Kerry Bone
Educational Article

Herbs and Cytokine Storm Risk

by Kerry Bone

Concerns have been raised that certain herbs acting on the immune system might deleteriously enhance the cytokine response during acute respiratory viral infections. These concerns are not supported by a detailed analysis of the published scientific and traditional literature.

What are cytokines?

Cytokines are a large group of molecules comprising proteins, peptides and glycoproteins that are secreted by specific cells of the immune system. They are signalling molecules that mediate and regulate both immunity and inflammation. Cytokine is a general term: other group names are used based on function, cell of secretion or target of action. For example, cytokines made by lymphocytes can also be referred to as lymphokines, while interleukins are made by one leukocyte and act on other leukocytes. Chemokines are cytokines with chemotactic activities. Interferons are named for their ability to indirectly interfere with viral infection.[1]

Cytokines are in effect the language of the immune system and play a critical communicative role in initiating and sustaining both the innate and adaptive immune responses to an invading pathogen. Just because an agent (such as a medicinal plant) facilitates cytokine signalling release in the early stages of an immune response does not necessarily mean it will drive that cytokine response to an excessive level in the later rampant stage of an infection. In other words, improving efficiency does not imply subsequent overproduction. The opposite is more likely to be true (see below).

Cytokine storm

Exuberant immune responses induced by the later stages of an infection have been described as a “cytokine storm” and are associated with excessive levels of proinflammatory cytokines and widespread tissue damage.[2] A range of pathogens have been observed to cause this response, but the reasons why the cytokine storm affects only certain individuals during an infection and not others are not fully understood. The term was first used in 1993 to describe the effects of graft-versus-host disease. In 2003, cytokine storm was shown to be associated with severe reactions to influenza viruses and subsequently to various viral, bacterial or fungal infections. While there is no agreed definition of what a cytokine storm exactly is, it is characterised by a marked severity of infection due to an activation cascade

that leads to an auto-amplification of cytokine production.[3] It is in fact an **autotoxicity** induced by the pathogen.

It is worthwhile to explore how a cytokine storm develops during a viral infection. It has been proposed that our response to a respiratory virus occurs in three stages: stage I, an asymptomatic incubation period with or without detectable virus; stage II, a non-severe symptomatic period with the presence of virus; stage III, a severe respiratory symptomatic stage with a high viral load.[4] During the incubation and non-severe stages, a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to the severe stage. This in turn requires a dynamic innate immune response, which will of course involve the efficient local release of cytokines as signalling agents. Therefore, any strategies that boost immune responses at the early stages are regarded as important.[4]

When a protective immune response is impaired, the virus will propagate, and massive destruction of affected tissues may occur. In this event, damaged host cells induce chaotic innate inflammatory responses in the lungs that are largely mediated by proinflammatory macrophages and granulocytes, and a cytokine storm results.[4] In other words, a cytokine storm is a late stage manifestation of the viral disease that occurs only when the immune system fails to contain the virus. It is not the manifestation of an overactive immune response directly targeted at the infection, in fact it is quite the opposite. Surely this argues for the intensive use of immune support during stages I (late stage prevention) and II (early acute management) to avoid its occurrence?

Overview of herbs and cytokine storm risk

While cytokine storm was first linked to a viral infection in only 2003, it has clearly been a feature of such infections since time immemorial. Hence, we are not dealing with a new phenomenon when it comes to observations about herbs and their role to prevent and reduce infection. There is no suggestion from traditional western herbal writings, including those of such well-documented groups like the Eclectics (who accumulated considerable experience during the Spanish flu pandemic[5]), that the use of immune herbs aggravated viral infections. Also, a range of traditional Chinese formulations (several containing the immune herb Astragalus) have been used extensively in China during various recent viral epidemics, with no suggestion of their exacerbating cytokine storm.

Echinacea

First it should be pointed out that the key role of Echinacea root is for infection prevention. In the modern prescribing context, it plays a secondary role during the actual viral infection. Antiviral herbs such as licorice and sweet wormwood (the latter in pulsed doses) and other immune herbs such as Andrographis and holy basil become more important in acute phase management (although Ellingwood very much regarded it as a frontline remedy during all

acute infections, see below). Hence, concerns about cytokine storm and Echinacea are not really that relevant to its current best clinical use.

