Review

Life or death: Neuroprotective and anticancer effects of quercetin

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Abstract

Ethnopharmacological relevance: Quercetin is a ubiquitous flavonoid that is present in numerous plants that are utilized in many different cultures for their nervous system and anticancer effects. To better understand the neuroprotective and antiproliferative activities of quercetin, we present a comprehensive review of the divergent actions that contribute to the ethnopharmacological profile of these plants.

Results: The pharmacological activities of quercetin that modulate antioxidation/oxidation/kinase-signaling pathways might be differentially elicited in neurons compared with malignant cells, ultimately promoting cell survival or death in a cell type- and metabolism-specific manner. Whereas the broad antioxidation and anti-inflammatory activities of quercetin are important for neuronal survival, the oxidative, kinase- and cell cycle-inhibitory, apoptosis-inducing effects of quercetin are essential for its anticancer effects. The diverse mechanistic interactions and activities of quercetin that modulate the phosphorylation state of molecules as well as gene expression would alter the interconnected and concerted intracellular signaling equilibrium, either inhibiting or strengthening survival signals. These mechanisms, which have been mainly observed in in vitro studies, cannot be easily translated into an explanation of the divergent simultaneous neuroprotective and anticancer effects observed in vivo. This is in part due to low bioavailability in plasma and in the brain, as well as the nature of the actual active molecules.

Conclusions: Numerous studies have demonstrated the beneficial effects of chronic quercetin intake, which is ethnopharmacologically meaningful, as many plants that are chronically ingested by people contain quercetin. Although quercetin and quercetin-containing plants exhibit potential as therapeutic modalities in neuropathology and in cancer, the data collectively highlight the need to elucidate issues such as bioavailability as well as its correlation with effectiveness at biomarkers in vivo. There would be an increased potential of these plants for chemoprevention and neuropathology prevention.

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1. Introduction: Flavonoids, quercetin

The flavonoids, a large family of naturally occurring benzo-g-pyrone derivatives, are natural constituents of plants, flowers and vegetables that exhibit a vast structural diversity and multiple functions in nature. Numerous studies have demonstrated the beneficial effects of flavonoid-rich foods, including anticancer, anti-inflammatory, and cardiovascular protective effects, as well as a protective role in degenerative diseases (Hertog et al., 1993; Benavente-García and Castillo, 2008; McCullough et al., 2012). Nonetheless, whereas some meta-analyses have previously suggested positive associations between flavonoid intake and human health, others have not supported such a correlation (Park and Pezzuto, 2012). Controversial and divergent data regarding different flavonoid molecules from both basic research and clinical studies have hampered the formation of a unified and comprehensive hypothesis on the mechanisms of action of flavonoids. A better understanding of the pharmacological activity of flavonoids might improve our understanding of the mode(s) of action of many plant extracts that are widely used around the world. To this end, we have performed a comprehensive review of both in vitro and in vivo studies of quercetin, a representative flavonoid molecule, focusing on its neuroprotective and anticancer effects, two of the numerous activities that have been described for this molecule.

Quercetin, (3’,4’,5,7-pentahydroxy-flavone) is a ubiquitous molecule present in most plants, fruits and vegetables that can reach levels in the human diet as high as 16–25 mg/day (Hertog et al., 1993a). A broad spectrum of beneficial properties have been described for quercetin, including anti-inflammatory effects, benefits for human endurance exercise capacity, atherosclerosis, thrombosis, hypertension, and arrhythmia as well as modulation of cancer-related multidrug resistance, among others. (Reviews available on these fields include: Hertog et al., 1993b; Formica and Regelson, 1995; Bischoff, 2008; Chen et al., 2010; Kessler et al., 2011; Mendoza and Burd, 2011; Larson et al., 2010; Russo et al., 2012).

2. Ethnopharmacological relevance of quercetin

As an example of its wide distribution, quercetin is present in 19 of 112 plants that are widely utilized in Chinese medicine (Caia et al., 2004). Quercetin is also present in plant extracts that are ethnopharmacologically important in terms of neuroprotective and anticancer effects. In connection with neuroprotection, in traditional Oriental medicine, Uncaria rhynchophylla has been used to lower blood pressure and to relieve various neurological symptoms. It was shown to significantly protect hippocampal CA1 neurons against 10-min transient forebrain ischemia (Zhu et al., 1997; Li et al., 2011). Among the numerous plants utilized in Ayurvedic medicine, the traditional Indian system of medicine, a few select plants have long been classified as enhancers of intellect or cognition. Such plants include Ginkgo biloba, Kava-kava, St John’s wort, Valerian, Bacopa monniera and Convolvulus pluricaulis, widely used for their effectiveness in brain disorders (Kumar, 2006). Quercetin has been identified in G. biloba, B. monniera and C. pluricaulis (Kumar et al., 2007). The use of Valerian, Kava-kava and Saint John’s wort has traditionally had an emphasis in affective disorders, and whereas G. biloba is widely used to treat dementia (Weismann et al., 2010), B. monniera has been recognized as a “brain tonic” for years and has also been demonstrated to elicit neuroprotective effects in experimental studies of oxidative aluminum damage in the rat hippocampus (Jyoti and Sharma, 2006). Centella asiatica is another example of a plant that is utilized for its activities on the nervous system, which have been experimentally demonstrated to affect the amyloid cascade and to alter the amyloid beta pathology in the brains of the transgenic PSAPP mice model of Alzheimer’s disease (Dhanasekaran et al., 2009).

The ethnopharmacological relevance of quercetin-containing plants that are commonly used for cancer treatment has been shown by a sample of plants taken from an article by Graham et al. (2000): Hydrocotyle sibthorpioides, Glycyotrobus pensilis, Solanum lyratum (from China) Fabiana imbricata (from Chile) Castilleja tenuiflora (from México) Uncaria tomentosa (from Perú), Oldenlandia diffusa (from Singapore) and Azadiracta indica (from Nigeria).

3. A comprehensive review of the neuroprotective and anticancer effects of quercetin

As mentioned above, quercetin exhibits numerous actions on multiple biological targets that we do not yet understand. Although its antioxidant effects comprise its most well-accepted pharmacological role, it is certainly responsible for several other effects. Some of its pharmacological activities have been postulated several years ago to result from its interactions with protein signaling cascades, which continue to be a source of much question and research. In this sense, neurons and cancer cells are good examples of the importance of regulatory signaling mechanisms. Simultaneously analyzing the many in vitro and in vivo experiments that have assessed the effects of quercetin on neurons and tumor cells, with emphasis on both antioxidation and signaling might help to understand its global mechanisms of action, which in turn would advance our understanding of the ethnopharmacological activity of plants utilized for nervous system pathologies and cancer therapy. Additionally, it is important to analyze the contradictory actions in terms of cellular protection (neurons) and cellular death induction (cancer cells) elicited by quercetin, as neurological diseases and cancer are two main global causes of death and as a significant portion of the world population still depends on these plant extracts for the symptomatic alleviation of disease.

