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Review

The use of herbal extracts in the control of influenza

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Influenza A virus poses a continuing threat to the health of humans and farmed animals, and predictions of impending pandemics are commonplace. This review discusses the unique combination of genetic features that make this virus such a threat, and explains why current control measures are inadequate. However, in spite of this, certain herbal extracts rich in polyphenols could play an important role in controlling influenza virus outbreaks and alleviating symptoms of the disease. One of the attractions of herbal treatment is the broad spectrum of potential viral targets, since components of these herbs can interact with different viral proteins and are not constrained by viral strain differences and drug-resistant mutations; consequently any influenza virus is susceptible. In addition these extracts often have antibacterial, anti-inflammatory, and anti-oxidant properties, all of which would be beneficial during influenza infection.

Key words: Influenza virus, avian 'flu, swine 'flu, antiviral, pandemic, cytokines, anti-inflammatory, herbal extracts, polyphenols.

INTRODUCTION

Influenza viruses are ubiquitous, they have been around for hundreds of years, and are likely to remain with us for a long time. They produce significant annual morbidity and mortality throughout the world, and the occasional pandemic with potentially devastating consequences for human and animal health and the global economy (Cannell et al., 2008; Suzuki, 2009). There are three types of influenza viruses: A, B and C, the latter two being confined mainly to humans, in which they produce relatively mild seasonal outbreaks. However, the greatest impact is derived from Influenza A virus, which has been associated with several well known human pandemics during the last century, and an increasing number of epidemics (epizootics) in domestic birds (Cannell et al., 2008; Michaelis et al., 2009; Neuman et al., 2009; Suzuki, 2009) (Table 1). The consensus is that influenza A virus originated in wild birds, possibly waterfowl such as ducks and geese, and that these birds act as reservoirs and vectors for the many known sub-types (strains) of influenza A virus (Boyce et al., 2009).

THE NATURE OF INFLUENZA A INFECTIONS

The classical symptoms of human influenza include cough, malaise and fever, often accompanied by sore throat, nasal obstruction, and sputum production, which resolve spontaneously in most healthy individuals, although immune compromised and elderly individuals tend to be more vulnerable. Complications may include bronchitis and pneumonia, and exacerbation of asthma and chronic obstructive pulmonary disease (COPD) (Johnston, 2002).

More serious disease in healthy individuals, especially during pandemics, is often accompanied by excessive overreaction of the innate immune response with the secretion of dangerous levels of cytokines ("cytokine storms") and other inflammatory mediators (Baskin et al., 2009). Also the importance of concurrent bacterial infection cannot be overlooked, since this may lead to more serious outcomes (Brundage and Shanks, 2008). Thus, an ideal control agent should be able to prevent or reduce the replication and spread of the virus, as well as any potentially pathogenic bacterial infection, and also counteract the overproduction of inflammatory mediators. There are also many other "influenza-like" infections, which could benefit from a similar multi-targeted approach.

Currently, the prevailing strains of Influenza A virus are H3N2 and H1N1 in humans; and H5N1 and several H7 viruses in domestic birds; but new pathogenic strains could emerge anytime from the avian reservoir (Table 1).

Table 1. Summary of influenza pandemics 20th - 21st centuries.

Year	Virus subtype	Global Deaths (est)	Source of viral genes
1918-19 "Spanish flu"	H1N1	20-50 million	All gene segments of avian origin
1957 "Asian flu"	H2N2	2-4 million	5 segments from H1N1 3 segments of avian origin
1968 "Hong -Kong flu"	H3N2	1-2 million	6 segments from H2N2 2 segments avian origin
1977 "Russian flu"	H1N1	< 1million	Identical to "Spanish flu"
2009 "swine-origin flu"	H1N1	In progress	3 segments from North American swine virus; 2 segments from N.A. avian virus; 2 segments Eurasian swine flu; 1 segment H3N2
2009/10 ?	H5N1, H7N3	Possibly millions of poultry	Re-assortment; intergenic recombination?

Adapted from Michaelis et al. (2009).

The so-called "swine flu" H1N1, or more correctly "swine-origin flu" virus (S-OIV), which has now been declared a pandemic, is still spreading and causing morbidity and mortality in many countries as they enter a new winter 'flu season' (Suzuki, 2009).

WHY IS INFLUENZA A VIRUS SUCH A THREAT?