But even given this, there is no evidence that Echinacea root will inappropriately stimulate the cytokine response during an acute viral infection and cause harm.

From the monograph I wrote in *Principles and Practice of Phytotherapy* (second edition):

Cytokine antibody arrays were used to investigate changes in pro-inflammatory cytokines released from human bronchial epithelial cells exposed to a rhinovirus.[6] Virus infection stimulated the release of at least 31 cytokine-related molecules and most of these were reversed by simultaneous exposure to the Echinacea extracts. The lipophilic extract of *E. purpurea* root was less active than the expressed juice of the aerial parts in this regard. However, in uninfected cells these cytokines were stimulated by Echinacea, with the lipophilic extract being more active.

There is still much to understand about the way Echinacea root impacts the human immune system. Each *in vitro* study by its nature can provide just a narrow insight into a few specific aspects of immune function, with any clinical relevance potentially confounded by bioavailability, dosage issues and local tissue factors. The *in vitro* studies probably of most relevance are the ones investigating alkylamides, since these compounds have proven bioavailability.

Research has been particularly insightful into one aspect of the mode of action of Echinacea alkylamides.[7] A lipophilic extract of *E. purpurea* strongly stimulated TNF-alpha mRNA synthesis in peripheral monocytes, but not TNF-alpha protein production. In other words, the Echinacea-induced new TNF-alpha transcripts (mRNA) were not translated into TNF-alpha itself. When monocytes were treated with LPS (lipopolysaccharide or endotoxin, a powerful stimulator of the immune system) TNF-alpha protein production was substantially increased. However, co-incubation of monocytes with LPS and Echinacea extract resulted in a strong inhibition of this effect of LPS. Investigation over a longer time-span revealed that the lipophilic Echinacea extract, via interaction with CB2 receptors, modulated and prolonged TNF-alpha production following immune stimulation. The results of this study suggest that Echinacea acted more as a modulator or facilitator of the immune response, rather than as an immune stimulant. In resting monocytes it prepared them for a quicker immune response by inducing TNF-alpha mRNA. However, in overstimulated monocytes (as in the case of LPS or viral damage that induces cytokine storm) it first reduced, and then extended their response in terms of TNF-alpha production. In particular, these key findings challenge the concept that traditional Echinacea extracts will “overstimulate and wear out” the immune system if taken continuously.

So, on the evidence we have to date, a lipophilic extract of Echinacea root rich in alkylamides will prime the immune response before virus exposure but will then tone it

down and sustain it once the virus takes hold. Exactly the opposite of the misinformed concerns based on a superficial and one-dimensional analysis of the published literature.

Interestingly, the Eclectic physician Ellingwood actually noted the value of a lipophilic extract of Echinacea root for conditions that seem quite akin to cytokine storm (we now know that **sepsis** is typically characterised by an initial intense inflammatory response or cytokine storm) when he wrote in in 1919:[8]

"It is the remedy for blood poisoning, if there is one in the Materia Medica. Its field covers acute auto-infection, slow progressive blood taint, faults of the blood from imperfect elimination of all possible character, and from the development of disease germs within the blood. It acts equally well, whether the profound influence be exerted upon the nervous system, as in puerperal **sepsis** and uraemia…

In **pleuritis**, in **bronchitis**, in peritonitis, especially pelvic peritonitis from **sepsis**; in hepatitis and nephritis and cystitis **always at the beginning of the acute stage** before much structural change has occurred, it may be given, and will retard and often throw off the attack."

and again:[8]

"I am convinced that success in certain cases depends upon the fact that the patient must have at times, a sufficiently large quantity of this remedy in order to produce full antitoxic effects on the virulent infections. I would therefore emphasize the statement which I have previously made that it is perfectly safe to give *echinacea* in massive doses—from two drams to half an ounce every two or three hours—for a time at least, when the system is overwhelmed with these toxins."

and:[8]

"In septic peritonitis it (Bryonia) may be given alternately with *aconite*, or *aconite* and *echinacea*, **the latter remedy directly controlling the sepsis**."

