Antioxidant activities of quercetin and its complexes for medicinal application

Dong Xu 1, Meng-Jiao Hu 1, Yan-Qiu Wang 1, Yuan-Lu Cui 1*

1Research Center of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China;
*Correspondence: cuiyl@tju.edu.cn; Tel.: +86-22-59596170; Fax: +86-22-59596170

Abstract: Quercetin is a widely existing chemical constituent in botanical medicine and traditional Chinese medicine, which has strong antioxidant activity. In recent years, the antioxidant activities of quercetin have been studied widely, including the effects on glutathione (GSH), enzymatic activity, signal transduction pathways and reactive oxygen species (ROS) caused by environmental and toxicological factors. The chemical study of antioxidant activity of quercetin mainly embodies complex of metal ion and complex ion on the influence of antioxidant activity. In this review, we highlight the advances related to antioxidant in the biological activities, chemical research, and medicinal application of quercetin.

Keywords: quercetin; antioxidant activity; complex; medicine

1. Introduction

Quercetin (Figure 1) is a polyphenolic flavonoid compound [1]. It abundantly presents in kales, onions, berries, apples, red grapes, broccoli and cherries, and the most abundant is in tea and red wine [2, 3]. Modern studies have shown that quercetin prevents various diseases, such as osteoporosis, some forms of cancer, tumor, lung and cardiovascular diseases and etc., for whose prevention and treatment the antioxidant effects of quercetin plays a significant role[4]. Moreover, owing to enhance its solubility and bioavailability, quercetin may also exhibit a good antioxidant activity after forming a complex or an inclusion as well as some novel preparations[5-8]. These good results can be applied to human health care. At the same time, according to the bibliometric analysis results based on Web of Science database (Figure 2), the antioxidant study of quercetin has become a research hotspot[9, 10]. Nevertheless, there is little review and no an incomplete summary from the perspective of antioxidant activity for this area in recent years[11, 12]. Therefore, this paper will discuss the antioxidant effects of quercetin from two aspects, biological activity and chemical research, and summarize the research on the antioxidant direction of quercetin in recent years. Meanwhile, the review talks about the application of antioxidation in the medical field. The review hopes to provide some guidance and reference for the latter antioxidant research of quercetin.
Molecules 2019, 24, x FOR PEER REVIEW

Figure 1. Chemical structure of quercetin.

Figure 2. co-occurrence map of quercetin. The figure is based on data in the WOS database range from 2000 to 2017 years, then drawn by CiteSpace. The diameter of a node represents the number of occurrences of keywords. The larger the diameter, the more the appearance.

2. Antioxidant activity of quercetin in vivo

The antioxidant activity of quercetin is mainly manifested in the effect on GSH, enzymatic activity, signal transduction pathways, and ROS caused by environmental and toxicological factors. Quercetin shows a strong antioxidant potential by maintaining oxidative balance.

2.1. Directly effects on GSH

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) can quickly capture \( \text{O}^2_- \) and transform it into \( \text{H}_2\text{O}_2 \), and then catalyze \( \text{H}_2\text{O}_2 \) to decompose into the non-toxic \( \text{H}_2\text{O} \). This reaction requires GSH as a hydrogen donor. Animal and cell studies had shown that quercetin induces GSH synthesis[13, 14]. Renal ischemia/reperfusion (I/R) also showed that GSH levels are increased with quercetin therapy aiming at enhancing the antioxidant capacity of rats[15]. But in quercetin treatment of high doses, the dynamic balance of GSH (Under the action of GSH peroxidase, \( \text{H}_2\text{O}_2 \) is converted to \( \text{H}_2\text{O} \) and GSH is oxidized to GSSG. Under the action of GSH reductase, GSSG in the liver and red blood cells receives H and restores to GSH.) is produced and that may cause inhibition of GSH levels in low doses that is 0.5% in the literature[16].

2.2. Effects on enzymatic activity

The -OH groups on the side phenyl ring of the quercetin are combined with important amino acid residues at the active site of two enzymes. Thus, it has a stronger inhibitory effect against key enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) that are associated with oxidative properties[17]. Quercetin can also alleviate the decline of manganese-induced antioxidant
enzyme activity, the increase of AChE activity, hydrogen peroxide generation and lipid peroxidation
level in rats, and therefore relieving the condition of manganese poisoning [18].

