The influence of traditional herbal formulas on cytokine activity

By: J.J. Burns, Lijun Zhao, Ethan Will Taylor, and Kevin Spelman

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Abstract:

Many of the botanical "immunomodulators", a class of herbal medicines widely recognized in traditional medical systems such as Chinese Medicine (TCM) and Ayurvedic Medicine, alter immune function and may offer clinically relevant therapeutics or leads to therapeutics. Many of these traditional remedies are prepared from combinations of medicinal plants which may influence numerous molecular pathways. These effects may differ from the sum of effects from the individual plants and therefore, research demonstrating the effects of the formula is crucial for insights into the effects of traditional remedies. In this review we surveyed the primary literature for research that focused on combinations of medicinal plants and effects on cytokine activity. The results demonstrate that many extracts of herb mixtures have effects on at least one cytokine. The most commonly studies cytokines were IL-4, IL-6, IL-10, TNF and IFN-γ. The majority of the formulas researched derived from TCM. The following formulas had activity on at least three cytokines; Chizukit N, CKBM, Daeganghwal-tang, Food Allergy Formula, Gamcho-Sasim-Tang, Hachimi-jio-gan, Herbkines, Hochuekki, Immune System Formula, Jeo-Dang-Tang, Juzen-taiho-to, Kakkon-to, Kan jang, Mao-Bushi-Saishin-to, MSSM-002, Ninjin-youei-to, PG201, Protec, Qing-huo-bai-du-yin, Qingfu Guanjieshu, Sambucol Active Defense, Seng-fu-tang, Shin-Xiao-Xiang, Tien Hsien, Thuja formula, Unkei-to, Vigconic, Wheeze-relief-formula, Xia-Bai-San, Yangyuk-Sanhwa-Tang, Yi-fey Ruenn-hou, and Yuldahansotang. Of the western based combinations, formulas with *Echinacea* spp. were common and showed multiple activities. Numerous formulas demonstrated activity on both gene and protein expression. The research demonstrates that the reviewed botanical formulas modulate cytokine activity, although the bulk of the research is *in vitro*. Therapeutic success using these formulas may be partially due to their effects on cytokines. Further study of phytotherapy on cytokine related diseases/syndromes is necessary.

Keywords: Cytokine | Herbal formula | Immunomodulator | Traditional medicine | Interleukin (IL) | Tumor necrosis factor (TNF)

Article:

1. Introduction

Traditional herbal pharmacotherapy is well known for combining plant species that results in complex phytochemical mixtures in the attempts to ameliorate pathophysiological processes. While research is necessary on isolated constituents and single herbal extracts to provide information about the molecular modes of activity, such studies have limited relevance to the practical use of herbs due to the traditional custom of dispensing herbal medicine in formulas (Walker, 2006). The rationale for formulating suggest that the introduction of the complex mixture of chemistry into a human system provides not only pharmacologically active compounds, but concomitant compounds that are important to the therapeutic effect (Spelman et al., 2006b). Supporting this view are numerous studies that have established that pharmacokinetic potentiation by way of altered absorption, distribution, metabolism and elimination is common place after ingestion of phytochemical mixtures.

Wagner (2005) points out that herbs can be advantageous in treating pathophysiology due to their chemical complexity. For example, an additive effect can be expected if two bioactive substances target the same pharmacological target, while a synergic activity commonly results if two or more compounds target different pharmacological sites (Wagner, 2005). Synergic effects have been estimated to increase activity 50–2000-fold compared to equivalent concentrations of a single compound (Tegos et al., 2002, Wagner, 2005). For example, rhein, an antimicrobial from *Rheum officinale* (Baill, Polygonaceae), potentiated bacterial killing up to 2000-fold when combined with a plant-based MDR efflux pump inhibitor (Tegos et al., 2002).

Given that plants' resistance to pests, including mammalian herbivores, has been shown to be due to mixtures of bioactive compounds (Dixon, 2001, Dyer et al., 2003; Firn and Jones, 2003; Fujita and Kubo, 2005, Mello and Silva-Filho, 2002, Thoison et al., 2004), this synergic effect is suggested to be the rule rather than the exception when medicinal plants interface with mammalian systems (Spelman et al., 2006b). Hence, phytotherapists suggest that multi-modal molecular activity is an integral aspect of herbal therapies and that this offers an advantage over isolated constituents (Spelman et al., 2006b, Wagner, 1999, Williamson, 2001). Zhu et al. (2002) illustrated this by demonstrating that individual herbs from a formula traditionally used for gastrointestinal issues failed to show the gastroprotective effect that the formula demonstrated at equivalent doses.

Inflammatory and immune-related illnesses have a notable history of being treated with herbal formulas that are considered immunomodulators (Mills and Bone, 2000). Immunomodulators may be defined as botanical medicines that alter the activities of the immune system via the dynamic regulation of messenger molecules—cytokines, adhesion molecules, nitric oxide, hormones, neurotransmitters, and other peptides (Spelman et al., 2006a). Reviews of the primary literature suggests many of the immune-related effects of medicinal plants may be via cytokine modulation (Calixto et al., 2004, Spelman et al., 2006a).

Cytokines are pleiotropic peptides and glycoproteins having multiple sources, multiple targets, and multiple functions. Although constitutive secretion is low to absent, virtually every nucleated cell type responds to injurious stimuli with cytokine secretion. Thus these compounds are critical to innate and adaptive inflammatory responses, as well as cell growth, differentiation, cell death, angiogenesis, developmental and bodily repair processes (Oppenheim, 2001).

Manipulation of cytokine activity shows promise in many disease states related to immune function including asthma (Stirling and Chung, 2000) and cancer (Oleksowicz and Dutcher, 1994). Considering the diverse and pleiotropic activities of cytokines, pharmacology based on cytokine signaling may also prove promising for disorders seemingly unrelated to immune function. For example, a number of cardiac diseases are associated with elevated cytokine expression, and can effect cardiac processes (Prabhu, 2004). Furthermore, the inflammatory milieu of cardiovascular disease is known to be influenced by cytokines from leukocytes, the liver, the heart, vessel walls, and adipose tissue (Rader, 2000).

Due to the regulation of different types of immune and somatic cells, cytokines have been widely researched for many diseases and syndromes. As a result of such diverse and far reaching effects of cytokines and the frequency of use of herbal formulas that are believed to impact immune function, this work provides a review of the primary literature on the effects of herbal formulas. We suggest that modulation of cytokine activity is a partial explanation for the observed activity of these formulas in traditional medicine.

2. Materials and methods

2.1. Search strategy

Titles were screened for all hits to the terms “herbs and cytokines,” “herb* formulas and cytokines” and “herbal* combinations and cytokines,” “medicinal plants and cytokines,” “Chinese Medicine and cytokines,” “Ayurvedic Medicine and cytokines,” “Ayurveda and cytokines.” A cutoff date of June 30, 2007 was used to keep the manuscript size manageable. These results were then searched with the key word “combination,” and again with a keyword of “formulas.” Databases utilized included Pubmed, Biosis, EBSCO and SciFinder Scholar, as well as a hand search through journals and bibliographies. No language restriction was observed.

2.2. Criteria for inclusion

The following parameters had to be met for study inclusion: firstly, investigations on combination of herbs were accepted. Research on isolated constituents or single herbs was rejected. Secondly, model types were considered; *in vitro* and *in vivo*, animal and human models were accepted. Thirdly, at least two of the following were required; method of preparation of the botanical medicine, concentration of the plant preparation and dose/exposure time. Lastly, only studies demonstrating statistically significant results of $p < 0.05$ with regards to cytokine activity were included.

385 titles and abstracts were reviewed for inclusion criteria. 326 studies were eliminated due to failing inclusion criteria such as constituent based research, or statistically not significant. Fifty-nine papers met the criteria.

Table 1A. Ingredients of formulations.

