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Focus on the high therapeutic potentials of quercetin and its derivatives

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ABSTRACT

Background: Polyphenols and particularly flavonoids are of constant interest to the scientific community. Flavonoids are investigated for their biological and pharmacological purposes, notably as antioxidant, anticancer, antiviral and for their anti-inflammatory activities. Certainly, one of the best-known flavonols recognized for its therapeutic and preventive properties is quercetin. Despite its biological interest, quercetin suffer from some drawbacks, mainly related to its bioavailability. Hence, its synthetic or biosynthetic derivatives have been the subject of intensive research. The health-promoting biological activities of flavonols and derivatives mainly arise from their capacity to disrupt the host-pathogen interactions and/or to regulate host cellular functions including oxidative processes and immunological responses. In the age of coronavirus pandemic, the anti-inflammatory and antiviral potential of flavonols should be put forward to explore these substances for decreasing the viral load and inflammatory storm caused by the infection.

Purpose of study: The present review will decipher and discuss the antioxidant, anti-inflammatory and antiviral capacities of major flavonol with a focus on the molecular basis and structure-activity relationships.

Study design: Current study used a combination of quercetin derivatives, pathway, antioxidant, anti-inflammatory, antiviral activities as keywords to retrieve the literature. This study critically reviewed the current literature and presented the ability of natural analogs of quercetin having superior antioxidant, anti-inflammatory and antiviral effects than the original molecule.

Results: This review allowed the identification of relevant key structure-activity relationship elements and highlight approaches on the mechanisms governing the antioxidant, antiviral and anti-inflammatory activities.

Conclusion: Through a critical analysis of the literature, flavonols and more precisely quercetin derivatives reviewed and found to act simultaneously on inflammation, virus and oxidative stress, three key factors that may lead to life threatening diseases.

1. Introduction

Polyphenols, commonly denoted as phenolic compounds, from plants are intensively studied over the past 30 years. Polyphenols are micro-constituents of plants and are provided in the diet by fruits, vegetables and derived beverages. Their consumption is estimated at around 1 g/day (Scalbert and Williamson, 2000) among average individuals. Intensive efforts are continuously devoted to provide epidemiological and/or experimental evidence of the protective effects of consuming polyphenol-rich foods against major pathologies such as cardiovascular diseases, cancer, diabetes, obesity, viral infections and neurological disorders. The wide range of biological activities and the potential health benefits of polyphenols have sparked growing attention from health professionals, food manufacturers and consumers. In this context, research on natural polyphenols and their synthetic analogues is a promising way to discover new efficient drugs (Breinbauer et al., 2002; Bulger et al., 2008).

According to their structure (number of phenolic nuclei, number and location of functions), polyphenols can be classified into 5 families: phenolic acids, flavonoids, lignans, stilbenes and curcuminoids. Flavonoids occurring in medicinal and aromatic plants, fruits and vegetables...
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Abbreviations

ACII adjuvant-carrageenan-induced inflammation
ACR acrylamide
ADV adenoviruses
ALI acute lung injury
AP-1 activator protein-1
ATP adenosine triphosphate
AVO acid vesicular organelles
BH-21 baby hamster kidney
BMDM Bone marrow-derived macrophages
CAT catalase
CCL-4 carbon tetrachloride
CDV canine distemper virus
CHIKV chikungunya virus
CHL chang liver
CRFK crandell-reese feline kidney
CRP C-reactive protein
DENV-2 dengue 2 virus
DNA Deoxyribonucleic acid
DNMT DNA methyltransferase
DPP-IV dipeptidyl peptidase-IV
EHV-1 equid herpesvirus 1
EMIQ enzymatically modified isoquercetin
EV-A71 enterovirus A71
FCV feline calicivirus
FDA food and drug administration
FLUAV influenza A virus
FRET fluorescence resonance energy transfer
GAE gallic acid equivalent
GES-1 gastric epithelial
GPX glutathione peroxidase
GR glutathione reductase
GSH glutathione
GSSG glutathione disulfide
GTP guanosine triphosphate
HAEcs human aortic endothelial cells
HBE human bronchial epithelial
HBV hepatitis B virus
HCMV human cytomegalovirus
HCV hepatitis C virus
HEL human embryonic lung
HepG2.2.15 human hepatoblastoma
HIV human immunodeficiency virus
HO-1 heme oxygenase-1
hRSV human Respiratory Syncytial Virus
HSV herpes simplex viruses
IARC international agency for research on cancer
IL-6 interleukin-6
IFN-α interferon-alpha
IFN-γ interferon-gamma
iNOS inducible nitric oxide synthase
IRF-1 interferon regulatory factor 1
JEV Japanese encephalitis virus
JNK c-Jun N-terminal kinase
LPS lipopolysaccharides
MAPK mitogen-activated protein kinases
MAYV mayaro virus
CCL-2 monocyte chemotactic protein-1
MDA malondialdehyde
MDCK madin-darby canine kidney
MHV mouse hepatitis virus
MNoV murine noroviruses
MPTP 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydroido-pyridine
MS multiple sclerosis
NF-κB nuclear kappa factor B
NO nitric oxide
Nrf2 NF-E2 bound factor 2
NSAIDs non-steroidal anti-inflammatory drugs
OBX olfactory bulbectomy
OH hydroxyl
PBMC peripheral blood mononuclear cells
PEDV porcine epidemic diarrhea virus
PGC-1α peroxisome proliferator-activated receptor gamma
coactivator 1-α
PQ paraquat
Q3G quercetin-3-glucoside
Q7R quercetin 7- rhamnoside
ROS reactive oxygen species
SIRT Sirtuin
SOD superoxide dismutase
STAT1 transcription signal activator 1
t-BHP tert-butyl hydroperoxide
TNF-α tumor necrosis factor-α
ZIKV zika virus

Quercetin is a flavonoid belonging to the flavonol subfamily, and it is one of the most studied polyphenols because of its numerous biological activities. It is also the most abundant flavonoid in nature. Quercetin is an ingredient in antioxidant and anti-allergic drugs that have been approved by the U.S. Food and Drug Administration (FDA; National Drug Code numbers are 65,448–3085, 65,448–3005) (Yi et al., 2004). Due to its potential benefits for human health, quercetin has become a nutraceutical ingredient of great interest in the food and pharmaceutical industries. Quercetin is known to have many pharmacological properties, including anti-inflammatory, antiviral, antineoplastic, cardio-protective, antitumor, antioxidant, anti-obesity and antibacterial activities (Salehi et al., 2020). In the context of the COVID-19 pandemic, quercetin has shown strong activity which could provide an interesting prospect for a quercetin-based treatment (Khazeei Tabari et al., 2021). Nevertheless, the pharmacological activity of quercetin is tightly linked to its bioavailability. In food, quercetin is generally present as quercetin glycoside where the quercetin aglycone is conjugated to sugar moieties such as glucose or rutinose. The conjugates being much more water-soluble explains why quercetin bioavailability is greater when it is consumed as an integral food component rather than quercetin alone. Greater bioavailability of quercetin conjugates results in higher physiological and pharmacological activity. Solubility can be impacted by glycosides and also by components of the food matrix (ethanol, fats and emulsifiers). (Hussain et al., 2012). Ingested, quercetin is rapidly metabolized and eliminated in the stool and urine. Most metabolites of quercetin have been identified, including quercetin-3-glucuronide, quercetin-3-sulfate and isorhamnetin-3-glucuronide (Patel et al., 2018). Application of quercetin in clinical studies is limited, mostly due to its poor water-solubility, chemical instability and short biological half-life, which may reduce its efficacy when used in food and pharmaceuticals (Cai et al., 2013; Khursheed et al., 2020). To overcome these...
hurdles, quercetin derivatives have been applied through various routes of administration (Khursheed et al., 2020).

Economically, quercetin and its derivatives market size has been increasing in recent years and it is expected that it will grow significantly over the period 2021–2028. Kaempferol, a quercetin derivative, would see its global market exceed 6.5 billion USD by 2025, representing an increase of 3.7% (“Kaempferol Market Share Analysis 2019–2025 | Growth Projections,” 2000, n.d.). There is an increase in research activities and approvals for utilization of these flavonoids in the tablets manufacturing and so is expected to propel the growth of quercetin and its derivatives market for years to come.

The aim of this review is to discuss the biological activities of quercetin and its derivatives, with a special focus on antioxidant, anti-inflammatory and antiviral activities. Whenever is possible, the mechanisms of action were discussed.

2. Sources of quercetin and derivatives

Quercetin is found in fruits and vegetables especially onions, peppers, cranberries, capers, tomatoes, lettuce, asparagus, broccoli, coriander, blueberries, apples, cherries, grapes, nuts, seeds, bark, black tea, wine and various fruit juices (USDA, 2018). Table 1 where they occur as aglycone, bound with glycosides and/or alcohols (Ander, 2015; Erlund, 2004). Quercetin derivatives are also found in food, beverages, grains, Spices, Herbs & shrubs. The bioavailability of quercetin, its derivatives and its chemical structure is composed of five hydroxyl groups at 3,5,7,3′ and 4′ position of the basic skeleton (Fig. 1).

Table 1

| Food                  | Source            | Quercetin contents (mg/100 g) | Food                  | Source            | Quercetin contents (mg/100 g) |
|-----------------------|-------------------|------------------------------|-----------------------|-------------------|------------------------------|
| Vegetables            |                   |                              | Fruits               |                   |                              |
| Arugula, raw          | 8.0               | Fruits                       | Acerola               | 4.7               |
| Asparagus, raw        | 14.0              |                              | Apricots, raw        | 1.6               |
| Bay leaves, fresh     | 3.2               |                              | Bayberries, raw      | 4.4               |
| Beans, snap, green, raw | 2.7            |                              | Bilberry, raw        | 3.0               |
| Broccoli, raw         | 3.3               |                              | Blackberries, raw    | 3.6               |
| Cabbage, chinese (pak-choi), raw | 2.1 |                              |                      |                   |
| Chard, swiss, red leaf, raw | 7.5 |                          | Blueberries, frozen  | 4.6               |
| Chicory greens, raw   | 6.5               |                              | Blueberries, raw     | 14.4              |
| Chives, raw           | 4.8               |                              | Cherries, raw        | 2.3               |
| Collards, raw         | 2.6               |                              | Chokeberry, raw      | 18.5              |
| Coriander leaves, raw | 53.0              |                              | Cranberries, raw     | 16.6              |
| Cowpeas, immature seeds, raw | 5.5 |                          | Crowberries, raw     | 5.5               |
| Fennel, leaves, raw   | 48.8              |                              | Crowberries, raw     | 5.5               |
| Garlic, raw           | 1.7               |                              | Goji berry           | 13.6              |
| Hartwort, leaves      | 29.3              |                              | Grapes, white or green, raw | 1.1   |
| Haworth leaves, raw   | 241.0             |                              | Guava, white-fleshed | 1.2               |
| Kale, raw             | 22.6              |                              | Jabuticaba, raw      | 1.1               |
| Lettuce, green leaf, raw | 4.2           |                          | Jujube, raw          | 1.3               |
| Lovage, leaves, raw   | 170.0             |                              | Juniper berries, ripe | 46.6             |
| Mustard greens, raw   | 8.8               |                              | Lemons, raw, without peel | 1.1   |
| Okra, raw             | 21.0              |                              | Lingonberries (cowberries), raw | 13.3 |
| Onions, raw           | 20.3              |                              | Mulberries, raw      | 2.5               |
| Onions, red, raw      | 39.2              |                              | Pitanga, raw         | 5.8               |
| Peppers, ancho        | 27.6              |                              | Plums, raw           | 0.9               |
| Radicchio, raw        | 31.5              |                              | Rowanberries, raw    | 7.4               |
| Radish leaves, raw    | 70.4              |                              | Strawberries, raw    | 1.1               |
| Rocket, wild, raw     | 66.2              |                              | Cocoa mix, powder    | 2.0               |
| Spinach, raw          | 4.0               | Tomatoes, cherry, raw        | 2.8                   | Beverages          |                              |
| Taro, raw             | 2.9               | Turmeric, steamed            | 4.9                   | Tea, black, brewed  | 2.2                           |
| Watercress, raw       | 30.0              | Turmeric, steamed            | 4.9                   | Tea, green, brewed, decaffeinated | 2.8 |
| Spices, Herbs & shrubs |                  |                              |                       |                   |
| Canned capers         | 172.6             | Beverages                    | Tea, oolong, brewed  | 1.3               |
| Oregano, fresh        | 7.3               |                              | Buckwheat            | 15.4              |
| Tarragon, fresh       | 10.0              | Nuts, Seeds and Cereal grains |                      | Chia seeds, raw    | 18.4                          |

3. Generality on quercetin and derivatives

Quercetin [2-(3,4-dihydroxyphenyl)−3, 5,7-trihydroxy-4Hchromen-4-one] belongs to the flavonoid family and the subfamily flavonols. Its chemical structure is composed of five hydroxyl groups at 3,5,7,3′ and 4′ position of the basic skeleton (Fig. 1).