Despite their functional differences, neurons and cancer cells share a common metabolic profile, as they both use glucose to cope with the energy demands of synaptic activity and massive growth, respectively. The increased requirements for ATP from mitochondrial oxidative phosphorylation generates free oxygen radicals, which creates oxidative stress conditions that could eventually promote cell death. To respond to this challenge, neurons and cancer cells utilize glucose as a source of energy. Glycolytic metabolism predominates in tumor cells, as Warburg demonstrated more than one hundred years ago. Furthermore, Vaughn and Deshmukh (2008) have recently demonstrated that coupling the pentose phosphate pathway with release of cytochrome c maintains a restrictive environment for cytochrome c-mediated apoptosis. Cytochrome c, a component of the mitochondrial electron transfer chain, initiates caspase activation when released from mitochondria during apoptosis. Thus, neurons and cancer cells maintain control over programmed cell death through the regulation of cytochrome c release, while efficiently using glucose as a source of energy. These metabolic adaptations are critical for the prolonged survival of neurons and for the continuous proliferation of cancer cells (Ruckenstuhl et al., 2009), and the examination of how quercetin might contribute these metabolic signaling that results in divergent endpoints, such as cellular survival or death, will help to improve our understanding of the ethnopharmacological profile of this flavonoid.
Research on the many pharmacological activities of quercetin in diverse biological systems, such as in neuron protection or cancer cell death, has revealed the controversial issues surrounding both topics. This review will critically summarize the available data and compare the current hypotheses as a basis for future research.

4. Quercetin and Neuroprotection

Studies have shown that treatment with quercetin can increase the survival of neurons cultured in vitro against oxidative lethal stimuli (reviewed by Dajas et al. (2003a) and Ossola et al. (2009)). A fundamental issue with many of the neuroprotection studies analyzed in this review is that the studies have been conducted using PC12 cells, a cell line derived from a pheochromocytoma of the rat adrenal medulla. Thus, it is more accurate to infer from these studies that quercetin protects tumor cells from oxidative insults. In fact, PC12 cells are extensively utilized because they stop dividing and terminally differentiate when treated with nerve growth factor (NGF). After exposure to NGF, PC12 cells begin to form branching varicose processes similar to those produced by primary sympathetic neurons cultured in vitro (Greene and Tischler, 1976). Notably, quercetin has been demonstrated to elicit NGF-like effects when it is added to PC12 cells, promoting differentiation with a potency similar to that of NGF (Blasina et al., 2009). Although the underlying mechanisms remain unknown, the well-characterized survival-inducing capacity of NGF (Rydén et al., 1997) is likely related to the differentiation-inducing effects of quercetin.

Neuroprotection conferred by quercetin treatment has been observed in the primary cultures of cortical or hippocampal neurons after a range of cytotoxic insults, such as treatment with glutamate, amyloid β peptide and H₂O₂. (Dajas et al., 2005; Jakubowicz-Gil et al., 2008; Ossola et al., 2009). The protective effects are obtained with concentrations of quercetin between 25 and 50 μM, whereas toxic effects are observed with concentrations exceeding 100 μM. In in vitro experiments, quercetin has been frequently applied during oxidative stress, indicating a non-specific action that might result from the direct interaction of the flavonoid with the specific oxidant. Nonetheless, quercetin increased neuronal survival even when applied 24 h before an oxidative insult and was no longer detected in the nucleus of the cells that were treated with quercetin and NGF, whereas toxic effects are observed with concentrations exceeding 100 μM. In in vitro experiments, quercetin has been frequently applied during oxidative stress, indicating a non-specific action that might result from the direct interaction of the flavonoid with the specific oxidant. Nonetheless, quercetin increased neuronal survival even when applied 24 h before an oxidative insult and was no longer detected in the neurons of the media at the moment of the oxidative insult, suggesting that the neuroprotective effects in vitro are specific at a molecular level (Arredondo et al., 2010). When applied to neurons in culture, quercetin rapidly enters the cells, and upon reaching the nucleus, greatly increases the potential for interactions with cytosolic and nuclear molecules (Arredondo et al., 2010). The capacity to interact with multiple cellular targets is likely the basis of the therapeutic and toxicity actions of quercetin.

In contrast with the in vitro results, the administration of aqueous quercetin in vivo have not elicited neuroprotection in studies using models, such as experimental Parkinson’s disease (Dajas et al., 2003a; Kääriäinen et al., 2008; Ossola et al., 2009). A number of studies have administered quercetin in different ways to assess its protective effects against diverse neurological insults. Kumar et al. (2008) studied the protective effects of quercetin after intracerebroventricular administration of colchicine. The daily oral administration of quercetin over a period of 25 day (20 and 40 mg/kg) significantly improved the colchicine-induced cognitive impairment, as demonstrated by the Morris water maze and plus-maze performance tests. Chronic administration of quercetin also attenuated elevated lipid peroxidation and restored depleted glutathione levels. Memory improvement was also observed by Patil et al. (2003) after quercetin was administered intraperitoneally for seven days to mice suffering from age-related or lipopolysaccharide treatment-induced cognitive impairment. In this case, the passive avoidance and elevated plus maze tests were utilized and the improvement was associated with the inhibition of cyclooxygenase-2 and inducible nitric oxide synthase. Mice fed for eight weeks with quercetin (5 and 10 mg/kg per day) exhibited significantly improved learning ability and memory compared with control mice injected daily with d-galactose (d-Gal) (50 mg/kg per day), as demonstrated by the step-through and Morris water maze tests (Lu et al., 2006). The d-gal-induced senescence mouse model is ideal for studying brain aging, and in this model, quercetin also increased superoxide dismutase activity and decreased malondialdehyde levels. Beyond the recovery of cognition after the induction of lesions in the brain, the beneficial effects of quercetin on memory have also been described for its ability to activate signaling pathways and to induce vascular effects capable of promoting new nerve cell growth in the hippocampus (Spencer, 2009). We will revisit these aspects of quercetin activity below. All of these in vivo experiments required the chronic administration of quercetin to elicit beneficial effects on the induced cognitive deficits, improvements that appear to be related to its antioxidant activity. With the exception of one study that observed anxiety-like activity at 60 min after oral administration of quercetin (Vissiennong et al., 2012), the acute neuroprotective effects of quercetin have been observed in rat models of repeated cerebral ischemia (Pu et al., 2007), compression trauma (Schültke et al., 2010) and hypoperfusion (Takizawa et al., 2003). In the first case, two doses of quercetin (50 mg/kg) improved spatial memory impairment in the 8-arm radial maze test and reduced neuronal cell death in the hippocampal CA1 area induced by repeated cerebral ischemia. Schültke et al. (2010) administered quercetin intraperitoneally at intervals ranging from one single injection to two or three injections daily for 10 day in a model of spinal cord compression injury. Approximately 50% of the animals recovered sufficient motor function to walk. Stepping/walking were observed in two of six animals receiving a single injection and in one of six animals receiving three injections.