Formula name	*Genus species* or pharmaceutical nomenclature
Allergina	*Schizonepetae herba*, *Forsythiae fructus*, *Ledebouriellae radix*, *Angelicae radix*, *Cindii rhizome*, *Paeoniae radix alba*, *Angelicae dahuricae radix*, *Bupleuri radix*, *Aurantinii fructus*, *Scutellariae radix*, *Fructus angelicae*, *Platycodi radix*, *Glycyrrhizae radix*, *Trichosanthis radix*, *Taraxaci herba*, *Lonicerae flos*
AT2	*Hirudo*, *Turtle shell*, *Panax notoginseng*
Bouum-Myunyuk-Dan	*Hedyotis diffusa*, *Astragalus membranaceus*, *Paeonia lactiflora*, *Angelica sinensis*, *Ophiopogon japonicus*, *Atractylodes maceocephala*, *Adenophora triphylla*, *Rehmannia glutinosa*, *Spatholobus suberectus*, *Citrus unshin*, *Hordeum vulgare*, *Callusgallus domesticus*, *Ulmus pumila*, *Anemarrhena asphodeloides*, *Phellodendron amurense*, *Glycyrrhizae uralensis*
CH-100	Unspecified
Chizukit N	*Echinacea purpurea*, *Propolis*, *Sucrose and Orange Oil*
CKBM	*Panax ginseng*, *Schisandra chinensis*, *Fructus crataegi*, *Zizyphus jujube*, *Glycine max*
CPD 861	*Not specified*
Daeganghwal-tang	*Angelicae koreanae radix*, *Cimicifuga rhizome*, *Araliae cordatae radix*, *Atractylodes rhizome*, *Sinomeni caulis et rhizome*, *Clematidis radix*, *Atractylodes rhizome alba*, *Angeliaca gigantis radix*, *Poria*, *Alismatis rhizome*, *Glycyrrhizae radix*
Dang-gui-bu-xue-tang	*Angelica sinensis*, *Astragalus membranaceus*
Echinacea Formula	*E. angustifolia radix*, *E. purpurea radix*, *E. purpurea herba*, *Thymus vulgaris*, *Mentha piperita*
Echinacea/Thuja Formula	*Thujae summitates*, *Baptisia tinctoriae radix*, *E. purpurea radix*, *E. pallidae radix*
FAHF-1	*Ganoderma lucidum*, *Aconiti Carmichaeli Praeparata*, *Pruni Mume*, *Zanthoxyli Bungeana*, *Asarum europaeum*, *Coptis trifolia*, *Phellodendron amurense*, *Zingiber officinalis*, *Cinnamomum cassia*, *Panax ginseng*, *Angelica sinensis*
FAHF-2	*Ganoderma lucidum*, *Fructus pruni mume*, *Pericarpium zanthoxyli bungeana*, *Rhizoma coptidis*, *Cortex phellodendri*, *Rhizoma zingiber officinalis*, *Ramulus cinnamomum cassia*, *Radix ginseng*, *Corpus radix Angelica sinensis*
Fei-shu-ling	*Platycodon grandiflorum*, *Angelica sinensis*, *earth worm*, *Raphanus sativus*
Gamcho-Sasim-Tang	*Glycyrrhiza uralensis*, *Scutellaria baicalensis*, *Zingiber officinale*, *Pinellia ternata*, *Panax ginseng*, *Coptis japonica*
Hachimi-jio-gan	*Rehmannia radix*, *Cornus fructus*, *Dioscorea rhizome*, *Alismatis rhizoma*, *Poria*, *Moutan cortex*, *Cinnamomum cortex*, processed *Aconitum tuber*
Herbkines	*Atractylodes macrocephala*, *Dioscorea batatas*, *Glycyrrhiza uralensis*, *Cinnamomum cassia*, *Rubus coreanus*, *Liriope platyphylla*, *Astragalus membranaceus*, *Cornus officinalis*
Hochuekki	*Astragali radix*, *Ginseng radix*, *Atractylodes rhizome*, *Angelicae radix*, *Zizyphi fructus*, *Aurantii nobilis pericarpium*, *Bupleuri radix*, *Glycyrrhizae radix*, *Cimicifugae rhizome*, *Zingiberis rhizoma*
Hwanglyun-Haedok-Tang	*Scutellaria baicalensis*, *Coptis japonica*, *Phellodendron amurense*, *Gardenia jasminoides*
Immune System Formula (Sambucol Active Defense)	*38% Black Elderberry*, *Glucose*, *Raspberry extract*, *Citric acid*, *Honey*, *Echinacea augustifolia*, *Echinacea purpurea*, *Propolis*, *Ascorbic Acid*, *Zinc Gluconate*
Jeo-Dang-Tang	*Rhei rhizome*, *Tabanus*, *Irubo*, *Persicae semen*
Juzen-taiho-to	*Astragalus membranaceus*, *Cinnamomum cassia*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Cnidium officinale*, *Atractylodes lancea*, *Angelica acutiloba*, *panax ginseng*, *Poria cocos*, *Glycyrrhiza uralensis*
Kakkon-to	*Puerlae radix*, *Ephedrae herba*, *Cinnamomum ramulus*, *Paeoniae alba radix Glycyrrhiza radix*, *Zingiber recens rhizome*, *Jujubae fructus*, *Etradix notopterygii rhizome*, *Angelicae pubescentis radix*, *Chuanxiong rhizome*, *Bupleuri radix*
Kan jang	*Andrographis paniculata*, *Eleutherococcus senticocus*

Formula name	*Genus species* or pharmaceutical nomenclature
Kanzo-bushi-to	*Glycyrrhizae radix*, *Aconitum tuber*, *Atractylodis lancease rhizome*, *Cinnamomum cortex*
Keyuling	*Astragalus membranaceus*, *Panax ginseng*, *Epimedium sagittatum*
Liu-Shen-Wan	*Moschus berezovskii*, *Bos taurus domesticus*, *Bufo Bufo gargarizans*, *Drybalanops aromaticua*, *Pteria martensii*
Mao-Bushi-Saishin-to	*Asarum heterotropias*, *Ephedra sinica stapf*, *Aconiti lateralis preparata*

Table 1B. Ingredients of formulations.

Formula name	*Genus species* or pharmaceutical nomenclature
MSSM-002	*Perilla frutescens*, *Descurainia Sophia*, *Prunus armeniaca*, *Scutellaria baicalensis*, *Sophora flavescens*, *Angelica sinensis*, *Platycodon grandiflorum*, *Glycyrrhiza urlensis*, *Zizyphus jujube*, *Zingiber officinale*, *Pteria margaritiferi*, *Ganoderma lucidum*
Nao-yi-an	*Not specified*
Ninjin-to	*Panax ginseng*, *Atractylodes lancea*, *Zingiber officinale, Glycyrrhiza uralensis*
Ninjin-youei-to	*Formula not specified*
PanaWang	*Panax ginseng*, *Bos Taurus*, *Corydalis yanhusuo*, *Torilis japonica*, *Allium sativum*, *Magnolia obovata*, *Paeonia lactiflora*, *Cnidium officinale*, *Cinnamomum cassia*, *Astragalus membranaceus*
PG201	*Chaenomeles speciosa*, *Achyranthes bidentata*, *Angelica sinensis*, *Cnidium officinale*, *Gastrodia elata*, *Acanthopanax senticosus*, *Carthamus tinctorius*, *Cinnamomum aromaticum*, *Gentiana macrophylla*, *Ledebouriella sesloides*, *Clematic chinensis*, *Pholmis umbrosa*
Protec	*Echinacea purpurea*, *Echinacea angustifolia*, *Propolis*, *Vitamin C*, *Rosa canina*
QFGJS	*Caulis Sinomenii*, *Aconiti lateralis preparata*, *Rhizoma Curcumae longae*, *Radix Paeoniae alba*, *Cortex Moutan*
Qing-huo-bai-du-yin	*Astragalus membranaceus*, *Lonicera japonica*, *Scutellaria baicalensis*, *ophiopogon japonicus*, *Eriobotrya japonica*
Sambucol Black Elderberry Syrup	*38% Black Elderberry*, *Glucose*, *Raspberry extract*, *Citric acid*, *Honey*
Sambucol for Kids	*19% Elderberry*, *Raspberry extract*, *Citric acid*, *Echinacea angustifolia*, *Echinacea purpurea*, *Propolis*
Sairei-to	*Bupleuri radix*, *Glycyrrhizae radix*, *Cinnamomi cortex*, *Scutellariae radix*, *Alismatis rhizome*, *Pineliae tuber*, *Poluporus*, *Hoelen*, *Atractylodislanceae rhizome*, *Zizyphi fructus*, *Ginseng radix*, *Zingiberis rhizome*
Seng-fu-tang	*Not specified*
Sesim-Tang	*Poria cocos*, *Zizyphus spinosa*, *Pinellia ternate*, *Tricticum sativum*, *Panax ginseng*, *Citrus unshiu*, *Aconitum carmichaeli*, *Acorus gramineus*, *Glycyrrhiza uralensis*
Shang Jong Shiah Tong Yong Tong Feng Wan	*Cortex phellodendri*, *Rhizoma atractylis*, *Rhizoma arisaematis*, *Lignum cocculi trilboi*, *Radix gentianae*, *Radix heraclei*, *Massa medicate fermentata*, *Cirtex cinnamomii*, *Radix clematidis*, *Flos carthamic*, *Rhizoma notopterygii*, *Semen persicae*
Shaur Yau Gan Tsao Tang	*Radix paeoniae*, *Radix glycyrrhizae*
Shi-bi-lin	*Fructus xanthii*, *Radix Angelicae dahuricae*, *Radix Gentianae*, *Herba Verbenae*, *Radix*, *Saposhnikovia*, *Flos Magnoliae*
Shi-ka-ron	*Ginseng radix*, *Lithospermi radix*, *Angelicae radix*, *Houttuyniae herba*, *Astragali radix*, *Cniddi rhizome*, *Coicis semen*, *Glycyrrhiza radix*
Shin + Xiao + Xiang	*Shin-yi-san*

Formula name	*Genus species* or pharmaceutical nomenclature
	Magnolia lili-flora, *Asarum heterotropoieds*, *Liquisticum sinense*, *Saposhnikovia divaricata schischk*, *Angelica dahurica*, *Liqusticum wallichi franch*, *Cimicifuga foetida*, *Akebia quinata*, *Glycyrrhiza uralensis*
	Xiao-qing-long-tang
	Ephedra sinica stapf, *Paeonia lactiflora*, *Asarum heterotropoides*, *Zingiber officinale*, *Glycyrrhiza uralensis*, *Cinnamomum cassia*, *Pinellia ternate*, *Schisandra chinesis*
	Xiang-sha-liu-jun-zi-tang
	Panax ginseng, *Atractylodes macrocephala koidz*, *Poria cocos*, *Glycyrrhiza uralensis*, *Citrus reticulata*, *Pinellia terrnata*, *Amomum xanthioides*, *Saussurea lappa*
Sho-saiko-to	*Bupluerum radix*, *Pinellia tuber*, *Scutellariae radix*, *Jujube fructus*, *Ginseng radix*, *Glycyrrhiza radix Zingiber rhizome*
Sho-seryu-to	*Ephedra rhizome*, *Paeoniae radix*, *Asarum radix*, *Zingiber rhizome*, *Glycyrrhiza radix and rhizome*, *Cinnamomi rhizome*, *Pinellia rhizome*, *Schisandra fructus*
Shu Jin Lih An Saan	*Radix saposhnikoviae*, *Radix angelicae grosseserratus*, *Rhizoma ligustics*, *Rhizoma notopterygii*, *Radix angelicae*, *Hoelen*, *Radix achyranthis*, *Radix glycyrrhizae*, *Radix rehmanniae Rhizoma atractylodis*, *Radix paeoniae*, *Flos carthami*, *Semen persicae*, *Rhizoma arisaematis*, *Exocarpium citri sinensis*, *Fructus chanomelis speciosae*, *Radix simomenii Radix clematidis*, *Fructus forsythiae*, *Lignum mutang*, *Radix scutellariae*, *Radix gentianae*, *Radix aconite*, *Caulis bambusae*

Table 1C. Ingredients of formulations.