3.1. Toxicity and bioavailability of quercetin

Quercetin is not classified in the list of carcinogenic compounds for humans according to the International Agency for Research on Cancer (IARC) (Okamoto, 2005; Utesch et al., 2008). Experiments with descendents of mice lacking deoxyribonucleic acid (DNA) repair mechanisms show that quercetin increases the prevalence of malignant tumors (Vanhees et al., 2011). Administration of quercetin for several months at a concentration above 1000 mg/day did not show side effects on serum electrolytes, blood parameters of renal and hepatic functions or hematology. Hence, no evidence of toxicity was found, however long-term safety data at high doses of quercetin are lacking (Wang et al., 2004). The co-administration of quercetin and some drugs with a narrow therapeutic index like digoxin should be restricted (Harwood et al., 2007). First pass effect in the intestine and liver metabolizes the majority of food quercetin which reduces the potential toxicity.

Several factors affect the bioavailability of quercetin. The main factor is due to its poor water solubility. Despite the presence of five polar hydroxyl groups, quercetin is lipophilic. Moreover, it has been reported that poor bioavailability of quercetin is linked to its propensity, to be refluxed back into the intestinal tractus following enteroocyte uptake
plasma vitamin C may contribute to quercetin intersubjective bioavailability (Bruno, 2015). Some studies have suggested that the differences in gender and age influence on the bioavailability (Guo and Guo, 2014).

### 3.2. Activities of quercetin derivatives

Quercetin derivatives in plants occur frequently in their glycosidic forms. Indeed, most quercetin derivatives bear oses mainly at the 3-OH position. Among these oses, glucose (isoquercitrin), galactose (quercetin 3-O-galactoside), rhamnosyl (quercetin 3-O-rhamnoside), rutinoside (rutin) and arabinofuranose (avicularin) are frequently found. Some derivatives can have polyoses as isoquercetrin which has up to 10 glucose moieties can be found fully or partially acylated.

Quercetin derivatives where the phenol groups are methylated are called quercetin-3-rhamnoglucoside or rutin. The latter shows antiviral activity against herpes simplex virus (HSV), dengue 2 virus (DENV-2) and human immunodeficiency virus (HIV), among others (Tao et al., 2007; Zandi et al., 2011a). It is known to exert various protective activities such as antioxidant, anti-inflammatory, cardioprotective and anti-tumor activities (Gullon et al., 2017). Quercetin 3-O-rhamnoside (quercitin) is known for its antioxidant, anti-inflammatory, anticancer and anti-tumor activities (Gullon et al., 2017). Quercetin 3-O-glucoside (isoquercitrin) exerts antioxidant, anti-inflammatory, antihypertensive activities, cytoprotection, inhibiting melanogenesis and Ca++-induced lipid peroxidation inhibitory activities (Cincin et al., 2014; Uppugundula et al., 2009). Quercetin-3-O-glucoside (isouqueritrin) exerts antioxidant, anti-inflammatory, antihypertensive activities, cytoprotection, inhibiting melanogenesis and Ca++-induced lipid peroxidation (Gonzales et al., 2015; Kwon et al., 2010; Ohguchi et al., 2010; Valentova et al., 2014). Quercetin 3-O-galactoside (hyperoside) presents antioxidant, antimicrobial and anti-inflammatory activities, as well as preventing hypertension and cardiovascular diseases (Khanavi et al., 2013; Li et al., 2013; Ola et al., 2009). Isoquahematin protects against hypertension, induces antioxidant, anti-tumor and cardioprotective activities (Ibarra et al., 2003; Zhao et al., 2015).

### 4. Molecular mechanisms of the antioxidant activity

The formation of reactive oxygen species (ROS) has been reported to contribute to diabetes, atherosclerosis, hypertension, ischemic heart disease and heart failure (Moris et al., 2017). Quercetin acts as an antioxidant by preventing oxidative stress throughs ability to scavenge free radicals and bind transition metal ions (de Souza and De Giovanni, 2004). The antioxidant activity of quercetin and its derivatives are summarized in Table 3 and schematized in Fig. 2. The major structural consideration for the antioxidant activity of flavonoids is the hydroxylation pattern of the B-ring (Fig. 1), which confers higher stability to the radical form and participates in electron delocalization (Rice-évans et al., 1995). The other property that confers radical scavenging activity to flavonoids is the C2-C3 double bond in conjugation with the 4-oxo function in the C-ring, responsible for electron delocalization from the B-ring. Moreover, the 3- and 5-hydroxyl groups together with the 4-oxo...

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**Table 2**

| Derivatives             | Food source | Contents (mg/100 g) | Reference |
|------------------------|-------------|---------------------|-----------|
| Quercetin 3-O-galactoside | Mango       | 7.6-147.0           | Berardini et al., 2005 |
|                        | Plums       | – 3.5               | Kim et al., 2003 |
|                        | Blueberry   | 14.6                | Zheng and Wang, 2003 |
|                        | Cranberry   | 9.7                 |           |
|                        | Chokeberry  | 41.5                |           |
|                        | Ligonberry  | 11.7                |           |
| Quercetin 3-O-glucoside | Mango       | 7.7-104.5           | Berardini et al., 2005 |
|                        | Beans       | 10.0-69.0           | Chang and Wong, 2004 |
|                        | Plums       | 0.2-2.2             | Kim et al., 2003 |
|                        | Onions      | 0.9-3.7             | Nemeth and Piskula, 2007 |
| Quercetin 3-O-xylloside | Mango       | 1.1-27.8            | Berardini et al., 2005 |
| Quercetin 3-O-rutinoside | Mango     | 7.6                 |           |
|                        | Cherries    | 2.8-7.7             | Kim et al., 2003 |
|                        | Chokeberry  | 1.8-13.7            | Gonzalves et al., 2004 |
|                        | Tomatoes    | 0.3-0.9             | Slimestad et al., 2005 |
|                        | Buckwheat  –leave | 21.70-34.30 × 10³ | Vollmannová et al., 2021 |
|                        | Buckwheat  –grains   | 1.29-6.29 × 10³    | Vollmannová et al., 2021 |
|                        | Chokeberry  | 71.0                | Slimestad et al., 2005 |
| Quercetin 3-O-diglucoside | Beans      | 12.0-64.0           | Chang and Wong, 2004 |
| Quercetin 3,3- dimethyl ether | Honey     | 0.03-0.2            | Yao et al., 2003 |
| Quercetin 3-O-glucuronide | Lettuce    | 0.73-0              | Nicolle et al., 2004 |
|                        | Chicory     | 8.1-106.5           | Innocenti et al., 2006 |
| Quercetin 3-O-6′- acetylglucoside | Beans | 1.0-5.0           | Chang and Wong, 2004 |
| Quercetin 3-methyl ether | Honey      | 0.2-0.3             | Yao et al., 2003 |
| Quercetin 3-O-rhamnoside | Mango  –fruits | 0.1-1.6          | Berardini et al., 2005 |
|                        | Pepper  –fruits | 11.3-99.3       | Materska et al., 2003 |
|                        | Cranberry   | 5.5                 | Zheng and Wang, 2003 |
|                        | Ligonberry  | 10.9                |           |
| Quercetin 7-O-glucoside  | Beans       | 2.0-12.0            | Chang and Wong, 2004 |
| Quercetin 3,4-diglucoside | Onions     | 16.9-137.2         | Nemeth and Piskula, 2007 |

![Fig. 1. Structure and numbering of quercetin.](image-url)
According to Wang et al. (Wang et al., 2006), the antioxidant activity of flavonoid aglycones, including fisetin, kaempferol, morin, myricetin and quercetin is demonstrated by the 4′-OH at the ring B. It was reported that glycosylation at C-(4′)-OH decreased the hydrogen donor capacity (Goupy et al., 2003), while the C-(3)-OH derivatives of quercetin exhibited a reducing potential comparable to that of free aglycone (Burda and Oleszek, 2001). Hence, it can be admitted that the lower antioxidant activity of quercetin derivatives is mainly due to the blockade of hydroxyl groups by sugar substituents. In vitro and in vivo studies have shown that quercetin activates the synthesis of glutathione (GSH). GSH acts as a hydrogen donor; it allows the enzyme superoxide dismutase (SOD) to capture $O_2^-$ anion. The latter is converted to $H_2O_2$, then broken down into nontoxic $H_2O$ (Kobori et al., 2015).

### 4.1. Antioxidant activity in animal cells

Polyphenols-rich extracts from the medicinal plants *Antirhea* borbonica, *Doratoxylon apetalum* and *Gouania mauritiana* were analyzed for their content of flavonoids: rutin, kaempferol and quercetin were found as major components. These extracts (25 μM GAE: Gallic acid equivalent) protected 3T3-L1 preadipocytes against $H_2O_2$ by down regulating the production of ROS and the secretion of pro-inflammatory markers, interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1/CCL-2), tumor necrosis factor-α (TNF-α) in response to lipopolysaccharides (LPS) (Marimoutou et al., 2015).

### 4.2. Antioxidant activity in human cells

Oxidative damage can occur in the lungs through the generation of ROS due to the intentional or accidental ingestion of paraquat (PQ), a common herbicide. In A549 (adenocarcinomic human alveolar basal epithelial cells), quercetin (40 mM) reduced PQ-induced cytotoxicity. A remarkable reduction in the level of ROS as well as an increase in the level of total cellular GSH occurred when cells exposed to PQ were treated with quercetin. The results suggest that quercetin can be used to reduce the oxidative stress by inhibiting the generation of ROS (Zerin et al., 2013).

**Table 3**

| In vitro experiments Molecules | Dose | Cell line | Effects | Ref |
|-------------------------------|------|-----------|---------|-----|
| Cells from Animal Rutin, kaempferol and quercetin | 25 μM | 3T3-L1 | Decreasing ROS production | (Marimoutou et al., 2015) |
| Cells from human Quercetin | 40 mM | A549 | Reducing cytotoxicity, level of ROS and increasing GSH | (Zerin et al., 2013) |
| Quercetin | 25, 50, 100 mM | GES-1 | Increasing cell viability and decreasing apoptosis and ROS production | (Jia et al., 2015) |
| Quercetin | 300 μM | 16HBE | Regulating ROS production | (Jin et al., 2016) |
| Quercetin | 20 μM | HaCaT | Decreasing apoptosis, flow of cytochrome c and ROS production | (Zhu et al., 2017) |

| In vivo experiments Molecules | Dose | Model | Effects | Ref |
|-------------------------------|------|-------|---------|-----|
| Quercetin | 20 mg/kg | Male | Decreasing in serum enzyme marker, increasing in GSH, SOD and CAT activities | (Kalantari et al., 2018) |
| Quercetin | 25 mg/kg | BALB/c | Decreasing ROS | (Jia et al., 2015) |
| Quercetin 3-O-glucoside | 30 mg/kg | Male | Decreasing mucus myeloperoxidase activity, production of NO, expression of TNF-α, levels of MDA and total GSH | (Joo et al., 2015) |
| Quercetin | 25 mg/kg | ICR | Increasing expression of the mRNA of PGC-1α and SIRT1. | (Dajas et al., 2015) |
| Quercetin | 10 mg/kg | Wistar rats | Reducing levels of dopamine, interferon-γ and 8-hydroxyguanosine and restoration of serotonin levels | (Zargar et al., 2016) |

**Fig. 2.** Antioxidant mechanisms of quercetin and its derivatives.
role in the pathogenesis of gastric disorders (Bhattacharyya et al., 2014). Human gastric epithelial cells (GES-1) were pretreated with quercetin (25, 50 and 100 mM) and then exposed to H₂O₂ (400 mM). Pretreatment by quercetin can protect against oxidative damage by significantly decreasing the loss of cell viability, apoptosis and ROS induced by H₂O₂ (Hu et al., 2015). It has been recognized that quercetin (330 µM) can stimulate 16HBE (human bronchial epithelial cell line) cells to repair oxidative damage after exposure to fine particles (Jin et al., 2016). In keratinocyte cells (HaCaT), quercetin (20 µM) exerted a significant protective effect by inhibiting UVB irradiation-induced apoptosis through its ROS scavenging ability (Zhu et al., 2017).

