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# Developing Phytocompounds from Medicinal Plants as Immunomodulators

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## ABSTRACT

Imbalance or malfunction of the immune systems is associated with a range of chronic diseases including autoimmune diseases, allergies, cancers and others. Various innate and adaptive immune cells that are integrated in this complex networking system may represent promising targets for developing immunotherapeutics for treating specific immune diseases. A spectrum of phytochemicals have been isolated, characterized and modified for development and use as prevention or treatment of human diseases. Many cytotoxic drugs and antibiotics have been developed from phytocompounds, but the application of traditional or new medicinal plants for use as immunomodulators in treating immune diseases is still relatively limited. In this review, a selected group of medicinal herbs, their derived crude or fractionated phytoextracts and the specific phytochemicals/phytocompounds isolated from them, as well as categorized phytocompound groups with specific chemical structures are discussed in terms of their immunomodulatory bioactivities. We also assess their potential for future development as immunomodulatory or inflammation-regulatory therapeutics or agents. New experimental approaches for evaluating the immunomodulatory activities of candidate phytomedicines are also discussed.

## I. INTRODUCTION

During the past few decades, there has been a paradigm shift in medicine, with interest moving from disease-treatment to disease-prevention health care. Medical care is being evaluated not only according to diagnosis, prevention and treatment of diseases but also according to the enhancement of life quality, maintenance of health and the use of nutritional or medicinal foods. In this context, new strategies for drug discovery with advanced experimental approaches are of importance for the modernization of medicine. Currently, mainstream pharmaceutical research and development still concentrates on single compounds, biochemicals or biologics as candidate drugs or lead compounds, that aim at specific targets associated with a disease. This drug discovery strategy, however, seems to have reached a bottleneck, as it becomes ever more time consuming, labour intensive and costly to develop new drugs (Chen *et al.*, 2008). Such ''traditional'' Western medical research expects that single compound chemicals confer high potency, low toxicity and high selectivity for targeted molecular/cellular targets and diseases. However, in reality, these ideals are proving hard to achieve.

Therefore, the development of drug candidates from various traditional or alternative and complementary medicines is receiving an increasing worldwide attention (Aravindaram and Yang, 2010; Tu, 2011).

Drug discovery is being transformed from a "game of chance" (mass screening) or overdependence on brute-force new high-throughput technology (Patwardhan and Mashelkar, 2009). A better understanding of approaches, the adaptation of a variety of approaches and cross-disciplinary learning that draws from traditional wisdom are now being considered by many scientists to be critical to make a significant difference (Schmid and Smith, 2004). Drug discovery strategies and development based on systematic and modernized investigation of complementary and alternative systems of medicines (CAM) or/and the traditional systems of medicines are re-emerging as an attractive approach for many pharmacology and pharmaceutical researchers. According to the definition of the National Center for Complementary and Alternative Systems of Medicine (NCCAM), CAM is a group of diverse medical and health-care systems, practices and products that are not generally considered part of "conventional medicine" (Western medicine) (Mansky and Wallerstedt, 2006). Although defining CAM can be arduous, it can generally be categorized into several groups including natural products, mind and body medicine, manipulative and body-based practices and other CAM practices. Speaking in a broad sense, other CAM practices may also include ancient and "self-integrated" medical systems such as the Ayurvedic medicines and traditional Chinese medicines (TCM). It is estimated that more than 70% of the developing world's population still relies primarily on CAM (Azaizeh *et al*., 2010). Plant materials are the major sources of various therapeutic agents in the CAM categories of natural products, Ayurvedic medicine and TCM. In fact, within TCM, plant-derived medicines have been used for prevention and treatment of various diseases and documented in a systematic way for over five millennia (Lam *et al*., 2010). Within this context, it can be expected that a spectrum of medicinal plants with a long history of use will be quickly re-recognized as highly valuable for future drug discovery and development, as recently commented (Lam *et al*., 2010; Tu, 2011).

An imbalance in specific immune systems or their coordination in general is known to be involved in the pathogenesis of various diseases including infection, dermatitis, inflammatory bowel diseases, metabolic syndrome, cancers and a spectrum of inflammation-related diseases (Mantovani *et al*., 2008; Nestle *et al*., 2009). Modulation of the immune systems has hence been considered a vital approach for the treatment or control of various immune-related diseases (Cho, 2008; Ouchi *et al*., 2011). The recent advent and breakthroughs in omics technology and systems biology experimental

approaches have created a new era for the investigation and development of novel therapeutics and drugs for diverse disease systems, especially complex immune-related disorders. These technologies and approaches include various genomic, proteomic, metabolomic, cellomic, lipidomic and phenomic approaches, as well as the associated bioinformatics sciences and databases. In general, phytomedicines, including phytoextracts, their subfractions derived from partitioning using organic solvent systems or isolated single phytocompounds or phytochemicals with a long history of medicinal use, are believed to interact with multiple targets to confer pharmacological or physiological effects at the cellular, tissue or organ levels. Experimental uses seem to suggest that they may be relatively safe. An increasing number of studies have shown that traditional phytomedicines can confer a variety of immunomodulatory activities, as recently revealed by others' and our own studies (Hou *et al.*, 2010; Shyur and Yang, 2008). The process of discovering and developing phytocompounds as immunomodulatory agents by evaluation using different experimental approaches and omics platforms is shown in Fig. 1. Here, we review a group of specific medicinal herbs, their derived plant extracts, fractions, and the derived phytochemicals that have been studied for their immunomodulatory bioactivities and assessed for their potential as immunomodulatory and/or inflammation-regulatory therapeutics agents. The functional genomics and proteomics approaches used for characterization of the bioactivities outlined here can be employed as key strategies in future applications. The accompanying findings are discussed in detail and their implications for phytomedicine research are contemplated.

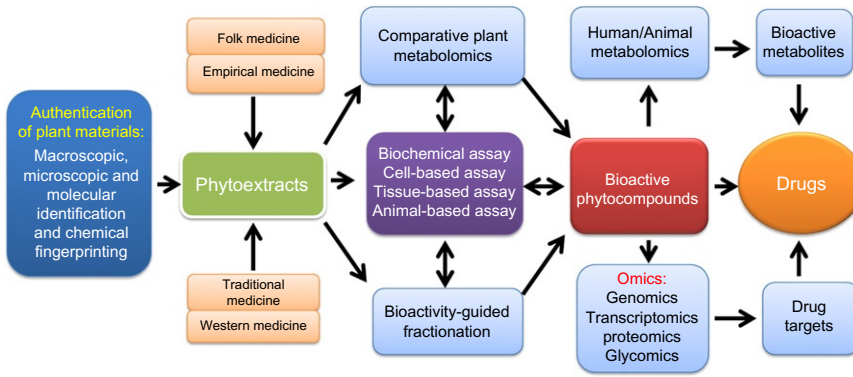



Fig. 1. Schematic representation of technological systems for drug discovery from phytocompounds of medicinal herbs as immunomodulatory agents using various experimental approaches.

# II. MODULATION OF THE IMMUNE SYSTEM

## A. IMMUNE SYSTEMS AND IMMUNE-RELATED DISORDERS

The immune system is, in nature, a uniquely complex network that protects the host body from foreign pathogens, stresses, insults and the resultant illnesses. It can govern the various and interconnecting pathways of inflammation, microbial recognition, microbial clearance, cell and tissue damage and death and wound healing. The homeostatic system requires the well-timed interplay of multiple immune cell types and crosstalk with the specific tissue microenvironment to maintain immune homeostasis. The immune system in vertebrates, at least, is traditionally divided into two types, innate immunity and adaptive immunity (Ullrich, 2010; Vesely *et al.*, 2011), although the distinctions between innate and adaptive immunity have become more intertwined in recent studies (Lanier and Sun, 2009). Both play critical roles in functioning as a defence system against the invasion of microbial pathogens present in our environment. It also provides a regulatory system that controls normal cell turnover and eliminates damaged cells and tumour cells. Typically, innate immunity has been considered to be the first line of defence against pathogens such as bacteria, viruses or fungi. It exhibits characteristic features such as rapid response, infection halting and lack of memory in functions (Schiller *et al.*, 2006). The innate immunity system may include dendritic cells (DCs), macrophages, mast cells, neutrophils, basophils, eosinophils, invariant natural killer cells (NK cells), NKT cells and γδ T cells (Garg *et al.*, 2010). In comparison, the adaptive immune system or acquired immune response is a relatively slow process mediated by T cells and B cells. It employs diverse antigen receptors that are not encoded in germ line cells but rather *de novo* generated through DNA rearrangement mechanisms in the somatic immune tissues of mammalian organisms (Iwasaki and Medzhitov, 2010; Krogsgaard and Davis, 2005). Characteristics of various immune cell types involved in innate and adaptive immunity are summarized in Fig. 2. A number of recent findings focusing on the specific cellular functions, as well as the complexity and functional specialization of immune cells, have drastically expanded our knowledge of immunity (Medzhitov *et al.*, 2011; Vivier *et al.*, 2011). For example, NK cells were originally defined as effector lymphocytes of innate immunity and were endowed with constitutive cytolytic functions. Recent studies, however, disclosed that NK cells can also mount a form of antigen-specific immunologic memory (Vivier *et al.*, 2011). Therefore, NK cells may also be classified as a new type of immune cell that can exert sophisticated biological functions that contribute to both innate and adaptive immunities. These properties render

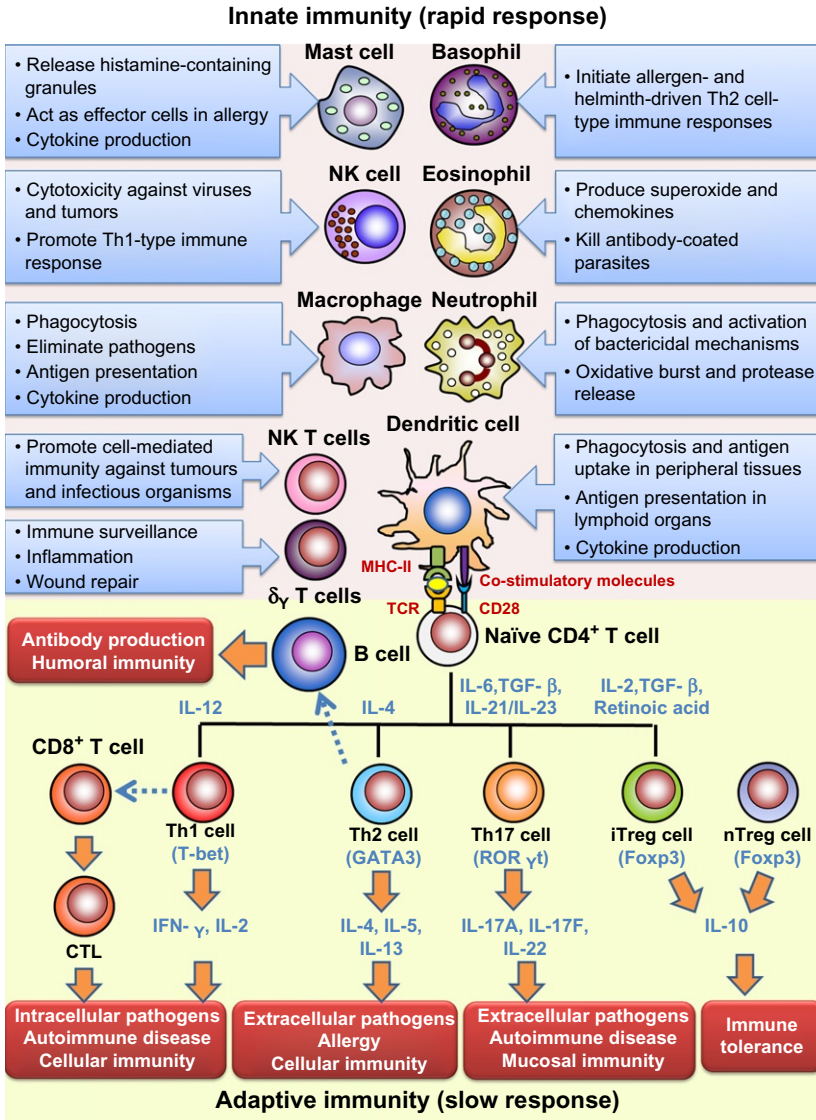



Fig. 2. Characteristics and functions of various innate and adaptive immune cells in the immune system. The immune system can be divided into innate immunity and adaptive immunity. The innate immune system involves the participation of dendritic cells, macrophages, mast cells, granulocytes (neutrophils, eosinophils and basophils), NK cells, NKT cells, δγ T cells and others. The key functions of each cell type are described in the blue grid. The adaptive immune system involves $CD4^+$ T cells, $CD8^+$ T cells, B cells and others. $CD4^+$ T cells can differentiate into Th1, Th2, Th17 and inducible Treg (iTreg) cells under different microenvironments specialized by interactive cytokines and chemokines, and distinct activation of specific transcription

NK cells highly specific and selective in various cellular functions, and thereby able to respond to a broad spectrum of antigens. These new findings and increased appreciation of the importance of the immune systems have led, over the past two decades, to considerable effort being spent on understanding how immune responses against various immune-related diseases are governed and modulated.

Most immune-associated diseases, including viral or bacterial pathogen-mediated infectious diseases, allergic diseases, inflammatory bowel diseases, cancers and a number of chronic diseases, are now known to be correlated with inflammation. Inflammation is probably the most vital immune response induced by noxious stimuli or conditions (Schmid-Schonbein, 2006). Inflammation underlies a wide variety of physiology and pathological processes, enables survival and tissue repair during or after tissue infection or injury and maintains the organ and body homeostasis (Medzhitov, 2008). Inflammation has been known to humans for thousands of years due to observations and experiences with wounded tissue and infections (Medzhitov, 2010). Traditionally, the symptoms of inflammation were characterized by five cardinal signs, redness, swelling, heat, pain as well as the disturbance of functions (Medzhitov, 2010). A typical inflammatory response is composed of four key components: (1) inflammatory inducers, as the signals to initiate inflammation; (2) specialized sensors that detect the inducers; (3) inflammatory mediators induced by the sensors; and (4) the target tissues that are functionally altered by the inflammatory mediators, that is, the effectors of inflammation (Medzhitov, 2008). These components and their relationships are shown in Fig. 3. Each component can be presented in multiple forms and their combinations can result in distinct inflammatory pathways.

