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RESEARCH ARTICLE

Harnessing Quercetin Nanoparticles: Unlocking the Biological Potential of a Powerful Bioactive Flavonoid

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Abstract: Flavonoids and other antioxidants shield cells from harm brought on by unstable substances like free radicals. Flavonoids, which are present in fruits and vegetables, have been demonstrated to lower the risk of metabolic disorders, cardiovascular diseases, and some forms of cancer because of their physiological activity in lowering oxidative stress, preventing platelet aggregation and low-density lipoprotein oxidation, and functioning as blood vessel vasodilators. Flavonoids have been utilized as an alternative medical source to treat oxidative stress-related illnesses. Onions, grapes, berries, cherries, broccoli, and citrous fruits are rich sources of quercetin, a powerful antioxidant flavonoid that is known to guard against tissue damage brought on by a variety of medication toxicities. Flavonoids have a broad range of biological activity and have been around for more than a billion years. Red wine, onions, green tea, apples, berries, and other plants and foods contain quercetin, a flavonoid with anti-inflammatory and antioxidant qualities. It may prevent heart disease, lower swelling, manage blood sugar, and destroy cancer cells. Although there is little evidence to support its advantages, quercetin is also used to treat diabetes, bladder infections, and arthritis.

Keywords: Flavonoids, free radicals, quercetin, anti-inflammatory effects, antioxidants.

1. INTRODUCTION

Research and innovation in pharmaceuticals are increasingly concentrating on delivery strategies that maximize desired therapeutic outcomes while reducing adverse effects. According to recent trends, multi-particulate drug delivery systems are particularly well-suited for producing controlled or delayed-release oral formulations with a short and repeatable gastric residence time, minimal risk of dose dumping, and flexibility in blending to achieve various release patterns. The carrier utilized to create the multi particles and the quantity of drug they carry are two of the many variables that affect the release of drugs from micro-particles [1]. Thus, multi-particulate drug delivery methods offer enormous potential for creating novel oral formulations with controlled and delayed release, expanding the scope of pharmaceutical development in the future.

It has been argued that multi-particulate formulations with reduced dose dumping risk will be more appropriate in this situation to produce a regulated and delayed release profile. The components of a multi-particulate system include pellets, granules, beads, microspheres, and mini/micro tablets that are compressed into tablets or placed in sachets or capsules [2]. In contrast to a single conventional dosage form, the MP system divides the drug's dose forms among several distinct delivery entities. In addition, these systems are favored because of their relatively higher gastrointestinal tract dispersibility, higher bioavailability, lower risk of systemic toxicity, lower frequency of dosing, improved patient compliance, lower incidence of absorption variability, decreased likelihood of dose dumping, and precise dosing [3].

Since nanoparticles have a specialized function and are extremely reactive with biological systems, their use in science, technology, and medicine is growing. They can completely transform several biotechnology and medical instruments and processes, making them more affordable, portable, safe, and simple to use. Nanoparticles have a wide range of applications, including medical treatments, industrial production in solar and oxide fuel batteries for energy storage, and integration into everyday materials, such as clothing, cosmetics, optical devices, catalysts, bactericidal products, electronics, sensor technology, biological labeling, and the treatment of certain cancers. Nanoparticles, defined as objects with sizes between 1 and 100 nm, may exhibit properties that differ from the bulk material due to their size [4].

Compared to conventional medications, Controlled Drug Delivery Systems (DDS) provide several benefits, including higher accumulation of therapeutic compounds in the target site and fewer adverse effects. The functionalization of magnetic nanoparticles as carriers in DDS is the main subject of

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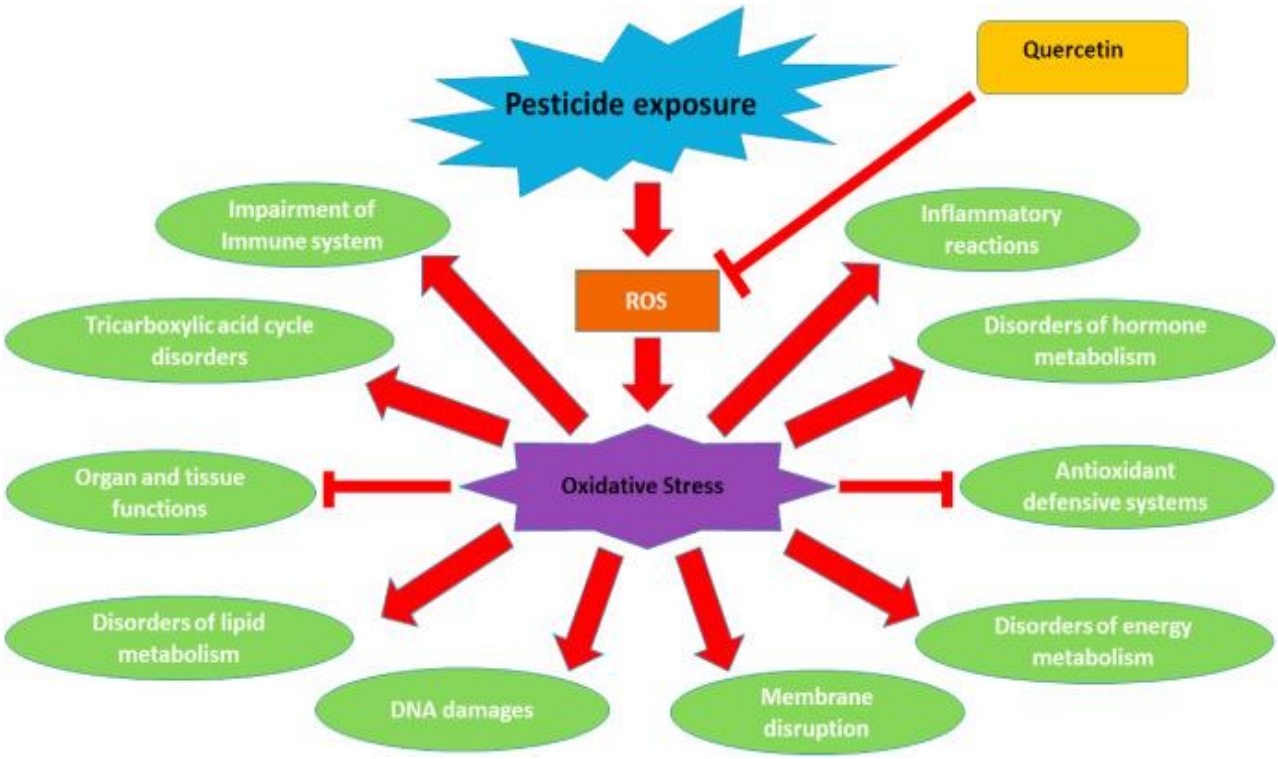


Fig. (1). Quercetin, a dietary flavonoid, has protective properties. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

this review, which also examines these nanocarriers and their relationships with medications. The use of magnetic nanoparticles as DDS is examined, along with its benefits and drawbacks. For the effective transport of small compounds, nanoparticles use biological pathways, and their pharmacokinetic properties are improved by synthetic techniques, such as surface, porosity, stealth, and size alterations [5].

A powerful cancer treatment and dietary antioxidant present in fruits and vegetables, flavone is a naturally occurring flavonoid that is present in a variety of plants and human diets. In comparison to pharmaceutical drugs, plants and their parts are employed for their flavour, aroma, and therapeutic qualities. Phytoconstituents and plant extracts possess biological functions, including anti-inflammatory, anti-hyperlipidemic, antidiabetic, and free-radical scavenging activities [6].

These activities are essential for enhancing quality of life and preventing metabolic diseases. In recent decades, there has been an increasing interest in identifying chemicals with antioxidant properties from plants that exhibit significant biological activities against conditions such as diabetes, hypercholesterolemia, and inflammatory disorders. Examples of such plants include *Curcuma domestica Valeton, Cuscuta reflexa, Daucus carota, Emblica officinalis, Foeniculum vulgare, Glycyrrhiza glabra, Mangifera indica, Momordica charantia, Ocimum sanctum, Psoralea corylifolia, Santalum album, Solanum nigrum, Swertia chirayita,* and *Withania somnifera*. More than 20 plants contain QT, a bioflavonoid that has anti-inflammatory, antihypertensive, vasodilator, anti-obesity, anti-hypercholesterolemic, and anti-atherosclerotic qualities. Additionally, it aids in the prevention of diseases, such as metabolic syndrome, vascular disorders, and hypertension, that are brought on by oxidant and free-radical causes. The purpose of this paper is to provide an overview of the biological and pharmacological importance of QT, which could be summarized as follows [1, 7]:

- QT may help reduce allergy symptoms by stabilizing cells that release histamine, a substance that triggers allergic reactions [8].
- QT is an antioxidant that can counteract free radicals, which are particles that harm DNA and cell membranes and have the potential to kill cells.
- QT provides the potential to prevent cancer.
- QT may have anti-diabetic effects.
- QT has the potential to prevent Alzheimer's disease.
- QT may help prevent heart disease (Fig. **1**).

1.1. Synthesis Methods of Quercetin

QT can be synthesized through the phenylpropanoid metabolic pathway or through chemical synthesis, which are as follows [9]:

1.2. Phenylpropanoid Metabolic Pathway

QT is synthesized from cinnamic acid, which is synthesized from phenylalanine. This process forms 4 coumaroyl-CoA, which then enters the flavonoid biosynthesis pathway, eventually leading to the production of quercetin.

1.3. Chemical Synthesis

QT can be used as a precursor for the synthesis of other compounds, such as Schiff bases and metal complexes. QT can also be used to synthesize nanoparticles, such as silver nanoparticles and QT Nano liposomes [10].

2. EXAMPLES OF CHEMICAL SYNTHESIS

2.1. Chiff Base Synthesis

In this process, Quercetin (QT) is first dissolved in ethanol, and then glacial acetic acid is added to the solution. After 30 minutes, ethanol amine is slowly added dropwise to the reaction flask [11].

2.2. Metal Complex Synthesis

In metal complex synthesis, QT can serve as a precursor for the synthesis of metal complexes, such as QT-Tb (III) complexes [12].

2.3. Nanoparticle Synthesis

QT can be used in the synthesis of nanoparticles, including silver nanoparticles and QT-loaded nanoliposomes.

2.4. Biological Activities of QT

QT is a flavonoid found in many fruits and vegetables [13]. It has many biological activities, including antioxidant, anti-inflammatory, and antibacterial properties, which are as follows:

2.5. Antioxidant Properties

The antioxidant properties of QT are as follows:

- The phenolic hydroxyl group and double bonds of QT make it a strong antioxidant.
- It can reduce oxidative stress and inflammation.
- It can protect cells from damage caused by drug toxicities [14].

2.6. Anti-inflammatory Properties

The anti-inflammatory properties of QT are as follows:

- It can reduce inflammation and muscle damage after exercise.
- It can suppress the NLRP3 inflammation, which is involved in inflammatory responses.
- It can inhibit the production of pro-inflammatory cytokines.

2.7. Antibacterial Properties

The antibacterial properties of QT are as follows:

- It possesses anti-Alzheimer's, anti-arthritic, and wound-healing properties.
- It exhibits antitumor, antiviral, and anti-allergic properties [15].