4.3. Antioxidant activity in vivo

An experimental study carried out on a mouse model (male Swiss albino mice) of hepatotoxicity induced by tert-butyl hydroperoxide (t-BHP) revealed the hepatoprotective effect of quercetin at a dose of 20 mg/kg against hepatic lesions. The results made it possible to determine the hepatoprotective and antioxidant effects of quercetin in a dose-dependent manner, as shown by a significant decrease in the marker of serum enzymes and an increase in GSH, superoxide dismutase (SOD) and catalase (CAT) activities (Kalantari et al., 2018). Chemiluminescence imaging showed that quercetin (25 mg/kg) attenuated the production of ROS and gastric damage in acute lesions of the gastric mucosa in mice BALB/c mice. This could be attributed to the inhibition of oxidative stress, the regulation of mitochondrial dysfunction, the initiation of antioxidant defense and the inhibition of apoptosis (Hu et al., 2015).

In a rat-induced colitis model (male Sprague-Dawley) with 2,4,6-trinitrobenzene sulfonic acid, isoquercetin at 30 mg/kg decreased the activity of mucous myeloperoxidase, production of nitric oxide (NO), expression of TNF-α, levels of malondialdehyde (MDA) and total ROS and the development of apoptosis due to the action of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) and the release of cytochrome c (Olanow and Tatton, 1999). Male ICR (Institute of cancer research) mice supplemented for 7 days with quercetin (25 mg/kg) showed an increase in markers of mitochondrial biogenesis in skeletal muscle and brain, namely the expression of the mRNA of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α), sirtuin 1 (SIRT1) and the concentration of cytochrome c (Davis et al., 2009).

Thus, targeted mitochondrial effects appear to be a process by which quercetin could prevent neurodegeneration (Dajas et al., 2015). Acrylamide (ACR) is formed in food during cooking and is known to be neurotoxic. The intraperitoneally treatment of rats with quercetin (10 mg/kg) contributed to a decrease in ACR-mediated neurotoxicity, as evidenced by reduced levels of dopamine, interferon-gamma (IFN-γ) and 8-hydroxy-2′-deoxyguanosine with concomitant restoration of serotonin levels. This study seeks that quercetin could be considered as potential therapeutic agent to prevent oxidative damage to neurons (Zargar et al., 2016).

5. Molecular mechanisms of antiviral activity

Quercetin, its derivatives and plant extracts containing quercetin have been extensively studied for their antiviral properties. Indeed, quercetin can reduce the viral load by preventing the virus from entering cells (Li et al., 2016). Quercetin also boosts the innate immune response by reducing in particular the gene expression of cytokines, chemokines and interferons, molecules involved in systemic inflammation (Li et al., 2016). Finally, quercetin can bind to the functional sites of viruses and interfere with their ability to mobilize the resources of the host cells for their own needs and thus limit their ability to replicate (Wu et al., 2015). These activities are summarized in Table 4 and schematized in Fig. 3.

Colorimetric enzyme immunoassay for the quantitative determination of retroviral reverse transcriptase activity was evaluated with recombinant HIV-1 enzyme, using a non-radioactive HIV-1 RT colorimetric ELISA kit. Using the latter test, it has been shown that quercetin of a Brazilian propolis at 200 µg/mL induced activity against HIV-1 inhibition (Silva et al., 2019). The presence of prenyl groups on flavonoids may increase their anti-HIV activity (Kurapati et al., 2015; Mengelman et al., 2001).

Quercetin showed significant inhibition towards the 3C-like protease (3CLₚᵡᵩ) with an IC₅₀ of 73 µM (Nguyen et al., 2012). 3CLₚᵡᵩ of coronavirus associated with severe acute respiratory syndrome (SARS-CoV) is vital for the replication of SARS-CoV and is now considered as a promising drug target. The proteolytic activity of 3CLₚᵡᵩ was measured using a fluorescence resonance energy transfer (FRET) assay. Another study presented the ability of quercetin to inhibit SARS-CoV 3CLpro (Ryu et al., 2010). Hence, in the context of the COVID-19 pandemic, quercetin and its derivatives may be an interesting avenue for controlling SARS-CoV-2 infection.

Otherwise, acetylated quercetin derivatives were found to bind to the M2–1 protein of human Respiratory Syncytial Virus (hRSV). It is an important anti-termination factor for the transcription process that prevents premature dissociation of the polymerase complex, making it a potential target for the development of inhibitors of viral replication. Studies have shown that acetylated derivatives of quercetin allow the development of new treatments against viral infections, by inhibiting the replication process of hRSV (Guimarães et al., 2018).

5.1. Antiviral activity in insect and animal cells

Zandi et al. demonstrated that quercetin (IC₅₀: 35.7 µg/mL) exhibits significant anti-DENV type 2 (DENV-2) replication properties on C6/36 and VERO cells. Quercetin affected intracellular replication of DENV but not the processes of attachment and entry of DENV (Zandi et al., 2011b). However, according to a study of Mir et al. using the molecular docking approach, it was found that quercetin interacts with protein E and can therefore block the entry process of the virus by inhibiting conformational changes in the hinge regions, thus preventing the fusion process. These compounds function as inhibitors of subsequent stages of dengue virus replication (Mir et al., 2016). Protein E plays a crucial role in the fusion of the viral membrane with the target cell membrane, for the inhibition of DENV infection, it is necessary to stop this early event. The flavonoid quercetin present in papaya Carica, apple and lemon could exert antiviral activity against the fusion mechanism of DENV-2 by blocking the conformational rearrangement of the envelope protein (Mir et al., 2016). On BHK-21 (baby hamster kidney) fibroblasts cells, quercetin (155 µg/mL) and quercitrin (467 µg/mL) had an anti-DENV-2 effect. A synergy of these two compounds was demonstrated by improving the cytopathicity of the treatment and thus increasing the antiviral effect against the DENV (Chiow et al., 2016). The same authors evaluated the anti-MHV (mouse hepatitis virus) effect of these flavonoids on CCL-9.1, a Mus musculus (mouse) liver epithelial cell line. Quercetin at IC₅₀: 116.50 µg/mL showed antiviral effects, which is not the case for quercitrin (Chiow et al., 2016). Moreover, the glycosylated quercetin, rutin was tested and showed beneficial effect on the two cell lines and viruses mentioned above.

It was shown that quercetin 7'-rhamnoside (Q7R) inhibits viral replication of porcine epidemic diarrhea virus (PDEV) at 10 µg/mL on VERO cells (Choi et al., 2009). In the same study, several flavonoids were tested, and a structure-activity relationship was established. Among the tested flavonoids, flavones (apigenin and luteolin), flavonol (7-rhamnoside quercetin) and flavanol (catechin), which all have ortho-dihydroxy groups at C-3′ and C-4′ positions, each showed significant anti-PEDV activity. However, the anti-PEDV activity of quercetin was less pronounced. This indicates that the presence of sugar groups at C-7 is an important characteristic for the anti-PEDV activity of flavonoids. A study showed that isorhamnetin, a glycosylated derivative of
Table 4
Antiviral activities of quercetin and its derivatives.

| Molecules                          | Dose       | Cell line | Effects            | Mechanisms                                                                 | Ref                                      |
|-----------------------------------|------------|-----------|--------------------|-----------------------------------------------------------------------------|------------------------------------------|
| **Cells from insect or Animals**  |            |           |                    |                                                                             |                                          |
| Quercetin                         | IC_{50} 35.7 µg | C6/36 and VERO | Anti-DENV-2        | Inhibition of DENV-2 replication                                             | (Zandi et al., 2011b)                   |
| Quercetin                         | 467.27 µg/mL | BHK-21    | Anti-PR8           | –                                                                            | (Chiu et al., 2016)                     |
| Quercetin                         | CC_{50} 116.38 µg/mL | CCL1.1 | Anti-MHV           | –                                                                            | (Chiu et al., 2016)                     |
| Quercetin                         | 5-50 µM    | VERO      | Anti-HSV-1         | Inhibition of HSV-1 replication                                               | (Lyu et al., 2005)                      |
| Quercetin                         | IC_{50} 212.1 µg | VERO | Anti-HEV           | –                                                                            | (Johari et al., 2012)                   |
| Quercetin and isquercetin         | 10 µg/mL   | VERO      | Anti-PEDV          | Early inhibition of PEDV replication after infection                         | (Choi et al., 2009)                     |
| Isoquercetin                      | 2 µM       | MDCK and VERO | Anti-OH7, PR8 and B / Lee / 40 | Early inhibition of OH7, PR8 and B / Lee / 40 replication after infection     | (Kim et al., 2010)                      |
| Quercetin and rutin               | 15 and 30 µg/mL | VERO | Anti-CDV           | Direct inactivation of virus, by binding irreversibly viral particles or by destabilizing viral ligands essential to the infectious process, such as envelope glycoproteins | (Carvalho et al., 2013)                 |
| Quercetin                         | 300 µM     | CRFK      | Anti-FCV           | Reduction of viral titers of FCV in pre-treatment                           | (Seo et al., 2016)                      |
| Quercetin                         | 100 µM     | RAW 264,7 | Anti-MNV           | Reduction of viral titers of MNV in pre-treatment                           | (Seo et al., 2016)                      |
| Quercetin                         | 100 µM     | RAW 264,7 | Anti-MnOv          | Upregulating the expression of antiviral cytokines (IFN-α, IFN-β, and TNF-α) and interferon-stimulating genes (Mx and ZAP) | (Seo and Choi, 2017)                    |
| Baicalein, fisetin, and querceatin | Respectively: IC_{50} 6.997 µM, 29.5 µM and 43.52 µM | BHK-21 | Anti-CHIKV         | Affects CHIKV RNA production and viral protein expression                   | (Lai et al., 2016)                      |
| Quercetin and querceatin          | Respectively: IC_{50} 10 µg/mL, > 100 µg/mL | VERO | Anti-MAYV          | Inhibition of MAYV replication                                                | (dos Santos et al., 2014)               |
| Quercetin and querceatin          | Respectively: IC_{50} 83.4 µM, IC_{90} 9.02 µM | VERO | Anti-HIV-luc/SARS  | –                                                                            | (Yi et al., 2004)                       |
| Quercetin and querceatin          | Respectively: IC_{50} 4.93 µg/mL, 6.43 µg/mL | MDCK | Anti-influenza A viruses (A/PR/8/34 (H1N1), A/Victoria/3/75 (H3N2), A/WS/33 (H1N1) and influenza B viruses (B/Maryland/1/59, B/Lee/40) | vRNA expression was significantly reduced with a subsequent blocking effect on the influenza PB2 protein | (Nile et al., 2020)                     |
| Quercetin and querceatin          | 10 µM      | VERO      | Anti-VSV-EBOV, VSV-SUDV and VSV-REST | Inhibition of virus entry into cells                                         | (Qiu et al., 2016)                      |
| **Cells from human**              |            |           |                    |                                                                             |                                          |
| Quercetin                         | 0.1-5 µM   | HCV-G1    | Anti-HCV           | Inhibition of HCV replication by blocking oxidative/nitrosative stress and subsequent modulation of PI3K-LXRα-mediated lipogenesis associated with the development of steatosis and hepatic C progression. | (Pisonero-Vaquero et al., 2014)         |
| Quercetin and querceatin          | Respectively: IC_{50} 4.5 µg/mL and 1.5 µg/mL | Huh7i-1 | Anti-HCV           | Inhibition of the virus at the post-entry level of the virus into the cell   | (Cryer et al., 2017)                    |
| Quercetin and querceatin          | CE_{50} 22.6–60 mg/L | BCC-1/KMC | Anti-HSV-1, HSV-2 and ADV-3, ADV-8, ADV-11 | Early inhibition of viral replication after infection                        | (Chiang et al., 2003)                   |
| Quercetin and querceatin          | IC_{50} 3.2 µM | HEL 299  | Anti-ADV-11        | –                                                                            | (Evers et al., 2005)                    |
| Quercetin and querceatin          | IC_{50} 3.2 µM | HEL 299  | Anti-HCMV          | Inhibition of various stages of HCMV replication                            | (Cotin et al., 2012)                    |
| Baicalein, quercetin and querceatin | Respectively: IC_{50} 165 µM and 145 µM | Hep2 | Anti-HSV-1          | Inhibition of HSV-1 replication                                               | (Cotin et al., 2012)                    |
| Baicalein, quercetin and querceatin | Respectively: IC_{50} 88.98 µM and 20.43 µM | TZM-bl | Anti-VIH-1 Bal     | –                                                                            | (Pasetto et al., 2014)                  |
| Baicalein, quercetin and querceatin | Respectively: IC_{50} 38.78 µM and 29.76 µM | H9     | Anti-VIH-MN and VIH 89,6 | –                                                                            | (Pasetto et al., 2014)                  |
| Baicalein, quercetin and querceatin | Respectively: IC_{50} 22.91 µM and 1.76 µM | H9     | Anti-VIH-MN and VIH 89,6 | –                                                                            | (Pasetto et al., 2014)                  |
| Fisetin and rutin                 | Respectively: IC_{50} 85 µM and 110 µM | RD     | Anti-EV-A71         | Inhibition of EV-A71 replication                                              | (Lin et al., 2012)                      |
| Quercetin and rutin               | 10 µg/mL   | HepG2.2.15 | Anti-HBV           | Inhibition of HBV replication by forming stable complexes with viral Pol/RT. | (Parvez et al., 2019)                   |
| Isoquercitrin                     | IC_{50} 32, 50 and 15 µM | A549, Huh-7 and SH-SY5Y | Anti-ZIKV         | Inhibition of ZIKV by decreasing viral RNA and viral protein production     | (Gaudry et al., 2018)                   |

