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Review Article

Anti-Influenza Nutraceuticals: Antiviral and Anti-Inflammatory Effects

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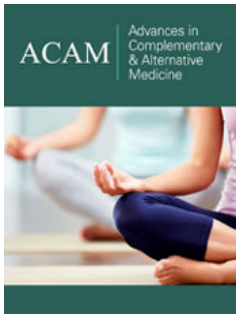

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Abstract

Influenza viruses cause upper-respiratory infections in their hosts with symptoms such as severe lassitude, headache, chills, muscle aches and delayed mild cough with signs of fever. These systemic symptoms are due to the release of cytokines by the bronchial epithelial and macrophage cells. However, influenza can cause more than just unpleasant symptoms - it can also be fatal through pneumonia superinfection or extreme cytokine reactions. There are several different methods of inhibiting influenza from entering or being effective inside the bronchial epithelial cells. The most commonly used drug is a Neuraminidase (NA) inhibitor called, oseltamivir, which prevents newly formed viruses from finalizing their budding from an infected cell. There are also several herbs and nutraceuticals that inhibit influenza viruses through this mechanism and others in addition to decreasing the cytokines being produced by the cells. The cytokine inhibition is often through block of the NF-κB pathway. This paper will discuss the anti-influenza and anti-inflammatory effects of eight of these nutraceuticals, Black Currant, Jamaican Sorrel, bee pollen, Echinacea Purpurea, Siberian Ginseng, honey, bee propolis, and Goldenseal. It will also discuss the anti-influenza and anti-inflammatory effects of four often recurring components of these nutraceuticals, luteolin, apigenin, quercetin, and chlorogenic acid.

Keywords: Black currant; Jamaican sorrel; Bee pollen; Echinaforce; Siberian ginseng; Honey; Bee propolis and goldenseal; Mechanism of action; NF-κB; Hibiscus sabdariffa

Introduction

Influenza is an upper respiratory infection that causes mild to severe symptoms, sometimes resulting in hospital visits and even death. There are often other complications related to influenza as well, such as pneumonia, ear and sinus infections; plus, influenza can augment preexisting chronic medical conditions [1]. The CDC estimates that since 2010 there have been 9.3-49 million cases of influenza in the United States (USA) annually. Of these cases, 140,000-960,000 resulted in hospitalizations, creating a heavy burden on our health care system. In addition, the CDC estimates that around 12,000-79,000 deaths have been caused annually in the USA since 2010 by influenza [2].

A recent review of the influenza's mechanism of viral infection details how influenza infects its host. It enters through the lungs, binding to sialic acid receptors on the surface of the bronchial epithelia. This binding causes lipid-raft clustering, the activation of Epidermal Growth Factor Receptor (EGFR), a tyrosine kinase that assists with clathrin-mediated endocytosis [3]. Recent studies show that influenza virus binding also can stimulate endocytosis through activation of Platelet Derived Growth Factor Receptor β (PDGFRβ), which stimulates uptake of the virus into endosomes from GM3-rich rafts [4]. After endosomal acidification, the viral M2 channel opens, which allows protons to enter the endosome and weaken the viral core by weakening the protein interactions in the core. By the late endosome, the Hemagglutinin (HA) on the viral envelope undergoes an irreversible conformational change due to the low pH. This causes the viral envelope to fuse with the membrane of the endosome and the release of viral ribonucleoproteins (vRNPs) into the cytoplasm. The vRNPs are imported to the cell's nucleus for transcription of the viral RNA (vRNA), which allows more viruses to be produced and released by the cell [5]. Neuraminidase (NA) then cleaves sialic acid from the cell's surface, allowing the new virion to be released from the cell. NA also helps the virus move through the mucus to the bronchial cells in the respiratory tract [6].

While influenza is in the endosome, it activates Toll-Like Receptor (TLR) 3 and TLR7, activation of TLR7 causes activation of Myeloid Differentiation primary response 88 (MyD88) which then activates Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB), a transcription factor for many various cytokines. These cytokines are signaling molecules used to alert other cells of the virus. They can have both antiviral and pro-viral effects. It is important to note that in the context of influenza, when NF-κB gets activated and releases cytokines it is often referred to as a "Cytokine Storm" due to the intense systemic inflammation they can cause. When influenza enters the cell it also activates the Nucleotide binding domain and Leucine-rich Repeat containing Protein 3 (NLRP3) inflammasome which then causes the transcription of capsase-1 which converts pro-IL-1 and pro-IL-18 into their active form (caspase-1 can also activate caspase-3 to induce apoptosis). The newly formed IL-1 can then bind to its receptor, IL-1R, and induce inflammatory gene production through MyD88 signaling. In addition, once the influenza vRNPs enter the cytosol, Retinoic Acid-Inducible Gene 1 (RIG-1) gets activated which can stimulate NF-κB as well [7-11].

Of the cytokines released, IL-6, and Tumor Necrosis Factor-α (TNF-α) are particularly pathogenic. The Janus Kinase/Signal Transducer and Activator of Transcription proteins (JAK/STAT) pathway is also important in the cellular response to influenza [12]. When this pathway is activated, various antiviral proteins such as Myxovirus Resistance Protein A (MxA) are transcribed [13,14].

Often NA inhibitors like oseltamivir or zanamivir are used as an early treatment for influenza virus infections. However, due to the high rate of mutation in influenza, some strains have become resistant, or at least less sensitive to oseltamivir. This was particularly evident during the winter 2008-2009 season with H1N1. NA inhibitors can also have negative side effects, like nausea, vomiting, and psychiatric effects [15].

Fortunately, there are many plants and nutraceuticals such as Jamaican sorrel, honey, bee pollen, bee propolis, Black Currant Berries, Echinacea purpurea, and Goldenseal that have molecular components that have both anti-influenza and anti-inflammatory properties. This is accomplished through blocking NA, HA, NF-κB, and other proteins and pathways involved in the influenza infection. Several recent reviews discuss the use of polyphenols and flavonoids for influenza virus infections [16-22]. The purpose of this review will be to discuss the recently discovered mechanisms for the anti-influenza effects as well as the less-appreciated anti-inflammatory properties of the above-named nutraceuticals. While there is a variety of known and unknown compounds in plants effective against influenza, four classes often reoccur in several different nutraceuticals: three structurally related flavones, luteolin, apigenin, and quercetin, and chlorogenic acid with its numerous variants. These compounds will be addressed first followed by a discussion of the eight natural products, many of which are rich in the above compounds. These products have been selected due to their particular effectiveness towards inhibiting influenza based on the literature. The studies used were chosen for their detail in describing the inhibition of the various compounds or product towards influenza.

Recurring components of nutraceuticals

While there are a variety of known and unknown compounds in plants that are effective against influenza, four often reoccur in several different nutraceuticals. Therefore, to avoid unnecessary repetition, these four-luteolin, apigenin, quercetin, and chlorogenic acid- will be addressed separately here. When they occur in a given nutraceutical, they will be mentioned as being present, but their effects won't be further elaborated.

Luteolin: The flavone luteolin (Figure 1), 2-(3,4-dihydroxyphenyl)-5,7-diihydroxychromen-4-one has been shown to possess anti-influenza properties via block of NA. Lee et al. [22], Liu et al. [23], and Sithisarn et al. [24] found that it inhibited various strains of the influenza virus (Table 1). Lee et al. [22] used a fluorometric method to determine luteolin's ability to inhibit the viral NA in Madin-Darby Canine Kidney cells (MDCK) cells. Liu et al. [23] used a standard fluorometric assay to determine the amount of inhibition luteolin has against NA. In each case, μM efficacy is observed. Sithisarn et al. [24] used an NA inhibition assay to test luteolin's ability to inhibit an H5N1 viral NA in A549 human bronchial cells.

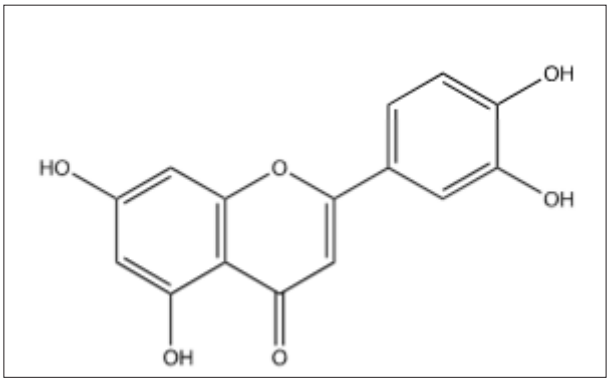

Figure 1: Luteolin.

Table 1: The Luteolin effect on influenza.

	IC_{50}±S.D.μM	Proposed Mechanism
H1N1[1]	10.7±0.2μM	NA inhibition
H5N1[1]	12.6±0.8μM	NA inhibition
H3N2[1]	25.6±8.3μM	NA inhibition
A/PR/8/34 (H1N1)[2]	33.7±6.4μM	NA inhibition
A/Jinan/15/90 (H3N2)[2]	32.6±9.8μM	NA inhibition
B/Jiangsu/10/2003[2]	53.3±11μM	NA inhibition
H5N1[3]	20.07±11.83μM	NA inhibition

[1]Lee et al. [22];

[2]Liu A. et al. [23];

[3]Sithisarn et al. [24]

Jia et al. [25] and Pratheeshkumar et al. [26] found that luteolin can also inhibit influenza-induced inflammatory pathways.