Pretreatment with quercetin significantly enhanced the expression levels of endogenous
antioxidant enzymes such as Cu/Zn SOD, Mn SOD, catalase and GSH peroxidase in the
hippocampal CA1 pyramidal neurons of animals suffering from ischemic injury, which generates a
strong protection for the hippocampal area CA1 pyramidal neurons from I/R injury. Thus,
pretreatment shows a strong neuroprotective effect on transient ischemia[19].

In addition, as one of the most metabolically active tissues of the body, bone undergoes a
continuous and complicated process of remodeling throughout life. In particular, osteoblasts play a
critical role in this cycle and derived from osteoprogenitor cells that they rise from self-renewing,
pluripotent stem cells. Their primary function is to generate a new bone matrix and, as osteocytes to,
support the bone structure itself. Damage of osteoblasts thus can result in several dysfunctions.
Quercetin can reduce the fracture healing damage of smokers due to their poor bone mass and
stability by the means of removing free radicals and up-regulating the expression of HO-1 and
SOD-1 to protect primary human osteoblasts exposed to cigarette smoke[20].

Quercetin also can prevent heart damage through the clearance of oxygen free radicals after
lipopolysaccharide (LPS)-induced endotoxemia. LPS can induce histopathological and biochemical
effects of damaged myocardium in the endotoxemia model. In the experiment, rats in the LPS group
showed a significant increase of MDA level in tissues and decrease of SOD and catalase (CAT) in
heart tissues. Nevertheless, quercetin increased the level of SOD and CAT and reduced the level of
MDA after LPS induction, hence enhanced the antioxidant defense system[21].

2.3. Effects on signal transduction pathways

By activating or inhibiting, up-regulating or down-regulating signal transduction of the body,
quercetin can improve the antioxidant performance of the body, and repair injury such as spinal
cord injury, atherosclerosis, lead or cadmium toxicity and damage in the organs to cure the disease.
Figure 3 is the signal pathway of antioxidation regulated by quercetin.

Through the influence on signal transduction pathways, quercetin affects related enzymes or
antioxidant active substances so that enhance antioxidant properties and helps treat diseases.
Studies have shown that the protective mechanism of quercetin for acute spinal cord injury may rely
on inhibiting the p38MAPK/iNOS signaling pathway, down-regulating the content of MDA and
up-regulating the activity of SOD to achieve the purpose of antioxidation[22]. In the case of treating
psoriasis with quercetin, the mechanism might downregulate the expression of NF-κB, IKK, NIK and RelB, upregulate TRAF3, increase the activity of GSH, CAT and SOD, reduce the accumulation of MDA in skin tissue induced by imiquimod (IMQ), and enhance the body’s antioxidant performance[23]. There are also signaling pathways that are affected by enzymes to enhance antioxidant properties, such as oxidative stress protection. Quercetin reduced oxLDL-inhibited AMPK activation and oxLDL-activated NADPH oxidase expression, thereby maintained AKT/eNOS function and reduced NF-κB signal transduction to combat atherosclerosis[24]. Besides, it can promote oxidation or enhance antioxidant capacity through the impact on the signal pathway. For example, quercetin controls the development of atherosclerosis induced by high fructose diet by the way of inhibiting ROS and enhancing PI3K/AKT. It also advances the functional recovery of moving medium after cerebral ischemia by promoting the signal transduction of anti-oxidation and resistance to apoptosis, and inhibiting TGFβ2/ PI3K/AKT activation to enhance the antioxidant capacity[25-27]. It can also be used to prevent or treat damage or toxicity of the body by directly enhancing the antioxidant properties by affecting signal transduction pathways as shown in Table 1.

