Received: 12 October 2016 | Revised: 21 February 2017 | Accepted: 13 March 2017

DOI: 10.1002/rmv.1930

WILEY

REVIEW

Nature nominee quercetin's anti-influenza combat strategy—Demonstrations and remonstrations

Enkhtaivan Gansukh[1] | Manikandan Muthu[1] | Diby Paul[2] | Gopal Ethiraj[1] | Sechul Chun[1] | Judy Gopal[1]

[1] Department of Bioresource and Food Science, Konkuk University, Seoul, South Korea

[2] Environmental Microbiology, Department of Environmental Engineering, Konkuk University, Seoul, South Korea

Correspondence
Dr. Judy Gopal, Assistant Professor, Department of Bioresource and Food Science, Konkuk University, Seoul 143-701, Korea.
Email: jejudy777@gmail.com

Summary

Nature's providences are rather the choicest remedies for human health and welfare. One such is quercetin, which is nature's nominee for cancer cure and recently demonstrated against influenza attack. Quercetin is highly recognized for its anticancer applications. This review emphasizes on yet another gift that this compound has to offer for mankind, which is none other than combating the deadly evasive influenza virus. The chemistry of this natural bioflavonoid and its derivatives and its modus operandi against influenza virus is consolidated into this review. The advancements and achievements made in the anti-influenza clinical history are also documented. Further, the challenges facing the progress of this compound to emerge as a predominant anti-influenza drug are discussed, and the future perspective for breaking its limitations through integration with nanoplatforms is envisioned.

KEYWORDS

bioflavonoid, challenges, influenza, natural product, quercetin, virus

1 | INTRODUCTION

Incidence of influenza A virus (IAV) outbreaks and seasonal pandemics worldwide is seriously impacting public health, as well as the country's economy. Of late, the one that is causing greater concern world over is the H1N1 subtype of swine influenza lineages that are circulating among humans. Its pandemic potential[1,2] is a serious concern these days. The highly pathogenic avian IAV (H5N1) causes acute respiratory distress syndrome and multiorgan failure with approximately 60% lethality[3] with the first case of the disease being found in China[4,5] and now widespread all over the world too. The reassorted IAV (H7N9) is found leading to extrapulmonary complications, registering a fatality rate of more than 34%.

The classification of different IAV subtypes has been based on the 2 surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA).[6] Genetic variation of IAVs has resulted from genetic drift and genetic shift caused by selective pressure from the environment or via host immune response, making it almost impossible to produce a timely and sufficiently effective vaccine to prevent epidemic outbreaks.[7,8] Consequently, development of novel strategies is the need of hour to prevent further spread of IAV. Among all strategies, formulation of anti-influenza agents is the most effective intervention control tool.

Based on drug target locations, 2 classes of anti-influenza drugs have been identified: one targeting the matrix 2 (M2) ion channel and the other group targeting NA expressed on the viral envelope. The M2 ion channel inhibitor drugs such as amantadine (trade name: Symmetrel) and rimantadine (trade name: Flumadine) are only effective against type A virus. Matrix 2 inhibitors block the release and migration of the virus ribonucleoprotein into the nucleus of the host

List of abbreviations: IAV, Influenza A virus; HA, Hemagglutinin; NA, Neuraminidase; M2, Matrix 2; RNP, Ribonucleoprotein; NAI, Neuraminidase inhibitor; BBB, Brain blood barrier; vRNP, Viral ribonucleic protein; CPE, Cytopathic effect; PA, Polymerase acidic protein; PB1, Polymerase basic protein 1; PB2, Polymerase basic protein 2; GTP, Guanosine triphosphate; RNA, Ribonucleic acid; mRNA, Messenger ribonucleic acid; PAMP, Pathogen-associated molecular pattern; PRR, Pattern recognition receptor; IFN, Interferon; TLR, Toll-like receptor; RIG-I, Retinoic acid inducible gene-I; NOD, Nucleotide oligomerization domain; NLRP3, NOD-like receptor family pyrin domain containing 3; DC, Dendritic cell; TNF, Tumor necrosis factor; NOS2, Nitric oxide synthase 2; IL, Interleukin; Th-2, T helper cell 2; ROS, Reactive oxygen species; EPR, Enhanced permeability and retention.

cells.[9] Currently, influenza A H3N2 and pandemic A (H1N1 pdm09) viruses are reported to be resistant to M2 inhibitors as are many H5N1 viruses.[9] These drugs have also been vindicated as causatives of neurological side effects and widespread drug resistance.[10-12] Neuraminidase inhibitors (NAIs), such as oseltamivir (trade name: Tamiflu) and zanamivir (trade name: Relenza), are already in use for treatment and prevention of acute uncomplicated flu caused by influenza A and B.[13] The drug peramivir (trade name: Rapivab) is the only available intravenous formulation amidst anti-influenza NAIs.[14,15]

Unfortunately, issues such as continually emerging NAI resistance limit their further development and working efficacy and raise the need to improvise. In addition, dual resistance to both oseltamivir and amantadine has also been detected.[12,13,16-22] Thus, with the marketed drugs hitting a dead end, there is a strong need to explore new antiviral drugs for anti-influenza combat. Nature is said to be the next possible resort and in this case a probable resort. Of the various natural remedies in highlight, quercetin is recently gaining paramount importance.

2 | QUERCETIN: SOURCE, CHEMISTRY, AND APPLICATION

Quercetin (3,3′,4′,5-7-pentahydroxyflavone), belonging to the chemical family of the glycoside rutin, is a marked flavonoid, which belongs to plant pigments that contribute towards the varied colors evident in fruits, flowers, and vegetables. Drawing the attention of many researchers around the world from the day Nobel Prize winner Albert Szent-Gyorgyi made his discovery of both vitamin C and flavonoids in 1937,[23,24] quercetin has for the past 8 decades been under extensive scientific scrutiny.

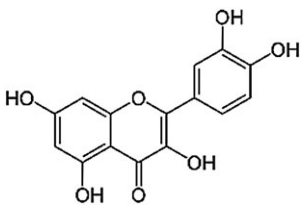
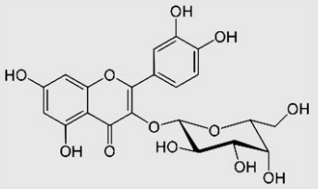
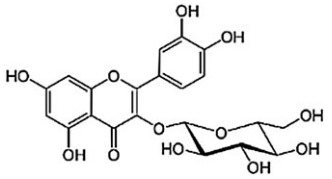
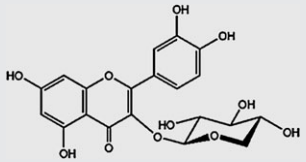
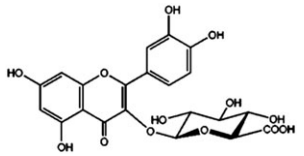
Of over 4000 naturally available plant phenolics,[23-25] quercetin is a rather unique one. The plant kingdom with a wide distribution of quercetin-type flavonols, primarily as quercetin glycosides, is the most abundant of the flavonoid molecules. They are abounding in a variety of foods such as onions, tomatoes, Brassica vegetables, capers, apples, berries, black grapes, shallots, tea, as well as many seeds, nuts, flowers, barks, and leaves. Their occurrence can rightfully be termed abundant in nature. Quercetin is also present in reputed medicinal plants, including *Ginkgo biloba*, *Hypericum perforatum* (St John's wort), and *Sambucus canadensis* (elder).[26-29] Table 1 gives an overview of the various quercetin derivatives, their sources, and antiviral properties.

Flavonoid compounds are classified into 6 subclasses (Table 1). and quercetin, categorized as a flavonol, is one among them. Flavonoids are a family of plant compounds that share a similar flavone backbone (a 3-ringed molecule with hydroxyl [OH] groups attached). Numerous other substitutions are also possible, giving rise to many subclasses of flavonoids with different compounds found within these subclasses. Flavonoids also manifest either as glycosides (with attached glycosyl groups) or as aglycones (without attached glycosyl groups).[30] Figure 1 elucidates the structure of few such predominant quercetin derivatives. Flavonoids, such as quercetin, are basically antioxidants. They can scavenge particles in the body known as free radicals that damage cell membranes, tamper with DNA, and even go to the extent of exterminating the cell. Making use of the inherent property of antioxidants to neutralize free radicals, it can be extended to prevent free radical damage. Although some of biological activities of quercetin are highly related with their antioxidant property, there is no concrete evidence to ascertain that all of the other biological activities such as antiproliferative, antibacterial, anticancer, anti-inflammatory, neuroprotective, hepatoprotective, and antiviral activity would be a result of quercetin's antioxidative effect. For instance, some researchers have explained that high neuroprotective activity has been detected in quercetin owing to their radical scavenging ability.[31] However, quercetin as caspase activator especially on cancer cells operates through inhibition of signal transducer and activator of transcription 3 signaling.[32] On the other hand, quercetin as an antimicrobial agent is operational through blocking of bacterial DNA polymerase, DNA binding, and DNA cleavage activity.[33,34] Moreover, yet another research has demonstrated that quercetin inhibited HIV-1 interferase and thereby influenced viral replication and virion production.[35] Thus, the modus operandi of quercetin appears to be not necessarily limited to or emerging from its antioxidant property The past decades have thus proven quercetin's commendable biological activities that include antiproliferative,[36] antioxidative,[11,37] antibacterial,[38] anticancer,[39,40] anti-inflammatory,[41,42] neuroprotective,[43] hepatoprotective,[44] and antiviral[45,46] effects.

