

## DIFFERENT TECHNIQUES OF EXTRACTION AND ANTIVIRAL ACTIVITIES OF QUERCETIN AGAINST VIRUSES SUCH AS CORONAVIRUS, INFLUENZA VIRUS, EBOLA VIRUS, ZIKA VIRUS, AND OTHER VIRUSES

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### ABSTRACT

Quercetin (QCT) is a flavonoid, existed as a pigment in various plants. It is a bioactive compound that has a favorable effect on human health. Our work concerns the selection of different rapid techniques for QCT extraction, published on the different scientific databases, as ultrasound-assisted enzymatic extraction process, supercritical CO<sub>2</sub> extraction, microwave-assisted extraction and consists of researching the antiviral activity of QCT and derivatives against viruses such as coronaviruses, influenza virus, human respiratory syncytial virus, Epstein-Barr virus gastric tumor, anti-hepatitis B virus, Zika virus, and Ebola. Following this research, we found that this molecule has a broad-spectrum antiviral activity. Is it effective in controlling this new form of coronavirus, this devastating virus, which currently affects thousands of people?

**Keywords:** Ultrasound-assisted extraction, Microwave-assisted extraction, Antiviral activities, Coronavirus, Influenza virus.

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### INTRODUCTION

Flavonoids represent a group of naturally occurring polyphenolic compounds that existed as a pigment in various fruits, vegetables, and pharmaceutical plants [1,2]. Polyphenols are known by their biological activity, including anti-viral, anti-oxidant, anti-bacterial, anti-cancer, vasodilatory, and anti-diabetic activities [3]. Quercetin (QCT) is one of the natural antioxidants [3] and the phenolic hydroxyl groups on the backbone of QCT can inhibit the oxidative damage caused by reactive oxygen species (ROS) [4,5]. Recent studies have also demonstrated the antiviral activity of these compounds against several of pathogens, including Ebola virus, hepatitis B virus (HBV), Chikungunya virus (CHIKV), hepatitis C virus (HCV), Mayaro virus, Epstein-Barr virus (EBV), and influenza virus (IAV) [6-8]. Our work concerns the selection of different rapid technics for QCT extraction, published on the different scientific databases, and we present several works on the antiviral effect of QCT and its derivatives against viruses.

### SOURCES OF QCT

QCT (3, 3', 4', 5, 7-pentahydroxyflavone) or Quercetol, Quertin, Xanthaurine (Fig. 1) is an organic compound of the flavonoid family [9]. It is a secondary metabolite present in some plants. Its role is to ensure the pigmentation of flowers and fruits [10]. It is known for its anti-inflammatory actions; antihistamines, anti-oxidant, anti-bacterial, anti-cancer, vasodilatory, anti-diabetic activities, and tonics for the body [11-19]. It cannot be produced in the human body [20,21]. It is one of the most abundant dietary flavonoids found in fruits, vegetables, and grains (Fig. 2) [22,23].

The highest concentrations of flavonols were found in vegetables such as onions and broccoli, fruits such as apples, cherries, and berries (blueberries, cranberries, currants, etc.), and drinks such as tea and red wine. The USDA classifies the major food plants rich in QCT [24]. We find caper (*Capparis spinosa*) with 1808-328 mg/kg, lovage (*Levisticum officinale*) 1700 mg/kg, hot pepper 14.7 mg/100 g, black elderberry (*Sambucus nigra*) 42 mg/100 g, *Theobroma cacao* 25 mg/100 g, wild blueberries (*Vaccinium myrtillus*) 7.7 mg/100 g, blackcurrants (*Ribes nigrum*) 5.7 mg/100 g, raw broccoli (*Brassica oleracea*) 3.3 mg/100 g,

green tea 2.5 mg/100 g, cherry (*Prunus cerasus*) 1.2 mg/100 g, red wine 8.3 g/l, and apple 1.5 mg/100 g [9,21,24,25]. The amount of QCT found varies considerably depending on the variety cultivated, the growing conditions, and the time of harvest. Here are some average values (Table 1).

