021

The suggested rationale for using antioxidant supplementation during chemotherapy, is to compensate the total antioxidant decline (measured by total radical antioxidant parameter/serum micronutrients) due to depletion of antioxidants after treatment, as some studies tried to investigate the effect of a single or a combination of antioxidants with chemotherapy; yet the evidence for such depletion isn't conclusive (67).

In this regard, several studies concluded that polyphenols in higher concentrations then serve as prooxidants (75,76), e.g., quercetin at higher concentrations (>50 μM) can initiate ROS generation especially $O_2^{\bullet-}$;

https://pmc.ncbi.nlm.nih.gov/articles/PMC9941246/

A Comprehensive Study on the Anti-cancer Effects of Quercetin and Its Epigenetic Modifications in Arresting Progression of Colon Cancer Cell Proliferation 2023

Quercetin is a plant pigment, extracted from vegetables and fruits having high anti-oxidant, anti-inflammatory, and anti-proliferative activity (Datta et al. 2022). Quercetin's anti-inflammatory activities have been explored in many in vitro and in vivo studies (Boly et al. 2011; Jiang et al. 2022). In addition, many researchers have fascinated attention to quercetin as an anti-inflammatory plant product since it exerts specific effects only on cancer cells rather than on normal and non-transformed cells (Bhatiya et al. 2021).

https://pmc.ncbi.nlm.nih.gov/articles/PMC5037516/

Molecular Targets Underlying the Anticancer Effects of Quercetin: An Update 2016

Quercetin is a key member of the polyphenol family and is largely found in various vegetables and fruits, such as capers, lovage, dill, cilantro, onions, various berries (e.g., chokeberries, cranberries, and lingonberries), and apples. Quercetin is well known for its anticarcinogenic potential. The anticancer property of quercetin is due to various cell signaling mechanisms and its ability to inhibit enzymes responsible for the activation of carcinogens. Moreover, quercetin exerts anticancer effect by binding to cellular receptors and proteins [9,10].

The studies presented here suggest the potential effects of quercetin in cancer therapy. Numerous in vitro and in vivo experiments have shown various mechanisms of action that could suppress multiple oncogenic signaling pathways. Quercetin is safe with no reported toxicity when applied for the treatment of human cancer. Since quercetin and its derivatives have great benefits, it is the need of the hour to investigate further the effects of these molecules in the prevention and intervention of cancer. However, there is still no conclusive evidence regarding its exact mode of action in order to enhance its clinical application in the treatment of human cancer. Therefore, the future perspective of research should concentrate on the evaluation of quercetin's precise mechanisms of action.

https://pubmed.ncbi.nlm.nih.gov/38889494/

Exploring the therapeutic potential of quercetin in cancer treatment: Targeting long non-coding RNAs 2024

Among natural compounds, quercetin, a phenolic compound abundantly present in fruits and vegetables has garnered attention due to its significant anticancer properties. Quercetin demonstrates the ability to inhibit cancer cell growth and induce apoptosis-a process often impaired in malignant cells. In this comprehensive review, we delve into the therapeutic potential of quercetin in cancer treatment, with a specific focus on its intricate interactions with lncRNAs. We explore how quercetin modulates lncRNA expression and function to exert its anticancer effects.

https://pubmed.ncbi.nlm.nih.gov/31261749/

The Anti-Cancer Effect of Quercetin: Molecular Implications in Cancer Metabolism 2019

Quercetin is ubiquitously present in fruits and vegetables, being one of the most common dietary flavonols in the western diet. The anti-cancer effects of quercetin include its ability to promote the loss of cell viability, apoptosis and autophagy through the modulation of PI3K/Akt/mTOR, Wnt/-catenin, and MAPK/ERK1/2 pathways. Quercetin (QUE; 3,5,7,3′,4′-pentahydroxyflavone) is the major representative of the flavonoid subclass of flavonols. Quercetin is ubiquitously present in fruits and vegetables, being one of the most common dietary flavonols in the western diet. According to the US Department of Health and Human Services, the average daily intake of QUE in humans is about 25 mg [41], a value which is also supported by French and Finnish studies [42,43]. Onions are among the foods particularly high in this flavanol, being 0.03–0.28 mg/100 g of the fresh weight (FW) of white and yellow onions, with red onion varieties exhibiting the highest content (around 1.31 mg/100 g FW) [44,45,46].

