The Pharma Innovation Journal 2023; 12(3): 1254-1260

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(3): 1254-1260

www.thepharmajournal.com
Received: 12-01-2023
Accepted: 28-02-2023

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An insight into physiochemical property, bioavailability and pharmacology of Quercetin: A bioflavonoid

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Abstract
Fruits, plants, vegetables, tea, bark, bulbs, stem, roots and wine all contain a class of natural compounds called flavonoids. Polyphenolic chemicals is also found in the blooms of Smith's *Rhododendron arboreum*. There have been numerous attempts to segregate these natural compounds, which are valued for their positive effects on health. Today, flavonoids are recognised as a crucial ingredient in a variety of cosmetic, pharmacological, and therapeutic compositions. The primary polyphenolic flavonoid, quercetin is widely distributed among plants is frequently present in foods and consumed on a daily basis, especially fruits and vegetables. Quercetin has long been used to treat a various conditions, including arthritis, cardiovascular diseases, cancer, eye and viral infections. It has been tested pharmacologically against a variety of microbes and parasites, including viruses and dangerous bacteria. Due to its inhibitory impact against acetylcholinesterase, it has also demonstrated therapeutic effects against Alzheimer's disease (AD). Additionally, it has been shown to have antioxidant, anti-fungal, anti-carcinogenic, and cardioprotective properties. According to research, quercetin is excreted by the respiratory, renal, and faecal systems and amasses in the liver, lungs, small intestine and kidneys with lower quantities in the spleen, heart and brain.

Keywords: antioxidants, flavonoids, quercetin, therapeutic benefits

Introduction
R. arboreum Smith (*Ericaceae*) is the Uttarakhand's state flower and Nepal's national flower. It is dispersed across the Himalayan and mountainous region at a height of 1500-3300 m. It has strong medical, profitable and sprititual values. In temples, flowers are presented to gods and goddesses. The flowers are used to treat diarrhoea and bloody dysentery in traditional Nepalese medicine. Jam, local brew, jelly and squash are all made from flowers that have a sweet and sour flavour. To make pickles, jellies, and *sharbat*, fresh petals are used. Although the young leaves are thought to be deadly, they are applied to the forehead as a headache remedy [1]. *R. arboreum is one of the essential components of the Ayurvedic drug "Asoka Aristha," which exhibits estrogenic, oxytocic, and prostaglandin synthetase-inhibitory activity* [2]. According to reports, *R. arboreum's* different sections contain a wide variety of bioactive phytochemical components. Quercetin-3-rhamnoside, rutin, coumaric acid, and quercetin are all said to be present in flowers [3]. Quercetin is a yellow, crystalline powder with a density of 1,799 g/cm^3, a molar mass of 302,236 g/mol and a melting point of 316 °C [4]. It is prevalent in plants in the natural world. Figure 1 depicts the chemical structure formula and has the molecular formula $C_{15}H_{10}O_7$. The first carbon of the quercetin molecule contains a basic oxygen atom and a ketocarbonyl group that enable it to form salts with potent acids. Four active groups are present in the compound's molecular structure: a 4-carbonyl group, a double bond between the C2 and C3 locations, an o-dihydroxy group in the B ring, and a dihydroxy group between the A and C rings. Quercetin has a potent antioxidant effect because it contains double bonds and a phenolic hydroxyl group. Its anti-inflammatory and antioxidant effects are strongly associated to the prevention and treatment of cancer and cardiovascular illnesses [5].
The bioactive phytochemicals known as polyphenols are those that are most frequently found in plants, such as red wine, chocolate, fruit juices, cereals, dry legumes, fruits, vegetables, and cereal-based foods. The natural antioxidant properties of polyphenols, which are particularly significant in the prevention of cancer and cardiovascular disease, are well established. Studies have shown that dietary sources of quercetin and its derivatives are widespread to reduce the risk of cancer and coronary heart disease by chelating transition metal ions and free radicals that lead to the oxidation of low-density lipoproteins (LDL) [6].

Physicochemical properties of quercetin

One of the six flavonoid chemical subclasses are called flavonols, and quercetin belongs to this group. The name, which was inspired by the Quercus tree and has been in use since 1857, originates from the Latin term quercetum, which means "oak forest." It is an organic polar auxin transport inhibitor [7]. Quercetin's scientific name is 3,31,41,5,7-pentahydroxyflvanone according to the International Union of Pure and Applied Chemistry (IUPAC) (or its synonym 3, 31, 41, 5, 7-pentahydroxy-2-phenylchromen-4-one). This indicates that the OH groups are joined to quercetin at locations 3, 5, 7, 31, and 41. Figure 1 depicts the typical types of quercetin.