Formula Name	*Genus species* or pharmaceutical nomenclature
Tien Hsien	*Cordyceps sinensis*, *OldenLandia diffuse*, *Indigo pulverata*, *Polyporus umbellatus*, *Astragalus membranaceus*, *Panax ginseng*, *Solanum nigrum*, *Pogostemon cablin*, *Atractylodis macrocephalae*, *Trichosenthes kirilowii*, *Clematis chinensis*, *Margarita*, *Ligustrum lucidum*, *Glycyrrhiza uralensis*, *Ganoderma lucidium*, *Dioscorea batatas*, *Codonopsis pilosula*, *Lycium barbarum*
Unkei-to	*Ophiopogon japonicus*, *Pinellia ternata*, *Glycyrrhiza uralensis*, *Angelica acutiloba*, *Cnidium officinale*, *Paeonia suffruticosa*, *Evodia rutaecarpa*, *Zingiber officinale*, *Asini corii collas*
Vigconic	*Radix Ginseng*, *Cornu cervi*, *Cordyceps sinensis*, *Radix Salviae miltiorrhizae*, *Semen Allii*, *Fructus Cnidii*, *Fructus Evodiae*, *Rhizoma Kaempferiae*
Wheeze-relief-formula	*Fritillariae cirrhosae*, *Cordyceps sinensis*, *Astragalus mongholicus*, *Stemona sessilifolia*, *Scutellariae baicalensis*
Xia-Bai-San	*Morus alba*, *Lycium chinense*, *Glycyrrhiza glabra*
Xin-feng	*Astragalus membranaceus*, *Coix lacryma jobi*, *Scolopendra*, *Tripterygium wilfordii*
Yangyuk-Sanhwa-Tang	*Rehmanniae radix*, *Lonicera japonica*, *Forsythiae fructus*, *Gardeniae fructus*, *Menthae herba*, *Anemarrhena rhizome*, *gypsum fibrosum*, *Schizonepetae herba*, *Ledebouriellae radix*
Yi-fei Ruenn-hou	*Gycyrrhiza uralensis*, *Panax quinquefolis*, *Paeonia suffruticosa*, *Camellia sinensis*
Yuldahansotang	*Pueraria montana var. thomsonii*, *Astragalus membranaceus*, *Ligustici tenuissima*, *Raphani Satovi*, *Angelicae Dahuricae*, *Veratrum viride*, *Platycodon Grandiflora*
Zemaphyte	*Ledebouriella seseloides*, *Potentilla chinensis*, *Clematis armandii*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrstris*, *Glycyrrhiza glabra*, *Schizonepeta tenuifolia*

Table 2A. *In vivo*.

Formula name	Preparation used	Daily dose	Duration of exposure	Tissue	Model	Cytokines affected	T helper influence	Author/date
Antitumor-I	Capsule	800 mg/kg	8 days	NK spleen Murine	Tumor bearing	IL-2↑,6↑	Th0	Lei and Chu (1996)
Dang-gui-bu-xue-tang	Aqueous	360 mg	7 days	Lymphocytes Murine	None	IL-2↑	Th1	Chen (1994)
Food Allergy Herbal Formula-1	Aqueous	21 mg BID, Intragastric gavage	7 weeks	Splenocytes Murine	Peanut allergen	IL-4↓,5↓,13↓	Th1	Li et al. (2001)
Food Allergy Herbal Formula-2	Aqueous	20 mg BID, Intragastric gavage	7 weeks	Splenocytes Murine	Peanut allergen	IL4↓,5↓,13↓ IFN-γ↑	Th1	Srivastava et al. (2005)
Hochuekki	Aqueous	1000 mg/kg PO	2 days before to 4 days after infection	Bronchioles Murine	Influenza	IL-1α↓,6↓ GM-CSF	Th0	Mori et al. (1999)
Hochuekki	Methanol	1000 mg/kg OD, Intragastric gavage	2 days before to 2 days after infection	Bronchioles Murine	Influenza	[a]IFN-α↓↑	–	Mori et al. (1999)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen cells Murine	OVA	IL-4↓,5↑ IFN-γ↑	Th0	Ishimitsu et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen and lung cells Murine	OVA	IL-4↓,5↑	–	Ishimitsu et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen cells Murine	*L. monocytogens*	IFN-γ↑	–	Yamaoka et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen cells Murine	Anti CD24 and/or anti CD3	IFN-γ↑	–	Yamaoka et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	21 days	Gastric mucosa Murine	*H. pylori*	IFN-γ↑	–	Yan et al. (2002)
Hochuekki	Aqueous	1000 mg/kg QD, PO	18 days	Ear Murine	Trinitro chlorobenzene	IL-4↓	–	Nakada et al. (2002)

OVA: ovalbumin.

[a]IFN-α was initially up-regulated and by the end of infection down-regulated as compared to the control group.

Table 2B. *In vivo*.

Formula name	Preparation used	Daily dose	Duration of exposure	Tissue	Model	Cytokines affected	T helper influence	Author/date
Kakkon-to	Aqueous	5.0 mg TID, PO	8 days	Serum Murine	Influenza	IL-4↓	–	Kurokawa et al. (2002)
Keyuling	Aqueous	0.18 mg/kg	30 days	Serum Murine	Radiation	TNF↑ IL-18↑	–	Jiang et al. (2004)
Nao-yi-an	Aqueous	4920 mg/kg	7 days	Brain Murine	Collagenase	IL-6↑	–	Xiao et al. (2002)

Formula name	Preparation used	Daily dose	Duration of exposure	Tissue	Model	Cytokines affected	T helper influence	Author/date
PG201	25% Ethanol	10 mg/mL QD, PO	18 days	Ankle tissue Murine	Rheumatoid Arthritis	IL-1β↓ TNF-α↓	–	Shin et al. (2003b)
PG201	25% Ethanol	10 mg/mL QD, PO	18 days	Serum Murine	Rheumatoid Arthritis	IL-4↑	–	Shin et al. (2003b)
Qing-huo-bai-du-yin	Aqueous	4000 mg BID, PO	5 days	Serum Murine	Burn model	IL-1β↓,4↑,6↓,10↑	Th2	Luo et al. (2004)
Qing-huo-bai-du-yin	Aqueous	4000 mg BID, PO	10 days	Serum Murine	Burn model	IL-6↓,8↓,10↑ TNF↓	Th2	Luo et al. (2004)
Qing-huo-bai-du-yin	Aqueous	4000 mg BID, PO	20 days	Serum Murine	Burn model	TNF↓	–	Luo et al. (2004)
Qingfu Guanjieshu	80% Ethanol	1940 mg/kg QD, PO	30 days	Serum Murine	Rheumatoid Arthritis	IL-6↓	–	Cai et al. (2005)
Qingfu Guanjieshu	80% Ethanol	3890 mg/kg QD, PO	30 days	Serum Murine	Rheumatoid Arthritis	IL-1β↓,6↓ TNF-α↓	–	Cai et al. (2005)
Shen-fu-tang	Aqueous	Unspecified IV	60 days	T cell subtype Human	Aplastic anemia	IL-2↓ TNF↓ IFN-γ↓	Th2	Wang et al. (2005)
Shi-ka-ron	Aqueous	400 mg/kg QD, PO	5 days	Spleen lymphocytes Murine	Con A	IL-2↑ IFN-γ↑	Th1	Jin and Kurashige (1996)
Shi-ka-ron And cyclophosphamide	Aqueous	300 mg/kg QD, PO	5 days	Spleen lymphocytes Murine	Con A	IL-2↑	–	Jin and Kurashige (1996)
Shi-ka-ron And cyclophosphamide	Aqueous	200 mg/kg QD, PO	5 days	Spleen lymphocytes Murine	Con A	IFN-γ↑	–	Jin and Kurashige (1996)
Shin + Xiao + Xiang	Powder	15,000 mg TID, PO	3 months	Lymphocytes, Human	PHA	IL-4↑,5↓,10↑,13↓	–	Yang et al. (2001)
Shin + Xiao + Xiang	Powder	15,000 mg TID, PO	3 months	Mononuclear cells Human	PHA	IFN-γ↓	–	Yang et al. (2001)

Con A: concanavalin A, LPS: lipopolysaccharide, PHA: phytohemagglutinin.

Table 2C. *In vivo*.