https://pubmed.ncbi.nlm.nih.gov/29898731/

Quercetin inhibits prostate cancer by attenuating cell survival and inhibiting anti-apoptotic pathways 2018

Quercetin led to apoptotic and necrotic cell death in PCa cells by affecting the mitochondrial integrity and disturbing the ROS homeostasis depending upon the genetic makeup and oxidative status of the cells. LNCaP and PC-3 cells that have an oxidative cellular environment showed ROS quenching after quercetin treatment while DU-145 showed rise in ROS levels despite having a highly reductive environment. Opposing effects of quercetin were also observed on the pro-survival pathways of PCa cells. PCa cells with mutated p53 (DU-145) and increased ROS showed significant reduction in the activation of pro-survival Akt pathway while Raf/MEK were activated in response to quercetin. PC-3 cells lacking p53 and PTEN with reduced ROS levels showed significant activation of Akt and NF-κB pathway. Although some of these changes are commonly associated with oncogenic response, the cumulative effect of these alterations is PCa cell death.

Quercetin treatment disrupts this new achieved ROS balance in PCa cells either by acting as an antioxidant or as a pro-oxidant depending upon the oxidation status of the cells. In PCa cells that have high basal level of ROS and lack PTEN (LNCaP and PC-3), quercetin serves as an anti-oxidant, whereas in DU-145 cells that have more reductive environment, it serves as a pro-oxidant. Interestingly, it is cytotoxic to all three PCa cell lines irrespective of its effects on ROS generation or the mode of induced cell death. **Quercetin treatment can increase ROS levels due to peroxidase-catalyzed oxidation or by lowering intracellular pool of glutathione (GSH) [52].** Quercetin can react with ROS forming harmful quinones [53] that are scavenged by GSH and ultimately leading to depletion depending on the GSH levels of cells [54, 55]. Quercetin-generated free radicals could lead to oxidative damage of nucleic acids, lipid peroxidation, and cell death as reported in human hepatocytes and epithelial cell lines [54, 55]. It could also induce apoptosis via AMPK-α or COX-2 signaling pathway [56]. ROS levels could be associated with apoptosis, p53, or RAS activation; NAD(P)H oxidase system; and mitochondrial integrity. Opposing effects of quercetin on ROS levels consequently reflect in its differential effect on the on MAPK, Akt, and NF-κB pathways in the two androgen-independent PCa cell types that inherently have low levels of activated Raf, MEK, and ERK.

https://pubmed.ncbi.nlm.nih.gov/36233051/

A Comprehensive Analysis and Anti-Cancer Activities of Quercetin in ROS-Mediated Cancer and Cancer Stem Cells 2022

Reactive oxygen species (ROS) induce carcinogenesis by causing genetic mutations, activating oncogenes, and increasing oxidative stress, all of which affect cell proliferation, survival, and apoptosis. When compared to normal cells, cancer cells have higher levels of ROS, and they are responsible for the maintenance of the cancer phenotype; this unique feature in cancer cells may, therefore, be exploited for targeted therapy. Quercetin (QC), a plant-derived bioflavonoid, is known for its ROS scavenging properties and was recently discovered to have various antitumor properties in a variety of solid tumors. Adaptive stress responses may be induced by persistent ROS stress, allowing cancer cells to survive with high levels of ROS while maintaining cellular viability. However, large amounts of ROS make cancer cells

extremely susceptible to quercetin, one of the most available dietary flavonoids. Because of the molecular and metabolic distinctions between malignant and normal cells, targeting ROS metabolism might help overcome medication resistance and achieve therapeutic selectivity while having little or no effect on normal cells. The powerful bioactivity and modulatory role of quercetin has prompted extensive research into the chemical, which has identified a number of pathways that potentially work together to prevent cancer, alongside, QC has a great number of evidences to use as a therapeutic agent in cancer stem cells. This current study has broadly demonstrated the function-mechanistic relationship of quercetin and how it regulates ROS generation to kill cancer and cancer stem cells. Here, we have revealed the regulation and production of ROS in normal cells and cancer cells with a certain signaling mechanism. We demonstrated the specific molecular mechanisms of quercetin including MAPK/ERK1/2, p53, JAK/STAT and TRAIL, AMPKα1/ASK1/p38, RAGE/PI3K/AKT/mTOR axis, HMGB1 and NF-κB, Nrf2-induced signaling pathways and certain cell cycle arrest in cancer cell death, and how they regulate the specific cancer signaling pathways as long-searched cancer therapeutics.