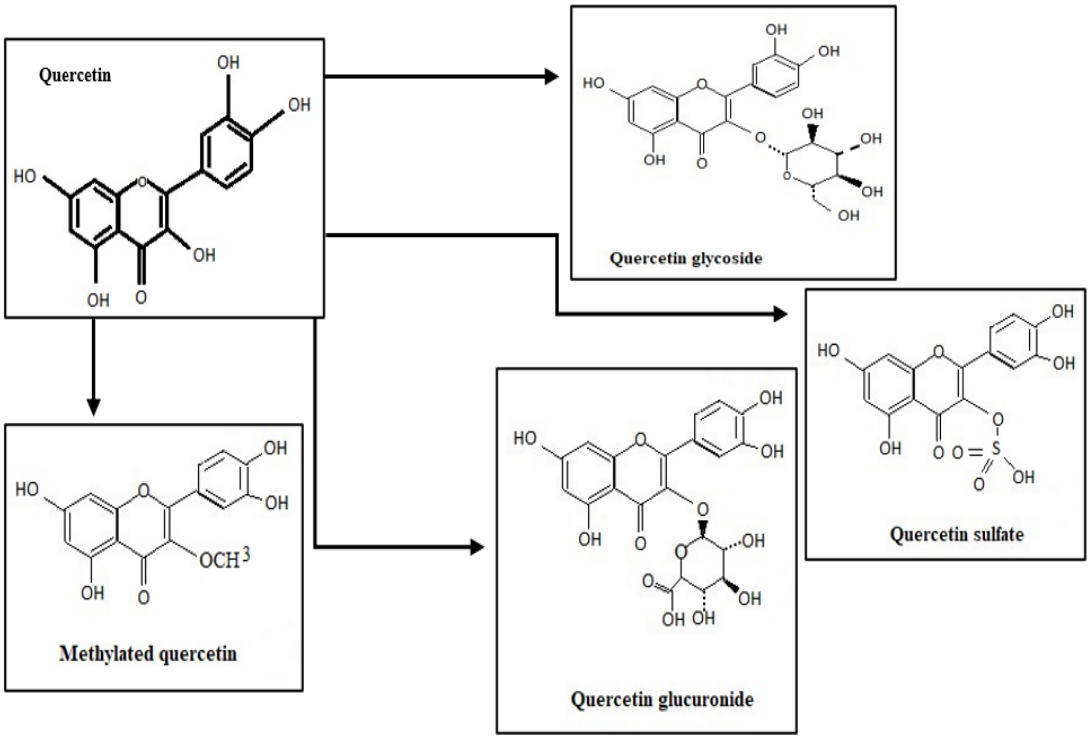

Fig 1: Molecular structure of quercetin glycoside, quercetin, quercetin sulphate, quercetin glucuronide and dimethyl quercetin

The aglycone quercetin (C15H10O7) is devoid of an associated sugar. It is a bright citron yellow needle crystal that dissolves reasonably well in lipids and alcohol but utterly refuses to mix with ice-cold water. A quercetin glycoside is produced when one of the OH groups is swapped out for a glycosyl group, which can be a sugar like glucose, rhamnose, or rutinose (commonly at position 3). The glycosyl group that is connected can have an impact on solubility, absorption, and *in vivo* effects. In general, quercetin glycoside is more water soluble than quercetin aglycone because it has a glycosyl group [8, 9].

The glycosyl group that is joined to a quercetin glycoside makes it distinctive. While the term "quercetin" should typically be used to refer to the aglycone, it is occasionally used in studies and the supplement business to refer to molecules of the quercetin family, including its glycosides.

Dietary Sources

Since 1857, quercetin has been known by this name. It is a translation of the Latin word Quercetum, named for the Quercus tree (oak) [10]. It is a flavonoid that is most frequently found in higher plants and in the glycosidal form, including hyperin, rutin and isoquercetin (quercetin-3-O-glucoside) (quercetin-3-O-galactoside). The most prevalent flavonoid molecules, quercetin-type flavonols, are found in a wide variety of plants, primarily as quercetin glycosides. In addition to various flowers, seeds, barks, nuts and leaves, they are present in a wide range of foods such as grapes, apples, Brassica vegetables, onions, tomatoes, tea, shallots and berries. *Sambucus canadensis*, *Ginkgo biloba*, and *Hypericum perforatum* are a few therapeutic plants that contain quercetin [11, 12]. The area closest to the root of red onions has the largest concentration of quercetin, while the outermost rings of red onions contain the most of it. Quercitin can be found in a variety of honeys made from diverse plant sources [13]. Quercetin is found in foods like fruits, vegetables, nuts, drinks, berries and other items of plant origin [14].

Absorption, bioavailablity and metabolism of quercetin

Absorption

Quercetin glycosides may absorb differently depending on the type of sugar linked [15]. Quercetin glucosides, which are mostly present in onion or shallot flesh, are thought to be more easily absorbed than their rutinoside counterparts (the major quercetin glycoside in tea). In the small intestine, beta-glucosidases efficiently hydrolyze glucosides to the aglycone form, which is then mainly absorbed [16]. The quercetin glycosides such as, quercetin glucoside, quercetin galactoside and quercetin arabinoside, present in foods (like onions), are deglycosylated to quercetin aglycone before being passively absorbed in the small intestine [17]. This initial response is thought to be mediated by either a beta-glucosidase from the gut microbiota or the enzyme lactase phlorizin hydrolase (a beta-glucosidase), depending on the kind of glycoside [18]. A significant and extensive biotransformation reaction results in the creation of glucuronidated, sulfated, and methylated

metabolites from the quercetin aglycone, and this suggests that the phase II enzymes UGT (uridine 5' -diphospho-glucuronosyltransferase), SULT (sulfotransferase), and COMT are involved (catechol-O-methyltransferase).
More readily absorbed than quercetin were its derivatives of sulfuric acid and quercetin glucuronic acid. The food chain from which it is consumed, variations in its glycosylation, and the simultaneous delivery of dietary components like fibre and fat all have an impact on how well it is absorbed after that [17]. As a result, the levels of absorption will differ based on the kinds of sugar and the locations where sugar groups can conjugate.