Pratheeshkumar et al. [26] used human Bronchial Epithelial cells (BEAS-2B), and mice to determine the effect of luteolin on inflammation when hexavalent chromium (an inflammation promoter) was exposed to the cells, and then luteolin was added. They found that luteolin decreased TNF-α expression of MCP-1, VCAM-1, NF-κB, IκBα, and IκB kinase B in a dose dependent manner with 1-2μM concentrations. Jia et al. [25] used an NF-κB transcriptional activity assay as well as immunoblotting analysis of IκB-α in male C57BL/6 mice to reduce the expression of AP-1, HIF-1α, COX-2, iNOS, IL-1β, IL-6, IL-8, MAPK, STAT-3, and TNF-α.

Apigenin: The structures of luteolin and apigenin (Figure 2, 2-(4-hydroxyphenyl)-5,7-diihydroxychromen-4-one) are very similar; in apigenin the catechol (3,4-dihydroxyphenyl) is converted to phenol, lacking the meta alcohol group. They have similar properties in regard to inhibiting influenza and inflammation (Table 2). Liu et al. [23] used the same procedure as with luteolin to find apigenin's inhibitory effect against NA. Sithisarn et al. [24] also used the same procedures to test apigenin as they did luteolin. Again, the efficacy is significant in the μM range. Apigenin also has been found to inhibit several components of inflammation. Basios et al. [27] found that apigenin inhibited IL-6, MPO, and TNF-α in male Wistar rats after they had had a bilio-pancreatic duct ligation. Palacz et al. [28] found that apigenin also inhibited COX-2, IL-2β, IL-10, TNF-α, and NF-κB expression in RAW-264.7 cells infected with lipopolysaccharide (LPS).

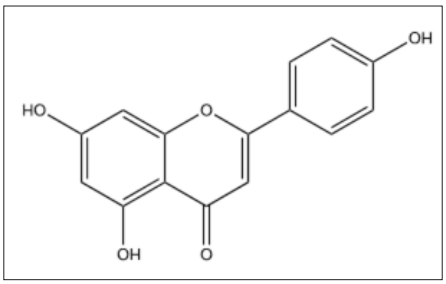

Figure 2: Apigenin.

Table 2: The Apigenin effect on influenza.

	IC_{50}±SD	Proposed Mechanism
A/PR/8/34 (H1N1)[1]	31.6±5.4μM	NA inhibition
A/Jinan/15/90 (H3N2)[1]	28.9±6.3μM	NA inhibition
B/Jiangsu/10/2003[1]	45.7±14μM	NA inhibition
A/Thailand /1(Kan^{-1})/04 (H5N1)[2]	16.01±4.33μM	NA inhibition

[1]Liu A. et al. [23];

[2]Sithisarn et. al. [24]

Quercetin: Quercetin (Figure 3, 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one) is also similar to luteolin, having an added hydroxyl at position 3 on the benzopyran. Wu et al. [29] used cytopathic effect (CPE) assays, Western Blots, immunofluorescence microscopy, and HA binding assays to determine that quercetin inhibits the membrane fusion process of influenza's entry into the cell by inhibiting the H2 subunit of the HA. Their results for inhibition of influenza infection in cell culture (Table 3) show strong efficacy for three strains. Lee et al. [22] used a fluorometric method as they did when they tested luteolin and found quercetin-3-sophoroside (Figure 4) extracted from Korean Papaver rhoeas bee pollen to be modestly effective towards inhibiting NA. Choi et al. [30] used CPE to demonstrate that quercetin-3-rhamnoside (Figure 5) inhibits A/WS/33 better than does oseltamivir-phosphate at comparable concentrations (Table 4). It should be noted that oseltamivir-phosphate, the prodrug, has been shown to be 100-fold less potent than the active metabolite, oseltamivir carboxylate, in MDCK cell CPE assays [31], but the activity of the quercetin analog is remarkable, nonetheless. For neither compound, did presoaking the virus sample in the compound produce the anti-viral effect, suggesting a post-endocytosis mechanism inhibition. Gel electrophoresis also demonstrated that, like oseltamivir-phosphate, quercetin-3-rhamnoside effectively inhibits the production of viral M segment RNA [30].

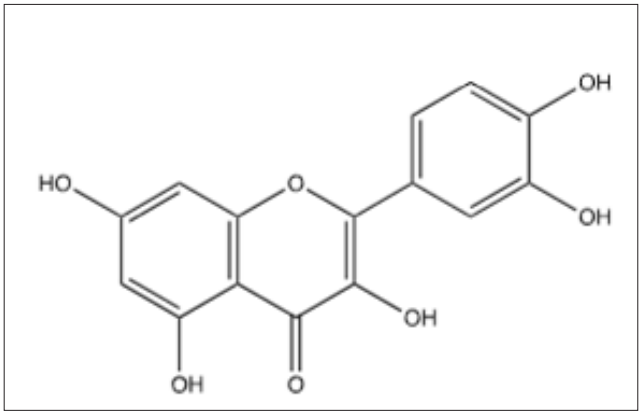

Figure 3: Quercetin.

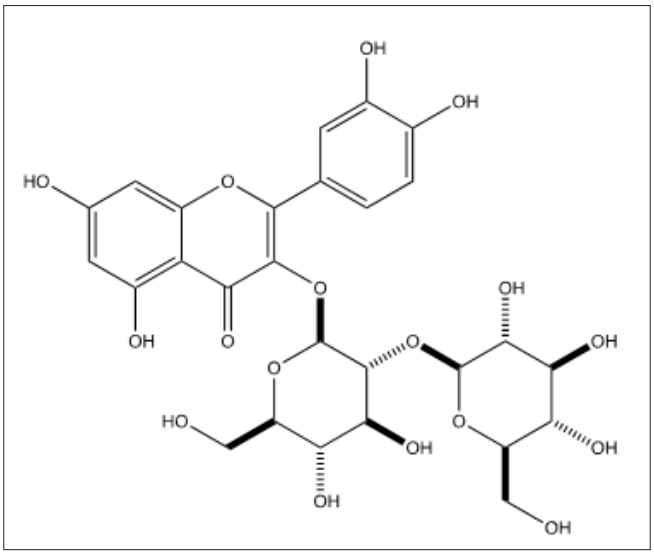

Figure 4: Quercetin-3-Sophoroside.

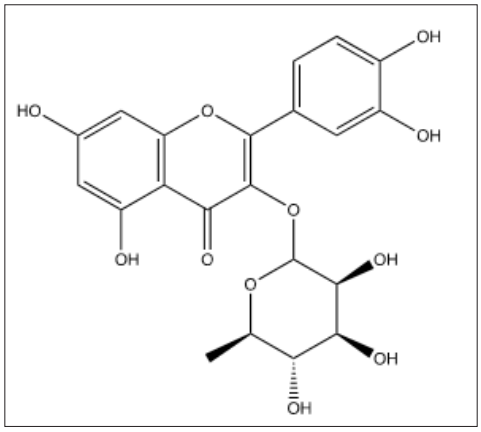

Figure 5: Quercetin-3-Rhamnoside.

Table 3: The Quercetin and Quercetin-3-sophoroside effects on influenza.

Quercetin[1]	EC_{50}±SD	Proposed Mechanism
A/Puerto Rico/8/34 (H1N1)	25.7±3.6μM	HA inhibition
A/FM-1/47/1 (H1N1)	20.6±0.467μM	HA inhibition
A/Aichi/2/68 (H3N2)	9.06±6.4μM	HA inhibition
Quercetin-3-Sophoroside[2]		
H1N1	88.3±3.0μM	NA inhibition
H5N1	75.1±8.7μM	NA inhibition
H3N2	112.8±8.2μM	NA inhibition

[1]Wu et al. [29];

[2]Lee et al. [22]

Table 4: The Quercetin-3-Rhamnoside effects on influenza[1].

	Percent Block of A/WS/33	Proposed Mechanism
223μM	86%	Post-endocytosis
22.3μM	66%	Post-endocytosis
Oseltamivir 244μM	58%	NA inhibition
Oseltamivir 24.4μM	49%	NA inhibition

[1]Choi et al. [30]

Takashima et al. [32] found that quercetin moderated the inflammation caused when mice had LPS administered to their trachea by inhibiting TNF-α, IL-1β, IL-6, and MMP-9. They also discovered that quercetin blocked TNF-α, IL-1β, IL-6 stimulated by LPS administration in mouse alveolar macrophage cell line AMJ2-C11. Maturu et al. [33] found that inflammation caused by hyperoxia in newborn mice could be relieved through the administration of quercetin. This was in part through the down regulation of NF-κB in lung and liver tissues as well as an upregulation in CYP1A1/CYP1B1/NQO1 mRNA. These results suggest that quercetin might inhibit the cytokine storm in influenza infections.