**In vivo experiments**

| Molecules                          | Dose       | Effect | Mechanisms | Ref                                      |
|-----------------------------------|------------|--------|------------|------------------------------------------|
| Isoquercitin                      | 10 mg/kg/day | Four-week-old female BALB/c mice | Reducing pulmonary viral titers levels | (Kim et al., 2010)                     |
quercetin, exhibited antiviral activity on influenza A and B viruses (Oh7, PR8 and B/Lee/40) on Madin-Darby canine kidney (MDCK) and VERO cells at 2 \( \mu \)M (Kim et al., 2010). Pre-incubation of influenza virus with isoquercetin did not decrease the viral titer, indicating that the antiviral effect of isoquercetin is not associated with direct viral neutralization or virucidal effect on influenza virus. Addition of isoquercetin to cells up to 4 h after viral infection reduced virus replication in a time-dependent manner. These results suggest that the antiviral mechanism of isoquercetin may act during the early stages of viral replication.

Carvalho et al. studied the antiviral activity of several flavonoids. Quercetin (15 and 30 \( \mu \)g/mL) at time 0 (adsorption), 1 h (penetration) and 2 h (intracellular) of the viral replication cycle and rutin (15 and 30 \( \mu \)g/mL) at time 0 and 1 h inhibited canine distemper virus (CDV) replication on VERO cells (Carvalho et al., 2013). Inhibitory effects observed with these flavonoids at the adsorption and penetration stages suggest direct inactivation of the virus, either by binding irreversibly to viral particles or by destabilizing viral ligands that are essential to the infectious process, such as envelope glycoproteins. Therefore, the role of flavonoids in the early stages of viral replication would reduce the number of infected cells and the formation of viral offspring.

It was shown that the antiviral activity of quercetin against feline calicivirus (FCV) and murine norovirus (MNV). At 300 \( \mu \)M, quercetin pre-treatment reduced the viral titers of FCV on Crandell-Reese feline kidney (CRFK) cells and reduced at 100 \( \mu \)M those of MNV on RAW 264.7 mouse monocyte macrophage cell line. Co and post-treatment experiments did not significantly reduce the viral titers of these viruses on the two cell lines. Only the pre-treatment showed some efficacy (Seo et al., 2016). The same authors reported that quercetin pre-treatment (100 \( \mu \)M) on RAW 264.7 cells showed antiviral activity by inhibiting murine noroviruses (MNoV), by upregulating the expression of antiviral cytokines (IFN-\( \alpha \), IFN-\( \lambda \), and TNF-\( \alpha \)) and interferon-stimulating genes (Mx and ZAP) (zinc finger CCCH type antiviral protein 1) (Seo and Choi, 2017).

Baicalein, fisetin, and quercetagetin which are close analogs of quercetin showed potent inhibition of CHIKV (Chikungunya virus) infection on BHK-21 cells, with 50% inhibitory concentrations IC\(_{50}\) of 1.891 \( \mu \)g/mL (6.997 \( \mu \)M), 8.444 \( \mu \)g/mL (29.5 \( \mu \)M) and 13.85 \( \mu \)g/mL (43.52 \( \mu \)M), respectively, and with minimal cytotoxicity. The qRT-PCR, immunofluorescence and Western blot assays indicated that each of these flavonoids affects CHIKV RNA production and viral protein expression (Lani et al., 2016).

Dos Santos et al. studied the antiviral activity of quercetin and its derivatives on the alphavirus arthropod-borne Mayaro virus (MAYV). Quercetin IC\(_{50}\) 10 \( \mu \)g/mL and quercitrin 100 \( \mu \)g/mL inhibited the replication of MAYV on VERO cells. Extracts from leaves of Bauhinia longifolia (Bong.) Steud. containing guaijaverine, quercitrin, isoquercetin and hyperine were also tested in the same cell model and found to inhibit MAYV replication (dos Santos et al., 2014).

Quercetin and luteolin showed antiviral activity against human immunodeficiency virus (HIV)-luc/SARS pseudotyped SARS-CoV virus, in VERO cells with IC\(_{50}\) of 83.4 \( \mu \)M and 9.02 \( \mu \)M, respectively. However, the mechanism of action remains to be elucidated (Yi et al., 2004). The promising effect of quercetin and structurally related molecules on SARS-CoV could be a possible opportunity of investigation to combat
5.2. Antiviral activity in human cells

Quercetin showed antiviral activity against the hepatitis C virus (HCV). In HCV-G1 cells, quercetin at concentrations close to those found in the bloodstream (0.1 – 5 µM) inhibited HCV replication (Pisón-O-Vaquero et al., 2014). Quercetin inhibits HCV replication by blocking oxidative/nitrosative stress and subsequent modulation of PI3K-LXRα-mediated lipogenesis associated with the development of steatosis and hepatitis C progression. Aoki et al. showed that quercetin (IC50: 4.5 µg/mL) exhibited anti-HCV activity (IC50: 1.5 µg/mL) on HepG2 cells. The antiviral activity of quercetin was exerted after viral adsorption, suggesting inhibition of the virus at the post-entry level of the virus into the cell (Cryer et al., 2017). Quercetin was also tested but showed no significant antiviral activity.

On human skin basal cell line (BCC-1/KMC) quercetin inhibits viral replication of herpes viruses (HSV-1, HSV-2) and adenoviruses (ADV-3, ADV-8, ADV-11) at an EC50: 22.6–60 mg/L. The mechanism of action is not linked to the inhibition of virus adsorption but results from early inhibition of viral replication after infection. Indeed, quercetin inhibits viral replication between 0 and 2 h for HSV-1 and between 0 and 4 h for ADV-3 which represents the beginning of virus replication (Chiang et al., 2003).

Evers et al. demonstrated that quercetin at IC50 of 3.2 µM inhibited human cytomegalovirus (HCMV) on HEL299 (primary human embryonic lung fibroblasts) cells (Evers et al., 2005). Others have demonstrated that three flavonoids (baicalein, quercetin and quercetagetin) inhibit various stages of HCMV replication, with the most active anti-HCMV compound being baicalein (Cotin et al., 2012). The three compounds showed antiviral activity against the reference HCMV AD169 strain at IC50: 2.2, 4.8 and 23 µM, respectively on HEL (Human embryonic lung) cells. These molecules were tested on another cell type, Hep2 (human epithelial), with the HSV-1 virus and showed very low activity.

Pasetto et al. studied the antiviral effect of quercetin and several flavonoids on HIV. The study was conducted on three cell types, namely TZM-bl (HeLa cell line genetically engineered to express CD4, CCR5, and CXCR4), H9 (human embryonic stem cell) and PBMC (peripheral blood mononuclear cells). Quercetin showed moderate activity against HIV on the three cell types. On TZM-bl cells, quercetin with IC50: 88.98 µM inhibited HIV-1 Bal infection by 39%. On H9 cells quercetin inhibited ≥ 64% (IC50: 38.78 µM; 29.76 µM) on HIV-MN and HIV-89.6 respectively. On PBMC cells, quercetin inhibited 45% of the HIV-MN virus and 59% of the HIV-89.6 virus with respective concentrations IC50: 31.68 µM; 39.26 µM (Pasetto et al., 2014). Myricetin was also tested and showed greater antiviral activity than quercetin. Myricetin inhibited over 87% of HIV-1 Bal infection in TZM-bl cells (IC50: 20.43 µM). At IC50: 22.91 µM and 1.76 µM on H9 cells, myricetin inhibited the infection to HIV-1 MN or HIV-1 89.6 respectively by ≥ 86%. These two compounds differ from each other by only one hydroxyl group which is missing in quercetin at the 5’position.

A viral replication assay indicated that fisetin and rutin significantly reduced the cytopathic effect induced by EV-A71 (enterovirus A71) and viral plaque titers in cultured RD rabdomyosarcoma cells. The plaque reduction against EV-A71 was reached with IC50: 85 µM for fisetin and 110 µM for rutin. The study suggests that both fisetin and rutin inhibit the replication of EV-A71 (Lin et al., 2012).

Parvez et al. studied the antiviral activity of several phenolic compounds on HepG2.2.15 (human hepatoblastoma line, HepG2-derived) against HBV (Hepatitis B virus). Quercetin and rutin (10 µg/mL) inhibited HBV replication by 68% and 50%, respectively. Quercetin was found to be the most active compound while rutin showed only a moderate effect. HBV polymerase (Pol / RT) is the most important drug target. Docking studies of phenolic compounds indicated a strong interaction with the HBV Pol active site through formation of stable complexes (Parvez et al., 2019).

Isoquercitrin has been evaluated for the antiviral effect on different human cell lines (AS49 (human lung epithelial), Huh-7 (human-derived Huh-7 hepatoma cells) and SH-SY5Y (human neuroblastoma) against ZIKV (Zika virus) (Gaudry et al., 2018). Isoquercitrin was found to be a potent growth inhibitor on ZIKV by decreasing viral RNA and viral protein production with an IC50 of 32, 50 and 15 µM, respectively on AS49, Huh-7 and SH-SY5Y cells. They also studied which stages of ZIKV infection were targeted by isoquercitrin. The results showed that isoquercitrin primarily targets the initial stages of the infectious life cycle rather than viral replication or viral assembly and release of viral particles. Based on the results obtained with close structures, it was hypothesized that the sugar present on isoquercitrin could play a determining role in the capacity of the compound to inhibit the entry of the virus into human cells (Gaudry et al., 2018).

5.3. Antiviral activity in animals

An animal experiment on four-week-old female BALB/c mice infected with the PR8 virus adapted to mice (A/PR/8/34, H1N1) demonstrated the antiviral activity of isoquercitrin at 10 mg/kg/day, by reducing the pulmonary viral titers levels compared to those of untreated mice. Isoquercitrin treatment also significantly reduced IFN-γ, iNOS and RANTES levels in the lungs compared to the untreated group (Kim et al., 2010). In another study, isoquercitrin isolated from Polygala perfoliata L. was shown to induce antiviral activity against influenza A virus (FLUAV) at 6 mg/kg by suppressing virus-induced pulmonary edema on the murine Kunming gene model (Fan et al., 2011).

Another study showed that quercetin (12.5 mg/kg/day) administered orally to four-week-old male ICR mice for 7 days prior to challenge with influenza virus (influenza virus [A/Puerto Rico/8/34 (H1N1)]) (but not after) compensated for the stress-induced increase in morbidity, symptom severity and mortality (Davis et al., 2008).

Ferreira et al. studied the antiviral activity of quercetin on the EHV-1 (Equid herpesvirus 1) virus in a mouse model. On six to seven-week-old female C57BL/6 mice, quercetin at 90 mg/kg/day exerted antiviral activity by attenuating the aggravation of viral infection in EHV-1 mice. It was observed reduced clinical signs and mortality, increased body weight, and reduced lesion severity in the EHV-1 infected mouse model (Ferreira et al., 2018).

Q3G, exerted antiviral activity against the Ebola virus by suppressing mortality and decreasing clinical signs of disease. This study was conducted at a concentration of 50 mg/kg in the mouse model C57BL/6 and MA-EBOV infection (Qiu et al., 2016).

In conclusion, quercetin and its derivatives have broad antiviral activities, both in inhibiting viral replication and as a virucide. They are active on many viruses and these properties were confirmed through in vivo models.