### QCT EXTRACTION

A process about an ultrasound-assisted enzymatic extraction using an ultrasonic bath and viscozyme applied for the recovery of total flavonoid content (TFC) from pomegranate peels was optimized using response surface methodology (RSM) by applying central composite rotatable design [26]. The optimum conditions obtained were an ultra-sonication time of 41.45 min, enzyme concentration of 1.32 mL/100 mL, the incubation time of 1.82 h, and incubation temperature of 44.85° C, and the values of TFC at optimized conditions were 17.97 mg QE/g. Two strategies based on the solubility in supercritical CO<sub>2</sub>, in which CO<sub>2</sub> plays different roles, are used [27] to make QCT particles by supercritical fluid technologies. The results showed that micronized QCT particles with a mean particle size of 1.0–1.5 µm could be made through solution-enhanced dispersion by supercritical fluids process, in which CO<sub>2</sub> worked as turbulent anti-solvent. A new study aimed to investigate the effects of various solvents (water, aqueous-methanol, and aqueous-ethanol) and techniques maceration (M), ultrasound-assisted extraction (UAE), ohmic-assisted extraction (OAE), and decoction – infusion on extraction yield has been applied by Bahar *et al.* [28], the OAE with water as a solvent to score the highest rank in terms of overall efficiency. However, if the ranking is to be based on the isolation of bioactive materials at a reasonably short time, the UAE may be the preferred choice. Extracts obtained from two green extraction techniques, accelerated solvent extraction (ASE) and UAE, were evaluated [29] to inhibit the growth of bacteria implicated in alimentary pathologies and to avoid the oxidation reactions. Hydroalcoholic extracts obtained by UAE resulted to have higher antibacterial and antioxidant properties compared to aqueous extracts from ASE. A method of designing solvents for the optimal extraction of bioactive ingredients from natural resources was developed [30] using an alcohol-water binary solvent. Using the solubility parameter, the extraction efficiency of the bioactive ingredients was correlated

with the solvent polarity. A reversed-phase high-performance liquid chromatography (HPLC) method has been developed and applied to determine resveratrol, QCT, quercitrin, and rutin content in several grape berries samples in a single analysis [31]. A study by microwave-assisted extraction was evaluated by Diana *et al.* [32]. The influence of the irradiation time and solvent concentration on the yield of phenolic compounds was studied. In conclusion, microwave technology presents some advantages such as required short times and small amounts of solvents in contrast with conventional extraction methods. A study, using RSM, was introduced [33] for the extraction of antioxidant compounds from plant biomass for the standardization of extraction of compounds of industrial interest. The optimal extraction conditions determined by full factorial design were 90 min at 80°C in water, 90 min