The need for repeated doses to obtain a neuroprotective effect suggests a difficulty in the delivery of quercetin to the brain at effective concentrations after a single dose and further suggests the likely need for an accumulative concentration to obtain pharmacological efficiency. Thus, the observed neuroprotective effects of quercetin in vitro have not been consistently reproduced in acute brain pathology. The protective effects obtained with a single administered dose were observed mainly in cases where the blood brain barrier is usually broken, such as ischemia or trauma (Schültke et al., 2010; Pu et al., 2007). Accordingly, contradictory results have been attributed to the difficult delivery of quercetin across the blood-brain barrier (BBB) (Ossola et al., 2009). Nonetheless, this interpretation is controversial as quercetin has been demonstrated to cross the BBB (Youndim et al., 2004a; Faria et al., 2010). The BBB is an interface that selectively limits the passage of small polar molecules and macromolecules from the vascular circulation to the brain. In a review of the role of BBB on the delivery of circulating flavonoids into the brain, Youndim et al. (2004b) observed quercetin fluxes into different brain regions using a rat in situ brain perfusion model. Thus, beyond concerns about how cell culture models can fully recapitulate the physiological environment in the brain, some experimental evidence would not support the concept that the BBB totally prevents quercetin entering into the brain. Thus, conundrum regarding “active concentrations” of quercetin might be attributed to its circulating bioavailability and actual access to neurons (i.e., the compartmentalization between the cerebrospinal fluid, extracellular fluid and the different types of brain cells).
In this context, Rivera et al. (2008) utilized liposomes as a carrier for quercetin and showed protective effects in a permanent focal ischemia rat model. In this case, exsanguination and perfusion of rats to avoid brain sample contamination was performed, a procedure not generally described in in vivo neuroprotection experiments, although it should be noted when assessing the cerebral levels of flavonoids (Schaffer and Halliwell, 2012).

5. Quercetin neuroprotective mechanisms

Accounting for only 2% of total body weight, the brain represents approximately 20% of the total O2 consumption of the organism. This high metabolic rate generates reactive oxygen species (ROS) in the brain, and thus, a crucial concomitant need for neuronal antioxidant defenses. In this context, numerous studies have identified oxidative stress as central cause of neurodegenerative and vascular diseases pathologies of the brain (Dajas et al., 2005; Ossola et al., 2009). Brain ischemia triggers a variety of cellular processes, including the release of neurotransmitters, in particular glutamate, NMDA receptor activation, and the increase of calcium entry into the cells. Upon ischemia, there is a general activation of intracellular enzymes, and ROS and reactive nitrogen species are generated, leading to lipid-peroxidation, DNA damage and cell membrane disruption, ultimately leading to neuronal cell death (Smith, 2004) (Fig. 1A). Oxidative stress is also critically important in altering the progression of neurodegenerative diseases (Emerit et al., 2004). Interestingly, pre-treatment of primary hippocampal cultures with quercetin significantly attenuated amyloid beta-induced cytotoxicity, protein oxidation, lipid-peroxidation and apoptosis (Ansari et al., 2009). In the case of Parkinson’s disease, a defect in mitochondrial complex I has been identified that might contribute to neuronal degeneration, resulting from a depletion in cellular ATP, ROS generation, and the induction of apoptosis caused by the opening of the mitochondrial transition pore and the release of cytochrome c (Olanov and Tatton, 1999). While it is known that quercetin accumulates in the mitochondria (Fiorania et al., 2010), a recent study showed that treatment with quercetin protected Caco-2 cells against indomethacin-induced mitochondrial dysfunction, precisely by its ability to enter cells and accumulate in mitochondria (Carrasco-Pozo et al., 2012). This protective activity points to a potential benefit of quercetin treatment for conditions involving mitochondrial dysfunction associated with increased oxidative stress.

In fact, the central role of oxidative stress in brain pathology is the basis of the therapeutic potential of quercetin. Its potent ROS scavenging activity is attributed to its inherent number of hydroxyl substitutions, which correlates with its electron-donating ability (Morel et al., 1993; Rice-Evans et al., 1996; Boots et al., 2008). Nevertheless, this electron-donating capacity has also been positively correlated with toxicity (Echeverry et al., 2010); quercetin forms catechol oxidation products, such as semiquinones and quinones that could alter redox homeostasis, limiting the initial positive effects (Boots et al., 2002). This is likely the basis of one critical aspect of the neuroprotective profile of quercetin in vitro, resulting in a narrow concentration range of protective capacity. With the currently available data, it is not possible to evaluate the significance of this limitation for the neuroprotective activity of quercetin in vivo, but it should be considered in translational studies.

In addition to the direct scavenging of free radicals, other antioxidant mechanisms contribute to the potent action of quercetin against oxidative stress, such as the inhibition of enzymes including xanthine oxidase and nitric oxide synthase (Bindoli et al., 1985), as well as other biochemical mechanisms, such as the chelation of iron and calcium and the inhibition of lipid-peroxidation (Morel et al., 1993; Mira et al., 2002) (Fig. 1B).

Although severe increases of ROS can induce cell death, regulated levels of ROS might also function as signals to promote cellular proliferation and survival, maintaining the function of redox-sensitive proteins. Redox homeostasis is important for cell survival because it regulates the functions of transcription factors, signal transduction pathways, and mediators of cell death. Abrogation of redox homeostasis is likely the first step in the failure of oxidative equilibrium in neurons. Oxidative modification alters redox-sensitive interacting proteins, such as the transcription factor nuclear factor-erythroid-2-related factor 2 (Nrf2) and its repressor Kelchlike ECH-associated protein 1 (Keap1). Nrf2 regulates the synthesis of glutathione through the control of both the basal and induced expression of the genes encoding the heavy and light chains of glutamylcysteine synthetase (Acharya et al., 2010). Quercetin has been shown to influence the Nrf2 gene expression (Ishikawa et al., 1999; Arredondo et al., 2010) demonstrated that a key function of quercetin is the activation of Nrf2 in cerebellar granule cells after oxidative stress, resulting in the induction of genes encoding for γ-glutamylcysteine synthetase and in increased neuronal glutathione levels that restore redox homeostasis. Oxidative stimuli could also produce redox thiol modifications, influencing the activity of signaling cascades, the balance of which defines anti- or pro-apoptotic responses (Acharya et al., 2010). As an important result of antioxidant activities, quercetin re-establishes the redox regulation of proteins, transcription factors and survival signaling cascades that are otherwise inhibited by elevated ROS (Fig. 1B).