Transformation and Transportation
Following absorption, quercetin is processed in the liver, kidney, small intestine and colon. Biotransformation enzymes in the small intestine and liver create the sulfo-substituted, methylated, and glucuronidated forms of metabolites [19, 20]. According to a study on the distribution of quercetin in rat and pig tissues, the lungs, liver, and kidneys of both species contain the highest concentrations of quercetin and its metabolites [21].
In intestinal mucosal epithelial cells, enteric bacteria and enzymes convert quercetin and its derivatives into a variety of metabolites (phenolic acid). These metabolites are later ingested, changed, or eliminated. In addition, bacteria in the colon and small intestine break down the aglycon's ring structure, which causes quercetin to lose its backbone structure and produce smaller phenolics [22]. The liver have less quercetin derivatives than the plasma did, and the hepatic metabolites had a high level of methylation (90%–95%), according to an analysis of the metabolites found in the two samples of blood and liver [23]. A few researches indicate that the liver is where quercetin undergoes methylation, vulcanization, and glucuronidation.
When quercetin was consumed regularly, it gets accumulated in the blood and there is a considerable increase in the concentration of plasma, and this was highly correlated with the nutritious components of the diet [24].
Human blood contains quercetin in a conjugated form, with glycoside being the main structural variant. In addition to its isorhamnetin and glucoside acid-sulfated derivatives, quercetin also has glucuronoside and methylated forms as metabolites. Boulton also discovered that quercetin reduced the bioavailability of plasma protein in cells (albumin accounts for 99.4% of plasma protein) [25].

Excretion
The researchers discovered that quercetin and its metabolites tend to build up in the organs responsible for its metabolism and excretion. Additionally, mitochondria may contain quercetin in some cells, the kidney is a major excretory organ. Possible frequent metabolites of quercetin include benzoic acid derivatives [26]. Quercetin can be absorbed significantly by human subjects from food or supplements, and its half-life has been observed in range from 11 to 28 hours [27]. Quercetin typically has a 3.5-hour terminal half-life [28]. Depending on the person, the total recovery of C-quercetin in exhaled air, urine and faeces varies greatly [29]. The lungs eventually remove a significant amount of the extensively digested quercetin that was ingested [30]. Later studies revealed that quercetin in the aglycone form is less completely absorbed than quercetin that has been glycosylated, and quercetin's bioavailability is boosted when it is eaten alongside vitamin C, folate, and other flavonoids [31, 32]. All of these investigations show that quercetin glucosides are taken up in the upper small intestine, followed by biotransformation enzymes in the small intestine and liver, and then kidneys, which eventually is excreted in urine.

Pharmacological properties of quercitin
Anti-Inflammatory
Inflammation is a biological reaction that occurs when areas of the human body are subjected to unpleasant or harmful stimuli. This reaction serves as a form of self- defense and aims to eliminate damaged cells, infections, or any unpleasant stimuli while also kicking off the healing process. Infection does not always signify inflammation. In most circumstances, a virus, bacteria, or fungus causes an infection, whereas an inflammatory process is the body's attempt to repair itself. The capacity of quercetin to control inflammation is one of the substance's most outstanding fundamental characteristics. By blocking the inflammatory enzymes cyclooxygenase (COX) and lipooxygenase, quercetin lowers inflammatory mediators such as prostaglandins and leukotrienes [33, 34]. It has been shown that quercetin has strong anti-inflammatory properties and a lengthy half-life. Quercetin can exhibit strong anti-inflammatory potential in numerous cell types in both animal and human studies [35]. Many possible antiallergic medications use quercetin, a plant extract, as their primary active ingredient. Its capacity to inhibit IL-8 is greater than that of Cromolin (the antiallergenic medication disodium cromoglycate), and it also has the ability to inhibit IL-6 and raise cytosolic calcium levels [36]. Respiratory and food allergies have been successfully treated using its anti-inflammatory and anti-allergic characteristics [37].

Anti-Microbial Activity
Nearly all bacterial strains are known to be susceptible to quercetin's antibacterial activities, which primarily affect the gastrointestinal, respiratory, urinary, and cutaneous systems. Strong bacteriostatic activity has been demonstrated for quercetin against a variety of bacterial strains, including *S. aureus, Pseudomonas aeruginosa, P. fluorescens, Salmonella enterica serotype Typhimurium, Staphylococcus epidermidis, Yersinia enterocolitica, Helicobacter pylori, Micrococcus luteus, Campylobacter jejuni* [38]. Surprisingly, quercetin derivatives, such as quercetin 40,40,3,5,7-pentaphosphate (QPP), quercetin 50-sulfonic acid (QSA), and 40,40,3,5,7-diphosphate (QDP), resulted in highly soluble, biocompatible and potent antibacterial activity with 100 percent inhibition of *Listeria monocytogenes* [39]. In addition, quercetin demonstrated the most potent antifungal effects against *Candida albicans, Cryptococcus neoformans, and Aspergillus niger* [40].