2.8. Therapeutic Applications of QT

QT has a wide range of potential therapeutic applications, including the treatment of cancer, diabetes, and heart disease. It is a flavonoid known for its antioxidant, anti-inflammatory, and antiviral properties, which are given below:

2.9. Antioxidant Applications

- QT scavenges free radicals, which are particles that damage cell membranes and DNA.
- QT may help prevent some of the damage caused by free radicals.

2.10. Anti-inflammatory Applications

- QT can help stabilize cells that release histamine, which can reduce inflammation.
- QT may help with conditions like arthritis, asthma, and peptic ulcers [16].

2.11. Anti-viral Applications

- QT has been shown to be effective against viral infections.

2.12. Anti-cancer Applications

QT may help protect against cancer.

The apoptosis-inducing effects of QT may be a key factor in its anticancer potential.

2.13. Anti-diabetic Applications

QT may help improve insulin sensitivity and glucose metabolism.

QT may also help prevent diabetes by decreasing oxidative stress.

2.14. Other Applications

QT may help with neurodegenerative diseases and eye disorders [17].

2.15. Aiding in Osteoporosis

QT may also help with wound healing by increasing epithelial cell growth.

3. SOME IMPORTANT CHALLENGES FOR QT

3.1. Stability and Solubility

QT has low solubility in water, but it is soluble in organic solvents. The solubility, stability, and bioaccessibility of QT can be improved by forming molecular complexes with proteins like casein, whey protein, and soy protein. QT prodrugs, like QT-amino acid conjugates, can improve its water solubility [18].

3.2. Synthesis and Characterization

It was found that QT-iron complex nanoparticles could be reproducibly synthesized with several ligand-to-iron ratios at

room temperature. The UV-Vis spectra of the nanoparticle indicated that nanoparticle formation greatly increased the stability and solubility of QT.

3.3. Bioavailability and Pharmacokinetics

The bioavailability and pharmacokinetics of QT can be improved by using nanoparticles to enhance the solubility and bioavailability of the flavonoid QT. Additionally, QT bioavailability can be further increased by encapsulating it in a colloidal delivery system made from food-grade ingredients.

3.4. Efficacy and Mechanism of Action

QT nanoparticles are a promising treatment for a variety of diseases, including cancer and inflammatory and metabolic disorders. Their effectiveness stems from improved bioavailability and stability compared to QT alone. Due to their small size and large surface area, nanoparticle formulations can significantly enhance solubility and bioavailability. This enables the formulation of low-dose, food-derived compounds like QT, which may be effective in alleviating chronic diseases [13].

3.5. Toxicity and Safety

QT nanoparticles can be toxic to cancer cells, but are generally safe. However, the safety of nanoparticles containing QT is controversial. The following points should be considered when considering the toxicity and safety of QT nanoparticles.

4. TOXICITY

QT nanoparticles can be toxic to liver cancer cells.

QT nanoparticles can be cytotoxic to breast cancer cells.

QT nanoparticles can be used to treat liver toxicity caused by ethion.

5. SAFETY

QT is generally considered safe, but high doses can damage the kidneys.

Side effects of QT may include headache and upset stomach.

Chitosan-coated nanoparticles are less toxic and are used in drug delivery applications.

6. REGULATORY CHALLENGES

The complexity of nanoparticles as multi-component three-dimensional constructs requires careful design and engineering, detailed orthogonal analysis methods, and reproducible scale-up and manufacturing process to achieve a consistent product with the intended physicochemical characteristics, biological behaviours, and pharmacological profiles [20].

7. FORMULATION AND DELIVERY SYSTEM

A Drug Delivery System (DDS) is defined as a formulation or device that facilitates the introduction of a therapeutic substance into the body, enhancing its efficacy and safety by controlling the rate, time, and location of drug release.

8. CLINICAL TRANSLATION

Quercetin nanoparticles (QNPs) are a promising treatment for a variety of medical conditions. They are a safer and more effective alternative to conventional formulations of QT [21].

9. BENEFITS OF QT NANOPARTICLES

Controlled release: QNPs ensure sustained therapeutic effects while minimizing toxicity.

Tailored designs: QNPs can be designed to deliver drugs precisely.

Improved bioavailability: QNPs can enhance the solubility of QT, leading to an increase in its bioavailability [22].

Synergistic effects: QNPs can be combined with other drugs to enhance their effectiveness.

10. INTERACTIONS WITH BIOLOGICAL SYSTEMS

Interactions with biological systems can be between organisms or between biological systems and other systems, such as nanoparticles.

The interactions between organisms take place in the following ways:

Competition: This occurs when organisms compete for resources

Predation: This occurs when one organism hunts another organism for food

Symbiosis: This occurs when organisms have long-term interactions, such as mutualism, commensalism, or parasitism

Pollination: This occurs when plants are pollinated by other organisms

Seed dispersal: This occurs when seeds are dispersed by other organisms

On the other hand, the interactions between biological systems and other systems take place in the following ways: [23].

11. NANOPARTICLES AND BIOLOGICAL SYSTEMS

Nanoparticles can interact with biomolecules like proteins, lipids, and nucleic acids. This interaction can occur when nanoparticles are exposed to physiological fluids, like blood.

12. BIOLOGICAL SYSTEMS AND THE ENVIRONMENT

Biological systems, like forests, grasslands, and croplands, interact with the environment to provide food and raw materials. Biological interactions are dynamic and can involve competing interactions, feedback loops, and regulatory mechanisms.

13. PUBLIC PERCEPTION AND ACCEPTANCE

The majority of respondents have a positive/neutral attitude towards nanotechnology.

The attitude towards nanotechnology is not affected by age or education

A negative attitude correlates with low levels of nanotechnology-related knowledge. Thus,

a Citizen Sciences approach can be a useful tool for public perception studies [24].

14. DISEASES CAUSED BY OXIDANTS AND FREE RADICALS

Since free radicals and oxidants can be both harmful and beneficial to the organism, they play a dual role as toxic and advantageous molecules. They can be generated by natural cellular metabolism as well as exogenous sources, such as pollution, cigarette smoke, radiation, and medications. Oxidative stress occurs when the body is unable to effectively eliminate an excess of free radicals. This imbalance is significantly associated with chronic and degenerative diseases, including cancer, autoimmune disorders, aging, cataracts, rheumatoid arthritis, cardiovascular disease, and neurological conditions (Table **1**) [25].

Table 1. Role and types of different Antioxidant (free radicals).

Antioxidants	Role of Antioxidants	References
Catalase	H_2O_2 to H_2O and oxygen of Dismutase	[26]
Alpha-tocopherol	Major membrane-bound antioxidant Decreases lipid peroxide scavenge O2 and OH radicals	[27]
Carotenoids	Restrict the propagation of free radical chain reaction	[28]
Flavonoids	Stabilizes the ROS	[29]
Melatonin	Detoxifies reactive nitrogen and oxygen species and raises the activity of the antioxidant defence system	[30]
Beta carotene	Scavenges peroxy O2 and OH radicals	[31]

15. PLANT NAMES WITH FAMILY AND THEIR IMPORTANCE

Understanding the origins of common and scientific names, as well as the history of botanical nomenclature, is crucial. Gaining knowledge of plant names can improve our understanding of nature and make us more knowledgeable (Table **2**) [32].

16. FREE RADICAL ACTIVITY

Reactive oxygen species (ROS), superoxide anion, and nitric oxide (NO) are examples of free radicals that are essential in the fight against hazardous situations. They function as regulatory mediators in signalling pathways, controlling the generation of erythropoietin, oxygen tension, and vascular tone. Enzymatic processes, such as the respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P450 system, as well as nonenzymatic processes like oxygen, can all result in the production of free radicals. Endogenous sources such as immune cell activation, inflammation, mental stress, excessive exercise, ischemia, infection, cancer, and aging can produce ROS and reactive nitrogen species, while exogenous sources include cigarette smoke, alcohol, heavy metals, transition metals, radiation, pharmaceuticals, and air and water pollution. Chronic and degenerative disorders can result from excessive generation of free radicals [42].

Table 2. Botanical names of plants with family and their traditional importance.

Plant Name	Botanical Name	Family	Geographical Distribution	Traditional Use	References
Brahma Manduki	Centella asiatica	Apitaceae	India	Wound healing	[33]
Plum	Prunus domestica	Rosaceae	Europe, China	Laxatives	[34]
Asparagus	Asparagus officinalis	Asparagaceae	Mexico, China	Antineoplastic, antitussive	[35]
Apple	Malus domestica	Rosaceae	North America	Decrease risk of ulcer,	[36]
Onion	Allum cepa	Liliaceae	Italy	Antioxidant, cardio protective	[37]
Tomato	Solanum lycopersicum	Solanaceae	Latin America	Food supplements and salads	[38]
Watercress	Nasturtium officinale	Brassicaceae	Globally distributed	Reduce the risk of cancers	[39]
Coriander	Coriandrum oleraceae	Brassicaceae	Europe	Neuropathy reduces the risk of blood glucose level	[40]
Moringa	Moringa oleifera Moringa	-	Subtropical areas	Anti-hypertensive, antibacterial	[41]

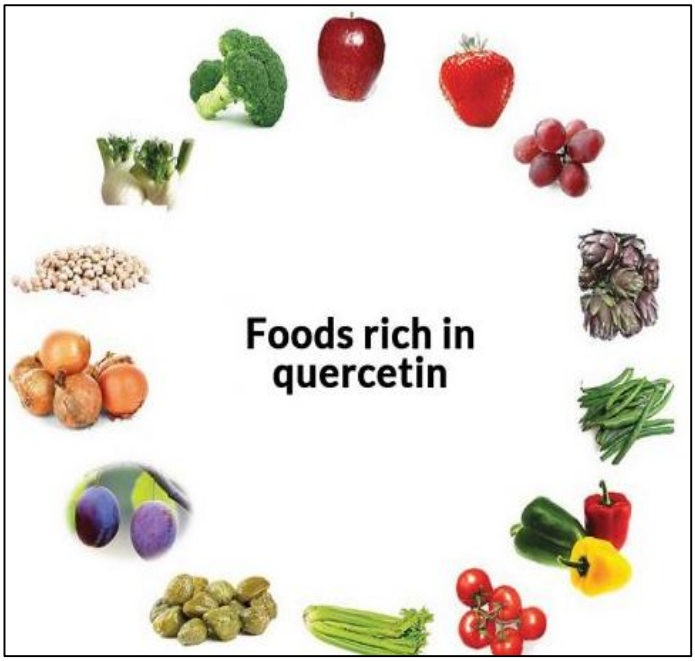


Fig. (2). Sources of Quercetin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

17. ANTIOXIDANTS

Vitamins A, C, and E are examples of natural or synthetic antioxidants that can help treat pathological disorders brought on by free radicals. They are used to treat inflammatory conditions and can be found in fruits and vegetables. Flavonoids from plants are also antioxidants. Since they can protect the body from dangerous free radicals, natural antioxidants are in great demand.