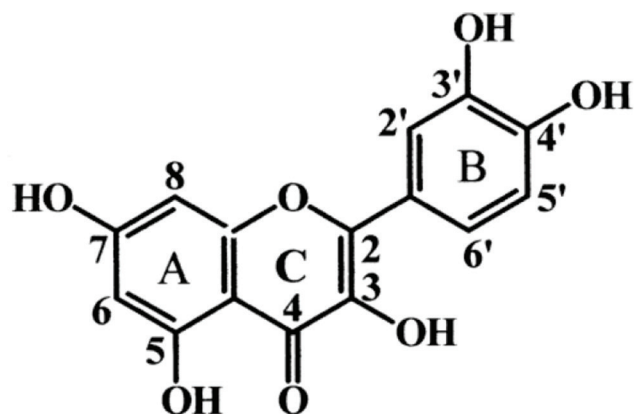


Fig. 1: Quercetin's chemical structure

at 80°C in 40% ethanol, and 90 min at 80°C in 40% acetone. Different methods as M, ASE, and supercritical fluid extraction (SFE) coupled with ASE were evaluated to obtain plant extracts with high antioxidant capacity. The most beneficial conditions were calculated for methanol and water:ethanol (50:50) extracts derived from the combination of SFE and ASE methodologies [34]. A study was introduced to extract and determine the total contents of phenolic and flavonoid compounds as well as to identify and quantify some flavonoids from Sarang semut (*Myrmecodia pendans*) [35]. The optimum extracting parameters were determined as follows: Extraction time, 4 h; ethanol/water composition, 80%; and solvent to sample ratio, 50 mL/g. Under these optimal conditions, a yield of 13.82% was obtained. An extraction method based on the application of an extracting solvent lighter than water in the ternary component solvent (aqueous solution: extracting solvent: disperser solvent) system was developed using inverted dispersive liquid-liquid microextraction and (HPLC-ultraviolet) [36]. Another study conducted by Pazhanichamy *et al.* [37] aimed to isolate and quantify flavonoids from the ethanol extract of *Costus igneus* rhizome. QCT (Rf - 0.72, 0.794%) and kaempferol (Rf - 0.35, 4.2%) were quantified by high-performance thin-layer chromatography (HPTLC) using solvent ratio of toluene:ethyl acetate:acetic acid:methanol (2.00:7.00:0.25:0.25) and toluene:ethyl acetate:methanol:formic acid (6.00:3.00:0.20:0.40), respectively. An ultrasonic-assisted extraction process has been applied by Yingpeng *et al.* [38] for QCT extraction from *Dendrobium officinale* using HPLC as a separative method. The amount of QCT obtained was 2.50–2.59 µg/g. A study investigated the application of subcritical water extraction (SWE) of QCT from onion skin. The maximum yield of QCT (16.29±0.75 mg/g onion skin) was obtained at an extraction temperature of 165° C, extraction time of 15 min, the mixture ratio of 1.5:2.5 for onion skin and diatomaceous earth. The SWE was compared with three conventional extraction methods

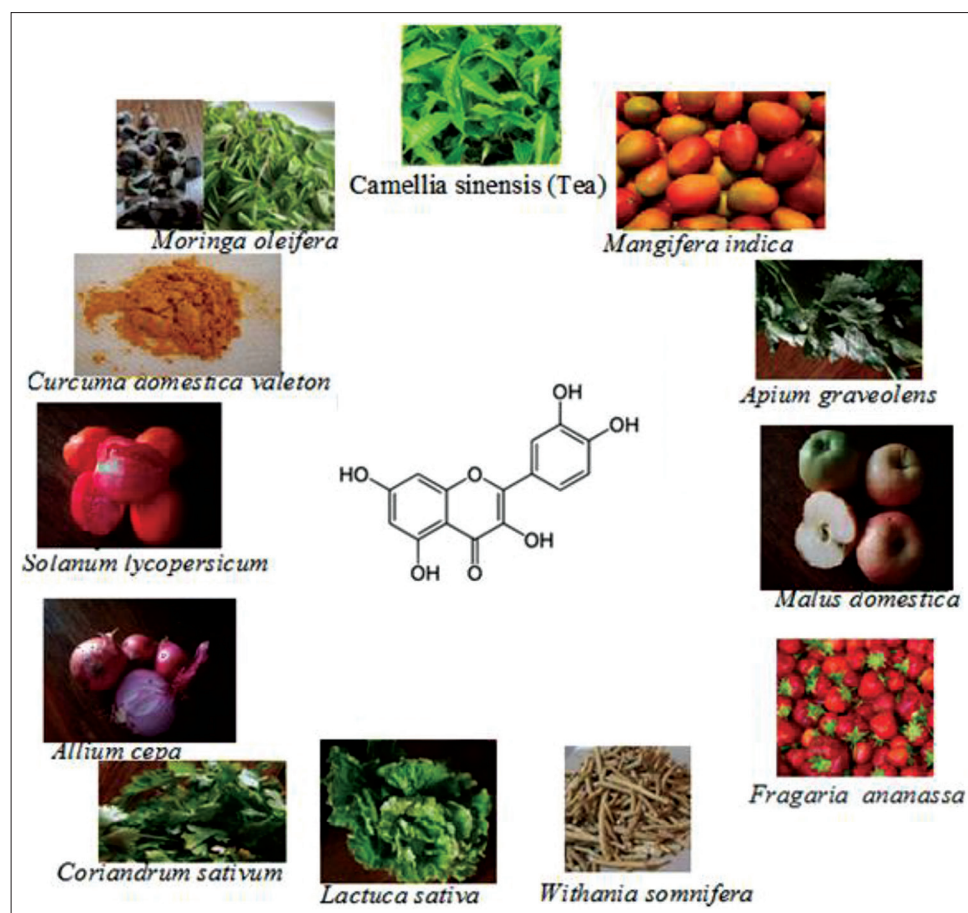


Fig. 2: The most common food plants that contain quercetin

Table 1: Food plants rich in quercetin (mg/100 g) [24]