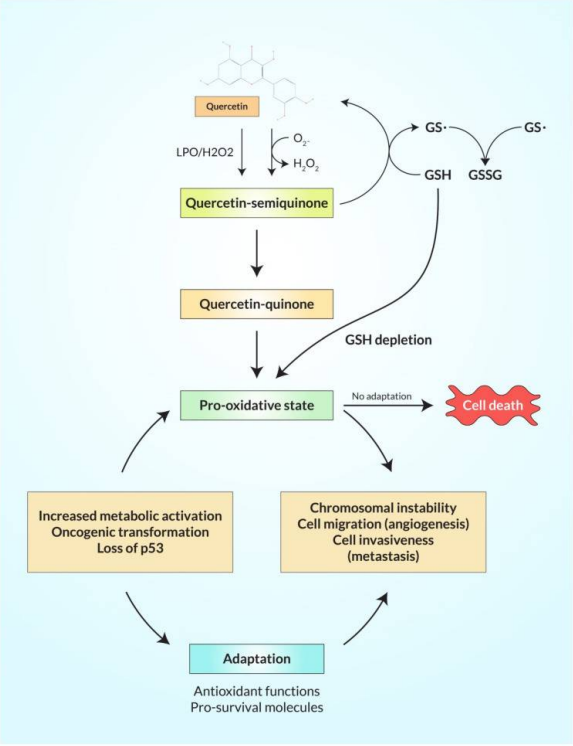
Quercetin (QC), which bears the chemical name "3,3′,4′,5,7-pentahydroxyflavone", is one of the most plentiful flavonoids under the flavonol group which has diverse biological activity for instant- antioxidant, anti-inflammatory, and antitumor activity, and is widely studied in several cancer models as a chemotherapeutic option [45,46,47]. It can disrupt ROS metabolism and trigger subsequent apoptosis, conversely, **significantly raising intracellular ROS levels by forming QC radicals** (QC-O•) after peroxidase-catalyzed oxidation to scavenge harmful reactive peroxyl radicals [48].

This current study has demonstrated the ROS regulation in normal cells, production of ROS in both cancer, and cancer stem cells, the potential role of ROS in cancer cell signaling, and quercetin's role in an unbalanced ROS state in cancerous cells. Additionally, the role of QC-dependent apoptosis, cell death, and major potential molecular mechanisms (for example, MAPK/ERK1/2 pathways, p53 pathway, and AMPKα1/ASK1/p38 pathway) for quercetin-induced cancer and cancer stem cell death is evaluated, and lastly, the future directions and precise investigations that are required to make quercetin a safe and effective anticancer pharmaceutical product are highlighted.

6. Quercetin Upregulate the ROS Levels in Cancerous Cells

As far as it is concerned, **QC can affect the formation of ROS and ultimately promote apoptosis**; it significantly enhances ROS levels within the cell as QC radicals (QC-O•) can form to scavenge reactive peroxyl radicals after peroxidase catalyzed oxidation [48]. For this purpose, QC could produce sufficient ROS which free radically-induced apoptosis at least by the signaling pathways including p38/ASK1/AMPKα1/COX2/AMPKα1 [118]. Thus, ROS generation proceeds to cause p38 and caspase-dependent activity, as well as activation of AMPKα and ASK1, which follow p38 recruitment and colocalization with protein kinase [119,120] and the COX-2 is a further downstream AMPKα1-mediate apoptosis-induced target [121].

Conversely, low concentrations of reduced GSH content, semiquinone, and quinone derivatives of quercetin react with thiols groups of protein and cause cell death; ultimately, as a result, low concentration and high concentration of GSH content of QC causes cell damage and leads to cell death which inhibits cell proliferation in cancerous cells to increasing levels of ROS, notably semiquinone and quinone, which are highly unstable and toxic for cell proliferation and for which **QC takes action as a pro-oxidant than antioxidant** as shown in Figure 6 [118].