6. Anti-inflammatory activity

Inflammation is regulated by several key regulators, of which the transcription factor, nuclear-kappa factor B (NF-κB), plays crucial roles. TNF-α is a cytokine that activates NF-κB that plays an important role in the inflammatory response by enhancing the induction of pro-inflammatory genes encoding the synthesis of new cytokines,
including TNF-α itself, chemokines, cell adhesion molecules, enzymes, growth factors and pro-inflammatory enzymes, such as cyclooxygenase COX-1 and COX-2, 5-lipoxygenase 5-LOX) and inductive nitric oxide synthase (iNOS) (“A current view on inflammation,” 2017). COX-2, 5-LOX and iNOS control the biosynthesis of essential synthase (iNOS) (the production of the inflammatory mediators, NO and TNF-α). TNF-α activates not only the NF-κB signaling pathway, which is central to the inflammatory process, but also other signaling cascades such as activator protein-1 (AP-1), mitogen-activated protein kinases (MAPK) and apoptotic pathways, contributing to the regulation of pro-life, gene expression, differentiation, survival and cell death (“A current view on inflammation,” 2017). More than 100 other cytokines are important in the inflammatory immune response (“A current view on inflammation,” 2017). IL-1/β, IL-6, interferon-γ (IFN-γ) and interleukin-α (IL-α) are examples of other well-known pro-inflammatory cytokines involved in the inflammatory process, while IL-10, IL-2 and transforming growth factor (TGF)-β are important anti-inflammatory cytokines responsible for the immune tolerance (“A current view on inflammation,” 2017). Long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of gastrointestinal and cardiovascular complications (Sostres et al., 2010). This is why there has been a definite interest in recent years in new anti-inflammatory drugs of natural origin. In this context, flavonoids and derivatives appear to be promising molecules with direct interactions with pro-inflammatory proteins, inhibition of the expression of genes related to inflammation and antioxidant and pro-oxidant effects (Hošek and Smejkal, 2015).

Anti-inflammatory properties of quercetin and its derivatives are summarized in Table S and schematized in Fig. 4.

### 6.1. Anti-inflammatory activity of quercetin and derivatives on animal cells

Quercetin (10 μM) showed anti-inflammatory activity by attenuating the production of the inflammatory mediators, NO and TNF-α, in BV-2 microglial cells stimulated by LPS. Mechanistically, quercetin induced negative regulation of the transcription factor NF-κB (Mrnová et al., 2015). In the same cell model, stimulated by endotoxin/cytokine, quercetin (10 μM) inhibited the expression of iNOS and NO production. Quercetin exerted their anti-inflammatory effect by the down-regulation of extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38, Akt, Src, Janus kinase-1, Tyk2, signal transducer and activator of transcription-1, and NF-κB (Kao et al., 2010). In addition, the study by Chen et al. (Chen et al., 2005) showed that LPS-induced activation of the kinase IκB (IKK), NF-κB and AP-1 and IFN-γ-induced activation of NF-κB, STAT1 and interferon regulatory factor 1 (IRF-1) in microglia was also decreased by quercetin (10 μM). Furthermore, quercetin and fisetin were found to inhibit the production of TNF-α in RBL-2H3 (rat basophilic leukemia cell line) cells with IC₅₀ of 5.6 and 4.3 μM, respectively (Mastuda et al., 2002).

Using a rat insulinoma cell line, quercetin (10 μM) significantly reduced nitrite production, the iNOS protein and its mRNA expression levels, and also inhibited phosphorylation IκBα, NF-κB activation and the activity of the iNOS promoter (Cho et al., 2012).

Boesch-Saadatmandi et al. studied the effect of quercetin and its major metabolites, Q3G and isorhamnetin on the expression of inflammatory genes in RAW264.7 mouse macrophages stimulated with LPS (Boesch-Saadatmandi et al., 2011). The NF-κB activity as determined by the nuclear translocation of p65 was inhibited by quercetin and isorhamnetin (10 μM). NF-κB is a master switch for inflammatory gene expression and regulates the expression of IL-1β, IL-6, iNOS and MIP-1α - biomarkers of inflammation that were all down-regulated by quercetin and isorhamnetin (Saluoi et al., 2001). Quercetin and isorhamnetin counteracted the LPS-induced increase miR-155 (an additional regulator of the inflammatory response). Q3G had no effect on inflammatory gene expression. Glucuronidation of Q3G, which masks important hydroxyl groups in the quercetin molecule, decreases its anti-inflammatory properties. Conversely, isorhamnetin has similar anti-inflammatory activity as quercetin, indicating that methylation is not associated with a loss of its biological properties.

The effect of several flavonoids was studied on bone marrow-derived macrophages (BMDM). Quercetin and kaempferol (25–50 μM) decreased the secretion of TNF-α induced by LPS. LPS induces iNOS expression and iNOS protein synthesis correlates with NO production (Xaus et al., 2000). Quercetin (< 50 μM) and kaempferol (100 μM) decreased iNOS expression. They also inhibited the release of NO at a concentration of (25–50 μM) and (50 μM) respectively. iNOS and TNF-α are both genes regulated by the transcription factor NF-κB. Under quiescent conditions, NF-κB is sequestered in cytosol by binding to the inhibitor protein IκB-α. Exposure of the cells to LPS triggers phosphorylation cascades that ultimately lead to phosphorylation and degradation of IκB-α. Once IκB-α dissociates from the complex, NF-κB translocates into the nucleus where binding to specific DNA motifs in the promoter region occurs, leading to increased genetic transcription. The phosphorylation of IκB-α by LPS was significantly reduced by quercetin treatment (10–50 μM). These results suggest that inhibition of the NF-κB pathway may be involved in the mechanism of action by inhibiting the phosphorylation of IκB-α. Quercetin was able to stimulate the expression of the anti-inflammatory cytokine IL-10 at low concentrations (< 50 μM) (Comalada et al., 2006).

Others have studied the same compounds (quercetin, kaempferol and isorhamnetin) on a mouse macrophage model of J774 stimulated by LPS. At 10 μM, both compounds decreased the production of NO but also the protein and mRNA expression of iNOS. These compounds also inhibited the activation of NF-κB, with a stronger effect for quercetin. Quercetin and kaempferol decreased nuclear levels of STAT-1, with more pronounced effect by quercetin and no effect for isorhamnetin. Considering that NF-κB and STAT-1 are important transcription factors for iNOS, the mechanism of action would lie in the inhibition of these pathways (Hämäläinen et al., 2007).

Effect of quercetin was studied on mouse model of bone marrow-derived dendritic cells (DCs) stimulated by LPS. TNF-α was down-regulated by quercetin in a dose-dependent manner (6.25–50 μM). It also decreased the secretion of cytokines (IL-1α, IL-1β, IL-6, IL-10, and IL-12 p70) and chemokines (CCL-2, MIP-1α, MIP-1β, and RANTES). Mechanistically, quercetin decreased the degradation of IκB-α and disrupted the activation of ERK, JNK, Akt, and NF-κB pathways. These results explain the powerful anti-inflammatory effect of quercetin in DCs (Huang et al., 2010).

On BMDM, quercetin (10–50 μM) in pre-treatment inhibited the secretion of TNF-α and IL-1β and the expression of iNOS induced by LPS. NF-κB and c-Jun N-terminal kinase (JNK) activation pathways, is well established that these pathways participate in the inflammatory response mediated by macrophages (Comalada et al., 2003; Ropert et al., 2001). Quercetin was not able to inhibit the c-Jun phosphorylation induced by LPS. These results suggest that JNK activation might not be implicated in the inhibition of TNF-α/IL-1β and iNOS expression induced by quercetin in these cells. Quercetin, but not quercitrin, inhibited in a dose-dependent manner the phosphorylation of the IκB-α protein induced by LPS treatment in macrophages, hence inhibiting the activation of the NF-κB pathway. So far, these results show that quercetin, but not quercitrin, exerts a potent in vitro anti-inflammatory effect which could be mediated through down-regulation of the NF-κB pathway (Comalada et al., 2005).

Moreover, it has been shown that in a dose dependent manner quercetin (6.25–25 μM) inhibits ERK1/2, JNK and p38MAPK signaling factors in 3T3-L1 and RAW264.7 cell models. It also inhibited protein levels of CCL-2 and TNF-α, a pro-inflammatory cytokine and chemokine. It decreased IL-1β, IL-6 and NO secretion and increased IL-10 secretion (Seo et al., 2015).
Table 5
Anti-inflammatory activities of quercetin and its derivatives.

| In vitro experiments | Molecules          | Dose   | Cell line | Effects                                                                 | Mechanisms                                                                 | Ref                                      |
|----------------------|--------------------|--------|-----------|-------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------|
| Cells from Animals   | Quercetin          | 10 µM  | BV-2      | Decrease of NO and TNF-α production                                       | Negative pathway regulation of NF-κB                                       | (Morváň et al., 2015)                   |
|                      | Quercetin          | 10 µM  | BV-2      | Inhibition of the expression of iNOS and NO production, down-regulation of extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38, Akt, Src, Janus kinase-1, Tyk2, signal transducer and activator of transcription-1, and NF-κB | –                                                                         | (Kao et al., 2010)                      |
|                      | Quercetin          | 10 µM  | BV-2      | Decrease in the rates of iKB (IKK), NF-κB, AP-1, STAT1 and IRF-1          | –                                                                         | (Chen et al., 2005)                     |
|                      | Quercetin and fisetin | Respectively IC₅₀: 5.6 and 4.3 µM | RBL-2H3 | Inhibition of the production of TNF-α                                    | –                                                                         | (Mastuda et al., 2002)                  |
|                      | Quercetin          | 10 µM  | RiNM5F    | Reduction of nitrite production and expression of iNOS, Inhibition of phosphorylation iKB and inactivation of NF-κB | –                                                                         | (Cho et al., 2012)                      |
|                      | Quercetin, quercetin-3-glucuronide and isorhamnettin | 10 µM  | RAW264.7 | Inhibition of p65 translocation, expression of IL-1α, IL-6, iNOS and MIP1α, miR-155 | –                                                                         | (Boesch-Saadatmandi et al., 2011)       |
|                      | Quercetin and kaempferol | 25–100 µ | BMDM  | Decrease of the secretion of TNF-α, decreased expression of iNOS, NO release, phosphorylation of IκB-α, increased expression of IL-10 | –                                                                         | (Comalada et al., 2006)                 |
|                      | Quercetin, kaempferol and isorhamnettin | 100 µM  | J774      | Decrease of the NO production, protein and mRNA expression of iNOS, inactivation of NF-κB and STAT-1 | –                                                                         | (Hämäläinen et al., 2007)               |
|                      | Quercetin          | 6.25–50 µM | DCs  | Decrease of secretion of TNF-α, IL-1α, IL-1β, IL-6, IL-10, IL-12 p70, CCL-2, MIP-1α, MIP-1β and RANTES | Decrease of the degradation of IκB and inhibition of activation of ERK, JNK, Akt, and NF-κB pathways. | (Huang et al., 2010)                     |
|                      | Quercetin          | 10–50 µM | BMDM  | Decrease of secretion of TNF-α and IL-1β and the expression of iNOS and phosphorylation of the IκB-α | Down-regulation of the NF-κB pathway.                                     | (Comalada et al., 2005)                 |
|                      | Quercetin          | 6.25–25 µM | 3T3-L1 and RAW264.7 | Inhibition of signaling factors ERK1/2, JNK and p38MAPK, protein levels of CCL-2 and TNF-α, secretion of IL-1β, IL-6 and NO and increased IL-10 secretion | –                                                                         | (Séo et al., 2015)                      |
| Cells from human Molecules | Quercetin and rutin | 20 µM  | THP-1     | Decreased expression and secretion of TNF-α, IL-1β and COX-2             | –                                                                         | (Wu et al., 2009)                       |
|                      | Quercetin          | 2 and 10 µM | HUASMC | Decreased expression and secretion of VCAM-1, ICAM-1 and CCL-2           | –                                                                         | (Winterbone et al., 2009)               |
|                      | Quercetin, quercetin-3-glucuronide, quercetin-3'-sulfate, 3'-methylquercetin | 2 and 10 µM | HUVEC | Decreased expression and secretion of VCAM-1, ICAM-1 and CCL-2           | –                                                                         | (Tribolo et al., 2008)                  |
|                      | Quercetin          | 40 µM  | HAE-Cs    | Decreased expression of ICAM-1                                          | –                                                                         | (Mochizuki et al., 2004)                |
|                      | Quercetin, quercetin-3-glucuronide, quercetin-3'-sulfate et la 3'-methylquercetin 3-glucuronide | 10 µM | Caco2     | Reduction expression of COX-2                                           | –                                                                         | (O’Leary et al., 2004)                  |
|                      | Quercetin and quercetin-3'-sulfate | 10 µM  | Caco2     | Inhibition of COX-2 activity                                             | –                                                                         | (O’Leary et al., 2004)                  |
|                      | Quercetin          | 5–200 µM | CHL      | Decreased concentration of iNOS, COX-2 and CRP, inhibition of expression of iNOS, COX-2 and CRP, Inhibition of IκBα and IκK (IκB kinase) α | Blocking of the transcription NF-κB pathway                                 | (García-Mediavilla et al., 2007)        |
|                      | Quercetin          | 1–50 µM | PBMC      | Inhibition of production and expression of TNF-α                         | –                                                                         | (Nair et al., 2006)                     |
|                      | Fisetin, quercetin and myricetin | 10–100 µM | A549    | Inhibition of PARP-1 and CXCL8 production                               | –                                                                         | (Geraets et al., 2007)                  |
|                      | Kaempferol, quercetin and fisetin | 40 µM  | HEK-293  | Inhibition of CXCL8 mRNA expression, phosphorylation and degradation of IκBα and translocation of NF-κB p65 | –                                                                         | (S. Lee et al., 2009)                   |
|                      | Fisetin and fisetin from hexane fraction of Rhus verniciflua Stokes | Respectively 0.1–10 µg/mL and 1–100 µg/mL | RA FLS | Decreased production and expression of TNF-α, IL-6, CXCL8, CCL-2 and VEGF | –                                                                         | (J.-D. Lee et al., 2009)                |
|                      | Quercetin, kaempferol and myricetin | 1, 10, 100 µM | hCBMCs | Inhibition of IL-6 release                                              | –                                                                         | (Kempuraj et al., 2005)                 |
|                      | Quercetin          | 10 and 100 µM | hCBMCs | Inhibition of CXCL8 and TNF-α release                                 | –                                                                         | (Kempuraj et al., 2005)                 |
|                      | Quercetin          | 10, 30 and 60 µM | hCBMCs | Inhibition of CXCL8 and TNF-α release                                 | –                                                                         | (Chuang et al., 2010)                   |
|                      |                   |        |           | (continued on next page)                                               |                                                                           |                                          |