Astragalus

In Traditional Chinese Medicine (TCM), Astragalus is generally contraindicated in acute infections, except where there is chi deficiency. However, as mentioned above, it has been used in TCM formulations to treat recent viral epidemics but is more often included in preventative formulations.[9] As per the TCM guidelines, Astragalus is particularly indicated for prevention when a person has compromised immunity and/or resilience.

Hence, Astragalus can be safely taken for prevention but is best stopped once acute symptoms develop (unless there is advice to the contrary from a skilled TCM practitioner). There is no suggestion from any research that its use only prior to an infection will increase the risk of cytokine storm once an infection takes hold (and the Astragalus has been subsequently stopped). In fact, this is extremely unlikely.

In one clinical trial, Astragalus (by injection) **reduced** inflammatory cytokines.[10] This was in patients undergoing heart valve replacement (HVR). Astragalus was found to decrease the inflammatory cytokines TNF-alpha and IL-8 and increase the level of the anti-inflammatory cytokine (IL-10), thereby exerting an anti-inflammatory activity in patients after HVR.

Elderberry

The use of the black elderberry (*Sambucus nigra*) during acute respiratory viral infections is relatively new, arising from research conducted in the 1970s. Initial investigations revealed antiviral activity, and this remains a research focus.[11] However, later research has indicated a potential role for the herb in enhancing immune responses, especially cytokine production.[12] Meta-analysis certainly supports its benefit when administered during acute viral infections.[13]

The exact mode of action of elderberry is not fully understood, and since its bioavailable components have not been determined (other than the polyphenolics which have relatively low bioavailability), *in vitro* studies need to be interpreted with great caution. As noted above, by their nature every *in vitro* study on a herb can provide just a narrow insight into a few specific aspects of immune function, with any clinical relevance potentially confounded by bioavailability, dosage issues and local tissue factors.

Hence, what we can glean from clinical studies is bound to be more reliable. One such trial in 473 patients (including many with confirmed influenza A and/or B) found that a combination of elderberry and Echinacea given as soon as possible for 10 days after symptoms developed was as effective as the antiviral drug oseltamivir.[14] There was no suggestion of harmful effects or induction of cytokine storm (the authors used the term septic shock to flag this possibility). In fact, adverse events were higher in the antiviral drug group. No hospitalisations were reported during the investigational period in either treatment group.

In another large trial involving 312 economy class passengers travelling from Australia to an overseas destination, participants took elderberry continuously from 10 days before flying overseas until five days after arriving at the travel destination.[15] Most cold episodes occurred in the placebo group (17 versus 12), however the difference was not significant ($p = 0.4$). Placebo group participants had a significantly longer duration of cold episode days (117 vs. 57, $p = 0.02$) and the average symptom score over these days was also significantly higher (583 vs. 247, $p = 0.05$). These data suggest a significant reduction of cold duration and severity in air travellers. The herbal treatment was well tolerated, with no serious adverse events.

These and other human trial results strongly imply that concerns over what is essentially a food precipitating a life-threatening adverse event during an infection (cytokine storm) are merely theoretical.

Medicinal mushrooms

As with Astragalus, the main role of medicinal mushrooms is for infection prevention and they can be discontinued during acute infection onset to make way for other higher priority treatments. Research suggests that the branched chain beta-glucan polymers found in the fruiting bodies of various mushroom species seem particularly adapted to heightening immune vigilance against potential pathogens.

The interaction of mushroom beta-glucans with immune cells involves distinct pathways, especially as revealed by the recent discovery of the dectin-1 receptor. Innate immune cells express pattern recognition receptors (PRRs) such as dectin-1, Toll-like receptors, and mannose receptors on their cell surfaces. These PRRs recognise pathogens by binding to highly conserved pathogen-associated molecular patterns such as beta-glucan (from fungi), mannan, and lipopolysaccharide (LPS). The immunomodulating activities of innate immune cells are augmented by the binding of beta-glucans to dectin-1 expressed by macrophages or dendritic cells. Upon binding beta-glucan, innate immune cells then activate adaptive immune cells such as B and T lymphocytes or natural killer cells by secreting various cytokines.[16] But as before, these cytokines are acting as signalling agents and are released only in low and localised amounts.

