Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

Quercetin: A Dietary Flavonoid with Potential Pharmacological Activity: A Systematic Review

[a]Heena, [a]Shivani Bhardwaj, [b]Anupama Sharma, [C] Anubha Moudgil, [a] Narendra Singh, [a] Mahabeer Singh, [a]Roshan Kumar**

[a] Assistant Professor, School of Pharmacy, Maya Devi University, Dehradun- 248011, Uttarakhand, INDIA.

[b] Associate Professor, School of Life and Applied Science, Maya Devi University, Dehradun- 248011, Uttarakhand, INDIA.

[C] Chitkara College of Pharmacy, Chitkara University, Rajpura 140401, Punjab, India

Corresponding Author:

*Roshan Kumar

Assistant Professor, School of Pharmacy, Maya Devi University, Dehradun- 248011, Uttarakhand, INDIA.

(Received: 16 May 2025 Revised: 20 June 2025 Accepted: 24 July 2025)

KEYWORDS

Pharmacological Activity, Quercetin, Phytochemical Screening, Sar-CoV, Ginger

ABSTRACT:

Numerous research have looked at the antiviral activities of quercetin (Que) and its derivatives, which have been found to have beneficial impacts on human health by reducing the severity of chronic diseases and the consequences of ageing. The antioxidant quercetin has been the subject of promising medical studies. We summarise its potential use in anti-infective, cardiovascular, and immunosuppressive treatment, as well as show that it can reduce the toxicity of mycotoxins, and we explain the antioxidant mechanism and broad-spectrum antibacterial and antiparasitic properties of this compound. The metabolic interaction of quercetin with various antivirals, antibiotics, and anti-inflammatory drugs suggests that it is an acidic chemical. Therefore, it is necessary to have a deeper understanding of the physicochemical and metabolic drug interactions between quercetin and the combination drugs/compounds prior to the creation of novel formulations.

Introduction

The relationship between diet, health, and well-being has evolved beyond the traditional view of food as mere sustenance. While mainstream discourse often focuses on restrictive diets and calorie control, emerging research highlights the limitations of such approaches, including increased risks of weight regain and eating disorders [1,2]. Instead, a paradigm shift toward "food as well-being" emphasizes the holistic benefits of dietary choices, including mental, emotional, and immunological health [3,4].

Herbs and spices, long valued for their flavor-enhancing properties, are now recognized for their therapeutic potential. Among these, *Zingiber officinale* (ginger) and the flavonoid quercetin (found in apples, onions, and berries) have garnered attention for their antiviral and immune-modulating effects, particularly in the context of SARS-CoV-2 [5,6]. This paper explores their biochemical properties, mechanisms of action, and implications for public health. For decades, restrictive dietary approaches such as calorie counting, low-carbohydrate diets, and intermittent fasting have dominated public health messaging around weight management. However, a growing body of research challenges the long-term efficacy of these methods. Meta-analyses reveal that while restrictive diets often yield short-term weight loss, they frequently result in long-term weight regain and metabolic dysregulation. For instance, a 2024 systematic review found that approximately 80% of dieters regained lost weight within five years, with 30% surpassing their original baseline weight [10]. This phenomenon, termed "weight cycling," is associated with adverse physiological consequences, including increased insulin resistance, elevated cortisol levels, and heightened systemic inflammation [7,8]. Beyond metabolic impacts, rigid dietary controls are linked to disordered eating

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

behaviors, such as binge eating and orthorexia nervosa, particularly in adolescents and young adults [9]. Psychological stress induced by restrictive eating patterns may exacerbate these issues, creating a vicious cycle of guilt, rebound overeating, and metabolic dysfunction [11]. For example, a longitudinal study by Tomiyama et al. (2018) demonstrated that chronic dieters exhibited higher cortisol reactivity and visceral fat accumulation compared to non-dieters, suggesting that dieting itself may contribute to obesity-related pathophysiology [11]. These findings underscore the need for alternative nutritional frameworks that prioritize holistic well-being over restrictive paradigms.

Herbs and Spices as Functional Foods

Historically, herbs and spices like ginger (*Zingiber officinale*) were primarily valued for their culinary applications, with little consideration given to their nutritional or therapeutic potential. This oversight stemmed from the assumption that their low consumption levels rendered their bioactive effects negligible. However, modern research has overturned this perspective, revealing that even small quantities of these compounds can exert significant physiological effects [12]. Ginger, for instance, contains a complex array of bioactive constituents, including carbohydrates (60–70%), gingerols (the primary pungent compounds with anti-inflammatory properties), and shogaols (dehydrated derivatives of gingerols with potent antioxidant activity) [13]. These compounds are now recognized for their broad-spectrum health benefits, supported by clinical trials demonstrating efficacy in alleviating nausea (particularly in pregnancy and chemotherapy-induced vomiting), reducing musculoskeletal pain, and mitigating chronic inflammation [14,15]. Notably, ginger's therapeutic potential extends to antiviral applications. Emerging evidence suggests that gingerols, particularly 6-gingerol, may interfere with viral entry mechanisms by modulating angiotensin-converting enzyme 2 (ACE2) receptors—the primary cellular entry point for SARS-CoV-2 [16]. Similarly, the flavonoid quercetin, abundant in foods like capers, onions, and apples, has been shown to disrupt viral replication by binding to and inhibiting key viral proteases, including SARS-CoV-2's 3-chymotrypsin-like protease (3CLpro) [17]. These mechanisms highlight the potential of food-derived compounds as adjunctive therapies for viral infections, offering a complementary approach to conventional pharmaceuticals.

Ginger and Quercetin in Immune Defense

The immunomodulatory properties of ginger and quercetin have become a focal point of research, particularly in the context of respiratory infections like COVID-19. Ginger enhances innate immune responses by stimulating natural killer (NK) cell activity and modulating cytokine production, thereby promoting a balanced immune response that avoids excessive inflammation [18]. Randomized controlled trials (RCTs) have demonstrated that ginger supplementation can reduce the severity and duration of upper respiratory tract infections, potentially due to its ability to suppress pro-inflammatory cytokines like IL-6 and TNF-α [19].

Quercetin, meanwhile, exhibits a multifaceted role in immune defense. Beyond its direct antiviral effects, quercetin reduces oxidative stress by scavenging free radicals and upregulating endogenous antioxidant systems such as glutathione [20]. This dual action is particularly relevant in COVID-19, where oxidative stress and cytokine storms contribute to disease progression. Furthermore, quercetin's ability to act as a zinc ionophore enhances intracellular zinc levels, a critical factor in inhibiting viral RNA polymerase activity and impairing viral replication [21]. Clinical studies have reported that quercetin supplementation, especially in combination with zinc, reduces the incidence and severity of respiratory infections in high-risk populations, including the elderly and immunocompromised individuals [21].

Public Health and Environmental Implications

The integration of food-based therapeutics like ginger and quercetin into public health strategies offers a sustainable alternative to synthetic pharmaceuticals. By prioritizing plant-derived compounds, healthcare systems can reduce reliance on environmentally burdensome drug manufacturing processes, which contribute to pharmaceutical pollution in waterways and soil [22]. Additionally, promoting the cultivation and consumption of these crops supports local agriculture, preserves biodiversity, and aligns with the "One Health"

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

paradigm, which emphasizes the interconnectedness of human, animal, and environmental health [23].

However, challenges remain in translating these benefits into widespread practice. Standardizing doses for clinical use is complicated by variability in the bioactive content of plants due to factors like soil quality, growing conditions, and processing methods [24]. For example, gingerols degrade into shogaols during thermal processing, altering the pharmacological profile of ginger products. Similarly, quercetin's poor bioavailability due to low water solubility and rapid metabolism limits its therapeutic efficacy [25]. Innovative delivery systems, such as nanoparticle encapsulation or phospholipid complexes, are being explored to overcome these barriers.