6.2. Anti-inflammatory activity of quercetin and derivatives on human cells

Wu et al. showed that treatment with quercetin and rutin at 20 μM significantly inhibits the expression of the pro-inflammatory genes and proteins TNF-α, IL-1β, and COX-2 on human monocytic THP-1 cells (Wu et al., 2008).

The anti-inflammatory effect of quercetin and its circulating metabolites on human umbilical vein smooth muscle cells (HUASMC) was conducted. HUASMC cells were activated with TNF-α to mimic the inflammatory conditions present at atherosclerotic sites. TNF-α induced an increase in the secretion and expression of VCAM-1 and ICAM-1 (adhesion molecules involved in the inflammatory and immune response) and COX-2. Quercetin at 10 μM decreased the secretion of VCAM-1 and ICAM-1 and downregulated gene expression. At 2 and 10 μM, quercetin decreased the secretion and expression of COX-2. Quercetin metabolites had no effect at all concentrations tested. The physiologically relevant metabolites of quercetin did not mimic the effects of quercetin on human vascular smooth muscle cell function in terms of reduced expression of adhesion molecules and a chemokine intimately involved in the inflammatory response (Winterbone et al., 2009). The same authors had shown that human umbilical vein endothelial cells (HUVEC) treated with a mixture of LPS and TNF-α to mimic pro-inflammatory conditions, there was a very marked increase in the surface expression of ICAM-1 and VCAM-1. Quercetin (2 and 10 μM) and quercetin-3 glucuronide (2 μM) decreased the surface expression of ICAM-1. Quercetin (10 μM), quercetin, quercetin-3-sulfate (2 μM), quercetin-3 glucuronide (2 μM) and quercetin-3-glucuronide (2 μM) reduced the surface expression of VCAM-1 whereas quercetin (10 μM) was the only to decrease the expression of ICAM-1. For the expression of CCL-2, only quercetin (10 μM) induced an inhibitory effect. These results indicate that quercetin and its metabolites, at physiological concentrations, can inhibit the expression of key molecules involved in monocyte recruitment during the inflammatory state (Tribolo et al., 2008). Other studies confirmed these effects. For example, Mochizuki et al. showed that quercetin 3-glucuronide had no effect on the expression of ICAM-1 induced by TNF-α in human aortic endothelial cells (HAECs) compared to quercetin at 40 μM (Mochizuki et al., 2004).

Quercetin and its metabolites (quercetin 3-glucuronide, quercetin 3′-sulfate and 3′-methylerucetin-3-glucuronide) reduced the expression of COX-2 mRNA in colon cancer cells (Caco2) not stimulated and stimulated by IL-1β. Quercetin and quercetin-3′-sulfate, in contrast to quercetin-3-glucuronide and 3′-methylerucetin-3-glucuronide, also inhibited COX-2 activity at 10 μM (O’Leary et al., 2004).

In the human hepatocyte-derived cell line Chang Liver (CHL), quercetin and kaempferol (5 – 200 μM) produced a decrease in the
concentration of iNOS, COX-2 and C-reactive protein (CRP). A more significant effect for kaempferol was noted at lower concentrations. Both flavonols also significantly inhibited the mRNA level of iNOS, COX-2 and CRP. Inhibitory effects of quercetin and kaempferol were also observed on the activation of NF-κB and on the protein concentration of the phosphorylated form of inhibitor IκB and IKK (IκB kinase) α. The mechanism involved would be the blocking of the activation of the NF-κB transcriptase pathway. The stronger effect of kaempferol at lower concentrations could be due to the absence of a hydroxyl group at the 3, compared to quercetin (García-Mediavilla et al., 2007).

Nair et al. studied the anti-inflammatory potential of quercetin on human peripheral blood mononuclear cells (PBMC). Results show that quercetin (1–50 μM) significantly inhibits TNF-α production and gene expression in a dose-dependent manner (Nair et al., 2006).

Another study showed that quercetin, myricetin and fisetin (10 – 100 μM) significantly inhibited the nuclear enzyme PARP-1 involved in acute or chronic inflammatory diseases on A549 lung epithelial cells treated with MNNG (N-methyl-N-′-nitro- N-nitrosoguanidine). In addition, the authors showed a decrease in CXCL8 production after LPS treatment of A549 cells in the presence of quercetin and fisetin (10 μM) (Geraets et al., 2007). These data suggest that their PARP-1 inhibitory activity may contribute to anti-inflammatory effects via inhibition of NF-κB. Indeed, PARP-1 has been reported to be a co-activator of NF-κB which plays a major role in the inflammatory and immune response and regulates the production of pro-inflammatory cytokines and chemokines such as CXCL8 (Hassa and Hottiger, 1999; Oliver et al., 1999).

Lee et al. showed that pre-treatment of human embryonic cells (HEK-293) with kaempferol, quercetin or fisetin (40 μM) exerted inhibition of CXCL8 mRNA expression that had been induced by TNF-α. The effect was more pronounced for fisetin. The authors evaluated the degradation of IκBα and the activation of NF-κB to determine whether they were modulated by flavonoids in HEK 293 cells stimulated by TNF-α. Pretreatment (40 μM) with these flavonoids induced a decrease in phosphorylation and degradation of IκBα, as evidenced by Western Blotting. Again, the effect with fisetin was more pronounced. To further explore the effects of flavonoids on TNF-α-induced NF-κB activation, the signal induced subcellular localization of NF-κB was evaluated by indirect immunofluorescence analysis. TNF-α-induced nuclear accumulation of NF-κB p65 was completely abolished by pretreatment of the cells with fisetin, whereas pretreatment with kaempferol, quercetin or chrysin were less effective at suppressing the TNF-α-induced nuclear accumulation of NF-κB p65. These flavonoids inhibited phosphorylation and degradation of IκBα and translocation of NF-κB p65 in HEK 293 cells stimulated by TNF-α, but the effectiveness of these flavonoids varied depending on the compound (Lee et al., 2009).

Fisetin showed a significant anti-inflammatory effect on RA FLS (Rheumatoid arthritis fibroblast-like synovial cells) stimulated by IL-1β. Indeed, fisetin in a dose dependent manner (0.1–10 μg/mL and 1–100 μg/mL respectively) significantly reduced the production and expression of TNF-α, IL-6, CXCL8, CCL-2 and VEGF (Lee et al., 2009).

Other studies have shown that quercetin, kaempferol and myricetin had anti-inflammatory activity on cultured mast cells derived from human umbilical cord blood (hCBMCs). All three flavonoids (1, 10, 100 μM) inhibited IL-6 release induced by anti-IgE. Only quercetin and kaempferol inhibit the release of CXCL8 (10 μM) and TNF-α (10 and 100 μM). These compounds differ only in the difference in hydroxyl groups on the B-ring (3 OH in myricetin, 2 OH in quercetin and 1 OH in kaempferol), therefore a structure-activity relationship can be considered (Kempuraj et al., 2005).

Quercetin (10, 30 and 60 μM) has attenuated the TNF-α-induced expression of inflammatory genes such as interleukin IL-6, IL-1β, CXCL8 and CCL-2 and the secretion of IL-6, CXCL8 and CCL-2. Quercetin attenuates the TNF-α-mediated phosphorylation of extracellular signal kinase and c-Jun-NH2-terminal kinase. Quercetin attenuates the TNF-α-mediated phosphorylation of c-Jun and degradation of inhibitory κB protein. Using primary human stromal vascular cells, quercetin, decreased the TNF-α induced transcriptional activity of the nuclear factor κB (Chuang et al., 2010).

The beneficial immunomodulatory effect of quercetin was evaluated on peripheral blood mononuclear cells (PBMC) isolated from multiple sclerosis (MS) patients and from normal healthy subjects. Quercetin reduced the production of several pro-inflammatory mediators crucial in the process of MS pathology namely IL-1α, TNF-α and MMP-9 in a dose-dependent manner (5–200 μM) (Sternberg et al., 2008).

Finally, quercetin (10 μM) showed anti-inflammatory effect on the HAEs stimulated by TNF-α, by decreasing very significantly the expression of NF-κB, p38MAPK and ERK1 and 2 (Chao et al., 2013).
6.3. Anti-inflammatory activity of quercetin and derivatives in vivo

Adult male Wistar rats having undergone olfactory bulbectomy (OBX) surgery were used as models to assess the anti-inflammatory effects of flavonoids. OBX leads to increased levels of pro-inflammatory cytokines such as IL-1β and TNF-α in the brain (Miynt et al., 2007) and promotes pathological damage by accompanying inflammatory reactions (Song et al., 2009). It was shown that OBX caused a significant increase in IL-6 and TNF-α levels in the cerebral cortex and hippocampal brain regions compared to the control group. Treatment with 40 and 80 mg/kg of quercetin significantly reduced IL-6 and TNF-α levels compared to the OBX group. This demonstrates the anti-inflammatory effect of quercetin (Rinw and Kumar, 2013).

Quercetin-3-glucoside (100 mg/kg) had an anti-inflammatory effect on female mice (C57BL/6) made diabetic by reducing levels of p65, a member of the NF-κB family of transcription factors (Tan et al., 2018).

Guardia et al. studied the anti-inflammatory effect of quercetin and rutin. Experimental arthritis was induced in female Wistar rats according to the method of adjuvant-carrageenan-induced inflammation (AChI). Rutin was much more effective than quercetin (80 mg/kg) in reducing edema, nodules and ankylosis. These 2 compounds differ by the presence of the rutinoside sugar in position 3. This substitution could be at the origin of the increased anti-inflammatory effect of rutin (Guardia et al., 2001).

Oral administration of fisetin (29 mg/kg) significantly suppressed the acute pulmonary inflammation induced by LPS in a C57BL/6 male mouse model. After 24 h LPS treatment, fisetin reduced the transcription of the cytokines IL-1β, IL-6 and TNF-α as well as the chemokines MIP-1α and MIP-2, suggesting that at this time frame, the NF-κB-mediated transcription was attenuated. In addition, the fisetin reduced the transcription of the inhibitory protein of NF-κB IkBα, suggesting that at this point, the LPS-induced activation of NF-κB was no longer increased (Geraets et al., 2009).