Formula name	Preparation used	Dose	Duration of exposure	Tissue	Model	Cytokines affected	T helper influence	Author/date
Xia-Bai-San	Aqueous	1 mg/kg PO	4 h	Lung fluid Murine	LPS	IL-1β↓,6↓ TNF-α↓	–	Yeh et al. (2006)
Xia-Bai-San	Aqueous	1 mg/kg PO	24 h	Lung fluid Murine	LPS	IL-10↑ IL-10 (mRNA)↑	–	Yeh et al. (2006)
Xinfeng	Capsule	4500 mg/day	3 months	Serum Human	Rheumatoid	IL-10↑ TNF-α↓	Th2	Liu et al. (2006)

Formula name	Preparation used	Dose	Duration of exposure	Tissue	Model	Cytokines affected	T helper influence	Author/date
Yangkyuk-Sanhwa-Tang	Aqueous	44,000 mg TID, PO	2 weeks	Serum Murine	Cerebral Infarct	IL-2↓,4↓,6↓ TNF-α↓ IFN-γ↑	–	Jeong et al. (2002)
Yi-fey Ruenn-hou	Aqueous	2 mg/mL QD, PO	6 months	Serum Murine	None	IL-10↑	–	Lin et al. (2004)
Yi-fey Ruenn-hou	Aqueous	8 mg/mL QD, PO	6 months	Serum Murine	None	IL-4↑,10↑	Th2	Lin et al. (2004)
Yi-fey Ruenn-hou	Aqueous	40 mg/mL QD, PO	3 months	Serum Murine	None	IL-4↑,10↑ IFN-γ↑	Th2	Lin et al. (2004)

LPS: lipopolysaccharide.

Table 3A. *Ex vivo*.

Formula name	Preparation used	Dose	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Cathay 100	Tablet ground in food	4 tablets/kg QD, PO	8 weeks	Liver Murine	Con A	TNF-α↓	Batey and Cao (2000)
Echinacea formula	Capsule	6000 mg day 1, 3000 mg × 9 days PO	10 days	Macrophages Human	URI	TNF↑	Barrett et al. (2002)
Echinacea/*Thuja Formula*	30% Ethanol	260 µL/kg QD, PO	3 days	Spleen cells Murine	LPS and Con A	IL-2↑ IFN-γ↑	Bodinet et al. (2002)
Echinacea/*Thuja Formula*	30% Ethanol	260 µL/kg QD, PO	3 days	Peritoneal macrophages	LPS	IL-1↑ TNF-α↑	Bodinet et al. (2002)
Hachimi-jio-gan	Aqueous	1000 mg/kg QD, PO	8 weeks	Kidney cells Murine	Anti-CD3 + anti-CD28 antibody	IL-4↑ IFN-γ↓ IL-12p35 (mRNA)↓ IL-12p40 (mRNA)↓	Furuya et al. (2001)
Hachimi-jio-gan	Aqueous	1000 mg/kg 5 days/week PO	4 weeks	Spleen cells Murine	Anti-CD40	IL-10↑,12p70↓ IL-12p35 (mRNA)↓ IL-12p40 (mRNA)↓ IL-18 (mRNA)↓	Furuya et al. (2002)
Juzen-taiho-to	Aqueous	1000 mg/kg QD, PO	2 weeks	Spleen lypmphocytes Murine	Con A	IL-4↑,5↑ IFN-γ↑	Matsumoto and Yamada (2000)
Juzen-taiho-to	Aqueous	1000 mg/kg QD PO	2 weeks	Gastric Lymphocytes Murine	Con A	IL-2↓,5↓,6↑ IFN-γ↑	Matsumoto and Yamada (2000)
Kakkon-to	Aqueous	5.0 mg TID, PO	8 days	Bronchioles Murine	Influenza	IL-12↑	Kurokawa et al. (2002)

Formula name	Preparation used	Dose	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Kanzo-bushi-to	Aqueous	50 mg/kg PO QOD	48 h incubation of spleen and T6S cells	T6S cells and spleen cell treated with herb Murine	None	IL-4↓	Kobayashi et al. (1994)
Liu-Shen-Wan	Powder	15 mg/kg PO	72 h	Plasma Human	Sepsis	TNF-α↓	Ma et al. (2006)
MSSM-002	Aqueous	360 mg/mL BID, PO	17 days	Spleen cells Murine	Allergies, Con A	IL-4↓, 5↓,13↓ IFN-γ↑	Li et al. (2000)

Con A: concanavalin A, LPS: lipopolysaccharide.

Table 3B. *Ex vivo*.

Formula name	Preparation used	Daily dose	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Ninjin-youei-to	Aqueous	100 mg/kg IP injection	1.5 and 3 h	Serum and Peritoneal cavity Murine	Unspecified	IL-1↑,6↑	Yonekura et al. (1992)
Ninjin-youei-to	Aqueous	1000 mg/kg PO 6× a week	24 weeks	Spleen Murine	Lupus	IFN-γ↑	Zhou et al. (1994)
Ninjin-youei-to + Prednisone	Aqueous	1000 mg/kg PO 6× a week	24 weeks	Spleen Murine	Lupus	IL-2↑ IFN-γ↓	Zhou et al. (1994)
Ninjin-youei-to	Aqueous	Unspecified	4 weeks	C57BL/6 and BALB Splenocytes Murine	Anti-CD3	IL-4↑ IFN-γ↑	Nakada et al. (2002)
PanaWang	Aqueous	12.2 mg/kg PO	7 days	Splenocytes Murine	ConA	IFN-γ↑	Tega et al. (2005)
Sairei-to	Unspecified	7200 mg/kg QD, PO	4 months	Spleen cells Murine	Con A Lupus	IL-4↑ IFN-γ↓	Ito et al. (2002)
Shin + Xiao + Xiang	Powder	15,000 mg TID, PO	3 months	Neutrophils Human	Allergic rhinitis	IL-8↑	Yang et al. (2002)
Sho-saiko-to	Aqueous	1000 mg/kg QD, PO	3 weeks	Lung Murine	LPS	IL-6↑	Ohtake et al. (2002)
Sho-seryu-to	5% Aqueous gum acacia solution	1000 mg/kg QD, PO	28 days	Spleen cells Murine	OVA, CD4 T cells, APC	IL-4↓ IFN-γ↑	Ikeda et al. (2002)
Echinacea purpurea, *E. angustifolia*, *Thuja*, *Baptisia,*	30% Ethanol	260 μL/kg QD PO	3 days	Spleen cells Murine	LPS and Con A	IL-2↑ IFN-γ↑	Bodinet et al. (2002)
Echinacea purpurea, *E. angustifolia*, *Thuja*, *Baptisia,*	30% Ethanol	260 μL/kg QD, PO	3 days	Peritoneal macrophages Murine	LPS	IL-1↑ TNF-α↑	Bodinet et al. (2002)

Formula name	Preparation used	Daily dose	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Xiao-chai-hu-tang	Aqueous	1600 mg/kg QD, PO	2 weeks	Spleen and Liver cells Murine	LPS	TNF↑	Haranaka et al. (1985)

Con A: concanavalin A, LPS: lipopolysaccharide, OVA: ovalbumin.

Table 4A. *In vitro*.

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Allergina	Aqueous	10 μg/mL incubation	24 h	T-cells Human	None	IL-4↑ IFN-γ↑	Jeong et al. (2003)
Allergina	Aqueous	100 μg/mL incubation	24 h	T-cells Human	None	IL-2↑	Jeong et al. (2003)
Allergina	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophages Murine	None	IL-12↑ TNF-α↑	Jeong et al. (2003)
Allergina	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophages Murine	IFN-γ	TNF-α↑	Jeong et al. (2003)
Allergina	Aqueous	1000 μg/mL incubation	24 h	Peritoneal macrophages Murine	IFN-γ	IL-12↑	Jeong et al. (2003)
Allergina	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophages Murine	IFN-γ + LPS	TNF-α↓	Jeong et al. (2003)
Bouum-Myunyuk-Dan	Aqueous	100 μg/mL incubation	24 h	T-cells Human	None	IL-2↑ IFN-γ↑	Jeong et al. (2004)
Bouum-Myunyuk-Dan	Aqueous	1000 μg/mL incubation	24 h	T-cells Human	None	IL-4↑ IFNγ↓	Jeong et al. (2004)
Bouum-Myunyuk-Dan	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophages Murine	None	IL-12↑	Jeong et al. (2004)
Bouum-Myunyuk-Dan	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophages Murine	IFN-γ	IL-12↑ TNF-α↑	Jeong et al. (2004)
Bouum-Myunyuk-Dan	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophages Murine	IFN-γ + polymyxin B	TNF-α↑	Jeong et al. (2004)

LPS: lipopolysaccharide.

Table 4B. *In vitro*.

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Chizukit N	Syrup	2 μL/mL incubation	24 h	Monocytes Human	None	IL-1β↓,6↓,10↑ TNF-α↓	Barak et al. (2002)

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
CKBM	Aqueous	20% incubation	18 h	THP-1 monocytes Human	None	IL-10↑ IFN-γ↑	Chan et al. (2005)
CKBM	Aqueous	15% incubation	18 h	THP-1 monocytes Human	A23187	IL-1β↑	Chan et al. (2005)
CKBM	Aqueous	5% incubation	18 h	THP-1 monocytes Human	A23187	IFN-γ↑	Chan et al. (2005)
CKBM	Aqueous	20% incubation	18 h	SupT1 and Ramos cells Human	LPS	IFN-γ↓	Chan et al. (2006)
CPD 861	Aqueous	5000 μg/mL incubation	48 h	HSC Murine	None	IL-6↓	You et al. (2001)
Daeganghwal-tang	Aqueous	100 μg/mL incubation	6 h	Mast cells Murine	PMA + A23187	IL-1β↓,6↓ TNF-α↓	Shin et al. (2003a)
Fei-shu-ling	Aqueous	50,000 μg/mL incubation	6 h	Lung macrophage Murine	LPS	TNF↓	Zhang et al. (1999)
Gamcho-Sasim-Tang	Aqueous	1000 μg/mL incubation	24 h	PBMC Human	PHA	IL-1β↓ IFN-γ↓, TNF-α↓	Kim et al. (2002b)

A23187: Ca^{2+}ionophore, LPS: lipopolysaccharide, PHA: phytohemagglutinin, PMA: phorphol myristate.

Table 4C. *In vitro*.