Other aspects of the pharmacological activity profile of quercetin, including its capacity to inhibit kinases (Walker et al., 2000) and to interact with a multitude of cellular proteins, have been much less explored in the context of its neuroprotective role. Quercetin has been considered a broad kinase inhibitor acting on signaling cascades involving phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/protein kinase B (Akt/ PKB), tyrosine kinase, protein kinase C (PKC), and mitogen-activated protein kinase (MAP kinase) (Williams et al., 2004). This activity was recognized more than twenty years ago by the works of Ferriola et al. (1989), who studied fifteen flavonoids and showed that fisetin, quercetin and luteolin were the most potent PKC inhibitors, inhibiting the enzyme in a dose-dependent manner. Another study identified a list of flavonoids that they similarly concluded could inhibit PI3K (Agullo et al., 1997). There are important reasons that this activity might be significant for neurons. PKC is an effector of transmembrane signals associated with the polyphosphoinositide pathway. Membrane phosphoinositide turnover is initiated by hormone, neurotransmitter and growth factor interactions with cell surface receptors. When activated, PKC phosphorylates many enzymes and proteins, activating signaling cascades. On the other hand, survival factors, by binding to tyrosine kinase receptors, recruit PI3K to the plasma membrane to generate the phosphoinositides that in turn lead to the activation of several kinases, including Akt/protein kinase B and ribosomal S6 kinase (RSK). The PI3K–Akt pathway is critical for trophic-factor-induced survival in neurons (Brunet et al., 2001). Aside from PKC and PI3K, some of the most well-characterized survival pathways include the MAP kinase-signaling pathway. Of these, one of the most well characterized MAPK pathways is governed by the mitogen extracellular signal-regulated protein kinase (ERK). ERK1/2 and c-Jun N-terminal kinase (JNK) are involved in apoptosis and various forms of cellular plasticity, and they are generally considered as exerting opposing actions. ERK1/2 is usually associated with pro-survival signaling through mechanisms that may involve the activation of the cyclic AMP regulatory binding protein (CREB) and the
upregulation of antiapoptotic proteins. Conversely, JNK has been strongly linked to transcription-dependent apoptotic signaling possibly through the activation of c-Jun (Williams et al., 2004).

Despite our lack of knowledge regarding the actual cerebral concentrations of quercetin that acts on molecular targets and signaling cascades, the inhibition of kinases can interfere with survival signals, as we will show below in the context of cancer.
In fact, one experimental in vitro study demonstrated that the interaction of quercetin with signaling cascades, such as PI3K and ERK, sufficed to induce neuronal death (Spencer et al., 2003). Nonetheless, not all inhibitory activities are associated with death signals; such inhibitory activities could also promote survival by modulating other cascades, as shown above. Aside from direct interaction with the ATP-binding sites of kinases, quercetin activates kinases and signaling cascades via redox mechanisms. The multiple and diverse mechanistic interactions of quercetin that alter the phosphorylation state of molecules and gene expression can modulate, in neurons subjected to oxidative stress, the concerted intracellular signaling equilibrium in terms of survival signaling, which we will describe below in the context of cancer cells. The particular sensitivity of each cell type to broad kinase inhibition or to changes in redox homeostasis is likely involved. Nonetheless, the extent of the effects of quercetin in inhibiting and/or activating these different targets has not yet been extensively explored in the context of the brain in vivo.

In addition to these neuronal molecular events, quercetin also affects the neuronal environment, i.e., the glia and vasculature. If prolonged, ischemia can lead to the development of an injured core, surrounded by a ‘penumbra’ of affected tissue with the potential for full recovery. This “penumbra’ region is a stressed, complex and unstable area that could be integrated into the ischemic core, depending on its defense mechanisms and the extent of the damage to the core (Del Zoppo et al., 2011). In addition to oxidative stress, the involvement of glia and microvessels is critical in this process. Inflammation during necrosis in the ischemic process involves microglia and reactive astrocytes that release neurotoxic mediators, such as nitric oxide, interleukin 1β (IL1β) and tumor necrosis factor α (TNFα) (Benn and Woolf, 2004). Chen et al. (2005) demonstrated that quercetin could inhibit lipopolysaccharide and interferon-gamma-induced nitric oxide (NO) production in BV-2 microglia, suggesting that it can suppress inflammation-related neuronal injury in cerebrovascular and neurodegenerative diseases, particularly at the microglial level (Bureau et al., 2008). Notably, quercetin vasodilator effects (Perez-Vizcalno et al., 2002) have been shown to increase blood flow and energy supply.

The structural diversity of flavonoids offers the possibility to identify the molecular substitutions required to afford different specific biological actions. The ortho-dihydroxy substitution in the B-ring and the presence of 2,3-unsaturation and a 4-carbonyl in the C-ring have been postulated to account for the antioxidant potency of quercetin (Rice-Evans et al., 1996). Interestingly, a recent study by Echeverry et al. (2010) showed that the ortho-dihydroxy substitution in the B-ring is not necessary for the neuroprotective effects of quercetin and may contribute to its neurotoxic effects. Therefore, the structural features implicated in the neuronal protective effects of quercetin are different from those that provide the free radical scavenging capacity, indicating that there are specific structural motifs that mediate differentially these survival effects (Fig. 2). The antioxidant capacity of quercetin is necessary but not sufficient for its neuroprotective effects.

6. Quercetin and anticancer effects

Numerous in vitro studies have shown consistent anticancer effects of quercetin in a variety of cancer cell lines and tumors, including U138MG (glioma, Braganhol et al., 2006); U2.US/MTX300 (osteosarcoma, Xie et al., 2010); HeLa (cervical cancer, Vidya Priyadarshini et al., 2010); CWR22Rv1 (prostate cancer, Hsieh and Wu, 2009); MDA-MB-453 (breast cancer, Choi et al., 2005); and oral cavity cancer (Kang et al., 2008); HT-29 (colorectal xenografts, Priego et al., 2008); myeloid leukemia (Duraj et al., 2005); and oral cavity cancer (Kang et al., 2010). The doses of quercetin that exhibited antiproliferative effects in vitro were in the range of 3 to 50 μM (Lamson and Brignall, 2000; Gibellini et al., 2011), concentrations that are generally lower than those that confer neuroprotection.