Chlorogenic acid: (Figure 6) is a thermally unstable ester that readily dissociates into its components, quinic acid (the tetrahydroxy-cyclohexanecarboxylic acid) and caffeic acid (Figure 7). It and several of its variants are found in several different plants, leaves, roots, and fruits. Green coffee beans, for instance, are a very rich source of chlorogenic acids [34]. Sinisi et al. [35] tested eight different compounds occurring in coffee from roasted green coffee beans that are variants of chlorogenic acid on various viruses such as influenza. The results from the two that were the most effective are in Table 5. Note that the two "R" groups in 3,4-O-dicaffeoyl-1,5-γ-quinide (Figure 8) both refer to ester linkages to caffeic acid groups (Figure 7). The mechanism of action for this chlorogenic acid was inhibition of influenza RNA synthesis, specifically through inhibiting the influenza virus RNA polymerase acidic (PA). It appears that the caffeic acid is the effective component, as it is equally effective alone. It may be advantageous to combine caffeic acid with one of the previous compounds that target sialic-acid binding sites to achieve synergy by blocking at multiple sites.

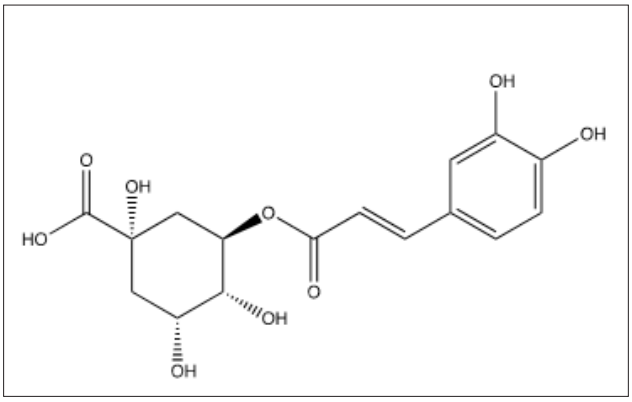

Figure 6: Chlorogenic acid.

Table 5: The Caffeic Acid and 3,4-O-dicaffeoyl-1,5-γ-quinide effects on influenza.

	Influenza Strain	IC_{50}(95% CI)[1]	EC_{50}(95% CI)[2]	Proteins Inhibited
Caffeic Acid[3]	A/PR/8/34	16 (12-22)	32 (20-51)	PA
3,4-O-dicaffeoyl-1,5-γ-quinide[3]	A/PR/8/34	34 (28-40)	19 (12-30)	PA

[1]Inhibition of endonuclease activity by the PA N-terminus

[2]vRNP reconstitution luciferase-based assay in human embryonic kidney (HEK293T) cells;

[3]Sinisi et al. [35].

Lin et al. [36] tested nine naturally occurring chlorogenic acid derivatives, in which caffeic acid(s) (Figure 7) was (were) esterized to different hydroxyls on quinic acid (Figure 9). It was found that five of them measurably inhibited viral RNA polymerase (Table 6), with the 4,5- and 3,4- variants being most potent.

Table 6: Caffeic acid derivative effects on influenza[1].

Compound1	Percent Inhibition of Viral Polymerase
3,4-dicaffeoylquinic acid	73%
1,5-dicaffeoylquinic acid	54%
4,5-dicaffeoylquinic acid	81%
3,5-dicaffeoylquinic acid	67%
1,3-dicaffeoylquinic acid	NE[2]
5-caffeoylquinic acid	26%
4-caffeoylquinic acid	NE
Quinic acid	NE
Caffeic acid	NE

[1]Lin et al. [36];

[2]No effect.

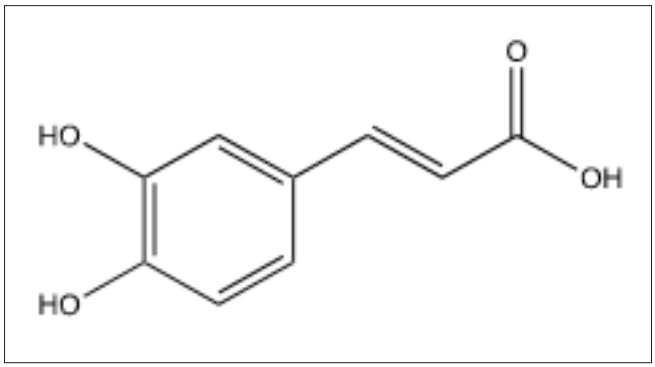

Figure 7: Caffeic acid.

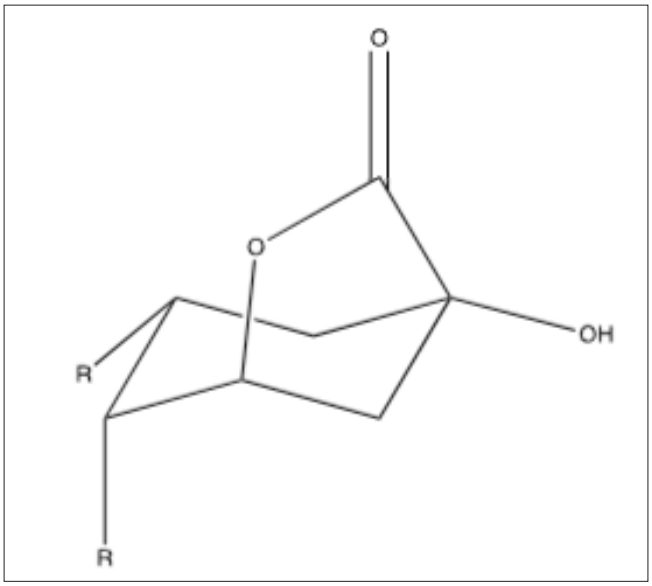

Figure 8: 3,4-O-dicaffeoyl-1,5-γ-quinide, R=caffeic acid.

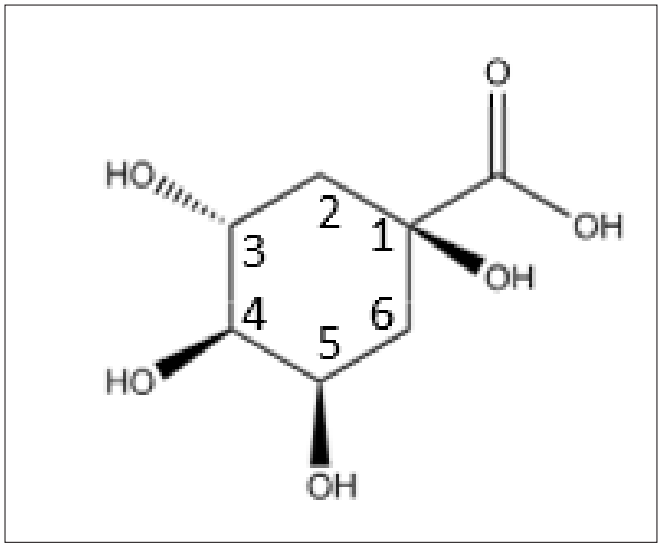

Figure 9: Quinic acid.

In cell culture with RAW264.7 cells, Ye et al. [37] found that cells pretreated with chlorogenic acid before LPS addition had lower levels of IL-6, TNF-α, Macrophage Inflammatory Protein-2 (MIP-2) and IL-1β. They further found that LPS injury to a mouse's kidney could be attenuated by the addition of chlorogenic acid. They also discovered that chlorogenic acid inhibits TNF-α, IL-1β, TLR-4 and IL-6 production in a dose dependent manner. This inhibition was done through the inhibition of IκB, and NF-κB p65 activity. The research done by Kim et al. [34] supports the research done by Ye et al. [37]. Kim et al. [34] pretreated RAW264.7 cells with chlorogenic acid prior to exposing them to LPS to test the suppression of cytokines and inflammatory factors by chlorogenic acid. They found that pretreatment with chlorogenic acid suppressed iNOS, Nitric Oxide (NO), IL-6, TNF-α, MIP-2, IL-β, and JAK2/STAT3. Therefore, chlorogenic acid is both effective against influenza virus, and blocks the cytokine pathways involved in inflammation.