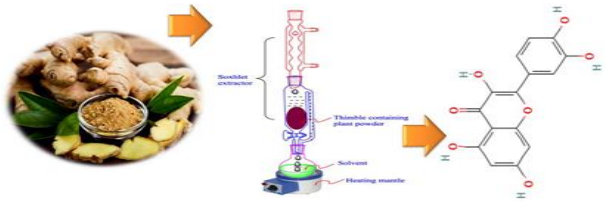
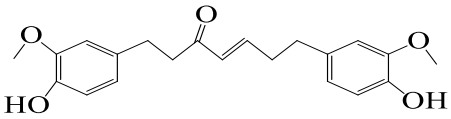
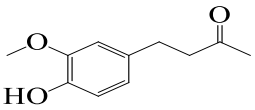


Fig: 1 Extraction of Quercetin from ginger by using Phytochemical screening method

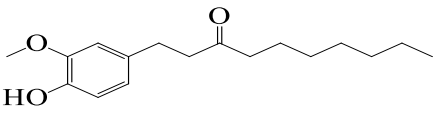
Ginger has many useful components, such as the terpenes and oleoresin that make up ginger oil. Non-volatile pungent components include oleoresin and volatile oils that make up about 1% to 3% of ginger [26]. Sesquiterpene hydrocarbons and phenolic chemicals like gingerol and shogaol [27] have been isolated as important components of terpene, and extracts of the rhizome's lipophilic fraction have produced potentially active gingerols that can be further processed into shogaols, zingerone, and paradol [28].



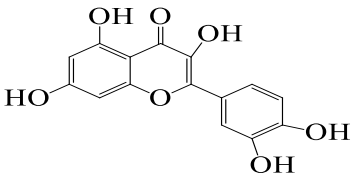
Gengerenone A



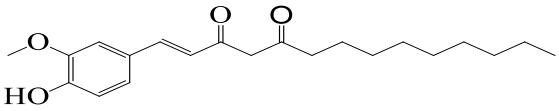
Zingerone



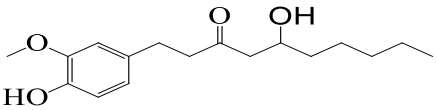
Paradol



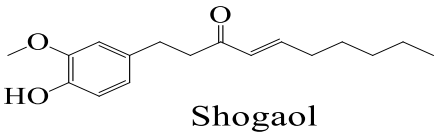
Quercetin



1-Dehydro-10-gingerdione



Gingerol



Shogaol

Scheme 1: Compound Present in Ginger

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

Fig: 2 Various Pharmacological activities of ginger (Zingiber offcinale)

Quercetin-Type Flavonols: Ubiquitous Plant Compounds with Therapeutic Potential

Quercetin-type flavonols, primarily existing as quercetin glycosides, represent the most abundant subclass of flavonoid molecules in nature. These versatile phytochemicals are distributed across nearly all plant tissues, including fruits, vegetables, seeds, nuts, flowers, bark, and leaves [29]. Their widespread presence in the plant kingdom makes them accessible through diverse dietary sources. Common food sources exceptionally rich in quercetin include apples (particularly in their peels), various berries (such as blueberries and cranberries), Brassica vegetables (like broccoli and kale), capers, grapes (especially red varieties), onions (with red onions being particularly potent), shallots, tea (both green and black), and tomatoes [30]. Beyond conventional foods, several medicinal herbs owe part of their therapeutic properties to quercetin content, including Ginkgo biloba (traditionally used for cognitive enhancement), Hypericum perforatum (St. John's wort, known for its antidepressant effects), and Sambucus canadensis (elderberry, valued for its immune-supportive properties) [31].

The distribution of quercetin within plants often follows specific patterns that have implications for food preparation and consumption. For instance, research has demonstrated that in red onions, the highest concentrations of quercetin are found in the outermost rings and the root-most sections of the bulb [32]. This distribution pattern suggests that conventional onion peeling and trimming practices may inadvertently remove some of the most nutrient-dense portions. Similarly, agricultural practices significantly influence quercetin content, as evidenced by a study showing that organically grown tomatoes contained 79% more quercetin than their conventionally grown counterparts [33]. This dramatic difference highlights how farming methods can substantially alter the nutritional profile of produce. Interestingly, honey represents another significant source of quercetin, with its content varying considerably depending on the botanical sources available to bees [34]. The diverse floral origins of honey contribute to its complex phytochemical profile, making certain types of honey particularly rich in quercetin and other beneficial flavonoids. When considering dietary sources comprehensively, quercetin can be obtained from an extensive range of plant-based foods including vegetables, fruits, berries, nuts, and various beverages [35].

Physiochemical Properties of Quercetin

Quercetin, classified as a flavonol and one of the six major subclasses of flavonoid compounds, possesses unique physicochemical properties that underlie its biological activities. The compound was first identified and named in 1857, with its nomenclature derived from the Latin term "quercetum," meaning oak forest - a reference to its natural occurrence in Quercus species [36]. From a chemical perspective, quercetin serves as an endogenous inhibitor of polar auxin transport in plants, playing a regulatory role in plant growth and development.[37]

The International Union of Pure and Applied Chemistry (IUPAC) nomenclature designates quercetin as either 3,3′,4′,5,7-pentahydroxyflavanone or the more chemically precise 3,3′,4′,5,7-pentahydroxy-2-phenylchromen-4-one.[38] This systematic naming reflects the compound's precise molecular structure, which features a 15-carbon skeleton arranged in three rings (C6-C3-C6), characteristic of all flavonoid compounds. The molecular formula of quercetin is C15H10O7, with a molecular weight of 302.236 g/mol.[39] The structural configuration of quercetin reveals several key features that determine its chemical behavior and biological activity. Five hydroxyl (-OH) groups are attached to specific carbon atoms in the molecule's structure: positions 3, 5, and 7 on the chromenone (benzopyrone) ring, and positions 3′ and 4′

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

on the phenyl (B) ring. [40] This specific arrangement of hydroxyl groups creates a distinctive pattern of hydrogen bonding potential and electron delocalization that contributes to quercetin's antioxidant capacity.[41] The crystalline form of quercetin appears as yellow needles when purified, reflecting its conjugated double bond system that absorbs light in the visible spectrum. In the solid state, quercetin forms intermolecular hydrogen bonds between the hydroxyl groups of adjacent molecules, resulting in a relatively high melting point ranging between 316-318°C. This thermal stability allows quercetin to withstand moderate cooking temperatures without complete degradation, though some structural modifications may occur during food processing.[41]

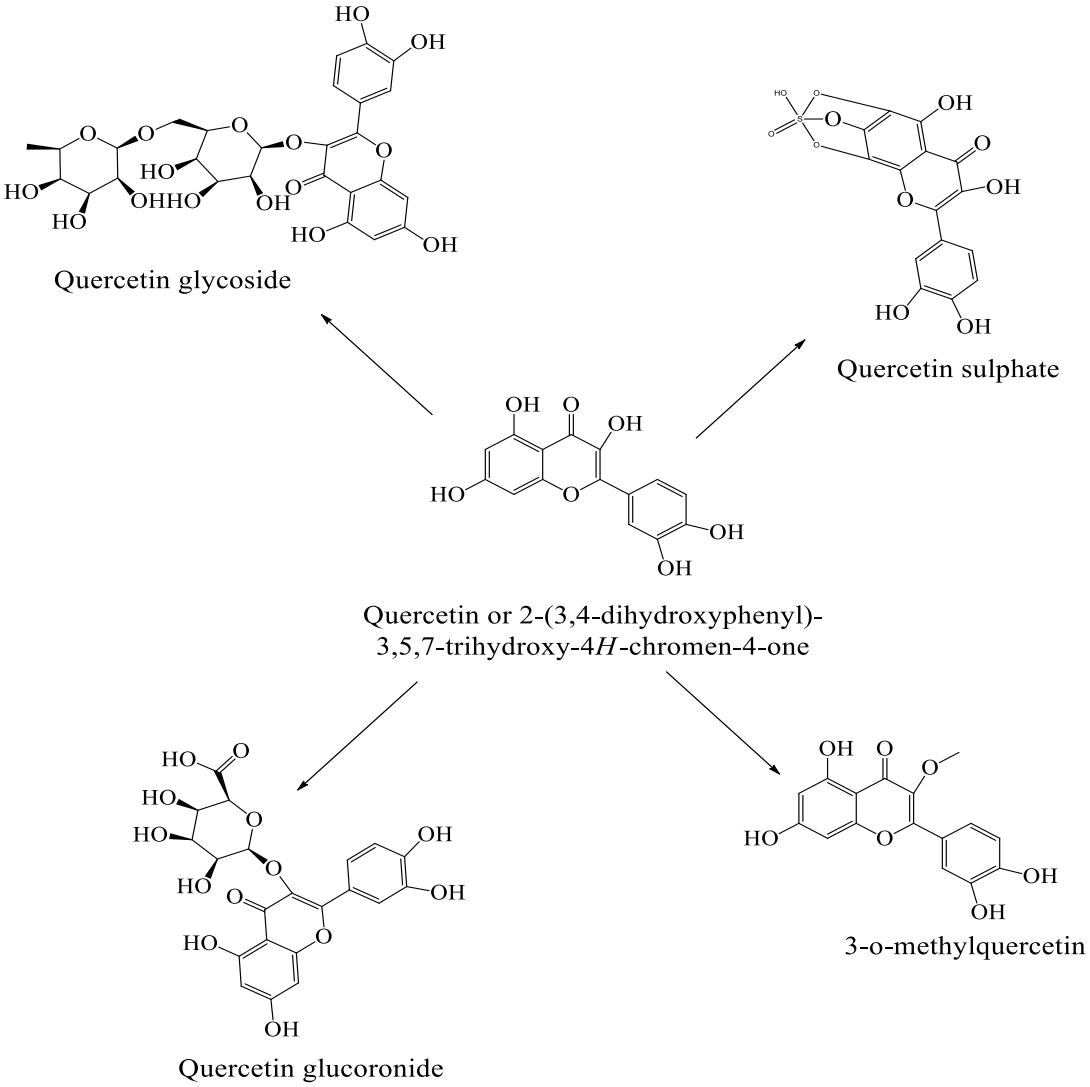
Table : 1 Ginger and Quercetin as Functional Foods