Plant name	Family	Teneur (mg/100 g)
<i>Allium fistulosum</i>	Amaryllidaceae	/
<i>Allium cepa</i> (red onions)	Liliaceae	39.2
<i>Apium graveolens</i>	Apiaceae	/
<i>Asparagus officinalis</i>	Asparagaceae	/
<i>Brassica oleracea</i> var. <i>italica</i> (Broccoli)	Brassicaceae	3.30
<i>Brassica oleracea</i> var. <i>sabellica</i> (Kale)	Brassicaceae	22.6
Blueberries, raw	Ericaceae	7.70
<i>Calamus scipionum</i>	Calamoideae	/
<i>Camellia sinensis</i> (black)	Theaceae	2.20
<i>Camellia sinensis</i> (green)	Theaceae	2.50
<i>Capparis spinosa</i>	Capparaceae	180.8–32.8
<i>Capsicum</i>	Solanacées	14.7
<i>Centella asiatica</i>	Apiaceae	/
<i>Coriandrum sativum</i>	Apiaceae	/
<i>Curcuma domestica</i> valetou	Zingiberaceae	/
<i>Cuscuta reflexa</i>	Convolvulaceae	/
<i>Daucus carota</i>	Apiaceae	/
<i>Emblica officinalis</i>	Euphorbiaceae	/
<i>Eruca vesicaria</i>	Brassicaceae	66.2
<i>Foeniculum vulgare</i>	Apiaceae	/
<i>Fragaria ananassa</i>	Rosaceae	/
<i>Glycyrrhiza glabra</i>	Fabaceae	/
<i>Hypericum hircinum</i>	Clusiaceae	/
<i>Hypericum perforatum</i>	Hypericaceae	/
<i>Lactuca sativa</i>	Asteraceae	1.40
<i>Levisticum officinale</i>	Apiaceae	70.0
<i>Malus domestica</i>	Rosaceae	1.50
<i>Mangifera indica</i>	Anacardiaceae	/
<i>Momordica charantia</i>	Cucurbitaceae	/
<i>Moringa oleifera</i>	Moringa	/
<i>Morus alba</i>	Moraceae	/
<i>Nasturtium officinale</i>	Brassicaceae	30.0
<i>Ocimum sanctum</i>	Lamiaceae	/
<i>Petroselinum crispum</i>	Apiaceae	1.00
<i>Prunus avium</i>	Rosaceae	/
<i>Prunus cerasus</i>	Rosaceae	1.20
<i>Prunus domestica</i>	Rosaceae	/
<i>Psoralea corylifolia</i>	Fabaceae	/
<i>Ribes nigrum</i>	Grossulariaceae	5.70
<i>Sambucus nigra</i>	Adoxaceae	420
<i>Santalum album</i>	Santalaceae	/
Scallions	Liliaceae	10.7
<i>Solanum lycopersicum</i>	Solanaceae	0.80
<i>Solanum nigrum</i>	Solanaceae	/
<i>Spinacia oleracea</i>	Amaranthaceae	4.00
<i>Swertia chirayita</i>	Gentianaceae	/
<i>Theobroma cacao</i>	Sterculiacées	25.0
<i>Vaccinium myrtillus</i>	Ericaceae	7.70
<i>Vaccinium oxycoccos</i>	Ericaceae	/
<i>Vigna unguiculata</i>	Fabaceae	17.2
<i>Vitis vinifera</i>	Vitaceae	8.30 mg/L
<i>Withania somnifera</i>	Solanaceae	/

in terms of efficiency. The QCT yield by SWE was over eight-, six-, and four-fold greater than those obtained using the ethanol, methanol, and water-at-boiling-point extraction methods, respectively [39]. Optimized ultrasonic extraction conditions were applied to extract rutin and QCT from dried stalks of *Euonymus alatus* (Thunb.) Sieb. The application was shown to be highly efficient compared with classical methods [40]. A new study introduced by Dmitrienko *et al.* [41] based on the scanning electron microscopy micrographs provided evidence of more rapid opening of plant cells treated by UAE in contrast to M. State of the art methods of the extraction, preconcentration, and determination of QCT and other flavonoids are described. Some examples of QCT determination in biological fluids, food products, biologically active food supplements, pharmaceutical preparations, and plant samples are given. The extraction yields of QCT from *Raphanus sativus* L leaves have been determined using different methods, including M, thermal digestion, Soxhlet, and UAE. UAE method at 50% of ultrasound intensity

(Frequency of 50/60 kHz) for 10 min in methanol proved to be the most efficient technique in QCT extracting (11.8% yield) [42].