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Herbkines	Aqueous	10 μg/mL incubation	24 h	T-cells Leukemic (MOLT-4) Human	None	IL-2↑ IFN-γ↑	Hong et al. (2005)
Herbkines	Aqueous	100 μg/mL incubation	24 h	T-cells Leukemic (MOLT-4) Human	None	IL-4↑	Hong et al. (2005)
Herbkines	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophage Murine	IFN-γ	IL-12↑ TNF-α↑	Hong et al. (2005)
Herbkines	Aqueous	10 μg/mL incubation	24 h	Peritoneal macrophage Murine	None	IL-12↑	Hong et al. (2005)
Hwanglyun-Haedok-Tang	Aqueous	1000 μg/mL incubation	6 h	Peritoneal mast cells Murine	Anti DNP IgE Ab	TNF-α↓	Kim et al. (1998)
Immune System Formula	Syrup	2 μL/mL incubation	24 h	Monocytes Human	None	IL-1β↑,6↑,8↑,10↑ TNF-α↑	Barak et al. (2002)
Jeo-Dang-Tang	Aqueous	1000 μg/mL incubation	24 h	Mononuclear cells Human	None	IL-4↑,10↑ TGF-β1	Jeong et al. (2003)

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Jeo-Dang-Tang	Aqueous	100 μg/mL incubation	25 h	Mononuclear cells Human	PHA	IL-4↓	Jeong et al. (2003)
Jeo-Dang-Tang	Aqueous	10 μg/mL incubation	25 h	Mononuclear cells Human	LPS	IL-4↓,10↓	Jeong et al. (2003)
Jeo-Dang-Tang	Aqueous	1000 μg/mL incubation	25 h	Mononuclear cells Human	PHA	IL-10↓	Jeong et al. (2003)
Jeo-Dang-Tang	Aqueous	1000 μg/mL incubation	25 h	Mononuclear cells Human	LPS	TGF-β1↓	Jeong et al. (2003)
Jeo-Dang-Tang	Aqueous	100 μg/mL incubation	25 h	Mononuclear cells Human	PHA	TGF-β1↓	Jeong et al. (2003)

Anti DNP IgE Ab: anti dinitrophenol IgE antibody, LPS: lipopolysaccharide, PHA: phytohemagglutinin.

Table 4D. *In vitro*.

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Kan jang	Aqueous	14 μg/mL incubation	72 h	Blood cells Human	PHA	TNF-α↑	Panossian et al. (2002)
Kan jang	Aqueous	35 μg/mL incubation	72 h	Whole blood cells Human	None	IFN-γ↑	Panossian et al. (2002)
Mao-Bushi-Saishin-to	Aqueous	10 μg/mL incubation	2 and 7 days	Peritoneal macrophages Murine	*Mycobacterium avium*	IL-10↓	Shimizu et al. (1999)
Mao-Bushi-Saishin-to	Aqueous	10 μg/mL incubation	4 weeks	Lung cells Murine	*Mycobacterium avium*	TNF-α (mRNA)↓ IFN-γ (mRNA)↓ TGF-β (mRNA)↓	Shimizu et al. (1999)
MSSM-002	Aqueous	50 μg/mL incubation	7 days	T cells Human	Allergies, conalbumin	IL-4↓,5↓,13↓	Li et al. (2004)
MSSM-002	Aqueous	1 μg/mL incubation	Unspecified	Spleen cells Murine	Allergies, Con A	IL-4↓,5↓ IFN-γ↑	Li et al. (2004)
MSSM-002	Aqueous	50 μg/mL incubation	Unspecified	D10 cells Murine	Allergies, Con A	IL-4↓,5↓	Li et al. (2004)
MSSM-002	Aqueous	1 μg/mL incubation	72 h	Spleen cells Murine	Conalbumin	IL-4↓,5↓	Srivastava et al. (2004)
MSSM-002	Aqueous	50 μg/mL incubation	72 h	Spleen cells Murine	Conalbumin	IFN-γ↑	Srivastava et al. (2004)
Protec	Syrup	2 μL/mL incubation	24 h	Monocytes Human	None	IL-1β↓,6↓,8↑,10↑ TNF-α↓	Barak et al. (2002)

Con A: concanavalin A, PHA: phytohemagglutinin.

Table 4E. *In vitro*.

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Sambucol Black Elderberry Syrup	Syrup	2 µL/mL incubation	24 h	Monocytes Human	None	IL-1β↑,6↑,8↑ TNF-α↑	Barak et al. (2001)
Sambucol Black Elderberry Syrup	Syrup	2 µL/mL incubation	24 h	Monocytes Human	None	IL-1β↑,6↑,8↑,10↑ TNF-α↑	Barak et al. (2002)
Sambucol for Kids	Syrup	2 µL/mL incubation	24 h	Monocytes Human	None	IL-1β↑,6↑,8↑,10↑ TNF-α↑	Barak et al. (2002)
Sesim-Tang	Aqueous	10 µg/mL incubation	18 h	Astrocytes Murine	LPS SP	IL-1↓ TNF-α↓	Kim et al. (2002a)
Shang Jong Shaur Tong Yong Tong Feng Wan	50% Ethanol	250 µg/mL incubation	48 h	Mononuclear cells Human	LPS	IL-2↓	Chou and Chang (1998)
Shaur Yau Gan Tsao Tang	50% Ethanol	100 µg/mL incubation	48 h	Mononuclear cells Human	LPS	IL-2↑	Chou and Chang (1998)
Shi-bi-lin	Aqueous	0.05 µg/mL incubation	7 h	HMC-1 Mast cells Human	PMA + A23187	IL-4↓,6↑,8↑	Zhao et al. (2005)
Shi-bi-lin	Aqueous	0.2 µg/mL incubation	7 h	HMC-1 Mast cells Human	PMA + A23187	IL-4↓,6↑ TNF↓	Zhao et al. (2005)
Shi-ka-ron	Aqueous	125 µg/mL incubation	24 h	Spleen lymphocytes Murine	Con A	IL-2↑	Jin and Kurashige (1996)
Shi-ka-ron	Aqueous	125 µg/mL incubation	24 h	Spleen lymphocytes Murine	Con A	IFN-γ↑	Jin and Kurashige (1996)
Sho-saiko-to	Aqueous	100 µg/mL incubation	48 h	Mononuclear cells, liver Human	Hep C	IL-10↑	Yamashiki et al. (1997)
Shu Jin Lih An Saan	50% Ethanol	250 µg/mL incubation	48 h	Mononuclear cells Human	LPS	IL-2↓	Chou and Chang (1998)
Tien Hsien	Aqueous	1 µg/mL	5 days	T-cells Whole blood Human	PHA, TT, *S. mutans*, GftD	IL-2↓,6↑,10↑ TNF-α↓	Sun et al. (2005)
Unkei-to	Aqueous	0.3 µg/mL incubation	48 h	Granulosa cells Human	None	IL-1β↑,8↑	Sun et al. (2004)
Unkei-to	Aqueous	3 µg/mL incubation	48 h	Granulosa cells Human	None	IL-6↑	Sun et al. (2004)

A23187: Ca^{2+}ionophore, Con A: concanavalin A, LPS: lipopolysaccharide, PHA: phytohemagglutinin, PMA: phorphol myristate, SP: substance P.

Table 4F. *In vitro*.

Formula name	Preparation used	Concentration	Duration of exposure	Cell type	Inducing agent	Cytokines affected	Author/date
Vigconic	Aqueous	100 µg/mL incubation	20 h	Lymphocytes Human	None	IL-8↑,10↑	Lee et al. (2006a)
Vigconic	Aqueous	1000 µg/mL incubation	20 h	Monocytes Human	None	IL-1β↑	Lee et al. (2006a)
Vigconic	Aqueous	400 µg/mL incubation	20 h	Monocytes Human	None	IL-8↑,10↑,12p70↑	Lee et al. (2006a)
Vigconic	Aqueous	100 µg/mL incubation	24 h	PBMC Human	None	mRNA: IL-1β↑	Pan-Hammarström et al. (2006)
Vigconic	Aqueous	100 µg/mL incubation	48 h	PBMC Human	None	mRNA: IL-1β↑,11,13↓	Pan-Hammarström et al. (2006)
Vigconic	Aqueous	100 µg/mL incubation	24 h	Spleen cells Human	None	mRNA: IL-1β↑,1α↑,4↑,6↑,8↑,19↑ IFN-γ ↑	Pan-Hammarström et al. (2006)
Vigconic	Aqueous	100 µg/mL incubation	48 h	Spleen cells Human	None	mRNA: IL-1β↑,1α↑,3↑,6↑,7↑,8↑ IL-12β2↓,12p35↓,12p40↑ IL-13↓,22↑ IFN-γ↑	Pan-Hammarström et al. (2006)
Vigconic	Aqueous	100 µg/mL incubation	48 h	Spleen cells Human	Polymixin	mRNA: IL-1α↑,6↑ IL-6↓(2nd donor) IFN-γ↑	Pan-Hammarström et al. (2006)
Vigconic	Aqueous	100 µg/mL incubation	24 h	Spleen cells Human	Polymixin	mRNA: IL-1α↑ IFN-γ↑	Pan-Hammarström et al. (2006)
Wheeze-relief-formula	Aqueous	1000 µg/mL incubation	18 h	Mononuclear cells Human	*Dermatophagoid espteronyssinus*	IL-5↓,10↓ TNF-α↓	Lee et al. (2006b)
Yuldahansotang	Aqueous	10 µg/mL incubation	24 h	Astrocytes Murine	LPS SP	IL-4↓ TNF-α↑	Choi et al. (2002)
Yuldahansotang	Aqueous	100 µg/mL incubation	24 h	Astrocytes Murine	LPS SP	IL-1↓,6↓	Choi et al. (2002)
Zemaphyte	Aqueous	0.1–100 µg/mL Best result not specified	4 days, every other day	Monocytes Human	Atopic dermatitis	IL-10↑	Novak et al. (2001)

LPS: lipopolysaccharide, SP: substance P.