Quercetin has a pro-oxidant effect rather than an antioxidant effect, so QC produced more ROS in PC-3 cell lines thus increasing ER stress, and G2/M phase arrest was evaluated using RT-PCR and Western blotting, and this combined therapy of QC+PTX caused PC-3 prostate cancer cell death [127].

https://pmc.ncbi.nlm.nih.gov/articles/PMC2736626/

Effects of low dose quercetin: Cancer cell-specific inhibition of cell cycle progression 2009

The resultant quercetin radicals enter the redox cycle to potentially increase ROS and subsequently cause oxidative DNA damage. **Quercetin as a pro-oxidant was proven by showing that the semiquinone formed by lactoperoxidase/H2O2 in the presence of 0.25 M ZnCl2** (to stabilize the semiquinone) disappeared on addition of 1 mM GSH [Metodiewa et al., 1999]. A fundamental question, which remains unanswered, is the differential effect of quercetin on cancer cells in comparison with normal cells. Previous studies have shown that reduced amounts of antioxidant enzymes, especially MnSOD, are found in a variety of cancer cells [Oberley and Buettner, 1979]; also, lowered amounts of CuZnSOD have been found in many, but not all, tumors. MnSOD and CuZnSOD are essential primary enzymes that convert O2·- to H2O2 and O2 within the mitochondria and cytoplasm, respectively. These observations suggest a rationale as to why tumor cells are more sensitive than normal cells to quercetin-induced reactive oxygen species [Yu et al., 2007]. This possibility needs to be investigated in the future.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3136711/

Quercetin and Cancer Chemoprevention 2011

Similarly, long exposure to Qu along with **high Qu concentration, causes a reduction in GSH content,** suggesting the inability of Qu to cope with ROS for that period. **As a consequence, the pro-oxidant effect of Qu could prevail over the antioxidant effect** and result in cell death by damaging cellular compartments [109, 110]. Antioxidant and pro-oxidant effects of Qu in the presence of low and high levels of reduced GSH. The antioxidant and pro-oxidant effects of Qu strongly depend upon the availability of intracellular reduced GSH.

As far as human clinical trials are concerned, no significant adverse effects were reported after oral administration of Qu at doses up to 1000 mg day^{-1}, corresponding to a high daily supplementation, for up to 12 weeks.

https://academic.oup.com/nutritionreviews/article-abstract/68/7/418/1821581?redirectedFrom=fulltext&login=false

Hormesis and synergy: pathways and mechanisms of quercetin in cancer prevention and management 2010

Quercetin is a unique dietary polyphenol because it can exert biphasic dose-responses on cells depending on its concentration. Cancer preventative effects of quercetin are observed at concentrations of approximately 1–40 μM and are likely mediated by quercetin's antioxidant properties. **Pro-oxidant effects are present at cellular concentrations of 40–100 μM. However, at higher concentrations, many novel pathways in addition to ROS contribute to its effects**. The potent bioactivity of quercetin has led to vigorous study of this compound and revealed numerous pathways that could interact synergistically to prevent or treat cancer. The effect of intake and concentration on emerging pathways and how they may interact are discussed in this review.

https://cellandbioscience.biomedcentral.com/articles/10.1186/s13578-020-00397-0

Quercetin and cancer: new insights into its therapeutic effects on ovarian cancer cells 2020

Ferry and colleagues have investigated the pharmacokinetic effects of intravenously injected quercetin in the patients with cancer at doses of 60–2000 mg/m^2. The safe dose of 945 mg/m^2 was identified by the researchers. At higher doses that were toxic, vomiting, high blood pressure, nephrotoxicity, as well as decreased serum potassium could be observed. The dispensation and removal half-life of quercetin applied intravenously, is 0.7–7.8 min, and 3.8–86 min, correspondingly. Elimination is 0.84 $L/min/m^2$, and dispensation content is 3.7 L/m^2 [28]. Pharmacokinetic characteristics of oral administration of 8, 20, and 500 mg quercetin aglycone were examined in healthy volunteers by Erlund et al. [29]. On the other hand, Graefe and colleagues examined the pharmacokinetic features of this agent at a dose of 200 mg. C_{max} as well as T_{max} of quercetin have been reported to be 2.3 ± 1.5 μg/mL and 0.7 ± 0.3 h, correspondingly [30].

https://ods.od.nih.gov/factsheets/ExerciseAndAthleticPerformance-HealthProfessional/