The application of quercetin in pharmaceuticals is limited because of its poor solubility and low bioavailability. However, absorption and brain blood barrier permeability are higher in various forms of quercetin glucosides.[31,47,48] Fortunately, natural quercetin derivatives such as glycosides at various positions determine its absorption ability.[48] Recently, it is reported that brain blood barrier permeability, absorption, and therapeutic effects of quercetin have been enhanced by nanoencapsulation with biodegradable materials.[31,47] Synthetic derivatives of quercetin are also in play. The synthesis and antiviral activities of various quercetin derivatives by substitution of C3, C3′, and C5 hydroxyl functions with various phenolic ester, alkoxy, and aminoalkoxy moieties are being actively researched. Some researchers have attempted to inhibit influenza virus infection using synthesized quercetin derivatives. Among them, quercetin-3-gallate is reported to show improved activity against influenza virus infection compared with natural quercetin derivatives. Synthetic quercetin derivatives include substituted derivatives, hybrid derivatives, and encapsulated types. These synthetic derivatives are well accomplished for their enhanced properties.[45,49-54]

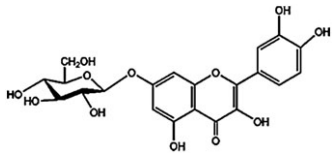
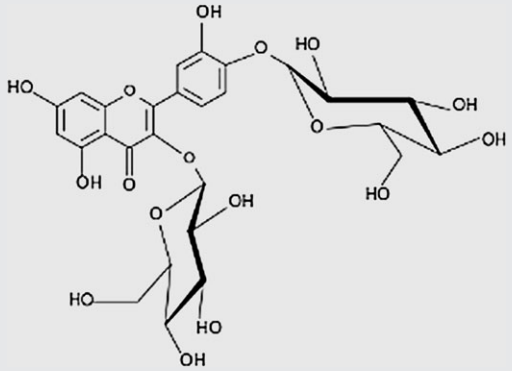
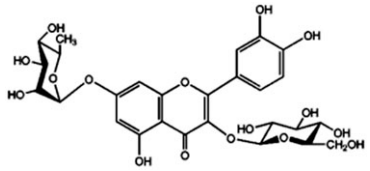
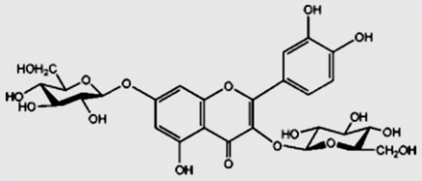
In recent times, a number of reports on quercetin have established that quercetin has the potent ability to inhibit influenza virus infection through induction of the cellular antiviral immune system, inhibiting viral mechanisms or viral particles at different phases.[11,55-57] Anti-influenza targets such as viral glycoproteins (HA and NA),[58,59] viral M2 protein,[60] and viral messenger RNA (mRNA) replication[61,62] are well known for anti-influenza drug development.[59] Most significant is quercetin and quercetin derivatives that exhibit promisingly stronger inhibitory activity against influenza virus through all anti-influenza targets. Figure 2 gives the scheme showing the mode of attack of quercetin and its derivatives on influenza virus.

TABLE 1 Consolidated list of quercetin and its derivatives and natural source

	Common Name (Systematic Name)	Molecular Formula (MW)	Structure	Example of Natural Source	Mechanism of Influenza Virus Target
1	Quercetin (3,5,7,3′,4′-pentahydroxyflavon)	C15H10O7 (302.2)		*Allium cepa*,[138,139] *Hippophae rhamnoides*,[107] *Phaseolus vulgaris*[140]	NA inhibitor,[141,142] reduce IL-6, IL-1β, and TNF-α,[143] NS1 protein inhibitor,[144] HA inhibitor,[66] IFN-γ inducer[145]
2	Hyperoside (quercetin-3-O-galactoside)	C21H20O12 (464.3)		*Mangifera indica*,[146] *Prunus*,[147] *Vaccinium corymbosum*,[148] *Vaccinium macrocarpon*,[148] *Aronia melanocarpa*,[148] *Vaccinium vitis-idaea*[148]	NA inhibitor[149]
3	Isoquercetin (quercetin-3-O-glucoside)	C21H20O12 (464.3)		*Aronia melanocarpa*,[148] *Hippophae rhamnoides*,[107] *Lepisorus contortus*,[150] *Mangifera indica*,[146] *Vigna sinensis*,[151] *Bauhinia variegate*,[152] *Prunus*,[147] *Allium cepa*,[138,153] *Vaccinium corymbosum*,[148] *Warburgia ugandensis*,[154]	IFN-γ inducer,[49] NA inhibitor,[43] RNA replication inhibitor[49]
4	Reynoutrin (quercetin-3-O-xyloside)	C20H18O11 (434.3)		*Mangifera indica*[146,155,156]	TNF-α reducer[157]
5	Miquelianin (quercetin-3-O-glucuronide)	C21H18O13 (478.3)		*Hypericum perforatum*,[158] *Hypericum hirsutum*,[159] *Phaseolus vulgaris*,[160] *Nelumbo nucifera*,[161] *Lactuca sativa*[162]	

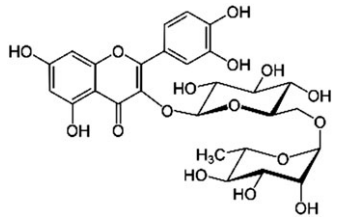
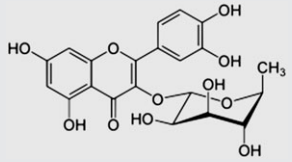
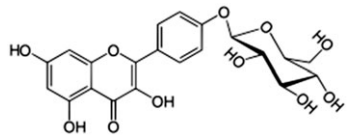
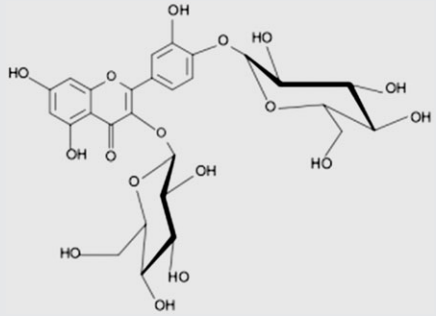
(*Continues*)

TABLE 1 (Continued)

	Common Name (Systematic Name)	Molecular Formula (MW)	Structure	Example of Natural Source	Mechanism of Influenza Virus Target
6	Quercimeritrin (quercetin-7-O-glucoside)	C21H20O12 (464.3)		*Chrysanthemum indicum*,[163] *Kummerowia striata*,[164] *Galinsoga parviflora*,[165] *Rumex luminiastrum*,[166] *Brasenia schreberi*,[167] *Vigna angularis*,[168] *Allium cepa*,[138] *Dianthus superbus*[11]	RNA polymerase (PB2) inhibitor, ROS reducer, autophagy blocker[11]
7	Quercetin 3,4′-diglucoside	C27H30O17 (626.4)		*Allium cepa*,[138,139] *Filipendula ulmaria*[169]	
8	Quercetin-3-glucoside-7-rhamnoside	C27H30O16 (610.5)		*Capsicum annuum*,[170] *Warburgia ugandensis*,[154] *Hippophae rhamnoides*[107]	
9	Quercetin 3,7-diglucoside	C27H30O17 (626.5)		*Cymbopetalum brasiliense*[171]	

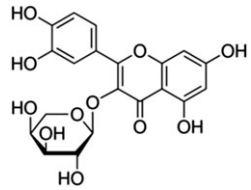
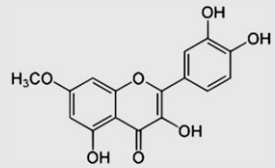
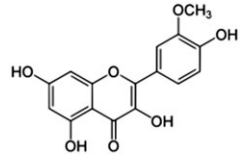
(*Continues*)

TABLE 1 (Continued)

	Common Name (Systematic Name)	Molecular Formula (MW)	Structure	Example of Natural Source	Mechanism of Influenza Virus Target
10	Rutin (quercetin-3-rutinoside)	C27H30O16 (610.5)		*Allium cepa*,[138,139] *Hippophae rhamnoides*,[107] *Prunus*,[147] *Prunus avium*[172]	NA inhibitor,[142,149] NS1 protein inhibitor[144]
11	Quercetrin (quercetin 3-O-rhamnoside)	C21H20O11 (448.4)		*Capsicum annuum*,[170] *Houttuynia cordata*,[173] *Mangifera indica*,[156] *Vaccinium macrocarpon*,[148] *Vaccinium vitis-idaea*,[148] *Warburgia ugandensis*[154]	Viral RNA replication blocker,[45] NS1 protein inhibitor[144]
12	Spiraeoside (quercetin 4-O-glucoside)	C21H20O12 (464.3)		*Allium cepa*,[138,139] *Filipendula ulmaria*[169]	TNF-α and IL-4 reducer[174]
13	Quercetin 4,7-O-diglucoside	C27H30O17 (626.5)		*Allium cepa*[138,139]	

(*Continues*)

TABLE 1 (Continued)

	Common Name (Systematic Name)	Molecular Formula (MW)	Structure	Example of Natural Source	Mechanism of Influenza Virus Target
14	Quercetin 3-O-arabinoside	C20H18O11 (434.3)		*Vaccinium corymbosum*,[148] *Vaccinium macrocarpon*,[148] *Vaccinium vitis-idaea*[148]	Cellular oxidation reducer[175]
15	Rhamnetin (quercetin 7-O-methyl)	C16H12O7 (316.2)		*Leptospermum* honey[176]	NA inhibitor,[177] cellular oxidation reducer,[178] TNF-α and IL-4 reducer, cellular oxidation reducer[179]
16	(quercetin 3′-methyl ether)	C16H12O7 (316.3)			Viral RNA replication inhibitor, NA inhibitor, ROS reducer, autophage blocker, HA inhibitor[180]

Abbreviations: HA, hemagglutinin; IFN, interferon; IL, interleukin; NA, neuraminidase; NS1; PB2, polymerase basic protein 2; ROS, reactive oxygen species; TNF, tumor necrosis factor.