## IN CORONAVIRUS

Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family Coronaviridae order Nidovirales. There are four generations within the subfamily Orthocoronavirinae, namely, alphacoronavirus ( $\alpha$ -CoV), betacoronavirus ( $\beta$ -CoV), gammacoronavirus ( $\gamma$ -CoV), and deltacoronavirus ( $\delta$ -CoV). The CoV genome is an enveloped, positive-sense, single-stranded RNA with a size varying between 26 kb and 32 kb, the largest genome of known RNA viruses. Both  $\alpha$ - and  $\beta$ -CoV genera are known to infect mammals, while  $\delta$ - and  $\gamma$ -CoVs infect birds. Two recent outbreaks of viral pneumonia caused by  $\beta$ -CoVs are severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [43]. In 2002, an outbreak of SARS was first reported

in China and then spread quickly worldwide, resulting in hundreds of deaths. In 2012, MERS first emerged in Saudi Arabia and subsequently spread to other countries. In both of these epidemics, the viruses likely originated from bats and then infected humans through other intermediate animal hosts, for example, the civet (*Pauguma larvata*) for SARS-CoV and the camel for MERS-CoV. Besides, more recently coronavirus disease (COVID-19) in December 2019. SARS-CoV-2 (initially named 2019-nCoV) was detected in December 2019 from a cluster of patients in Wuhan, China, who developed pneumonia of unknown causes [44]. No vaccine or specific treatment is currently available. Since the antiviral activity of some flavonoids is known, [45] a flavonoid library to probe inhibitory compounds have applied against MERS-CoV 3C-like protease (3CLpro). Herbacetin, isobavachalcone, QCT 3- $\beta$ -D-glucoside, and helicrysetin were found to block the enzymatic activity of MERS-CoV 3CLpro. In this way, another study [46] showed Chinese medical herbs that are commonly used in treating viral respiratory infections and also contain compounds that might directly inhibit 2019 novel coronavirus (2019-nCoV), an ongoing novel coronavirus that causes pneumonia. Recent studies [46] revealed that the genome sequence of SARS-CoV-2 is very similar to that of SARS-CoV. Here is a series of medicinal plants Chinese containing potential antiviral phytochemicals are screened against. The results of the analysis revealed that the top nine hits might serve as potential anti-SARS-CoV-2 lead molecules for further optimization and drug development process to combat COVID-19. An evaluation *in vitro* activities compounds in *Houttuynia cordata* (QCT, quercitrin, and rutin) conducted by Chiow *et al.* [47] against murine coronavirus and dengue virus indicated that they have much potential for the development of antiviral agents against coronavirus and dengue infection. In 2012 a series of QCT, derivatives are evaluated by Hye *et al.* [48] against the SARS-associated coronavirus (SARS-CoV, SCV) as well as HCV. An ethanolic extract and three flavones (apigenin, luteolin, and QCT) of *Torreya nucifera* [49] leaves were evaluated for SARS-CoV 3CLpro inhibition using fluorescence resonance energy transfer analysis (FRET). The ethanolic extract exhibited good SARS-CoV 3CLpro inhibitory activity (62% at 100  $\mu$ g/mL), and apigenin, luteolin, and QCT inhibited 3CLpro activity with IC<sub>50</sub> values of 28.0, 20.2, and 23.8  $\mu$ mol, respectively. Chen *et al.* [50] identified a natural compound called QCT-3-b-galactoside as an inhibitor of the 3CLpro by molecular docking, surface plasmon resonance/FRET-based bioassays, and mutagenesis studies. This study not only reveals a new class of compounds as potential drug leads against the SARS virus but also provides a solid understanding of the mechanism of inhibition against the target enzyme.