The different types of pathways triggered under given physiological and environmental conditions depend on the nature of the inflammatory inducers. Therefore, understanding and characterizing the types of inducers are a key issue that needs to be addressed in studies of inflammation. The inducers of inflammation are, in general, broadly classified into exogenous and

factors. $CD8^+$ T cells are responsible for confirming cytotoxicity against virus-infected cells or tumour cells. Treg cells are generally grouped into two classes, iTreg cells and natural Treg (nTreg) cells. They can regulate specific immune responses, especially immune tolerance, to maintain immune homeostasis. Abbreviations: Th1, T-helper type 1; Th2, T-helper type 2; Th17, T-helper type 17; Treg, T regulatory cells; NK, natural killer cells; NK T cells, natural killer T cells; MHC-II, major histocompatibility complex class II; TCR, T cell receptor; IFN-γ, interferon-gamma; TGF-β, transforming growth factor-beta; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; IL-12, interleukin-12; IL-17, interleukin-17; IL-21, interleukin-21; IL-23, interleukin-23.

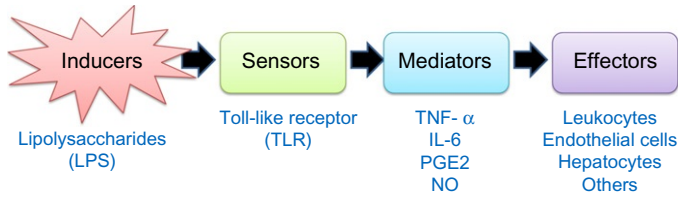



Fig. 3. Schematic representation of the inflammatory pathway. The inflammatory pathway consists of four major components: (1) inducers such as lipopolysaccharides (LPS); (2) sensors such as toll-like receptors (TLRs); (3) mediators such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), prostaglandin E2 (PGE2) and nitric oxide (NO); and (4) effectors such as leukocytes, endothelial cells, hepatocytes and others.

TABLE I

*Classification of Inducers of the Inflammatory Pathway (Modified from Medzhitov, 2008)*

| | | | |
|---|---|---|---|
| Inducers | Exogenous | Microbial | 1. PAMPs<br>2. Virulence factors |
| | | Non-microbial | 1. Allergens<br>2. Irritants<br>3. Foreign bodies<br>4. Toxic compounds |
| | Endogenous | Cell derived<br>Tissue derived<br>Plasma derived<br>ECM derived | 1. Inducers released from malfunctioning, stressed or dead cells and from damaged tissues<br>2. Endogenous crystal<br>3. Products of ECM breakdown |

endogenous (Table I) (Medzhitov, 2008, 2010). Exogenous inducers are categorized into two subgroups: microbial and non-microbial. Further, there are two types of microbial inducer: pathogen-associated molecular patterns (PAMPs) and virulence factors. PAMPs are defined as a set of conserved molecular patterns that are characterized by all microorganisms of a given class (Medzhitov and Janeway, 1997). PAMPs are defined in the context that the host has evolved a corresponding set of pattern-recognition receptors (PRRs) that are responsible for detecting the presence of PAMPs. The second class of microbial inducers is composed of various virulence factors and is hence restricted to various pathogens. In contrast to PAMPs, virulence factors are not sensed directly by dedicated or specific receptors. Exogenous inducers of non-microbial origin include various allergens, irritants, foreign

materials and toxic compounds (Medzhitov, 2008, 2010). A variety of allergens are sensed because they mimic the virulence activity of parasites. Others may function as irritants on the mucosal epithelia. The inflammatory response induced by both types of inducers is quite similar as the action of the immune system against parasites and environmental irritants depends mainly on expulsion and clearance under the control of the mucosal epithelia. The sensors for allergens, however, are largely unknown.

In essence, endogenous inducers of inflammation are defined as the signals produced by malfunctioning, stressed or damaged cells or tissues and can trigger distinct types of inflammatory responses, suggesting that they can play a vital role in immune response (Medzhitov, 2008). The identity and features of these signals are currently not well defined or understood. However, they apparently belong to different functional classes specified according to the nature and level of the cell or tissue anomalies on which they report. An important and common theme, but not a universal one in detection of acute tissue injuries, is the sensing of the desequestration of cells, organelles or molecules which are normally maintained as separate entities in intact or undamaged cells and tissues. The sequestration activity of these components including various ligands and their receptors or enzymes is provided by various types of compartmentalization that normally and commonly occurs in normal tissues. Among them, some obvious examples are the sequestration bounded by cellular membranes, basement membranes, the surface epithelium and the vascular endothelium (Medzhitov, 2008). For example, for necrotic cell death, the integrity of the plasma membrane is damaged, resulting in release of a number of DAMPs and other constituents, including ATP, uric acid, $K^+$ ions and high-mobility group box 1 protein (HMGB1) (Bianchi, 2007). Another class of endogenous inducers, including crystals of monosodium urate, calcium pyrophosphate dihydrate and advanced glycation end products (AGEs), are correlated with chronic inflammatory conditions. Specific salt crystals can induce the inflammatory conditions gout and pseudogout. AGEs bind to advanced glycation end-product-specific receptor (RAGE, also known as AGER), and this mediates the induction of inflammation. The final class of endogenous inducers is breakdown products of the extracellular matrix (ECM) generated during tissue damage or malfunction (Medzhitov, 2008). One of the best-studied components in such processes is the glycosaminoglycan hyaluronate. Under normal conditions, hyaluronate is present as an inert high-molecular-weight polymer. Tissue injury causes its breakdown into low-molecular-weight fragments, which can induce inflammatory activity via activating toll-like receptor 4 (TLR4), resulting in a tissue-repair response (Jiang *et al.*, 2005; Medzhitov, 2008). This key conversion activity is regulated by reactive

oxygen species (ROS)-dependent signalling (Jiang *et al.*, 2007). In fact, a number of endogenous pathways that initiate inflammatory responses are known to be dependent on ROS activity. Therefore, ROS is considered as a promising target for immunomodulation or anti-inflammation.

Recent findings from a spectrum of immunology scientists (Medzhitov, 2008, 2010; Medzhitov *et al.*, 2011) have increased awareness that inflammation comes in distinct forms and modalities, regulated by different molecular and cellular mechanisms of induction, regulation and resolution. Undoubtedly, a well-controlled inflammatory response is beneficial for homeostasis (e.g. in providing protection against tissue injury and pathogen infection); however, it can become very detrimental if dysregulation of the process occurs (e.g. resulting in septic shock). Therefore, it is highly important to govern various dysregulated acute inflammatory disorders with appropriate drugs and specific therapeutics. Interestingly, during the past few decades, the research focus on prevailing inflammatory conditions has shifted from treating acute inflammatory reactions in response to infections or/and tissue wounds to the newly defined chronic inflammatory states that accompany, obesity, type 2 diabetes, atherosclerosis, asthma, cancers and various neurodegenerative diseases (Donath and Shoelson, 2011; Nguyen and Casale, 2011; Ouchi *et al.*, 2011).

### B. IMMUNOMODULATION AND IMMUNOMODULATORS

Therapeutics for immunomodulation can be referred to as a therapeutic approach to intervene or adjust the auto-regulating immune responses to a desired level via immune-stimulation, immune-suppression or induction of immunologic tolerance. An immunomodulator can be defined as a substance or agent that can elicit immunomodulatory activities by altering or affecting immune cell systems to produce the desired immune response through dynamic regulation of the target immune systems (Spelman *et al.*, 2006). Immunomodulators have been traditionally divided into three groups: immunosuppressive agents, immunostimulators and tolerogens. Immunostimulators, also known as immunostimulants, are substances that can stimulate the immune systems by inducing the activation or augmenting the activity of immune system components. They are usually used in the treatment or control of infections, immunodeficiency and cancers. Immunosuppressive agents, also known as immunosuppressants, are substances that can reduce the ability of the immune system by inhibiting activation or decreasing the activity of its components. These types of agents are often used in organ transplantation and/or autoimmune diseases. Tolerogens are recognized to induce immunologic tolerance and make the immune system non-responsive to target

antigens. Immunologic adjuvants can be considered as another type of immunomodulator, as they are agents that can stimulate the immune system and increase the response to a vaccine without possessing any specific antigenic effect alone. Various phytomedicines have been found to modulate the components of the inflammatory pathways including the various inducers, sensors, mediators and sensors mentioned above. Based on understanding of various immunomodulation activities and the profound effects of certain traditional medicines on these activities, we suggest that plant-derived secondary metabolites as natural products could be important resources for future development of immunomodulators into immunotherapies.

Taking the treatment of allergic disease as an example, immunomodulation aims at decreasing the pathologic immune response such as inflammation instead of causing an unwanted return to an immunologically naive or unresponsive state (Nguyen and Casale, 2011). On the basis of our knowledge of innate and adaptive immune responses at both the molecular and cellular levels, various immunomodulators for a number of allergic diseases, including asthma, allergic rhinitis and eosinophilic esophagitis, have been developed (Akdis *et al*., 2005; Chang *et al*., 2007). As several approaches for exploring immunomodulation activity in mouse models of allergic disease have not been effective to translate into useful results in human clinical trials, the pleiotropic nature of associated or related cytokines/chemokines and the underlying effector mechanisms of the varied phenotypes of these diseases need to be carefully investigated to develop future treatment for such diseases. The common goals for treating these diseases are to decrease the excessive T-helper 2 (Th2) response via various mechanisms such as (1) blocking critical Th2 cytokine activities, (2) inhibiting Th2 cytokine synthesis, (3) blocking critical Th2 effector molecules, (4) inhibiting key cell-type populations involved in Th2 response and (5) stimulating Th1 responses for balance (Nguyen and Casale, 2011). Therapies directed against specific effector molecules, including immunoglobulin E for targeting the IL-4/IL-13 receptor and augmenting the Th1/Th2 balance, are promising targets for immune-modulation therapy of allergic diseases. Herbal extracts from *Ganoderma lucidum*, *Glycyrrhiza radix* and *Sophorae flavescentis* Radix were found to reduce eosinophil infiltration of the lungs and inhibit airway hyperresponsiveness (AHR) in ovalbumin (OVA)-sensitized mice via reducing the levels of IgE and Th2-associated cytokines (IL-5, IL-4 and IL-13) and increasing the level of IFN-$\gamma$ secretion (Busse *et al*., 2010; Shen *et al*., 2011).

In addition to the suppression of inflammatory responses, an important approach for immunomodulation is to boost an individual's immune defence systems by giving either physiologic or supraphysiologic dosages of exogenous cytokines or therapeutic substances to treat the associated chronic

malignancies and viral infections (Nelson and Ballow, 2003). The most studied approaches consist of pathogen-derived vaccines, tumour cell-based vaccines, DC-based immunotherapy and peptide vaccines (Melief, 2008; Smyth *et al.*, 2001). A number of clinical studies for these approaches have demonstrated the safety, but not necessarily satisfying clinical efficacy of such experimental medicines (Robson *et al.*, 2010). Moreover, there is an emerging consensus that the most efficacious therapies will activate several specific components of the immune system (Whelan *et al.*, 2003). Cancer immunotherapy using cytokines is an important and attractive approach for cancer therapy; however, optimizing the pharmacological doses to avoid cytotoxic reactions remains a very challenging issue (Chada *et al.*, 2003). Several cytotoxic drugs such as paclitaxel have been shown to also confer immunomodulatory effects at relatively low doses and exhibit immunity-dependent curative effects in animal models (Mizumoto *et al.*, 2005; Shin *et al.*, 2003). Combinational therapies using low-dose anti-cancer agents and cytokines together have revealed some benefits in some studies. It has also been shown that inducing T-helper (Th) 1-promoting cytokines using specific adjuvants is vital for enhancing certain anti-tumour immunity, and thereby preventing or reducing tumour growth (Garg *et al.*, 2010; Wen *et al.*, 2011). Therefore, the development of specific phytocompounds from herbal medicines as immunomodulatory agents to be used as either adjuvants or therapeutics for cancer treatment or immunotherapy is an emerging clinical issue. For example, specific phytocompounds from *Dioscorea batatas* (DsCE-I) were shown to increase the promoter activities of nuclear factor kappa B (NF-κB)-inducible ELAM and GM-CSF promoter constructs and protect animals against certain test cancers (Su *et al.*, 2008). Another group of agents have been shown to have the potential to stimulate hematopoietic recovery in patients suffering from cytopenias resulting from disease- or therapy-related bone marrow suppression (Nelson and Ballow, 2003). For example, phytocompounds from *D. batatas* (DsCE-II) extracted using a different fractionation procedure was proposed as adjuvant therapy, to be used alongside chemotherapy (Su *et al.*, 2011b).

### C. VARIOUS IMMUNE CELLS INVOLVED IN THE IMMUNE RESPONSE

#### *1. Innate immune cells*

Innate immunity is the first line of host defence against malignant transformation and pathogen infection (Medzhitov and Janeway, 1997). In the inflammatory pathway shown in Fig. 2, the immune cells probably play a vital role in the components of sensors, mediators and effectors. Therefore, exploration and understanding of the roles of the various immune types in

the immune system and the underlying mechanisms and interactions in/between the cells related to pathogenesis to the immune-related disorders are critically important for developing immunotherapeutics or immunomodulator agents. As shown in Fig. 2, the innate immune mechanisms known to be involved in immunomodulation are orchestrated by an array of cells, including NK cells, NKT cells, γδ-T cells, macrophages, granulocytes (neutrophils, eosinophils and basophils) and DCs. Adaptive immunity is created by networking among B cells, naïve $CD4^+$ T cells, differentiated $CD4^+$ T cells including helper T cells (including Th1, Th2, Th17 cells), induced regulatory T cells (iTreg cells) and the natural regulatory T cells differentiated from thymus. The immune functions or dysfunction of some of the key immune cell types that play an essential role in various immune diseases are briefly described below.

Among cells involved in innate immunity, DCs not only act as front-line cells to confer phagocytosis and produce cytokines and chemokines against invading pathogens, but they are also the most specialized professional antigen-presentation cells (APCs) with a unique T-cell stimulatory ability that plays a vital role in the follow-up adaptive immune responses in most immune diseases. In general, APCs include DCs, macrophages and B cells, all of which play a crucial role in antigen presentation (Joffre *et al.*, 2009). They mature after encountering various "danger signals" and can initiate subsequent immune processes leading to activation of antigen-specific T-cell response. DCs are well known as key immune cells, as highlighted by the awarding of half the Nobel Prize in Physiology or Medicine 2011 to Ralph M. Steinman for his discovery of DCs and their role in adaptive immunity (Travis, 2011). Steinman demonstrated the presence of this new immune cell type in 1973.