### Table 1. The mechanisms that quercetin treat damage induced by various factors.

<table>
<thead>
<tr>
<th>Inductive factors</th>
<th>Damage name</th>
<th>Protection mechanisms</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS/ D-GalN</td>
<td>Acute liver injury</td>
<td>Inhibits the activation of NF-κB and MAPK signaling pathways and inhibits the expression of apoptosis related proteins induced by LPS/D-GalN</td>
<td>Decreases production of LPS/D-GalN induced by oxidation markers[28]</td>
</tr>
<tr>
<td>Toosendanin</td>
<td>Liver toxicity</td>
<td>Induces Nrf2/GCL/GSH antioxidant signal transduction pathways</td>
<td>Increases Nrf2-mediated GCLC/GCLM expression, thereby increases GSH content in cells[29]</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Liver damage</td>
<td>Regulates phosphoinositide 3-kinase/Akt/NF-κB and STAT3 pathways</td>
<td>Enhances the body’s antioxidant, anti-inflammatory and anti-apoptotic effects[30]</td>
</tr>
<tr>
<td>A variety of liver toxins</td>
<td>Liver toxicity</td>
<td>Induces p62 expression and inhibits the binding of Keap1 and Nrf2</td>
<td>Increases transcription expression of Nrf2 targeted antioxidant genes[31]</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Heart toxicity</td>
<td>Up regulates Bmi-1 expression to reduce oxidative stress</td>
<td>Reduces DNA damage at ROS levels and maintains cardiomyocyte viability[32]</td>
</tr>
<tr>
<td>CCl4</td>
<td>Liver damage</td>
<td>Improves antioxidant activity and regulates of TLR2 / TLR4 and MAPK/NF-κB signaling pathway</td>
<td>Inhibits ROS production in the liver and attenuates CCl4-induced oxidative damage[33]</td>
</tr>
<tr>
<td>Lead</td>
<td>Liver damage</td>
<td>Reduces oxidative stress in liver, inhibits JNK phosphorylation and increases PI3K, Akt levels</td>
<td>Effectively inhibits lead-induced endoplasmic reticulum stress[34]</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Cerebral cholinergic dysfunction</td>
<td>Reduces the production of ROS and protects the integrity of the line by regulating the protein</td>
<td>Regulates molecular targets involved in the signal conduction of</td>
</tr>
</tbody>
</table>
involved in apoptosis and MAPK signal conduction

brain cholinergic energy and reduces the neurotoxicity of cadmium[35]

Malignant cell transformation

Protects BEAS-2B cells from Cr (VI) induction by targeting miR-21-PDCD4 signaling

Reduces ROS production induced by Cr (VI) exposure in BEAS-2B cells[36]

Decreases free radicals, increases antioxidant enzyme activity, improves overall antioxidant capacity and slows down aging by improving Nrf2[37]

Cognitive impairment and neuron degeneration or loss

Improves the Nrf2-ARE signaling pathway

D-lactose

Regulates the transcription activities of NF-κB and AP-1

Receptor activator for NF-κB ligand

Osteoblast differentiation

Regulates the transcription activities of NF-κB and AP-1 mechanism activation[38]

2.4. Effects on ROS caused by environmental and toxicological factors

Oxidative damage in the body is mostly caused by ROS. Quercetin can remove ROS to achieve direct resistance against oxidation damage, including respiratory damage, ultraviolet radiation b(UVB) skin lesions caused by radiation, the oxidative damage induced by paraquat as well as sperm change associated with ROS and oxidative damage of gastric epithelial cells.

Respiratory damage refers to exposure to fine particulate matter (PM2.5) in the environment that weakens the cellular activity of 16HBE cells, increases the production of ROS and inhibits the expression of mitochondrial genes. Quercetin might stimulate 16HBE cells to repair oxidative damage after PM2.5 exposure by regulating ROS production and anti-inflammatory[39].

Human skin is the body's largest organ that can resist all kinds of environmental damage. However, UVB induces a transient increase in ROS and an imbalance of endogenous antioxidant systems, leading to increased levels of free radicals and inflammation that affect the organism. Some studies have shown that quercetin prevents UVB-induced radiation damage by removing ROS and preventing cell membrane and mitochondrion from attacks of ROS and inhibits cell membrane mobility and mitochondrial membrane depolarization. Consumption of quercetin also inhibits this imbalance and is used to prevent UVB skin damage[40, 41].

When herbicide paraquat treats with cells, ROS levels are significantly reduced and the total GSH levels are increased. The results show that quercetin can alleviate oxidative stress by reducing ROS production and increasing GSH in cells [42]. Gastric epithelial injury caused by ROS including H2O2 can be eased by quercetin which protects gastric epithelial GES-1 cells from oxidative damage and inhibits the production of ROS during acute gastric mucosal injury in mice [43]. Meanwhile, since quercetin has a significantly scavenging properties of ROS, it also prevents sperm changes induced by ROS and retains the function of male germ cells [44].