Antiviral Activity
A variety of viruses have been demonstrated to be susceptible to quercetin's antiviral effects. For example, studies have demonstrated quercetin's potency against the human T-lymphotropic virus 1 and the Japanese encephalitis virus (JEV), which causes the mosquito-borne illness Japanese encephalitis [41, 42]. Quercetin has also been shown to inhibit the nonstructural protein 3 protease, which is a key player in the spread of the hepatitis C and type-2 dengue viruses [43, 44]. It has been found that other quercetin formulations are

effective against the influenza A virus and the porcine epidemic diarrhoea virus, respectively. These compounds include quercetin-3-O-D-glucuronide, formulations with lecithin that has been enhanced, and quercetin 7-rhamnoside [45].

Antioxidant Activity

The body produces free radicals throughout metabolism, and they are one of the factors in many disorders. They can disrupt cell membranes, alter genes, hasten the ageing process, and cause a number of illnesses, including diabetes, heart disease, and liver damage [46, 47]. According to researchers quercetin is the flavonoid family's top free radical scavenger [48]. Because the benzo-dihydropyran ring of quercetin's polyphenol has four hydroxyl groups, It can combat the body's production of free radicals, has a potent antioxidant potential, and can help keep the body stable, researchers also additionally noted that by preventing lipid peroxidation, methylated quercetin metabolites, such as tamarixetin and isorhamnetin, demonstrated more antioxidant activity than quercetin [49]**.** Because it may neutralise reactive oxygen species, as quercetin has been shown to have antioxidant properties [50]. To stop the spread of many malignancies, including liver, lung, breast, prostate and cervical cancers, quercetin modulates oxidative stress factors and antioxidant enzymes.

Antiprotozoal Activity

Numerous studies have been reprted that quercetin slows the growth of a variety of protozoan parasites, including *Theileria*, *Toxoplasma*, *Babesia*, *Leishmania* and *Trypanosoma*. Interestingly, *T. brucei brucei*, *T. cruzi*, *Trypanosoma brucei rhodesiense* and *Leishmania donovani* parasites are all susceptible to the growth inhibitory effects of quercetin both in vitro and *in vivo* [51]. With an IC_{50} of 1.0 g/mL and 8.3 g/mL, respectively, it produced significant leishmanicidal and trypanocidal action in vitro. However, in an *in vivo* trial, only the flavonoid quercetin demonstrated *in vivo* efficacy by preventing the growth of *L. donovani*. Additionally, by inhibiting the production of heat shock proteins 90 (hsp90), 70 (hsp70), and 27, quercetin has been shown to have exceptional inhibitory effects against *Toxoplasma gondii*. This suppresses the induction of bradyzoite growth [52]. Quercetin's antiplasmodial efficacy against a chloroquine-sensitive (3D7) and chloroquine-resistant (7G8) strain of Plasmodium falciparum was first reported by some researchers [53]**.**

Anti-Cancer Activity

A lower risk of cancer has been associated with eating more fruits and vegetables, according to epidemiological research. Quercetin may be effective for cancer treatment due to its antiproliferative, growth factor-suppressive, and antioxidant characteristics [54]. Numerous tumour *in vivo* and in vitro models have demonstrated quercetin's capacity to fight cancer in a number of different ways. Quercetin greatly slows down the cell cycle, encourages cell death, and stops the growth and spread of blood vessels. It has been proven that quercetin has anticancer properties both in vitro and *in vivo*. The inhibition of angiogenesis in tamoxifen-resistant cancer was used in in vitro trials to determine quercetin's anticancer efficacy against various cell lines, while its antioxidant activity was used to explain its effectiveness *in vivo* [55, 56]. Experts consider quercetin to be a good candidate for an anticancer drug due to its ability to prevent metastasis and induce apoptosis in tumour cell lines [57]. Several malignancies, including lung, breast, liver, cervical, prostate and colon cancer, are prevented from spreading by quercetin, and it works via a variety of mechanisms, inhibiting enzymes that activate carcinogens, binding to cellular receptors, proteins and including cellular signalling [58]. Quercetin has recently been shown to boost breast cancer cells' chemosensitivity to the chemotherapy drug doxorubicin by lowering cell invasion and proliferation, which encourage cell death. Additionally, via modifying the expression of miR-146a, cell apoptosis induction, Caspase 3 activation, and mitochondrial pathways, quercetin reduced the proliferation of the human breast cancer cell lines MCF-7 and MDA-MB-231 [59]. It was found that quercetin blocked the NF-B pathway, negatively regulated B-cell lymphoma 2, and upregulated Bcl-2-associated X protein in the CACO-2 and SW-620 cells, significantly inhibiting the growth of human colon cancer cells. Along with TLR4 and NF-B-mediated signalling, quercetin also has properties that are anti-colon cancer [60].