#### IN HUMAN RESPIRATORY SYNCYTIAL VIRUS (hRSV) ADHESION

The hRSV is the main cause of acute lower respiratory tract infections in newborns, children, and the elderly. To date, treatments are only palliative and there is no vaccine available. Natural products show exceptional structural diversity and they have played a vital role in drug research. QCT is a flavonoid that presents several biological activities, including anti-hRSV role. QCT pentaacetate [51] could interact with F-protein with lower binding energy and better stability to block viral adhesion. These results show an alternative anti-hRSV strategy and contribute to drug discovery and development. Here, three types of flavonoids were investigated against the antiviral activity of CHIKV *in vitro* replication. Three compounds [52]: Silymarin, QCT, and kaempferol were evaluated for their *in vitro* antiviral activities against CHIKV using a CHIKV replicon cell line and a clinical isolate of CHIKV of Central/East African genotype. This study may have an important consequence for broadening the chance of getting effective antiviral for CHIKV infection. A study conducted by Weiss *et al.* showed that QCT (3, 30, 40, 5, 7-pentahydroxyflavone) [53] is an effective antioxidant in the prevention and treatment of viral upper respiratory illness (URI). It may be consumed as a supplement or within foods, such as broccoli, apples, berries, onions, and tea. In mice, it has been shown to counteract the increased URI susceptibility that is associated with exercise stress and to decrease viral replication, expression of cytokines, and airway hyperresponsiveness. The next work aimed to

develop solid lipid microparticles (SLMs) as dry powders containing QCT for direct administration to the lung. Santo *et al.* [54] has investigated a formulation and aerosol delivery to the lung of solid lipid QCT microparticles as a potential active pharmaceutical ingredient for asthma therapy. Through this study, it was demonstrated SLM particle technology could be used to deliver this naturally derived flavonoid for the treatment of a range of respiratory diseases. In another study conducted by Serena *et al.* [55] confirmed that a QCT supplementation in doses of 500 and 1000 mg/day for 12 weeks significantly increased plasma QCT levels with no reported side effects.

#### IN IAVS

IAVs cause seasonal pandemics and epidemics with high morbidity and mortality, which calls for effective anti-IAV agents. Influenza infection is a major public health threat. Drug resistance and side effects of chemical treatments have been observed, resulting in increased interest in alternative use of herbal medications for prophylaxis against this infection. Investigation of the antiviral and cytotoxic effect of QCT 3-glucoside (Q3G) from *Dianthus superbus* L. over IAV infection and replication was studied by Shivraj *et al.* [56]. IAV infection induced a higher ROS production; however, potentially reduced by Q3G treatment and significantly blocked virus infection-induced acidic vesicular organelles (AVO). Q3G from *D. superbus* showed potent antiviral activity against influenza A and B viruses with a suppressive effect on virus-induced cellular ROS generation and AVO formation. Thus, this study provided a new line of research for Q3G to develop possible natural anti-influenza drugs. The aim of the next study conducted by Parvaneh *et al.* [57] was to investigate the immunomodulatory properties of QCT-3-O- $\alpha$ -L-rhamnopyranoside isolated from *Rapanea melanophloeos* (L.) Mez. against IAVs. QCT-3-O- $\alpha$ -L-rhamnopyranoside at 150  $\mu$ g/mL decreased the viral titer. The expression of cytokines was also considerably affected by the compound treatment. Another study conducted by Wenjiao *et al.* [58] indicates that QCT showing inhibitory activity in the early stage of influenza infection provides a future therapeutic option to develop effective, safe, and affordable natural products for the treatment and prophylaxis of IAV infections. The next report [59] also showed that QCT 3-rhamnoside possessed antiviral activity against the influenza A/W5/33 virus *in vitro*. This study shows the benefit of short-term QCT feedings on susceptibility to respiratory infection following exercise stress.

#### IN EBV TUMOR GASTRIC

EBV is a human gamma-1 herpesvirus that establishes lifelong latency in over 90% of the world's population. Antiviral effects of QCT were investigated against EBV-associated gastric carcinoma [8,60], those studies demonstrated that QCT has promising anti-HBV activity, mediated by the reduction of hepatitis B surface antigen (HBsAg) and hepatitis Be antigen (HBeAg) secretion as well as viral DNA level *in vitro*. Therefore, these results revealed the potential of QCT as an effective anti-HBV agent with low toxicity.