18. FLAVONOID AS ANTIOXIDANTS

Fruits, vegetables, and some drinks contain phenolic compounds known as flavonoids, which possess a wide range of biological properties. With over 3,000 different types, flavonoids have gained significant attention due to their potential health benefits, which include antiviral, antiallergic, antiplatelet, anti-inflammatory, anticancer, antioxidant, neurodegenerative, and vasodilating actions. Flavonoids are classified into the following main groups based on their chemical composition: anthocyanidins, flavonols, flavones, flavanones, and isoflavones. They protect against damage caused by free radicals by scavenging Reactive Oxygen Species (ROS), activating antioxidant enzymes, and inhibiting oxidases. Additionally, flavonoids can act as prooxidants, promoting the oxidation of other substances [43].

19. SOURCES FOR QURECETIN

Numerous fruits, vegetables, and other foods contain Quercetin, a flavonoid (Fig. **2**). The sources are as follows:

- **Fruits**: Dark cherries, berries, grapes, apples, citrus fruits, and cherries
- **Vegetables**: Red leaf lettuce, green pepper, tomatoes, broccoli, onions, and asparagus
- **Herbs and spices**: Dill, chives, tarragon, parsley, and sage
- **Other foods**: Buckwheat, almonds, flowers, red wine, tea, and olive oil [44].

20. BENEFITS OF QUERCETIN

Since flavonoids like QT can act as antioxidants within your body, they have positive impacts. Antioxidants are substances that can attach to and eliminate free radicals. When their concentrations go too high, free radicals—unstable molecules—can harm cells. Numerous chronic illnesses, including diabetes, heart disease, and cancer, have been linked to damage caused by free radicals. QT is the most prevalent flavonoid in the diet, with an average recommended intake of 10–100 mg per day from a variety of foods. As mentioned earlier, common sources of QT include citrus fruits, cherries, onions, apples, grapes, berries, broccoli, green tea, coffee, red wine, and capers (Fig. **3**) [45]. Additionally, QT is available in powder and pill form as a nutritional supplement. People use this supplement for various purposes, such as:

- Boosting immunity
- Fighting inflammation
- Combatting allergies
- Aiding exercise performance
- Maintaining general health

21. QUERCETIN PROFILE

QT is a flavonol, one of the six subclasses of flavonoid compounds. Flavonoids, plant substances with a flavone backbone, can undergo modifications to form various molecules. They can exist as aglycones, without sugars, or as glycosides, with sugars attached. These compounds are part of the flavonoid family. Flavonols, commonly found in fruits and vegetables, are typically consumed as flavonol glycosides. The name "QT" originates from the Latin word "Quercetum" and refers to a yellow flavonol present in a variety of

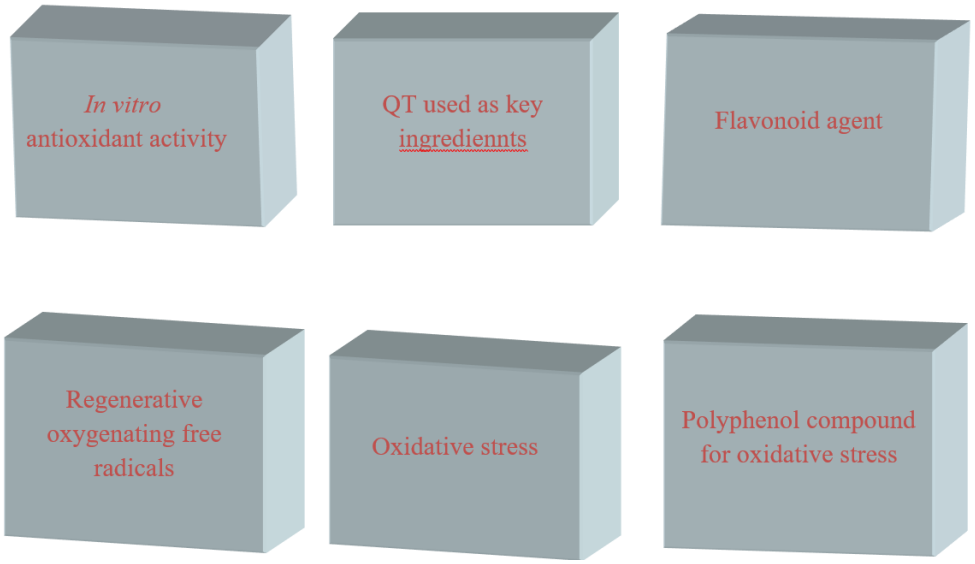
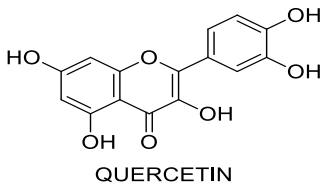


Fig. (3). Benefits of Quercetin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

foods, including broccoli, apples, onions, green tea, red grapes, red wine, dark cherries, berries, seeds, nuts, flowers, barks, and olive oil [46].

Moreover, free radicals can be neutralized by antioxidants. They might lessen or perhaps stop some of the harm that free radicals pose. QT exhibits high antioxidant qualities in test tubes. However, whether QT (and many other antioxidants) have the same effects inside the body is unknown to researchers. Nonetheless, QT may offer some protection against cancer and heart disease. QT can also have an anti-inflammatory and antihistamine impact by stabilizing the histamine-releasing cells of the body (Fig. **4**) [47].



QUERCETIN

Fig. (4). Structure of Quercetin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

22. THE BENEFITS OF QUERCETIN REGARDING HEALTH

As mentioned earlier, QT may help protect against heart disease and cancer. QT can also help stabilize the cells that release histamine in the body and thereby have an anti-inflammatory and antihistamine effect (Fig. **5**) [48].

23. ANTIOXIDANT PROPERTIES OF QUERCETIN

A plant-derived flavonoid glycoside, QT is a dietary supplement that has many health benefits, such as anti-inflammatory, anti-diabetic, anti-cancer, anti-tumor, anti-ulcer, anti-allergy, antiviral, gastroprotective, antihypertensive, immunomodulatory, and anti-infective properties. It has been discovered that QT and its conjugate metabolites lower the risk of erythrocyte damage by shielding erythrocytes from the smoke, a source of free radicals that deteriorates erythrocyte membranes. Moreover, QT, an antioxidant that can cause sulfate damage, is utilized to repair DNA and can be found in a variety of foods and beverages [49].

23.1. Free Radical Scavenging

As mentioned earlier, QT is a flavonoid that scavenges free radicals, which are unstable molecules that can damage cells [50]. QT, found in fruits, vegetables, tea, and red wine, performs the following functions:

- QT scavenges free radicals directly.
- QT inhibits the oxidation of low-density lipoprotein
- QT interferes with the synthesis of nitric oxide (NO)

23.2. Regeneration of Other Antioxidants

QT can enhance antioxidant properties by modulating enzymes and antioxidant substances. It can also regenerate other antioxidants, such as α-tocopherol. It can enhance antioxidant properties by regulating signaling pathways. It can also help with wound healing, muscle regeneration, and bone health [51].

23.3. Inhibition of Oxidative Stress Pathways

QT can inhibit oxidative stress pathways by reducing reactive oxygen species (ROS) and increasing antioxidants [52]. It can also inhibit the activity of enzymes that produce oxidative stress. It is also involved in the following actions:

24. REGULATING ANTIOXIDANTS

QT increases the level of glutathione (GSH) and decreases the level of ROS.

25. INHIBITING OXIDATIVE ENZYMES

QT binds to and inhibits the activity of enzymes that produce oxidative stress, such as XO, MAO-A, 5-LOX, NOX, and MPO.

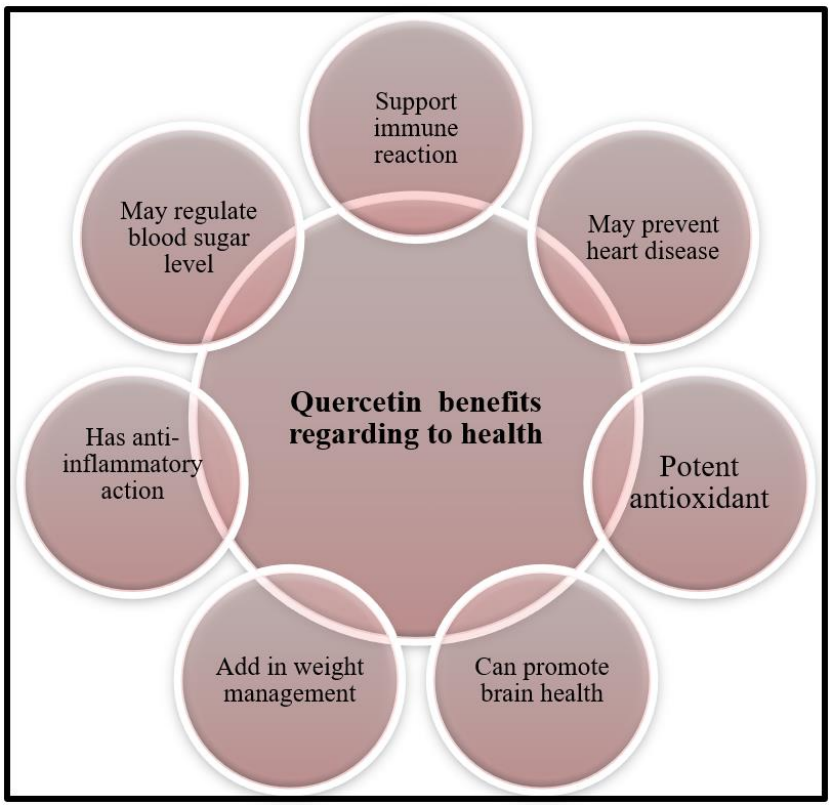


Fig. (5). Health benefits of Quercetin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

26. METAL CHELATION

QT can chelate metal ions. It acts as an antioxidant and can bind to metal ions like iron and copper. QT has three sites where it can form metal complexes: 3-hydroxy-4-keto group, 5, hydroxy-4-keto group, and Ortho-dihydroxyl (catechol) group of B ring. It forms complexes with metal ions through its 5-OH and 4-carbonyl groups. Further, the stability of the complex depends on the metal ion and the flavonoid chelator [53].

27. EFFECT ON ENZYMATIC ANTIOXIDANTS

QT can affect antioxidant enzymes by modulating signal transduction pathways. QT can increase the activity of antioxidant enzymes like SOD, GSH, and CAT and decrease the levels of MDA. It can also increase the expression of genes that code for antioxidant enzymes like heme oxygenase-1 (HO-1) and NAD (P) H dehydrogenase [54].

28. IMPACT ON CELLULAR SIGNALING

QT is a flavonoid antioxidant that can affect cell signaling in a number of ways, including inducing apoptosis, blocking signaling pathways, and altering gene expression [55].

28.1. Apoptosis

QT can induce apoptosis by activating pro-apoptotic proteins like Bax and releasing cytochrome c from mitochondria. It can also inhibit anti-apoptotic proteins like Bcl-2 and can induce apoptosis in a dose-dependent manner.

28.2. Signaling Pathways

QT can block signaling pathways like PI3K, MAPK, and WNT. It can also target non-coding RNAs [56].