Neurodegenerative Disorders

The most frequent cause of dementia is thought to be Alzheimer's disease (AD), a chronic neurodegenerative disorder that causes memory loss and cognitive abnormalities like aphasia, agnosia, and apraxia and is connected to neuro-inflammatory processes in the central nervous system [61, 62].There are various memory types, including verbal, olfactory, episodic, and visual. These are separated into explicit memory (active or passive retention of facts) and implicit memory (nonverbal habitual memory) [63]. The development of neurodegenerative illnesses involving AD also includes oxidative stress, which is brought on by an imbalance of free radicals in the body. Quercetin is one of several flavonoids with distinct vascular system activities that can change the cerebrovascular blood flow and, in turn, the neuronal morphology that results in neurogenesis and angiogenesis. Additionally, it can shield neurons from damage brought on by neurotoxins. Flavonoids, which are abundant in foods, prevent neurodegeneration and reverse age-related declines in cognitive function [64]. The effectiveness of quercetin's inhibitory activities against acetylcholinesterase (AChE) is attributed to its therapeutic benefits against AD [65].

The benefits of quercetin and ascorbic acid include preventing neuronal damage and decreasing the frequency of oxidative damage to human lymphocytes and neurovascular structures in the skin. It is well recognised to shield brain tissue from oxidative stress, which harms cells and causes Alzheimer's and other neurological diseases [66]. Thy have believed to be necessary for preventing neuronal damage [67]. Flavonoid has neuroprotective effects on the brain and has the capacity to shield neurons from damage brought on by neurotoxins. It also enhances memory, learning, and cognitive abilities while suppressing neuroinflammation. Additionally, it has been discovered that flavonoids have protective properties that can stop more severe degenerative diseases, as well as many types of cerebrovascular disease connected to dementia and stroke that primarily affect elderly people. By boosting existing neural function or by encouraging neuronal regeneration, flavonoid-rich plant or dietary supplements improve cognition functions and safeguard fragile neurons [68].

Ulcer and Gastritis: According to studies, quercetin acts as a gastro protective agent by preventing stomach acid secretion and lipid peroxidation of gastric cells in addition to the infection with *Helicobacter pylori* is also prevented [69]. A group of researchers investigated the antioxidant and antiulcer impact of quercetin 50 and 100 mg/kg against an ethanol-induced model of gastric mucosal injury in rats, and the results indicate towards quercetin's potentially beneficial antiulcer activity [70]. Because of its capacity to scavenge free radicals or because it causes an increase in stomach mucus production, quercetin has anti-ulcer capabilities [71].

Cardiovascular Protection

According to researchers, quercetin has positive benefits on cardiovascular conditions such as atherosclerosis, ischemia-reperfusion injury, hypertensionor cardiotoxicity [72, 73]. These conditions are strongly related to quercetin's anti-inflammatory and antioxidant capabilities. Systolic, diastolic, and mean arterial pressure are all decreased as part of quercetin's protective mechanism for the cardiovascular system. In addition, there were decreased levels of total free fatty acids, cholesterol, triglycerides, phospholipids, lipid peroxidation in the heart and blood, and ST segment in the serum. Both blood vessels and blood sugar can be healed by it. It can significantly lessen the aortic wall's thickness. Researchers discovered that stage 1 hypertension patients who consumed 730 mg of quercetin daily for 28 days saw a reduction in their systolic, diastolic, and mean arterial pressure [74]. In addition to its heart-inhibitory effects on LDL oxidation and endothelium-dependent vasodilation, research has shown that quercetin significantly reduces the influence of adhesion molecules and other inflammatory indicators. Additionally, 93 overweight or obese participants in a research who took 150 mg of quercetin daily for six weeks saw a significant reduction in the quantity of LDL in their blood that was being oxidised by systolic blood pressure and atherosclerosis [75]. These participants were at high risk for metabolic syndrome [76]. The term "protective effect" describes how nitrogen oxide (NO) affects endothelial function, how it prevents oxidative inflammation from damaging neurons, and how platelets have an anti-aggregation impact.

Conclusion

However, the paper focused on different portions of *R. arboreum* as a source of high-value phenolics and flavonoids that could be used in preventative medications and nutraceuticals. The flavonoid quercetin has antioxidant qualities. Numerous positive impacts on health are attributed to quercetin's power, including defence against conditions like lung cancer, osteoporosis, and cardiovascular disease. According to the studies, people who consumed a lot of flavonoids had a lower risk of cardiovascular disease. Quercetin has demonstrated effective therapeutic effects against a number of illnesses. It is anticipated that quercetin will develop into a novel medication through ongoing research that can both prevent and treat a number of disorders. Its potent antioxidant, anti-inflammatory and anti-tumor activities have promising clinical applications; in addition, it can enhance bodily processes and lessen stress responses. Consuming rhododendron flowers is therefore advantageous for preventing diseases like cancer, cardiovascular, neurodegenerative, and others.