No safety concerns reported for 1,000 mg/day or less for up to 8 weeks

https://pubmed.ncbi.nlm.nih.gov/34311541/

Emerging impact of quercetin in the treatment of prostate cancer 2021

Therapeutic effects of quercetin have been assessed in diverse cancers including prostate cancer through the establishment of in vitro and in vivo experiments. Moreover, this agent might prevent the initiation of this type of cancer as it indirectly blocks the activity of promoters of two important genes in the pathogenesis of prostate cancer i.e. androgen receptor (AR) and prostate specific antigen (PSA). Several in vitro investigations have identified the differential influence of quercetin on normal prostate cells versus neoplastic cells, emphasizing its specific cytotoxic effects on cancerous cells. The most appreciated route of quercetin effect on prostate cancer cells is the detachment of Bax from Bcl-xL and the stimulation of caspase families. Besides, quercetin might enhance the effects of other therapeutic options against prostate cancer. For instance, a combination of TNF-related apoptosis-inducing ligand (TRAIL) and quercetin has been recommended as a novel modality for the treatment of prostate cancer. These kinds of strategies might overcome resistance to apoptosis in cancer cells. In the current paper, we summarize the recent data about the preventive and therapeutic influences of quercetin in prostate cancer.

Notably, despite the high cytotoxic effects on cancer cells, quercetin has little or no harmful impacts on normal cells [2], since it does not affect proliferation of normal cells [4]. Besides, quercetin has cell-specific anti-proliferative impacts via stimulation of cell cycle arrest at the G1 stage. The effect of quercetin on cell cycle progression is mediated through regulation of p21 CDK inhibitor and suppression of pRb phosphorylation resulting in E2F1 sequestering. Moreover, the low dose of quercetin has brought minor DNA injury and Chk2 induction, through which quercetin regulates p21 expression. Besides, quercetin has a role in the reduction of cyclin B1 and CDK1 levels, important modules of G2/M cell cycle transition [4].

Quercetin has also suppressed the upsurge of hsp70 expression in prostate cancer cells following heat treatment and enhanced the quantity of subG1 cells. Quercetin has been shown to increase the heat-induced suppressive impact on cell growth and heat-associated apoptosis in prostate cancer cells, suggesting that quercetin might increase heat-associated cytotoxicity in prostate cancer cells via suppression of hsp70 expression [19].

https://onedaymd.aestheticsadvisor.com/2021/12/quercetin-101-heres-what-you-need-to.html

Most quercetin studies use a dosage of around 500mg per day, although some studies use a dosage of 500mg taken twice per day.

Most supplements have a similar dosage, offering 500mg to 1,200mg of quercetin per serving.

In some studies, researchers have given participants up to 5,000mg of quercetin per day with no reported side effects.

Quercetin has poor bioavailability. You might take a 1,200mg quercetin supplement, but your body only absorbs a small percentage of it. That's why many quercetin supplements contain vitamin C or bromelain, as some evidence suggests they boost absorption.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6470739/

Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application 2019

In recent years, antioxidant activities of quercetin have been studied extensively, including its effects on glutathione (GSH), enzymatic activity, signal transduction pathways, and reactive oxygen species (ROS) caused by environmental and toxicological factors.

Quercetin increases the body's antioxidant capacity by regulating levels of GSH. This is because, once oxygen free radicals are generated in the body, superoxide dismutase (SOD) quickly captures O^{2-} and transforms it into H_2O_2. This enzyme further catalyzes the decomposition of H_2O_2 to the non-toxic H_2O. This reaction requires GSH as a hydrogen donor.

https://pubmed.ncbi.nlm.nih.gov/16433026/

Anti- and pro-oxidant effects of oxidized quercetin, curcumin or curcumin-related compounds with thiols or ascorbate as measured by the induction period method 2006

Phenolic antioxidants, such as quercetin (QUE), curcumin (CUR) and the CUR-related compounds eugenol (EUG) and isoeugenol (IsoEUG), do not act in isolation in vivo but form an intricate antioxidant network together with ascorbate or glutathione (GSH). To clarify the antioxidant/prooxidant activity of these compounds in their interplay with ascorbate or GSH, the induction period (IP) and propagation rate (Rp) for mixtures of 2-mercapto-1-methylimidazole (MMI, a thiol) or L-ascorbyl-2,6-dibutyrate (ASDB, an ascorbate derivative) with QUE, CUR, EUG or IsoEUG were determined from differential scanning calorimetry (DSC) monitoring of the polymerization of methyl methacrylate (MMA), initiated by thermal decomposition of 1.0 mol% benzoyl peroxide (BPO, a PhCOO* radical) under nearly anaerobic conditions.

Polyphenolics not only exert antioxidant, but also prooxidant, activities under certain circumstances, such as anaerobic conditions. Oxidized phenolics can be recycled by interactions with antioxidants such as ascorbate and GSH, a process called antioxidant networking (20).