On the other hand, quercetin inhibits oxidative stress to achieve direct antioxidant damage. Oxidative stress is caused by the imbalance of oxidation and antioxidant in the body, and it tends to be oxidized. Once oxidized, it results in neutrophil inflammatory infiltration, increasing protease secretion and numerous oxidative intermediates. Quercetin regulates the balance of oxidative and antioxidant effects to inhibit oxidative stress which, in the experiment, embodies radiation brain damage in rats, oxidative damage in rats induced by acrylamide, nerve damage in retinas of diabetic rats, neurodegenerative diseases and oxidative stress induced by cadmium fluoride. By changing antioxidant levels in the body, quercetin enhances the antioxidant level of the body and protect the brain, nerve or other cells in the body from damage caused by oxidation[45-49].
Ionizing radiation induces various kinds of damages by forming free radicals, or causes cell damage and cell death by hydrolyzing ROS. Quercetin effectively protects cells from the genetic toxicity and damage induced by radiation and attributes to remove free radicals induced by radiation, and increases the endogenous antioxidant levels. The structure-activity relationship of these bioflavonoids is a reducing agent for hydrogen or electronic agents, which inhibits or reduces free radical toxicity and enhances the antioxidant properties of the body, thus provides protection against radiation[50-52].

Quercetin has antioxidant and hepatoprotective effects on acute liver injury in mice induced by tertiary butyl hydrogen peroxide. Because quercetin has a strong antioxidant effect and free radical scavenging effect. It inhibits lipid peroxidation and increases antioxidant activity and can be used to treat oxidative liver injury[53]. Quercetin also directly removes ROS, hydroxyl radicals in hypoxia and restore endogenous redox homeostasis by increasing glutathione levels and removing free radical enzyme systems, thereby it reverses hypoxia-induced memory impairment by reducing oxidative stress mediated neurodegeneration in the hippocampus[54].

Quercetin removes free radicals and strengthen antioxidant defense systems in the body. Thus, quercetin inhibits the oxidative stress including the production of ROS induced by nicotine in order to cure disease such as tobacco addiction[55].

3. Chemical studies on the antioxidant activity of quercetin

Due to poor water solubility and low bioavailability (5.3%) of quercetin, many researchers used quercetin as a lead compound for structural modification to increase its water solubility and bioavailability, thus enhancing its antioxidant activity[56]. The modification of quercetin is generally divided into two types, namely derivation of quercetin or recombination with the active group. The former changes the structure of quercetin and improves its solubility through derivation, while the latter produces a synergistic effect through the properties of the active group and quercetin, such as the metal complexes of quercetin. Moreover, the bioactivity and pharmacological action of quercetin are significantly enhanced after forming complexes with some metal or complex ion. Therefore, many researchers have tried to improve the antioxidant activity of quercetin by the method of complexes.

3.1. Complexes with metal ion

The combination of quercetin and metal ions improves reducibility of flavonoids, which are more easily oxidized by free radicals than unmatched flavonoids. Therefore, the complexes show excellent antioxidant activity. Through DPPH free radical scavenging, the scavenging capacity of quercetin combined with vanadium[57], copper[58, 59], magnesium[60], iron[61], ruthenium[62], cobalt and cadmium[63], calcium[64] and rare earth elements[65] are stronger than the pure quercetin, namely the antioxidant activity of the complexes is significantly higher than the pure quercetin. Most of these complexes are applied in medicine. For instance, vanadium quercetin complex weakens mammary cancer by regulating the P53, Akt/mTOR pathway and downregulating cellular proliferation connected with increased apoptotic events. Ruthenium quercetin complex forces the colon cancer cells to undergo apoptosis through p53 mediated pathway and has antiangiogenic activity through potential inhibition of VEGF. The solid quercetin rare earth (III) complexes have a better inhibition rate against the tested tumor cells compared with quercetin. Other new compounds are called for potential remedial and other application identification. But some metal ions, when combined with quercetin, reduce free radical scavenging and total antioxidant activity, such as lead[66] and terbium[67].