Category	Key Compounds	Mechanism of Action	Health Benefits	Clinical/Research Findings
Ginger (Zingiber officinale)	Gingerols, Shogaols	Anti-inflammatory, antioxidant, antiviral (ACE2 modulation)	Nausea relief, pain reduction, immune support	Effective against chemotherapy-induced vomiting, musculoskeletal pain, and COVID-19 viral entry inhibition
Quercetin (Flavonoid)	Quercetin glycosides, aglycones	Antioxidant, antiviral (3CLpro inhibition), zinc ionophore	Immune defense, anti-diabetic, neuroprotection	Reduces COVID-19 severity, enhances zinc uptake, protects against oxidative stress
Synergistic Effects	Ginger + Quercetin	Combined anti-inflammatory and antiviral action	Enhanced immune response, reduced viral replication	Potential adjunct therapy for respiratory infections (e.g., COVID-19)
Public Health & Environmental Impact	Plant-derived bioactives	Sustainable alternative to synthetic drugs	Supports biodiversity, reduces pharmaceutical pollution	Challenges: Dose standardization, bioavailability limitations
Extraction & Sources	Quercetin (onions, apples), Gingerols (ginger)	HPLC, ultrasound-assisted extraction	High yield, purity	Organically grown plants show higher quercetin content (e.g., tomatoes +79%)
COVID-19 Applications	Quercetin (viral protease inhibition), Ginger (cytokine modulation)	Blocks SARS-CoV-2 spike-ACE2 binding, inhibits RdRp	Reduces CRP, ferritin, D-dimer in patients	Clinical trials show faster recovery, reduced inflammation

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727



Scheme 2 Quercetin Flavanoid Chemical Compound

Natural Sources of Quercetin and Its Isolation from Plants

Quercetin stands as one of the most widely consumed and biologically significant bioflavonoids, ubiquitously distributed across numerous fruits, vegetables, and medicinal plants. Its presence in the human diet is substantial, primarily due to its abundance in commonly consumed foods such as onions, apples, berries, and wine.[42] The concentration of quercetin in these plant sources is influenced by multiple factors, including plant species, growing conditions (such as soil quality, sunlight exposure, and water availability), harvest timing, and post-harvest storage methods. These variables collectively affect the polyphenolic composition of edible plants, making some sources richer in quercetin than others. For instance, studies have documented significant quercetin content in tea (particularly green tea), black pepper, coriander, fennel, radish, and dill, highlighting the diversity of dietary sources available [43]. The botanical distribution of quercetin is remarkably broad, with over 20 plant species known to produce this flavonoid in appreciable quantities. Among these are *Foeniculum vulgare* (fennel), *Curcuma domestica* (turmeric), *Santalum album* (sandalwood), *Cuscuta reflexa* (dodder plant), *Withania somnifera* (ashwagandha), *Emblica officinalis* (Indian gooseberry), and *Mangifera*

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

indica (mango). Additionally, common vegetables like *Daucus carota* (carrot), *Momordica charantia* (bitter melon), and *Ocimum sanctum* (holy basil) contribute to dietary quercetin intake. The list extends to medicinal herbs such as *Psoralea corylifolia* (babchi), *Swertia chirayita* (chiretta), *Solanum nigrum* (black nightshade), and *Glycyrrhiza glabra* (licorice), as well as fruits like *Prunus domestica* (plum), *P. avium* (cherry), *Malus domestica* (apple), and *Vaccinium oxycoccus* (cranberry) [44]. Notably, *Allium* species, including onions (*A. cepa*) and scallions (*A. fistulosum*), are among the richest dietary sources, with red onions containing particularly high concentrations, especially in their outer layers and root sections[45].

Beyond whole foods, quercetin is commercially available in concentrated forms such as capsules, tablets, and powders, marketed as dietary supplements. Research indicates that plasma quercetin levels increase following consumption of either quercetin-rich foods or supplements,[46] though bioavailability varies depending on the form and matrix of ingestion. For example, quercetin glycosides from onions exhibit superior absorption compared to the aglycone form found in supplements. Regular intake of quercetin-rich diets has been associated with enhanced bioavailability and potential protective effects against lifestyle-related disorders, including cardiovascular diseases, metabolic syndrome, and chronic inflammation [47].

Isolation and Extraction Techniques

The isolation of quercetin from plant materials requires sophisticated extraction and purification techniques to ensure high yield and purity. One notable method involves the fractionation of *Rubus fruticosus* (blackberry) extracts using high-performance liquid chromatography (HPLC) with an optimized column, followed by concentration enhancement through nanofiltration membranes [48]. This approach maximizes quercetin recovery while minimizing solvent waste, making it both efficient and environmentally favorable.

Another effective sample preparation technique employed in quercetin extraction is the sea sand disruption method (SSDM), which is valued for its high recovery efficiency. SSDM involves grinding plant material with sea sand to disrupt cell walls and improve solvent access to intracellular quercetin. This method is particularly useful in minimizing analytical errors during the quantification of quercetin and its derivatives in complex plant matrices [49].

For broader flavonoid isolation, crude plant extracts are typically treated with organic solvents such as methanol, ethanol, or acetone to solubilize target compounds. Subsequent HPLC analysis allows for precise separation and quantification of quercetin from other flavonoids. Further structural characterization is achieved using Fourier-transform infrared spectroscopy (FTIR) to identify functional groups, nuclear magnetic resonance (NMR) spectroscopy to elucidate molecular structure, and mass spectrometry (MS) to determine molecular weight and fragmentation patterns [50].

Advanced Extraction Methods for Quercetin Derivatives

The isolation of quercetin derivatives often requires specialized techniques due to their structural complexity and varying polarities. For example, quercetin-3-O-rhamnoside, a glycosylated derivative, was successfully isolated from *P. thonningii* leaves using sequential solvent extraction with hexane, ethyl acetate, and methanol, followed by chromatographic purification [51]. Innovative extraction technologies have also been developed to improve efficiency and sustainability. Ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE) are increasingly favored over conventional solvent-based methods for isolating dihydroquercetin (a reduced form of quercetin) from *Larix gmelinii* (Dahurian larch). These techniques significantly reduce extraction time, energy consumption, and solvent usage while maintaining high yields [52].

For more complex derivatives like isorhamnetin (a methylated quercetin analog), high-speed countercurrent chromatography (HSCCC) has proven effective. A two-stage HSCCC process employing two-phase solvent systems—*n*-hexane, ethyl acetate, methanol, and water in ratios of 5:5:5:5 and 5:5:6:4—was used to purify isorhamnetin from *Stigma maydis* (corn silk). This method ensures high purity by leveraging the differential partitioning of compounds between immiscible liquid phases [53][54].