Eight nutraceuticals

Black currant (Ribes nigrum folium): Black Currant leaves, and black currant berries have both been shown to have antiviral effects. Ehrhardt et al. [38] found that LADANIA067, an extract preparation from black currant berry leaves, was effective against oseltamivir-resistant strains in influenza (Table 7) in A549 cells, a human alveolar type II epithelial cell line. In addition, the virus didn't develop resistance to LADANIA067 like it did with amantadine (an M2 channel blocker). This viral inhibition was also found in mouse models with aerosolized LADANIA067. Hemagglutination by IAV *in vitro* was not inhibited by the compound, nor is sialic-acid based lectin-induced hemagglutination, indicating that LADANIA067 neither occludes the sialic-acid binding sites on the virus, nor occludes sialic-acid on the respiratory cell. LADANIA067 inhibited EGFR phosphorylation when virus was present, indicating that its mechanism involves inhibiting receptor-mediated endocytosis and viral uptake into the cell. The compound neither activated NF-κB nor inhibited receptor-mediated NF-κB activation. A549 cells did not take up nor metabolize LADANIA067. It was best administered

in aerosolized form. Teaupa et al. [39] found that an aqueous extract of black currant berries inhibited A/CA/07/09 (H1N1) with a half maximal response (EC_{50}) of 0.016±0.002mosmol/kg (±SEM) in MDCK cells. It is interesting to note that Ehrhardt et al. [38] pretreated their cells with the extract, whereas Teaupa et al. [39] pretreated their cells with virus first; and in both cases the virus was inhibited. However, not too many parallels can be drawn between the two studies without further research since Teaupa et al. [39] used the berries, and Ehrhardt et al. [38] used the leaves (Table 7).

Table 7: Black Currant effects on influenza.

Compound/Plant Extract	Type of Influenza	Efficacy
LADANIA067[1]	A/Nordrhein-Westfalen/173/09(H1N1)[2]	87.0%[3]
LADANIA067[1]	A/Puerto-Rico/8/34(H1N1)	58.60%
LADANIA067[1]	A/FPV/Bratislava/79(FPV) (H7N7)	77.70%
Black Currant Berries[4]	A/CA/07/09(H1N1)	0.016±0.002mmol/kg[5]

[1]Ehrhardt et al. [38]"

[2]Osteltamivir resistant pandemic 2009 strain;

[3]Percent reduction in viral titer in A549 cell culture medium in presence of compound at 50µg/ml 8 hours post infection;

[4]Teaupa et al. [39];

[5]EC50±SEM in MDCK cell 48-hour CPE assay.

Black currant has also been found to have anti-inflammatory properties too, despite Ehrhardt et al. [38] not finding any NF-κB inhibition with LADANIA067. Desjardins et al. [40] found that an extract with black currant was effective in alleviating toxicity caused by nicotine in oral epithelial cells. The effective concentrations they found ranged from 25-50µg/mL when the extract was used prior to nicotine. They also tested Cyanidin-3-O-glucoside, a major anthocyanin in black currant (Figure 10), for its effect against inflammation, and found that it protected the cells too. It was also found that black currant extract decreased the secretion of IL-6 by 37% in macrophages preincubated with the extract and then exposed to nicotine. Cyanidin-3-O-glucoside decreased the production of IL-6 by 22% or 46% when 5µg/mL or 25µg/mL of extract was preincubated with the macrophages prior to exposure to nicotine, respectively. Therefore, Black Currant can produce anti-inflammatory effects due to Cyanidin-3-O-glucoside, and anti-influenza properties when prepared as the extract LADANIA067.

Table 8: Black Currant's Effects on Inflammation[1].

Extract/Compound	Cytokine Inhibited	Concentration: Percent Inhibited
Black Currant Extract	IL-6	5µg/mL:5% 25µg/mL:37%
Cyanidin-3-O-glucoside	IL-6	5µg/mL:22% 25µg/mL:46%

[1]Desjardins et al. [40]

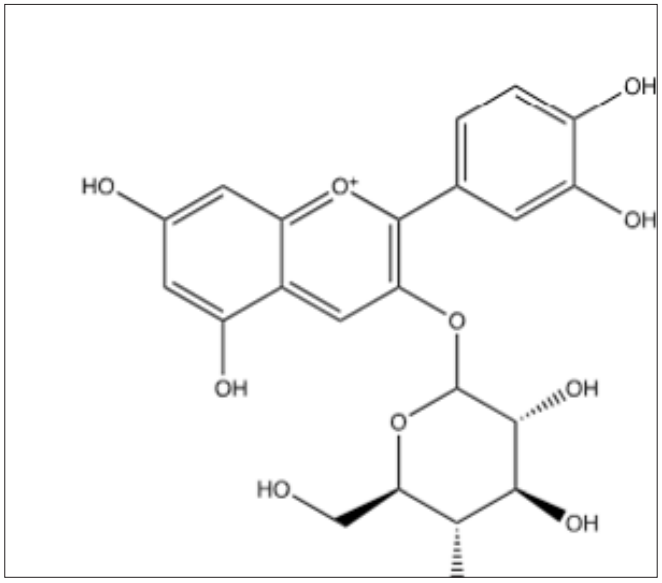

Figure 10: Cyanidin-3-O-glucoside.

Jamaican Sorrel: (Hibiscus sabdariffa), otherwise known as Roselle, has been shown to be effective against different strains of influenza. Baatartsogt et al. [41] found that an aqueous extract of Hibiscus (2 grams boiled in 100mL water for one hour, then centrifuged in a concentrator filter device) was effective against several types of influenza when the virus was mixed with the extract for either 10 seconds or 10 minutes then incubated with MDCK cells for 5 days (Table 9). They hypothesized that this block was from HA inhibition. Using MDCK cells, Teaupa et al. [39] also found that an aqueous extract of Hibiscus was effective against A/CA/07/09 (H1N1) with an EC_{50} of 0.0313±0.0014mmol/kg (±SEM) (Table 10). Da-Costa-Rocha et al. [42], found that Hibiscus has quercetin (Figure 3), luteolin (Figure 1), and chlorogenic acid (Figure 7), and Ramirez et al. [43] found that Hibiscus has quercetin and chlorogenic acid. Since luteolin, quercetin, and chlorogenic acid can independently inhibit influenza as discussed earlier, the combination of all three of these compounds is most likely the cause of the Hibiscus inhibition of influenza observed by Baatartsogt et al. [41] and Teaupa et al. [39].

Table 9: The Jamaican sorrel effect on influenza[1].

Influenza Virus Type	Log 10 Reduction in the Viral Titer after 10 Minutes of Virus and Extract Being Mixed	Log 10 Reduction in the Viral Titer after 10 Seconds of Virus and Extract Being Mixed
Avian/ Japan/9UO0036/09	≥4.0	N/A
Avian/ Japan/11OG1083/11	≥4.0	N/A
Chicken/Ibaraki/8/05	≥4.7	N/A
Whistling swan/Shi-mane/499/83	≥4.0	N/A
Duck/Hong Kong/820/80	≥3.3	N/A
Chicken/Yamagu-chi/7/04	≥5.0	≥5.0
Whooper swan/Hokkai-do/1/08	≥5.0	3
Chicken/VN-HT/33/2003	≥5.0	≥4.7
Molly duck/VN-HN/77/07	≥5.2	2.7
Chicken/VN-HT/30/10	≥5.0	2

[1]Baatartsgt et al. [41]

Table 10: The Jamaican sorrel effect on influenza.

Type of Influenza	EC_{50}±SEM
A/CA/07/09 (H1N1)[1]	0.0313±0.0014mmol/kg

[1]Teaupa et al. [39]

Jamaican sorrel also has anti-inflammatory properties, most likely due to it containing luteolin, quercetin, and chlorogenic acid as discussed. Chou et al. [44] observed that Hibiscus effectively attenuated urinary tract infections for those in long-term care facilities. To further determine the Hibiscus effect on inflammation, they injected mice with LPS and then gave them a hibiscus drink. After seven days they were sacrificed. ELISA tests were done on the serum of the mice to determine cytokine levels. A cell culture assay with a strain of immortalized hepatic cells (HepG2 cells) was also performed with LPS and Hibiscus to determine the cytokine levels. It was discovered that Hibiscus inhibits NF-κB *in vitro*, and IL-1β *in vivo*. It also suppressed IL-6, IL-22, Chemokine (C-X-C motif) ligand 2 (CXCL2), Chemokine (C-C motif) ligand 12 (CCL12), COX2 and iNOS genes. One of the key molecules involved is delphinidin-3-sambubioside (Figure 11) which acts on NF-κB and MAPK to suppress iNOS, NO, IL-6, MCP-1 and TNF-α.

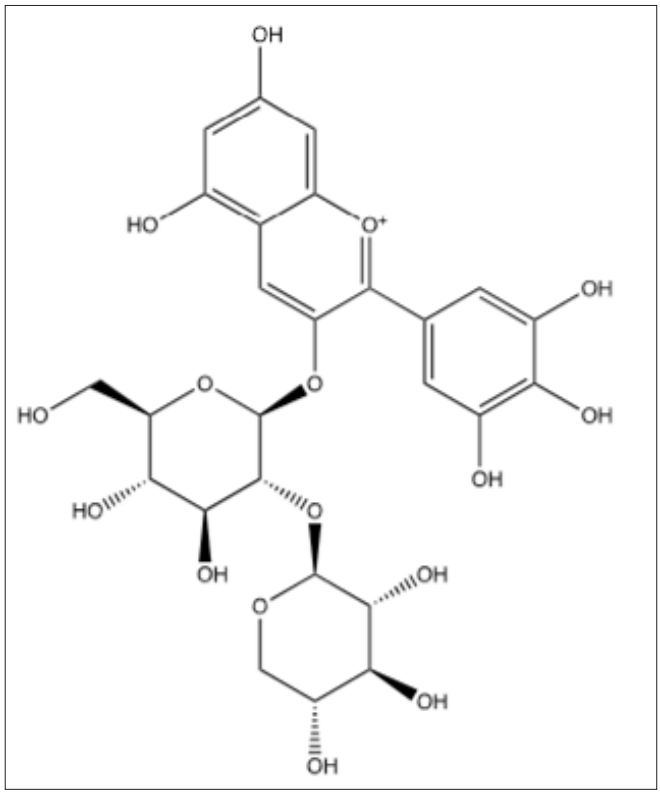

Figure 11: Delphinidin-3-Sambubioside.