3. Results

Table 1A, Table 1B, Table 1C list the formula compositions. The majority of the studies utilized the well known Chinese formulas. In the case that the formula is used in traditional Japanese medicine the Japanese nomenclature of the formula is listed as well. Much of the phytotherapy in the Western countries includes TCM based formulas, which may explain why there appears to be less emphasis on the investigation of western herbal formulas.

Much of the primary literature does not include a full listing of the *Genus species* of plants used, especially if they are listed in pharmaceutical notation which includes *Genus* and plant part used, but does not list plant species. Conversely, if the *Genus* species is listed, then the plant part used was commonly not listed. As a result of these omissions Table 1A, Table 1B, Table 1C lists either the *Genus species or* the pharmaceutical nomenclature as denoted in the reviewed study.

Table 2A, Table 2B, Table 2C, Table 3A, Table 3B, Table 4A, Table 4B, Table 4C, Table 4D, Table 4E, Table 4F list, by formula, the results of the cytokines produced in response to formulas. Table 2A, Table 2B, Table 2C, Table 3A, Table 3B list the *in vivo* and *ex vivo* results respectively, while Table 4A, Table 4B, Table 4C, Table 4D, Table 4E, Table 4F list the *in vitro* work. The tables are partitioned into columns denoting the formula, type of preparation/extraction (aqueous, ethanolic, powder, etc.), concentration/dosage used, duration of exposure, the cell type, inducing agent and model (*in vivo*, *ex vivo* or *in vitro*). If one of these variables differed in an investigator's series of experiments, there are multiple listings of the same investigation to report the differing conditions in which an experiment was run.

For the *in vivo* data tabulated in Table 2A, Table 2B, Table 2C there is also a column suggesting the effects on T helper (Th) cells. Although in some cases more data is needed to predict a Th1 or Th2 biasing effect, with the information provided we have made a prelimary prediction of the direction (Th0, Th1 or Th2) of effect. This is based on the pattern of cytokine secretion that the formula showed in the *in vivo* models. In the following cases we declined to predict Th bias effects due to limited data; an effect on only one cytokine, an up or down-regulation on cytokines that have contradictory effects on Th cells, or cytokines whose effects have not been clearly elucidated in regard to Th effects. We also declined to make Th bias predictions on the *ex vivo* or *in vitro* models due to uncertainity in the accuracy of such models.

The vast majority of herbal preparations used in this literature were aqueous extractions. Less frequently, ethanolic extractions were utilized. Rarely glucose or sucrose-based syrups were tested. For the *in vivo* investigations, aqueous extractions were the most common method of administration. Exceptions to this included powdered herb mixed into rat or mouse chow.

The concentrations/dosages used varied considerably. For the *in vitro* work concentrations of extracts varied from 0.3 μg/mL to 1 g/mL. For the *in vivo*/*ex vivo* work the dosages ranged from 0.18 mg/mL (murine) to 44 g (human). If there were 2 or more different concentrations used, for example in the case of demonstrating a dose dependent response, the lowest concentration that demonstrated a statistically significant effect is reported. Incubation times varied widely from 6 h to 4 weeks in the *in vitro* cell culture work and 1.5 h to 6 months in the *in vivo*/*ex vivo* work.

The most common cell types utilized were splenoctyes, T cells, monocytes and macrophages and induction of these cells was clustered around a few stimulants: Con A, PHA and LPS. In some cases cytokines themselves were used as stimulants. In a number of investigations there were no inducers used and accordingly, this is notated as "none." As seen by the listing of Table 4A, Table 4B, Table 4C, Table 4D, Table 4E, Table 4F the most common model type was *in vitro* work. If any of the above variables were altered in a group's experimental protocols, for instance if different inducers were tested, there is a separate listing for each variation of the model.

The outcome of particular studies is listed under cytokines affected. The majority of investigations measured cytokine protein/peptide levels. However, a few groups measured transcriptional activity as well as protein levels. In these cases mRNA is listed to indicate that genes and not proteins were up or down regulated.

4. Discussion

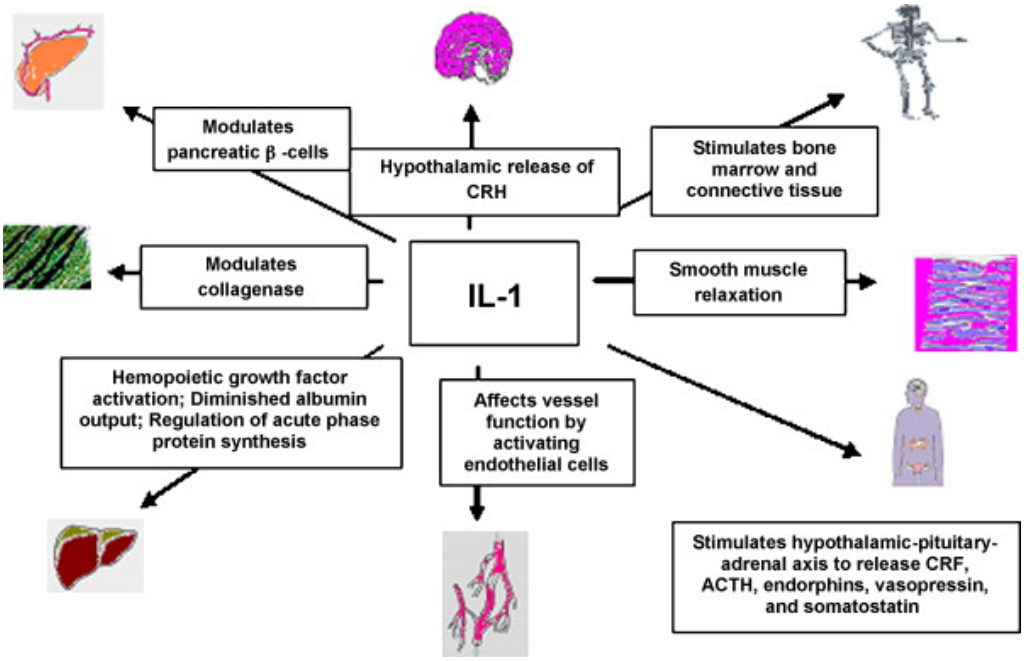

Figure 1. Influences of IL-1 on human physiology (Th2 bias) (Illustrations by: Sariah Burns. Skeleton by: Microsoft Office Clipart. Endocrine System by: Merriam-Webster Inc.).

Pharmacological therapy based on medicinal plants, such as the immunomodulators, is frequently based on combinations of herbs. Therefore, we reviewed the primary literature for formulas that demonstrate cytokine activity and listed the results in Table 2A, Table 2B, Table 2C, Table 3A, Table 3B, Table 4A, Table 4B, Table 4C, Table 4D, Table 4E, Table 4F. The limitations of the data in this review are due to the use of *in vitro* assays for the majority of the investigations reviewed and animal models in the remaining investigations. Replicating physiologically relevant models of human physiology are difficult with *in vitro* methods (Freeman and Spelman, 2008). Cell culture conditions provide a markedly alien environment for cells. Genetic engineering generates cell lines that are stressed and incompletely understood. Therefore cultured cell lines response to experimental conditions should be carefully scrutinized. In addition, the absence of digestive and metabolic processing of complex extracts *in vitro* calls

into question the significance of data gathered from such methodology. Further, concentrations utilized for *in vitro* models often do not correspond to physiologically relevant serum concentrations. For example, in the *in vitro* models investigating Allergina (Jeong et al., 2003) and Bouum-Myunyuk-Dan (Jeong et al., 2004) the researchers used up to 1 mg/mL, a concentration lacking physiological relevance (Fig. 1).

Animal models also may misrepresent human physiology. Artificially generated pathology, confounding variables, differences in anatomy and biochemical pathways all call into question the validity of data gathered from animal models. Unfortunately, a previous review on herbs and cytokines found that most *in vivo* models are animal studies and that human studies are rare (Spelman et al., 2006a).

Traditional use of medicinal plants can offer leads to their pharmacological activity. Seventy-five percent of new drugs made from natural products were "discovered" by following leads from traditional use of medicinal plants (Cott, 1995). For example, of 6350 proven antimicrobial species ~63% have ethnobotanical documentation as antimicrobials (Mahady, 2005). Of the 90 prescription drugs in use today in cancer treatment derived from plant species ~74% of these were "discovered" by investigating traditional uses (Aggarwal et al., 2004). Hence, data from traditional use combined with outcomes from laboratory studies offers insights into possible modes of activity by the medicinal plants in question. The data in this review, combined with indications of traditional use, does offer insight into the effect of these herbal extracts on cytokine activity. Moreover, given the broad spectrum activity of cytokines, it is likely that at least some of the organ and tissue effects of these herbal remedies observed in traditional use are due, at least in part, to modulation of cytokine activity.

The Th1/Th2 paradigm offers a useful perspective in viewing the many cytokine activities of the reviewed formulas. From this perspective, cytokines influence the balance between cell-mediated responses (Th1) and humoral immunity (Th2). Naïve T cells are activated to a Th0 cell, which show characteristics of both Th1 and Th2 cells, by numerous cytokines including IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, as well asTNF-α and IFN-γ. After differentiation cytokines which induce a cell-mediated response (IL-2, IL-3, IL-12, IFN-γ, TNF-α and TNF-β), shifting the immune response away from the humoral response, are known as Th1 cytokines (Fig. 2, Fig. 4, Fig. 5). Conversely, cytokines that shift the immune response towards humoral immunity (IL-4, IL-5, IL-6, IL-10 and IL-13) and away from cell-mediated responses are considered Th2 cytokines (Fig. 1, Fig. 3). Pharmacological agents that modulate the Th1 or a Th2 balance are therefore useful, depending on the state of the cellular milieu and the nature of any pathogens involved (e.g., intracellular parasites and viruses requiring a Th1 response, vs. extracellular microbes requiring Th2 response). Th2 cytokines are also important for immunity against cancer cells, but can contribute to pathology in allergy and various autoimmune disorders.