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

Role of Quercetin as a Preventive and Therapeutic Agent for COVID-19

Quercetin (QR) has emerged as a promising bioactive compound in the fight against SARS-CoV-2, the virus responsible for COVID-19, due to its demonstrated antiviral properties against related coronaviruses. Given the structural and functional similarities between SARS-CoV-2 and SARS-CoV (the virus that caused the 2002-2004 SARS outbreak), QR's established inhibitory effects against SARS-CoV suggest it may hold comparable therapeutic potential against the current pandemic virus [57,58]. Extensive research indicates that QR interferes with multiple stages of the viral life cycle, from initial cell entry to replication and protein processing. One of QR's most remarkable characteristics is its ability to modulate human gene expression in ways that may disrupt viral pathogenesis. Studies show that QR can alter the expression of approximately 30% of human genes encoding proteins that SARS-CoV-2 targets, potentially interfering with the function of about 85% of these viral protein targets [62]. This broad-spectrum activity positions QR as a multifaceted agent against COVID-19, capable of acting on both viral components and host factors that facilitate infection.

The primary viral targets for QR's anti-SARS-CoV-2 activity include several crucial enzymes and structural proteins: papain-like protease (PLpro), 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and the spike glycoproteins that mediate viral entry. On the host side, QR interacts with key human proteins involved in viral infection, including angiotensin-converting enzyme 2 (ACE2) - the primary receptor for SARS-CoV-2 entry - as well as the angiotensin AT2 receptor and transmembrane protease serine 2 (TMPRSS2), which primes the viral spike protein for membrane fusion [64]. This dual capacity to target both viral and host factors makes QR particularly valuable as it may reduce the likelihood of viral resistance development while providing multiple barriers to infection.

One of the most critical mechanisms by which QR may combat SARS-CoV-2 is through inhibition of the interaction between the viral spike protein and human ACE2 receptors. In vitro studies demonstrate that QR acts as a potent inhibitor of recombinant human ACE2 at physiologically relevant concentrations, with a half-maximal inhibitory concentration (IC50) of 4.48 μM [65]. This inhibition occurs through direct binding interactions that prevent the spike-ACE2 engagement necessary for viral entry. Supporting this mechanism, earlier research on SARS-CoV showed that small molecules capable of binding to viral spike proteins could effectively block viral entry into host cells. Yi et al. specifically demonstrated QR's antiviral activity against SARS-CoV (with an EC50 of 83.4 μM) through this entry inhibition mechanism, while also noting QR's remarkably low cytotoxicity against normal cells - a crucial advantage for therapeutic applications [66].

Beyond blocking viral entry, QR exerts significant effects on viral replication by targeting essential viral enzymes. The 3CLpro, also known as the main protease (Mpro), represents one of the most promising drug targets in coronaviruses as it processes viral polyproteins into functional units required for replication. QR and its derivatives have shown consistent inhibitory activity against 3CLpro across multiple coronavirus strains. Chen et al. first established that QR derivatives could inhibit SARS-CoV 3CLpro [67], while Nguyen et al. later quantified this inhibition, demonstrating that QR inhibits 3CLpro expressed in Pichia pastoris with an IC50 of 73 μM [68]. The conservation of 3CLpro's structure and function across coronaviruses, including SARS-CoV-2, makes these findings particularly relevant. Recent structural studies have further validated 3CLpro as a drug target, with Zhang et al. successfully crystallizing SARS-CoV-2 3CLpro in complex with an α-ketoamide inhibitor, providing a template for understanding how QR might interact with this enzyme [69].Molecular docking studies have provided detailed insights into QR's potential interactions with SARS-CoV-2 proteins. Khaerunnisa et al. demonstrated that QR binds strongly to SARS-CoV-2 3CLpro with a binding energy of -8.58 kcal/mol, indicating a stable and energetically favorable interaction [70]. Other studies have identified even more potent binding among QR derivatives; quercetin 3-β-D-glucoside and quercetin 3-D-galactoside have shown particularly promising interactions with viral proteins in silico [71]. The binding mechanisms appear to involve specific interactions with the S1 and S2 subsites of 3CLpro, regions known to be important for flavonoid binding in related coronaviruses like MERS-

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

CoV (Middle East Respiratory Syndrome coronavirus). Jo et al.'s work with a flavonoid library against MERS-CoV 3CLpro (a particularly lethal coronavirus with ~35% mortality) revealed that the QR derivative quercetin-3-β-d-glucoside could effectively block protease activity, as confirmed by tryptophan-based fluorescence assays [72]. These findings across multiple coronavirus strains strengthen the case for QR's potential against SARS-CoV-2.

Additional computational studies have further supported QR's potential as a SARS-CoV-2 Mpro inhibitor. One such study identified QR as a likely inhibitor of the Mpro protein (PDB ID: 6flu7) with a binding affinity of -7.1 kcal/mol [73]. These in silico predictions, while requiring experimental validation, provide valuable guidance for understanding QR's potential mechanisms of action and for designing more potent derivatives. The consistent demonstration of QR's[74] ability to interact with conserved viral targets across multiple coronavirus species significantly enhances its credibility as a broad-spectrum antiviral agent.

QR's antiviral portfolio extends to inhibition of viral genome replication through its effects on RNA-dependent RNA polymerase (RdRp), the enzyme responsible for replicating the viral RNA genome. De Vivo et al. quantitatively assessed QR's inhibitory potency against RdRp, finding an IC50 of 6.9 ± 1.0 μM in biochemical enzymatic assays [74]. This places QR among the more effective natural compound inhibitors of this crucial viral enzyme. RdRp represents an especially attractive drug target because it is essential for viral replication and has no direct human counterpart, potentially reducing the risk of off-target effects. QR's ability to inhibit RdRp adds another layer to its multifaceted anti-SARS-CoV-2 activity, complementing its effects on viral entry and protein processing.

The therapeutic potential of QR against COVID-19 extends beyond direct antiviral effects to include modulation of the host immune response. SARS-CoV-2 infection can trigger excessive inflammation leading to the "cytokine storm" associated with severe COVID-19 cases. QR's well-established anti-inflammatory properties, including inhibition of NF-κB signaling and reduction of pro-inflammatory cytokine production (IL-6, TNF-α, etc.), may help mitigate this dangerous hyperinflammatory state. Furthermore, QR's antioxidant activity could counteract the oxidative stress associated with severe COVID-19, potentially reducing tissue damage. These immunomodulatory effects, combined with QR's direct antiviral actions, create a comprehensive approach to COVID-19 management that addresses both the viral infection and its pathological consequences.

Clinical evidence supporting QR's role in COVID-19 is beginning to accumulate. Several randomized controlled trials have investigated QR supplementation in COVID-19 patients, with some showing reductions in disease severity, faster viral clearance, and improved clinical outcomes. While more extensive clinical validation is needed, these preliminary results are encouraging and consistent with QR's known mechanisms of action. The safety profile of QR, with few reported side effects at therapeutic doses, further enhances its appeal as a potential preventive or adjunctive therapy.