Honey: Different kinds of honey, especially Manuka honey from New Zealand have been shown to have anti-influenza properties. Watanabe et al. [45] tested manuka honey, soba honey, kanro honey, acacia honey, and renge honey as possible anti-viral agents against A/WSN/33 (H1N1) influenza in MDCK cells. Of these, manuka honey performed the best (Table 11). Soba honey, kanro honey, acacia honey and renge honey followed manuka honey for effectiveness. Charyasriwong et al. [46] found that methylglyoxal (Figure 12) was an active ingredient in manuka honey with EC50 values of 180-420 μM against H1N1, H3N2, H5N2 and even oseltamivir-resistant H1N1. They even found that manuka honey had a synergistic effect when combined with NA inhibitors like oseltamivir. Teaupa et al. [39] tested a 1:1 combination of Manuka honey and bee pollen (which contains several NA inhibitors, see bee pollen section below) and found that this combination had an EC_{50} of 0.0313±0.0018mmol/kg (±SEM) which was more effective than just manuka honey or bee pollen individually. Charyasriwong et al. [47], found that the mechanism of methylglyoxal may not be through inhibition of HA or NA, at least not for influenza B, but may be involved in inhibiting the NF-κB pathway due to its suppression of TNF-α. In short, the exact mechanism of methylglyoxal and manuka honey's effect on influenza still needs to be elucidated, however they are effective against influenza, and act synergistically with NA inhibitors.

Table 11:

Honey Type	Strain of Influenza	EC_{50}
Manuka[1]	A/WSN/33 (H1N1)	3.6±1.2mg/mL (±S.D.)
Soba[1]	A/WSN/33 (H1N1)	6.7±0.5mg/mL (±S.D.)
Kanro[1]	A/WSN/33 (H1N1)	8.6±1.8mg/mL (±S.D.)
Acacia[1]	A/WSN/33 (H1N1)	10.3±2.7mg/mL (±S.D.)
Renge[1]	A/WSN/33 (H1N1)	11.3±3.7mg/mL (±S.D.)
1:1 Manuka honey and bee pollen[2]	H1N1	0.0313±0.0018 mmol/kg(±SEM)

[1]Watanabe et al. [45];

[2]Teaupa et al. [39].

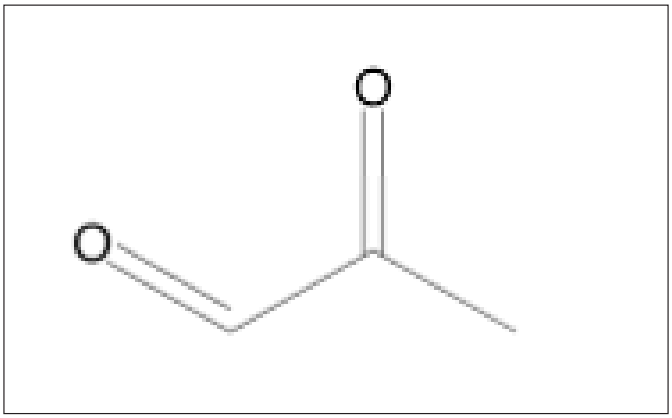

Figure 12: Methyglyoxal.

Gelam and Tualang honey have been shown to be effective against inflammation and to inhibit similar pathways influenza induces. Hussein et al. [48] studied the effects Gelam honey had on rat paw inflammation stimulated by carrageenan. They found that pretreatment of Gelam honey inhibited NF-κB, IκBα, COX-2, and TNF-α in the rat paws. Ahmad et al. [49] found that Tualang honey protected murine epidermal keratinocyte cells from UVB exposure by inhibiting NF-κB and the degradation of IκBα. It also inhibited IL-1β, IL-6, and TNF-α release from PAM212 keratinocytes exposed to UVB, and decreased expression of COX-2 and Prostaglandin E2. Ahmad et al. [49] & Kogilavanee et al. [50] reviewed the literature on Taulang honey in regard to inflammation, and found several studies discussing honey's anti-inflammatory effects. In conclusion, Tualang and Gelam honey have been shown to inhibit influenza-induced cytokines, so they could each have an effect on the cytokine storm.

Kaempferol: The flavone kaempferol (Figure 13) is a variant of quercetin (Figure 3) in which the catechol is converted to phenol. Bee pollen is rich in kaempferol glycosides [22]. The common glycosides are shown in Figure 14-17. The "X" on each glycoside represents a hydroxyl that is eliminated in forming the ether bond to kaempferol at its 3-hydroxy group (designated as OR). As discussed earlier, Lee et al. [22] tested several different compounds for their effectiveness against influenza in general, and specifically NA. Although not as effective as luteolin, they found that four derivatives of Kaempferol were effective towards inhibiting influenza though NA inhibition (Table 12).

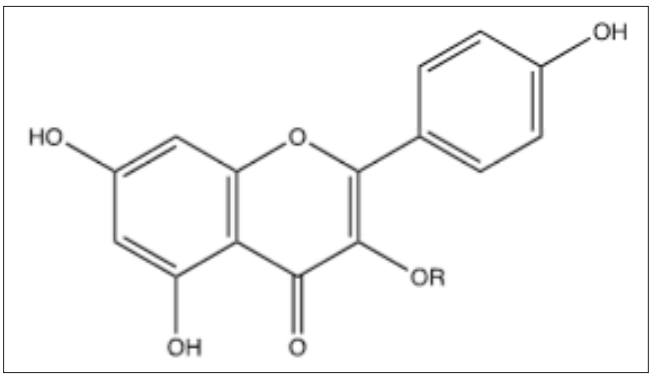

Figure 13: Kaempferol.

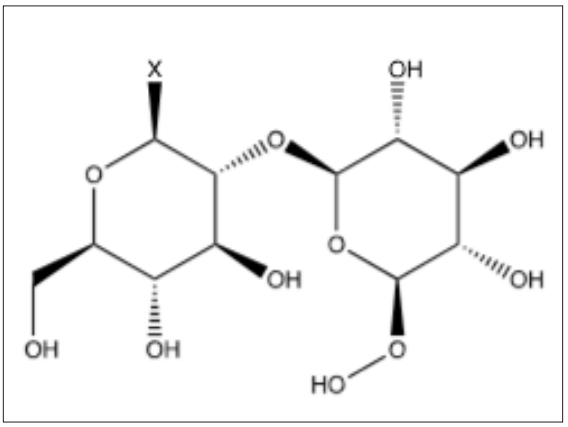

Figure 14: Kaempferol-3-Sophoroside.

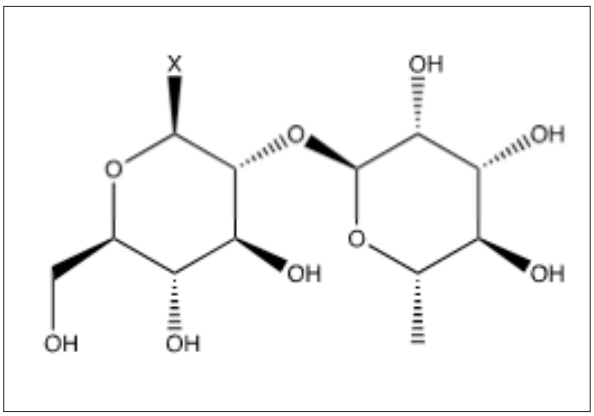

Figure 15: Kaempferol-3-Neohesperidoside.

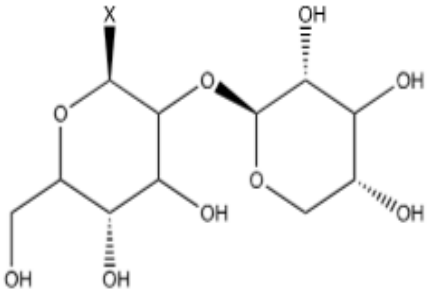

Figure 16: Kaempferol-3-Sambubioside.

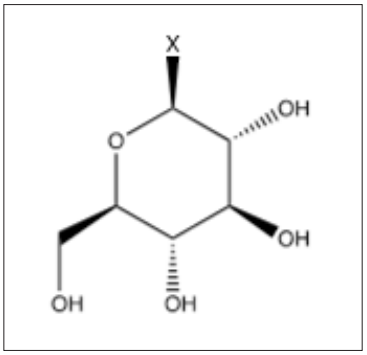

Figure 17: Kaempferol-3-Oβ-D-glucoside.