Thus an adequate GSH level should be maintained when supplementation with QUE is performed (10). A study of oxygen activation by polyphenolic phenoxyl radicals with GSH has previously been reported, showing that the polyphenolics were metabolized by peroxidase in the presence of GSH, but that catalytic effectiveness for oxygen activation preferentially appeared in CUR, but not in QUE (11). However, the existence of a phenoxyl-type CUR radical induced by oxidation suggests that CUR does not react with oxygen and is unlikely to cause oxygen activation (29), and our findings indicate that CUR does not cause oxygen activation. This discrepancy may result from the experimental differences between aerobic and anaerobic conditions. A similar oxygen-dependent difference in antioxidant activity has been reported for the potent antioxidants vitamin C and vitamin E, indicating that these compounds are not efficient antioxidants under anaerobic conditions (23). Under anaerobic conditions, QUE, with a catechol ring, may be more prooxidant than CUR, with a phenol ring.

In the present study, ASDB, an ascorbate derivative, acted as a prooxidant in the CUR antioxidant network (29). Cancer cells are anaerobic in their metabolism (8, 9) and have very poor mechanisms for absorbing adequate amounts of antioxidants. The exception is ascorbate, which is remarkably similar in chemical structure to glucose. Since cancer cells preferentially take up and metabolize glucose, they selectively absorb more ascorbate than do normal cells (30). Our findings may indicate a possible chemopreventive mechanism of CUR against cancer cells, in which CUR enhances the prooxidant activity of ascorbate which may, in turn, trigger apoptotic cell death. It is well established that CUR acts as a chemopreventive agent against cancer (31)

https://pmc.ncbi.nlm.nih.gov/articles/PMC4189461/

Quercetin Regulates Sestrin 2-AMPK-mTOR Signaling Pathway and Induces Apoptosis via Increased Intracellular ROS in HCT116 Colon Cancer Cells 2013

Quercetin increased apoptotic cell death though generating intracellular reactive oxygen species (ROS), and it was responsible for Sestrin 2 expression. Increased Sestrin 2 expression was accompanied by AMPK activation. Interestingly, mTOR activity by Sestirn 2 expression was dependent on AMPK phosphorylation. On the other hand, the expression of Sestrin 2 by quercetin-generated intracellular ROS was independent of p53.

In this study, we investigated the anti-proliferation and induced apoptosis effects by Quercetin via increased intracellular ROS in HCT 116 colon cancer cells.

Thus, we hypothesized that quercetin-generated intracellular ROS induced apoptosis through the inhibition of mTOR via Sestrin 2 transcription, and it accompanied by AMPK phosphorylation. Our result shown that quercetin suppressed proliferation by expression of Sestrin 2 and AMPK phosphorylation, whereas inhibited mTOR activity. Moreover, quercetin by increasing intracellular ROS can transcript Sestrin 2 directly, and it was confirmed that the upstream function in the AMPK signaling pathway.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3835130/

Interfering with ROS Metabolism in Cancer Cells: The Potential Role of Quercetin 2010

However, excessive ROS levels render cancer cells highly susceptible to quercetin, one of the main dietary flavonoids. **Quercetin depletes intracellular glutathione and increases intracellular ROS to a level that can cause cell death.**

Several studies indicate that p53 impacts ROS levels. Under normal physiologic conditions, p53 can upregulate several antioxidant genes, such as GPx, MnSOD2, the tumor protein p53-inducible nuclear protein 1 (TP53INP1), Tp53-induced glycolysis and apoptosis regulator (TIGAR), and the sestrins, SESN1 and SESN2, which encode antioxidant modulators of PRDXs [24,25,26]. In p53-deficient cancer cells, the lack of p53-dependent antioxidant modulation can increase the redox stress within the cell, allowing ROS accumulation.

Several studies investigated the ability of GSH depleting agents to selectively sensitize cancer cells to overbalanced ROS, so as to cause cell death. GSH is one of the main cellular scavengers of free radicals.

Moreover, in contrast to their activity as antioxidants, certain types of flavonoids act as pro-oxidants, and induce apoptosis in cancer cells, by increasing ROS levels or by modulating detoxifying enzymes, or both.