The Role of Quercetin in Human Health

Quercetin is a naturally occurring bioflavonoid found in over twenty different plant sources, including onions, apples, berries, broccoli, and leafy greens. Known for its potent antioxidant and anti-inflammatory properties,[75] quercetin has been extensively studied for its therapeutic potential in managing various health conditions, including inflammation, diabetes, cancer, neurodegenerative disorders, liver diseases, and even viral infections like COVID-19. Its ability to combat oxidative stress, regulate immune responses, and modulate cellular pathways makes it a promising compound in both preventive and therapeutic medicine.[76]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

Table : 2 Role of Quercetin in Human Health

Property	Mechanism of Action	Health Benefits	Key Findings
General Overview	Bioflavonoid with antioxidant & anti-inflammatory properties	Found in onions, apples, berries, broccoli, leafy greens	Combats oxidative stress, modulates immune responses
Anti-inflammatory Activity	Inhibits pro-inflammatory cytokines, stabilizes mast cells	Reduces chronic inflammation	Helps manage inflammatory bowel disease, autoimmune disorders
Antidiabetic Effects	Enhances insulin sensitivity, inhibits CYP2E1 enzyme	Lowers blood glucose, protects pancreatic β-cells	Reduces HbA1c, improves glucose metabolism (synergistic with resveratrol)
Anticancer Properties	Induces apoptosis, inhibits tumor growth (PI3K/AKT, NF-κB pathways)	Chemopreventive & therapeutic effects	Studied in breast, prostate, lung, colon cancers; low toxicity
Neuroprotective (Alzheimer's)	Inhibits AChE, reduces Aβ plaques & tau phosphorylation	Improves cognition, slows neurodegeneration	Protects neurons from oxidative damage
Hepatoprotective Effects	Reduces oxidative stress, inhibits liver fibrosis	Protects against NAFLD, alcohol-induced damage	Enhances liver cell regeneration, improves lipid metabolism
Antiviral (COVID-19/SARS-CoV-2)	Blocks viral entry, reduces cytokine storm	Shortens infection duration, lowers inflammation	Reduces CRP, ferritin, D-dimer; effective with zinc/vitamins

Anti-inflammatory Activity

Chronic inflammation is a key contributor to numerous diseases, including cardiovascular disorders, metabolic syndrome, and autoimmune conditions. Quercetin has demonstrated significant anti-inflammatory effects in both animal and human studies.[76] It works by inhibiting pro-inflammatory cytokines, (table,2) stabilizing mast cells, and reducing oxidative stress. Additionally, quercetin exhibits immunomodulatory properties by suppressing dendritic cell activity, which plays a crucial role in immune responses. Its cytoprotective effects in the digestive tract further highlight its potential in managing inflammatory bowel diseases. By modulating inflammatory pathways, quercetin helps mitigate tissue damage and supports overall immune health.

Antidiabetic Effects

Diabetes mellitus, particularly type 2 diabetes (T2D), is associated with oxidative stress, insulin resistance, and pancreatic β-cell dysfunction. Quercetin has shown promising antidiabetic effects by improving glucose metabolism and reducing oxidative damage. In diabetic animal models, quercetin administration lowered blood glucose levels, enhanced insulin sensitivity, and protected pancreatic β-cells from oxidative injury. It also inhibited the liver enzyme CYP2E1, (Table 2) which is linked to diabetic liver damage. Furthermore, quercetin reduced obesity-related complications, such as hypercholesterolemia and hyperinsulinemia, in high-fat diet-induced diabetic mice.

When combined with resveratrol, another polyphenol, quercetin synergistically improved lipid and glucose metabolism, further supporting its role in diabetes management. Studies also indicate that quercetin

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

reduces glycosylated hemoglobin (HbA1c) levels and enhances pancreatic function, making it a potential adjunct therapy for diabetes.

Anticancer Properties

Cancer remains one of the leading causes of death worldwide, and natural compounds like quercetin are increasingly being explored for their chemopreventive and therapeutic effects. As a potent antioxidant, quercetin neutralizes free radicals, reduces DNA damage, and inhibits cancer cell proliferation. It has been studied in various cancers, including breast, prostate, lung, and colon cancer, where it induces apoptosis (programmed cell death) and suppresses tumor growth. Quercetin's ability to modulate signaling pathways involved in cancer progression—such as PI3K/AKT, NF-κB, and MAPK—makes it a valuable candidate for combination therapy with conventional chemotherapy drugs.(Table 3) Unlike synthetic drugs, quercetin exhibits minimal toxicity, making it a safer alternative or complementary treatment option. Its widespread availability in dietary sources further enhances its appeal as a preventive measure against cancer.

Neuroprotective Effects in Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-beta (Aβ) plaque accumulation, tau protein hyperphosphorylation, and chronic neuroinflammation. Quercetin has shown neuroprotective effects by inhibiting acetylcholinesterase (AChE), (Table 2) an enzyme that breaks down acetylcholine, a neurotransmitter essential for memory and cognition. By increasing acetylcholine levels, quercetin helps improve cognitive function. Additionally, quercetin reduces oxidative stress and inflammation in the brain, protecting neurons from damage. It also prevents Aβ aggregation and tau protein phosphorylation, two hallmark pathological features of AD. These multifaceted mechanisms suggest that quercetin could be a promising therapeutic agent in slowing Alzheimer's progression and improving brain health.[77]

Hepatoprotective Effects

The liver is vital for detoxification, metabolism, and nutrient processing, making it susceptible to oxidative damage and inflammation. Quercetin exerts hepatoprotective effects by reducing oxidative stress, enhancing antioxidant enzyme activity, and inhibiting liver fibrosis. Studies have shown that quercetin mitigates liver damage induced by toxins, alcohol, and high-fat diets.[78][79]

Its ability to modulate inflammatory cytokines and improve lipid metabolism further supports liver health. By preventing lipid peroxidation and promoting liver cell regeneration, quercetin may help in managing conditions like non-alcoholic fatty liver disease (NAFLD) and hepatitis.

Antiviral Activity Against SARS-CoV-2 (COVID-19)

The COVID-19 pandemic highlighted the need for effective antiviral therapies, and quercetin emerged as a potential candidate due to its broad-spectrum antiviral properties. Research suggests that quercetin inhibits SARS-CoV-2 replication by blocking viral entry into host cells and reducing the activity of key viral enzymes. Additionally, its anti-inflammatory effects help mitigate the cytokine storm—a severe immune overreaction seen in COVID-19 patients.Clinical trials have demonstrated that quercetin supplementation reduces inflammatory markers such as C-reactive protein (CRP), ferritin, and D-dimer in COVID-19 patients. It also accelerates viral clearance, [79][80][81][82] shortening the duration of symptoms. When combined with zinc and vitamins, quercetin enhances immune defense, making it a viable adjunct therapy for respiratory infections.

Conclusion

Quercetin, a naturally occurring flavonoid found abundantly in fruits, vegetables, and medicinal plants, has emerged as a compound of significant pharmacological interest due to its wide-ranging biological activities. Extensive preclinical and clinical studies have demonstrated its therapeutic potential in managing various diseases, including viral infections, metabolic disorders, cancer, neurodegenerative conditions, and liver diseases. Its ability to modulate oxidative stress, inflammation, and immune responses

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

makes it a versatile candidate for both preventive and therapeutic applications.

One of the most compelling areas of research is quercetin's antiviral activity, particularly against SARS-CoV-2, the virus responsible for COVID-19. Quercetin disrupts viral entry by inhibiting key host receptors such as ACE2 and TMPRSS2, which are essential for viral attachment and cell fusion. Additionally, it targets viral replication by interfering with crucial enzymes like 3-chymotrypsin-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp). Beyond direct antiviral effects, quercetin mitigates the hyperinflammatory response seen in severe COVID-19 cases by reducing pro-inflammatory cytokines and oxidative stress markers such as C-reactive protein (CRP), D-dimer, and ferritin. Clinical trials have suggested that quercetin, especially when combined with zinc and vitamin C, accelerates recovery and reduces symptom severity, highlighting its potential as an adjunctive therapy for respiratory infections. Inflammation is a common underlying factor in many chronic diseases, and quercetin's anti-inflammatory and immunomodulatory properties make it particularly valuable. It suppresses key inflammatory pathways, including NF-κB and NLRP3 inflammasome activation, which are central to conditions like arthritis, cardiovascular diseases, and autoimmune disorders. Furthermore, quercetin stabilizes mast cells, preventing excessive histamine release, and modulates dendritic cell activity, promoting a balanced immune response. These mechanisms suggest that quercetin could be beneficial in managing chronic inflammatory conditions, allergies, and immune-mediated diseases. Quercetin also exhibits antidiabetic and metabolic benefits, making it a promising candidate for managing type 2 diabetes (T2D) and obesity-related complications. It enhances insulin sensitivity, protects pancreatic β-cells from oxidative damage, and inhibits enzymes like CYP2E1, which contribute to diabetic liver injury. Animal and human studies have shown that quercetin supplementation reduces fasting blood glucose levels, HbA1c, and lipid peroxidation. When combined with other polyphenols like resveratrol, it demonstrates synergistic effects in improving glucose metabolism and reducing oxidative stress, further supporting its role in metabolic syndrome management.