References

1. Manandhar NP. Plants and people of Nepal. Timber press, 2002.
2. Middelkoop TB, Laba RP. Evaluation of Asoka Aristha, an indigenous medicine in Sri Lanka. Journal of Ethnopharmacology. 1983;8(3):313-320.
3. Rangaswami S, Sambamurthy K. Crystalline chemical components of the flowers of *Rhododendron nilagiricum* Zenk, 'Proceedings of the Indian Academy of Sciences-Section. 1960;51(6):322-327.
4. Smith C, Lombard KA, Peffley EB, Liu W. Genetic analysis of quercetin in onion (*Allium cepa* L.) 'Lady Raider'. Texas Journal of Agriculture and Natural Resources. 2003;16(5):24-28.
5. Manach C, Mazur A, Scalbert A. Polyphenols and prevention of cardiovascular diseases. Current Opinion in Lipidology. 2005;16(1):77-84.
6. Collins AR. Assays for oxidative stress and antioxidant status: applications to research into the biological effectiveness of polyphenols. The American Journal of Clinical Nutrition. 2005; 81(1):261-267.
7. Fischer C, Speth V, Fleig-Eberenz S, Neuhaus G. Induction of zygotic polyembryos in wheat: influence of auxin polar transport. The Plant Cell. 1997;9(10):1767-1780.
8. Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. Annual Review of Nutrition. 2002;22(8):19-34.
9. Hollman PC, Bijsman MN, Van Gameren Y, Cnossen EP, De Vries JH, Katan MB. The sugar moiety is a major determinant of the absorption of dietary flavonoid glycosides in man. Free Radical Research. 1999;31(6):569-573.
10. Rahman MH, Bajgai J, Fadriquela A, Sharma S, Trinh TT, Akter R, Jeong YJ, *et al*. Therapeutic potential of natural products in treating neurodegenerative disorders and their future prospects and challenges. Molecules 2021;26(17):5327.
11. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. The American Journal of Clinical Nutrition. 2005;81(1):230-242.
12. Wiczkowski W, Romaszko J, Bucinski A, Szawara-Nowak D, Honke J, Zielinski H, *et al*. Quercetin from shallots (*Allium cepa L. var. aggregatum*) is more bioavailable than its glucosides. The Journal of Nutrition. 2008;138(5):885-888.
13. Petrus K, Schwartz H, Sontag G. Analysis of flavonoids in honey by HPLC coupled with colorimetric electrode array detection and electrospray ionization mass spectrometry. Analytical and Bioanalytical Chemistry. 2011;400(8):2555-2563.
14. Tutelian VA, Lashneva NV. Biologically active substances of plant origin. Flavonols and flavones: prevalence, dietary sourses and consumption. Voprosy Pitaniia. 2013;82(1):4-22.
15. Scholz, Williamson G. Interactions affecting the bioavailability of dietary polyphenols *in vivo*. International Journal for Vitamin and Nutrition Research. 2007;77(3):224-235.
16. Ader P, Wessmann A, Wolffram S. Bioavailability and metabolism of the flavonol quercetin in the pig. Free