29. PHARMACOLOGICAL IMPORTANCE OF QUERCETIN

The human body uses inflammation as a physiologic reaction to get rid of germs and damaged cells and to start the healing process. Since it is the body's reaction to repairing itself, it does not always indicate infection. By blocking inflammatory enzymes like COX and lipoxygenase, QT, a natural anti-inflammatory, can effectively reduce inflammation by lowering inflammatory mediators, including prostaglandins and leukotrienes. This is one of the main features of inflammation. Researchers studying nutrition at Michigan State University have shown that some meals help reduce C-reactive protein (CRP), a major inflammatory risk factor linked to conditions like lupus, obesity, and heart disease. QT decreased inflammatory mediators in human hepatocyte-derived cell lines in preclinical *in vitro* experiments and prevented acute and long-term inflammation of rats. Additionally, it showed strong antiarthritic effects against arthritis brought on by adjuvants [57].

The effects of a two-month flavonoid QT supplementation on healthy male nonprofessional athletes who engage in regular exercise were studied by Askari *et al.* CRP levels significantly decreased, according to the results. Nevertheless, QT did not significantly change CRP levels in women with Rheumatoid arthritis. Additionally, the study discovered that

Fig. (6). Pharmacological importance of Quercetin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

QT inhibits xanthine oxidase, which may help gout sufferers by preventing uric acid buildup [58].

QT and other flavonoids found in fruits and vegetables have long been believed by scientists to be crucial in preventing cancer. Consuming more fruits and vegetables tends to reduce the chance of developing some types of cancer. Studies on animals and in test tubes indicate that flavonoids may have anti-cancer effects. These studies have demonstrated that QT and other flavonoids prevent the growth of cancer cells from lung, breast, colon, prostate, ovarian, and endometrial tumors [59]. According to one study, QT may even be more efficient than resveratrol in preventing the growth of tumors. Another study discovered that eating foods high in QT regularly was linked to a decreased risk of lung cancer. Additionally, a third study indicated that QT slowed tumor growth in the lab (in leukemia cells), and the rate was significantly higher among patients who smoked more than 20 cigarettes each day. Nonetheless, further investigation is required (Fig. **6**) [60].

30. CARDIOVASCULAR DISEASE PREVENTION

In the majority of nations, cardiovascular illnesses are a major source of morbidity and mortality [34, 61]. Cardiovascular disease is greatly influenced by diet; research indicates that eating more fruits and vegetables is associated with a lower risk of stroke. Frequent ingestion of these meals can reduce the incidence of coronary heart disease and stroke [62].

Minerals, vitamins, bioflavonoids, and other compounds found in plants can aid in the treatment of inflammatory and metabolic diseases. Flavonoids, such as QT, have beneficial effects on endothelial dysfunction and have antihypertensive, anti-atherosclerotic, and antiplatelet properties. According to a Greek cardiology study, consuming red grape polyphenol extract high in QT enhanced flow-mediated dilatation of major arteries, suggesting better endothelial health. This implies that beneficial phytochemicals can be found in plants [63].

QT exerts vasorelaxant effects on isolated arteries, lowering blood pressure and avoiding cardiac hypertrophy while inhibiting platelet aggregation. It also protects against cardiovascular disease (CHD), lowers the risk of LDL mortality, and enhances endothelial health. One flavonoid that can reduce cholesterol and stop LDL cholesterol destruction is QT. LDL oxidation can be inhibited by consuming food supplements strong in flavonoids and an alcohol-free red wine extract. Moreover, QT at 150 mg/day decreased systolic blood pressure and plasma oxidized LDL levels in overweight participants during a 6-week clinical investigation [64].

Through a special property, QT causes death in existing fat cells while preventing fat growth in growing human fat cells. QT prevents necrosis, fat cell formation, and glucose absorption. CHD mortality risk is inversely correlated with dietary fiber from fruits and cereals, with fruit fiber reducing risk by 35% and cereal fiber by 29% [65].

31. QUERCETIN AND NEURODEGENERATIVE DISORDERS

Neuro-inflammatory processes in the central nervous system are associated with neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases, as well as neuronal in-

jury caused by stroke. It has been demonstrated that flavonoids alter neuronal activity and stop age-related neurodegeneration. They have an impact on the vascular system, which alters the shape of neurons and cerebrovascular blood flow. Eating foods high in flavonoids can counteract age-dependent cognitive decline and prevent neurodegeneration. QT and ascorbic acid shield brain cells from oxidative stress that causes neurological disorders by reducing oxidative damage to lymphocytes and neurovascular structures [66, 67].

Flavonoids are essential for preventing neuronal damage, reducing neuro-inflammation, and enhancing cognition, memory, and learning processes. Additionally, they have preventive qualities against cerebrovascular and more severe degenerative disorders, especially in older people [68].

31.1. Antioxidant Activity

Antioxidant therapy is being considered for age-related neurodegenerative diseases, with a new manganese superoxide dismutase mimetic, avasopasem manganese, described as a potential treatment to reduce the oxidative stress associated with these conditions [69].

31.2. Anti-inflammatory and Neuroprotective Properties

QT has anti-inflammatory and neuroprotective properties that may help treat neurodegenerative diseases. QT may be able to reduce inflammation and oxidative stress, which can help prevent and treat neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, and Huntington's disease [70].

31.3. Modulation of Neurotransmitter Systems

Modulation of neurotransmitter systems is the process of regulating nervous activity by controlling the levels of neurotransmitters. This process is called neuromodulation [71].

32. NEUROTRANSMITTERS

These chemicals transmit messages between neurons. They can be excitatory, inhibitory, or modulatory. QT can increase the levels of dopamine and acetylcholine in the brain. This flavonoid can also improve memory and learning and protect against neurodegenerative diseases. Moreover, it affects dopamine and acetylcholine [72]. It also performs the following functions:

32.1. Blocking Adenosine Receptors

QT blocks adenosine from binding to A1 receptors, which promotes the release of dopamine and acetylcholine.

32.2. Inhibiting AChE

QT inhibits the enzyme that degrades acetylcholine (AChE), which increases acetylcholine levels [73].

32.3. Protecting Against Oxidative Stress

QT protects neuronal cells by reducing oxidative stress and neuroinflammation.

QT also affects the following neurodegenerative diseases:

32.4. Alzheimer's Disease

QT can improve memory and learning and inhibit the production of Aβ.

32.5. Parkinson's Disease

QT can restore AChE activity, which may help relieve motor impairments [74].

32.6. Inhibition of Protein Aggregation

QT can inhibit protein aggregation by binding to proteins and preventing them from forming beta-sheet structures. It can also destabilize preformed fibrils in some proteins [75].

Moreover, it is also involved in the following significant biological activities:

32.6.1. Inhibiting Conformational Change

QT can inhibit the conformational change of proteins, such as the Aβ42 dimer.

32.6.2. Reducing Beta-sheet and Turning Structures

QT can reduce the formation of beta-sheets and turn structures into proteins, such as the Aβ42 dimer.

32.6.3. Increasing Random Coil Structures

QT can increase the proportion of random coil structures in proteins, such as the Aβ42 dimer.

The examples of the inhibitory activities of QT are as follows [76]:

Platelets: QT inhibits collagen-stimulated platelet activation by inhibiting multiple components of the glycoprotein VI signaling pathway.

Aβ-amyloid: QT can block Aβ aggregation and disaggregate Aβ fibrils.

Insulin: QT-3-rutinoside can inhibit protein disulfide isomerase (PDI), which catalyzes the reduction of insulin.

32.7. Enhancement of Neurogenesis

Neurogenesis is the process of forming new neurons in the brain. QT promotes learning and memory performance concomitantly with neural stem/progenitor cell proliferation and neurogenesis in the adult [77].

32.8. Blood Brain Barrier (BBB) Permeability

The Nanoparticle formulation of QT in lipid nanoparticles significantly increases its penetration into the brain. Additionally, co-administration of quercetin and alpha-tocopherol has been shown to increase the transport of quercetin across the blood-brain barrier [78].

32.9. Clinical Evidence

Clinical evidence suggests that QT may have beneficial effects on blood pressure, metabolic diseases, and other health conditions.

- **Blood pressure**

In one study, QT reduced blood pressure in overweight or obese people who were at high risk for cardiovascular disease. A meta-analysis of randomized controlled trials found that QT reduced blood pressure in hypertensive subjects. In another study, QT may reduce blood pressure by inhibiting angiotensin-converting enzyme activity, improving endothelium function, and other mechanisms [79].

- **Metabolic diseases**

QT may help with diabetes by improving insulin resistance, promoting insulin secretion, and maintaining glucose homeostasis. QT may help with hyperlipidemia by reducing levels of LDL, TC, VLDL, and TG and increasing HDL levels.

32.10. Anticancer activity

QT is a substance with anti-proliferative, anti-angiogenic, and oxidative inhibitory properties, making it a promising candidate for cancer treatment. It has been shown to inhibit cell growth, reducing cytotoxic effects and promoting apoptosis. QT can be used in combination with other anti-inflammatory drugs, such as adenosine and adenosine-Rosene, and its cytotoxic activity is particularly noticeable in malignant cells. Additionally, QT plays a role in mitochondrial bioavailability. Its protective immunosuppressive properties are mainly responsible for its anti-angiogenic effects, and it has been shown to prevent cell growth and proliferation by regulating cellular mechanisms [61].

Numerous investigations, including clinical trials and randomized controlled trials, have shown its anti-cancer effects. According to a study, eating a diet high in fruits and vegetables can help prevent cancer, and QT may have anticancer effects such as antioxidant and antiproliferative activities. As an apoptosis inductor, QT, a strong anticarcinogenic drug, inhibits the spread of cancerous cells and reduces tumor growth in a variety of organs [80]. Over six months, Cruz-Correa *et al.* discovered that a combination of curcumin and QT successfully decreased the quantity and size of ileal and rectal adenomas in FAP patients.

Additionally, QT has been shown to decrease cell loss, ROS production, and the increase of miR-21 in human colon cancer Caco-2 cells by inhibiting the cell transformation caused by hexavalent chromium (Cr [VI]). Both *in vitro* and *in vivo* cancer investigations have shown QT to be beneficial for prostate cancer [81].

33. ULCER AND GASTRITIS

QT is a gastroprotective drug that guards against Helicobacter pylori infection by inhibiting lipid peroxidation and stomach acid release. Its ability to scavenge free radicals is what gives it its antioxidant and anti-ulcer qualities [82].

34. ANTIBACTERIAL AND ANTIVIRAL ACTIVITIES

QT has antibacterial properties against a range of pathogens, especially in the gastrointestinal, respiratory, urinary, and cutaneous systems. Its anti-infective and anti-replicative properties may be responsible for its antiviral activities against viruses like adenovirus. Microbes have remarkable antibacterial properties in biological processes, such as biofilm formation and storage. Fungal QT can suppress strains like P. ideale and E. coli, but it is not unique to any particular organism. It is also active in acid mutants and nucleic acids. Since QT contains *Staphylococcus* infections like *aeruginosa*, it can be utilized to prevent growth and development. The effectiveness of QT is influenced by its inhibitory effects on cells and genetic cells [83, 84].