Influenza A virus is an RNA virus and therefore subject to a high rate of mutation, a process referred to as genetic or antigenic "drift". In addition the RNA genome is unique in that it comprises 8 discrete segments, making it amenable to mixing (re-assorting) between different virus sub-types, and consequently the generation of novel sub-types, some of which could be more virulent (pathogenic) than the parental viruses. This process is completely unpredictable and is referred to as genetic or antigenic "shift". It is aided by the relative ease of transmission of the virus between species, including birds to mammals. The two outer proteins of the virus are the HA (hemagglutinin) and NA (neuraminidase), which are responsible for virus entry and dissemination into and between cells. Significant mutations in their genes (HA or H gene, and NA or N gene) can result in the host immune system (and vaccines) no longer recognizing them. There are 16 known sub-types of the HA gene (H1 to H16), and 9 subtypes of the N/NA gene, all of which have been found in wild birds (Boyce et al., 2009; Suzuki, 2009).

CONTROL OF INFLUENZA: THE INADEQUACY OF EXISTING STRATEGIES

Vaccines represent the first line of attack against many infectious agents, and they are generally advocated for routine application during each influenza seasonal outbreak, based on the prevailing strain of the previous season; but because of the unpredictable nature of influenza epidemics one cannot be sure of the success of any vaccine. Once a novel virus strain has been isolated and characterized it then becomes plausible to produce a more appropriate vaccine, a process that could take up to 6 months, although there is no guarantee that community protection by a given vaccine will be adequate, especially if the virus becomes progressively more virulent. In fact several experts have questioned the wisdom of wide-spread vaccination (Cannell et al., 2008; Jefferson et al., 2009; Fedson, 2009).

Numerous antiviral drugs for use in infected patients have been tested experimentally, in animal models and in humans, but none has proven satisfactory. The most recent synthetic compounds are the neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®). However, apart from the usual risk of side effects with any new drug, there is also the likelihood of resistant mutants being selected during the course of treatment, in a manner analogous to antibiotic-resistant bacteria. In fact drug resistant strains of human and avian Influenza viruses have been documented with increasing frequency, including the current S-OIV (Jefferson et al., 2006; Cheng et al., 2009).

THE HERBAL ALTERNATIVE

Some innovative molecular approaches have been suggested, based on cellular signaling pathways utilized by the virus for its replication (Ludwig, 2009; Fedson, 2009). Herbal remedies, including traditional Chinese Medicine (TCM) have also been suggested as alternatives (Wang et al., 2006). These generally may be safer than chemical drugs, and are less likely to encounter resistant viruses, because of their multivalent functions. In addition certain herbal preparations can target both the virus itself and the symptoms of influenza

infection, many of which are due to the overproduction of inflammatory mediators, such as cytokines, which are induced by the virus infection (Baskin et al., 2009; Sharma et al., 2009a). Some of them also possess antibacterial and anti-oxidant activities.

Geranium (*Geranium sanguineum* L.):

Aqueous and alcoholic extracts of the dried aerial roots of Geranium have traditional uses in Bulgaria (and presumably other countries) to counteract various gastro-intestinal disorders, infections, and inflammatory conditions (Serkedjieva and Hay, 1998). Laboratory investigations in cell cultures and animal models have revealed impressive antiviral activities against a number of human, avian and equine strains of Influenza A virus, including amantadine resistant virus (Serkedjieva et al., 2008). The extracts apparently interfere with an early stage in virus replication, at concentrations as little as 10 µg/ml. They are also virucidal at > 50 µg/ml, at which level cytotoxicity also becomes evident. The authors concluded however that the extract appeared to be relatively more potent *in vivo*, in a mouse-influenza model, than in cell cultures. This was probably a reflection of the additional bio-activities manifest *in vivo*, which included a stimulation of various macrophage functions which had been suppressed by the virus, as well as reversal of virus-induced oxidative stress in the infected mice (Murzakhmetova et al., 2008). Intranasal application of the extract, particularly in the form of an aerosol, and preferably both before and after virus infection, was the most effective treatment protocol in reducing lung virus load and pathology and prolonging viability.

The alcoholic extracts are rich in various polyphenols, including flavonoids, phenolic acids, catechins and gallotannins; thus it is tempting to assign the antiviral and anti-oxidative bioactivities to these compounds. However, the more recent investigations on the anti-influenza activities revealed that isolated individual compounds were no more effective, on a weight basis, than the crude ethanol extract. These results suggest that the combination of phenolic compounds acting in synergy is more important than any individual compound, or alternatively that other uncharacterized components might contribute to the anti-viral activity. On the basis of these results, the Geranium extract could be a useful adjunct treatment in influenza infections, because of its wide spectrum of beneficial activities.