Table 12: The effects of Kaempferol derivatives on influenza.

	IC_{50}±SD(μM)	Proteins Inhibited
Kaempferol-3-Sophoroside[1]		
H1N1	85.6±1.4	NA
H5N1	111.6±1.0	NA
H3N2	61.0±0.7	NA
Kaempferol-3-Neohesperidoside[1]		
H1N1	56.2±1.1	NA
H5N1	80.2±4.8	NA
H3N2	51.6±1.5	NA
Kaempferol-3-Sambubioside[1]		
H1N1	45.3±1.9	NA
H5N1	51.2±3.1	NA
H3N2	52.2±2.9	NA
Kaempferol-3-Oβ-D-glucoside[1]		
H1N1	36.3±1.5	NA
H5N1	61.1±2.1	NA
H3N2	54.0±1.2	NA

[1]Lee et al. [22]

Bee pollen also has anti-inflammatory properties, inhibiting inflammatory pathways similar to those activated by influenza. Huang et al. [51] tested Schisandra chinensis bee pollen on the liver and kidneys of Sprague Dawley rats after the rats had bee pollen and cisplatin (an inflammatory agent) injected into their intraperitoneal region. They found that NF-κB, IL-1β, and IL-6 were decreased in the rats injected with bee pollen compared to the controls. Devi et al. [52] reviewed literature on kaempferol, observing that kaempferol reportedly inhibits COX-1, COX-2, iNOS, MAPK, Extracellular Signal-Regulated Kinases (ERK), STAT3, NF-κB, TNF-α, and other inflammatory pathways. Thus, kaempferol compounds augment the anti-viral and anti-inflammatory effects of luteolin and quercetin in bee pollen discussed above.

Bee propolis: Takemura et al. [53] found that Brazilian Green Propolis contains chlorogenic acid (Figure 6), caffeic acid (Figure 7), and several other compounds, including 3,4,5-tricaffeoylquinic acid, artepillin C, baccharin, p-coumaric acid, isosakuranetin, drupanin and ferulic acid. They also studied the effect of bee propolis on A/WSN/33 (H1N1) intranasally infected BALB/c mice (Table 13). They found that 3,4-dicaffeoylquinic acid Figures 7 and 9; (Table 6) was one of the major constituents of bee propolis that gave it an antiviral effect. However, they also mentioned that other yet-to-be quantified components of bee propolis probably had an effect against influenza as well. The mechanism of this inhibition involved increased Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), which induced the apoptosis of influenza virus infected cells; they also found that the propolis had an unknown cytoprotective mechanism. Búfalo et al. [54] found that propolis contains caffeic acid (Figure 7) and apigenin (Figure 2) which have been shown to be effective against influenza; it also contains caffeoylquinic acid, derivatives of which have been shown to inhibit influenza (Table 6); [23].

Table 13: The Bee Propolis effect on influenza.

Treatment[1] (Orally administered in 5% Arabic Gum)	n	Dose	Treatment duration in days post-infection (dpi)	Survival time (dpi, mean±SE)	Statistical Significance
5% Arabic gum	9		0-5	7.4±0.7	
Oseltamivir	8	0.5mg twice/kg/day	0-5	>120.0#	**
Propolis Water Extract	9	100 mg twice/kg/day	0-5	10.0±0.9	*
Propolis Ethanolic Extract	9	100mg twice/kg/day	0-5	10.1±0.9	*

3,4-dicaffeoylquinic acid	7	50mg twice/ kg/day	0-5	10.3±1.5	*
Chlorogenic Acid	9	50mg twice/ kg/day	0-5	8.1±0.8	N.S.

#Standard error not determined;

*P<0.05; **P<0.01; N.S. not significant.

[1]Takemura et al. [53].

Bee propolis is also capable of inhibiting several cytokines associated with the cytokine storm induced by influenza. Song et al. [55] found that caffeic acid phenethyl ester (CAPE, like chlorogenic acid (Figure 6), but with phenethyl alcohol replacing quinic acid), a component of bee propolis, was effective against blocking TNF-α, IL-8, and IκB-α in human middle ear epithelial cells when they were exposed to LPS. Búfalo et al. [54] also found that caffeic acid and propolis were effective in suppressing p38 MAPK, C-Jun N-Terminal kinase ½ (JNK1/2), NO, and NF-κB in Raw 264.7 cells when they were exposed to LPS. Therefore, bee propolis is effective against influenza virus itself, and affects some of the inflammatory pathways involved in the cytokine storm.

Echinaforce®: Rauš et al. [15] performed a randomized, double blind, multicenter, controlled clinical trial on 473 patients to compare Echinaforce®, an *Echinacea purpurea* extract, against oseltamivir. Both the oseltamivir and Echinaforce® groups showed a similar fever reduction after the start of treatment over a period of two days. The Echinaforce® group also showed an almost statistically significant decrease in complications (P=0.076). The Echinaforce® group had five times less adverse effects than the oseltamivir group; these effects were usually gastrointestinal issues like nausea and vomiting. Schapowal et al. [56] indicated that Echinaforce® affects HA and NA, and that influenza doesn't get resistant to Echinaforce® like it does to oseltamivir [57]. In fact, oseltamivir resistant virus was still susceptible to Echinaforce®. Sharma et al. [58] found that Echinaforce® inhibited H3N2 infections of MDCK cells in the CPE assay (Table 14). Pleschka et al. [53] used MDCK cells to test Echinaforce® inhibition of H3N2 (Table 15), as well as H1N1, H5N1, and H7N7. They observed that the extract could inactivate 99% or more of the virus at concentrations ranging from 0.16 to 53.3μg/ml. Pleschka et al. [57] also determined that Echinaforce® inhibited HA (Table 16) using a hemagglutination assay.

Table 14: The Echinaforce effect on influenza H3N2.

	EC_{50}
H3N2[1]	0.58±0.22μg/mL

[1]Sharma et al. [58]

Table 15: The Echinaforce effect on influenza H3N2 virus titer.

Echinaforce®'s Effect on H3N2	
Echinaforce®Dilution (μg/mL)	**Virus titer (PFU, % of control)**
1:30 (53.3)	<0.1
$1:10^2$ (16)	<0.1
$1:10^3$ (1.6)	<0.1
$1:10^4$ (0.16)	1.0±0
$1:10^5$ (0.016)	110±7.8

[1]Pleschka et al. [57].

Table 16: The Echinaforce effects on influenza HA protein.

Influenza strain[1]	Positive Control	Negative Control	Concentration that had a Significant Inhibition of HA
S-OIV (H1N1)	+	-	50μg/mL
KAN-1 (H5N1)	+	-	400μg/mL
FPV (H7N7)	+	-	400μg/mL

[1]Pleschka et al. [57].

Echinaforce® also has anti-inflammatory effects. Sharma et al. [58] found that Echinaforce® blocked release of CXCL1 (GRO-α), CXCL8 (IL-8), CCL2 (MCP-1), CCL5 (RANTES), IL-1α, IL-5, IL-6, TNF-α, IL-6, and IL-8 in BEAS-2 (human bronchial epithelial) cells exposed to influenza. Vimalanathan et al. [59] used BEAS-2 cells to determine how well Echinaforce® blocks virus-upregulated bacterial adhesion receptors on the cell surface for H. influenzae and S. aureus to prevent these bacteria from causing a superinfection (which is usually pneumonia). It was found that Echinaforce® does indeed inhibit expression of these receptors, so it could inhibit these bacteria from getting to the bronchial cells and infecting them too. They also found that Echinaforce® reduced NF-κB, IL-6, and IL-8 in cells exposed to LPS. Sharma et al. [58] found that Echinaforce® contains chlorogenic acid (Figure 6), caffeic acid (Figure 7), and several caffeic-acid containing compounds, namely echinacoside (Figure 18), cynarin (Figure 19), caftaric acid (Figure 20), and cichoric acid (Figure 21), which, given their caffeic acid components, may be responsible for Echinaforce®'s effects on influenza and inflammation.

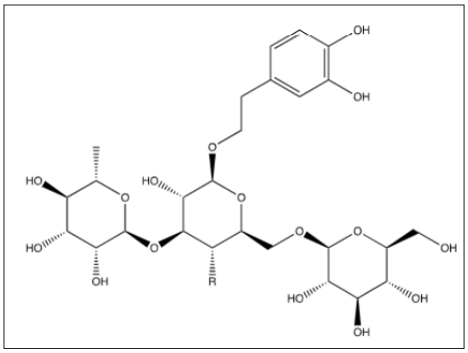

Figure 18: Echinacoside.

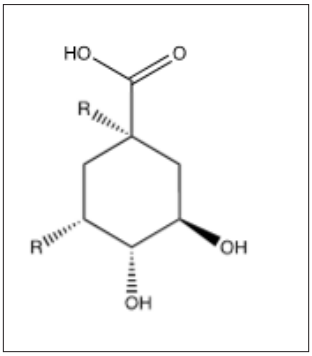

Figure 19: Cynarin, R=caffeic acid.