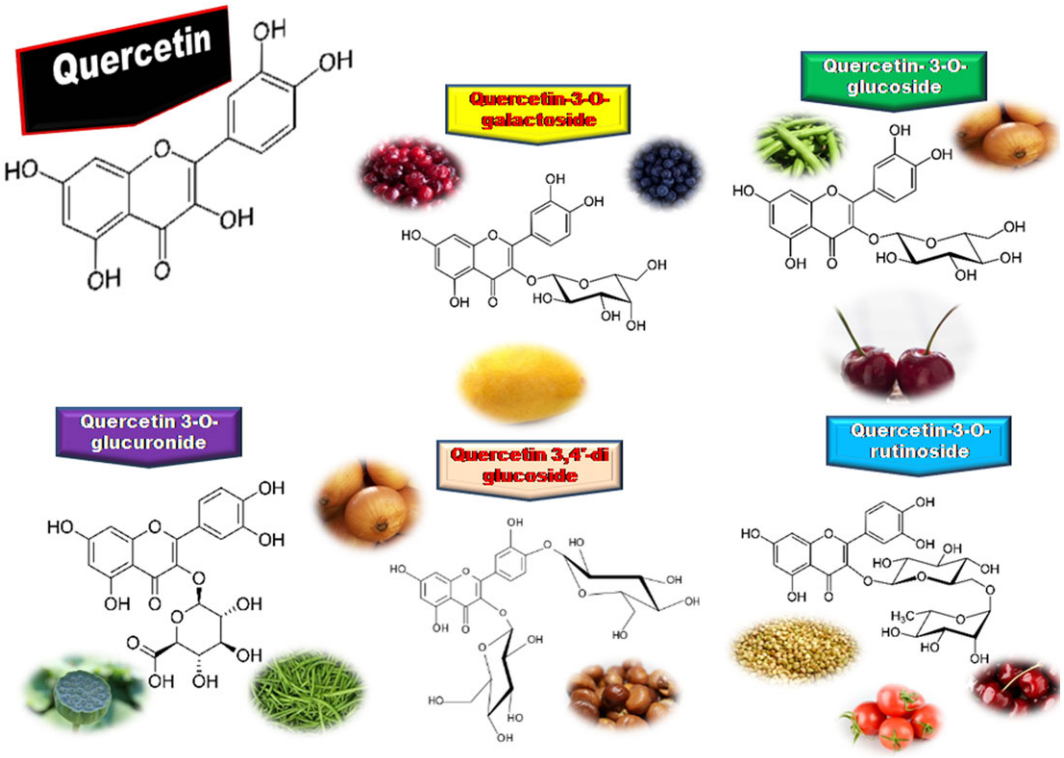


FIGURE 1 Quercetin structure and illustration showing source and chemistry of its derivatives

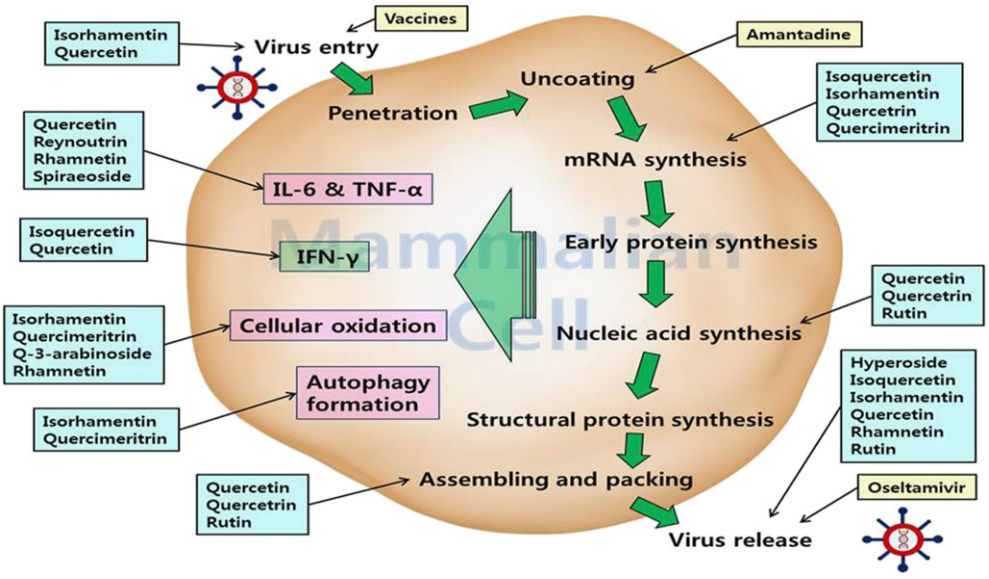


FIGURE 2 Schematic showing the varied site of attack of various quercetin derivatives on influenza virus. IL, interleukin; IFN, interferon; mRNA, messenger RNA; TNF, tumor necrosis factor

3 | QUERCETIN VS INFLUENZA VIRUS: MODUS OPERANDI

3.1 | Inhibiting influenza virus entry via blocking of HA

In the viral replication cycle, stage 1 is virus entry; so prevention of viral entry will be the first line of defense against viral infectivity, this by itself is an attractive antiviral strategy.[63,64] The influenza virus envelope protein HA plays a critical role in facilitating viral entry.[65] Firstly, HA is responsible for the virus binding to the cell surface; the binding of the virus to host cells leads to subsequent membrane fusion within the late endosomes. Following binding, the virus is internalized by endocytosis. Within the low-pH (5.0-5.5) environment of the endosome, HA undergoes conformational rearrangements. This results in the exposure of the fusion peptide, which subsequently enters the endosomal membrane of the host cells. The HA2 subunit in the stem region leads to viral cell membrane fusion. After fusion, the viral ribonucleic proteins are released into the cytosol and transported into the nucleus, where replication occurs.[63] It is now known that quercetin

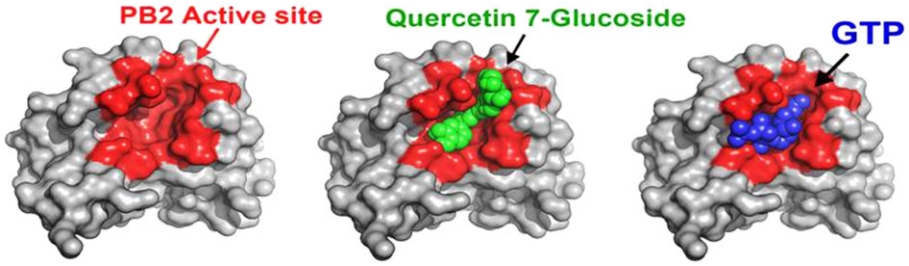


FIGURE 3 Comparison between quercetin 7-glucoside (green) and guanosine 3-phosphate (blue) docked on cap-binding domain of influenza virus PB2 subunit of RNA-dependent RNA polymerase (red colored residues indicate active site). GTP, guanosine triphosphate; PB2, polymerase basic protein 2

blocks influenza virus entry via influenza viral HA protein. Mechanistic investigations revealed that quercetin engages in active interaction with the HA2 subunit. Moreover, it has been established that quercetin is capable of inhibiting the entry of the H5N1 virus using the pseudo virus-based drug screening system.[66]

3.2 | Inhibiting influenza virus via blocking of NA

Most of the licensed and commercialized antiviral drugs against influenza A and B mainly target the viral surface protein NA for inhibiting viral infection in the human body.[67] Neuraminidase activity leads to the release of progeny virions from a host cell by cleaving terminal sialic acid from glycoproteins on the host cell surface.[68] The NA inhibitors inhibit release of newly formed virions from the host cell surface.[9] By blocking of NA of influenza virus, the newly formed influenza viral virions infected other noninfected cells.[9] There are 2 NA inhibitors licensed internationally for the treatment and inhibition of influenza such as Relenza (zanamivir) and Tamiflu (oseltamivir).[9] In addition, lower clinical efficacy of oseltamivir has been reported in case of children infected with influenza B than in those infected with influenza A.[69]

Many research findings validate that the plant-derived quercetin and quercetin derivatives inhibited influenza virus infection through NA inhibition pathway.[67,68,70] Quercetin from a Chinese traditional plant showed higher binding affinity to the active NA sites of A/PR/8/34 (H1N1), and this was confirmed by in vitro and in vivo experiments.[58] That treatment of quercetin-reduced influenza virus–induced cytopathic effect was confirmed by computational studies showing that the chemical structure of quercetin was able to suppress the NA crystal structure *in silico*.[58] Additionally, researchers identified that quercetin and quercetin derivatives reduced lung damages such as lung inflammation induced by influenza virus infection in vivo.[46,58] Moreover, it increased survivalists and the lung index of quercetin-treated group was higher and more or less similar to the placebo and normal.[46,58]

3.3 | Inhibiting influenza virus via blocking of viral RNA polymerase

In modern practice, antiviral researchers propose influenza viral polymerase as a target for influenza drug development, since it is subject to almost no significant structural and genetic change across different influenza virus types and strains.[61,71] RNA polymerase consists of PA, PB1, and PB2 subunits, which play an important role in viral RNA synthesis.[72] This viral polymerase, using the well-known "cap-snatching" mechanism, uses host pre-mRNA as a primer for transcription of viral mRNA. When host pre-mRNA (7-methylated guanosine triphosphate [GTP] on 5′ end of host pre-mRNA) is bound to PB2, it is cleaved by the PA endonuclease subunit to the primer.[73] Then the conserved polymerase domain of PB1 with the assistance of that primer elongates the viral mRNA transcription.[61] Jassim and Naji[57] reported some flavonoids including quercetin and their derivatives to inhibit RNA virus infections through blocking of viral polymerase.[40] Moreover, quercetin 3-rhamnoside exerted stronger inhibitory activity on influenza viral mRNA synthesis[45] as proved by in vivo investigations.[46] In 2016, another quercetin derivative known as quercetin 7-glucoside was reported as a blocker of influenza H1N1 virus polymerase via occupying the binding site of 7-methylated GTP on PB2 subunit by RNA polymerase inhibition assay using molecular docking studies.[11] Figure 3 gives the comparison between quercetin 7-glucoside and 7-methylated GTP on the PB2 subunit of RNA-dependent RNA polymerase. However, till date, quercetin aglycone has not been confirmed of its influenza viral polymerase blocker status.