Green Tea (*Camellia sinensis*)

Aqueous extracts of *C. sinensis*, especially green tea, have been shown to possess antiviral, antibacterial, antifungal, and antioxidant activities, as well as other bioactivities. These activities appear to be due mainly to the dominant polyphenolic components, the catechins and their chemically related theaflavins, which together can amount to 10% of the dry weight of the leaves (Friedman, 2007).

Various strains of influenza A and B virus are susceptible, as are also some other respiratory viruses. The antiviral effects against influenza seem to be multifunctional, inasmuch as viral hemagglutinin, neuraminidase, and viral RNA synthesis, were all inhibited in cell culture studies. The extract worked best when added to cells around the time of virus adsorption. However, these could all be consequences of an early stage interaction between the active compounds and individual virus components (Imanishi et al., 2002; Song et al., 2005).

Not all the individual polyphenols were active however, and EGC [(-) epigallocatechin] and theaflavin digallate were much more active than their structural analogues, possibly due to differences in binding affinities with the viral target proteins. Interestingly, the active catechins were no more active, on a weight basis, than the whole extract or a mixture of the polyphenol components, suggesting that they act synergistically.

Some authors have discussed the significance of tea polyphenols in terms of their limited bioavailability and their pharmacodynamics in intestinal tissues, the normal destination of tea consumption (Friedman, 2007). However, upper respiratory viruses and bacteria are not necessarily affected by intestinal bioavailability, since exposure of the organisms will initially occur in mucosal tissues; hence a mouth wash or gargle would be more effective *in vivo* than traditional tea drinking. In this connection a preliminary trial was conducted with a gargled solution of green tea catechins for its ability to prevent influenza infection. The results suggested a possible benefit, but the numbers involved were too small to be really significant (Yamada et al., 2006).

In another study based on subjective symptom scores related to ”cold and flu”, individuals consumed daily either capsules made from a standardized green tea rich in polyphenols, equivalent to consumption of about 10 cups of tea per day, or a placebo. The green tea group recorded about one-third fewer symptoms (Rowe et al., 2007). Unfortunately, in the absence of microbial/viral characterization, it is difficult to relate such results to influenza specifically, although it appears that consumption of green tea on a regular basis during the flu season could be beneficial.

Cistus incanus

Cistus species are found throughout the Mediterranean Region and the Caucasus, where they have been used traditionally for the treatment of various ailments, including skin and inflammatory diseases. The aqueous extracts are rich in polyphenols, particularly high molecular weight compounds such as pro-anthocyanidins (Ehrhardt et al., 2007). *C. incanus* (pink rockrose) extracts were the subject of recent investigations on anti-

bioactivities. These activities appear to be due mainly to the dominant polyphenolic components, the catechins influenza activities. At non-cytotoxic concentrations, the extract was very effective in reducing the replication of several human and avian influenza virus strains in cell culture (50 µg/ml resulting in 99% reduction without adversely affecting several parameters of cell viability and function). Evidently, the extract inhibited a very early stage in the replication cycle, possibly by binding to the virus and preventing entry into the cells. Continued passage of virus in the presence of the extract did not result in the emergence of resistant mutants, in contrast to amantadine which was tested in parallel (Ehrhardt et al., 2007).

C. incanus extracts were also evaluated in mice infected with a mouse-adapted avian influenza virus. Because of possible limited bioavailability of the high molecular weight polyphenols, an aerosol formulation was used. In fact a normal oral administration of *Cistus* extract gave no protection at all, whereas in contrast mice treated with the aerosol preparation did not develop the usual symptoms of disease, or mortality, and viral titers in the lungs were substantially reduced. However, the extract had to be applied prior to virus infection in order to be protective (Droebner et al., 2007). This suggests that if the high molecular weight polyphenols were involved, as proposed, then they would presumably have to remain available in the mucosa to allow subsequent contact with the virus inoculum. Bronchial epithelial cells from treated mice showed normal histology, indicating that such a preparation is safe and could be beneficial in human influenza.

In a more recent report, Kalus et al. (2009) described a study in which 300 patients, given either capsules prepared from *C. incana* or freshly brewed green tea, subjectively recorded upper respiratory symptoms over a period of time. Placebos were not considered ethically acceptable for this study. In spite of the limitations inherent in such an analysis, the *Cistus* preparation appeared to be superior to the green tea extract in terms of overall symptom scores.