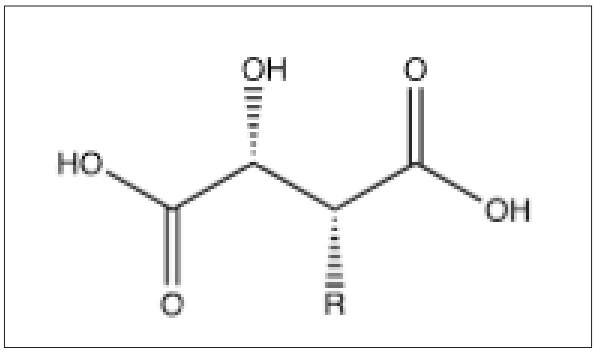

Figure 20: Caftaric acid, R= caffeic acid.

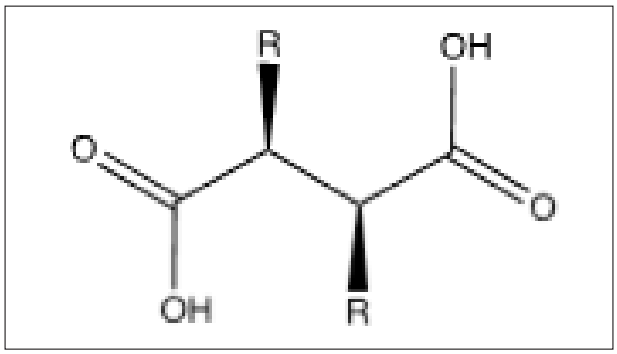

Figure 21: Cichoric acid, R= caffeic acid.

Goldenseal: It has anti-influenza properties due to berberine (Figure 22). Cecil et al. [60] tested this isoquinoline alkaloid, a component of goldenseal, barberry (*Berberis vulgaris*), coptis (*Coptis chinensis*), and Oregon grape (*Mahonia aquifolium*), on H1N1 in RAW264.7 macrophage-like cells, A549 human lung epithelial-derived cells, murine bone marrow derived macrophages, and MDCK cells. Berberine was effective at inhibiting the virus production in all the cell lines except for the MDCK cells. In RAW 264.7 cells, berberine had EC_{50} values of 0.01 and 0.44μM for the two H1N1 virus strains tested, much lower than amantadine which had an EC_{50} of 27μM (Table 17). They found that the mechanism behind this inhibition is most likely related to post-translational effects on transport or maturation of viral proteins inside the cell.

Table 17: The Berberine effect on influenza.

	EC_{50}
Berberine[1] vs. A/PR/8/34 (H1N1)	0.01μM
Berberine vs. A/WS/33 (H1N1)	0.44μM
Amantadine vs. A/PR/8/34 (H1N1)	27μM

[1]Cecil et al. [60].

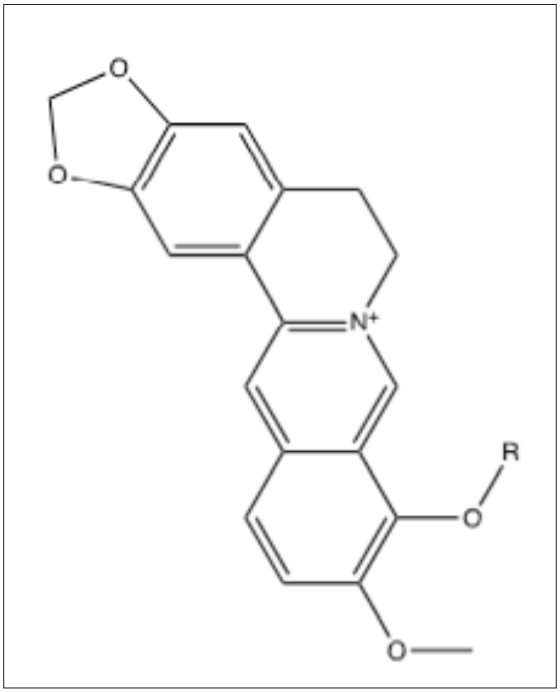

Figure 22: Berberine.

Enkhtaivan et al. [61] tested berberine-piperazine derivatives for their effects on A/PR/8/34 (H1N1), A/Vic/3/75 (H3N2), B/Lee/40, and B/Maryland/1/59 strains of influenza in MDCK cells compared to oseltamivir. Table 18 shows results for the five derivatives berberine with adducts attached as ethers to its "OR" via their terminal pentyl carbons, shown in Figure 23-27 found to be most effective against A/PR/8/34 (H1N1). They also tested the binding affinity of the different compounds to NA. Cecil et al. [60] also found that Berberine and goldenseal extracts inhibit TNF-α, and PGE2. Li et al. [59] found that berberine decreased IL-1β, IL-4, IL-5, IL-6, IL-13, IL-17 through inhibiting NF-κB p65, p-NF-κB

p65 and p-IκBα in a dose dependent manner. These tests were done with male Wister rats that had ovalbumin injected into their intraperitoneal cavity to induce asthma [62]. Therefore, Goldenseal in general, and specifically the root, is effective against influenza virus infection and the resulting cytokine storm mostly due to it containing berberine and derivatives thereof.

Table 18: The Berberine-Piperizine[1] derivative effects[2] on influenza.

Berberine-Piperizine	A/PR/8/34 (H1N1)	A/Vic/3/75 (H3N2)	B/Lee/40	B/Maryland/1/59
A[3]	97.7±0.0323	88.6±0.25	66.4±0.092	74.7±0.10
B[3]	57.4±0.0034	54.1±0.03	51.2±0.051	47.6±0.13
C[3]	100.2±0.20	82.0±0.84	83.8±0.13	90.0±0.010
D[3]	103±0.20	95.8±0.016	84.6±0.007	90.3±0.027
E[3]	105±0.34	92.2±0.079	86.9±0.045	96.4±0.11
Oseltamivir[4]	51.5±0.29	77.4±1.3	176±0.16	159±0.090

[1]Enkhtaivan et al. [61];

[2]EC50±experimental uncertainty (μM).

[3]Berberine adducts are the piperizine variants shown in Figure 24-28.

[4]Oseltamivir phosphate ester, i.e. Tamiflu, which is weakly active in cell culture compared to the active agent, oseltamivir phosphate carboxylate.

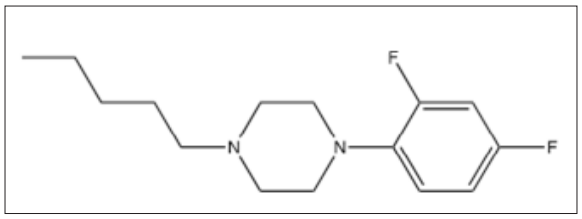

Figure 23: Berberine adduct A.

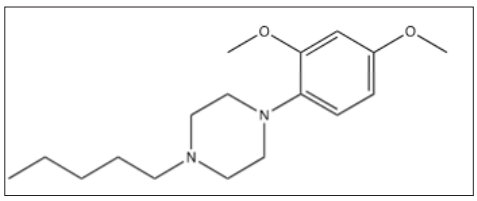

Figure 24: Berberine adduct B.

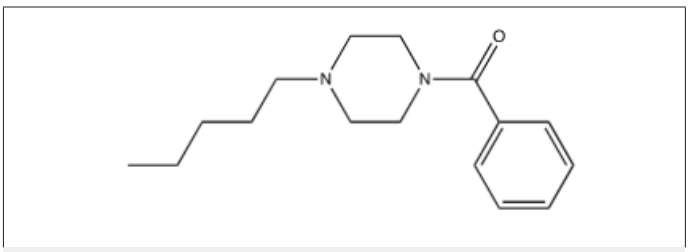

Figure 25: Berberine adduct C.

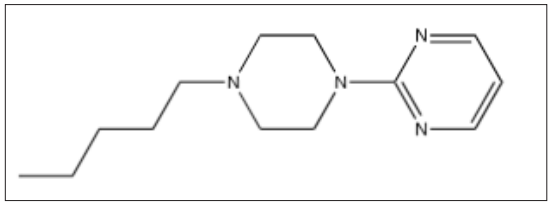

Figure 26: Berberine adduct D.

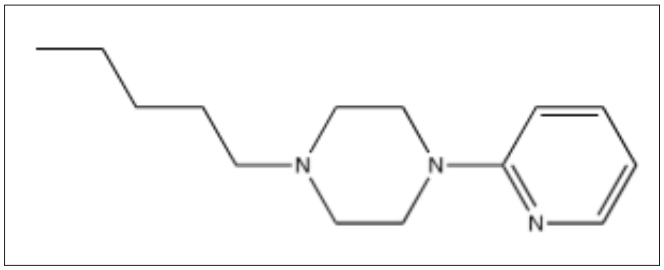

Figure 27: Berberine adduct E.