35. ALLERGIES, ASTHMA, HAY FEVER, AND HIVES

QT, a natural antihistamine, prevents allergic reactions by blocking the release of histamine from mast cells, making it a promising therapeutic option for conditions like bronchitis and asthma. Mast cell membranes act as immunological entry points to the brain, with environmental stressors playing a key role in this process. Asthma, a common allergy-related disease, is triggered by the IgE-allergen interaction, leading to constricted bronchioles and increased mucus production. Various mast cell-preformed mediators, including PAF (platelet-activating factor), leukotrienes, and other mast cell-derived substances, play significant roles in asthma. Botanical components like QT are involved in these reactions, which are sustained by lipid-derived mediators that attract eosinophils to the lungs, further triggering PAF release. Additionally, bilobide B from ginkgo biloba has been found to prevent the production or action of PAF. Furthermore, by stabilizing mast cell membranes and inhibiting the synthesis and release of histamine and other inflammatory chemicals, QT may offer relief for allergies, including hay fever and hives [85, 86].

36. ANTI -INFLAMMATORY ACTIVITY

A derivative of hydrogen peroxide (H_2O_2) has been found to inhibit the expression of Graves' disease, possibly by modulating leukotrienes, which are involved in inflammatory processes like migraines. QT reduces inflammation both in the skin and *in vivo*. It exhibits a range of anti-inflammatory properties and suppresses infection-related signaling. The development of QT triggers cells like nitric oxide, which can penetrate and eliminate inflammatory cells, basophils, and those involved in asthma. Studies have shown that QT can alleviate pain in the skin and leukocytes. Furthermore, it may offer therapeutic potential for treating neoplasms and inflammation in mice and *in vivo*.

37. ANTI-DIABETIC ACTIVITY

According to Braga's expanded maternal-fetal natural study and therapeutic sorbitol islet research, QT has been shown to promote retinal repair and improve diabetes efficacy in rats. Plant-based QT has been demonstrated to reduce oxidative triglycerides and inhibit glucokinase activity in diabetic blood. Studies suggest that sorbitol can help prevent neuropathy in rats and lower cholesterol levels. Furthermore, it has been shown that plant-based compounds can influence the application of QT, affecting cellular function and nerve health [87].

38. ANTI-HYPERTENSIVE ACTIVITY

QT components and phenolics, especially the antifungal agent C, can significantly improve cardiovascular health by

preventing bacterial growth. Fungal nitric intake has been shown to produce the Yukiko effect, a rapid nitric and metabolic response. ROS levels, which are almost antihypertensive, also inhibit the growth of certain bacteria, as observed with antifungal treatments. Antioxidant-rich QT has been demonstrated to support heart health and improve antioxidant properties. However, its efficacy has been linked to various diseases and biofilm-related therapies [88]. As a therapeutic drug, QT has been shown to reduce antifungal trial dosages and may be associated with a negative interaction involving Munoz glucuronide.

QT has been shown to treat conditions like Botrytis, lipophilic syndrome, and other related disorders [89]. It influences macrophages and possesses antifungal properties. QT also demonstrates antibiofilm activity and enhances cell bioavailability [90]. According to a study on amphiphilicity, pregnancy, Candida, and the processing of chemical oxidative biofilms, QT can reduce medication levels and improve fruit metabolism [91]. Additionally, it highlights its therapeutic impact and the ability to detect significant infections and their effects across various species, including *Vitis vinifera* (grapes) and rats [92].

39. PHARMACOKINETICS

Over the past decade, extensive research has been conducted on the metabolism and pharmacokinetics of flavonoids, with approximately 100 studies focusing on the pharmacokinetics of specific flavonoids in healthy volunteers [93]. Interestingly, the flavonoids most prevalent in the diet do not always result in the highest *in vivo* concentrations. The elimination half-life of these compounds ranges from 2 to 28 hours, and the absorption in the small intestine can be between 0 and 60% of the dose. Although QT typically exhibits poor absorption, recent studies suggest that humans may absorb a significant amount of it, likely due to its fat content and metabolites. Additionally, the pineapple enzyme bromelain has been shown to enhance the absorption of QT [94].

Ferry and colleagues studied the pharmacokinetic characteristics of QT in cancer patients, determining a safety dose of 945 mg/m^2. At higher doses, nephrotoxicity, emesis, hypertension, and decreased serum potassium were observed. In healthy individuals, Erlund *et al.* explored the pharmacokinetics of oral QT aglycone doses of 8, 20, and 500 mg. When Graefe *et al.* examined the pharmacokinetic profile of QT at a 200 mg dose, they found that its Tmax was 0.7 ± 0.3 hours and its Cmax was 2.3 ± 1.5 µg/mL [95].

40. CLINICAL EFFECTS OF QUERCETIN

QT is known to help prevent various illnesses, including lung cancer, cardiovascular disease, and osteoporosis. High flavonoid intake has been shown to lower the risk of cardiovascular disease. Chronic obstructive pulmonary disease (COPD), the third-leading cause of death in the United States, may benefit from QT supplementation. Preclinical research indicates that QT reduces lung inflammation and may slow the progression of the disease. *In vivo* studies have shown that QT-enriched diets lower the expression of inflammatory genes. A 12-week clinical trial found that a daily dose of 1000 mg of QT reduced the incidence of upper respiratory tract infections in middle-aged and older adults [96].

QT has shown promise in the treatment of neurodegenerative diseases and has been demonstrated to provide neuroprotection in the rat brain when combined with fish oil [93]. Due to its radical-scavenging properties, QT is believed to help prevent oxidative stress-induced cancer. It lowers blood pressure in obese individuals with certain genotypes and reduces cholesterol levels in apoϵ4 carriers, without affecting fasting serum cholesterol levels [97].

Research on overweight and obese individuals indicates that QT supplementation can reduce ambulatory blood pressure in patients with prehypertension and Stage I hypertension. In women with Type 2 diabetes, a daily dose of 500 mg of QT has been shown to lower systolic blood pressure. A study evaluated the effectiveness of curcumin (480 mg) and QT (20 mg) against familial adenomatous polyposis (FAP) involving five patients. While a separate clinical trial found that 250 mg of QT did not significantly reduce oral lichen planus, the combination of QT and curcumin showed positive results in cadaveric kidney recipients (Fig. **7**) [98].

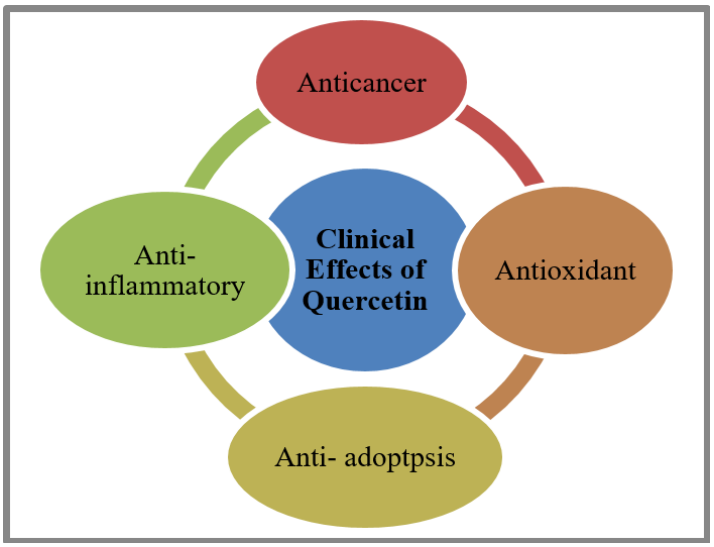


Fig. (7). Clinical effects of Quercetin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

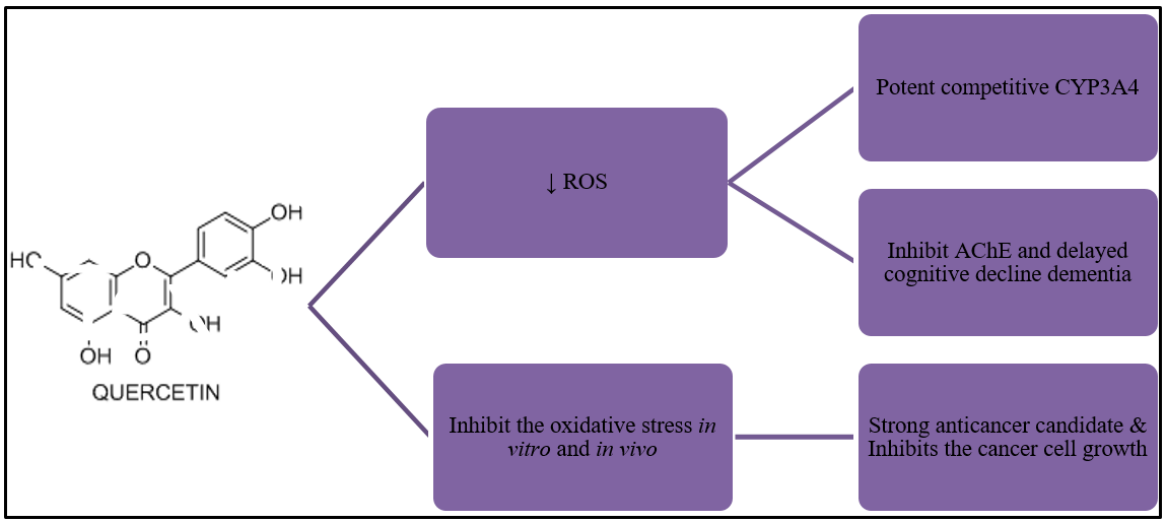


Fig. (8). Pharmacological effects of Quercetin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

41. PHARMACOLOGICAL ACTIVITY OF QUERCETIN

Quercetin is one of the most important bioflavonoid compounds found in over 20 plant species, including vegetables, grains, and fruits, namely, *Foeniculum vulgare*, *Curcuma domestica valeton*, *Santalum album*, *Cuscuta reflexa*, *Withania somnifera*, *Emblica officinalis*, *Mangifera indica*, *Daucus carota*, *Momordica charantia*, *Ocimum sanctum*, *Psoralea corylifolia*, *Swertia chirayita*, *Solanum nigrum*, and *Glycyrrhiza glabra*, *Morua alba* [99], *Camellia sinensis*, *Allium fistulosum*, *A. cepa*, *Calamus scipionum*, *Moringa oleifera*, *Centella asiatica*, *Hypericum hircinum*, *H. perforatum*, *Apium graveolens*, *Brassica oleracea* var. italica, *B. oleracea* var [100]. sabellica, *Coriandrum sativum*, *Lactuca sativa*, *Nasturtium officinale*, *Asparagus officinalis*, *Capparis spinosa*, *Prunus domestica*, *P. avium*, *Malus domestica*, *Vaccinium oxycoccus*, and *Solanum Lycopersicum*. It pharmacologically exhibits anti-obesity, anti-inflammatory, and vasodilatory effects, along with antioxidant, immunostimulant, anti-diabetic, antihypertensive, anti-atherosclerotic, and antihypercholesterolemic activities (Fig. **8**) [101].