References

1. Alizadeh, S. R., & Ebrahimzadeh, M. A. (2022). Quercetin derivatives: Drug design, development, and biological activities, a review. *European Journal of Medicinal Chemistry, 229*, 114068. https://doi.org/10.1016/j.ejmech.2021.114068

2. Alizadeh, S. R., & Ebrahimzadeh, M. A. (2022). O-Glycoside quercetin derivatives: Biological activities, mechanisms of action, and structure–activity relationship for drug design, a review. *Phytotherapy Research, 36*(2), 778–807. https://doi.org/10.1002/ptr.7352

3. Amić, A., & Mastiľák Cagardová, D. (2022). DFT study of the direct radical scavenging potency of two natural catecholic compounds. *International Journal of Molecular Sciences, 23*(22), 14497. https://doi.org/10.3390/ijms232214497

4. Buhaș, M. C., Gavrilaș, L. I., Candrea, R., Cătinean, A., Mocan, A., Miere, D., & Tătaru, A. (2022). Gut microbiota in psoriasis. *Nutrients, 14*(14), 2970. https://doi.org/10.3390/nu14142970

5. Carullo, G., Mazzotta, S., Koch, A., Hartmann, K. M., Friedrich, O., Gilbert, D. F., ... & Aiello, F. (2020). New oleoyl hybrids of natural antioxidants: Synthesis and in vitro evaluation as inducers of apoptosis in colorectal cancer cells. *Antioxidants, 9*(11), 1077. https://doi.org/10.3390/antiox9111077

6. Chen, S., Tang, Y., Gao, Y., Nie, K., Wang, H., Su, H., ... & Dong, H. (2022). Antidepressant potential of quercetin and its glycoside derivatives: A comprehensive review and update. *Frontiers in Pharmacology, 13*, 865376. https://doi.org/10.3389/fphar.2022.865376

7. Chen, Y. B., Zhang, Y. B., Wang, Y. L., Kaur, P., Yang, B. G., Zhu, Y., ... & Cui, Y. L. (2022). A novel inhalable quercetin-alginate nanogel as a promising therapy for acute lung injury. *Journal of Nanobiotechnology, 20*(1), 272. https://doi.org/10.1186/s12951-022-01483-w

8. Costa, P. C. T. D., de Souza, E. L., Lacerda, D. C., Cruz Neto, J. P. R., Sales, L. C. S. D., Silva Luis,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1351-1368 | ISSN:2251-6727

C. C., ... & de Brito Alves, J. L. (2022). Evidence for quercetin as a dietary supplement for the treatment of cardio-metabolic diseases in pregnancy: A review in rodent models. *Foods, 11*(18), 2772. https://doi.org/10.3390/foods11182772

9. da Silva, A. P. G. (2021). Fighting coronaviruses with natural polyphenols. *Biocatalysis and Agricultural Biotechnology, 37*, 102179. https://doi.org/10.1016/j.bcab.2021.102179
10. Deepika, & Maurya, P. K. (2022). Health benefits of quercetin in age-related diseases. *Molecules, 27*(8), 2498. https://doi.org/10.3390/molecules27082498
11. Diez-Echave, P., Ruiz-Malagón, A. J., Molina-Tijeras, J. A., Hidalgo-García, L., Vezza, T., Cenis-Cifuentes, L., ... & Lozano-Pérez, A. A. (2021). Silk fibroin nanoparticles enhance quercetin immunomodulatory properties in DSS-induced mouse colitis. *International Journal of Pharmaceutics, 606*, 120935. https://doi.org/10.1016/j.ijpharm.2021.120935
12. Feng, S., Yi, J., Li, X., Wu, X., Zhao, Y., Ma, Y., & Bi, J. (2021). Systematic review of phenolic compounds in apple fruits: Compositions, distribution, absorption, metabolism, and processing stability. *Journal of Agricultural and Food Chemistry, 69*(1), 7–27. https://doi.org/10.1021/acs.jafc.0c05481
13. Gong, Y., Li, J., Li, J., Wang, L., & Fan, L. (2023). In vitro inhibitory effects of polyphenols from Flos sophorae immaturus on α-glucosidase: Action mechanism, isothermal titration calorimetry and molecular docking analysis. *Foods, 12*(4), 715. https://doi.org/10.3390/foods12040715
14. Ha, A. T., Rahmawati, L., You, L., Hossain, M. A., Kim, J. H., & Cho, J. Y. (2021). Anti-inflammatory, antioxidant, moisturizing, and antimelanogenesis effects of quercetin 3-O-β-D-glucuronide in human keratinocytes and melanoma cells via activation of NF-κB and AP-1 pathways. *International Journal of Molecular Sciences, 23*(1), 433. https://doi.org/10.3390/ijms23010433
15. Huang, T., Zhang, K., Wang, J., He, K., Zhou, X., & Nie, S. (2023). Quercetin alleviates acrylamide-induced liver injury by inhibiting autophagy-dependent ferroptosis. *Journal of Agricultural and Food Chemistry, 71*(19), 7427–7439. https://doi.org/10.1021/acs.jafc.3c01725
16. Iglesias-Carres, L., & Neilson, A. P. (2021). Utilizing preclinical models of genetic diversity to improve translation of phytochemical activities from rodents to humans and inform personalized nutrition. *Food & Function, 12*(22), 11077–11105. https://doi.org/10.1039/D1FO02112A
17. Jin, T., Zhang, Y., Botchway, B. O., Huang, M., Lu, Q., & Liu, X. (2023). Quercetin activates the Sestrin2/AMPK/SIRT1 axis to improve amyotrophic lateral sclerosis. *Biomedicine & Pharmacotherapy, 161*, 114515. https://doi.org/10.1016/j.biopha.2023.114515
18. Kandemir, K., Tomas, M., McClements, D. J., & Capanoglu, E. (2022). Recent advances on the improvement of quercetin bioavailability. *Trends in Food Science & Technology, 119*, 192–200. https://doi.org/10.1016/j.tifs.2021.12.004
19. Kang, Q., Sun, J., Wang, B., & Sun, B. (2023). Wine, beer and Chinese baijiu in relation to cardiovascular health: The impact of moderate drinking. *Food Science and Human Wellness, 12*(1), 1–13. https://doi.org/10.1016/j.fshw.2022.07.001
20. Lyu, M., Wang, Y., Chen, Q., Qin, J., Hou, D., Huang, S., ... & Cui, H. (2022). Molecular mechanism underlying effects of wumeiwan on steroid-dependent asthma: A network pharmacology, molecular docking, and experimental verification study. *Drug Design, Development and Therapy, 16*, 909–929. https://doi.org/10.2147/DDDT.S347397
21. Mahmoud, N. N., Qabooq, H., Alsotari, S., Tarawneh, O. A., Aboalhaija, N. H., Shraim, S., ... & Abu-Dahab, R. (2021). Quercetin-gold

nanorods incorporated into nanofibers: Development, optimization and cytotoxicity. *RSC Advances, 11*(33), 19956–19966. https://doi.org/10.1039/D1RA02842G

22. Mohd Zaid, N. A., Sekar, M., Bonam, S. R., Gan, S. H., Lum, P. T., Begum, M. Y., ... & Fuloria, S. (2022). Promising natural products in new drug design, development, and therapy for skin disorders: An overview of scientific evidence and understanding their mechanism of action. *Drug Design, Development and Therapy, 16*, 23–66. https://doi.org/10.2147/DDDT.S356767

23. Moon, H., Lertpatipanpong, P., Hong, Y., Kim, C. T., & Baek, S. J. (2021). Nano-encapsulated quercetin by soluble soybean polysaccharide/chitosan enhances anti-cancer, anti-inflammation, and anti-oxidant activities. *Journal of Functional Foods, 87*, 104756. https://doi.org/10.1016/j.jff.2021.104756

24. Prabhu, S., Vijayakumar, S., Ramasubbu, R., Praseetha, P. K., Karthikeyan, K., Thiyagarajan, G., ... & Prakash, N. (2021). Traditional uses, phytochemistry and pharmacology of Bauhinia racemosa Lam.: A comprehensive review. *Future Journal of Pharmaceutical Sciences, 7*(1), 1–18. https://doi.org/10.1186/s43094-021-00210-w