Pomegranate (*Punica granatum*)

Polyphenol rich extracts of pomegranate were recently studied for anti-influenza virus activity. And, like the other extracts described above, they showed activity which was manifest at a very early stage in the virus replication cycle, probably a consequence of its ability to block viral HA and entry into cells (Haidari et al., 2009). The activity was attributed to the major polyphenol punicalagin, although the antiviral potency did not appear to be as good as the other extracts discussed above. However, in an interesting extension of the study, punicalagin was able to synergize with the neuraminidase inhibitor oseltamivir.

Echinacea (*Echinacea purpurea* and other species)

Traditionally, various types of extract, prepared from aerial parts and roots of several species of *Echinacea*, were used in North America in the treatment of respiratory infections, wounds, and other inflammatory conditions (Barrett, 2003). In recent decades they have become very popular in many parts of the world as “cold and flu” remedies. Most of the commercial preparations are based on pressed juice or ethanol tinctures of aerial parts of *E. purpurea*, or root extracts of *E. angustifolia*, although other species are sometimes used. Polysaccharides were originally proposed to be the main bioactive constituents; but more recent investigations have focused on alkylamides and caffeic acid derivatives (Barnes et al., 2005). A variety of antiviral, antibacterial, antifungal, antioxidant and immune-modulatory activities have been described in studies *in vitro* and *in vivo*, but it has not proved possible to correlate these activities with specific compounds (Barnes et al., 2005; Hudson et al., 2005; Vimalanathan et al., 2009). However, there are clear differences between extracts derived from different species and plant parts, and the need for standardized extracts has been emphasized (Vohra et al., 2009).

In connection with influenza, this virus and other membrane containing viruses are very susceptible to direct contact with *E. purpurea* preparations (more than 3 $\log_{10}$ inactivation at dilutions of 1:100 or more, equivalent to one tenth of the recommended oral dose), although viruses without membranes, such as rhinoviruses (common cold viruses) and adenoviruses, are more resistant. A very early stage in the virus replication cycle, possibly at the level of virus entry or penetration into the cell, is the target of the *Echinacea* (unpublished data), and polyphenolic components may be responsible for this antiviral activity.

Echinacea extracts also show potent bactericidal activity against several bacteria associated with “cold and flu” symptoms such as sore throat (*Streptococcus pyogenes*) and respiratory complications (*Hemophilus influenzae*, *Legionella pneumophila*). However, other bacteria are relatively resistant, indicating the selectivity of the antibiotic effect. This should be considered beneficial since many normal resident oral bacteria (“friendly” bacteria) would be spared.

Many respiratory viruses and bacteria, including those resistant to direct attack by *Echinacea*, induced the secretion of pro-inflammatory cytokines and related mediators, as well as mucin secretion, in epithelial cell models of nasal, mucosal and tracheo-bronchial tissues. And in all of these models a standardized potent tincture of *E. purpurea* (Echinaforce®), intended for oral consumption, reversed the inflammatory responses (Sharma et al., 2008b; 2009a; 2009b). The responses were mediated by a large number of transcription factors, such as NFkB and many others, which were activated by the infectious agents and consequently led to increased

expression of inflammatory genes. *Echinacea,* however, inhibited these transcription factors, leading to repression of cytokine and mucin secretion (Altamirano et al., 2009).

Some clinical trials have been conducted with *Echinacea* extracts, although the objective in these trials was invariably to determine possible prevention or therapy of "common colds", rather than influenza. Furthermore, few of them utilized adequately characterrized *Echinacea* preparations or satisfactory statistical analyses. Nevertheless, there was an overall trend towards beneficial effects of the *Echinacea*, and equally importantly the safety of the preparations was confirmed (Schoop et al., 2006). A more comprehensive trial that includes influenza virus and other respiratory viruses, in addition to a well characterized *Echinacea* extract, is needed to confirm the benefits of oral *Echinacea* use.

CONCLUDING REMARKS

The studies described above have revealed a number of common features among the anti-influenza herbal extracts. Various polyphenols are present, and the antiviral activities have been attributed to them. Animal and human studies have invariably supported the studies in cell culture systems. The extracts also possess antibacterial, antioxidant and anti-inflammatory activities. Since influenza virus and several respiratory bacteria induce the secretion of certain pro-inflammatory cytokines and chemokines, then a reversal of these "cytokine storms" would be beneficial for the control of various symptoms associated with the infection. In general the polyphenol-rich extracts were more effective, on a weight basis, than individual isolated components, suggestive of synergism. All of these herbal extracts appear to be safe for human consumption, and could therefore provide benefits in influenza infected individuals. Furthermore, any measure that decreases the "virus load" in a community would be a valuable aid in control of influenza.

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