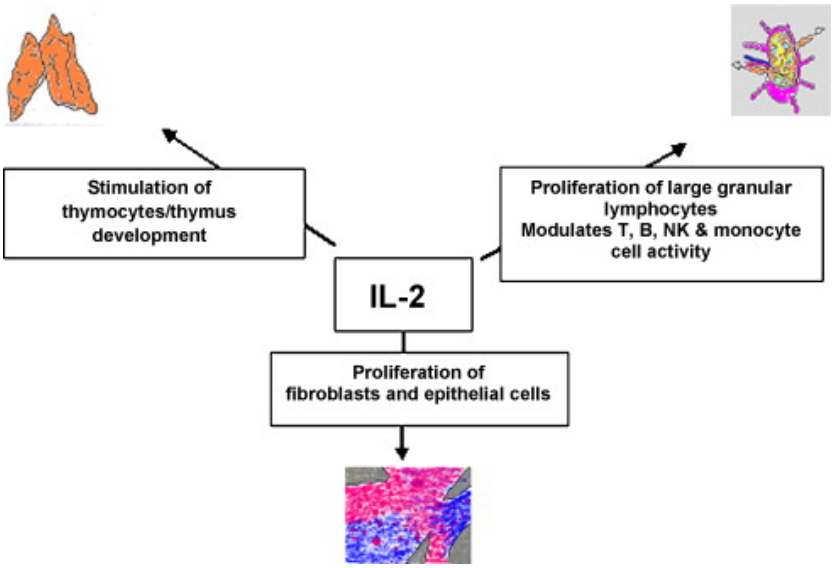

Figure 2. Influences of IL-2 on human physiology (Th0 and Th1 bias) (Illustrations by: Sariah Burns).

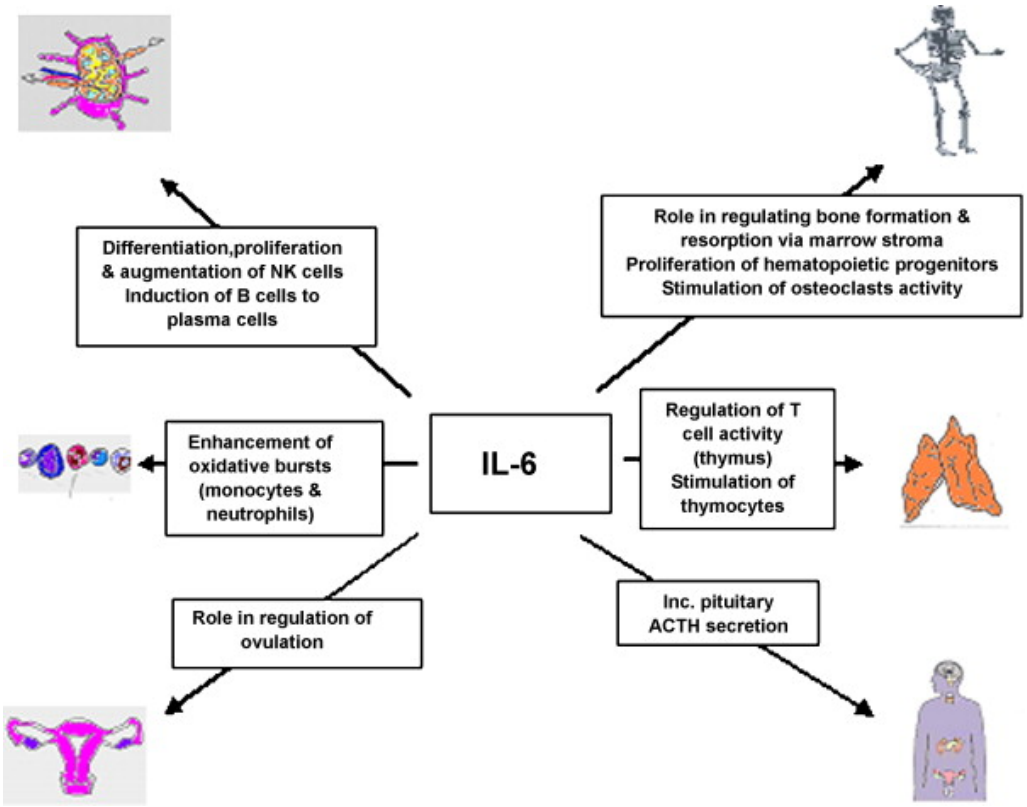

Figure 3. Influences of IL-6 on human physiology (Th0 and Th2 bias) (Illustrations by: Sariah Burns. Skeleton by: Microsoft Office Clipart. Endocrine System by: Merriam-Webster Inc.).

From Table 2A, Table 2B, Table 2C it can be seen that not all formulas appear to have a cytokine stimulation pattern and as a result, are difficult to categorize in terms of Th1/Th2 response. However, some formulas appear to down regulate Th2 response and others are

reported to down regulate Th1 response. For example, “Food allergy formula I” (Table 2A) down regulates the Th2 cytokines IL-4, IL-5 and IL-13. As a result the immune response is shifted away from a Th2 response, resulting in a reduction in the allergic response. Similarly, Qing-huo-bai-du-yin, is shown in Table 2B to induce the Th2 cytokines (IL-4, IL-6, IL-10), which in the burn model utilized in these investigators model increases antibody production to fight the susceptibility to infection resulting from third degree burns (Luo, Zhou et al., 2004). In these examples, the constituents of the herbal formulation appear to induce a cytokine profile that “makes sense” in terms of the pharmacological applications of the formulas.

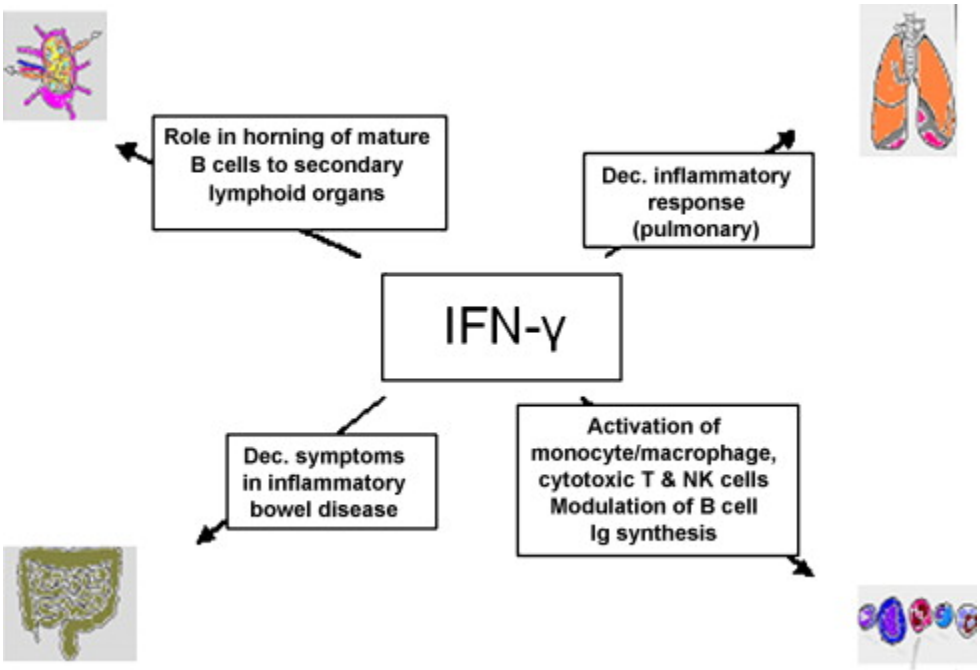

Figure 4. Influences of IFN-γ on human physiology (Th0 and Th1 bias) (Illustrations by: Sariah Burns).

As previously mentioned in regard to traditional use, the data can be extrapolated to aid in the understanding of traditional use of many of the reviewed formulas. For example, Sho-saiko-to, a traditional Japanese formula affecting cytokine activity, has undergone considerable research for immune and hepatic effects. This formula was found to repair “abnormalities in the cytokine cascades” and correct “deteriorated biological defense mechanisms”. Specifically, Sho-saiko-to increased depressed IL-10 levels found in hepatitis C patients, while decreasing elevated levels of IL-4 and IL-5 to normal levels (Yamashiki et al., 1997). A double-blind multi-center clinical trial of patients with chronic active hepatitis found Sho-saiko-to to lessen serum markers for liver injury (Hirayama et al., 1989). Other groups have found that Sho-saiko-to induces local IL-6 stimulation in pulmonary tissue (Fig. 3). On fractionation of Sho-saiko-to, both a hydrophilic and a moderately hydrophobic fraction demonstrated IL-6 stimulation, suggesting that multiple constituents are responsible for the IL-6 activity (Ohtake et al., 2000). It may be that to repair “deteriorated biological defense mechanisms” multi-component therapeutics is advantageous; while certain phytochemicals may potentiate ADME properties, others may enhance pharmacodynamics (Eder and Mehnert, 1998, Spelman et al., 2006b).