#### ZIKA

Zika virus (ZIKV) is a member of the *Flaviviridae* family and *Flavivirus* genus. The *flavivirus* genus is the largest among the *Flaviviridae* family with 53 different species. The first human cases of ZIKV infections were reported in Africa in 1950 and later in Asia but remained restricted to these regions until 2007 when a large outbreak occurred in Yap Island, the Federated States of Micronesia, followed by outbreaks in French Polynesia, New Caledonia, and the Cook Islands in 2013 and 2014. In May 2015, ZIKV spread across the Pacific Ocean and was introduced in Brazil, where it caused more than one million cases. As of May 2019, the virus rapidly spread to 84 countries, territories, or subnational areas and became a public health problem worldwide. Here, for the first time, it has discovered that QCT inhibits Zika NS2B-NS3pro [6]. Its inhibitory activity was quantified with IC<sub>50</sub> of 26.0 $\pm$ 0.1  $\mu$ M; and Ki of 23.0 $\pm$ 1.3  $\mu$ M. A study conducted by Mariana *et al.* [61], about the anti-ZIKV effects of Q3G on Vero cells *in vitro*, demonstrated that Q3G exerts antiviral

activity against ZIKV in both tissue culture and knockout mice and that post-exposure *in vivo* treatment with Q3G could have a beneficial effect. The following studies conducted by Roy *et al.*, Hee-jung *et al.*, and Zou *et al.* [62-64] demonstrate that several flavonoids Galangin, kaempferide, QCT, myricetin, and epigallocatechin gallate were found to reduce ZIKV, induced plaques, and viral RNA copies with negligible cytotoxic effects on host cells. Furthermore, inhibition of ZIKV propagation by flavonoids showed a structure-activity relationship. These results demonstrate flavonoids as inhibitors of ZIKV entry and NS2B-NS3 protease. Hence, these flavonoids could be used as potential bi-functional drugs for treating ZIKV infections.

#### ANTIHEPATITE B AND OTHER VIRUSES

A study conducted by Zhikui *et al.* [8] demonstrates that QCT reduces significantly HBsAg and HBeAg, secretion, and HBV genomic DNA levels in both cell lines. Recently, Parvez *et al.* [65] showed *in vitro* HBV activity of *Guiera senegalensis* leaves and identified QCT and other flavonoids by HPTLC. The two isolated bioactive compounds were identified as QCT and myricetin-3-O-rhamnoside. QCT significantly inhibited the synthesis of HBsAg and HBeAg by about 60% and 62%. QCT 7-rhamnoside (Q7R) could be considered as a lead compound for the development [66] of anti-porcine epidemic diarrhea virus (anti-PEDV) drugs to may be used during the early stage of PEDV replication and the structure-activity data of Q7R may usefully guideline to design another related antiviral agent [66]. However, the effects of QCT [67] feeding on the antioxidative status should be investigated to validate the health-protecting effects of QCT feeding in neonatal calves.

#### EBOLA

Ebola is a severe viral disease that spreads in West African countries, whose search for an effective drug is a necessity. The VP30 protein is known as an essential activator of transcription for the Ebola virus. Oleuropein, kaempferol, and QCT are bio-active components, originally from several plants, and which are known by their ability to inhibit viral transcription activators such as HIV. A study conducted by Kasmi [68] showed that the components are linked with the active sites of VP30 with a free energy score estimated near-8 kcal/mol and an average distance of  $1.8/10^{10}$  m. It concludes that oleuropein, kaempferol, and QCT components may be an effective treatment for Ebola virus. Most promisingly, antiviral activity against two distinct species of Ebola virus was seen. This study serves as a proof of principle that Q3G has potential as a prophylactic against Ebola virus infection.

#### CONCLUSION

Following these various works, this molecule has a broad-spectrum antiviral activity. Is it effective in controlling this new form of COVID-19, this devastating virus, which currently affects thousands of people? QCT has inhibitory properties against coronavirus and maybe 1 day could offer an alternative, both preventive and curative, about the epidemic threat.

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#### CONFLICTS OF INTEREST

The authors have declared that they have no conflicts of interest in this study.

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