3.4 | Quercetin impact on virus-related immune system in host cells

Influenza A virus infection leads to the recognition of pathogen-associated molecular patterns by pattern recognition receptors that initiate antiviral signaling cascades. This signaling results in the production of interferons (IFNs), cytokines, and chemokines.[74,75] Three main categories of pattern recognition receptors are involved in the recognition of influenza A infection and the induction of an IFN response. These include toll-like receptors, retinoic acid inducible gene I receptors, and nucleotide oligomerization domain–like receptor family pyrin domain containing 3.[76-78] All these pathways eventually result in the transcription of proinflammatory cytokines, chemokines, and IFNs that activate the antiviral response and the recruitment of neutrophils, activation of macrophages, and maturation of dendritic cells.[74,75] Type I IFNs include IFN-α and IFN-β both of which play an important part in limiting viral replication.[79,80] IFN-γ is the main type II IFN and contributes to the establishment of an effective adaptive cytotoxic T-cell response against influenza virus infections.[81] Type III IFNs, like IFN-λ, are reported to control influenza A infections of the lung.[82]

Besides, activated macrophages enhance their proinflammatory cytokine response (interleukin [IL] 6 and tumor necrosis factor

[TNF] α).[83,84] Alveolar macrophages have a direct role in limiting the spread of virus through phagocytosis of apoptotic infected cells[85,86] and by phagocyte-mediated opsonophagocytosis of influenza virus.[87] In contrast to these beneficial effects, alveolar macrophages also pose a negative effect, since their activation also results in the production of nitric oxide synthase 2 and TNF-α, which in turn results in severe pathological symptoms from influenza virus infections.[88-90] Food-derived flavonoids, in particular quercetin, critically modulate a variety of inflammatory processes and immune functions as widely researched and reviewed.[91-93] Recent reports ascertain that quercetin reduces inflammatory cytokine levels, whereby expressions of IL-1β, IL-4, IL-6, and TNF-α mRNA and protein were markedly downregulated in rats treated with quercetin.[94] These inferences suggest that the beneficial immunostimulatory effects of quercetin may be mediated through the induction of T helper cell 1–derived cytokine, IFN-γ, and inhibition of T helper cell 2–derived cytokines, IL-1β, IL-4, IL-6, and TNF-α.[95-97]

3.5 | Quercetin impact on virus-induced cellular oxidation

Influenza infection highly enhances reactive oxygen species (ROS) generation in host cells.[11] A higher level of ROS generation increases viral pathogenesis in vitro and in vivo.[98] Moreover, researchers have found that influenza virus–induced ROS produces systematic symptoms such as weight loss and body temperature changes.[99] Additionally, they reported that natural compounds were successful in reducing influenza viral titer by approximately 50% owing to their antioxidant properties.[100] Some researchers claim that the oxidation of the conserved tryptophan 153 residue in the receptor-binding site inactivates influenza HA binding using chlorine dioxide.[101] Quercetin has a higher reduction potential both in vivo and in vitro.[102] This implies that quercetin is able to block influenza HA through antioxidant properties.[103-106] Gansukh et al reported that quercetin derivatives extracted from *Dianthus superbus* exhibited inhibitory effect on influenza virus–induced ROS production and subsequently it inhibits viral infection during early stages of binding, fusion, and replication.[11] Additionally, Enkhtaivan et al reported a strong correlation between antioxidant and anti-influenza agents from *Hippophae rhamnoides* L. extracts.[107] They have reported that quercetin and quercetin monoglucoside are effective in vitro inhibitors on both oxidant and influenza infections by reducing virus-induced cytopathic effects.[107] Researchers have concluded that quercetin's antiviral activity is a result of a variety of multiple actions. Some of the primary mechanisms may include one or more of the following: (1) reducing the ability of a virus to infect cells (infectability),[108] (2) inhibiting the ability of infected cells to replicate and reproduce,[108] and (3) reducing resistance of infected cells to pharmaceutical drug therapy.[109] It is reported that within each of these categories, quercetin has demonstrated (in vivo) chemical interactions of multiple cellular pathways that inhibit or promote the production of critical viral proteins. The basic effect of quercetin's multifaceted interference could be to block viral activity at every possible level of its existence. Thus, it is certainly a potentially powerful neutraceutical therapy, which could be put to promising and effective use.

3.6 | Challenges and future perspective for quercetin in anti-influenza strike

One of the major challenges that quercetin faces when put to clinical use is its poor water solubility, instability in physiological media,[110] and subsequent poor bioavailability.[111] Thus, optimizing ideal drug (quercetin), delivery options are necessary to facilitate the harnessing of maximum benefits from quercetin. Moreover, quercetin is a versatile compound that can trigger off a number of responses to its active interaction once inside the human system. Hence, before beginning a full-fledged application routine, it is necessary that all the interactions and pros and cons in vivo are completely researched. Current research on some interactions have revealed that there is concern that quercetin may reduce the effectiveness of certain antibiotics.[112-115] Quercetin may render corticosteroids staying longer in the body. Quercetin may interfere with the body's absorption of cyclosporine, which is used to suppress the immune system.[113] Concomitant use may increase the risks of digoxin and fluoroquinolones. Quercetin is suspected to enhance the effect of anticoagulants, increasing risk of bleeding. Test tube and animal trials suggest that quercetin may enhance the effects of doxorubicin and cisplatin, which are 2 chemotherapy medications used to treat cancer.[112-115] Quercetin is generally considered safe. Side effects may include headache and upset stomach. Preliminary evidence suggests that a by-product of quercetin can lead to a loss of protein function. Moreover, very high doses of quercetin may damage the kidneys. Periodic breaks from taking quercetin are highly recommended. In addition, pregnant women, breastfeeding women, and people with kidney disease should avoid quercetin. At doses greater than 1 g per day, there have been reports of damage to the kidneys.[116-118]

These uncertainties and established and silent threats are the limitations facing the harnessing of the complete benefits of this bioflavonoid. Thus, it is crucial that quercetin is not let loose into the system but delivered through targeted drug delivery carriers. Targeted delivery can be actively or passively achieved. Active targeting is by conjugating the therapeutic agent or carrier system to a tissue or cell-specific ligand.[119] Passive targeting is said to be achieved by incorporating the therapeutic agent into a macromolecule or nanoparticle that passively reaches the target. Thus, drugs encapsulated within nanoparticles or drugs coupled to macromolecules can passively target specific viral cells through the enhanced permeability and retention effect. In this direction, liposomes have been demonstrated to be useful for delivering pharmaceutical agents, via "contact-facilitated drug delivery," which involves binding or interaction with the target cell membrane. Biodegradable polymeric micelles are regarded as excellent candidates for anticancer drug delivery. Anticancer drugs delivered by amphiphilic polymer micelles are already documented,[120,121] and more recently, polymer micelles have been used for quercetin formulation too.[122] The polymer micelles have been reported to have enhanced the oral bioavailabilty of quercetin too.[123] Thus, numerous approaches are underway involving the use of promising drug delivery systems such as inclusion complexes, liposomes, nanoparticles, or micelles, which appear to provide higher solubility and bioavailability to combat quercetin's limitations.

Yet another interesting offer is from topical prodrugs that are obtained by chemical modification of a drug into a bioreversible form

to improve drug bioavailability and therapeutic efficacy. Upon administration, regeneration of the parent drug occurs in vivo by either enzymatic or chemical processes.[124] Quercetin-amino acid conjugates, QC-3,5,7,3,4-pentamethylether, QC-3-O-acyl esters (I-VI), and QC-polymethacrylic acid conjugated quercetin-based prodrugs, have been synthesized and demonstrated for their enhanced pharmacokinetic properties including water solubility, stability against chemical or enzymatic hydrolysis, and cell permeability.[124-126]

A recent researcher has described that sugars on quercetin derivatives are highly correlated with their anti-influenza and anticancer effects.[107] Depending on the correlation between metabolites and biological activities, aglycones and monoglycosides are better targets in influenza viral drug development while diglycoside and triglycoside are involved in inhibiting the growth of cancer cells.[107] Moreover, monoglycoside of quercetin (quercetin 7-glucoside) has been proved as influenza PB2 polymerase subunit blocker tested in vitro and *in silico*.

In a more recent review Cai et al[127] have surveyed the wholesome options available for solving the bioavailability issues of quercetin. They report an excellent compilation of accomplishments attained via quercetin inclusion complexes,[110,128] quercetin nanocrystals,[129,130] quercetin microemulsions,[131] quercetin phospholipid formulations,[132] and encapsulated polymer nanoparticles and micelles.[133-137] This review finds it interesting that most of these quercetin exultations are yet to be tested and applied in real time. This review calls to attention the available expertise and solutions offered to promote quercetin, which is a testing away from being launched as a successful drug.