Physiologically, DCs act as sentinels in peripheral tissues where they encounter invading pathogens or other danger signals in the course of an infection. PRRs on the DCs recognize general PAMPs from microbial signatures and enable DCs to detect these molecular species from different pathogens including bacteria and viruses. With binding of PAMPs to PRRs on DCs, this ligand–receptor activity can instigate DC activation and induction of the maturation process (Diebold, 2008; Reis e Sousa, 2001). During their maturation, DCs perform the uptake, processing and presentation of antigen-containing or antigen-expressing materials as epitopes from their environment (Mellman and Steinman, 2001). Immature DCs (iDCs) can usually pick up foreign materials from their environment, but they are inefficient in antigen presentation (Mellman and Steinman, 2001). Activity antigen processing and presentation from the ingested materials are only induced once DCs are activated and undergo maturation (Robson *et al.*, 2010). Particularly, since

recycling of these molecules and their passage through the endosomal class II-rich compartments cease upon DC activation, the levels of major histocompatibility complex class II (MHC-II) molecules on the cell surface are elevated (Petersen *et al.*, 2010). Consequently, DCs increase the levels of antigen at the cell surface and impart a snapshot of antigens derived from the target pathogen they encountered during infection. Subsequently, DCs cease to take up and process any new antigenic materials from their environment (West *et al.*, 2004). Further, the DC maturation process entails a change in the upregulation of co-stimulatory molecules such as CD40, CD80 and CD86 molecules on the DC surface which can act as maturation markers and in an increase in chemokine receptor expression level of CCR7 (Scandella *et al.*, 2004). Expression of CCR7 accompanied by inflammatory mediators such as prostaglandin E2 at the site of infection enables DCs to migrate from the inflamed tissue to the draining lymph node (Scandella *et al.*, 2004). Once they arrive in the draining lymph node, the activated DCs interact with naïve T cells. The key determinants of DC-derived signals that induce these interactions and immune response are the levels of antigen presentation (signal 1), the expression level of co-stimulatory molecules (signal 2) and the presence of immunomodulatory factors such as specific cytokines (signal 3) (Diebold, 2008).

Increased levels of antigen presentation and the expression of co-stimulatory molecules on DCs are very important for the expansion of antigen-specific T cells, whereas they are not sufficient for the induction of effector functions (Diebold, 2008). Immunomodulatory factors such as cytokines (signal 3) can determine the differentiation of expanded T cells into effector cells (Sporri and Reis e Sousa, 2005). The ability of DCs to induce differentiated effector functions in T cells enables the immune system to adjust its response to combat diverse classes of pathogens or stimuli. As shown in Fig. 2, the different cytokine expression patterns from DCs can help differentiate distinct forms of effector T cells or regulatory T cells. Dysfunction of DCs is involved in pathogenesis of a variety of immune diseases including type 1 diabetes, rheumatic disease, psoriatic arthritis, inflammation, microbial infection and cancer. Therefore, due to their various unique and multifacet features, DCs are a promising therapeutic target for skewing differentiation of T cells to treat a variety of immune diseases, especially cancers. We believe that a spectrum of phytochemicals, derived from plant secondary metabolites from traditional medicines, may be applicable for use as immunomodulators for regulating various DC functions. For instance, we showed that phytocompound mixtures extracted from the butanol fraction (BF) of a stem and leaf (S + L) extract of *Echinacea purpurea* ([BF/S + L/Ep]) can modulate DC mobility and related cellular physiology in mouse immune systems (Wang *et al.*, 2008a; Yin *et al.*, 2010).

Macrophages are other key players in the innate immunity system (Fig. 2). They are critical effectors and regulators of inflammation and the immediate arm of the immune system; they can, however, also confer antigen-presentation ability. They are the resident cells which perform phagocytosis in lymphoid and non-lymphoid tissues and are involved in steady-state tissue homeostasis via the clearance of cell debris from both apoptotic and necrosis cells, and the production of various growth factors (Geissmann *et al.*, 2010; Qian and Pollard, 2010). Macrophages can use a broad range of pathogen-recognition receptors (PPRs) to become efficient at phagocytosis and induce production of pro-inflammatory cytokines. Timely and efficient production of pro-inflammatory cytokines and nitrogen species as well as extensive production of reactive oxygen from macrophages may serve as protective mechanisms. Different types of macrophages have been recently characterized according to their functional participation in particular immunological responses (Qian and Pollard, 2010). The ''activated'' macrophages (M1) are defined as cells involved in the responses of type I helper T (Th1) cells to pathogens such as bacteria. This population is activated by IFN-γ and engagement of TLRs and has the characteristics of elevated expression level of MHC-II, production of IL-12 and TNF-α, generation of nitric oxide (NO) and ROS and the ability to kill pathogens and undesirable or stressed host/endogenous cells. In contrast, ''alternatively activated'' macrophages (M2) that can differentiate in response to IL-13 and IL-4 play a key role in Th2-type responses, including wound healing and humoral immunity (Qian and Pollard, 2010). The developmental origin and the function of tissue macrophage subsets are very diverse and include microglia, dermal macrophages and liver macrophages (Kupffer cells). These cells remain poorly understood (Qian and Pollard, 2010). Nonetheless, it has been shown that they do play an important role in sepsis, inflammation, liver disease, obesity and cancers (Qian and Pollard, 2010). The use of phytomedicines as immunomodulatory agents for treating macrophage-related immune diseases may be a promising approach for developing new generation of therapeutics. Taking specific phytocompounds as examples, we showed that shikonin selectively inhibits the expression of TNF-α at the mRNA splicing level (Chiu and Yang, 2007) and also significantly inhibits the early mRNA expression of inflammatory cytokines including TNF-α, IL-1β and IL-4 and chemokines CCL4 and CCL8 (Chiu *et al.*, 2010). Caffeic acid derivatives, ethyl caffeate, a natural phenolic compound isolated from *Bidens pilosa* plant, markedly suppressed lipopolysaccharide (LPS)-induced NO production, mRNA and protein expression of inducible nitric oxide synthase (iNOS), and PGE2 production in RAW 264.7 macrophages and significantly inhibited the TPA-induced COX-2 expression in mouse skin tissues (Chiang *et al.*, 2005).

NK cells are known as effector lymphocytes of the innate immune system and control various types of tumour growth and microbial infection mechanistically by limiting their spread and subsequent tissue damage (Vivier *et al.*, 2008). NK cells have a number of traits in common with $CD8^+$ T cells (Sun *et al.*, 2009b). Recent studies have shed light on a new role for NK cells in different immune responses, suggesting that these innate lymphocytes have the characteristics of both innate and adaptive immunities (Cooper *et al.*, 2009; Vivier *et al.*, 2011). Activation of NK cells through NKG2D can result in cytotoxicity and cytokine production. This activation may be triggered by the disappearance of class I MHC molecules from the cell surface of tumour cells or by exposure to antigens such as MHC class I-related chains A and B (MICA and MICB), which are NKG2D ligands. Their expression is induced by DNA damage in tumour cells (Garg *et al.*, 2010). Phytochemical-derived medicines may prove to be the highly useful resources for developing immunomodulatory agents for controlling NK cell activity. For example, oral administration of the total flavones and polysaccharides of *Epimedium* at doses of 240 mg/kg for 30 days was shown to significantly enhance the activities of NK cells in aged rats (Ma *et al.*, 2011). Another study indicated that the aqueous extract of *Nigella sativa* can significantly enhance NK cytotoxic activity against specific cancer cells, suggesting that the documented anti-tumour effects of *N. sativa* may be in part due to its ability to stimulate NK anti-tumour activity (Majdalawieh *et al.*, 2010).

Natural killer T cells (NKT cells) are lipid antigen-reactive, CD1d-restricted, immunoregulatory T lymphocytes that can enhance cell-mediated immunity against infectious organisms such as bacteria and some self or endogenous antigenic determinants as from tumours (Godfrey *et al.*, 2010). The invariant natural killer T (iNKT) cells are a subset of αβ T-cell receptor $(\alpha\beta TCR)^+$ T cells which are restricted by CD1d molecules. They can modulate the activities of DC cells and B cells and can increase DC-induced B- and T-cell responses. The iNKT cells can amplify TLR-derived signals. It is thought that combinations of specific compounds that can activate iNKT cells may provide a formulation that could serve as a vaccine adjuvant (Cerundolo *et al.*, 2009). In addition, iNKT cells express an invariant T-cell receptor α chain that recognizes glycolipid antigens presented by CD1d molecules present on the surface of tumour cells, allowing receptor/ligand action NKT cells to subsequently elicit their anti-tumour effects primarily via secretion of IFN-γ and directly effect cytotoxicity. iNKT cells are recognized as a unique population of T cells with immunomodulatory properties that can link innate and adaptive immune responses (Cerundolo *et al.*, 2009; Godfrey *et al.*, 2010).

*2. Adaptive immune cells*

The adaptive immune system includes two major types of lymphocytes, T cells and B cells, that are made up of several subsets (Fig. 2). B cells can differentiate into plasma cells that secrete antibodies. T lymphocytes or T cells are further divided into two classes, $CD4^+$ T cells and $CD8^+$ T cells (Janeway, 2005). $CD8^+$ T cells can differentiate into cytotoxic T cells, which kill virus-infected cells and tumour cells, whereas $CD4^+$ T cells differentiate into different subsets of $CD4^+$ T cells which can activate other cell types for execution of specific immune functions.

B lymphocytes are required for the induction of effective antibody-based immunity following pathogen challenge. The antibody response of B cell-mediated humoral immunity can be activated by T-helper cell type-2 (Th2 cells). Currently available vaccines have been mostly developed to explore the specificity of antibodies produced by B lymphocytes, for protection against diseases such as diphtheria, tetanus, hepatitis, measles and pneumococcal and meningococcal infections (Makela, 2000). Phytocompounds, phytochemicals or phytoextracts which can regulate B-lymphocyte effector functions have the potential to be employed as a useful tool for the maintenance of protective immunity; however, the efficacy of specific vaccines is currently limited. For example, Quan *et al*. (2007) reported that the intranasal co-administration of inactivated influenza virus A and *Panax ginseng* on days 0 and 14 significantly increased the levels of influenza virus-specific IgG in the serum as compared to that control in mice, possibly due to high saponin content. In this study, *P. ginseng* was shown to elevate the mouse lung IgA level at 15 days post-challenge with influenza virus, suggesting that phytochemicals from *P. ginseng* can apparently modulate systemic and mucosal immunity and may act as a powerful mucosal adjuvant for vaccination.

$CD8^+$ T cells (cytotoxic T lymphocytes, CTLs) are very potent professional killers, particularly important for protection against virus-infected cells and tumour cells. Some reports suggest that one single activated CTL cell can eliminate hundreds of target tumour cells (Garg *et al*., 2010). Previous studies also showed that oral administration of *S. cerevisiae*-derived β-glucan in mice elevated the levels of $CD8^+$ intraepithelial lymphocytes (IELs) in comparison with control mice (Tzianabos, 2000).

$CD4^+$ T cells are the major orchestrators and conductors of the adaptive immune response. Upon interaction with antigen-presenting cells such as DCs, naïve CD4+ T cells can differentiate into a variety of effector subsets, including the classic T-helper cells (Th1 and Th2 cells), as well as recently defined Th17 cells and inducible regulatory T (iTreg) cells (Zhou *et al*., 2009), as described in Fig. 2. Differentiation is determined predominantly by the specific cytokines present in the microenvironment and by the strength of the

interaction between the T cell antigen receptor and target antigen (Sakaguchi *et al.*, 2008). Traditionally, Th1 cells produce IFN-γ and contribute to cellular immunity against intracellular microorganisms such as bacteria. IL-12 is effectively produced by innate immune cells such as DCs, and the IFN-γ produced by both T cells and NK cells can skew the polarization of cells towards Th1 cell differentiation through action of T box transcription factor (T-bet). Th2 cells can produce cytokines IL-4, IL-5 and IL-13, which are essential for humoral immunity in control of infection from helminths and other extracellular pathogens. Th2 cell differentiation attributes to the action of GATA3, which occurs downstream of IL-4 action. Th17 cells can produce IL-17A, IL-17F and IL-22, and they play vital roles in clearance of extracellular fungi and bacteria, especially in mucosal immunity (Medzhitov *et al.*, 2011). Th17 cell differentiation is mediated by retinoid-related orphan receptor (ROR)γt, a transcription factor that is activated by TGF-β in combination with the pro-inflammatory cytokines such as IL-6, IL-23 and IL-21 (Sakaguchi *et al.*, 2008). Regulatory T (Treg) cells are characterized by the expression of Forkhead box P3 $(FOXP3)^+$ genes and can be classified into two categories: iTreg cells differentiated from naïve $CD4^+$ T cell and natural Treg (nTreg) cells that arise from the thymus. Aberrant control or malfunction of Th1 and Th17 cell responses may contribute to organ-specific autoimmunity, whereas Th2 cells contribute to atopy, allergy and asthma. Treg cells play crucial roles in regulating these effector T cell responses, thereby preventing the body from potential pathogenic effects (Sakaguchi *et al.*, 2010). Various phytochemicals, phytocompounds or phytoextracts from traditional medicines may be of use to maintain or optimize our immune system via the modulation of the different subsets of helper T cells. For instance, *Tripterygium wilfordii* Hook. F (TWHF) has been evaluated for treating autoimmune diseases including rheumatoid arthritis (RA). Triptolide, the diterpene purified from this plant, was shown to inhibit peripheral $CD4^+$ T lymphocytes but increase $CD8^+$ T lymphocyte in Peyer's patches of mice in a collagen-induced mouse arthritis model (Zhou *et al.*, 2006).

## III. MEDICINAL HERBS WITH IMMUNOMODULATORY ACTIVITIES

Five medicinal herbs have been selected in this section for detailed review. All have a long history of human use as traditional or folk medicines. Echinacea was a top-selling herbal remedy in the USA between 1995 and 2005 and has been used as a traditional medicine or nutraceutical in the

USA and Europe for decades or perhaps centuries. The other four medicinal plants have been extensively used in TCM or Taiwanese traditional medicine as single herbs or in formulation with other herbs for specific indications. Evidence accumulated from a series of studies by our group (Chiu *et al*., 2010; Wang *et al*., 2006, 2008a,b; Yin *et al*., 2010) has demonstrated the immunomodulatory activities of *E. purpurea*, *Lithospermum erythrorhizon* and *D. batatas* through *in vitro* and *in vivo* biological assay systems using transgenic and omics research approaches. Artemisinin from *Artemisia annua* has recognized benefit and use in the treatment of malaria, and Dr. Tu recently won the 2011 Lasker Award in medical research for her findings relating to the plant (Tu, 2011). The research revealed the importance of *A. annua* phytochemicals not only for use in malaria but also for its potential application in inflammatory diseases (Tu, 2011). *T. wilfordii* Hook. F has been traditionally used for treating autoimmune diseases including RA (Brinker and Raskin, 2005; Tao *et al*., 2008). One of its well-known bioactive components, triptolide, has been shown to possess a strong immunosuppressive effect and has the potential to treat a series of autoimmune diseases.