3.2. Complexes with complex ion

Quercetin does not enhance the activity of SOD, CAT, and GSH-PX in the ARPE-19 cells treated by H2O2 and does not effectively reduce the content of ROS and MDA in the ARPE-19 cells. However, quercetin phospholipid complex significantly increases the activity of these enzymes and
significantly reduces ROS and MDA levels. These data jointly show that compared with free quercetin, the antioxidant activity of quercetin phospholipid complex is increased. Because the low water solubility of quercetin limits its use, the quercetin phospholipid complex is developed to improve its water solubility, which is better absorbed through the gastrointestinal tract and increases bioavailability[68, 69]. The bioavailability of quercetin is also increased by the structural modification with glucoside/sulfate conjugates. Studies have shown that after oral administration of quercetin, about 93.3% of quercetin is metabolized in the intestinal tract and only 3.1% in the liver. When it forms the structure of quercetin with glucoside/sulfate conjugates, no significant intestinal liver recirculation is observed for the metabolites of quercetin and its conjugation. It is indicated that the bioavailability of free quercetin is improved after the synthesis of the conjugate, and the antioxidant activity of the free quercetin is further strengthened[56].

Some complex ionic complexes, such as glucan - quercetin conjugate[70], calcium phosphate-quercetin nanocomplex(CPQN)[71] and quercetin-germanium nanoparticles[72], have higher antioxidant activity than free quercetin after forming complexes. Just like the function of complexes with metal ion, complexes with complex ion also are applied in medicine and other aspects to serve mankind.

4. Application of antioxidant activity in the medical field

Given the clinical importance of oxidative damage, antioxidants are expected to treat some diseases. Therefore, quercetin can be well applied in medicine because of its strong antioxidant properties. This basic principle of antioxidant activity of quercetin is shown in the Figure 4.

Figure 4. Basic principle of antioxidant activity of quercetin.

4.1. Effects on tumor

The effects of quercetin on tumor are mainly reflected on the effect of the malignant tumor, including the malignant tumor of epithelial tissue and the malignant tumor of interlobular tissue. The term "cancer" generally refers to all malignant tumors, including cancer and sarcoma.

Quercetin is used in cancer prevention, and blocks the spread of various cancers, such as lung, prostate, liver, breast, colon and cervical. Anticancer properties come into play through various mechanisms involving cell signaling and the ability of enzymes to inhibit the activation of carcinogens. This article focuses on the treatment or prevention of quercetin for cancer. The continuous accumulation of ROS induces oxidative stress, which leads to the over-activation of signal transduction pathways and promotes cell proliferation, survival and metabolic adaptation to the tumor microenvironment. Therefore, this may induce the generation of the tumor. Quercetin regulates both internal and external pathways of ROS-mediated Protein kinase C (PKC) signaling. PKC is a key regulator of cell growth and differentiation in mammalian cells and its activation partially depends on ROS signaling, inhibits cell proliferation and survival and induces apoptosis in cancer. Quercetin also induces the anticancer effect by up-regulating p53 which
is the most common inactivated tumor suppressor and BAX which is the most downstream of p53 or the most famous pro-apoptotic gene in HepG2 cells[73, 74].

Beyond that, quercetin prevents cancer by influencing oxidative stress markers and antioxidant enzymes. In the experiment, histology and oxidative stress markers lipid peroxidation (LPO), H$_2$O$_2$, and antioxidant GSH level in rats were measured. The result showed that LPO, H$_2$O$_2$, in (carcinogen + testosterone) treated rats are increased and GSH level is decreased, whereas the quercetin-treated rats reverted back to normal level. This means that quercetin may be used to target the signaling molecules, and it attributes to remedy of prostate cancer which is the second highest cancer-related deaths in men[75]. Other studies have confirmed that prostate cancer induces a significant decrease in antioxidant enzymes and apoptotic proteins in animals as well as a significant increase in antioxidant enzymes and apoptotic proteins after quercetin supplementation. When insulin-like growth factor receptor 1 (IGFIR), AKT, androgen receptor (AR), cell proliferation and anti-apoptotic proteins are increased in cancer induction, supplement with quercetin reduces its expression[76].Quercetin also significantly increases antioxidant enzyme levels, including GSH, SOD, and catalase, and inhibits lipid peroxides, thereby weakening the skin cancer induced by 7, 12-dimethyl Benz (a) anthracene(DMBA)and croton oil in mice. Histology and enzyme activity suggest that oral quercetin in the daily diet may affect the occurrence of skin cancer, thus achieve some protective effect on skin cancer[77].