This review also finds ample gaps between reports on quercetin and clinical testings, most of the information on the side effects and interactions and adverse effects remain on websites and private domains and not on scientific publications or authentic science engines. Nature's nominee is still unnominated, this review is expected to be a wake-up call for researchers to put to test the clinical expertise of quercetin and the claims of enhanced quercetin modifications in real time. To unleash what quercetin holds, it is required that limitations are overcome and recent advancements made are put to trial.

ACKNOWLEDGEMENTS

This work was supported by the KU Research Professor Program of Konkuk University.

CONFLICT OF INTEREST

The authors have no competing interest.

REFERENCES

1. Garten RJ, Davis CT, Russell CA, et al. Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans. *Science*. 2009;325:197-201.
2. Barr IG, McCauley J, Cox N, et al. Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: Basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009-2010 Northern Hemisphere season. *Vaccine*. 2010;28:1156-1167.
3. Nakajima N, Tin NV, Sato Y, et al. Pathological study of archival lung tissues from five fatal cases of avian H5N1 influenza in Vietnam. *Mod Pathol*. 2013;26:357-369.
4. Li Q, Zhou L, Zhou MH, et al. Epidemiology of Human Infections with Avian Influenza A(H7N9) Virus in China. *N Engl J Med*. 2014;370:520-532.
5. Uyeki TM. Global epidemiology of human infections with highly pathogenic avian influenza A (H5N1) viruses. *Respirology*. 2008;13:S2-S9.
6. Smith GJ, Vijaykrishna D, Bahl J, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature*. 2009;459:1122-1125.
7. Bouvier NM, Palese P. The biology of influenza viruses. *Vaccine*. 2008;26:D49-D53.
8. Klenk HD. Evolution and infection biology of new influenza A viruses with pandemic potential. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2013;56:15-21.
9. McKimm-Breschkin JL. Influenza neuraminidase inhibitors: antiviral action and mechanisms of resistance. *Influenza Other Respir Viruses*. 2013;7(Suppl 1):25-36.
10. Leonov H, Astrahan P, Krugliak M, Arkin IT. How do amino-adamantanes block the influenza M2 channel, and how does resistance develop? *J Am Chem Soc*. 2011;133:9903-9911.
11. Gansukh E, Kazibwe Z, Pandurangan M, Judy G, Kim DH. Probing the impact of quercetin-7-O-glucoside on influenza virus replication influence. *Phytomedicine*. 2016;23:958-967.
12. Sheu TG, Fry AM, Garten RJ, et al. Dual Resistance to Adamantanes and Oseltamivir Among Seasonal Influenza A(H1N1) Viruses: 2008-2010. *Journal of Infectious Diseases*. 2011;203:13-17.
13. Spanakis N, Pitiriga V, Gennimata V, Tsakris A. A review of neuraminidase inhibitor susceptibility in influenza strains. *Expert Rev Anti Infect Ther*. 2014;12:1325-1336.
14. Komeda T, Ishii S, Itoh Y, et al. Post-marketing safety and effectiveness evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir (II): A pediatric drug use investigation. *J Infect Chemother*. 2015;21:194-201.
15. Komeda T, Ishii S, Itoh Y, et al. Post-marketing safety and effectiveness evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir (I): A drug use investigation. *J Infect Chemother*. 2014;20:689-695.
16. McKimm-Breschkin JL. Resistance of influenza viruses to neuraminidase inhibitors--a review. *Antiviral Res*. 2000;47:1-17.
17. Baranovich T, Bahl J, Marathe BM, et al. Influenza A viruses of swine circulating in the United States during 2009-2014 are susceptible to neuraminidase inhibitors but show lineage-dependent resistance to adamantanes. *Antiviral Res*. 2015;117:10-19.
18. Huang L, Zhou JF, Wei H, Shu YL. Neuraminidase inhibitors resistance in influenza viruses and the related mechanisms. *Bing Du Xue Bao*. 2012;28:572-576.
19. de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med*. 2005;353:2667-2672.
20. Fick J, Lindberg RH, Tysklind M, et al. Antiviral oseltamivir is not removed or degraded in normal sewage water treatment: implications for development of resistance by influenza A virus. *PLoS One*. 2007;2:e986
21. Stephenson I, Democratis J, Lackenby A, et al. Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. *Clin Infect Dis*. 2009;48:389-396.
22. Le QM, Kiso M, Someya K, et al. Avian flu: Isolation of drug-resistant H5N1 virus (vol 437, pg 1108, 2005). *Nature*. 2005;438:754-754.
23. Lesser S, Wolffram S. Oral bioavailability of the flavonol quercetin - A review. *Current Topics in Nutraceutical Research*. 2006;4:239-256.
24. Formica JV, Regelson W. Review of the biology of Quercetin and related bioflavonoids. *Food Chem Toxicol*. 1995;33:1061-1080.
25. Davis JM, Murphy EA, McClellan JL, Carmichael MD, Gangemi JD. Quercetin reduces susceptibility to influenza infection following

stressful exercise. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology*. 2008;295:R505-R509.

26. Hakkinen SH, Karenlampi SO, Heinonen IM, Mykkanen HM, Torronen AR. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. *J Agric Food Chem*. 1999;47:2274-2279.
27. Kunyanga CN, Imungi JK, Okoth MW, Biesalski HK, Vadivel V. Flavonoid content in ethanolic extracts of selected raw and traditionally processed indigenous foods consumed by vulnerable groups of Kenya: antioxidant and type II diabetes-related functional properties. *Int J Food Sci Nutr*. 2011;62:465-473.
28. Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. *Am J Clin Nutr*. 2005;81:243S-255S.
29. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr*. 2005;81:230S-242S.
30. Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. *Annu Rev Nutr*. 2002;22:19-34.
31. Suganthy N, Devi KP, Nabavi SF, Braidy N, Nabavi SM. Bioactive effects of quercetin in the central nervous system: Focusing on the mechanisms of actions. *Biomed Pharmacother*. 2016;84:892-908.
32. Seo HS, Ku JM, Choi HS, et al. Quercetin induces caspase-dependent extrinsic apoptosis through inhibition of signal transducer and activator of transcription 3 signaling in HER2-overexpressing BT-474 breast cancer cells. *Oncol Rep*. 2016;36:31-42.
33. Turumtay H, Midilli A, Turumtay EA, et al. Gram (-) microorganisms DNA polymerase inhibition, antibacterial and chemical properties of fruit and leaf extracts of Sorbus acuparia and Sorbus caucasica var. yaltirikii. *Biomed Chromatogr*. 2016;e3901. doi: 10.1002/bmc.3901.
34. Raza A, Xu X, Xia L, Xia C, Tang J, Ouyang Z. Quercetin-Iron Complex: Synthesis, Characterization, Antioxidant, DNA Binding, DNA Cleavage, and Antibacterial Activity Studies. *J Fluoresc*. 2016; 26:2023-2031.
35. Kim HJ, Woo ER, Shin CG, Park H. A new flavonol glycoside gallate ester from Acer okamotoanum and its inhibitory activity against human immunodeficiency virus-1 (HIV-1) integrase. *J Nat Prod*. 1998;61:145-148.
36. Delgado L, Fernandes I, Gonzalez-Manzano S, de Freitas V, Mateus N, Santos-Buelga C. Anti-proliferative effects of quercetin and catechin metabolites. *Food Funct*. 2014;5:797-803.
37. Robaszkiewicz A, Balcerczyk A, Bartosz G. Antioxidative and prooxidative effects of quercetin on A549 cells. *Cell Biol Int*. 2007; 31:1245-1250.
38. Li MY, Xu ZT. Quercetin in a lotus leaves extract may be responsible for antibacterial activity. *Arch Pharm Res*. 2008;31:640-644.
39. Atashpour S, Fouladdel S, Movahhed TK, et al. Quercetin induces cell cycle arrest and apoptosis in CD133(+) cancer stem cells of human colorectal HT29 cancer cell line and enhances anticancer effects of doxorubicin. *Iran J Basic Med Sci*. 2015;18:635-643.
40. Lu J, Papp LV, Fang J, Rodriguez-Nieto S, Zhivotovsky B, Holmgren A. Inhibition of Mammalian thioredoxin reductase by some flavonoids: implications for myricetin and quercetin anticancer activity. *Cancer Res*. 2006;66:4410-4418.
41. Lin CF, Leu YL, Al-Suwayeh SA, Ku MC, Hwang TL, Fang JY. Anti-inflammatory activity and percutaneous absorption of quercetin and its polymethoxylated compound and glycosides: The relationships to chemical structures. *Eur J Pharm Sci*. 2012;47:857-864.
42. Garcia-Mediavilla V, Crespo I, Collado PS, et al. The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells. *Eur J Pharmacol*. 2007;557:221-229.
43. Dajas F. Life or death: neuroprotective and anticancer effects of quercetin. *J Ethnopharmacol*. 2012;143:383-396.
44. Ying HZ, Liu YH, Yu B, Wang ZY, Zang JN, Yu CH. Dietary quercetin ameliorates nonalcoholic steatohepatitis induced by a high-fat diet in gerbils. *Food Chem Toxicol*. 2013;52:53-60.
45. Choi HJ, Song JH, Park KS, Kwon DH. Inhibitory effects of quercetin 3-rhamnoside on influenza A virus replication. *Eur J Pharm Sci*. 2009; 37:329-333.
46. Choi HJ, Song JH, Kwon DH. Quercetin 3-rhamnoside exerts antiinfluenza A virus activity in mice. *Phytother Res*. 2012;26:462-464.
47. Moreno LC, Puerta E, Suarez-Santiago JE, Santos-Magalhaes NS, Ramirez MJ, Irache JM. Effect of the oral administration of nanoencapsulated quercetin on a mouse model of Alzheimer's disease. *Int J Pharm*. 2017;517:50-57.
48. Wittig J, Herderich M, Graefe EU, Veit M. Identification of quercetin glucuronides in human plasma by high-performance liquid chromatography-tandem mass spectrometry. *J Chromatogr B Biomed Sci Appl*. 2001;753:237-243.
49. Chen L, Li J, Luo C, et al. Binding interaction of quercetin-3-beta-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): structure-activity relationship studies reveal salient pharmacophore features. *Bioorg Med Chem*. 2006;14:8295-8306.
50. Kim YJ, Narayanan S, Chang KO. Inhibition of influenza virus replication by plant-derived isoquercetin. *Antiviral Res*. 2010;88:227-235.
51. Song JM, Lee KH, Seong BL. Antiviral effect of catechins in green tea on influenza virus. *Antiviral Res*. 2005;68:66-74.
52. Nagle DG, Ferreira D, Zhou YD. Epigallocatechin-3-gallate (EGCG): chemical and biomedical perspectives. *Phytochemistry*. 2006; 67:1849-1855.
53. Roth M, Timmermann BN, Hagenbuch B. Interactions of green tea catechins with organic anion-transporting polypeptides. *Drug Metab Dispos*. 2011;39:920-926.
54. Thapa M, Kim Y, Desper J, Chang KO, Hua DH. Synthesis and antiviral activity of substituted quercetins. *Bioorg Med Chem Lett*. 2012; 22:353-356.
55. Gao ZH, Huang KX, Xu HB. Protective effects of flavonoids in the roots of Scutellaria baicalensis Georgi against hydrogen peroxide-induced oxidative stress in HS-SY5Y cells. *Pharmacol Res*. 2001; 43:173-178.
56. Chu ZY, Chu M, Teng Y. Effect of baicalin on in vivo anti-virus. *Zhongguo Zhong Yao Za Zhi*. 2007;32:2413-2415.
57. Jassim SAA, Naji MA. Novel antiviral agents: a medicinal plant perspective. *J Appl Microbiol*. 2003;95:412-427.
58. Liu ZK, Zhao JP, Li WC, et al. Computational screen and experimental validation of antiinfluenza effects of quercetin and chlorogenic acid from traditional Chinese medicine. *Sci Rep*. 2016;6:
59. Gong JZ, Fang H, Li MY, et al. Potential Targets and Their Relevant Inhibitors in Anti-influenza Fields. *Curr Med Chem*. 2009; 16:3716-3739.
60. Moorthy NSHN, Poongavanam V, Pratheepa V. Viral M2 Ion Channel Protein: A Promising Target for Anti-influenza Drug Discovery. *Mini-Reviews in Medicinal Chemistry*. 2014;14:819-830.
61. Clark MP, Ledeboer MW, Davies I, et al. Discovery of a Novel, First-in-Class, Orally Bioavailable Azaindole Inhibitor (VX-787) of Influenza PB2. *J Med Chem*. 2014;57:6668-6678.
62. Nakazawa M, Kadowaki SE, Watanabe I, Kadowaki Y, Takei M, Fukuda H. PA subunit of RNA polymerase as a promising target for anti-influenza virus agents. *Antiviral Res*. 2008;78:194-201.
63. Basu A, Antanasijevic A, Wang M, et al. New small molecule entry inhibitors targeting hemagglutinin-mediated influenza a virus fusion. *J Virol*. 2014;88:1447-1460.
64. Yang J, Li M, Shen X, Liu S. Influenza A virus entry inhibitors targeting the hemagglutinin. *Virus*. 2013;5:352-373.
65. Huang Q, Sivaramakrishna RP, Ludwig K, Korte T, Bottcher C, Herrmann A. Early steps of the conformational change of influenza