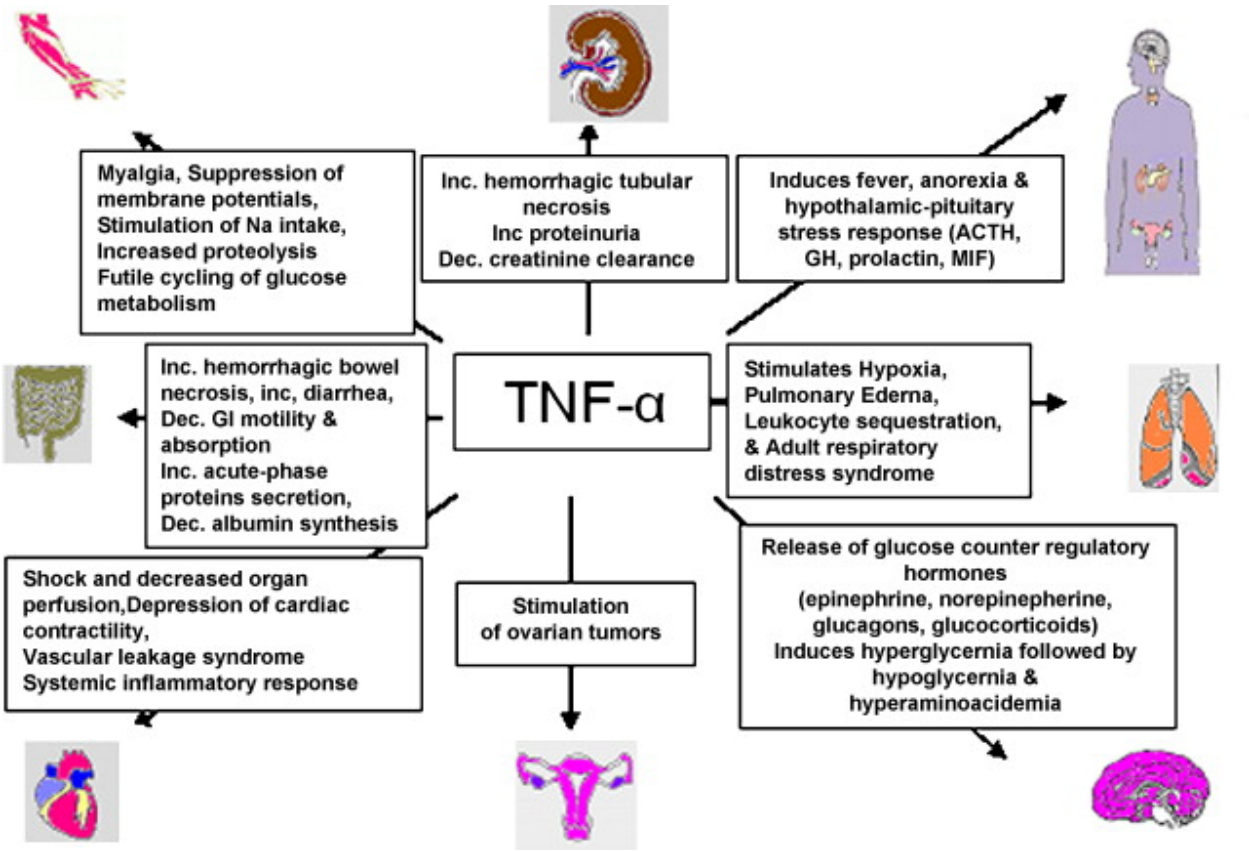

Figure 5. Influences of TNF-α on human physiology (Th0 and Th1) (Illustrations by: Sariah Burns. Endocrine System by: Merriam-Webster Inc.).

Zuo et al. (2003), in a human study of the pharmacokinetics of key constituents in an herbal formula, found that the absorption of the constituents was delayed, their C_{max} was higher and area under the curve was increased, compared to the same constituents if ingested as a single herb. They concluded that the concomitant constituents in the compound prescription increased efficiency and stability of the known active constituents. Of particular interest, human pharmacokinetic studies on Sho-saiko-to (containing *Scutellaria* baiclensis and *Glycyrrhiza glabra*) demonstrate efficient absorption of liquiritigenin and its glycoside liquiritin even though these constituents make up a mere 0.5% of this formula (Li et al., 1998). This suggests that absorption of these compounds may have been improved due to formulation (Zuo et al., 2003).

Chronic diseases are increasingly being seen as multifactorial disorders (Cooper, 2003). Accordingly, multivalent pharmacology is progressively becoming a prerequisite in clinical medicine, whether for the treatment of infectious diseases, psychiatry, or cardiovascular disorders. Lansky and Von Hoff (2005) point out that even without full understanding of the pharmacology represented by complex pharmacological mixtures such as within medicinal plants, they may nonetheless have advantages.

Intriguingly, medicinal plants are known to carry more than one active compound (Duke, 2007). Consequently the pharmacology associated with traditional remedies, especially formulas, is likely due to diverse modes of activity via various protein sites providing redundant and multiple pathway activity. Keith and Zimmermann (2004) suggest that many genes might need

complementary action to modify disease processes. In other words, modulating a multiplicity of sites may be an asset in clinical therapeutics (Morphy et al., 2004).

The partial perturbations of medicinal plants on a pharmacological network mimic physiological scenarios where hundreds of different enzyme systems and receptor types and subtypes act in concert (Ágoston et al., 2005). Recent research into cellular networks demonstrates that pharmacological agents that provide multiple signals can impact the complex equilibrium of whole cellular networks more favorably than drugs that act on a single target (Ágoston et al., 2005, Briskin, 2000, Csermely, 2004, Csermely et al., 2005, Keith et al., 2005, Keith and Zimmermann, 2004, Morphy et al., 2004, Werner, 2003). Additionally, multi-target agents need affect their targets only partially, which corresponds well with the presumed low-affinity interactions of medicinal plants (Ágoston et al., 2005). Broader specificity, lower affinity, multi-component compounds have been reported to be, in some cases, more efficient than high affinity, high specificity compounds (Csermely, 2004). This is compared to the complete elimination of a single network node (enzyme or receptor system), which is an unusual phenomenon not typically found in a physiological scenario (Csermely et al., 2005). Additionally, low-affinity, multi-target pharmacological strategies have demonstrated improved safety profiles (lower occurrence and reduced range of side-effects) than high affinity, single-target drugs (Csermely et al., 2005, Lipton, 2004, Rogawski, 2000).

Notably, although the majority of the studies did not include samples of single plants or known active constituents of plant species, those that did found that the active constituents or single plants, were not as effective as the tested herbal formulas (Ohtake et al., 2000, Pan-Hammarström et al., 2006, Yamashiki et al., 1992). For example, when bicalin and glycyrrhizin, considered to have significant roles in the activity of *S. baiclensis* and *G. glabra* respectively, were tested alone they could not induce IL-10 secretion as these herbs did in formula.

A further advantage of formulas is the reduction of adverse events by *buffering* toxicity that an herb or specific constituent may contain (Jia et al., 2004, Vickers and Zollman, 1999). For example, Aconitum carmichaeli, considered a powerful medicinal plant, is known as a low-dose botanical medicine due to the alkaloids aconitine, mesaconitine, and hypaconitine. At inappropriate doses these alkaloids can be toxic, but their metabolites are particularly effective antiiflammatories and antinociceptives (Hikino et al., 1980, Shu et al., 2006, Suzuki et al., 1994). Traditional practices include processes that are able to remove some, but not all, of the toxicity of *Aconitum* based medicine. The formula FAHF includes *Aconitum*. Li et al. (2001) reported that FAHF, at twice the therapeutic dose (42 mg/mouse) over 14 weeks, demonstrated no toxicity in a murine model. Additionally, the formula Mao-Bushi-Saishin-to, which contains *Aconitum*, did not demonstrate toxicity to mice or rats at a significant dose (100 mg/kg) for 13 weeks (Shimizu et al., 1999). Finally, QFGJS, also containing *Aconitum*, caused no mortality in a murine model at a single dose (33.6 g/kg) 346 times the suggested clinical dose for humans. Even after 3 months of dosing at 100 times the clinical dose, no obvious signs of toxicity have been reported (Cai et al., 2005). Kimura (2006) suggests that herbal formulations, as used in traditional systems of medicine, contain both yin and yang constituents that have mutually opposing pharmacological activities. Considering the toxicity of aconitine, mesaconitine, and hypaconitine from *Aconitum*, there may be “yin” principals opposing these “yang” alkaloids. Due to this paradoxical reversal of toxicity and the pharmacology complexity of multi-

component remedies, herbal formulas represent a particular methodological and technological challenge to study and thus, understand.

Pharmacological research on the immunomodulators and, more broadly on medicinal plant formulas, is progressing as instrumental prowess and research methodology advance. Immunomodulators may offer a reasonable strategy for subtle induction of a variety of cytokines in immune-related diseases and other disorders. Moreover, research into these complex phytochemical cocktails may lead to further therapeutic advances and ultimately assist in elucidating the non-linear, non-additive interactions between the genome and proteome.

5. Conclusion

The current data on the influence of herbal formulas on cytokine activity is limited by the paucity of human studies. Despite the fact that the majority of the research listed in this review is *in vitro* or animal models, there does appear to be substantial historical, empirical, and increasing scientific evidence that herbal formulas may provide therapeutic application in the modulation of cytokines. Given the reported therapeutic success of these formulas by traditional cultures and modern clinicians, the activity of these medicinal plant mixtures may be partially due to their effects on cytokines, although other modes of activity are also likely. In addition, pharmacodynamic and pharmacokinetic potentiation of active constituents, as well as buffering of toxic constituents, appear to be common strategies of traditional formulas. It is our hope, the data collated and reviewed here will serve to stimulate further research on this topic. Further study of herbal mixtures on diseases and syndromes involving cytokines is necessary.

Conflict of interest

None.

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