### A. *ECHINACEA PURPUREA*

*Echinacea* is a top-selling herbal remedy in the United States. It has been claimed to confer high immunostimulatory activity by acting as an immunopromoter (Ernst, 2002). It is reputed to alleviate respiratory infections and colds, including sore throats, coughs and other symptoms (S *et al*., 2011). *Echinacea angustifolia*, *Echinacea pallida* and *E. purpurea* are the three major species used in traditional medicine or nutraceutical applications in the United States and Europe (Borchers *et al*., 2000). The most common constituents of *Echinacea* are alkamides, caffeic acid derivatives (shown in Fig. 4), polysaccharides and lipoproteins (Pietta *et al*., 1998). The active components present in *Echinacea* may vary due to differences in plant age and organ portion, agricultural conditions, geographical location and tissue extraction methods (Perry *et al*., 2001).

An accumulating number of studies have reported the effects of *E. purpurea* from the perspective of immune functions and systems (Brush *et al*., 2006; Mishima *et al*., 2004). The most frequently reported pharmacological activities of *Echinacea* are the activation of macrophages and polymorphonuclear neutrophils immune cells (Goel *et al*., 2005; Sullivan *et al*., 2008). A recent study has shown that macrophage phagocytosis and NK cell activities can be strongly activated after *ex vivo* exposure of these cells to *E. purpurea* extracts (See *et al*., 1997). Reports of increased macrophage phagocytic activity from mouse liver and spleen following oral administration of *E. purpurea* extract

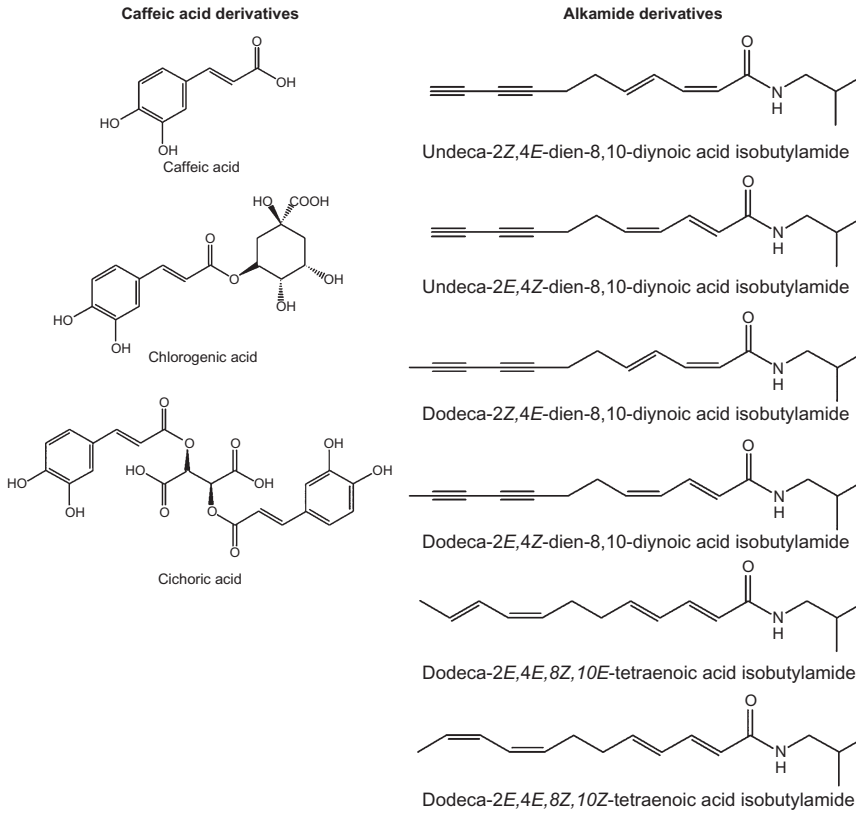



Fig. 4. Chemical structures of caffeic acid derivatives and alkamide derivatives from *Echinacea purpurea*.

have been shown to result in enhanced expression of cytokines including TNF-α, IL-1α, IL-1β, IL-6 and IL-10, and NO production (Rininger *et al.*, 2000). It was also determined that *E. purpurea* extract enhanced phagocytic activity in human peripheral blood mononuclear cells (Rininger *et al.*, 2000). Most recently, Sasagawa *et al.* (2006) found that low concentrations of the ethanolic extracts obtained from aerial portions of *E. purpurea* suppressed the ability of activated T cells to express IL-2, a key cytokine involved in the early phase of Jurkat T-cell activation. Moreover, a recent study reported that differential expression of key accessory molecules was detected in polysaccharide-enriched *E. purpurea* root extract and the ethanolic, alkamides-enriched *E. purpurea* leaf extract (Benson *et al.*, 2010). The *E. purpurea* root extract increased the expression of MHC class II, co-stimulatory markers (CD86 and CD54) and pro-inflammatory cytokines (IL-6 and TNF-α), while the

*E. purpurea* leaf extract decreased the expression of the tested markers and cytokines, suggesting that the root extract and leaf extract from the same *E. purpurea* plant stimulated and inhibited immune activities, respectively (Benson *et al.*, 2010). Similar effects were also observed in our investigation of the immunomodulatory effects of *E. purpurea* extracts on human monocyte-derived DCs and mouse bone marrow-derived DCs (Wang *et al.*, 2006, 2008a). We employed a chemically defined *E. purpurea* extract, termed [BF/S + L/Ep], containing hypoxanthine, chlorogenic acid, caffeic acid, cichoric acid, quercetin-3-*O*-rhamnosyl-(1–6)-galactoside, kaempferol-3-*O*-rhamnosyl-(1–6)-galactoside and rutin as index compounds (Wang *et al.*, 2008a). Our findings suggested that the [BF/S + L/Ep] phytochemical mixture was able to modulate cell adhesion-, cell mobility-, cytokine- and NF-κB signalling-related activities in primary cultures of mouse DCs, and it could also enhance the mobility of DCs to target specific lymphoid tissues in test mice in *in vivo* trafficking experiments (Yin *et al.*, 2010). These studies were performed using a network knowledge-based approach to analyse the genome-wide transcriptome activity *in vitro* and *in vivo*, and to correlate specific proteome activities and special functional genomic phenotypes in test cells (Wang *et al.*, 2006, 2008a). Further, we also showed that the alkamides can play an important role in anti-inflammatory activities of *Echinacea*, as revealed by comparative metabolomics approaches and cell- and gene-based assays (Hou *et al.*, 2010). Further, the possible receptors, cannabinoid (CB1 and CB2), were reported to mediate the bioactivities and pleiotropic effects of *E. purpurea* by manipulating the endocannabinoid system through molecular targeting to receptors, endocannabinoid transport and degradation (Chicca *et al.*, 2009; Hohmann *et al.*, 2011).

The harvest of medicinal herbs from different regions and at different periods of the year has been shown to play a role in the quantity of bioactive components found in plants and their associated pharmacological activities (Jia and Zhao, 2009; Liu *et al.*, 2007b). With *E. purpurea*, for example, plant extracts have been found to display differential profiles and varied amounts of phenolic compounds including caffeic acid, cichoric acid, chlorogenic acid and alkamides, in different seasons and months of plant growth and/or year of harvesting, and sometimes according to different post-harvest treatment (Hou *et al.*, 2010; Liu *et al.*, 2007b). Since some of the phytochemicals of this plant are bioactive components contributing to the immunomodulatory activities of *E. purpurea*, the differential amounts of these components may result in distinguishable biological effects.

Functional and comparative genomics analysis of the cellular and immunological effects of different anti-inflammatory phytoextracts or phytocompounds, especially via microarray analysis, is recognized as a promising

approach to distinguish the complex and specific bioactivities of candidate phytomedicines (Chiu *et al.*, 2010; Wang *et al.*, 2008a,b). However, combining this with other sets of data on protein expression such as proteomics or Western blot analyses is critically important for verification of the transcriptome result. For example, Wang *et al.* and her colleagues investigated the specific and differential gene expression in human iDCs in response to treatment with a BF containing defined bioactive phytocompounds extracted from the stems and leaves of *E. purpurea*, denoted as [BF/S + L/Ep] (Wang *et al.*, 2008a,b). The results from Affymetrix DNA microarray showed significant upregulation of specific genes for cytokines (IL-1β, IL-8 and IL-18) and chemokines (CCL-2, CCL-5 and CXCL-2) within 4 h after [BF/S + L/Ep] treatment of iDCs. Bioinformatics analysis of genes expressed in [BF/S + L/Ep]-treated DCs showed a key signalling network involving a number of immunomodulatory molecules, possibly leading to the activation of a downstream molecule, adenylate cyclase 8. Confirmed with proteomic analysis, results also showed upregulation of antioxidant defence enzymes such as Mn-SOD and downregulation of cytoskeletal proteins such as cofilin after treatment with [BF/S + L/Ep] and cichoric acid. These data were further verified by Western blot analyses.

### B. *DIOSCOREA BATATAS*

*Dioscorea* species are widely used plants not only in Eastern traditional medicine but also in modern Western medicine. *D. batatas* (yam), which is widely distributed in East Asia, has long been used as a supplement as a major source of steroid precursors (Li and Ni, 2011) or prescribed to treat poor appetite, chronic diarrhoea, asthma, frequent or uncontrollable urination, diabetes and even emotional instability (Hou *et al.*, 2002). Several active components in tubers of *D. batatas* have been shown to exhibit immunomodulatory activities (Oh and Lim, 2009; Su *et al.*, 2011b). These phytochemicals include mucopolysaccharide, dioscorin, diosgenin (Fig. 5), batatasins and glycoproteins.

Dioscorin, a tuber protein, has been shown to exhibit systemic and mucosal immunomodulatory activities *in vivo* after oral administration (Liu *et al.*, 2009). Dioscorins, the storage protein of *D. batatas* tuber, can enhance the proliferation of $CD4^+$, $CD8^+$ and $CD19^+$ cells in spleen (Lin *et al.*, 2009). Dioscorin also can act as a TLR4 activator and induce macrophage activation via the typical TLR4-signalling pathways via stimulation of multiple signalling molecules (NF-κB, ERK, JNK and p38) and induction of the expression of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) (Fu *et al.*, 2006). The mucopolysaccharide in *D. batatas* can significantly

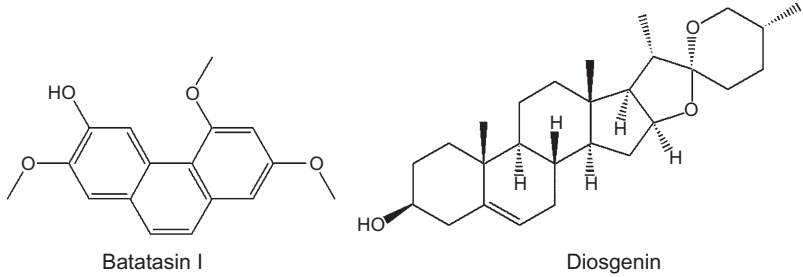



Fig. 5. Chemical structures of diosgenin and batatasin I from *Dioscorea batata*.

increase IFN-γ production in treated splenocytes, suggesting that it may induce cell-mediated immune responses (Choi *et al*., 2004). Besides, these mucopolysaccharides (50 μg/ml) were found to increase the uptake capacity and lysosomal phosphatase activity of test peritoneal macrophages (Choi *et al*., 2004). Batatasin I (Fig. 5), with a well-identified structure of 6-hydroxy-2,4,7-trimethoxyphenanthrene, was shown to inhibit the generation of prostaglandin D2 and leukotriene C4 and degranulation activity in mouse bone marrow-derived mast cells (Lu *et al*., 2011c). Some glycoproteins in *D. batatas* were shown to inhibit the expressions of IL-4 and IL-10 through modulation of GATA-3, STAT-6, p44/42 MAPK and p38 MAPK in mouse lymphocytes (Lin *et al*., 2009), leading to the possibility that glycoproteins in such plants may be usefully applied for use as nutraceuticals or health supplements for prevention of Th2-mediated immune disorders (Oh and Lim, 2009). In addition, *Dioscorea* glycoproteins significantly increased the trafficking of macrophages, lymphocytes, neutrophils and monocytes into the peritoneal cavity (Huong *et al*., 2011). Further, in addition to significant enhancement of proliferation of T cells and B cells in splenocytes of glycoprotein-treated mice, the non-specific cytolytic activity of NK cells and macrophages was significantly increased (Huong *et al*., 2011). These glycoproteins also can stimulate specific immune system functions, including macrophage activation via increasing the expression levels of iNOS, IL-1β and TNF-α (Huong *et al*., 2011). In our previous study, we found that a fraction of the *D. batatas* tuber extract significantly increased the GM-CSF promoter activity in normal and inflamed skin tissues (Su *et al*., 2008). Our previous study reported that a 50–75% ethanol-partitioned fraction of the tuber extract of *D. batatas* (DsCE-II) may confer immunogenic activities (Su *et al*., 2011b). DsCE-II contained polysaccharides with a high abundance of 1,4-linkage mannose (64%), which can preferentially promote the regeneration of CFU-GM cells in damaged bone marrow tissues in

5-fluorouracil-treated mice fed with DsCE-II (Su *et al.*, 2011b). DsCE-II efficacy level for bone marrow cell restoration was ~85% of that obtained by a subcutaneous administration of recombinant G-CSF proteins (5 μg/kg) in mice tested in parallel, suggesting that the DsCE-II fraction of *D. batatas* extract may be useful for further development as a dietary supplement for use alongside chemotherapy during cancer treatment (Su *et al.*, 2011b). Recently, we have also obtained results indicating that DsCE-I may be employed as an adjuvant for gene-based or protein subunit cancer vaccines (Yang *et al.*, 2011). In addition, the ethanol extract of bark of *D. batatas* was identified to confer anti-inflammatory bioactivity through inhibition of iNOS and COX-2 expression in RAW 264.7 cells, apparently via NF-κB and ERK1/2 inactivation (Jin *et al.*, 2010).