virus hemagglutinin to a fusion active state: stability and energetics of the hemagglutinin. *Biochim Biophys Acta*. 1614;2003:3-13.

66. Wu WJ, Li RC, Li XL, et al. Quercetin as an Antiviral Agent Inhibits Influenza A Virus (IAV) Entry. *Viruses-Basel*. 2016;8:
67. Rakers C, Schwerdtfeger SM, Mortier J, et al. Inhibitory potency of flavonoid derivatives on influenza virus neuraminidase. *Bioorg Med Chem Lett*. 2014;24:4312-4317.
68. Jeong HJ, Ryu YB, Park SJ, et al. Neuraminidase inhibitory activities of flavonols isolated from *Rhodiola rosea* roots and their in vitro anti-influenza viral activities. *Bioorg Med Chem*. 2009;17:6816-6823.
69. Sugaya N, Mitamura K, Yamazaki M, et al. Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. *Clin Infect Dis*. 2007;44:197-202.
70. Kim Y, Narayanan S, Chang KO. Inhibition of influenza virus replication by plant-derived isoquercetin. *Antiviral Res*. 2010;88:227-235.
71. Byrn RA, Jones SM, Bennett HB, et al. Preclinical Activity of VX-787, a First-in-Class, Orally Bioavailable Inhibitor of the Influenza Virus Polymerase PB2 Subunit. *Antimicrob Agents Chemother*. 2015;59:1574-1587.
72. Das K, Aramini JM, Ma LC, Krug RM, Arnold E. Structures of influenza A proteins and insights into antiviral drug targets. *Nat Struct Mol Biol*. 2010;17:530-538.
73. Zheng WJ, Tao YJ. Structure and assembly of the influenza A virus ribonucleoprotein complex. *FEBS Lett*. 2013;587:1206-1214.
74. Sanders CJ, Doherty PC, Thomas PG. Respiratory epithelial cells in innate immunity to influenza virus infection. *Cell Tissue Res*. 2011;343:13-21.
75. van de Sandt CE, Kreijtz JHCM, Rimmelzwaan GF. Evasion of Influenza A Viruses from Innate and Adaptive Immune Responses. *Viruses-Basel*. 2012;4:1438-1476.
76. Blasius AL, Beutler B. Intracellular Toll-like Receptors. *Immunity*. 2010;32:305-315.
77. Pang IK, Iwasaki A. Inflammasomes as mediators of immunity against influenza virus. *Trends Immunol*. 2011;32:34-41.
78. Takeuchi O, Akira S. Innate immunity to virus infection. *Immunol Rev*. 2009;227:75-86.
79. Van Hoeven N, Belser JA, Szretter KJ, et al. Pathogenesis of 1918 Pandemic and H5N1 Influenza Virus Infections in a Guinea Pig Model: Antiviral Potential of Exogenous Alpha Interferon To Reduce Virus Shedding. *J Virol*. 2009;83:2851-2861.
80. Szretter KJ, Gangappa S, Belser JA, et al. Early Control of H5N1 Influenza Virus Replication by the Type I Interferon Response in Mice. *J Virol*. 2009;83:5825-5834.
81. Bot A, Bot S, Bona CA. Protective role of gamma interferon during the recall response to influenza virus. *J Virol*. 1998;72:6637-6645.
82. Mordstein M, Kochs G, Dumoutier L, et al. Interferon-lambda contributes to innate immunity of mice against influenza A virus but not against hepatotropic viruses. *Cytokine*. 2008;43:307-307.
83. van Riel D, Leijten LME, van der Eerden M, et al. Highly Pathogenic Avian Influenza Virus H5N1 Infects Alveolar Macrophages without Virus Production or Excessive TNF-Alpha Induction. *PLoS Pathog*. 2011;7:
84. Becker S, Quay J, Soukup J. Cytokine (tumor necrosis factor, IL-6, and IL-8) production by respiratory syncytial virus-infected human alveolar macrophages. *J Immunol*. 1991;147:4307-4312.
85. Tumpey TM, Garcia-Sastre A, Taubenberger JK, et al. Pathogenicity of influenza viruses with genes from the 1918 pandemic virus: Functional roles of alveolar macrophages and neutrophils in limiting virus replication and mortality in mice. *J Virol*. 2005;79:14933-14944.
86. Kim HM, Lee YW, Lee KJ, et al. Alveolar macrophages are indispensable for controlling influenza viruses in lungs of pigs. *J Virol*. 2008;82:4265-4274.
87. Huber VC, Lynch JM, Bucher DJ, Le J, Metzger DW. Fc receptor-mediated phagocytosis makes a significant contribution to clearance of influenza virus infections. *J Immunol*. 2001;166:7381-7388.
88. Lin KL, Suzuki Y, Nakano H, Ramsburg E, Gunn MD. CCR2(+) monocyte-derived dendritic cells and exudate macrophages produce influenza-induced pulmonary immune pathology and mortality. *J Immunol*. 2008;180:2562-2572.
89. Jayasekera JP, Vinuesa CG, Karupiah G, King NJC. Enhanced antiviral antibody secretion and attenuated immunopathology during influenza virus infection in nitric oxide synthase-2-deficient mice. *J Gen Virol*. 2006;87:3361-3371.
90. Peper RL, Van Campen H. Tumor necrosis factor as a mediator of inflammation in influenza A viral pneumonia. *Microb Pathog*. 1995;19:175-183.
91. Middleton E, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer. *Pharmacol Rev*. 2000;52:673-751.
92. Kandaswami C, Middleton E Jr. Free radical scavenging and antioxidant activity of plant flavonoids. *Adv Exp Med Biol*. 1994;366:351-376.
93. Middleton E. Effect of plant flavonoids on immune and inflammatory cell function. *Flavonoids in the Living System*. 1998;439:175-182.
94. Zhang YF, Yi B, Ma JH, et al. Quercetin Promotes Neuronal and Behavioral Recovery by Suppressing Inflammatory Response and Apoptosis in a Rat Model of Intracerebral Hemorrhage. *Neurochem Res*. 2015;40:195-203.
95. Nair MPN, Kandaswami C, Mahajan S, et al. The flavonoid, quercetin, differentially regulates Th-1 (IFN gamma) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. *BBA-Mol Cell Res*. 2002;1593:29-36.
96. Casaschi A, Wang Q, Dang K, Richards A, Theriault A. Intestinal apolipoprotein B secretion is inhibited by the flavonoid quercetin: potential role of microsomal triglyceride transfer protein and diacylglycerol acyltransferase. *Lipids*. 2002;37:647-652.
97. Kandere-Grzybowska K, Kempuraj D, Cao J, Cetrulo CL, Theoharides TC. Regulation of IL-1-induced selective IL-6 release from human mast cells and inhibition by quercetin. *Br J Pharmacol*. 2006;148:208-215.
98. Vlahos R, Stambas J, Selemidis S. Suppressing production of reactive oxygen species (ROS) for influenza A virus therapy. *Trends Pharmacol Sci*. 2012;33:3-8.
99. He L, Zhang YM, Fang YQ, Liang WL, Lin JH, Cheng M. Classical swine fever virus induces oxidative stress in swine umbilical vein endothelial cells. *BMC Vet Res*. 2014;10:
100. Mata M, Morcillo E, Gimeno C, Cortijo J. N-acetyl-L-cysteine (NAC) inhibit mucin synthesis and pro-inflammatory mediators in alveolar type II epithelial cells infected with influenza virus A and B and with respiratory syncytial virus (RSV). *Biochem Pharmacol*. 2011;82:548-555.
101. Ogata N. Inactivation of influenza virus haemagglutinin by chlorine dioxide: oxidation of the conserved tryptophan 153 residue in the receptor-binding site. *J Gen Virol*. 2012;93:2558-2563.
102. Zhang M, Swarts SG, Yin LJ, et al. Antioxidant Properties of Quercetin. *Oxygen Transport to Tissue Xxxii*. 2011;701:283-289.
103. Chen TJ, Jeng JY, Lin CW, Wu CY, Chen YC. Quercetin inhibition of ROS-dependent and -independent apoptosis in rat glioma C6 cells. *Toxicology*. 2006;223:113-126.
104. Lee DE, Chung MY, Lim TG, Huh WB, Lee HJ, Lee KW. Quercetin Suppresses Intracellular ROS Formation, MMP Activation, and Cell Motility in Human Fibrosarcoma Cells. *J Food Sci*. 2013;78:H1464-H1469.
105. Sliwa A, Goralska J, Polus A, Gruca A, Dembinska-Kiec A. Influence of free fatty acids and quercetin on ROS generation and other mitochondrial function of human preadipocytes. *Free Radical Biology and Medicine*. 2013;65:S50-S50.