In vivo studies of the anticancer effects of quercetin have demonstrated that oral administration can prevent induced carcinogenesis, particularly in the colon (Murakami et al., 2008), and furthermore, quercetin can inhibit melanoma growth, invasion, and metastatic potential (Caltagirone et al., 2000). When administered in the diet, quercetin was able to inhibit the initiation, growth and/or dissemination of induced tumors in experimental animal models (Yang et al., 2001), although the results have been controversial, as independent studies have found either inhibition or no effect (Yang et al., 2001).

Studies concerning the in vivo anticancer effects of quercetin have been hampered by difficulties in interpretation regarding
the bioavailability and the identity of the specific active molecules; similar what has been the case with neuroprotection studies.

7. Anticancer mechanisms of quercetin

Experiments performed with mice that are deficient in either CuZn superoxide dismutase or glutathione peroxidase – enzymes believed to protect cells from oxidative damage by scavenging ROS – led to increased tumorigenesis (Elchuri et al., 2005). These and similar reports substantiate the notion that prolonged oxidative stress promotes damage to proteins, lipids, membranes and DNA, playing a central role in cancer development (Khandrika et al., 2009). To maintain increased cell growth, proliferation and survival, cancer cells undergo significant genetic and adaptive changes that result from the alterations and aberrations of hundreds of genes that ultimately modulate multiple pathways. One of these alterations includes oxidative changes, which activate antioxidant functions to upregulate pro-survival molecules. Cancer cells adapt to live with a controlled level of oxidative stress with persistently higher ROS than normal cells due to deregulated redox balance, which allows for the activation of the redox-regulated signals and cascades mentioned above, without triggering apoptosis (Acharya et al., 2010). Notably, although the maintenance of active redox survival signals represents an adaptive process that is important for promoting pro-survival and oncogenic activity, it also renders tumor cells particularly sensitive to oxidative stress (Montero and Jassem, 2011).

Intriguingly, some of the experimental results described above for the neuroprotective effects appear to contradict the therapeutic antiproliferative, anticancer activities of quercetin because strengthening the regulation of redox mechanisms would help to maintain deleterious effects, such as cancer proliferation. Nonetheless, a recent study by Gibellini et al. (2010) reviewed the role of quercetin in ROS-induced apoptosis in cancer cells. In contrast to reports of the neuroprotective increases in glutathione levels after quercetin treatment, they highlighted studies showing that glutathione is decreased after quercetin treatment in malignant cells at concentration ranges lower than those otherwise required for oxidative toxicity. By unknown mechanisms, the oxidative actions of quercetin dominate in the genetically modified cellular context of malignant cells, thereby promoting apoptosis by modulating the cancerous control of oxidative stress. In the anticancer papers reviewed above, the researchers show that quercetin modulates the complex balance of proteins linked to apoptosis as another way to induce cancer cell death. To maintain high proliferation rates and survival in hostile stromal contexts (hypoxia, low blood flow), cancer cells maintain tight control of the apoptotic process and impaired apoptosis is a crucial step in tumorigenesis, a notion that is strongly supported by experimental models (Cory and Adams, 2002).

Caspase activation leads to apoptosis through two main pathways (Cory and Adams, 2002) (Fig. 3A). One pathway involves a tumor necrosis factor (TNF) receptor at the cell surface, which recruits caspase-8 through the adaptor protein FAS-associated death domain (FADD) leading to the activation of caspase-8. The intrinsic pathway involves the release of cytochrome c from mitochondria, a key intermediate step in the apoptotic process that leads to the activation of caspase 9. Cytosolic cytochrome c binds to Apoptotic protease-activating factor-1 (Apaf-1), a cytosolic protein containing a caspase-recruitment domain (CARD) and a nucleotide-binding domain. The binding of nucleotides (dADP, ATP) triggers the formation of the apoptosome, a multimeric complex containing Apaf-1 and cytochrome c. The CARD domains of Apaf-1 become exposed in the apoptosome, which subsequently recruit multiple procaspase-9 molecules to the complex to promote their autoactivation (Wang, 2001). The B-cell lymphoma 2 (Bcl-2) family of proteins regulates the release of cytochrome c and other apoptogenic proteins from mitochondria and include the antiapoptotic members Bcl-2 and Basal cell lymphoma-extra large (Bcl-xl), which blocks the release of cytochrome c release, pro-apoptotic BCL2 agonist killer 1 (Bak), BCL-2 interacting mediator of cell death (Bim), BCL-XL/BCL-2-associated death promoter (Bad), and B-cell lymphoma 2-associated protein X (Bax). Pro-apoptotic molecules can function by heterodimerizing with anti-apoptotic molecules to inhibit their function. In the presence of a survival factor, BAD is phosphorylated and sequestered within the cytosol. Following a death signal, BAD is dephosphorylated and found to associate with BCL-XL and BCL-2. To date, several kinases have been shown to phosphorylate and inactivate BAD. For instance, Akt kinase downstream of phosphatidylinositol 3-kinase is site-specific for Ser136 (Gross et al., 1999). The concerted interaction of proteins in response to death or survival stimulus centers at the mitochondria as a critical effector of cell fate. Part of the electrons transported by the mitochondrial respiratory chain is transferred to oxygen, generating the superoxide anions that increase during pathological conditions, such as cancer and ischemia (Zielonka and Kalyanaraman, 2008). The effector is the mitochondrial permeability transition (MPT) that consists in the opening of the mitochondrial permeability transition pore (MPTP) in the inner mitochondrial membrane, which causes membrane depolarization, uncoupling, loss of metabolites and respiration factors (e.g., NADH), ATP depletion, and if prolonged, necrotic cell death (Baines et al., 2005). MPT and closure or opening of MPTP is critical for cell survival or death. While MPTP inhibition can protect from situations of high oxidative stress, it can also represent a tool for the elimination of unwanted cancer cells.

De Marchi et al. (2005) assessed the effects of quercetin on the MPT, observing the pore itself at the single-channel level in patch-clamp experiments. In contrast to other polyphenols (e.g., catechin), quercetin was able to inhibit the opening of the MPTP. The addition of quercetin to mitochondria suspended in a standard sucrose-based buffer containing phosphate and a respiratory substrate with added Ca2+ did not show inhibition of MPTP, as indicated by the induction of mitochondrial swelling. Furthermore, quercetin was associated with increased production of superoxide anions in these experiments. These results show that polyphenols, such as quercetin, can both inhibit or promote MPT, indicating its bi-directional nature in redox homeostasis. Interestingly, the authors proposed a redox-based interpretation of their results in which reduction of a disulfide group would cause channel closure, whereas its re-oxidation would trigger opening. Modulation of the redox state of mitochondria to either inhibit or to enhance MPT thus appears to be a process by which quercetin might protect neurons (antioxidation) or trigger cancer cell death (oxidation). As we will describe below, the different intracellular milieu, the time of exposure and concentrations of quercetin will determine the final output.