25. Sanlier, N., Kocabas, Ş., Erdogan, K., & Sanlier, N. T. (2022). Effects of curcumin, its analogues, and metabolites on various cancers: Focusing on potential mechanisms. *Food Reviews International, 38*(sup1), 1–21. https://doi.org/10.1080/87559129.2022.2029476

26. Shabir, I., Kumar Pandey, V., Shams, R., Dar, A. H., Dash, K. K., Khan, S. A., ... & Pandiselvam, R. (2022). Promising bioactive properties of quercetin for potential food applications and health benefits: A review. *Frontiers in Nutrition, 9*, 999752. https://doi.org/10.3389/fnut.2022.999752

27. Shastrala, K., Kalam, S., Damerakonda, K., Sheshagiri, S. B. B., Kumar, H., Guda, R., ... & Bedada, S. K. (2021). Synthesis, characterization, and pharmacological evaluation of some metal complexes of quercetin as P-gp inhibitors. *Future Journal of Pharmaceutical Sciences, 7*(1), 99. https://doi.org/10.1186/s43094-021-00235-1

28. Shatylo, V., Antoniuk-Shcheglova, I., Naskalova, S., Bondarenko, O., Havalko, A., Krasnienkov, D., ... & Vaiserman, A. (2021). Cardio-metabolic benefits of quercetin in elderly patients with metabolic syndrome. *PharmaNutrition, 15*, 100250. https://doi.org/10.1016/j.phanu.2020.100250

29. Shorobi, F. M., Nisa, F. Y., Saha, S., Chowdhury, M. A. H., Srisuphanunt, M., Hossain, K. H., & Rahman, M. A. (2023). Quercetin: A functional food-flavonoid incredibly attenuates emerging and re-emerging viral infections through immunomodulatory actions. *Molecules, 28*(3), 938. https://doi.org/10.3390/molecules28030938

30. Sinyani, A., Idowu, K., Shunmugam, L., Kumalo, H. M., & Khan, R. (2023). A molecular dynamics perspective into estrogen receptor inhibition by selective flavonoids as alternative therapeutic options. *Journal of Biomolecular Structure and Dynamics, 41*(9), 4093–4105. https://doi.org/10.1080/07391102.2022.2064335

31. Sofiullah, S. S. M., Murugan, D. D., Muid, S. A., Seng, W. Y., Kadir, S. Z. S. A., Abas, R., ... & Woon, C. K. (2023). Natural bioactive compounds targeting NADPH oxidase pathway in cardiovascular diseases. *Molecules, 28*(3), 1047. https://doi.org/10.3390/molecules28031047

32. Stepanić, V., & Kučerová-Chlupáčová, M. (2023). Review and chemoinformatic analysis of ferroptosis modulators with a focus on natural plant products. *Molecules, 28*(2), 475. https://doi.org/10.3390/molecules28020475

33. Uyanga, V. A., Amevor, F. K., Liu, M., Cui, Z., Zhao, X., & Lin, H. (2021). Potential implications of citrulline and quercetin on gut functioning of monogastric animals and humans: A comprehensive review. *Nutrients, 13*(11), 3782. https://doi.org/10.3390/nu13113782

34. Vishwas, S., Gulati, M., Kapoor, B., Gupta, S., Singh, S. K., Awasthi, A., ... & Kumar, V. (2021). Expanding the arsenal against Huntington's

disease—Herbal drugs and their nanoformulations. *Current Neuropharmacology, 19*(7), 957–989. https://doi.org/10.2174/1570159X18666201109090824

35. Wang, G., Wang, Y., Yao, L., Gu, W., Zhao, S., Shen, Z., ... & Yan, T. (2022). Pharmacological activity of quercetin: An updated review. *Evidence-Based Complementary and Alternative Medicine, 2022*, 1–20. https://doi.org/10.1155/2022/3997190

36. Wang, M., Chen, X., Yu, F., Zhang, L., Zhang, Y., & Chang, W. (2022). The targeting of noncoding RNAs by quercetin in cancer prevention and therapy. *Oxidative Medicine and Cellular Longevity, 2022*, 1–18. https://doi.org/10.1155/2022/4330681

37. Wani, T. A., Alanazi, M. M., Alsaif, N. A., Bakheit, A. H., Zargar, S., Alsalami, O. M., & Khan, A. A. (2022). Interaction characterization of a tyrosine kinase inhibitor erlotinib with a model transport protein in the presence of quercetin: A drug–protein and drug–drug interaction investigation using multi-spectroscopic and computational approaches. *Molecules, 27*(4), 1265. https://doi.org/10.3390/molecules27041265

38. Yi, H., Peng, H., Wu, X., Xu, X., Kuang, T., Zhang, J., ... & Fan, G. (2021). The therapeutic effects and mechanisms of quercetin on metabolic diseases: Pharmacological data and clinical evidence. *Oxidative Medicine and Cellular Longevity, 2021*, 1–20. https://doi.org/10.1155/2021/6678662

39. Yu, F., Goh, Y. T., Li, H., Chakrapani, N. B., Ni, M., Xu, G. L., ... & Yu, H. (2020). A vascular-liver chip for sensitive detection of nutraceutical metabolites from human pluripotent stem cell derivatives. *Biomicrofluidics, 14*(3), 034107. https://doi.org/10.1063/5.0012185

40. Yu, J., Hu, G., Cao, H., & Guo, X. (2022). Quercetin ameliorates lipopolysaccharide-induced duodenal inflammation through modulating autophagy, programmed cell death and intestinal mucosal barrier function in chicken embryos. *Animals, 12*(24), 3524. https://doi.org/10.3390/ani12243524

41. Zang, X., Cheng, M., Zhang, X., & Chen, X. (2021). Quercetin nanoformulations: A promising strategy for tumor therapy. *Food & Function, 12*(15), 6664–6681. https://doi.org/10.1039/D1FO01152E

42. Zhou, Y., Suo, W., Zhang, X., Lv, J., Liu, Z., & Liu, R. (2022). Roles and mechanisms of quercetin on cardiac arrhythmia: A review. *Biomedicine & Pharmacotherapy, 153*, 113447. https://doi.org/10.1016/j.biopha.2022.113447

43. Hoffmann, M., Kleine-Weber, H., Schroeder, S., et al. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, *181*(2), 271-280. https://doi.org/10.1016/j.cell.2020.02.052

44. Zhou, F., Yu, T., Du, R., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *The Lancet*, *395*(10229), 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3

45. Harvey, W. T., Carabelli, A. M., Jackson, B., et al. (2021). SARS-CoV-2 variants, spike mutations and immune escape. *Nature Reviews Microbiology*, *19*(7), 409-424. https://doi.org/10.1038/s41579-021-00573-0

46. Javed, Z., Sadia, H., Iqbal, M. J., et al. (2021). Rutin: A potential antiviral for repurposing as a SARS-CoV-2 main protease (Mpro) inhibitor. *Natural Product Communications*, *16*(4), 1934578X21991723.

47. Derosa, G., Maffioli, P., D'Angelo, A., & Di Pierro, F. (2021). A role for quercetin in coronavirus disease 2019 (COVID-19). *Phytotherapy Research*, *35*(3), 1230-1236. https://doi.org/10.1002/ptr.6887

48. Silveira, D., Prieto-Garcia, J. M., Boylan, F., et al. (2020). COVID-19: Is there evidence for the use of herbal medicines as adjuvant symptomatic

therapy? *Frontiers in Pharmacology*, *11*, 1479. https://doi.org/10.3389/fphar.2020.581840

49. Paniri, A., Hosseini, M. M., & Akhavan-Niaki, H. (2021). Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19: Role of lncRNAs in cytokine storm modulation. *Life Sciences*, *267*, 118923. https://doi.org/10.1016/j.lfs.2020.118923

50. Li, Y., Yao, J., Han, C., et al. (2016). Quercetin, inflammation and immunity. *Nutrients*, *8*(3), 167. https://doi.org/10.3390/nu8030167

51. Rojas, A., Del Campo, J. A., Clement, S., et al. (2021). Effect of quercetin on hepatitis C virus life cycle: From viral to host targets. *Scientific Reports*, *11*(1), 1-13. https://doi.org/10.1038/s41598-021-81759-7