106. Sohn UD, Cho JH, Song HJ, Sun YH, Hwang WK. Protective Effects of Quercetin-3-O-beta-D-Glucuronopyranoside (QGC) On Ethanol-Induced Cell Damage Involve Inhibitions of ROS Generation and Downstream Activation of the ERK in Feline Esophageal Epithelial Cells. *Gastroenterology*. 2009;136:A442-A442.
107. Enkhtaivan G, Maria John KM, Pandurangan M, Hur JH, Leutou AS, Kim DH. Extreme effects of Seabuckthorn extracts on influenza viruses and human cancer cells and correlation between flavonol glycosides and biological activities of extracts. *Saudi Journal of Biological Sciences*. 2016; doi:10.1016/j.sjbs.2016.01.004.
108. Nair. The Flavonoid, Quercetin, Inhibits HIV-1 Infection in Normal Peripheral Blood Mononuclear Cells. *American Journal of Infectious Diseases* 2009; 5:135-141.
109. Wu CP, Calcagno AM, Hladky SB, Ambudkar SV, Barrand MA. Modulatory effects of plant phenols on human multidrug-resistance proteins 1, 4 and 5 (ABCC1, 4 and 5). *FEBS J*. 2005;272:4725-4740.
110. Pralhad T, Rajendrakumar K. Study of freeze-dried quercetin-cyclodextrin binary systems by DSC, FT-IR, X-ray diffraction and SEM analysis. *J Pharm Biomed Anal*. 2004;34:333-339.
111. Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MNVR. Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. *J Control Release*. 2006;113:189-207.
112. Schulman RA, Dean C. *Solve it with supplements : the best herbal and nutritional supplements to prevent and heal more than 100 common health problems*. Emmaus, Pa: Rodale: Distributed to the book trade by Holtzbrinck Publishers; 2007.
113. Vrolijk MF, Haenen GR, Opperhuizen A, Jansen EH, Schiffers PM, Bast A. The supplement-drug interaction of quercetin with tamsulosin on vasorelaxation. *Eur J Pharmacol*. 2005;746:132-137.
114. Center MS-KC. Quercetin. About Herbs. November 2, 2009; March 24, 2009.
115. Faculty TR. Quercetin. Find a Vitamin or Supplement 2009; 2009.
116. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcino genic properties. *Food Chem Toxicol*. 2007;45:2179-2205.
117. Kobylinska A, Janas KM. Health - promoting effect of quercetin in human diet. *Postepy Higieny I Medycyny Doswiadczalnej*. 2015;69:51-62.
118. Boots AW, Li H, Schins RPF, et al. The quercetin paradox. *Toxicol Appl Pharmacol*. 2007;222:89-96.
119. Lamprecht A, Ubrich N, Yamamoto H, et al. Biodegradable nanoparticles for targeted drug delivery in treatment of inflammatory bowel disease. *Journal of Pharmacology and Experimental Therapeutics*. 2001;299:775-781.
120. Hamaguchi T, Matsumura Y, Suzuki M, et al. NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumour activity and reduce the neurotoxicity of paclitaxel. *Br J Cancer*. 2005;92:1240-1246.
121. Nakanishi T, Fukushima S, Okamoto K, et al. Development of the polymer micelle carrier system for doxorubicin. *J Control Release*. 2001;74:295-302.
122. Gao X, Wang BL, Wei XW, et al. Anticancer effect and mechanism of polymer micelle-encapsulated quercetin on ovarian cancer. *Nanoscale*. 2012;4:7021-7030.
123. Dian LH, Yu EJ, Chen XN, et al. Enhancing oral bioavailability of quercetin using novel soluplus polymeric micelles. *Nanoscale Res Lett*. 2014;9:
124. Montenegro L, Carbone C, Maniscalco C, et al. In vitro evaluation of quercetin-3-O-acyl esters as topical prodrugs. *Int J Pharm*. 2007; 336:257-262.
125. Kim MK, Park KS, Yeo WS, Choo H, Chong Y. In vitro solubility, stability and permeability of novel quercetin-amino acid conjugates. *Bioorg Med Chem*. 2009;17:1164-1171.
126. Puoci F, Morelli C, Cirillo G, et al. Anticancer activity of a quercetin-based polymer towards HeLa cancer cells. *Anticancer Res*. 2012;32:2843-2847.
127. Cai X, Fang Z, Dou J, Yu A, Zhai G. Bioavailability of quercetin: problems and promises. *Curr Med Chem*. 2013;20:2572-2582.
128. Kale R, Saraf M, Juvekar A, Tayade P. Decreased B16F10 melanoma growth and impaired tumour vascularization in BDF1 mice with quercetin-cyclodextrin binary system. *J Pharm Pharmacol*. 2006;58:1351-1358.
129. Kakran M, Shegokar R, Sahoo NG, Shaal LA, Li L, Muller RH. Fabrication of quercetin nanocrystals: comparison of different methods. *Eur J Pharm Biopharm*. 2012;80:113-121.
130. Gao L, Liu G, Wang X, Liu F, Xu Y, Ma J. Preparation of a chemically stable quercetin formulation using nanosuspension technology. *Int J Pharm*. 2011;404:231-237.
131. Rogerio AP, Dora CL, Andrade EL, et al. Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. *Pharmacol Res*. 2010;61:288-297.
132. Singh D, Rawat MS, Semalty A, Semalty M. Quercetin-phospholipid complex: an amorphous pharmaceutical system in herbal drug delivery. *Curr Drug Discov Technol*. 2012;9:17-24.
133. Kakran M, Sahoo NG, Li L, Judeh Z. Fabrication of quercetin nanoparticles by anti-solvent precipitation method for enhanced dissolution. *Powder Technol*. 2012;223:59-64.
134. Zhao L, Shi Y, Zou S, Sun M, Lil L, Zhail G. Formulation and in vitro evaluation of quercetin loaded polymeric micelles composed of pluronic P123 and D-a-tocopheryl polyethylene glycol succinate. *J Biomed Nanotechnol*. 2011;7:358-365.
135. Tan BJ, Liu Y, Chang KL, Lim BK, Chiu GN. Perorally active nanomicellar formulation of quercetin in the treatment of lung cancer. *Int J Nanomedicine*. 2012;7:651-661.
136. Wang BL, Gao X, Men K, et al. Treating acute cystitis with biodegradable micelle-encapsulated quercetin. *Int J Nanomedicine*. 2012;7:2239-2247.
137. Khonkarn R, Mankhetkorn S, Hennink WE, Okonogi S. PEG-OCL micelles for quercetin solubilization and inhibition of cancer cell growth. *Eur J Pharm Biopharm*. 2011;79:268-275.
138. Aziz AA, Edwards CA, Lean MEJ, Crozier A. Absorption and excretion of conjugated flavonols, including quercetin-4 '-O-beta-glucoside and isorhamnetin-4 '-O-beta-glucoside by human volunteers after the consumption of onions. *Free Radic Res*. 1998;29:257-269.
139. Olsson ME, Gustavsson KE, Vagen IM. Quercetin and Isorhamnetin in Sweet and Red Cultivars of Onion (*Allium cepa* L.) at Harvest, after Field Curing, Heat Treatment, and Storage. *J Agric Food Chem*. 2010;58:2323-2330.
140. Konar N. Non-isoflavone phytoestrogenic compound contents of various legumes. *Eur Food Res Technol*. 2013;236:523-530.
141. Nguyen PH, Nguyen TNA, Kang KW, et al. Prenylated pterocarpans as bacterial neuraminidase inhibitors. *Bioorg Med Chem*. 2010; 18:3335-3344.
142. Liu AL, Wang HD, Lee SMY, Wang YT, Du GH. Structure-activity relationship of flavonoids as influenza virus neuraminidase inhibitors and their in vitro anti-viral activities. *Bioorg Med Chem*. 2008; 16:7141-7147.
143. Takashima K, Matsushima M, Hashimoto K, et al. Protective effects of intratracheally administered quercetin on lipopolysaccharide-induced acute lung injury. *Respir Res*. 2014;15:
144. Ahmad A, Ahad A, Rao AQ, Husnain T. Molecular docking based screening of neem-derived compounds with the NS1 protein of Influenza virus. *Bioinformation*. 2015;11:359-365.
145. Abood WN, Fahmi I, Abdulla MA, Ismail S. Immunomodulatory effect of an isolated fraction from Tinospora crispa on intracellular expression of INF-gamma, IL-6 and IL-8. *BMC Complement Altern Med*. 2014;14:205