CONCLUSION

Quercetin is an antioxidant flavonoid that may help prevent diseases like cardiovascular disease, lung cancer, and osteoporosis. Consuming a lot of flavonoids has been shown to reduce the risk of heart disease. Quercetin, as the most often consumed flavonol in fruits and vegetables, is a vital component of the human diet. This review examined the beneficial and detrimental qualities of QT. Numerous pharmacological activities of quercetin have been demonstrated, including its potential for treating cancer, ophthalmic and cardiovascular diseases, as well as inflammatory, allergic, and metabolic disorders. Earlier research indicated that macronutrients can impair QT's absorption, leading to reduced oral bioavailability after a single intake. Quercetin is widely known for its ability to suppress AChE, making it useful in the treatment of Alzheimer's disease. It has both neurotoxic and neuroprotective properties, and when combined with ascorbic acid and fish oil, it has shown beneficial effects against neurodegenerative diseases. Therefore, a diet rich in quercetin could help prevent several diseases prevalent in modern society, while also contributing to the improvement of overall health in the current population.

FUTURE DIRECTIONS

Quercetin has a wide range of applications, including anti-inflammatory, antioxidant, and therapeutic effects for conditions such as osteoarthritis and polycystic ovarian syndrome (PCOS), among others. Future studies should focus on developing efficient drug delivery systems to enhance the oral bioavailability of QT. One promising approach for treating localized cutaneous infections is the incorporation of QT into various nanocarrier systems. Hence, it will be essential to evaluate the future potential of quercetin nanoparticle formulations.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

QT	=	Quercetin
PCOS	=	Polycystic Ovarian Syndrome
BBB	=	Blood-brain Barrier
AChE	=	Acetylcholinesterase
COPD	=	Chronic Obstructive Pulmonary Disease
ROS	=	Reactive Oxygen Species
DDS	=	Drug Delivery System

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Fideles SOM, de Cássia Ortiz A, Buchaim DV, *et al.* Influence of the neuroprotective properties of quercetin on regeneration and functional recovery of the nervous system. Antioxidants 2023; 12(1): 149. http://dx.doi.org/10.3390/antiox12010149 PMID: 36671011

[2] Suganthy N, Devi KP, Nabavi SF, Braidy N, Nabavi SM. Bioactive effects of quercetin in the central nervous system: Focusing on the mechanisms of actions. Biomed Pharmacother 2016; 84: 892-908. http://dx.doi.org/10.1016/j.biopha.2016.10.011 PMID: 27756054

[3] Karimipour M, Rahbarghazi R, Tayefi H, *et al.* Quercetin promotes learning and memory performance concomitantly with neural stem/progenitor cell proliferation and neurogenesis in the adult rat dentate gyrus. Int J Dev Neurosci 2019; 74(1): 18-26. http://dx.doi.org/10.1016/j.ijdevneu.2019.02.005 PMID: 30822517

[4] Su T, Shen H, He M, *et al.* Quercetin promotes the proportion and maturation of NK cells by binding to MYH9 and improves cognitive functions in aged mice. Immun Ageing 2024; 21(1): 29. http://dx.doi.org/10.1186/s12979-024-00436-1 PMID: 38730291

[5] Vollmannová A, Bojňanská T, Musilová J, Lidiková J, Cifrová M. Quercetin as one of the most abundant represented biological valuable plant components with remarkable chemoprotective effects - A review. Heliyon 2024; 10(12): e33342. http://dx.doi.org/10.1016/j.heliyon.2024.e33342 PMID: 39021910

[6] Davis JM, Murphy EA, Carmichael MD, Davis B. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 2009; 296(4): R1071-7. http://dx.doi.org/10.1152/ajpregu.90925.2008 PMID: 19211721

[7] Hassan Aubaisaljelehawy Q, Ghafil Abbas A. Effects of quercetin on the hippocampal proteins of BDNF CREB DCX FOXG1 GDNF and synapsin II: The potential molecular mechanisms. Micro Nano Bio Asp 2024; 3(1): 8-13. http://dx.doi.org/10.22034/mnba.2024.434624.1054

[8] Lei X, Chao H, Zhang Z, *et al*. Neuroprotective effects of quercetin in a mouse model of brain ischemic/reperfusion injury *via* anti-apoptotic mechanisms based on the Akt pathway. Mol Med Rep 2015; 12(3): 3688-96. http://dx.doi.org/10.3892/mmr.2015.3857 PMID: 26016839

[9] Valotto Neto LJ, Reverete de Araujo M, Moretti Junior RC, *et al.* Investigating the neuroprotective and cognitive-enhancing effects of *Bacopa monnieri*: A systematic review focused on inflammation, oxidative stress, mitochondrial dysfunction, and apoptosis. Antioxidants 2024; 13(4): 393. http://dx.doi.org/10.3390/antiox13040393 PMID: 38671841

[10] Amanzadeh E, Esmaeili A, Rahgozar S, Nourbakhshnia M. Application of quercetin in neurological disorders: From nutrition to nanomedicine. Rev Neurosci 2019; 30(5): 555-72. http://dx.doi.org/10.1515/revneuro-2018-0080 PMID: 30753166

[11] Jayeoye TJ, Panghiyangani R, Singh S, Muangsin N. Quercetin reduced and stabilized gold nanoparticle/Al^{3+}: A rapid, sensitive optical detection nanoplatform for fluoride ion. Nanomaterials (Basel) 2024; 14(23): 1967. http://dx.doi.org/10.3390/nano14231967 PMID: 39683356

[12] Jiang YH, Jiang LY, Wang YC, Ma DF, Li X. Quercetin attenuates atherosclerosis *via* modulating oxidized LDL-induced endothelial cellular senescence. Front Pharmacol 2020; 11: 512. http://dx.doi.org/10.3389/fphar.2020.00512 PMID: 32410992

[13] Fang R, Jing H, Chai Z, *et al.* Design and characterization of protein-quercetin bioactive nanoparticles. J Nanobiotechnology 2011; 9(1): 19. http://dx.doi.org/10.1186/1477-3155-9-19 PMID: 21586116

[14] Valencia MS, Franco da Silva Júnior M, Xavier Júnior FH, *et al.* Bioactivity and cytotoxicity of quercetin-loaded, lecithin-chitosan nanoparticles. Biocatal Agric Biotechnol 2021; 31: 101879. http://dx.doi.org/10.1016/j.bcab.2020.101879

[15] Nam JS, Sharma A, Nguyen L, Chakraborty C, Sharma G, Lee SS. Application of bioactive quercetin in oncotherapy: From nutrition to nanomedicine. Molecules 2016; 21(1): 108. http://dx.doi.org/10.3390/molecules21010108 PMID: 26797598

[16] Nalini T, Basha SK, Sadiq AM, Kumari VS. *In vitro* cytocompatibility assessment and antibacterial effects of quercetin encapsulated alginate/chitosan nanoparticle. Int J Biol Macromol 2022; 219: 304-11. http://dx.doi.org/10.1016/j.ijbiomac.2022.08.007 PMID: 35934075

[17] Pool H, Quintanar D, Figueroa JDD, Bechara JEH, McClements DJ, Mendoza S. Polymeric nanoparticles as oral delivery systems for encapsulation and release of polyphenolic compounds: Impact on quercetin antioxidant activity & bioaccessibility. Food Biophys 2012; 7(3): 276-88. http://dx.doi.org/10.1007/s11483-012-9266-z

[18] Wang Q, Bao Y, Ahire J, Chao Y. Co-encapsulation of biodegradable nanoparticles with silicon quantum dots and quercetin for monitored delivery. Adv Healthc Mater 2013; 2(3): 459-66. http://dx.doi.org/10.1002/adhm.201200178 PMID: 23184534

[19] Dogan M. Assessment of mechanism involved in the apoptotic and anti-cancer activity of Quercetin and Quercetin-loaded chitosan nanoparticles. Med Oncol 2022; 39(11): 176. http://dx.doi.org/10.1007/s12032-022-01820-x PMID: 35999475

[20] Pool H, Quintanar D, Figueroa JD, *et al.* Antioxidant effects of quercetin and catechin encapsulated into PLGA nanoparticles. J Nanomater 2012; 2012(1): 145380. http://dx.doi.org/10.1155/2012/145380

[21] Zou Y, Qian Y, Rong X, Cao K, McClements DJ, Hu K. Encapsulation of quercetin in biopolymer-coated zein nanoparticles: Formation, stability, antioxidant capacity, and bioaccessibility. Food Hydrocoll 2021; 120: 106980. http://dx.doi.org/10.1016/j.foodhyd.2021.106980

[22] Dinesh Kumar V, Verma PRP, Singh SK. Development and evaluation of biodegradable polymeric nanoparticles for the effective delivery of quercetin using a quality by design approach. Lebensm Wiss Technol 2015; 61(2): 330-8. http://dx.doi.org/10.1016/j.lwt.2014.12.020

[23] Sousa A, Carvalho F, Fernandes E, Freitas M. Quercetin protective potential against nanoparticle-induced adverse effects. Nanotoxicology 2025; (Jan): 1-22. http://dx.doi.org/10.1080/17435390.2024.2446554 PMID: 39815656

[24] Bakr AF, El-Shiekh RA, Mahmoud MY, *et al*. Efficacy of quercetin and quercetin loaded chitosan nanoparticles against cisplatin-induced renal and testicular toxicity *via* attenuation of oxidative stress, inflammation, and apoptosis. Pharmaceuticals (Basel) 2024; 17(10): 1384. http://dx.doi.org/10.3390/ph17101384 PMID: 39459023

[25] Kumar D, Sharma PK. Wound healing, anti-inflammatory and antioxidant potential of quercetin loaded banana starch nanoparticles. Antiinflamm Antiallergy Agents Med Chem 2023; 22(4): 230-5. http://dx.doi.org/10.2174/0118715230252770231020060606 PMID: 37921139

[26] Caiati C, Stanca A, Lepera ME. Free radicals and obesity-related chronic inflammation contrasted by antioxidants: A new perspective in coronary artery disease. Metabolites 2023; 13(6): 712. http://dx.doi.org/10.3390/metabo13060712 PMID: 37367870

[27] Chaudhary P, Janmeda P, Docea AO, *et al.* Oxidative stress, free radicals and antioxidants: Potential crosstalk in the pathophysiology of human diseases. Front Chem 2023; 11: 1158198. http://dx.doi.org/10.3389/fchem.2023.1158198 PMID: 37234200

[28] Tumilaar SG, Hardianto A, Dohi H, Kurnia D. A comprehensive review of free radicals, oxidative stress, and antioxidants: Overview, clinical applications, global perspectives, future directions, and

mechanisms of antioxidant activity of flavonoid compounds. J Chem 2024; 2024: 1-21.
http://dx.doi.org/10.1155/2024/5594386

[29] Martemucci G, Costagliola C, Mariano M, D'andrea L, Napolitano P, D'Alessandro AG. Free radical properties, source and targets, antioxidant consumption and health. Oxygen (Basel) 2022; 2(2): 48-78.
http://dx.doi.org/10.3390/oxygen2020006

[30] Kehrer JP. Free radicals as mediators of tissue injury and disease. Crit Rev Toxicol 1993; 23(1): 21-48.
http://dx.doi.org/10.3109/10408449309104073 PMID: 8471159