4.2. Effects on heart diseases

Due to the antioxidant activity of quercetin, it is used to therapy cardiovascular diseases threatening human health. As one of the most common cardiovascular diseases, coronary heart disease is based on acute myocardial infarction (AMI). The recent study shows that oxidative stress is an important factor for facilitating the development of AMI. Quercetin significantly decreases MDA content, increases SOD and CAT activity, and regulates other indicators combined with anti-inflammatory and anti-apoptosis to effectively protect against myocardium injury[78]. At the same time, quercetin protects the heart from secondary cardiac dysfunction mediated by oxidative stress and inflammation. Because quercetin significantly attenuates ROS overproduction, decreases trauma-induced viability, and increases TNF-α and Ca$^{2+}$ overload in myocardial cell injury. Therefore, quercetin can efficiently prevent injury induced by oxidative stress[79].

4.3. Effects on depression

Depression is a common mental disease that severely endangers human physical and mental health. Chronic stress is connected with depression and anxiety. Research shows that quercetin treatment significantly lower oxidative and inflammatory stress and prevent neural damage through the regulation of oxidative stress markers that are TBARS, nitric oxide, antioxidants that are total thiol, catalase, and pro-inflammatory cytokines in the hippocampus[80].Meanwhile, quercetin has a significant antidepressant effect in the Olfactory bulbectomy (OB) ,an animal model of depression. Quercetin reduced the immobility time in the forced swimming test and tail suspension test, increased the time spent grooming, the activity of SOD, and the lipid hydroperoxide content (LOOH) in the hippocampus to give play to antidepressant potential[81].As a result, quercetin efficiently prevents stress induced by neurological complications, and enhances total antioxidant activity in the body to treat depression and related diseases.

4.4. Effects on diseases caused by poisoning

Quercetin affects diseases induced by pathogenic factors. These diseases usually are caused by imbalance between oxidation/antioxidation in the body. Quercetin protects the body from urotoxicity induced by cyclophosphamide (CYP) via that inhibits oxidative stress and restores pro-inflammatory /anti-inflammatory cytokines balance. Compared with the normal group, CYP injection showed a marked reduction in bladder levels of catalase, SOD, and IL-10. However, quercetin reversed the change of biochemical markers and histopathology to treat urotoxicity[82].
inhibiting CYP 2E1 activity, quercetin reduces the production of ROS and peroxide oxidation and prevents antioxidant depletion to prevent liver injury in Type I diabetes[83]. Simultaneously, quercetin has certain therapeutic effect for diseases induced by manganese[84], ciprofloxacin[85], glycosides from thunder god vine [86], cadmium (Cd) [87], Procarbazine (PCZ)[88], arsenic[89], LPS[90], cisplatin(Cis.)[91]. Through increasing the body’s total antioxidant activity and related antioxidant enzymes, quercetin can be used to treat diseases caused by oxidative damage.

4.5. Effects on other diseases

The diseases such as necrotizing enterocolitis (NEC), diabetes, lung injury and diseases correlated with oxidation, quercetin has a better therapeutic effect. For the NEC, quercetin changes the total antioxidant status of serum, MDA and GSH levels[92]. For the type II diabetes, a study has shown that quercetin intake is inversely related to the prevalence of diabetes, showing a protective effect[93]. In the meantime, quercetin is suggested to a remedy for idiopathic pulmonary fibrosis (IPF) due to restoring a disturbed pulmonary redox balance combined with inflammation[94]. Quercetin is also beneficial to acute lung injury by reducing the levels of oxidative stress markers and increasing the antioxidant enzyme activities[95].