### C. *ARTEMISIA ANNUA*

*A. annua* is an ancient Chinese medicine still in common use today. It has long been utilized to treat malarial and autoimmune diseases, including systemic lupus erythematosus and RA (Christen and Veuthey, 2001). As shown in Fig. 6, artemisinin, also known as qinghaosu, was identified as

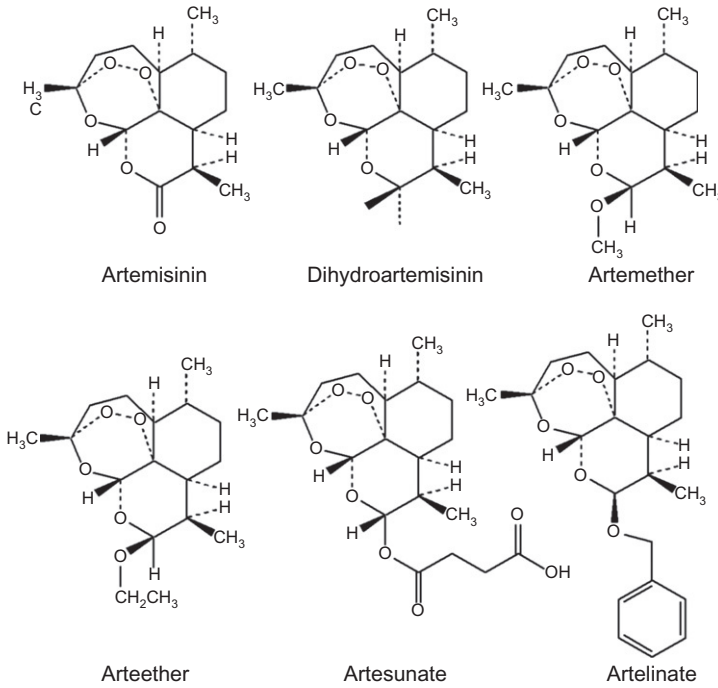



Fig. 6. Chemical structures of artemisinin and its derivatives.

the major active compound isolated from *A. annua* (Christen and Veuthey, 2001). Artemisinin is a sesquiterpene trioxane lactone, and its chemical structure contains a peroxide bridge, considered to be critical for its bioactivity and unique among antimalarial drugs (van Agtmael *et al.*, 1999). From the perspective of drug metabolism, artemisinin is primarily converted to inactive metabolites, while its derivatives, namely, artesunate, artelinate, artemether and arteether, can serve as parent compounds all exhibiting a very short half-life ($<10$ min), and be converted to the highly potent active metabolite, dihydroartemisinin (DHA), which has a much longer half-life ($\sim 1$ h) (Balint, 2001). The antimalarial mechanisms of artemisinin were shown to involve the interference of parasite transport proteins that can disrupt the function of parasite mitochondria, and most important, modulate the host immune response function (Golenser *et al.*, 2006).

Currently, the first-line antimalarial treatment for *Plasmodium falciparum* recommended by the World Health Organization (WHO) is the artemisinin combination therapy (Reyburn, 2010). Several such therapeutic approaches have been developed, for example, the formulation of one of artemisinin-derived phytochemical and one clinically therapeutic antimalarial drug, such as the combination of artemether and lumefantrine (Olliaro and Taylor, 2004). Artemisinin has also been reported to suppress LPS-induced proteolytic degradation of IκB, the translocation of NF-κB, and thus inhibit iNOS transcription, leading to the blockade of NO synthesis (Aldieri *et al.*, 2003). Artemisinin, artesunate and DHA were shown to enhance DNA synthesis by treatment with alloantigens or Con A and increase IL-2 production in mouse splenocytes, indicating that artemisinin and its derivatives may selectively promote T-cell function and accelerate immune reconstitution. These activities may be applicable for future therapy for the restoration of immune function (Yang *et al.*, 1993). Artemisinin has also been reported to inhibit the protein expression of p65 unit of NF-κB, the mRNA expression of NF-κB and TGF-β 1 and the levels of TNF-α and IL-6 in test mice with lupus nephritis, suggesting that artemisinin may be a reliable and effective treatment for lupus nephritis (Wu *et al.*, 2010). Artemisinin can also reduce angiotensin II-induced cardiac hypertrophy via inhibition of the NF-κB binding activity, and the mRNA expression levels of IL-6, TNF-α and MCP-1 (Xiong *et al.*, 2010). Artemisinin was also reported to prevent atherosclerosis via an inhibition of activation of THP-1 monocytes (Wang *et al.*, 2011b). Recently, artemisinin and its derivatives have been found to inhibit generation of NO in the RAW 264.7 mouse macrophage cell line (Konkimalla *et al.*, 2008). Among the compounds studied, artesunate showed the highest NO inhibition activity. Microarray analyses showed that the effects of artesunate in macrophages are associated mainly with NO metabolism and signalling (Konkimalla *et al.*, 2008).

### D. *TRIPTERYGIUM WILFORDII*

TWHF, sometimes named leigongteng (thunder god vine) from the Chinese, is another member of the traditional Chinese pharmacopoeia. The portion of TWHF plant in empirical TCM use is the debarked root, which has been anecdotally used for treating autoimmune diseases including RA, immune complex nephritis, systemic lupus erythematosus, organ transplantation; it has and even been used as an anti-cancer agent (Brinker and Raskin, 2005; Tao *et al.*, 2008). Starting in the 1970s, a series of TWHF-associated products claimed to have high therapeutic value were developed, patented and commercialized. Leigongteng was developed as a multi-glycoside tablet. A number of triterpenes, diterpenes and macrocyclic alkaloids have been identified as secondary metabolites from TWHF plant (Brinker and Raskin, 2005). Triptolide ($C_{20}H_{24}O_6$), a diterpene triepoxide, is the most well-studied component derived from TWHF and was the first recognized diterpenoid triepoxide containing an 18(4+3) abeoabietane skeleton shown in Fig. 7 (Kupchan *et al.*, 1972). Triptolide has been reported to exhibit multiple pharmacological activities including anti-inflammatory (Krakauer *et al.*, 2005), anti-neoplastic, proapoptotic (Antonoff *et al.*, 2009) and anti-angiogenic properties (Zhu *et al.*, 2010). Triptolide can suppress TLR-induced NF-κB activation and downregulate TLR4 and TRIF proteins (Premkumar *et al.*, 2010). Triptolide also can ameliorate Th1-mediated chronic colitis and the disordered immune state in IL-10(−/−) mice (Wei *et al.*, 2008). Triptolide has been shown to suppress the nuclear concentration of NF-κB and the secreted levels of IL-17, IL-21 and IFN-γ in parallel, showing greater potency in Th17 cells from young mice as opposed to older mice (Huang *et al.*, 2008). In addition, the triptolide-mediated inhibition of LPS-induced activation of PI3K/Akt and NF-κB was found to involve the downregulation of COX-2 and CCR7 expression resulting in impaired migration to secondary lymphoid organs of test DCs (Liu *et al.*, 2007a).

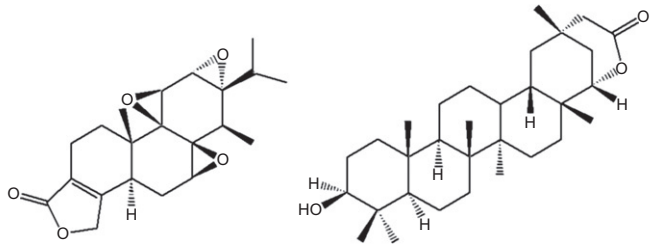


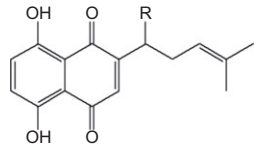

Fig. 7. Chemical structures of triptolide and wilforlide A from *Tripterygium wilfordii*.

Triptolide can inhibit staphylococcal exotoxin-stimulated T-cell proliferation and the expression of IL-1β, IL-6, TNF, IFN-γ, MCP-1, MIP-1α and MIP-1β in human PBMCs (Krakauer *et al*., 2005). Previous studies showed that triptolide inhibited the secretion of RANTES, TARC and IP-10 from LPS-stimulated DCs, resulting in impaired DC-mediated chemoattraction of neutrophils and T cells under both *in vitro* and *in vivo* test conditions (Liu *et al*., 2006b). Triptolide, at a high concentration, was also observed to induce apoptosis of DCs through sequential activity in p38 MAP kinase phosphorylation and caspase-3 activation (Liu *et al*., 2004). It decreased the expression of CD80 and CD86 and the secretion of IL-12p40 and IL-12p70 in THP-1 cells leading to impaired antigen-presenting functions (Liu *et al*., 2004). In Jurkat T cells, triptolide inhibited phorbol myristate acetate (PMA)/Iono-stimulated IL-2 transcription through regulation of purine-box/antigen receptor response element (ARRE)/nuclear factor of activated T cells (NF-AT) and NF-κB transcriptional activation (Qiu *et al*., 1999). In a functional genomics study, triptolide treatment affected the expression of 22.5% of 195 immune signalling genes (Premkumar *et al*., 2010). Shao *et al*. (2004) further provided evidence that triptolide could significantly attenuate TNF-α-induced COX-2, iNOS, PGE2 and NF-κB and suppress the subsequent NO production in human RA synovial fibroblasts (Shao *et al*., 2004). Triptolide ameliorated the clinical signs of experimental autoimmune encephalomyelitis by induction of heat shock protein 70 and stabilization of NF-κB/IκBα transcriptional complex (Kizelsztein *et al*., 2009). Triptolide also significantly reduced the inflammatory responses and cartilage damage in the joint tissues in test mice with collagen-induced arthritis (CIA), apparently by interfering with the CIA-induced expression of matrix metalloproteinase (MMP)-13 and -3 and by augmenting tissue inhibitors of metalloproteinases (TIMP) 1 and 2 (Lin *et al*., 2007). Triptolide significantly inhibited the generation of Th17 cells from murine splenocytes and purified $CD4^+$ T cells in a dose-dependent manner via inhibition of the transcription of IL-17 mRNA and the IL-6-induced phosphorylation of STAT3 (Wang *et al*., 2008b). Further, triptolide effectively inhibited the expression of IFN-γRα, pJak2, pSTAT1 and ICAM-1 in HaCaT cells (Hongqin *et al*., 2011). IL-12 and IL-23 produced by antigen-presenting cells are known as key factors for the generation and function of Th1 and Th17 cells, respectively, and they have been strongly implicated in the pathogenesis of a number of autoimmune disorders (Wei *et al*., 2011). Triptolide was able to inhibit the expression of the *p40* gene at the transcriptional level in part through the activation of CCAAT/enhancer-binding protein-α (C/EBPα), thus inhibiting p40 expression (Zhang and Ma, 2010). Triptolide can activate the transcription of C/EBPα and enhance the phosphorylation

of Ser21 and Thr222/226 which are critical for C/EBPα inhibition of p40 (Zhang and Ma, 2010). C/EBPα activation by triptolide is dependent on the upstream kinases ERK1/2 and Akt-GSK3β activities (Zhang and Ma, 2010). Triptolide also inhibited the migration of lymphoma cells to lymph nodes *in vitro*, and blockage of the SDF-1/CXCR4 axis by triptolide may contribute to a potential anti-metastatic effect (Zhang *et al.*, 2006). Triptolide also effectively blocked the induction of miR-155 RNA (Matta *et al.*, 2009). Wilforlide A (Fig. 7), another tripterygium glycoside, has also been found to confer efficacious anti-inflammatory and immune suppressive activities in carrageenan-induced rat pedal swelling and tampon-induced rat granulation models (Xue *et al.*, 2010).

### E. *LITHOSPERMUM ERYTHRORHIZON*

The dried root of *L. erythrorhizon*, known as zicao or purple gromwell and referred to as *shikon* in Japanese, is a commonly used traditional Chinese herbal medicine in China and Taiwan (Novosel'tseva *et al.*, 1979). It has been used for thousands of years for treatment of macular eruptions, measles, smallpox, eczema, carbuncles and burns (Novosel'tseva *et al.*, 1979). Shikonin and its derivatives are the primary active components isolated from root tissues of the traditional Chinese medicinal herb *L. erythrorhizon* and have recently garnered considerable interest for their broad spectrum of anti-inflammatory activities and significant anti-tumour activities (Chen *et al.*, 2002; Staniforth *et al.*, 2004; Su *et al.*, 2008). The chemical structure of shikonin and its derivatives are shown in Fig. 8. In this section, we focus on the primary active compound, shikonin. Our previous study showed that shikonin drastically suppressed the transcriptional activity of GM-CSF promoter by inhibiting the binding of the TFIID protein complex to the TATA box (Su *et al.*, 2008). In addition, shikonin effectively inhibited the promoter/transcriptional activity of the pro-inflammatory cytokine TNF-α (Staniforth *et al.*, 2004). Interestingly, at a relatively low concentration (0.1 μM), shikonin also specifically blocked the splicing of TNF-α pre-mRNA (Chiu and Yang, 2007). Shikonin can further confer a drastic and acute effect in human monocytes at the genomic and proteomic levels (Chiu *et al.*, 2010). We demonstrated that shikonin significantly inhibited the early expression (within 0.5 h) of approximately 50 genes, notably cytokines TNF-α, IL-1β and IL-4, chemokines CCL4 and CCL8 and inflammatory modulators NFATC3 and PTGS2 (Chiu *et al.*, 2010). Previous studies from others have shown that shikonin can possess multiple pharmacological properties such as anti-tumour (Lee *et al.*, 2008; Min *et al.*, 2008), antioxidant (Wang *et al.*, 2010), anti-platelet (Ko *et al.*, 1995) and anti-atherosclerosis




| Compound | R |
|---|---|
| Deoxyshikonin | H |
| Shikonin (*R*) or Alkanin (*S*) | OH |
| Acetylshikonin | $OCOCH_3$ |
| Isobutylshikonin | $OCOCH(CH_3)_2$ |
| β,β-Dimethylacrylshikonin | $OCOCH{=}C(CH_3)_2$ |
| Isovalerylshikonin | $OCOCH_2CH(CH_3)_2$ |
| α-Methyl-*n*-butylshikonin | $OCOCH(CH_3)CH_2CH_3$ |
| β-Hydroxyisovalerylshikonin | $OCOCH_2C(CH_3)_2(OH)$ |

Fig. 8. Chemical structures of shikonins from *Lithospermum erythrorhizon*.

(An *et al*., 2007) activities. More recently, it has been reported that the anti-tumour effects of shikonin may be due to its induction of ROS (Chang *et al*., 2010; Mao *et al*., 2008), inhibition of proteasome activity (Yang *et al*., 2009) and the circumvention of cancer drug resistance via induction of necroptosis (Han *et al*., 2007). Shikonin is also considered as a potential drug for treating allergic diseases by inhibition of PMA + cAMP-induced IL-4 and IL-5 expression through downregulation of the expression of GATA-3 and Maf (Lee *et al*., 2011). Shikonin significantly prolonged the survival and recovered or increased numbers of $CD3^+$ and $CD19^+$ cells (Long *et al*., 2011). Other study suggests that the anti-inflammatory effect of shikonin may be due to its proteasome inhibitory activity, resulting in accumulation of IκB-α and ubiquitinated proteins and blockage of p65-NF-κB translocation from the cytoplasm to the nucleus. Further, shikonin was also shown to induce apoptosis and cell death in rat primary macrophage cultures (Lu *et al*., 2011b). Other reports have revealed that the wound-healing activity of shikonin could result in active proliferation of fibroblasts, an increase in the collagen fibre levels of granuloma tissues and an increase in $CD11b^+$ cell population in granulation tissues (Kaith *et al*., 1996; Sakaguchi *et al*., 2001). Accumulating evidence showed that shikonin may serve as a naturally occurring, low-molecular-weight pan-chemokine receptor inhibitor for CCL1, CCL2, CCL3, CCL5, CXCL12 and C5a (Chen *et al*., 2001, 2002; Chiu *et al*., 2010). Shikonin downregulated surface expression of CCR5, a

primary HIV-1 co-receptor, constituting a basis for the development of novel anti-HIV therapeutic agents (Chen *et al.*, 2003). These findings collectively and strongly suggest that shikonin may confer a spectrum of cellular and molecular activities that can induce specific chemokines and subsequent chemotaxis activities in various and specific immune-responsive cell types.