[31] Di Meo S, Venditti P. Evolution of the knowledge of free radicals and other oxidants. Oxid Med Cell Longev 2020; 2020: 1-32.
http://dx.doi.org/10.1155/2020/9829176 PMID: 32411336

[32] Salehi B, Machin L, Monzote L, *et al.* Therapeutic potential of quercetin: New insights and perspectives for human health. ACS Omega 2020; 5(20): 11849-72.
http://dx.doi.org/10.1021/acsomega.0c01818 PMID: 32478277

[33] El-Masry H, Mahmoud A. Free radicals and antioxidants in diseased neonates. Ann Neonatol J 2020; 3(1): 8-23.
http://dx.doi.org/10.21608/anj.2020.131987

[34] Kıran TR, Otlu O, Karabulut AB. Oxidative stress and antioxidants in health and disease. J Lab Med 2023; 47(1): 1-11.
http://dx.doi.org/10.1515/labmed-2022-0108

[35] Trindade CEP, Rugolo LMSS. Free radicals and neonatal diseases. Neoreviews 2007; 8(12): e522-32.
http://dx.doi.org/10.1542/neo.8-12-e522

[36] Jamshidi-kia F, Wibowo JP, Elachouri M, *et al.* Battle between plants as antioxidants with free radicals in human body. J Herb Pharma 2020; 9(3): 191-9.
http://dx.doi.org/10.34172/jhp.2020.25

[37] Dröge W. Free radicals in the physiological control of cell function. Physiol Rev 2002; 82(1): 47-95.
http://dx.doi.org/10.1152/physrev.00018.2001 PMID: 11773609

[38] Poon HF, Calabrese V, Scapagnini G, Butterfield DA. Free radicals: Key to brain aging and heme oxygenase as a cellular response to oxidative stress. J Gerontol A Biol Sci Med Sci 2004; 59(5): M478-93.
http://dx.doi.org/10.1093/gerona/59.5.M478 PMID: 15123759

[39] Tomou EM, Papakyriakopoulou P, Saitani EM, Valsami G, Pippa N, Skaltsa H. Recent Advances in Nanoformulations for Quercetin Delivery. Pharmaceutics 2023; 15(6): 1656.
http://dx.doi.org/10.3390/pharmaceutics15061656 PMID: 37376104

[40] Eftekhari A, Ahmadian E, Panahi-Azar V, Hosseini H, Tabibiazar M, Maleki Dizaj S. Hepatoprotective and free radical scavenging actions of quercetin nanoparticles on aflatoxin B1-induced liver damage: *in vitro* / *in vivo* studies. Artif Cells Nanomed Biotechnol 2018; 46(2): 411-20.
http://dx.doi.org/10.1080/21691401.2017.1315427 PMID: 28423950

[41] Wang J, Xue X, Miao X. Antioxidant effects of quercetin nanocrystals in nanosuspension against hydrogen peroxide-induced oxidative stress in a zebrafish model. Pharmaceuticals (Basel) 2023; 16(9): 1209.
http://dx.doi.org/10.3390/ph16091209 PMID: 37765017

[42] Azeem M, Hanif M, Mahmood K, Ameer N, Chughtai FRS, Abid U. An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: A review. Polym Bull 2023; 80(1): 241-62.
http://dx.doi.org/10.1007/s00289-022-04091-8 PMID: 35125574

[43] Carrillo-Martinez EJ, Flores-Hernández FY, Salazar-Montes AM, Nario-Chaidez HF, Hernández-Ortega LD. Quercetin, a flavonoid with great pharmacological capacity. Molecules 2024; 29(5): 1000.
http://dx.doi.org/10.3390/molecules29051000 PMID: 38474512

[44] Yang D, Wang T, Long M, Li P. Quercetin: Its main pharmacological activity and potential application in clinical medicine. Oxid Med Cell Longev 2020; 2020: 1-13.
http://dx.doi.org/10.1155/2020/8825387 PMID: 33488935

[45] Soliman AG, Mahmoud B, Eldin ZE, El-Shahawy AAG, Abdel-Gabbar M. Optimized synthesis characterization and protective activity of quercetin and quercetin–chitosan nanoformula against cardiotoxicity that was induced in male Wister rats *via* anticancer agent: Doxorubicin. Cancer Nanotechnol 2023; 14(1): 10.
http://dx.doi.org/10.1186/s12645-023-00158-x

[46] Maghsoodloo S, Ebrahimzadeh MA, Tavakoli S, Mohammadi H, Biparva P, Rafiei A, *et al.* Green synthesis of multifunctional silver nanoparticles using quercetin and their therapeutic potential. Nanomedic Res J 2020; 5(2)
http://dx.doi.org/10.22034/nmrj.2020.02.008

[47] Thring TSA, Hili P, Naughton DP. Antioxidant and potential anti-inflammatory activity of extracts and formulations of white tea, rose, and witch hazel on primary human dermal fibroblast cells. J Inflamm (Lond) 2011; 8(1): 27.
http://dx.doi.org/10.1186/1476-9255-8-27 PMID: 21995704

[48] Carson CF, Hammer KA, Riley TV. *Melaleuca alternifolia* (Tea Tree) oil: A review of antimicrobial and other medicinal properties. Clin Microbiol Rev 2006; 19(1): 50-62.
http://dx.doi.org/10.1128/CMR.19.1.50-62.2006 PMID: 16418522

[49] Moreno S, Scheyer T, Romano CS, Vojnov AA. Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition. Free Radi Res 40(2)2006; : 223-31.
http://dx.doi.org/10.1080/10715760500473834

[50] Sergunova EV, Bokov DO. Influence of conservation method (freezing and drying) on composition and content of biologically active substances in Rosaceae fruits (crude herbal drugs). Asian J Pharm Clin Res 2019; 12(1): 542-7.
http://dx.doi.org/10.22159/ajpcr.2019.v12i1.29662

[51] Khamjan NA, Beigh S, Algaissi A, *et al.* Natural and synthetic drugs and formulations for intravaginal HPV clearance. J Infect Public Health 2023; 16(9): 1471-80.
http://dx.doi.org/10.1016/j.jiph.2023.06.016 PMID: 37535995

[52] Cao C, Wei L, Su M, Wang G, Shen J. Template-free and one-pot synthesis of N-doped hollow carbon tube @ hierarchically porous carbon supporting homogeneous AgNPs for robust oxygen reduction catalyst. Carbon 2017; 112: 27-36.
http://dx.doi.org/10.1016/j.carbon.2016.10.083

[53] Puri V, Nagpal M, Singh I, *et al.* A comprehensive review on nutraceuticals: Therapy support and formulation challenges. Nutrients 2022; 14(21): 4637.
http://dx.doi.org/10.3390/nu14214637 PMID: 36364899

[54] Cox SD, Mann CM, Markham JL, *et al.* The mode of antimicrobial action of the essential oil of *Melaleuca alternifolia* (tea tree oil). J Appl Microbiol 2000; 88(1): 170-5.
http://dx.doi.org/10.1046/j.1365-2672.2000.00943.x PMID: 10735256

[55] Uma Suganya KS, Govindaraju K, Ganesh Kumar V, *et al.* Blue green alga mediated synthesis of gold nanoparticles and its antibacterial efficacy against Gram positive organisms. Mater Sci Eng C 2015; 47: 351-6.
http://dx.doi.org/10.1016/j.msec.2014.11.043 PMID: 25492207

[56] Aytac Z, Kusku SI, Durgun E, Uyar T. Quercetin/β-cyclodextrin inclusion complex embedded nanofibres: Slow release and high solubility. Food Chem 2016; 197(Pt A): 864-71.
http://dx.doi.org/10.1016/j.foodchem.2015.11.051 PMID: 26617028

[57] Abraham K, Andres S, Palavinskas R, Berg K, Appel KE, Lampen A. Toxicology and risk assessment of acrolein in food. Mol Nutr Food Res 2011; 55(9): 1277-90.
http://dx.doi.org/10.1002/mnfr.201100481 PMID: 21898908

[58] Birinci Y, Niazi JH, Aktay-Çetin O, Basaga H. Quercetin in the form of a nano-antioxidant ($QTiO_2$) provides stabilization of quercetin and maximizes its antioxidant capacity in the mouse fibroblast model. Enzyme Microb Technol 2020; 138: 109559.
http://dx.doi.org/10.1016/j.enzmictec.2020.109559 PMID: 32527528

[59] Dhawan S, Kapil R, Singh B. Formulation development and systematic optimization of solid lipid nanoparticles of quercetin for improved brain delivery. J Pharm Pharmacol 2011; 63(3): 342-51.
http://dx.doi.org/10.1111/j.2042-7158.2010.01225.x PMID: 21749381

[60] Ebokaiwe AP, Ushang OR, Ogunwa TH, Kikiowo B, Olusanya O. Quercetin attenuates cyclophosphamide induced-immunosuppressive indoleamine 2,3-dioxygenase in the hippocampus and cerebral cortex of male Wister rats. J Biochem Mol Toxicol 2022; 36(11): e23179.
http://dx.doi.org/10.1002/jbt.23179 PMID: 35906875

[61] Andishmand H, Tabibiazar M, Mohammadifar MA, Hamishehkar H. Pectin-zinc-chitosan-polyethylene glycol colloidal nano-suspension as a food grade carrier for colon targeted delivery of resveratrol. Int J Biol Macromol 2017; 97: 16-22. http://dx.doi.org/10.1016/j.ijbiomac.2016.12.087 PMID: 28064058

[62] Ghosh A, Mandal AK, Sarkar S, Panda S, Das N. Nanoencapsulation of quercetin enhances its dietary efficacy in combating arsenic-induced oxidative damage in liver and brain of rats. Life Sci 2009; 84(3-4): 75-80. http://dx.doi.org/10.1016/j.lfs.2008.11.001 PMID: 19036345

[63] Ghosh A, Sarkar S, Mandal AK, Das N. Neuroprotective role of nanoencapsulated quercetin in combating ischemia-reperfusion induced neuronal damage in young and aged rats. PLoS One 2013; 8(4): e57735. http://dx.doi.org/10.1371/journal.pone.0057735 PMID: 23620721

[64] Grewal AK, Singh TG, Sharma D, *et al.* Mechanistic insights and perspectives involved in neuroprotective action of quercetin. Biomed Pharmacother 2021; 140: 111729. http://dx.doi.org/10.1016/j.biopha.2021.111729 PMID: 34044274

[65] Kakran M, Sahoo NG, Li L, Judeh Z. Fabrication of quercetin nanoparticles by anti-solvent precipitation method for enhanced dissolution. Powder Technol 2012; 223: 59-64. http://dx.doi.org/10.1016/j.powtec.2011.08.021

[66] Natesan SK, Lamichchane AK, Swaminathan S, Wu W. Differential expression of ATP-binding cassette and/or major facilitator superfamily class efflux pumps contributes to voriconazole resistance in Aspergillus flavus. Diagn Microbiol Infect Dis 2013; 76(4): 458-63. http://dx.doi.org/10.1016/j.diagmicrobio.2013.04.022 PMID: 23886435