Extracellular survival signals inhibit apoptosis by activating the IP3K/Akt signaling pathway. Akt phosphorylation also activates CREB, resulting in the elevated transcription of genes encoding for antiapoptotic proteins, such as Bcl-2 and Bcl-XL. By controlling the activation of this and other survival cascades, such as the Ras Sarcoma/Rapidly Accelerated Fibrosarcoma/ERK Kinase/ERK (Ras/Raf/MEK/ERK) pathway, which activates p90 ribosomal S6 kinase (Rsk) that also targets Bad and CREB, the molecular mutations in cancer can act synergistically to sustain cancerous cell survival (Fig. 3A).

In the papers cited above, Duraj et al. (2005) demonstrated that quercetin treatment of leukemia cells induces the
upregulation of pro-apoptotic Bax and the increased phosphorylation of anti-apoptotic Bcl-2 and ERK. Similar effects were recently observed by Xie et al. (2010) in osteosarcoma cells (U2-OS/MTX300), accompanied by a significant reduction of mitochondrial membrane potential and the direct activation of caspase-3. Similar caspase activation was also reported in oral cavity cancer cells (Kang et al., 2010). Choi et al. (2008) also reported increased Bax expression during quercetin-induced apoptosis. Priego et al. (2008) showed that the effects of quercetin were mediated through the inhibition of NFkB. Quercetin has also

Fig. 3. Schematic view of the main signaling cascades activated in cancer and their relationship with the mitochondria and apoptosis. (A) PI3K/AKT cascade: Activated PI3K induces the activation of Akt. Survival signals from PI3K/Akt pathways are transduced mainly through the phosphorylation and inactivation of pro-apoptotic proteins, such as BAD (Bcl-xL/Bcl-2-associated death promoter) and caspase-9. Akt phosphorylation activates CREB (cyclic AMP response element-binding protein), resulting in elevated transcription of genes encoding antiapoptotic Bcl-2 family proteins. (B) Activation of the Ras/Raf/MEK/ERK (Rat Sarcoma/Rapidly Accelerated Fibrosarcoma/ERK Kinase/Extracellular signal-regulated kinase) pathway, results in the activation of Rsk (p90 ribosomal S6 kinase). Bad and CREB are also the targets of Rsk, which may act synergistically with Akt to activate the survival pathway. (Abbreviation: TRAIL: Tumor necrosis factor-α-TNFα-related apoptosis-inducing factor; Trk: tyrosine kinase receptor). (B) Quercetin interaction with intracellular signaling cascades in cancer. Through inhibition of the major PI3K/AKT and RasRaf/MEK/ERK1/2/RSK signaling pathways, among others, which are crucial for cell survival, quercetin promotes apoptosis. Effects of PI3K/Akt also involve the results of crosstalk with other signaling cascades, such as JNK.
been shown to modulate apoptosis by stimulating the proteolytic activity of caspase-3 and caspase-9, by altering the expression of BCL-2 protein family, by inhibiting the phosphorylation of AKT, ERK 1/2 and PKC, and by upregulating c-jun N-terminal kinase (JNK) in a time- and concentration-dependent manner (Granado-Serrano et al., 2008). Globally, it appears that in malignant cells, quercetin might interact with different proteins (BCL-2 proteins, caspases) directly or indirectly to inhibit survival signaling cascades in cancer (including PI3K/Akt, MAPKs, ERK, and PKC) to promote the release of cytochrome c and the activation of caspases, thereby triggering apoptotic cell death (Fig. 3B). Notably, the antiproliferative effects observed appear to be a specific effect of quercetin in the context of cancer cells, as these effects were not observed in non-cancerous cell line of the same origin. One example of this has been demonstrated in prostatic cancer cells (Guo et al., 2007). The specificity of the effects of quercetin on cancer cells, particularly in regard to cellular metabolism, requires caution when interpreting the results from the neuroprotection studies that use tumor-derived cells, such as the human neuroblastoma cell line SH-SY5Y (Kim et al., 2008; Lee et al., 2010a; Wu et al., 2011).

Another important aspect of the anticancer effects of quercetin is its interaction with cell cycle regulatory proteins. Braganhol et al. (2006) found that quercetin triggers a G2/M phase cell cycle arrest in vitro, which, in the case of human cervical cancer (HeLa) cells, appears to be mediated through the activation of the p53 tumor suppressor protein, a transcription factor that induces apoptosis and that has been suggested as a potential target for cancer therapy (Haupt et al., 2003). Quercetin also appears to stabilize and to reactivate p53-dependent cell cycle arrest in other cancer cells (Tanigawa et al., 2008).

8. The bioavailability of quercetin

The identification of the molecular forms of quercetin circulating in the blood and their corresponding pharmacological effects has been a matter of long debate, but unfortunately, that matter is beyond the scope of this review. Nonetheless, further discussion regarding the different studies in context is warranted to understand controversial results. The issue of intestinal absorption, for instance, has previously been a point of discussion (Boots et al., 2008). Dietary quercetin is mostly present as glycosides that are subject to deglycosidation by enterobacteria for the absorption in the intestines, where metabolic conversion (glucuronidation and sulfation) begins (Crespy et al., 2001; Murota and Terao, 2003; Sesink et al., 2003). Studies have postulated that quercetin is metabolized by the intestinal microflora to its corresponding hydroxyphenylacetic acids (Vissiennnon et al., 2012). The magnitude of this process in relation to deglycosidation/metabolization is currently unknown. The percent of quercetin that enters the bloodstream as an aglycone undergoes metabolism into glucuronide, sulphoglucuronide and methylated forms. Initial studies described non-detectable plasma concentrations of quercetin; however, improvements in analytical procedures have since facilitated the detection of plasma quercetin concentrations in the nanomolar to micromolar range (Bischoff, 2008; Manach et al., 1995).