9. Quercetin Interferes with ROS Metabolism

Quercetin (3,3',4',5,7-pentahydroxyflavone, Qu) is an important dietary flavonoid, present in different vegetables, fruits, seeds, nuts, tea, and red wine (reviewed in [103]). Interestingly, Qu can interfere with ROS metabolism and can cause subsequent apoptosis. On the one hand, Qu strongly increases intracellular ROS levels, as Qu radicals (Qu-O•) can be formed after peroxidase-catalyzed oxidation in order to scavenge reactive peroxyl radicals [104]. In certain situations, Qu can generate enough ROS to cause free radical-induced apoptosis through, at least, the ROS/AMPKα1/ASK1/p38 and the AMPKα1/COX2 signaling pathways [105]. Accordingly, the generation of ROS determines the subsequent activations of AMPKα1 and ASK1, which are, in turn, accompanied by p38 activation and recruitment of caspases [106,107]. COX-2 is another AMPKα1 downstream target mediating Qu-induced apoptosis [108].

On the other hand, Qu can alter ROS metabolism by directly lowering the intracellular pool of GSH [102,109,110]. By choosing the U937 monoblastic and CEM lymphocytic cell lines as models, we showed that long time exposure to Qu resulted in a decrease in H2O2 and a reduction in GSH content, suggesting that an inability of Qu to cope with ROS for a long period [111]. By reacting with ROS, Qu can form potentially toxic oxidation products, i.e., semiquinone radical and quinone radicals [112], that are highly reactive toward thiols; these radicals thus preferentially react with GSH [113]. Qu depletes GSH in a concentration-dependent manner; the higher the Qu concentration, the more GSH is depleted, presumably because GSH reacts with Qu-derived semiquinone and quinine radicals. In a model system of isolated rat liver nuclei, Qu reduces, in a dose-dependent manner, both the nuclear GSH content and the glutathione S-transferase activity [114]. Then, in the presence of Qu-induced GSH depletion, apoptosis is triggered trough mitochondrial depolarization (Figure 1), as described in several models [115,116,117,118,119,120]. In particular, during Qu-induced apoptosis, loss of mitochondrial membrane potential, phosphatidilserine exposure, and decrease of mitochondrial mass are early events that precede permeability to propidium iodide and loss of DNA [117,121]. GSH depletion is also responsible for the efficacy of the Qu-arsenic trioxide combination therapy in U937 cells [110]. Considering that the detoxification of arsenic trioxide essentially depends on glutathione S-transferases, and that arsenic trioxide is highly reactive towards thiols [122], intracellular GSH depletion may result in the increase of intracellular free arsenic trioxide concentration, and hence, increase protein damage.

Owing to the biological and biochemical differences between cancerous and normal cells, the targeting of ROS metabolism could help bypass drug resistance and achieve selectivity of treatment, while maintaining a weak or null impact on normal cells. Because normal, non-transformed cells have a lower basal intracellular ROS level, and have a full antioxidant capacity, they should be less vulnerable to the ROS stress that is induced by Qu.

https://pubmed.ncbi.nlm.nih.gov/16298752/

Essential requirement of reduced glutathione (GSH) for the anti-oxidant effect of the flavonoid quercetin 2005

We have analyzed the anti- or pro-oxidant effects of the flavonoid quercetin (QU) by evaluating, in U937 cell line, hydrogen peroxide (H(2)O(2)), superoxide anion reduced glutathione (GSH) content, mitochondrial membrane potential, DNA content, phosphatidylserine exposure on the outer face of the plasma membrane and cell viability. Polychromatic flow cytometry was used to evaluate in the same cells several functional parameters. For short periods of treatment QU exerted an anti-oxidant effect (decrease in H(2)O(2) levels), whereas for long periods it showed a pro-oxidant activity (increase in). **In these conditions, GSH content was reduced, and this correlated with a lack of anti-oxidant activity of QU**, which in turn could be correlated with proapoptotic activity of this molecule. Thus, QU can exert different effects (anti-/prooxidant) depending on exposure times and oxidative balance, and in particular on stores of GSH.

https://pmc.ncbi.nlm.nih.gov/articles/PMC5122222/

Quercetin and ovarian cancer: An evaluation based on a systematic review 2016

Among flavonoids, quercetin (Q) is the most common flavonoid in nature[10] with a wide variety of biological activities[11] that mostly present in leafy vegetables, apples, onions, broccoli, tea, and berries.[12]