5. Conclusion

Quercetin, a typical flavonoid, generally exists in fruits and vegetables, and its antioxidant activity in vivo is implied to contribute to human health[96]. Simultaneously, some study shows quercetin also is used as a nutraceutical for protection against various diseases[96]. It is of great significance for the treatment and prevention of human diseases through the influence on glutathione, enzymes, signal transduction pathways and ROS caused by other factors. The application of quercetin is limited in pharmaceutical field and it is difficult to be absorbed in body own to its poor solubility, low bioavailability, poor permeability and instability[97]. When it forms complexes with metal ions or complex ion, its bioavailability and antioxidant effect are enhanced and strengthened. In addition to the study of complex, the preparations of quercetin are also a hot research in recent years, including nanoparticles loaded with quercetin[96, 98-101], polymeric micelle of quercetin[102], quercetin-loaded mucoadhesive nanoemulsion[103], quercetin-loaded gel[104], and others[105, 106]. These preparations well solve the solubility and bioavailability of quercetin to improve its related property or clinical efficacy in favor of new drug research and development.

As a result, the solubility and bioavailability of quercetin are firstly solved, and its property such as antioxidant activity, anti-microbial and others will be well exhibited. Quercetin, as a rich natural drug resource, will be made full use to contribute to the development of human health and medicine.

Conflicts of Interest: The authors declare that they have no competing interests.

Acknowledgments: The authors are thankful to Tianjin University of Traditional Chinese Medicine for help in conducting this study.

Funding statement: This work was supported by the National Natural Science Foundation of China (81741119).

Reference


436 45. Kale, A., Pişkin, Ö., Baş, Y., Aydin, B. G., Can, M., Elmas, Ö., & Büyükuysal, Ç. Neuroprotective effects of
438 46. Zargar, S., Siddiqi, N. J.; Ansar, S.; Alsaumani, M. S.; El Ansary, A. K. Therapeutic role of quercetin on
442 48. Heo, H. J.; Lee, C. Y. Protective effects of quercetin and vitamin C against oxidative stress-induced
444 49. Zargar, S., Siddiqi, N. J.; Al Daithan, S. K.; Wani, T. A. Protective effects of quercetin on cadmium fluoride
446 50. Patil, S. L.; Rao, N. B.; Somashekaraappa, H. M.; Rajashekar, K. P. Antigenotoxic potential of rutin and
Quercetin protects radiation-induced DNA damage and apoptosis in kidney and bladder tissues of rats.
450 52. Patil, S. L.; Malliaiah, S. H.; Patil, R. K. Antioxidative and radioprotective potential of rutin and quercetin in
452 53. Kalantari, H.; Forouzandeh, H.; Khodayar, M. J.; Siahpoosh, A.; Saki, N.; Kheradmand, P. Antioxidant and
hepatoprotective effects of Capparis spinosa L. fractions and Quercetin on tert-butyl hydroperoxide-
hypoxia-induced hippocampal neurodegeneration and improves memory function in the rat. High. Alt.
456 55. Yarahmadi, A.; Zal, F.; Bolouki, A. Protective effects of quercetin on nicotine induced oxidative stress in
Pharm. Res. 2005, 22, 892-901.
regulating the P53, Akt/mTOR pathway and downregulates cellular proliferation correlated with
462 58. Bratu, M.; Birghila, S.; Miresan, H.; Negreanu-Pirjol, T.; Prajitura, C.; Calinescu, M. Biological Activities of
Zn(II) and Cu(II) Complexes with Quercetin and Rutin: Antioxidant Properties and UV-Protection
Spectrosc. 2015, 151, 807-813.
Antioxidant, DNA Binding, DNA Cleavage, and Antibacterial Activity Studies. J. Fluoresc. 2016, 26,
2013-2031.
underlying the in vitro and in vivo chemotherapeutic efficacy of ruthenium quercetin complex in colon
472 63. Trifunscii, S.; Ardelean, D. Synthesis, Characterization and Antioxidant Activity of Co(II) and Cd(II)
474 64. Simoes, V. D.; Favarin, L. R. V.; Cabeza, N. A.; de Oliveira, T. D.; Fiorucci, A. R.; Stropa, J. M.; Rodrigues,
D. C. M.; Cavalheiro, A. A.; dos Anjos, A. Synthesis, characterization and study of the properties of a new
478 66. Ravichandran, R.; Rajendran, M.; Devapriam, D. Structural characterization and physicochemical


550 77. Ali, H.; Dixit, S. Quercetin attenuates the development of 7, 12-dimethyl benz (a) anthracene (DMBA) and croton oil-induced skin cancer in mice. J. Biomed. Res. 2015, 29, 139-144.


© 2019 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license \( \text{http://creativecommons.org/licenses/by/4.0/} \).