When 20 mg of quercetin were administered orally to rats as an aglycone, free plasma quercetin was detected at a concentration of 1.8 µM (Morand et al., 2000). Concentrations of 12 µM were detected in humans after the intravenous administration of 100 mg of quercetin (Lasmon and Brignall, 2000). In humans, a meal rich in plants (with 87 mg of quercetin) yielded mean plasma concentrations of 373 nM at three hours post ingestion, and a meal of fried onions (225 g) increased plasma concentrations to 516 nM (Kelly, 2011). These results suggest that one acute administration of quercetin does not reach the effective threshold of pharmacological plasma concentration that, according to in vitro experiments, could confer protection in brain tissue or anticancer effects in cell lines. These findings demonstrate that the active concentrations of quercetin applied in vitro cannot be translated linearly into in vivo situations. However, chronic administration of quercetin represents a different situation. Plasma levels of approximately 100 µM have been detected after rats were fed a diet containing quercetin for long periods of time (from 3 to 11 weeks) (Manach et al., 1995; De Boer et al., 2005). After oral gavage administration of St. John’s wort extract for a 9-day period, quercetin accumulated in the rat brain and elicited an antidepressant pressure (Paulke et al., 2008). A single oral dose (600 mg/kg) of the Ginkgo biloba extract EGB 761 resulted in plasma concentrations of 176 ng/ml of quercetin, whereas repeated administration of the same dose for 8 day produced an approximate 4.5-fold increase (Rangel-Ordóñez et al., 2010). Plasma quercetin concentrations of 12.5 ng/ml were detected after the supplementation with Achyrocline satureioides extracts, which are rich in quercetin aglycone and quercetin glycosides, into the animals’ daily water intake for 20 day. Cerebral levels of 1.65 ng/ml were detected after this latter treatment (Rivera, F., personal communication). The chronic administration of quercetin to humans (50–150 mg orally for 2 weeks) significantly increased plasma concentrations of quercetin (Kelly, 2011). Although there was one report showing that the long-term dietary intake of quercetin did not lead to its plasma accumulation (Bieger et al., 2008), available evidence shows that repeated quercetin administration markedly increases plasma (and brain) bioavailability.

Studies evaluating the protective effects of quercetin in the brain have focused on the antioxidant and protective targets and generally have not reported on working concentrations of quercetin. One study estimated a cerebral quercetin concentration of approximate 0.64 µM at 30 min after intraperitoneal liposomal quercetin administration (Dajas et al., 2003b). Thus, the recorded brain levels of quercetin after acute quercetin administration fall consistently below the active in vitro pharmacological concentrations, unlike when quercetin is administered chronically or using carriers that provide metabolic protection. Regarding toxicity the toxic in vivo concentrations remain unknown. Taken together, the data indicate the possibility that quercetin metabolites are pharmacologically active, as postulated by some studies (Spencer, 2009; Vissiennnon et al., 2012). Ishisaka et al. (2011) showed that the long-term (one month) oral administration of quercetin resulted in its accumulation as metabolite forms with antioxidant activity in the brain tissue of rats.

This low bioavailability might be related to the fact that most human studies have shown that quercetin has small effects on plasma antioxidant biomarkers and no effects on antioxidant indices, such as antioxidant status, oxidized LDL, inflammation or metabolism (Williamson and Manach, 2005; Egert et al., 2008; Kelly, 2011). In a twelve-week study, doses of 500 or 1000 mg/day of quercetin elicited no effects on plasma F (2) b-isoprostanes, oxidized LDL, glutathione, the ferric-reducing ability of plasma (FRAP) or oxygen radical absorbance capacity (ORAC) (Shanely et al., 2010). In apparent contrast to these results, a review of clinical studies highlighted evidence that quercetin could reduce the risk of lung cancer and development of colon cancer and reported an association between dietary quercetin intake and a decreased risk of renal cancer in male smokers (Kelly, 2011). When attempting to understand the discrepancies concerning the antioxidant capacity of quercetin with its lack of correlation with biomarkers and its apparently effective chemopreventive effects, the explanation proposed by Egert et al. appears quite probable:
the majority of the studies performed on the bioavailability of quercetin and its antioxidant effects explore its nutritional properties, and generally, the amounts administered are below levels of putative pharmacological activity. Plasma levels obtained with a flavonoid-rich diet might confer chemopreventative effects in the case of cancer, but considerably higher plasma concentrations would be necessary for anticancer effects. In clinical trials, such as those conducted on patients with chronic prostatitis (Shokes et al., 1999), beneficial effects have been observed only after the administration of high oral doses of quercetin (500 mg twice a day). In the only reported Phase I clinical trial in which quercetin showed improvement in two of eleven cancer patients doses utilized were of of 1400 mg/m² (Ferry et al., 1996). In this context, the demonstration that plasma levels of quercetin can be enhanced upon supplementation or chronic administration is of particular importance. Thus, although numerous in vitro and in vivo studies provide evidence for the inhibition of carcinogenesis by quercetin, the applicability to human cancer treatment still requires further research.

This context has provided a strong basis for numerous studies that have, at present, started to utilize different delivery vehicles for quercetin plasma transport that protects the molecule from metabolism and that facilitates more direct action on cellular and molecular targets. Different types of liposomes have been utilized with success in cases of experimental ischemia (Rivera et al., 2008; Sarkar and Das, 2006). Liposomal delivery in cases of cancer demonstrated that quercetin significantly inhibited tumor growth in vivo in a dose-dependent manner, showing that pegylated liposomal preparations could significantly improve the solubility and bioavailability of quercetin (Yuan et al., 2006). This approach offers great promise, although much research concerning the hemodynamic safety and efficacy is still needed.

9. Quercetin: Neuroprotection and anticancer effects taken together

Beyond the antioxidation/oxidation and kinase modulation mechanisms described above for neurons and cancer cells, whether there might be other molecular targets that could account for the results described above remains an open question.

Considering the metabolic similarities between neurons and tumor cells in terms of their glucose utilization, it would be meaningful determining how the known quercetin-mediated activation of AMP-activated protein kinase (AMPK), a common sensor for energy production and energy expenditure, might contribute to its neuroprotective and anticancer activities. AMPK activation requires phosphorylation by key upstream kinases, such as the serine-threonine kinase and tumor suppressor liver kinase B1 (LKB1) (Hardie, 2011). LKB1-AMPK influences the mammalian target of rapamycin (mTOR) pathway, which controls cell growth and is deregulated in most human cancers. The regulation of mTORC1 and p53 by AMPK contributes to LKB1-dependent tumor suppression (Shackelford and Shaw, 2009).

Several studies have highlighted the fact that the activation of AMPK by quercetin can sensitize cancer cells to apoptosis, indicating a role for quercetin as a modulator of signaling proteins, such as cyclooxygenase 2, apoptosis signal regulating kinase 1 (ASK-1), p53, and heat shock protein 709 (HSP70) (Jung et al., 2010; Lee et al., 2010b). Although a study that describes the neuroprotective capacity of quercetin through AMPK activation in a high cholesterol mouse model (Lu et al., 2006) would show a beneficial therapeutic effects on cancer and nervous protection through AMPK, a review showed that the role of AMPK in neuroprotection is highly controversial with conflicting experimental evidence of neuronal survival and death (Spasic et al., 2009).