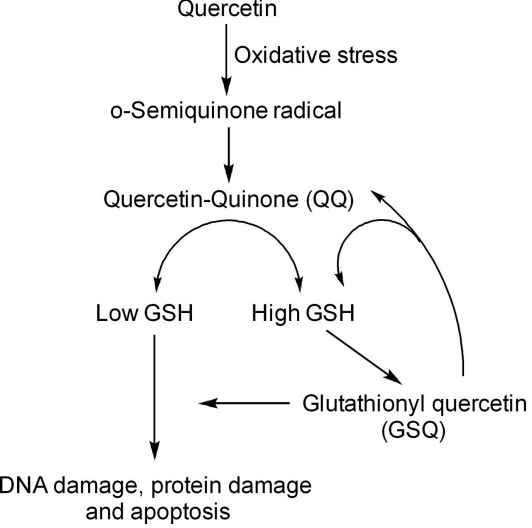
The antioxidant and pro-oxidant effects of Q depend on the concentration of intracellular reduced glutathione (GSH). In an oxidative stress, in the presence of peroxidases, Q reacts with H_2O_2 to form a Q-quinone (QQ) that has a pro-oxidant effect. Its high reactivity toward protein thiols and DNA can cause cell damage and cytotoxicity. QQ also reacts with GSH to form relatively stable protein-oxidized Q adducts such as 6-glutathionyl-Q (6-GSQ) and 8-GSQ. The reversibility of this reaction allows the continuous breakdown of GSQ into GSH and QQ. In the high concentrations of GSH, QQ reacts with GSH to form GSQ again and QQ cannot cause its cytotoxic effects.[28]

https://onlinelibrary.wiley.com/doi/full/10.1002/cam4.1411

Quercetin as an innovative therapeutic tool for cancer chemoprevention: Molecular mechanisms and implications in human health 2019

Quercetin is well known for its antioxidant and cell protective effects. However, quercetin also displays strong pro-oxidant effects and increases the cellular levels of ROS to cytotoxic levels in B16F10 melanoma cells and many other cancer cells 18, 36. Therefore, quercetin may be used to selectively killing cancer cells and be therapeutically useful.

The **switching between antioxidant and pro-oxidant behavior of quercetin is often decided by the availability of intracellular reduced glutathione (GSH)**, a tripeptide redox buffer present in living cells (Fig. 4). During oxidative stress conditions, quercetin reacts with hydrogen peroxide (H2O2) to form o-semiquinone radical and quercetin–quinone products (QQ) 37. QQ products are cytotoxic and induce cell death through their interaction with protein thiols and DNA 38. Notably, QQ products react reversibly with GSH to form glutathione–quercetin adducts such as 6-glutathionylquercetin (6-GSQ) and 8-glutathionylquercetin (8-GSQ) which dissociate persistently back into GSH and QQ 37. In case of high GSH level, QQ reacts preferably with GSH, resulting in the formation of GSQ and in this case, QQ fails to induce cell death; whereas in case of low GSH level, QQ reacts with protein thiols and thereby causes cellular damage and apoptosis. Similarly, extended exposure with high concentration of quercetin causes a substantial decline in GSH levels, impairing the ability of quercetin to scavenge ROS. As a result, pro-oxidant effect of quercetin overdominates its antioxidant effect, resulting in DNA damage and cell death.



Direct proapoptotic effects of quercetin

Apoptosis plays a central role in chemoprevention strategies. Quercetin can activate both intrinsic and extrinsic pathways of apoptosis. Quercetin activates intrinsic pathway of apoptosis (e.g., in MDA-MB-231 cells) through Ca2+-mediated dissipation of mitochondrial membrane potential (MMP) and activation of caspase-3, -8, and -9 44 (Fig. 6). Alternatively, quercetin can activate apoptosis (e.g., in HepG2 cells) through redistribution of Bcl-2 family proteins, increased translocation of Bax to the mitochondrial membrane, activation of caspases, and concomitant blockade of the PI3K/Akt and ERK signals 18, 45

It is interesting to know that when p53 is inhibited, cancer cells become vulnerable to quercetin-induced apoptosis 59. A new model, based on the cardinal role of p53 in redox homeostasis, has been propounded to explain this observation 60 (Fig. 7). It is believed that end consequence of p53 activation in cell depends highly on the nature and intensity of redox stress. If there is no or minimal redox stress, p53 elevates enzymatic antioxidant defense system including GPX1, Mn-SOD2, and catalase, which together detoxify ROS (Fig. 7). However, in case of high redox stress, p53 promotes transcription of many pro-oxidant and proapoptotic genes such as Bax, Puma, and Noxa, leading to induction of apoptosis 61.