Recently, it was shown that shikonin may be involved in the inhibition of acetylcholine-induced aorta relaxation response and NO generation in RAW 264.7 cells (Yoshida *et al.*, 2010). Shikonin also downregulated the expression of SREBP-1c and the subsequent expression of PPARγ and C/EBPα, resulting in downregulation of lipid metabolizing enzymes and reduced fat accumulation (Lee *et al.*, 2010b). Shikonin effectively suppressed the maturation of OVA and thymic stromal lymphopoietin-induced bone marrow DCs *in vitro* via downregulation of IL-4, IL-5, IL-13 and TNF-α, and it inhibited allergic inflammation and AHR in a murine model of asthma (Lee *et al.*, 2010a). In addition, shikonin may also be further evaluated for its potential therapeutic effect on allergic asthma by blocking histamine release from human basophils via suppression of Syk-dependent phosphorylation and inhibition of leukotriene B4 and 5-hydroxyeicosatetraenoic acid (Takano-Ohmuro *et al.*, 2008). Shikonin also significantly inhibited the expression of MMP-1 and upregulated TIMP-1 in mice with CIA, suggesting that shikonin could be developed as a candidate cartilage protective medicine for RA (Dai *et al.*, 2009; Kim *et al.*, 2010).

## IV. CATEGORIZED PHYTOCOMPOUNDS WITH IMMUNOMODULATORY ACTIVITIES

Natural product-derived medicines can be traced back for more than 5000 years, while Western medicine has a relatively short history of a few hundred years (Goldman, 2001). In their review, Balunas *et al.* stated that the medicinal use of more than 85,000 plant species has been documented worldwide (Balunas and Kinghorn, 2005). The WHO also estimated that up to 80% of people in the world, mostly in developing countries, rely on herbal medicines for treatment of various diseases including immune diseases (Licciardi and Underwood, 2011). Moreover, approximately 30% of all FDA-approved drugs are derived from a botanical origin (Licciardi and Underwood, 2011; Onaga, 2001). Based on this evidence, it is important to investigate the chemical structures from traditional phytomedicines to evaluate their usefulness as immunomodulatory agents for immune disorders. Below, we provide examples of phytocompounds whose specific chemical structures

and immunomodulating activities have been elucidated. The representative phytocompounds with their chemical structures, molecular targets and associated diseases are summarized.

## A. POLYPHENOL

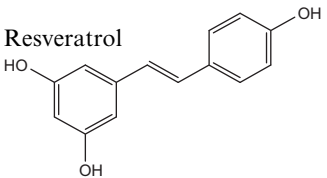
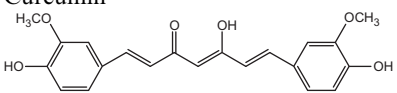
A "polyphenol" or "phenolic" is defined as a substance that has an aromatic ring with one or more hydroxyl substituents, including functional derivatives (esters, glycosides, etc.) (Shahidi *et al*., 2005). Polyphenols in foods or natural health products originate from one of the main classes of plant secondary metabolites derived from tyrosine or phenylalanine (Fraga, 2010; Shahidi *et al*., 2005).

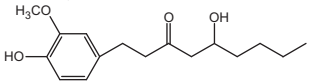
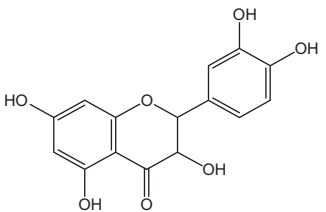
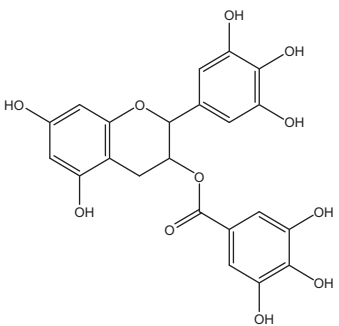
### *1. Stilbene derivatives*

Stilbenes are phenolic compounds that consist of two aromatic rings linked by an ethene bridge (C6–C2–C6) (Lamoral-Theys *et al*., 2010). Resveratrol (*trans*-3,5,4′-trihydroxystilbene) is well known as a kind of phytoalexin that belongs to the stilbene class (Table II). It is a component of grapes, berries and other TCM such as *Polygonum cuspidatum* and is known to mediate its effects through the modulation of many different pathways (Harikumar and Aggarwal, 2008). Resveratrol has been shown to bind to a wide range of inflammation-related cell-signalling molecules (Harikumar and Aggarwal, 2008; Wood *et al*., 2010). It has also been shown to regulate various transcription factors (e.g. nuclear factor erythroid-derived 2-like 2 (Nrf-2), NF-κB, activator protein-1 (AP-1), signal transducer and activator of transcription-3 (STAT3), β-catenin and peroxisome proliferator-activated receptor-gamma (PPAR-γ)), inhibit activation of some protein kinases (e.g. PI3K, JNK and AKT), induce expression of antioxidant enzymes (e.g. catalase, superoxide dismutase (SOD) and hemoxygenase-1(HO-1)), inhibit the expression of inflammatory biomarkers (e.g. cyclooxygenase-2 (COX-2), iNOS, C-reactive protein (CRP) and TNF-α) and inhibit the expression of metastatic and angiogenic genes (e.g. MMPs, vascular endothelial growth factor (VEGF), cathepsin D and intercellular adhesion molecule-1 (ICAM-1)) (Harikumar and Aggarwal, 2008). A number of animal studies have demonstrated that this polyphenol holds promise for use in a variety of age- and inflammation-associated diseases including cancer, diabetes, Alzheimer's disease, cardiovascular and pulmonary diseases as well as in ageing (Richard *et al*., 2011).

TABLE II

*Chemical Classes, Plant Sources and Molecular Targets of Representative Immunomodulatory Polyphenol Phytocompounds*

| Group/class | Compound/structure | Plant sources | Molecular targets | Targeted diseases | References |
|---|---|---|---|---|---|
| Polyphenol Stilbenes | Resveratrol  | Grapes (*Vitis vinifera* L.), *Polygonum cuspidatum* | Nrf-2, NF-κB, STAT3, HIF-1α, β-catenin and PPAR-γ, PI3K, JNK and AKT, catalase, SOD, HO-1, MMP2/9, ROS | Inflammation, ageing, cancer, diabetes, Alzheimer's disease, cardiovascular and pulmonary diseases | Harikumar and Aggarwal (2008), El-Mowafy *et al.* (2011), Csiszar (2011), Bereswill *et al.* (2010) |
| Hydroxycinnamic acids | Curcumin  | Turmeric (*Curcuma longa*) | Nrf-2, NF-κB, AP-1, STAT3, PKCα, PI3K, GSK-3β, ERK, JNK, AKT, COX-2, iNOS, IL-6, TNF-α, PGE2, MMP-2/9, VEGF, ROS | Inflammation, arthritis, allergy, asthma, cancer, atherosclerosis, heart disease, Alzheimer's disease, diabetes | Surh (2003), Lamoral-Theys *et al.* (2010), Goel and Aggarwal (2010) |

| | | | | | |
|---|---|---|---|---|---|
| | 6-Gingerol  | Ginger (*Zingiber officinale*) | NF-κB, AP-1, PKCα, cyclin D1, COX-2, iNOS, IL-6, TNF-α | Inflammation, hyperlipidaemia, hyperglycaermia, analgesic | Aggarwal and Shishodia (2006), Al-Suhaimi *et al.* (2011), Kim *et al.* (2005) |
| Flavonoids | Quercetin (belongs to flavonol)  | Grapes, tea, onions, apples, berries | Nrf-2, NF-κB, AKT, iNOS, PGE2, COX-2, TNF-α, IL-1β, IL-6, ROS | Inflammation, ageing, neurodegerative diseases, inflammatory bowel diseases, cancer | Bacon *et al.* (2003), Conforti and Menichini (2011), Dihal *et al.* (2006), Gomes *et al.* (2008), Pan *et al.* (2009) |
| | EGCG (belongs to flavanol)  | Tea (*Camellia sinensis*) | EGFR, AKT, NF-κB, AP-1, cyclin D1, VEGF, COX-2, iNOS, MMP-2/-9, IL-12, VCAM-1 | Inflammation, ageing, hepatitis, cancer, upper respiratory tract infections, cardiovascular disease | Babu and Liu (2008), Melgarejo *et al.* (2010), Peairs *et al.* (2010), Shan *et al.* (2008), Shirakami *et al.* (2008) |

*2. Hydrocinnamic acid derivatives*

Curcumin (diferuloylmethane) is a diferuloyl derivative containing 19 carbon atoms (C6–C7–C6) and is a major pigment isolated from *Curcuma longa* (from the Zingiberaceae or Ginger family) (Table II) (Aggarwal, 2010). Curcumin has long been used as part of the daily diet in Asian countries without toxicity (Ammon and Wahl, 1991). It can also be used as a food preservative, drug, a yellow colouring agent and a component in cosmetics. Further, it has probably been most studied as a highly pleiotropic molecule with anti-inflammatory, antioxidant, anti-metabolic, chemopreventive, chemosensitization and radiosensitization activities (Goel and Aggarwal, 2010; Gupta *et al.*, 2011; Lamoral-Theys *et al.*, 2010). The activities of *C. longa* may be due to its modulation of factors at the transcriptional level (e.g. Nrf-2, NF-κB, AP-1 and STAT3), interference with some protein kinases (e.g. PKCα, PI3K, GSK-3, JNK and AKT), enhancement of expression of antioxidant enzymes (e.g. HO-1), suppression of the expression of inflammatory biomarkers (e.g. COX-2, iNOS, IL-6 and TNF-α) and inhibition of metastatic and angiogenic gene expression (e.g. MMP2/9 and VEGF) (Aggarwal, 2010; Goel and Aggarwal, 2010; Yadav and Aggarwal, 2011). The multiple activities of curcumin has meant that it has come to be thought of as somewhat of "a magic bullet" targeted at a broad spectrum of diseases including asthma, allergy, arthritis, atherosclerosis, heart disease, Alzheimer's disease, diabetes and metabolic syndrome (Carroll *et al.*, 2011; Kanai *et al.*, 2011; Sharma *et al.*, 2004). It has already entered clinical trials for cancer treatment at the phase I and II levels in the past 10–15 years (Bayet-Robert *et al.*, 2010; Carroll *et al.*, 2011; Kanai *et al.*, 2011). Another hydrocinnamic acid derivative, 6-gingerol, also shows similar patterns of activity as curcumin (Table II) (Kim *et al.*, 2005; Lee *et al.*, 2009; Park *et al.*, 2008).

*3. Flavonoids*

Flavonoids are one of the most abundant naturally occurring compounds and are ubiquitous in vascular plants (Gomes *et al.*, 2008). Almost all plant tissues can synthesize flavonoids (Pan *et al.*, 2008b), and at least 2000 naturally occurring flavonoids have been found (Pan *et al.*, 2008b). Flavonoids are characterized by a basic backbone of 15 carbon atoms (C6–C3–C6) (Gomes *et al.*, 2008). According to their chemical structures, in general, they are categorized into seven groups: flavones, flavanones, flavonols, flavanonols, isoflavones, flavanols and anthocyanidins (Gomes *et al.*, 2008). They usually exist as a form of aglycone or a form of flavonoid glycoside. Flavonoid glycosides are mainly distributed in the leaves, flowers or fruits, while aglycones appear mainly in woody tissues. Seeds may contain both flavonoid aglycones and glycosides. In addition to their well-known antioxidant

activity, flavonoids have long been reported to possess anti-inflammatory, anti-hepatotoxic, anti-atherogenic, anti-osteoporotic, anti-allergic and anti-cancer activities (Gomes *et al.*, 2008). Here, we provide two examples of flavonoids as shown in Table II. Quercetin is a flavonol that is found in grapes, tea, onions, apples and leafy green vegetables. Epigallocatechin-gallate (EGCG) is a potent antioxidant which is the most recognized active component in tea. As shown in Table II, it is not only a potent antioxidant and anti-inflammatory agent that protects human body from the harmful effects induced by free radicals (Conforti and Menichini, 2011) but can also modulate phase I and phase II enzymes (Bacon *et al.*, 2003). The anti-inflammatory mechanisms of action of quercetin and EGCG are believed to be through the inhibition of transcriptional factors (e.g. NF-κB, AP-1) and the enhancement of Nrf-2, resulting in a reduction of pro-inflammatory mediators (Conforti and Menichini, 2011; Fraga, 2010; Shahidi *et al.*, 2005). With these features, these compounds are under evaluation for development as therapies for inflammation-related diseases, ageing, neurodegenerative diseases, inflammatory bowel diseases, cancer and diabetes.

## B. TERPENOIDS

Among natural products, phenolic compounds and terpenoids are the major phytochemicals present in vegetables, fruits and other dietary or medicinal foods (Salminen *et al.*, 2008). Terpenoids are composed of five-carbon isoprene units ($C_5H_8$) which are also often named isoprenoids (de las Heras and Hortelano, 2009). On the basis of biosynthesis and chemical structures, the terpenoids can be divided into five subgroups: (1) monoterpenoids (10 carbons), (2) sesquiterpenoids (15 carbons), (3) diterpenoids (20 carbons), (4) triterpenoids (30 carbons) and (5) carotenoids (40 carbons) (Salminen *et al.*, 2008).

### *1. Monoterpenoids*

The monoterpenoids are, in general, formed from two isoprene units, and have the molecular formula $C_{10}H_{16}$. They are usually present in nature in acyclic, monocyclic or bicyclic forms modified by oxidation, methylation or glycosylation (Bouvier *et al.*, 2005). Most of monoterpenes are volatile in nature. Some monoterpenes have been employed for human used since antiquity. The monoterpene limonene (Fig. 9), originally obtained from citrus fruits, cherries and apricots, was shown to suppress NF-κB activation (Berchtold *et al.*, 2005), and geniposide (Fig. 9), the major ingredient of the fruits of *Gardenia jasminoides*, a traditional herbal medicine used to treat inflammation, fever, headache and hepatic disorders, can inhibit NF-κB and iNOS expression (Koo *et al.*, 2004).