Radical Biology and Medicine. 2000;28(7):1056-1067.
17. Guo Y, Mah E, Davis CG, Jalili T, Ferruzzi MG, Chun OK, *et al*. Dietary fat increases quercetin bioavailability in overweight adults. Molecular Nutrition and Food Research. 2013;57(5):896-905.
18. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly) phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxidants and Redox Signaling. 2013;18(14):1818-1892.
19. Hollman PC, Katan MB. Absorption, metabolism and bioavailability of flavonoids. In Flavonoids in Health and Disease. Ed by Rice-Evans C.A, Packer L, Marcel Dekker Inc, New York, USA, 1998, 483–522.
20. Day AJ, Bao Y, Morgan MR, Williamson G. Conjugation position of quercetin glucuronides and effect on biological activity. Free Radical Biology and Medicine 2000;29(12):1234-1243.
21. De Boer VC, Dihal AA, van der Woude H, Arts IC, Wolffram S, Alink GM, *et al*. Tissue distribution of quercetin in rats and pigs. The Journal of Nutrition 2005;135(7):1718-1725.
22. Kim DH, Kim SY, Park SY, Han MJ. Metabolism of quercitrin by human intestinal bacteria and its relation to some biological activities. Biological and Pharmaceutical Bulletin. 1999;22(7):749-751.
23. Manach C, Texier O, Morand C, Crespy V, Regerat F, Demigne C, *et al*. Comparison of the bioavailability of quercetin and catechin in rats. Free Radical Biology and Medicine. 1999;27(12):1259-1266.
24. Koli R, Erlund I, Jula A, Marniemi J, Mattila P, Alfthan G. Bioavailability of various polyphenols from a diet containing moderate amounts of berries. Journal of Agricultural and Food Chemistry. 2010;58(7):3927-3932.
25. Boulton DW, Walle UK, Walle T. Extensive binding of the bioflavonoid quercetin to human plasma proteins. Journal of Pharmacy and Pharmacology. 1998;50(2):243-249.
26. Graefe EU, Derendorf H, Veit M. Pharmacokinetics and bioavailability of the flavonol quercetin in humans. International Journal of Clinical Pharmacology and Therapeutics. 1999;37(5):219-233.
27. Manach C, Mazur A, Scalbert A. Polyphenols and prevention of cardiovascular diseases. Current Opinion in Lipidology. 2005;16(1):77-84.
28. Konrad M, Nieman DC. Evaluation of quercetin as a countermeasure to exercise-induced physiological stress. In: *'Antioxidants in Sports Nutrition'*. Lamprecht, M., Ed. CRC Press: Boca Raton, Florida, 2015, 155-170.
29. Moon YJ, Wang L, DiCenzo R, Morris ME. Quercetin pharmacokinetics in humans. Biopharmaceutics and Drug Disposition. 2008;29(4):205-217.
30. Manach C, Mazur A, Scalbert A. Polyphenols and prevention of cardiovascular diseases. Current Opinion in Lipidology. 2005;16(1):77-84.
31. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. Food and Chemical Toxicology. 2007;45(11):2179-2205.
32. Xiao X, Shi D, Liu L, Wang J, Xie X, Kang T, *et al*. Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. PloS One. 2011;6(8):22934-22951.
33. Warren CA, Paulhill KJ, Davidson LA, Lupton JR, Taddeo SS, Hong MY, *et al*. Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. The Journal of Nutrition. 2009;139(1):101-105.
34. Geraets L, Moonen HJ, Brauers K, Wouters EF, Bast A, Hageman GJ. Dietary flavones and flavonoles are inhibitors of poly (ADP-ribose) polymerase-1 in pulmonary epithelial cells. The Journal of Nutrition. 2007;137(10):2190-2195.
35. Mlcek J, Jurikova T, Skrovankova S, Sochor J. Quercetin and its anti-allergic immune response. Molecules. 2016;21(5):623-631.
36. Jurikova T, Mlcek J, Sochor J, Hegedusova A. Polyphenols and their mechanism of action in allergic immune Response Immune response. Global Journal of Allergy. 2015;1(2):037-039.
37. Wang S, Yao J, Zhou B, Yang J, Chaudry MT, Wang M, *et al*. Bacteriostatic effect of quercetin as an antibiotic alternative *in vivo* and its antibacterial mechanism *in vitro*. Journal of Food Protection. 2018;81(1):68-78.
38. Osonga FJ, Akgul A, Miller RM, Eshun GB, Yazgan I, Akgul A, *et al.* Antimicrobial activity of a new class of phosphorylated and modified flavonoids. ACS Omega 2019;4(7):12865-12871.
39. Batiha GES, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, *et al*. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: Quercetin. Foods. 2020;9(3):374-381.
40. Johari J, Kianmehr A, Mustafa MR, Abubakar S, Zandi K. Antiviral activity of baicalein and quercetin against the Japanese encephalitis virus. International Journal of Molecular Sciences. 2012;13(12):16785-16795.
41. Coelho-dos-Reis JGA, Ab Gomes O, Bortolini DE, Martins ML, Almeida MR, Martins CS, *et al*. Evaluation of the effects of Quercetin and Kaempherol on the surface of MT-2 cells visualized by atomic force microscopy. Journal of Virological Methods. 2011;174(2):47-52.
42. Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, Abu Bakar S. Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virology Journal. 2011;8(1):1-11.
43. Bachmetov L, Gal-Tanamy M, Shapira A, Vorobeychik M, Giterman-Galam T, Sathiyamoorthy P, *et al*. Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity. Journal of Viral Hepatitis. 2012;19(2):81-88.
44. Ramadan MF, Selimasker MM. Antimicrobical and antivirial impact of novel quercetin-enriched lecithin. Journal of Food Biochemistry. 2009;33(4):557-571.
45. Ullah F, Iqbal N, Ayaz M, Sadiq A, Ullah I, Ahmad S, *et al*. DPPH, ABTS free radical scavenging, antibacterial and phytochemical evaluation of crude methanolic extract and subsequent fractions of Chenopodium botrys aerial parts. Pakistan Journal of Pharmaceutical Sciences. 2017;0(3):761-766.
46. Ghosh N, Chakraborty T, Mallick S, Mana S, Singha D,