52. Colunga Biancatelli, R. M. L., Berrill, M., Catravas, J. D., & Marik, P. E. (2020). Quercetin and vitamin C: An experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). *Frontiers in Immunology*, *11*, 1451. https://doi.org/10.3389/fimmu.2020.01451

53. Dabeek, W. M., & Marra, M. V. (2019). Dietary quercetin and kaempferol: Bioavailability and potential cardiovascular-related bioactivity in humans. *Nutrients*, *11*(10), 2288. https://doi.org/10.3390/nu11102288

54. Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition*, *79*(5), 727-747. https://doi.org/10.1093/ajcn/79.5.727

55. Lombard, K. A., Geoffriau, E., & Peffley, E. (2005). Flavonoid quantification in onion by spectrophotometric and HPLC analyses. *HortScience*, *40*(3), 534-537. https://doi.org/10.21273/HORTSCI.40.3.534

56. Pinto, J. T., & Rivlin, R. S. (2017). Antiproliferative effects of allium derivatives from garlic. *Journal of Nutrition*, *131*(3), 1058S-1060S. https://doi.org/10.1093/jn/131.3.1058S

57. Hertog, M. G., Hollman, P. C., & Katan, M. B. (1993). Content of potentially anticarcinogenic flavonoids of tea infusions, wines, and fruit juices. *Journal of Agricultural and Food Chemistry*, *41*(8), 1242-1246. https://doi.org/10.1021/jf00032a015

58. Mitchell, A. E., Hong, Y. J., Koh, E., et al. (2007). Ten-year comparison of the influence of organic and conventional crop management practices on the content of flavonoids in tomatoes. *Journal of Agricultural and Food Chemistry*, *55*(15), 6154-6159. https://doi.org/10.1021/jf070344+

59. Boots, A. W., Haenen, G. R., & Bast, A. (2008). Health effects of quercetin: From antioxidant to nutraceutical. *European Journal of Pharmacology*, *585*(2-3), 325-337. https://doi.org/10.1016/j.ejphar.2008.03.008

60. Ryu, Y. B., Jeong, H. J., Kim, J. H., et al. (2010). Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. *Bioorganic & Medicinal Chemistry*, *18*(22), 7940-7947. https://doi.org/10.1016/j.bmc.2010.09.035

61. Day, A. J., Canada, F. J., Diaz, J. C., et al. (2000). Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Letters*, *468*(2-3), 166-170. https://doi.org/10.1016/S0014-5793(00)01211-4

62. Graefe, E. U., Wittig, J., Mueller, S., et al. (2001). Pharmacokinetics and bioavailability of quercetin glycosides in humans. *The Journal of Clinical Pharmacology*, *41*(5), 492-499. https://doi.org/10.1177/00912700122010366

63. Nemeth, K., Plumb, G. W., Berrin, J. G., et al. (2003). Deglycosylation by small intestinal epithelial cell β-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans. *European Journal of Nutrition*, *42*(1), 29-42. https://doi.org/10.1007/s00394-003-0397-3

64. Hollman, P. C., van Trijp, J. M., Buysman, M. N., et al. (1997). Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. *FEBS Letters*, *418*(1-2), 152-

156. https://doi.org/10.1016/S0014-5793(97)01367-7

65. Moon, Y. J., Wang, X., & Morris, M. E. (2006). Dietary flavonoids: Effects on xenobiotic and carcinogen metabolism. *Toxicology in Vitro*, *20*(2), 187-210. https://doi.org/10.1016/j.tiv.2005.06.048

66. Kawai, Y., Nishikawa, T., Shiba, Y., et al. (2008). Macrophage as a target of quercetin glucuronides in human atherosclerotic arteries: Implication in the anti-atherosclerotic mechanism of dietary flavonoids. *Journal of Biological Chemistry*, *283*(14), 9424-9434. https://doi.org/10.1074/jbc.M706571200

67. Walle, T., Vincent, T. S., & Walle, U. K. (2003). Evidence of covalent binding of the dietary flavonoid quercetin to DNA and protein in human intestinal and hepatic cells. *Biochemical Pharmacology*, *65*(10), 1603-1610. https://doi.org/10.1016/S0006-2952(03)00151-5

68. Aura, A. M., Martin-Lopez, P., O'Leary, K. A., et al. (2005). In vitro metabolism of anthocyanins by human gut microflora. *European Journal of Nutrition*, *44*(3), 133-142. https://doi.org/10.1007/s00394-004-0502-2

69. Kumar, P., Sharma, G., Kumar, R., et al. (2016). Promises of a biocompatible nanocarrier in improved brain delivery of quercetin: Biochemical, pharmacokinetic and biodistribution evidences. *International Journal of Pharmaceutics*, *515*(1-2), 307-314. https://doi.org/10.1016/j.ijpharm.2016.10.024

70. Pool, H., Quintanar, D., de Dios Figueroa, J., et al. (2012). Antioxidant effects of quercetin and catechin encapsulated into PLGA nanoparticles. *Journal of Nanomaterials*, *2012*, 1-12. https://doi.org/10.1155/2012/145380

71. Shoba, G., Joy, D., Joseph, T., et al. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Medica*, *64*(4), 353-356. https://doi.org/10.1055/s-2006-957450

72. Liao, W., Ning, Z., Chen, L., et al. (2020). Intracellular antioxidant detoxifying effects of diosmetin on 2,2-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced oxidative stress through inhibition of reactive oxygen species generation. *Journal of Agricultural and Food Chemistry*, *68*(8), 2286-2296. https://doi.org/10.1021/acs.jafc.9b02624

73. Wu, L. Y., Zheng, Z. Q., Qian, C., et al. (2015). A novel quercetin derivative with potent antioxidant activity: 8-(3″,4″-dihydroxyphenyl)-3,4-dihydro-2H,5H-pyrano[3,2-g]chromene-3,5,7(8H)-trione. *Bioorganic & Medicinal Chemistry Letters*, *25*(2), 196-198. https://doi.org/10.1016/j.bmcl.2014.11.073

74. Semalty, A., Semalty, M., Rawat, M. S., & Franceschi, F. (2010). Supramolecular phospholipids-polyphenolics interactions: The PHYTOSOME® strategy to improve the bioavailability of phytochemicals. *Fitoterapia*, *81*(5), 306-314. https://doi.org/10.1016/j.fitote.2009.11.001

75. D'Andrea, G. (2015). Quercetin: A flavonol with multifaceted therapeutic applications? *Fitoterapia*, *106*, 256-271. https://doi.org/10.1016/j.fitote.2015.09.018

76. Zhuang, Z., Zhong, J., Bian, Y., et al. (2022). A research update on the potential effects of flavonoids on the SARS-CoV-2 infection. *Phytotherapy Research*, *36*(1), 119-129. https://doi.org/10.1002/ptr.7289

77. Pandey, P., Rane, J. S., Chatterjee, A., et al. (2021). Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: An in silico study for drug development. *Journal of Biomolecular Structure and Dynamics*, *39*(17), 6306-6316. https://doi.org/10.1080/07391102.2020.1796811

78. Ohashi, H., Watashi, K., Saso, W., et al. (2021). Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment. *iScience*, *24*(4), 102367. https://doi.org/10.1016/j.isci.2021.102367

79. Liu, H., Ye, F., Sun, Q., et al. (2022). Scutellaria baicalensis extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease in vitro. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *36*(1), 497-503. https://doi.org/10.1080/14756366.2021.1873977

80. Jo, S., Kim, S., Shin, D. H., & Kim, M. S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *35*(1), 145-151. https://doi.org/10.1080/14756366.2019.1690480

81. Su, H. X., Yao, S., Zhao, W. F., et al. (2020). Anti-SARS-CoV-2 activities in vitro of Shuanghuanglian preparations and bioactive ingredients. *Acta Pharmacologica Sinica*, *41*(9), 1167-1177. https://doi.org/10.1038/s41401-020-0483-6

82. Khan, M. B., Khan, S. A., Khan, A. K., et al. (2022). A computational and bioinformatic analysis of ACE2: An elucidation of its dual role in COVID-19 pathology and finding its associated partners as potential therapeutic targets. *Journal of Biomolecular Structure and Dynamics*, *40*(4), 1813-1829. https://doi.org/10.1080/07391102.2020.1833760