The anti-inflammatory activity of kaempferol by modulating the cyclooxygenase pathway via inhibition of nitric oxide synthesis was investigated. In male Wistar rats, kaempferol administered orally at doses of 50 and 100 mg/kg showed significant inhibition of carrageenan-induced nitrite production and prostaglandin-E2 generation. Modulation of the cyclooxygenase pathway via inhibition of nitric oxide synthesis contributes significantly to the anti-inflammatory activity of kaempferol (Mahat et al., 2010).

The anti-inflammatory properties of quercetin were confirmed in vivo in female C57BL/6 mice fed quercetin-enriched diets (0.1 mg/g diet). Results highlights that plasma levels of TNF-α were decreased with the quercetin supplemented diet (Boesch-Saadatmandi et al., 2011).

In BALB/c mouse model, carbon tetrachloride (CCl₄) induced necrotic areas and inflammation in the liver and obvious alteration of the sinusoidal and tubular architecture of the liver. These morphological changes and inflammation were improved in the group of mice given quercetin orally (50 mg/kg/day). F4/80 and CD68 macrophage markers were increased in livers after chronic CCl₄ injury compared to control livers. Macrophage infiltration into livers was significantly reduced in fibrotic mice treated with quercetin. Mice receiving quercetin treatment also had decreased mRNA expression levels of TNF-α, IL-1β, IL-6 and CCL-2 (Li et al., 2018).

In a Sprague-Dawley rat model with acute lung injury (ALI) induced by LPS, quercetin (50 mg/kg) counter-squared the increased secretion of TNF-α, CXCL8, IL-1β, IL-6 in bronchoalveolar lavage fluid samples. Due to its anti-inflammatory action, quercetin may have therapeutic potential in the prevention of ALI (Huang et al., 2015).

Male Wistar rats were treated orally with 50% ethanol, which resulted, among other effects, in inflammatory infiltration. This inflammation resulted in increased levels of cytokines such as IL-1β, IL-1, IL-6, CXCL8 and TNF-α in rat plasma and decreased levels of IL-10. In this in vivo model, preventive treatment with quercetin at 5, 10 and 20 mg/kg counteracts the inflammatory effect induced by ethanol (Chen, 2010).

Males ICR mice were exposed to nickel sulfate to induce liver damage and an inflammatory state. Quercetin treatments (40 and 80 mg/kg) decreased total DNA methyltransferase (DNMT) activity and the level of DNA methylation of NF-E2-bound factor 2 (Nrf2) DNA in the livers of nickel-treated mice. Quercetin also induced nuclear translocation of Nrf2 and heme oxygenase-1 (HO-1) activity. In addition, quercetin decreased the production of pro-inflammatory markers including TNF-α, IL-1β and iNOS. Quercetin significantly inhibited p38 and the transcription signal activator 1 (STAT1) transducer and activator, which in turn inactivated NF-κB and inflammatory cytokines in the liver of nickel-treated mice. In conclusion, these results suggest that quercetin’s inhibition of nickel-induced inflammation is associated with its ability to modulate the Nrf2/HO-1 and p38/STAT1/NF-κB signaling pathway (Liu et al., 2015).

In a model of Male Wistar rats made diabetic by streptozotocin (70 mg/kg), treatment with quercetin (45 mg/kg) inhibited the transcription pathway NF-κB, the protein level of IκBα and upregulated the protein level IκKα and iNOS. Treatment with quercetin, by suppressing the IκK/NF-κB signal transduction pathway demonstrates strong anti-inflammatory activity (Dias et al., 2005).

Seo et al. showed that quercetin (6.25–25 μM) decreased NO generation in a zebrafish model with a high-fat diet. The same authors demonstrated the anti-inflammatory activity of quercetin (25–100 mg/kg) in a model of ICR male mice also fed a high-fat diet by inhibiting the signaling factors ERK, JNF and p38MAPK. Quercetin treatment also decreased CCL-2, TNF-α, IL-1β and IL-6 concentrations and increased IL-10 (Seo et al., 2015).

The efficacy of the combination of quercetin and sitagliptin, a selective dipeptidyl peptidase-IV (DPP-IV) inhibitor, in the management of streptozotocin (STZ)-induced diabetic rats was realized. Quercetin alone or in combination with sitagliptin at 50 mg/kg in adult male Wistar rats normalized serum levels of TNF-α and NF-κB relative to the diabetic control group. These results demonstrate the anti-inflammatory effect of quercetin in a diabetes-induced inflammatory model (Etah et al., 2019).

On the same animal model, intraperitoneal application of quercetin (50 mg/kg) prior to induction of ischemia has a direct effect on the overexpression of the anti-inflammatory cytokine IL-10 in the jejunal wall tissues and its serum concentration in the blood (Curgali et al., 2018). According to Ciccia et al. (Ciccia et al., 2010), IL-10 plays a key role in the maintenance of intestinal immune homeostasis, which strongly suggests the potential of the IL-10 pathway as a strategy to restore intestinal homeostasis in human intestinal inflammation. Preventive application of quercetin prior to induction of jejunal ischemia stimulates faster restoration of the jejunal mucosa and appears to have immunomodulatory and anti-inflammatory effects.

Mascaraque et al. (Mascaraque et al., 2014) studied the anti-inflammatory effect of rutin in the CD4 + CD62L + T cell transfer model of colitis, one of the closest to human disease. Colitis was induced by the transfer of CD4 + CD62L + T cells to Rag1-/- mice. Rutin was administered by gavage in post-treatment (57 mg/kg/day). Treatment with rutin decreased the secretion of pro-inflammatory cytokines (IFN-γ and TNF-α) by cells of the mesenteric lymph nodes ex vivo. Colonic expression of pro-inflammatory genes, including IFN-γ, TNFα, CXCL1, S100A8 and IL-1β, was significantly reduced by more than 80%. Rutin exerts intestinal anti-inflammatory activity in chronic T-cell dependent colitis.

In summary, quercetin and its derivatives are very promising anti-inflammatory molecules. They act on the inhibition of the expression and secretion of many cytokines and chemokines such as TNF-α, iNOS and NO, IL-1β, IL-6, CCL-2, RANTES, COX-2... The main pathways involved are NF-kB, ERK1/2, JNK and p38MAPK. These molecules therefore have a wide range of action.
7. Conclusion

Quercetin is a bioactive polyphenolic flavonol that is abundant in fruits and vegetables. It is known for its various beneficial properties to human health such as the antioxidant effects on glutathione, enzymes, signal transduction pathways and ROS production. It is also very effective in combating viral infections. However, its application in the pharmaceutical field still limited, mainly due to its poor bioavailability. Some quercetin derivatives have shown better activities than the parent compound. A structure-activity relationship (SAR) can be put forward. Based on SAR studies, the design of new quercetin derivatives would improve the bioavailability of the compound, reduce toxicity and potentiate the biological properties. Studies demonstrated that quercetin and its derivatives possess a series of important antiviral activities against the various stages of replication in vitro and in vivo by affecting intracellular replication or the process of attachment and entry of several viruses. Quercetin acts against the fusion mechanism by blocking target proteins involved in the fusion of the viral membrane with the cell membrane, the analysis of the relationship between the chemical structures of the compounds and their antiviral activities may point to putative sites that could be used as models for the design of new antiviral agents. As resistance to antiretrovirals drugs is increasing, there is a need to develop new agents that are not as expensive and toxic as those currently used. The fundamental challenge that remains is to develop targeted therapy using novel compounds to bypass drug resistance or to replace antivirals with unwanted cytotoxic effects. Future experiments are still necessary to determine the inhibitory mechanism displayed by flavonoids and phenolic acids in order to assess their applicability as an antiviral therapeutic agent. The future challenge is to infer the optimal benefits of quercetin and its derivatives with SAR studies that provide information to increase the efficacy of parent molecules. In the age of COVID-19 pandemic, polyphenols are being regarded as molecular allies to prevent the infection and decrease the inflammatory storm induced by the SARS virus. As discussed in this review, the antiviral and anti-inflammatory potential of quercetin and derivatives are clearly in favor of this potential.

Author statement

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Bullets points

- Quercetin is one of the most potent antioxidants among polyphenols.
- Quercetin and its derivatives are good candidates as antiviral agents.
- Quercetin derivatives should exhibit better biological activity, selectivity towards biological target of interest, increased bioavailability and reduced toxicity.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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References

A current view on inflammation, 2017. Nat Immunol 18, 825–825. 10.1038/nl.3978.
Berga, N., Fezer, R., Conrad, J., Befus, U., Carle, R., Schier, A., 2005. Screening of mango (Mangifera indica L) cultivars for their contents of flavonol O- and xanthone C-glycosides, anthocyanins, and pectin. J. Agric. Food Chem. 53, 1563–1570, 10.1021/jf0480469.
Bhattacharyya, A., Chattopadhyay, R., Mitra, S., Crowe, S.E., 2014. Oxidative Stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol. Rev. 94, 329–354. https://doi.org/10.1152/physrev.00040.2012.
Boesch-Saadatmandi, C., Loboda, A., Wagner, A.E., Stachurska, A., Jozkowicz, A., Polak, J., Diering, F., Wodziana, G., 2011. Effect of quercetin and its metabolites isorhamnetin and quercetin-3-glucuronide on inflammatory gene expression: role of miR-155. J. Nutr. Biochem. 22, 293–299. https://doi.org/10.1016/j.jnutbio.2010.02.006.
Booth, A.W., Haenen, G.R.M.M., Bart, A., 2008. Health effects of quercetin: from antioxidant to nutraceutical. Eur. J. Pharmacol. 585, 325–337. https://doi.org/10.1016/j.ejphar.2008.03.008.
Breinbauer, R., Vetter, J.R., Waldmann, H., 2002. From protein domains to drug candidates—natural products as guiding principles in the design and synthesis of compound libraries. Angew. Chem. Int. Ed. Engl. 41, 2878–2890. https://doi.org/10.1002/1521-3773(20020816)41:23<2878::AID-ANCI3>3.0.CO;2-H.
Bulger, P.G., Bagal, S.K., Marriott, R., 2008. Recent advances in biomimetic natural product synthesis. Nat. Prod. Rep. 25, 254–297. https://doi.org/10.1039/b709098h.
Burdz, S., Oleszek, W., 2001. Antioxidant and antiradical activities of flavonoids. Pharmacol. Rep. 53, 775–781. 10.1016/S1422-1381(01)70011-2.
Cai, X., Fang, Z., Dou, J., Yu, A., Zhai, G., 2013. Bioavailability of quercetin: problems and promises. Curr. Med. Chem. 20, 2572–2582. https://doi.org/10.2174/092987713509990120.
Carvalho, O.V., Botelho, C.W., Ferreira, C.G.T., Ferreira, H.C.C., Santos, M.R., Dávila, M.A., Oliveira, T.T., Soares-Martins, J.A.P., Almeida, M.R., Silva Júnior, A., 2013. In vitro inhibition of canine distemper virus by flavonoids and phenolic acids: implications of structural differences for antiviral design. Res Vet Sci 95, 717–724. https://doi.org/10.1016/j.rvsc.2013.04.013.
Chang, Q., Wang, Y.-S., 2004. Identification of flavonoids in Hakmeitau beans (Vigna sinensis) by high-performance liquid chromatography-electrospray mass spectrometry (LC-ESI/MS). J. Agric. Food Chem. 52, 6694–6699. https://doi.org/10.1021/jf040911a.
Chao, P.-Y., Huang, Y.-P., Hsieh, W.-B., 2013. Inhibitive effect of purple sweet potato leaf extract and its components on cell adhesion and inflammatory response in human aortic endothelial cells. Cell Adh. Migr. 7, 237–245. https://doi.org/10.4162/cam.2013.7.3.08.
Chen, J.-C., Ho, F.-M., Chao, C.-P., Jeng, K.-C.G., Hsu, H.-B., Lee, S.-T., Wu, Wen Tung, Lin, W.-W., 2005. Inhibition of iNOS gene expression by quercetin is mediated by the inhibition of IkB kinase, nuclear factor-kappa B and STAT1, and depends on heme oxygenase-1 induction in mouse BV-2 microglia. Eur. J. Pharmacol. 521, 9–20. https://doi.org/10.1016/j.ejphar.2005.08.005.
Chen, X., 2010. Protective effects of quercetin on liver injury induced by ethanol. Phcog. Mag. 6, 135–141. https://doi.org/10.3945/ajcn.2010.29807.
Berardini, N., Fezer, R., Conrad, J., Befus, U., Carle, R., Schier, A., 2005. Screening of mango (Mangifera indica L) cultivars for their contents of flavonol O- and xanthone C-glycosides, anthocyanins, and pectin. J. Agric. Food Chem. 53, 1563–1570, 10.1021/jf0480469.
Ciccio, F., Accardo-Palumbo, A., Giardina, A., Maggio, P.D., Principato, A., Bombardieri, M., Rizzo, A., Alessandro, R., Ferrante, A., Principe, S., Peralta, S., Conte, F., Drago, S., Craxi, A., Leo, G.D., Triolo, G., 2010. Expansion of intestinal CD4+ T cells in patients with ankylosing spondylitis: a putative role for interleukin-10 in preventing intestinal Th1 response. A&R 62, 3625–3634, 10.1002/art.27699.
Cincin, Z.B., Urdn, M., Kiran, I., Birellar, E.S., Baran, Y., Cakmakoglu, B., 2014. Molecular mechanisms of quercetin-induced apoptosis in non-small cell lung cancer. Arch. Med. Res. 45, 445–454. 10.1016/j.arcmed.2014.08.002.
Comalada, M., Ballester, I., Ballein, E., Sierra, S., Xaus, J., Galvez, J., Medina, F.S., de Zarruzelo, A., 2006. Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: analysis of the structure–activity relationship. Biochem. Pharmacol. 71, 1010–1021. https://doi.org/10.1016/j.bcp.2006.07.016.
Comalada, M., Camaesco, B., Sierra, S., Ballester, I., Xaus, J., Galvez, J., Zarruzelo, A., 2005. In vivo quercetin anti-inflammatory effect involves release of quercetin,
which inhibits inflammation through down-regulation of the NF-κB pathway. Eur. J. Immunol. 35, 584–592. doi: 10.1002/eji.200425778.