Ghosh B, *et al*. Synthesis, characterization and study of antioxidant activity of quercetin–magnesium complex. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2015;151(12):807-813.
47. Hanasaki Y, Ogawa S, Fukui S. The correlation between active oxygens scavenging and antioxidative effects of flavonoids. Free Radical Biology and Medicine. 1994;16(6):845-850.
48. Lesjak M, Beara I, Simin N, Pintac D, Majkic T, Bekvalac K, *et al*. Antioxidant and anti-inflammatory activities of quercetin and its derivatives. Journal of Functional Foods. 2018;40(1):68-75.
49. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. European Journal of Pharmacology. 2008;585(3):325-337.
50. Tasdemir D, Kaiser M, Brun R, Yardley V, Schmidt TJ, Tosun F, Ruedi P. Antitrypanosomal and antileishmanial activities of flavonoids and their analogues: in vitro, *in vivo*, structure-activity relationship, and quantitative structure-activity relationship studies. Antimicrobial Agents and Chemotherapy. 2006;50(4):1352-1364.
51. Weiss LM, Ma YF, Takvorian PM, Tanowitz HB, Wittner M. Bradyzoite development in Toxoplasma gondii and the hsp70 stress response. Infection and immunity. 1998;66(7):3295-3302.
52. Lehane AM, Saliba KJ. Common dietary flavonoids inhibit the growth of the intraerythrocytic malaria parasite. BMC Research Notes. 2008;1(1):1-5.
53. Lakhanpal P, Rai DK. Quercetin: a versatile flavonoid. Internet Journal of Medical Update. 2007;2(2):22-37.
54. Oh SJ, Kim O, Lee JS, Kim JA, Kim MR, Choi HS, *et al*. Inhibition of angiogenesis by quercetin in tamoxifen-resistant breast cancer cells. Food and Chemical Toxicology. 2010;48(11):3227-3234.
55. Baghel SS, Shrivastava N, Baghel RS, Agrawal P, Rajput S. A review of quercetin: antioxidant and anticancer properties. World Journal of Pharmacy and Pharmaceutical Sciences. 2012;1(1):146-160.
56. Gibellini L, Pinti M, Nasi M, Montagna JP, De Biasi S, Roat E, *et al*. Quercetin and cancer chemoprevention. Evidence-Based Complementary and Alternative Medicine. 2011;(4):1-16.
57. Rauf A, Imran M, Khan IA, ur-Rehman M, Gilani SA, Mehmood Z, *et al*. Anticancer potential of quercetin: A comprehensive review. Phytotherapy Research. 2018;32(11):2109-2130.
58. Tao SF, He HF, Chen Q. Quercetin inhibits proliferation and invasion acts by up-regulating miR-146a in human breast cancer cells. Molecular and Cellular Biochemistry. 2015;402(1):93–100.
59. Zhang XA, Zhang S, Yin Q, Zhang J. Quercetin induces human colon cancer cells apoptosis by inhibiting the nuclear factor-kappa B Pathway. Pharmacognosy Magazine. 2015;11(42):404-409.
60. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: An overview of environmental risk factors. Environmental Health Perspectives. 2005;113(9):1250-1256.
61. Choi GN, Kim JH, Kwak JH, Jeong CH, Jeong HR, Lee U, *et al*. Effect of quercetin on learning and memory performance in ICR mice under neurotoxic trimethyltin exposure. Food Chemistry. 2012;132(2):1019-1024.
62. Arlt S. Non-Alzheimer's disease—related memory impairment and dementia. Dialogues in Clinical Neuroscience. 2022;15(4):465-473.
63. Vauzour D, Vafeiadou K, Rodriguez-Mateos A, Rendeiro C, Spencer JP. The neuroprotective potential of flavonoids: a multiplicity of effects. Genes & Nutrition. 2008; 3(3):115-126.
64. Choi GN, Kim JH, Kwak JH, Jeong CH, Jeong HR, Lee U, *et al*. Effect of quercetin on learning and memory performance in ICR mice under neurotoxic trimethyltin exposure. Food Chemistry. 2012;132(2):1019-1024.
65. Lakhanpal P, Rai DK. Quercetin: a versatile flavonoid. Internet Journal of Medical Update. 2007;2(2):22-37.
66. Vauzour D, Vafeiadou K, Rodriguez-Mateos A, Rendeiro C, Spencer JP. The neuroprotective potential of flavonoids: a multiplicity of effects. Genes & Nutrition. 2008;3(3):115-126.
67. Youdim KA, Joseph JA. A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects. Free Radical Biology and Medicine. 2001;30(6):583-594.
68. Suzuki Y, Ishihara M, Segami T, Ito M. Anti-ulcer effects of antioxidants, quercetin, α-tocopherol, nifedipine and tetracycline in rats. The Japanese Journal of Pharmacology. 1998;78(4):435-441.
69. De La Lastra A, Martin MJ, Motilva V. Anti-ulcer and gastroprotective effects of quercetin: a gross and histologic study. Pharmacology. 1994;48(1):56-62.
70. Terao J. Factors modulating bioavailability of quercetin-related flavonoids and the consequences of their vascular function. Biochemical Pharmacology. 2017;139(9):15-23.
71. Guillermo Gormaz J, Quintremil S, Rodrigo R. Cardiovascular disease: a target for the pharmacological effects of quercetin. Current Topics in Medicinal Chemistry. 2015;15(17):1735-1742.
72. Edwards RL, Lyon T, Litwin SE, Rabovsky A, Symons JD, Jalili T. Quercetin reduces blood pressure in hypertensive subjects. The Journal of Nutrition 2007;137(11):2405-2411.
73. Brull V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Muller C, *et al*. Acute intake of quercetin from onion skin extract does not influence postprandial blood pressure and endothelial function in overweight-to-obese adults with hypertension: a randomized, double-blind, placebo-controlled, crossover trial. European Journal of Nutrition. 2017;56(3):1347-1357.
74. Egert S, Bosy-Westphal A, Seiberl J, Kurbitz C, Settler U, Plachta-Danielzik S, *et al*. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. British Journal of Nutrition. 2009;102(7):1065-1074.
75. Vita JA. Polyphenols and cardiovascular disease: effects on endothelial and platelet function. The American Journal of Clinical Nutrition. 2005;81(1):292-297.
76. Song JH, Shim JK, Choi HJ. Quercetin 7-rhamnoside reduces porcine epidemic diarrhea virus replication via independent pathway of viral induced reactive oxygen species. Virology Journal. 2011;8(1):1-6.