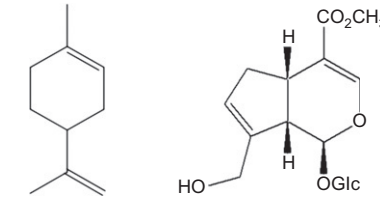



Fig. 9. Chemical structures of representative monoterpenoids.

*2. Sesquiterpenoids*

Sesquiterpenes are generally defined as substances that consist of three isoprene units which can form mono-, bi- or tricyclic compounds (Salminen *et al.*, 2008). Many traditional natural remedies or herbal medicines contain sesquiterpenoids which are modified and structurally rearranged from sesquiterpene structures. Up to the present, more than 7000 sesquiterpene structures have been identified and characterized; however, sesquiterpene lactones are recognized as those most frequently found in nature (Robles *et al.*, 1995). Sesquiterpene lactones are often found to exhibit potential medicinal properties including chemoprevention of certain inflammatory diseases and cancers (Robles *et al.*, 1995; Salminen *et al.*, 2008). Recently, a number of studies suggest that sesquiterpene lactones can be developed into therapeutics for certain diseases (Lee *et al.*, 2010c; Miller and Su, 2011; Shyur *et al.*, 2011). Among them, artemisinin (Fig. 10) is probably the most well known. Artemisinin was isolated from the leaves of *A. annua*, a traditional Chinese medicinal plant (Tu, 2011) (see Section III.C). Artemisinin has been used as an effective antimalarial drug, especially against multi-drug-resistant malaria. Artemisinin and its derivatives have also been shown to confer antifungal, anti-cancer, anti-angiogenesis and immunosuppressive properties (Cui and Su, 2009; Miller and Su, 2011). The NF-κB transcription signalling system was suggested to be the target and mode of mechanistic action of artemisinin, resulting in a strong inhibition of inflammation. Further examples of sesquiterpene lactones are the elephantopin derivatives (Fig. 10). They include isodeoxyelephantopin and deoxyelephantopin and are isolated from the *Elephantopus scaber* plant (Ichikawa *et al.*, 2006). Isodeoxyelephantopin and deoxyelephantopin have been shown to not only possess anti-inflammatory activities but also confer anti-cancer activities, again via suppression of NF-κB activation (Huang *et al.*, 2010; Ichikawa *et al.*, 2006; Su *et al.*, 2011a).

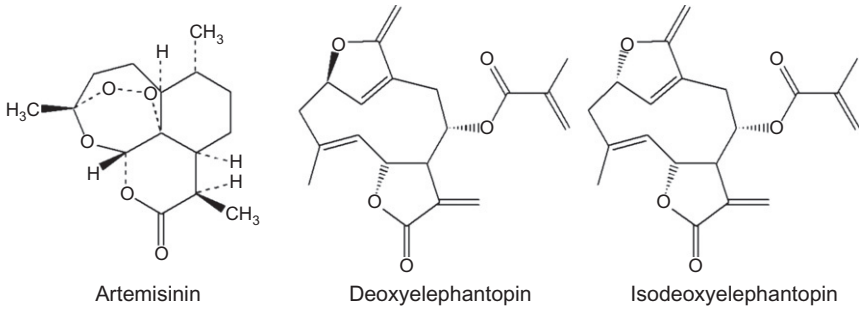



Fig. 10. Chemical structures of representative sesquiterpenoids.

*3. Diterpenoids*

Diterpenes consist of four isoprene units and have a basic structure of $C_{20}H_{32}$ (Ajikumar *et al.*, 2008; Robles *et al.*, 1995). Diterpenoids are generally modified and structurally rearranged from diterpene structures. They may be acyclic, but in general, they are present as mono-, bi-, tri-, tetra- or macrocyclic compounds (Ajikumar *et al.*, 2008). Oleoresin from the conifer plant species usually contains a number of diterpenoids (Salminen *et al.*, 2008). Traditionally and clinically, diterpenoid-containing medicines have been applied to a variety of diseases including arthritis, atherosclerosis, cancer and inflammation (Salminen *et al.*, 2008; Thoppil and Bishayee, 2011). Physiologically, these typically active diterpenoids include retinol derivatives, taxanes, phorbols, forskolin and gibberellins (Pan and Ho, 2008).

The retinoids, including all-*trans*-retinoic acid and retinol, are reputed to play essential roles in the function and maintenance of human vision (Pan and Ho, 2008). Another well-known example is taxol, a complex polyoxygenated diterpenoid originating from the bark of the Pacific yew tree, *Taxus brevifolia*. This potent anti-cancer drug is clinically used for treating a number of cancer diseases under the generic name of paclitaxel. Two major bioactive diterpenoids derived from TCM are reputed to be useful for treating various inflammatory diseases: triptolide (Fig. 11), originally isolated from TWHF, and tanshinone IIA (Fig. 11), the major active diterpene quinone from the roots of *Salvia miltiorrhiza*. *S. miltiorrhiza* is a common TCM herb which has been used to treat immunological disorders, cardiovascular diseases, osteoporosis and breast cancer (Gao *et al.*, 2011; Yuan *et al.*, 2003). Studies have shown that tanshinone IIA can inhibit NF-κB signalling and the associated inflammatory mediators (Gao *et al.*, 2011). Another series of diterpenoids containing specific chemical structures of the abietane type have also been found to be potent immunomodulators with potential application to a broad spectrum of diseases. Prevention or blocking of the inducer

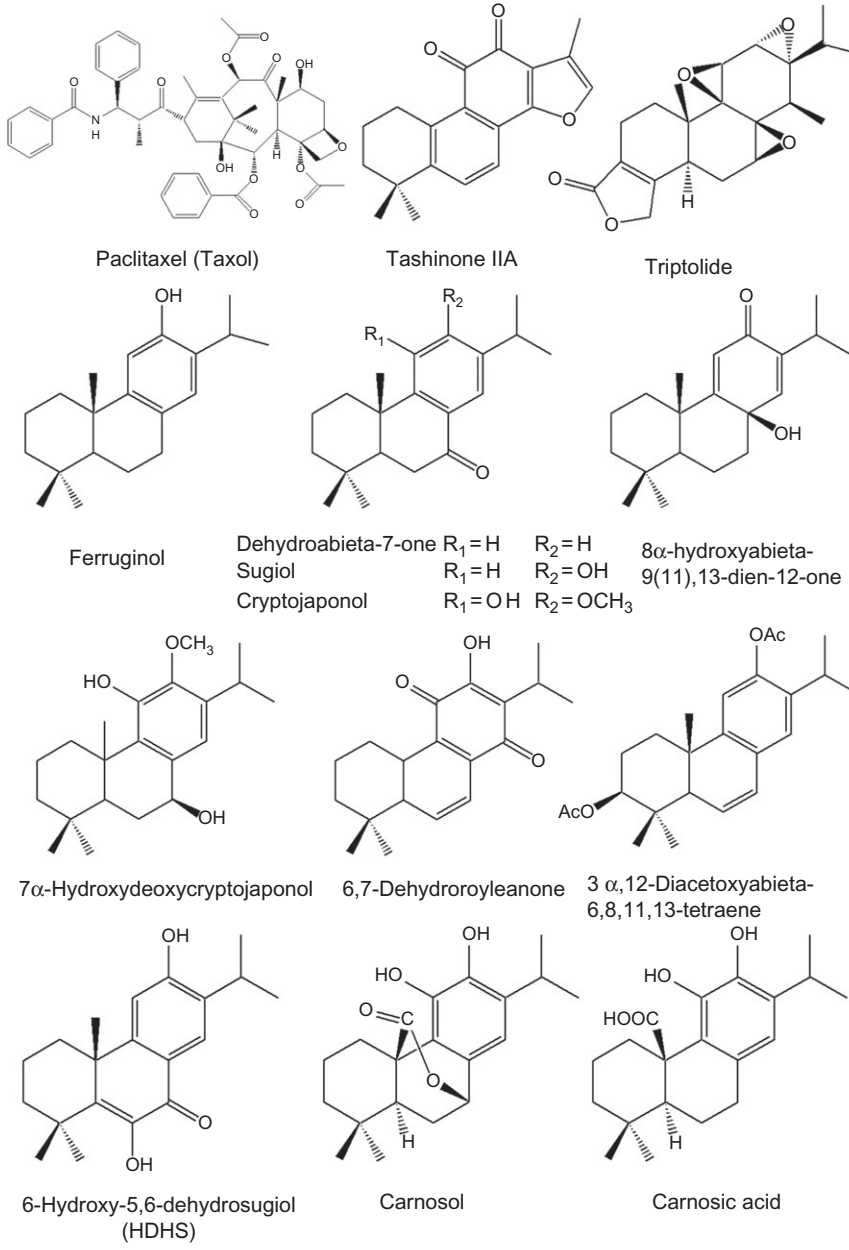



Fig. 11. Chemical structures of representative diterpenoids.

from an exogenous pathogen from initiating the inflammatory pathway may be taken as an approach for preventing the specific immune responses. For example, severe acute respiratory syndrome (SARS) is caused by infection with a coronavirus, SARS coronavirus (SARS-CoV), and is characterized by a cytokine storm in the host following infection leading to serious damage to the human body (Skowronski *et al*., 2005). Our previous study showed that 10 diterpenoids, 8 abietane-type diterpenoids and 2 labdane-type diterpenoids (Fig. 11) can suppress SARS-CoV replication, hence suggesting that they could be further evaluated for use as antiviral agents (Wen *et al*., 2007). Another two abietane-type diterpenoids, carnosol and carnosic acid have been found in high abundance in Rosemary extracts (*Rosmarinus officinalis*), a frequently used traditional herbal remedy (Salminen *et al*., 2008). Both of these compounds possess antioxidant and anti-inflammatory activities, probably via the induction of Nrf-2-activated HO-1 expression and inhibition of activation of NF-κB signalling (Pan and Ho, 2008; Salminen *et al*., 2008). Lin *et al*. (2008) also reported an abietane-type diterpenoid, 6-hydroxy-5,6-dehydrosugiol (HDHS) (Fig. 10) isolated from the stem bark of *Cryptomeria japonica*, can suppress tumour growth in prostate cancer (PCa)-xenografted mice. Based on the various diverse bioactivities of these abietane-type diterpenoids, additional research efforts may need to focus on classifying them into specific subgroups, for example, with regard to whether they suppress or enhance NF-κB signalling directly or indirectly, or serve as an inflammation-modulatory agent or immune-stimulatory agent, depending on their structure/activity relationship. For instance, taxol was reported to activate NF-κB signalling via the TLR4 receptor complex (Li *et al*., 2004; Tsuda *et al*., 2007). Further, most of the diterpenoids mentioned above, such as carnosol, possess anti-inflammatory and other therapeutic effects. Taken together, these findings suggest that diterpenoids may serve as a group of promising candidates for drug development.

*4. Triterpenoids*

Triterpenes are composed of 6 isoprene units and have 30 carbons. There are more than 20,000 naturally occurring triterpenoids which have cyclic structures (Ajikumar *et al*., 2008; Liby *et al*., 2007). Triterpenoids, synthesized in many plants by the cyclization of squalene, are widely used in various traditional and folk medicines (Phillips *et al*., 2006). Celastrol is a quinone methide pentacyclic triterpenoid and is extracted from the TCM, TWHF (Yang *et al*., 2006). It has been reported to possess antioxidant, anti-inflammatory and anti-cancer activities (Pinna *et al*., 2004). Celastrol may act in part through the suppression of NF-κB signalling inhibiting inflammation and tumour growth (Kim *et al*., 2009; Pinna *et al*., 2004). Ursolic acid is a

different type of pentacyclic triterpene which is the main active ingredient of some traditional herbal remedies, such as rosemary leaves (Liu, 1995). As shown in Fig. 12, ursolic acid is well known to possess a broad spectrum of biological functions that can counteract exogenous and endogenous biological stimuli (Ikeda *et al*., 2008). In addition, it has been reported to confer various medicinal effects including anti-hyperlipidaemia, anti-cancer and hepatoprotective activities (Ikeda *et al*., 2008; Pan and Ho, 2008; Salminen *et al*., 2008). It was reported to inhibit NF-κB activation contributing to the suppression of LPS-induced pro-inflammatory mediators in mouse macrophages and TPA-induced skin tumour promotion (Ikeda *et al*., 2008). You *et al*. (2001) showed that ursolic acid can also induce NF-κB activation, resulting in release of pro-inflammatory mediators in non-stimulated mouse macrophages. Therefore, it is speculated that, depending on the biological status of test cells and tissues, ursolic acid may exert contrasting anti- and pro-inflammatory activities (Ikeda *et al*., 2008). Other lupane-type triterpenoids, such as betulinic acid and its derivatives (Fig. 12), have also been considered to have therapeutic potential against pathogen infections (e.g. HIV),

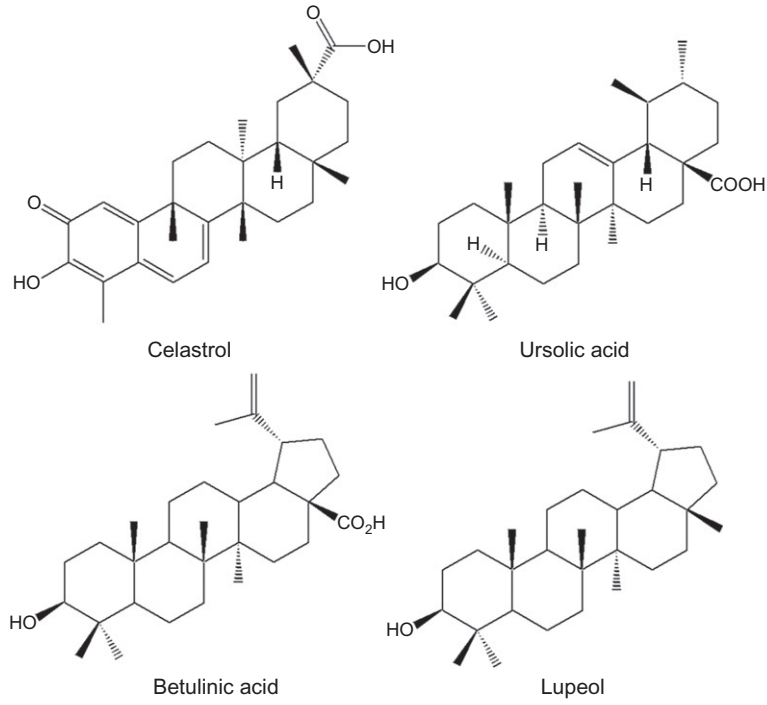



Fig. 12. Chemical structures of representative triterpenoids.

cancers (e.g. melanoma) and different types of inflammation (Fulda, 2009; Takada and Aggarwal, 2003). It was also observed that betulinic acid inhibited the activation of IKKα and NF-κB induced by various NF-κB activators (Takada and Aggarwal, 2003). Our previous study showed that betulinic acid conferred anti-SARS-CoV activities (Wen *et al.*, 2007). Lupeol has a similar chemical structure to betulinic acid and is one of the major constituents of a number of common vegetables, fruits and medicinal herbs (Salminen *et al.*, 2008). It has been studied for possible therapeutic effects for specific cancers (Siddique and Saleem, 2011) and inflammatory disorders (Fernandez *et al.*, 2001; Saleem, 2009). It was shown to inhibit NF-κB signalling via phosphorylation of IκBα protein, NF-κB-dependent reporter gene activity or DNA binding of NF-κB complex (Lee *et al.*, 2004; Saleem *et al.*, 2004). Lupeol can apparently also inhibit other signalling pathways, such as Akt-dependent pathways, and these activities may contribute to its various anti-cancer and anti-inflammatory properties (Fernandez *et al.*, 2001; Salminen *et al.*, 2008).