Interaction of mushroom beta-glucans with the dectin-1 receptor may even be able to "train" the innate immune response.[17] Trained (innate) immunity (TI) can be induced by a variety of stimuli, of which BCG (Bacillus Calmette–Guérin vaccine) and beta-glucan have been particularly studied. Both BCG (via NOD2 signalling) and beta-glucan (via dectin-1) can induce epigenetic changes that lead to TI. Interestingly, because of the discovery of TI, BCG is currently being investigated as a preventative for acute respiratory viral infection amongst 4000 healthcare workers.[18] There is clearly no concern about triggering a cytokine storm with this powerful agent, presumably because its role, like the medicinal mushrooms, is preventative.

Herbs and fever management

One aspect that seems to have been largely overlooked when discussing herbs for managing viral infections is the important role of diaphoretic herbs in stage II. Their appropriate use could prove to be critical in preventing the development of cytokine storm.

A diaphoretic is an agent that literally is used to promote sweating, and in the context of a fever, diaphoretic herbs were used to manage the febrile phase of an infection. In modern herbal practice, diaphoretic herbs are still considered appropriate in fever management, including remedies such as *Mentha x piperita* (peppermint), Achillea (yarrow), Sambucus (elderflower), Matricaria (chamomile), Tilia (lime flowers), *Eupatorium perfoliatum* (boneset) and *Asclepias tuberosa* (pleurisy root). Their objective is to help to facilitate the fever as a "slow burn" (usually the range 100–102°F or 37.8–38.9°C), ensuring that this important physiological response is supported, but kept at a level that is comfortable, restorative and not harmful to the person. They work best when taken hot, as in an infusion or decoction.

In the classical model of pathogenesis, induction of fever is mediated by the release of pyrogenic cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and interferons into the bloodstream in response to exogenous pyrogens from infecting agents.[19] These are the same cytokines that are largely responsible for cytokine storm. Hence, diaphoretic herbs might well reduce the risk of developing cytokine storm during an infection.

This might be disregarded as idle speculation, except for the Eclectic experience with diaphoretic herbs during the Spanish flu pandemic, where they were regarded as key remedies. Drawing from just one of the many testaments to the value of diaphoretic herbs from that time, as reviewed by Abascal and Yarnell:[5]

"One physician, who saw 10–35 patients with influenza per day during the epidemic began treatment by mixing 2 teaspoons of boneset and 1 teaspoon of pleurisy root tinctures in a cup of hot water. This was given immediately with a second dose 15 minutes later, a third dose half an hour later, and a fourth dose an hour after the first dose. He reported that this treatment typically reduced a fever of 103–104ºF by 3–4º in a few hours. Yet another physician reported that boneset was always a significant remedy in influenza."

Conclusions

Concerns have been raised that certain immune acting herbs might deleteriously enhance the cytokine response during acute respiratory viral infections and trigger or increase the risk of cytokine storm. Such concerns do not differentiate between the initial role of cytokines during an infection as immune signalling agents versus their later role in promoting an inflammatory response. In particular, cytokine storm is a chaotic, intense and unregulated response to massive necrotic tissue destruction that is unlikely to be capable of further augmentation by any agent, much less a relatively benign medicinal plant.

Neither traditional use, clinical trials nor modern pharmacology (when interpreted in the appropriate context) support any concerns about common immune herbs increasing the risk of cytokine storm during an infection. In fact, the opposite is more likely to apply since these herbs will support a focussed initial immune response and thereby reduce the risk of any infection progressing to the stage III development of cytokine storm.

Herbs are best given in combination, and such informed use of herbal prescribing can lower the risk of side effects and improve clinical outcomes. In the context of reducing the risk of cytokine storm after an infection has taken hold, the potentially valuable role for the inclusion of diaphoretic herbs in the treatment protocol needs to be given due attention.

Kerry Bone
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For the professional education of healthcare practitioners.

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