Siberian Ginseng: Otherwise known as *Acanthopanax senticosus*, or *Eleutherococcus senticosus*, has anti-influenza properties through a number of flavonoids it contains. Liu et al. [63] ran an ultra-performance liquid chromatography coupled with electrospray ionization time-of-flight mass spectrometry to determine the various components of Siberian Ginseng [64]. They found that it contained syringin (also known as eleutheroside B, Figure 28), chlorogenic acid (Figure 6), caffeic acid (Figure 7), eleutheroside E (Figure 29), and isofraxidin (Figure 30). Yang et al. [34] found that it contained eleutheroside B_1 (Figure 31). Wang et al. [65] used MDCK cells to find that eleutheroside B_1 was effective against A/PR/8/34 (H1N1), A/Guangzhou/GIRD07/09 (H1N1), and A/Aichi/68 (H3N2), but it had no effect on avian influenza viruses like A/Duck/Guangdong/2009 (H6N2), A/Duck/Guangdong/1994 (H7N3), or A/Chicken/Guangdong/1996

(H9N2) (Table 19). Therefore, it is reasonable to conclude that eleutheroside B_1 inhibits influenza by a hemagglutinin specific mechanism. For Siberian Ginseng extracts, this could combine with anti-viral effects from chlorogenic acid, eleuthroside B and some of its other components.

Table 19: The Eleutheroside B_1 effects on influenza[1];

Eleutheroside B_1	EC_{50}
A/PR/8/34 (H1N1)	276μM
A/Guangzhou/GIRD07/09 (H1N1)	167μM[2]
A/Aichi/68 (H3N2)	325μM[2]
A/Duck/Guangdong/2009 (H6N2)	No Effect
A/Duck/Guangdong/1994 (H7N3)	No Effect
A/Chicken/Guangdong/1996 (H9N2)	No Effect

[1]Wang et al. [65]

[2]These units, μM, are based on corrections to the published units, which are clearly erroneous, i.e. high by a factor of 1000.

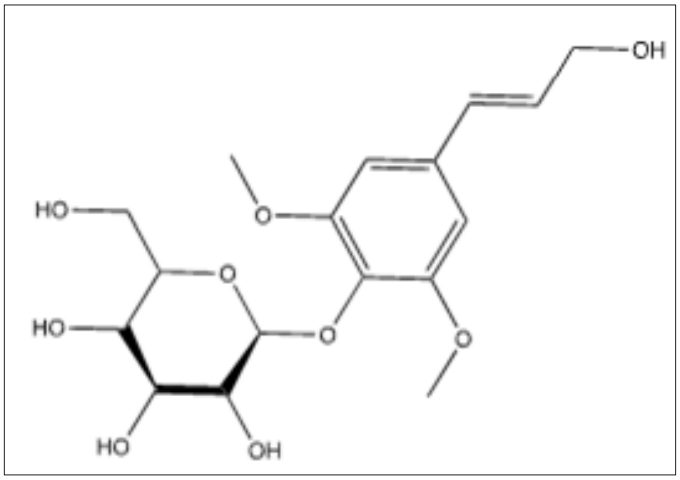

Figure 28: Syringin.

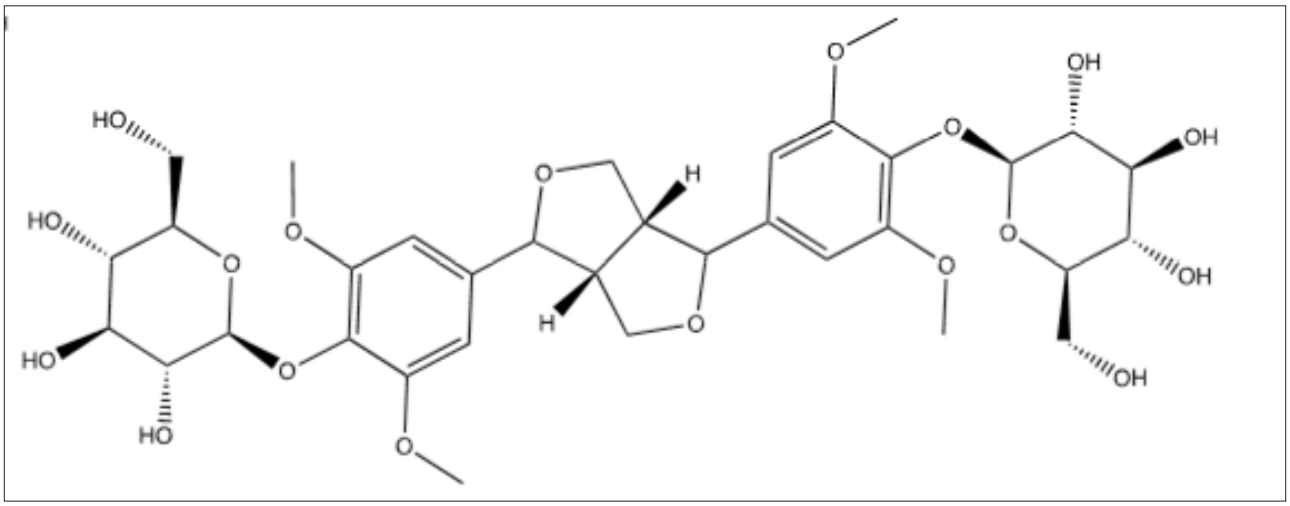

Figure 29: Eleutheroside E.

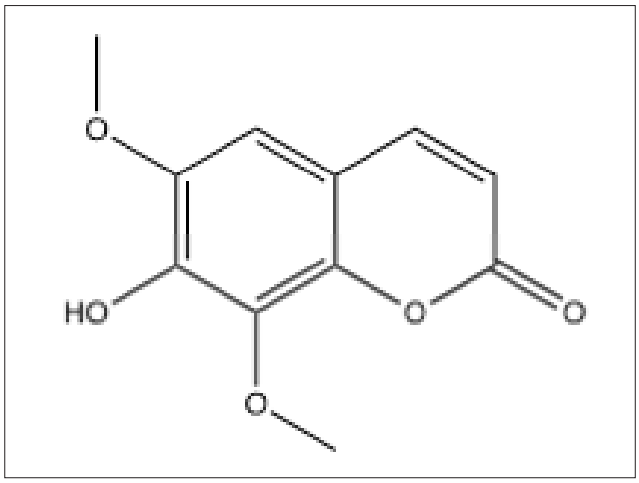

Figure 30: Isofraxidin.

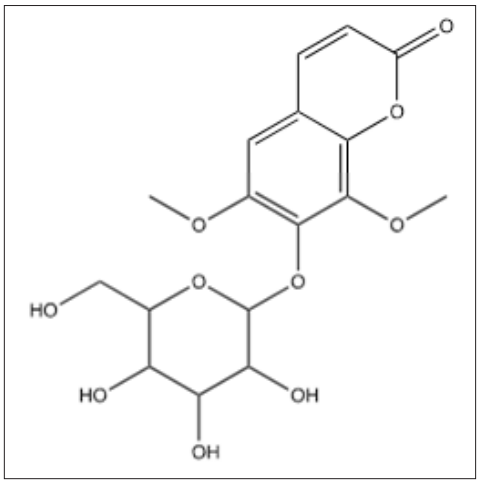

Figure 31: Eleutheroside B1.

Siberian Ginseng also confers some anti-inflammatory effects. Wang et al. [65] found that eleutheroside B_1 suppressed influenza-induced expression of CXCL-8, CCL-2 and IL-6 in A549 cells. Han et al. [66] injected piglets with LPS or saline in the intraperitoneal cavity. They then gave Siberian Ginseng polysaccharides (800mg/kg dietary supplement) to half of the piglets and not to the control group. They determined that Siberian Ginseng decreased expression of IL-1β, IL-6, and TNF-α. Therefore, Siberian Ginseng may have a similar effect on inflammation due to eleutheroside B_1, and chlorogenic acid; some of the other components may play a role as well.

Conclusion

In conclusion, influenza is a major disease that usually just causes minor symptoms, but it can prove fatal. The systemic symptoms are due to the release of cytokines by the body. Traditionally oseltamivir is used to treat influenza infections. In particular, Echinaforce® performed admirably in a clinical trial against oseltamivir. But there are other compounds that may also be effective against influenza and may also aid in abating the cytokine storm. Some of these compounds include luteolin, apigenin, quercetin, and chlorogenic acid. These compounds and others can be found in various nutraceuticals like the eight described in this paper. It should be noted though that there is some thought that these compounds, and other catechol and phenolic compounds may constitute Pan-Assay Interference Compounds (PAINS) which have a variety of binding sites, but not specific activity against one protein [67]. Therefore, these compounds may be useful for developing a combo-therapy since they work *in vitro*, however they are not as beneficial for guiding medicinal chemistry (which is focused on improving the potencies and patentability of different compounds) since these compounds have non-specific binding sites. Perhaps through combining these compounds with others that have shown effective against influenza, more effective drug combinations could be made to treat this potentially deadly disease.

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