Comalli, G.S., Xue, X., Al-Saadi, A.F., Lopez-Cruz, J.G., Gelada, A. 2003. PKC is involved in JNK activation that mediates LPS-induced TNF-α, which induces apoptosis in macrophages. Am. J. Physiol. Cell Physiol. 285 doi: 10.1152/ajpcell.2003.285.5.C1235-C1245.

Cotin, S., Callieste, C., M.-C. Hantz, S., Duroux, J.-L., Ravvoldin, W.D., Ploy, M.-C., Alain, S. 2012. Eight flavonoids and their potential as inhibitors of human cytomegalovirus replication. Antiviral Res. 96, 181–186. doi: 10.1016/j.antiviral.2011.07.003.
Liu, C.-M., Ma, J.-Q., Xie, W.-R., Liu, S.-S., Feng, Z.-J., Zheng, G.-H., Wang, A.-M.,
Lin, Y.-J., Chang, Y.-C., Hsiao, N.-W., Hsieh, J.-L., Wang, C.-Y., Kung, S.-H., Tsai, F.-.Li, X., Jin, Q., Yao, Q., Xu, B., Li, L., Zhang, S., Tu, C., 2018. The flavonoid quercetin
Kwon, E.-K., Lee, D.-Y., Lee, H., Kim, D.-O., Baek, N.-I., Kim, Y.-E., Kim, .H.-Y., 2010.
Kim, D.-O., Chun, O.K., Kim, Y.J., Moon, H.-Y., Lee, C.Y., 2003. Quantification of
Kim, Y., Narayanan, S., Chang, .K.-O., 2010. Inhibition of influenza virus replication by
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N.,
Khanavi, M., Moghaddam, G., Oveisi, M., Narnat, B., Rostami, M.,
Sanghvi, S., Rau, R., Bhatnagar, D., 2013. Hyperosorh and anthocyanin content of ten
different pomegranate cultivars. Pak. J. Biol. Sci. 16, 636-644. https://doi.org/
Kanzawa, H., Marimoutou, M., Le Sage, F., Smadja, J., Lefebvre d'O, 2012. Flow cytometry
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N.,
Cetrou, C.L., Theoharides, T.C., 2005. Flavonoids inhibit proinflammatory mediator release,
intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br. J. Pharmacol. 145, 934-944. https://doi.org/10.1038/j.
bjp.0702646.
Khanavi, M., Moghaddam, G., Oveisi, M.R., Sadeghi, N., Jannat, B., Rostami, M.,
Sanghvi, S., Rau, R., Bhatnagar, D., 2013. Hyperosorh and anthocyanin content of ten
different pomegranate cultivars. Pak. J. Biol. Sci. 16, 636-644. https://doi.org/
Kanzawa, H., Marimoutou, M., Le Sage, F., Smadja, J., Lefebvre d'O, 2012. Flow cytometry
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N.,
Cetrou, C.L., Theoharides, T.C., 2005. Flavonoids inhibit proinflammatory mediator release,
intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br. J. Pharmacol. 145, 934-944. https://doi.org/10.1038/j.
bjp.0702646.
Khanavi, M., Moghaddam, G., Oveisi, M.R., Sadeghi, N., Jannat, B., Rostami, M.,
Sanghvi, S., Rau, R., Bhatnagar, D., 2013. Hyperosorh and anthocyanin content of ten
different pomegranate cultivars. Pak. J. Biol. Sci. 16, 636-644. https://doi.org/
Kanzawa, H., Marimoutou, M., Le Sage, F., Smadja, J., Lefebvre d'O, 2012. Flow cytometry
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N.,
Cetrou, C.L., Theoharides, T.C., 2005. Flavonoids inhibit proinflammatory mediator release,
intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br. J. Pharmacol. 145, 934-944. https://doi.org/10.1038/j.
bjp.0702646.
Khanavi, M., Moghaddam, G., Oveisi, M.R., Sadeghi, N., Jannat, B., Rostami, M.,
Sanghvi, S., Rau, R., Bhatnagar, D., 2013. Hyperosorh and anthocyanin content of ten
different pomegranate cultivars. Pak. J. Biol. Sci. 16, 636-644. https://doi.org/
Kanzawa, H., Marimoutou, M., Le Sage, F., Smadja, J., Lefebvre d'O, 2012. Flow cytometry
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N.,
Cetrou, C.L., Theoharides, T.C., 2005. Flavonoids inhibit proinflammatory mediator release,
intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br. J. Pharmacol. 145, 934-944. https://doi.org/10.1038/j.
bjp.0702646.
Khanavi, M., Moghaddam, G., Oveisi, M.R., Sadeghi, N., Jannat, B., Rostami, M.,
Sanghvi, S., Rau, R., Bhatnagar, D., 2013. Hyperosorh and anthocyanin content of ten
different pomegranate cultivars. Pak. J. Biol. Sci. 16, 636-644. https://doi.org/
Kanzawa, H., Marimoutou, M., Le Sage, F., Smadja, J., Lefebvre d'O, 2012. Flow cytometry
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N.,
Cetrou, C.L., Theoharides, T.C., 2005. Flavonoids inhibit proinflammatory mediator release,
intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br. J. Pharmacol. 145, 934-944. https://doi.org/10.1038/j.
bjp.0702646.
Khanavi, M., Moghaddam, G., Oveisi, M.R., Sadeghi, N., Jannat, B., Rostami, M.,
Sanghvi, S., Rau, R., Bhatnagar, D., 2013. Hyperosorh and anthocyanin content of ten
different pomegranate cultivars. Pak. J. Biol. Sci. 16, 636-644. https://doi.org/
Kanzawa, H., Marimoutou, M., Le Sage, F., Smadja, J., Lefebvre d'O, 2012. Flow cytometry
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N.,
Cetrou, C.L., Theoharides, T.C., 2005. Flavonoids inhibit proinflammatory mediator release,
intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br. J. Pharmacol. 145, 934-944. https://doi.org/10.1038/j.
bjp.0702646.
predominant human metabolites on adhesion molecule expression in activated human vascular endothelial cells. Atherosclerosis 197, 50-56. https://doi.org/10.1016/j.atherosclerosis.2017.03.023.

Uppungundla, N., Engelbert, A., Vandhana Ravindranath, S., Clausen, E.C., Lay, J.O., Gidden, J., Carrier, D.J., 2009. Switchgrass water extracts: extraction, separation and biological activity of rutin and quercetin. J. Agric. Food Chem. 57, 7763-7770, https://doi.org/10.1021/jf900996q.

Urquiaga, I., Leighton, F. 2000. Plant polyphenol antioxidants and oxidative stress. Biol. Res. 33, 55-64. https://doi.org/10.1016/s0736-976x(00)00020-0.

USDA. 2018. USDA database for the flavonoid content of selected foods, Release 3.3. https://doi.org/10.1002/jn.130.8.2073s.

Vanhees, K., de Bock, L., Godschalk, R.W.L., van Schooten, F.J., van Waa bijl van Doorn-Khosrowshahi, S.B., 2011. Prenatal exposure to flavonoids: implication for cancer risk. Toxicon. Sci. 120, 59-67. https://doi.org/10.1016/j.toxsci.2014.05.008.

Verhoeyen, M.E., Boyv, A., Collins, G., Muir, S., Robinson, S., de Vos, C.H.R., Collier, S., 2002. Increasing antioxidant levels in tomatoes through modification of the flavonoid biosynthetic pathway. J. Exp. Bot. 53, 2099-2106. https://doi.org/10.1038/jcb.04f004.

Vollmannova, A., Musilova, J., Lidikova, J., Jarvay, J., Snicr, M., Toth, T., Bojtanska, T., Cissova, I., Kreft, I., Germ, M., 2021. Concentrations of polyphenolic acids are different genetically determined in leaves, flowers, and grain of common buckwheat (Fagopyrum esculentum Moench). Plants 10, 1142. https://doi.org/10.3390/plants10111142.

Wang, Y.-H., Cao, P.-D., Hsu, S.-L., Wen, K.-C., Hou, Y.-C., 2004. Lethal quercitin-lipoxin interaction in pigs. Life Sci 74, 1191-1197. https://doi.org/10.1016/j.blood.2003.06.044.

Winterbone, M.S., Tribudo, S., Needs, P.W., Kroon, P.A., Hughes, D.A., 2009. Physiologically relevant metabolites of quercetin have no effect on adhesion molecule or chemokine expression in human vascular smooth muscle cells. Atherosclerosis 202, 431-438. https://doi.org/10.1016/j.atherosclerosis.2008.04.040.

Wu, C.-H., Wu, C.-F., Huang, H.-W., Yao, J.-C., Yen, G.-C., 2009. Naturally occurring flavonoids attenuate high glucose-induced expression of proinflammatory cytokines in human monocyte THP-1 cells. Mol. Nutr. Food Res. 53, 984-995. https://doi.org/10.1002/mnfr.2008000495.

Wu, W., Li, Y., Li, X.-E., Xue, J., Jiang, S., Li, S., Yang, J., 2015. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. Viruses 8, E6. 10.3390/v8010006.

Xau, J., Comalada, M., Valledor, A.F., Lloberas, J., Lazaro-Campos, S., 2014. Modulation of PI3K-LXR activation, antioxidant and antiinflammatory effects of flavonoids. J. Agric. Food Chem. 54, 9796-9804. https://doi.org/10.1021/jf5020719.

Yao, L., Datta, N., Tomita, K., 2019. Antiviral and anti-inflammatory effects of flvone and quercetin. A J. Mol. Biol. 53, 64. https://doi.org/10.1080/0306426X.2019.1638051.

Yao, L., Fujisawa, K., Nakagawa, T., Tomita, K., 2019. Antiviral mechanism of quercetin against influenza A virus (IAV) infection. Virology 547, 200-210. https://doi.org/10.1016/j.virol.2019.09.006.

Zargar, S., Siddiqui, N.A., Ansari, M., Alam, M.A., 2015. Metabolites of isolated from multiple sclerosis patients. J. Neuroimmunol. 205, 142-146. https://doi.org/10.1016/j.jneuroim.2009.01.011.

Zandi, K., Teoh, B.-T., Sam, S.-S., Wong, P.-F., Mustafa, M.R., AbuBakar, S., 2011b. Quercetin reduces oxidative stress and induces antidepressent-like effect in olfactory bulbectomized rats. Neurosci. J. 67, 383. https://doi.org/10.3109/10715769509145649.

Zhang, Y.-H., Zhao, P.-Y., Yang, Q.-D., 2007. In vitro anti-HIV and -HSV activity and safety of sodium rutin sulfate as a potential of quercetin as a cardiovascular agent. Eur. J. Med. Chem. 155, 889-894. https://doi.org/10.1016/j.ejmech.2018.06.053.