146. Berardini N, Fezer R, Conrad J, Beifuss U, Carle R, Schieber A. Screening of mango (*Mangifera indica* L.) cultivars for their contents of flavonol O- and xanthone C-glycosides, anthocyanins, and pectin. *J Agric Food Chem*. 2005;53:1563-1570.

147. Kim DO, Chun OK, Kim YJ, Moon HY, Lee CY. Quantification of polyphenolics and their antioxidant capacity in fresh plums. *J Agric Food Chem*. 2003;51:6509-6515.

148. Zheng W, Wang SY. Oxygen radical absorbing capacity of phenolics in blueberries, cranberries, chokeberries, and lingonberries. *J Agric Food Chem*. 2003;51:502-509.

149. Rakers C, Schwerdtfeger SM, Mortier J, et al. Inhibitory potency of flavonoid derivatives on influenza virus neuraminidase. *Bioorg Med Chem Lett*. 2014;24:4312-4317.

150. Yang JH, Kondratyuk TP, Jermihov KC, et al. Bioactive Compounds from the Fern Lepisorus contortus. *J Nat Prod*. 2011;74:129-136.

151. Chang Q, Wong YS. Identification of flavonoids in hakmeitau beans (*Vigna sinensis*) by high-performance liquid chromatography-electrospray mass spectrometry (LC-ESI/MS). *J Agric Food Chem*. 2004;52:6694-6699.

152. Farag MA, Sakna ST, El-fiky NM, Shabana MM, Wessjohann LA. Phytochemical, antioxidant and antidiabetic evaluation of eight Bauhinia L. species from Egypt using UHPLC-PDA-qTOE-MS and chemometrics. *Phytochemistry*. 2015;119:41-50.

153. Nemeth K, Piskula MK. Food content, processing, absorption and metabolism of onion flavonoids. *Crit Rev Food Sci Nutr*. 2007;47:397-409.

154. Manguro LOA, Ugi I, Lemmen P, Hermann R. Flavonol glycosides of Warburgia ugandensis leaves. *Phytochemistry*. 2003;64:891-896.

155. Chen YK, Xie SG, Chen SQ, Zeng S. Glucuronidation of flavonoids by recombinant UGT1A3 and UGT1A9. *Biochem Pharmacol*. 2008; 76:416-425.

156. Dorta E, Gonzalez M, Lobo MG, Sanchez-Moreno C, de Ancos B. Screening of phenolic compounds in by-product extracts from mangoes (*Mangifera indica* L.) by HPLC-ESI-QTOF-MS and multivariate analysis for use as a food ingredient. *Food Res Int*. 2014;57:51-60.

157. Shah KA, Patel MB, Patel RJ, Parmar PK. *Mangifera indica* (mango). *Pharmacogn Rev*. 2010;4:42-48.

158. Wei Y, Xie QQ, Dong WT, Ito Y. Separation of epigallocatechin and flavonoids from *Hypericum perforatum* L. by high-speed counter-current chromatography and preparative high-performance liquid chromatography. *J Chromatogr A*. 2009;1216:4313-4318.

159. Crockett SL, Boeve JL. Flavonoid Glycosides and Naphthodianthrones in the Sawfly Tenthredo zonula and its Host-Plants, *Hypericum perforatum* and *H. hirsutum*. *J Chem Ecol*. 2011;37:943-952.

160. Plumb GW, Price KR, Williamson G. Antioxidant properties of flavonol glycosides from green beans. *Redox Rep*. 1999;4:123-127.

161. Kashiwada Y, Aoshima A, Ikeshiro Y, et al. Anti-HIV benzylisoquinoline alkaloids and flavonoids from the leaves of *Nelumbo nucifera*, and structure-activity correlations with related alkaloids. *Bioorg Med Chem*. 2005;13:443-448.

162. Nicolle C, Carnat A, Fraisse D, et al. Characterisation and variation of antioxidant micronutrients in lettuce (*Lactuca sativa* folium). *J Sci Food Agric*. 2004;84:2061-2069.

163. Sun Y, Ma X, Liu J. Compounds from fraction with cardiovascular activity of *Chrysanthemum indicum*. *Zhongguo Zhong Yao Za Zhi*. 2012;37:61-65.

164. Park KY, Lee SH, Min BK, et al. Inhibitory effect of luteolin 4 '-O-glucoside from *Kummerowia striata* and other flavonoids on interleukin-5 bioactivity. *Planta Med*. 1999;65:457-459.

165. Bazylko A, Stolarczyk M, Derwinska M, Kiss AK. Determination of antioxidant activity of extracts and fractions obtained from *Galinsoga parviflora* and *Galinsoga quadriradiata*, and a qualitative study of the most active fractions using TLC and HPLC methods. *Nat Prod Res*. 2012;26:1584-1593.

166. Abd el-fattah H, Gohar A, el-Dahmy S, Hubaishi A. Phytochemical investigation of Rumex luminiastrum. *Acta Pharm Hung*. 1994;64:83-85.

167. Legault J, Perron T, Mshvildadze V, et al. Antioxidant and anti-inflammatory activities of quercetin 7-O-beta-D-glucopyranoside from the leaves of *Brasenia schreberi*. *J Med Food*. 2011;14:1127-1134.

168. Morina F, Takahama U, Yamauchi R, Hirota S, Veljovic-Jovanovic S. Quercetin 7-O-glucoside suppresses nitrite-induced formation of dinitrosocatechins and their quinones in catechin/nitrite systems under stomach simulating conditions. *Food Funct*. 2015;6:219-229.

169. Williamson G, Plumb GW, Uda Y, Price KR, Rhodes MJ. Dietary quercetin glycosides: antioxidant activity and induction of the anticarcinogenic phase II marker enzyme quinone reductase in Hepalclc7 cells. *Carcinogenesis*. 1996;17:2385-2387.

170. Materska M, Perucka I. Antioxidant activity of the main phenolic compounds isolated from hot pepper fruit (*Capsicum annuum* L.). *J Agric Food Chem*. 2005;53:1750-1756.

171. Santos DYAC, Salatino MLF. Foliar flavonoids of Annonaceae from Brazil: taxonomic significance. *Phytochemistry*. 2000;55:567-573.

172. Goncalves B, Landbo AK, Knudsen D, et al. Effect of ripeness and postharvest storage on the phenolic profiles of cherries (*Prunus avium* L.). *J Agric Food Chem*. 2004;52:523-530.

173. Choi HJ, Song JH, Park KS, Kwon DH. Inhibitory effects of quercetin 3-rhamnoside on influenza A virus replication. *Eur J Pharm Sci*. 2009;37:329-333.

174. Kim JK, Seo YK, Park S, et al. Spiraeoside inhibits mast cells activation and IgE-mediated allergic responses by suppressing phospholipase C-gamma-mediated signaling. *Biochem Cell Biol*. 2015;93:227-235.

175. Zhao MH, Jiang ZT, Liu T, Li R. Flavonoids in *Juglans regia* L. leaves and evaluation of in vitro antioxidant activity via intracellular and chemical methods. *Scientific World Journal*. 2014;2014: 303878

176. Yao LH, Datta N, Tomas-Barberan FA, Ferreres F, Martos I, Singanusong R. Flavonoids, phenolic acids and abscisic acid in Australian and New Zealand Leptospermum honeys. *Food Chem*. 2003;81:159-168.

177. Liu AL, Shu SH, Qin HL, Lee SMY, Wang YT, Du GH. In vitro Anti-Influenza Viral Activities of Constituents from *Caesalpinia sappan*. *Planta Med*. 2009;75:337-339.

178. Kim YJ. Rhamnetin Attenuates Melanogenesis by Suppressing Oxidative Stress and Pro-inflammatory Mediators. *Biol Pharm Bull*. 2013;36:1341-1347.

179. Zhang W, Li B, Guo Y, et al. Rhamnetin attenuates cognitive deficit and inhibits hippocampal inflammatory response and oxidative stress in rats with traumatic brain injury. *Cent Eur J Immunol*. 2015;40:35-41.

180. Abdal Dayem A, Choi HY, Kim YB, Cho SG. Antiviral effect of methylated flavonol isorhamnetin against influenza. *PLoS One*. 2015;10: e0121610

How to cite this article: Enkhtaivan G, Manikandan M, Paul D, Gopal E, Chun S, Gopal J. Nature nominee quercetin's anti-influenza combat strategy—Demonstrations and remonstrations. *Rev Med Virol*. 2017;27:e1930. https://doi.org/10.1002/rmv.1930