However, this pathway also interacts with hypoxia-inducible factor 1 (HIF1), an important transcription factor that regulates cellular metabolism and survival during hypoxia by modulating transcriptional targets that include angiogenic factors, several glycolytic enzymes and multiple members of the glucose transporter family. The activation of glycolytic genes by HIF-1 is considered critical for metabolic adaptation to hypoxia through the increased conversion of glucose to pyruvate and eventually to lactate. In tumor cells, HIF plays a major role in the metabolic switch that shunts glucose metabolites from mitochondrial respiration to glycolysis (Lu et al., 2002). Hypoxia is a common circumstance faced by neurons in cerebrovascular pathology and proliferating cancer cells, and it has been hypothesized that quercetin activates HIF-1α in all steps of its signaling pathway (Wilson and Poellinger, 2002). Thus, the activation of HIF-1α by quercetin might be a key signal for neuroprotection because HIF-1α activation has been demonstrated to contribute to protective brain preconditioning (Bergeron et al., 2000). In cancer cells, quercetin inhibits the cell cycle through induction of the HIF system (Bach et al., 2010), consistent with its antiproliferative actions in other cases (Du et al., 2010).

Cells respond to heat exposure by expressing of a family of highly conserved proteins, the heat shock proteins (HSPs), which perform a variety of chaperone functions including folding and unfolding of polypeptides, proteins, and transport of proteins. HSPs are also expressed in response to metabolic perturbations and injuries, as part of a general stress response that is also linked with control of apoptosis (Lindquist and Craig, 1988). Several reports have shown that the overexpression of Hsp70, a 70-kD heat shock protein that is the most representative of the family, elicits protective effects in different models of nervous system damage (Yenari, 2002). In contrast, HSPs are overexpressed in a wide range of human cancers and are implicated in tumor cell proliferation, differentiation, invasion, and metastasis. HSPs have the ability to protect tumor cells from stress-induced lethal damage by interfering with antiapoptotic pathways and have furthermore been proposed as prognostic markers (Ciocca and Calderwood, 2005; Calderwood et al., 2006; Schmid and Multhoff, 2012). Accordingly, the reduction of HSPs expression in malignant cells, such as HeLa cells, promotes the induction of apoptosis (Jakubowicz-Gil et al., 2002, Jung et al., 2010).

The synthesis of HSP70 is inhibited by quercetin (Gonzalez et al., 2009; Wei et al., 1994) by interacting with HSF (heat shock protein factor), which inhibits the induction of HSPs after heat shock, resulting in the induction of apoptosis in malignant cells (Hosokawa et al., 1992). Thus, whereas the interaction of quercetin with HSF might result in therapeutic (pro-apoptotic) effects against malignant cells, it might worsen brain injury, as previously shown (e.g., by aggravating NMDA-induced seizures) (Ekimova et al., 2008).

The summary of the analysis of the last three cellular markers (AMPK, HIF and HSP) is a good final example that the specific effects of quercetin on neurons and cancer cells do not depend on particular actions on similar targets, but rather, on the significantly different intracellular milieus in which these molecular targets are immersed.

Other action of quercetin on cancer and the brain that should be considered is its inhibition of the of matrix metalloproteinases (MMPs) (Vijayababu et al., 2006; Saragusti et al., 2010). The extracellular matrix is a collection of fibrous proteins imbedded in a hydrated polysaccharide gel that are regulated by a system of proteolytic enzymes that are essential for cell proliferation, differentiation, and processes of apoptosis. MMPs represent the main group of these proteases and excessive expression of some
MMPs has been correlated with cancer susceptibility and mortality since invasion and metastasis of tumor cells depend on the degradation of the basal membrane and the extracellular matrix. Animal experiments confirm that MMPs play an important role in the genesis and progression of cancer although many of MMP inhibitors did not show clinical efficacy in cancer patients (Pytliak et al., 2012). The main role of MMPs in angiogenesis, tumor growth, metastasis and degradative activity of the extracellular matrix would give them an important role in cancer progression (Klein et al., 2004).

Besides, activation of MMPs mediates BBB disruption during cerebral ischemia. Lee et al. (2011) studied the effects of quercetin (25 µmol/kg intraperitoneally, starting 1 h after injury with continued treatment at 12-h intervals for 3 day) in adult rats that received focal ischemia by photothrombosis, assessing the results on BBB permeability and motor output. Results showed that post-ischemic increase in BBB permeability and brain oedema were decreased after quercetin that also significantly improved the behaviour in the rotarod test. Quercetin treatment markedly reduced ischemia-induced up-regulation of MMP-9 after ischemic injury. According to these results, inhibition of MMP might be one of the pharmacological activities of quercetin that would play a role in neuroprotection and cancer progression, although much research is still needed to clearly define its therapeutic potential in this field.

In summary, the pharmacological modulation of antioxidation/oxidation, kinase signaling axes by quercetin would modify the interconnected and concerted intracellular signaling equilibrium, promoting survival or death in the metabolically stressed neuron or the metabolically modified cancer cell. Whereas quercetin exhibits functions from broad anti-oxidation activity to kinase modulation of survival proteins that would be important for neuronal protection, its oxidative activity, apoptosis-promoting and other tumor suppressor activities would be the basis of its anticancer effects. Oxidative activity facilitating the release of death-promoting signals through the broad kinase inhibitory activities of quercetin would potentiate cell death in cancer while narrowing the protective capabilities in neurons (Fig. 4). These results would show the potential of quercetin as a therapeutic tool in neuroprotection and anticancer. Nonetheless, these conclusions are, at present, safely based only on in vitro studies. Low bioavailability and uncertainty about the active molecules hamper the translation of the in vitro results into an explanation of in vivo studies.

Controversial results, mainly from the in vivo studies emphasize the need for further research on the extent and the conditions of the antioxidant activity of quercetin in neurons and its oxidative actions in cancer in vivo, the relationship of its nuclear effects on gene expression, the identification of the active molecules and the improvement of their bioavailability through the use of transporters, such as liposomes.

One important conclusion from the evidence reviewed is that chronic intake of quercetin significantly results in its accumulation in the plasma and the brain, improving its effectiveness at biomarkers. This fact has particular ethnopharmacological relevance because, in general, people chronically ingest quercetin-containing plants for nervous ailments and cancer. Available evidence on the bioavailability and effectiveness at biomarkers points to chemoprevention and prevention of neuronal damage as the actual pharmacological effects of quercetin.

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