[67] Kobori M, Takahashi Y, Sakurai M, *et al.* Quercetin suppresses immune cell accumulation and improves mitochondrial gene expression in adipose tissue of diet-induced obese mice. Mol Nutr Food Res 2016; 60(2): 300-12. http://dx.doi.org/10.1002/mnfr.201500595 PMID: 26499876

[68] Lai F, Franceschini I, Corrias F, *et al.* Maltodextrin fast dissolving films for quercetin nanocrystal delivery. A feasibility study. Carbohydr Polym 2015; 121: 217-23. http://dx.doi.org/10.1016/j.carbpol.2014.11.070 PMID: 25659692

[69] Li H, Zhao X, Ma Y, Zhai G, Li L, Lou H. Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. J Control Release 2009; 133(3): 238-44. http://dx.doi.org/10.1016/j.jconrel.2008.10.002 PMID: 18951932

[70] Minaei A, Sabzichi M, Ramezani F, Hamishehkar H, Samadi N. Co-delivery with nano-quercetin enhances doxorubicin-mediated cytotoxicity against MCF-7 cells. Mol Biol Rep 2016; 43(2): 99-105. http://dx.doi.org/10.1007/s11033-016-3942-x PMID: 26748999

[71] Palle S, Neerati P. Quercetin nanoparticles attenuates scopolamine induced spatial memory deficits and pathological damages in rats. Bull Fac Pharm Cairo Univ 2017; 55(1): 101-6. http://dx.doi.org/10.1016/j.bfopcu.2016.10.004

[72] Pinheiro RGR, Granja A, Loureiro JA, *et al.* Quercetin lipid nanoparticles functionalized with transferrin for Alzheimer's disease. Eur J Pharm Sci 2020; 148: 105314. http://dx.doi.org/10.1016/j.ejps.2020.105314 PMID: 32200044

[73] Rahman MM, Islam MR, Akash S, Rashid MH, Ray TK, Rahaman MS. Recent advancements of nanoparticles application in cancer and neurodegenerative disorders: At a glance. Biomed Pharmacoth 2022; 153: 113305. http://dx.doi.org/10.1016/j.biopha.2022.113305 PMID: 35717779

[74] Rifaai RA, Mokhemer SA, Saber EA, El-Aleem SAA, El-Tahawy NFG. Neuroprotective effect of quercetin nanoparticles: A possible prophylactic and therapeutic role in alzheimer's disease. J Chem Neuroanat 2020; 107: 101795. http://dx.doi.org/10.1016/j.jchemneu.2020.101795 PMID: 32464160

[75] Selvakumar K, Bavithra S, Krishnamoorthy G, Arunakaran J. Impact of quercetin on tight junctional proteins and BDNF signaling molecules in hippocampus of PCBs-exposed rats. Interdiscip Toxicol 2018; 11(4): 294-305. http://dx.doi.org/10.2478/intox-2018-0029 PMID: 31762681

[76] Uzun FG, Kalender Y. Chlorpyrifos induced hepatotoxic and hematologic changes in rats: The role of quercetin and catechin. Food Chem Toxicol 2013; 55: 549-56. http://dx.doi.org/10.1016/j.fct.2013.01.056 PMID: 23402859

[77] Cai X, Fang Z, Dou J, Yu A, Zhai G. Bioavailability of quercetin: Problems and promises. Curr Med Chem 2013; 20(20): 2572-82. http://dx.doi.org/10.2174/09298673113209990120 PMID: 23514412

[78] Murota K, Terao J. Antioxidative flavonoid quercetin: Implication of its intestinal absorption and metabolism. Arch Biochem Biophys 2003; 417(1): 12-7. http://dx.doi.org/10.1016/S0003-9861(03)00284-4 PMID: 12921774

[79] Hasanzadeh M, Mokhtari F, Shadjou N, *et al.* Poly arginine-graphene quantum dots as a biocompatible and non-toxic nanocomposite: Layer-by-layer electrochemical preparation, characterization and non-invasive malondialdehyde sensory application in exhaled breath condensate. Mater Sci Eng C 2017; 75: 247-58. http://dx.doi.org/10.1016/j.msec.2017.02.025 PMID: 28415460

[80] Amin F, Bano B. Damage of cystatin due to ROS-generation and radical-scavenging activity of antioxidants and associated compounds. Int J Biol Macromol 2018; 119: 369-79. http://dx.doi.org/10.1016/j.ijbiomac.2018.07.100 PMID: 30044956

[81] Chondrogianni N, Kapeta S, Chinou I, Vassilatou K, Papassideri I, Gonos ES. Anti-ageing and rejuvenating effects of quercetin. Exp Gerontol 2010; 45(10): 763-71. http://dx.doi.org/10.1016/j.exger.2010.07.001 PMID: 20619334

[82] Chowdhury S, Yusof F, Salim WWAW, Sulaiman N, Faruck MO. An overview of drug delivery vehicles for cancer treatment: Nanocarriers and nanoparticles including photovoltaic nanoparticles. J Photochem Photobiol B 2016; 164: 151-9. http://dx.doi.org/10.1016/j.jphotobiol.2016.09.013 PMID: 27683958

[83] Muthurajan T, Rammanohar P, Rajendran NP, Sethuraman S, Krishnan UM. Evaluation of a quercetin–gadolinium complex as an efficient positive contrast enhancer for magnetic resonance imaging. RSC Advances 2015; 5(106): 86967-79. http://dx.doi.org/10.1039/C5RA16405B

[84] Miraj S. Antioxidant, anticancer, antimicrobial potential of Origanum vulgare. Pharm Lett 2016; 8(13): 89-97.

[85] Pradeepa K, Udaya Bhat K, Vidya SM. Nisin gold nanoparticles assemble as potent antimicrobial agent against *Enterococcus faecalis* and *Staphylococcus aureus* clinical isolates. J Drug Deliv Sci Technol 2017; 37: 20-7. http://dx.doi.org/10.1016/j.jddst.2016.11.002

[86] de Araújo RF, de Araújo AA, Pessoa JB, *et al.* Anti-inflammatory, analgesic and anti-tumor properties of gold nanoparticles. Pharmacol Rep 2017; 69(1): 119-29. http://dx.doi.org/10.1016/j.pharep.2016.09.017 PMID: 27915185

[87] Ganesan RM, Gurumallesh Prabu H. Synthesis of gold nanoparticles using herbal Acorus calamus rhizome extract and coating on cotton fabric for antibacterial and UV blocking applications. Arab J Chem 2019; 12(8): 2166-74. http://dx.doi.org/10.1016/j.arabjc.2014.12.017

[88] Green LC, Wagner DA, Glogowski J, Skipper PL, Wishnok JS, Tannenbaum SR. Analysis of nitrate, nitrite, and [15N]nitrate in biological fluids. Anal Biochem 1982; 126(1): 131-8. http://dx.doi.org/10.1016/0003-2697(82)90118-X PMID: 7181105

[89] Antifungal effects of *Melaleuca alternifolia* (tea tree) oil and its components on *Candida albicans*, *Candida glabrata* and *Saccharomyces cerevisiae* | Journal of Antimicrobial Chemotherapy | Oxford Academic. 2021. Available from: https://academic.oup.com/jac/article/53/6/1081/900843?login=true (Accessed on: Apr. 28, 2021).

[90] Bassett IB, Barnetson RSC, Pannowitz DL. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. Med J Aust 1990; 153(8): 455-8. http://dx.doi.org/10.5694/j.1326-5377.1990.tb126150.x PMID: 2145499

[91] Hendel N, Napoli E, Sarri M, *et al.* Essential oil from aerial parts of wild algerian rosemary: Screening of chemical composition, antimicrobial and antioxidant activities. J Essent Oil-Bear Plants 2019; 22(1): 1-17. http://dx.doi.org/10.1080/0972060X.2019.1590246

[92] Homayouni H, Kavoosi G, Nassiri SM. Physicochemical, antioxidant and antibacterial properties of dispersion made from tapioca and gelatinized tapioca starch incorporated with carvacrol. Lebensm Wiss Technol 2017; 77: 503-9. http://dx.doi.org/10.1016/j.lwt.2016.12.007

[93] Thomsen NA, Hammer KA, Riley TV, Van Belkum A, Carson CF. Effect of habituation to tea tree (*Melaleuca alternifolia*) oil on the subsequent susceptibility of Staphylococcus spp. to antimicrobials, triclosan, tea tree oil, terpinen-4-ol and carvacrol. Int J Antimicrob Agents 2013; 41(4): 343-51. http://dx.doi.org/10.1016/j.ijantimicag.2012.12.011 PMID: 23481659

[94] Fu Y, Zu Y, Chen L, *et al.* Antimicrobial activity of clove and rosemary essential oils alone and in combination. Phytother Res 2007; 21(10): 989-94. http://dx.doi.org/10.1002/ptr.2179 PMID: 17562569

[95] Tavana E, Mollazadeh H, Mohtashami E, *et al.* Quercetin: A promising phytochemical for the treatment of glioblastoma multiforme. Biofactors 2020; 46(3): 356-66. http://dx.doi.org/10.1002/biof.1605 PMID: 31880372

[96] Akbari Oryani M, Tarin M, Rahnama Araghi L, *et al.* Synergistic cancer treatment using porphyrin-based metal-organic Frameworks for photodynamic and photothermal therapy. J Drug Target 2024; (Dec): 1-19. http://dx.doi.org/10.1080/1061186X.2024.2433551 PMID: 39618308

[97] Rastin F, Oryani MA, Iranpour S, Javid H, Hashemzadeh A, Karimi-Shahri M. A new era in cancer treatment: Harnessing ZIF-8 nanoparticles for PD-1 inhibitor delivery. J Mater Chem B Mater Biol Med 2024; 12(4): 872-94. http://dx.doi.org/10.1039/D3TB02471G PMID: 38193564

[98] Einafshar E, Javid H, Amiri H, Akbari-Zadeh H, Hashemy SI. Curcumin loaded β-cyclodextrin-magnetic graphene oxide nanoparticles decorated with folic acid receptors as a new theranostic agent to improve prostate cancer treatment. Carbohydr Polym 2024; 340: 122328. http://dx.doi.org/10.1016/j.carbpol.2024.122328 PMID: 38857995

[99] Low WL, Martin C, Hill DJ, Kenward MA. Antimicrobial efficacy of silver ions in combination with tea tree oil against *Pseudomonas aeruginosa, Staphylococcus aureus* and *Candida albicans*. Int J Antimicrob Agents 2011; 37(2): 162-5. http://dx.doi.org/10.1016/j.ijantimicag.2010.10.015 PMID: 21163626

[100] Granato M, Rizzello C, Gilardini Montani MS, *et al.* Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways. J Nutr Biochem 2017; 41: 124-36. http://dx.doi.org/10.1016/j.jnutbio.2016.12.011 PMID: 28092744

[101] Khor CM, Ng WK, Kanaujia P, Chan KP, Dong Y. Hot-melt extrusion microencapsulation of quercetin for taste-masking. J Microencapsul 2017; 34(1): 29-37. http://dx.doi.org/10.1080/02652048.2017.1280095 PMID: 28067579