*5. Carotenoids*

Carotenoids are known as pigmented tetraterpenes typically containing a 40-carbon polyene chain, derived from eight isoprene units with conjugated double bonds, providing strong light absorption and brilliant colour, allowing them to take up excess energy from other molecules through a non-radiative energy transfer mechanism (Pan and Ho, 2008; Salminen *et al.*, 2008). Carotenoids are naturally occurring fat-soluble pigments that give bright colouration to host plants and animals. Plant carotenoids can play an essential role in maintenance of human health (Salminen *et al.*, 2008). They can serve as powerful antioxidants and are reputed to alleviate several chronic diseases, such as cardiovascular disease, osteoporosis and cancer. Some carotenoids such as β-carotene, lutein and lycopene can also offer protection against some inflammatory responses, possibly via modulation of redox-sensitive signalling pathways such as NF-κB and ROS signalling (Chew and Park, 2004; De Stefano *et al.*, 2007; Huang *et al.*, 2007). β-Carotene (Fig. 13) is the most common cyclic tetraterpene and the most potent pro-vitamin A in nature (Pan and Ho, 2008). It is stored in the liver and can be converted to vitamin A. The lipophilic xanthophylls, lutein (Fig. 13), is a dihydroxy derivative of β-carotene and is widely present in a variety of fruits and vegetables as well as in egg yolks. It can protect against oxidative stress and prevent age-related macular degeneration and exhibit a neuroprotective effect in retinal inflammation (Lee *et al.*, 2004; Sasaki *et al.*, 2009). Another acyclic tetraterpene, lycopene (Fig. 13), is the most abundant carotenoid present in the human body (Salminen *et al.*, 2008). It is present mainly in red-colour vegetables and fruits. Lycopene is a powerful

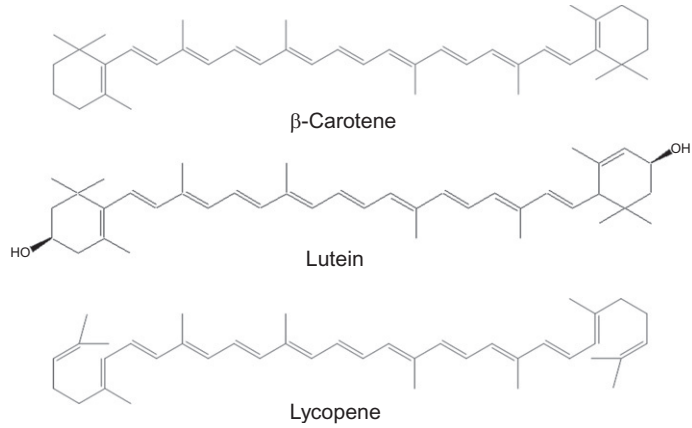



Fig. 13. Chemical structures of representative carotenoids.

antioxidant, more potent than vitamin E, and it can thus prevent cells from free radical attack during oxidative stress. It has also been claimed to reduce the risk for various chronic diseases, such as cardiovascular diseases, RA and atherosclerosis (Pan and Ho, 2008; Salminen *et al.*, 2008). These carotenoids exhibiting antioxidant activities may warrant future development as immunomodulators.

### C. ORGANOSULPHUR-CONTAINING COMPOUNDS

The organosulphur compounds are a special type of phytocompound found in various *Allium* species. The organosulphur compounds in garlic are known to differ slightly from those in onion varieties and consequently may have different health benefits. Two major kinds of organosulphur compounds are present in onion varieties, especially in garlic-γ-glutamyl-*s*-cysteines and cysteine sulphoxides (ca., alliin). When raw garlic cloves are crushed, chopped or chewed, an enzyme known as alliinase is released. Alliinase catalyses the formation of sulphenic acids from cysteine sulphoxides (Fig. 14). Sulphenic acids can spontaneously react with each other to form unstable thiosulphinates compounds. In the case of alliin, the resulting sulphenic acids react with each other to form a thiosulphinate (half-life in crushed garlic at 23 °C is 2.5 days) (Lawson *et al.*, 1998). Thiosulphinate formation is very rapid and can be completed within 10–60 s after crushing a garlic clove. Allicin breaks down and forms a variety of fat-soluble organosulphur compounds, including diallyl trisulphide (DATS), diallyl disulphide (DADS) and diallyl sulphide (DAS), or in the presence of oil or organic solvents, as ajoene and vinyldithiins

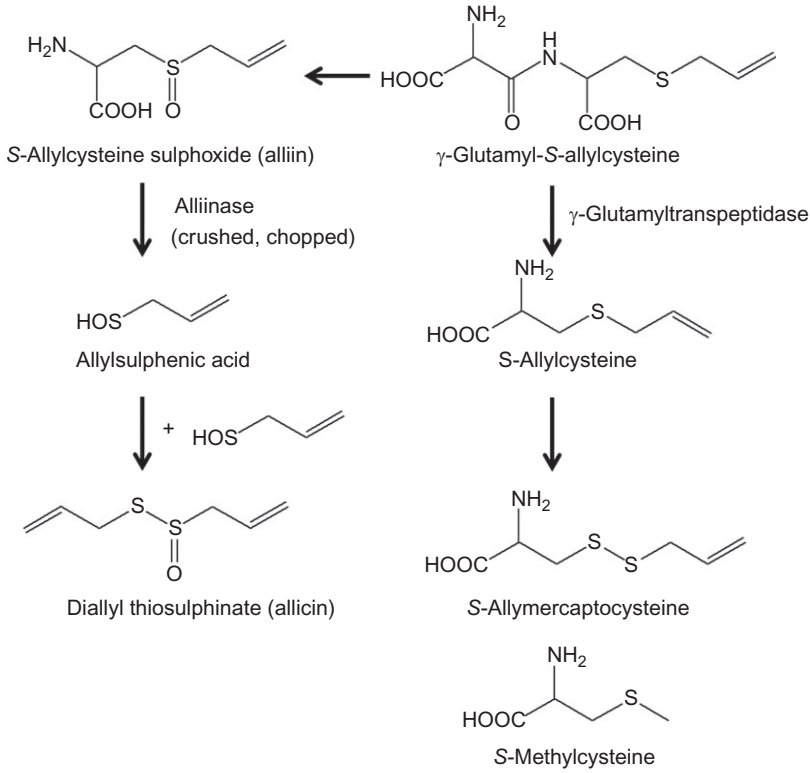



Fig. 14. Biosynthesis and transformation of various organosulphur-containing compounds.

(Block, 1985). Water-soluble organosulphur compounds, such as *S*-allylcysteine (SAC), are formed from γ-glutamylcysteines during long-term incubation of crushed garlic in aqueous solutions, as in the manufacture of mature garlic extracts (Fig. 14).

The oil-soluble organosulphur compound, allicin, is easily transformed into oil-soluble polysulphides, mostly DADS, DAS, DATS and also diallyl tetrasulphide (Fig. 15). Chemical compositions of the various preparations obtained by extraction of oil-soluble garlic fractions also depend on the specific extraction conditions such as temperature, treatment time interval and solvent polarity. Analysis of allicin solution that has been allowed to stand at room temperature for 20 h showed the following bioorganic composition: 66.7% DADS, 14.6% DATS, 13.3% DAS and 5.4% diallyl tetrasulphide (Lee *et al.*, 2003). Various findings suggest that higher polysulphides, such as diallyl penta-, hexa- or hepta sulphides, can be formed but

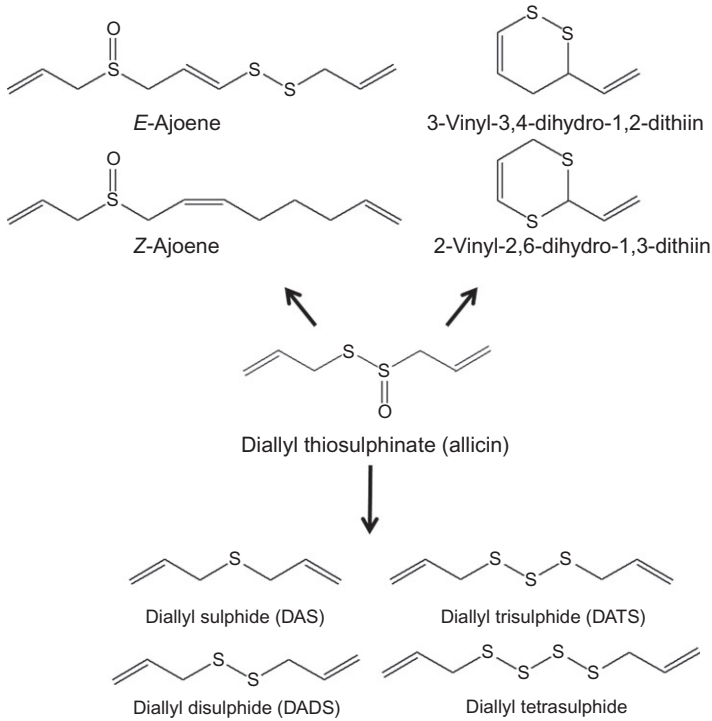



Fig. 15. Biotransformation of various oil-soluble compounds from allicin.

their concentrations are often low (O'Gara *et al.*, 2000). When extraction conditions are optimized, allicin can be transformed into vinyldithiin and structures of the *Z*- or *E*-ajoene type. The vinyldithiin compound was first identified by gas chromatographic analysis as a product of thermal degradation of allicin (Brodnitz *et al.*, 1971; Lee *et al.*, 2003). These structures are formed by dimerization of thioacrolein created via allicin β-elimination. Ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide) was generated via allicin S-thiolation and 2-propenesulphenic acid addition. Originally, ajoene was isolated from an ether fraction of garlic extract as a potential antithrombotic agent (Block *et al.*, 1984).

The reactions of allicin with —SH groups can yield SAC or *S*-allylmercaptocysteine (SAMC), both of which are water-soluble organosulphur compounds (Rabinkov *et al.*, 2000). Unlike oily sulphur compounds, water-soluble compounds are odourless and have a more delicate and less characteristic flavour (Kodera *et al.*, 2002). These phytocompounds are formed during aqueous garlic extraction, when the initial compound γ-glutamyl-*S*-allylcysteine (GSAC) is transformed into SAC. This reaction

is catalysed by γ-glutamyltranspeptidase (γ-GT) (Fig. 14). SAC along with its derivatives, *S*-methylcysteine (SMC) and SAMC, are components of aqueous extracts of garlic and possess various biological activities, under both *in vitro* and *in vivo* conditions.

Garlic- and onion-derived organosulphur compounds have been shown to suppress the *in vitro* activities of inflammatory enzymes such as cyclooxygenase and lipoxygenase (Ali *et al*., 2000) and to inhibit the expression of iNOS in inflammatory white blood cells (macrophages) (Dirsch *et al*., 1998). Some organosulphur compounds have been shown to inhibit expression of the inflammation signalling molecules in cultured macrophages and human peripheral blood mononuclear cells (Chang *et al*., 2005). Various findings have demonstrated that garlic extracts and their derived compounds can exhibit anti-inflammatory effects through inhibition of the NF-κB activity induced by various receptor agonists, including TNF-α and LPS (Keiss *et al*., 2003). Expression of iNOS was also shown to be inhibited by garlic extract in activated macrophages (Dirsch *et al*., 1998; Liu *et al*., 2006a). In addition, Youn *et al*. (2008) demonstrated that garlic extracts can modulate inflammatory responses through suppression of TLR activation.

### D. POLYSACCHARIDES

Over 300 types of bioactive polysaccharides have been identified from natural products (Jiang *et al*., 2010). According to the broad and diverse sources, they can be mainly divided into five categories, including the higher plant, fungal polysaccharides, bacterial, lichen and the algae (Cheung *et al*., 2009). Polysaccharides, one of main classes of various bioactive substances present in various traditional herbal medicines, have been shown or implicated to confer a spectrum of pharmacological activities, especially on immunomodulatory, anti-tumour effects or cancer chemopreventive effects (Guo *et al*., 2011). Unfortunately, however, their immunoregulatory activities in terms of molecular and cellular mechanisms are in general not well understood. According to the similarities and differences of their chemical structures, the plant polysaccharides can be roughly categorized into several groups, including the β(1 → 3)-D-glucans (Fig. 16A), α(1 → 3)-D-glucans (Fig. 16A), (1 → 3)-β-linked backbone with (1 → 6)-β-branches (Fig. 16A), acetylated glucomannans (Fig. 16B), sulphated polysaccharides, arabinans (Fig. 16C), arabinogalactans I, arabinogalactans II (Fig. 16D), rhamnogalacturonan I (RG-I) (Fig. 16E), RG II (Fig. 16F) and pectins (Fig. 16G).

A large volume of studies have reported that various plant polysaccharides can confer potent immunomodulatory activities through regulating the specific functions of various immune cells, including monocytes, macrophages,

NK cells, DCs, T lymphocytes, B lymphocytes and others (Chen *et al.*, 2009a; Thakur *et al.*, 2011; Zhang *et al.*, 2011b). They can be recognized or distinguished by the corresponding receptors on specific immune cells (Table III), and they can activate immune cells to generate a series of specific cellular or molecular events, including the innate immune and acquired immunities. Accumulating evidences have shown that DCs, the potent APCs, are the major immunomodulatory targets of polysaccharides in regulation of innate as well as acquired immunities (Chen *et al.*, 2011; Kim *et al.*, 2009; Li *et al.*, 2010a). Polysaccharides can increase the expression of MHC class II and the co-stimulatory molecules CD80 and CD86. Various polysaccharides can affect the morphological maturity of DCs, upregulate IL-12 and GM-CSF, downregulate phagocytosis and antigen uptake activities of DCs or promote DC differentiation (Jeurissen *et al.*, 2005; Khayrullina *et al.*, 2008). These

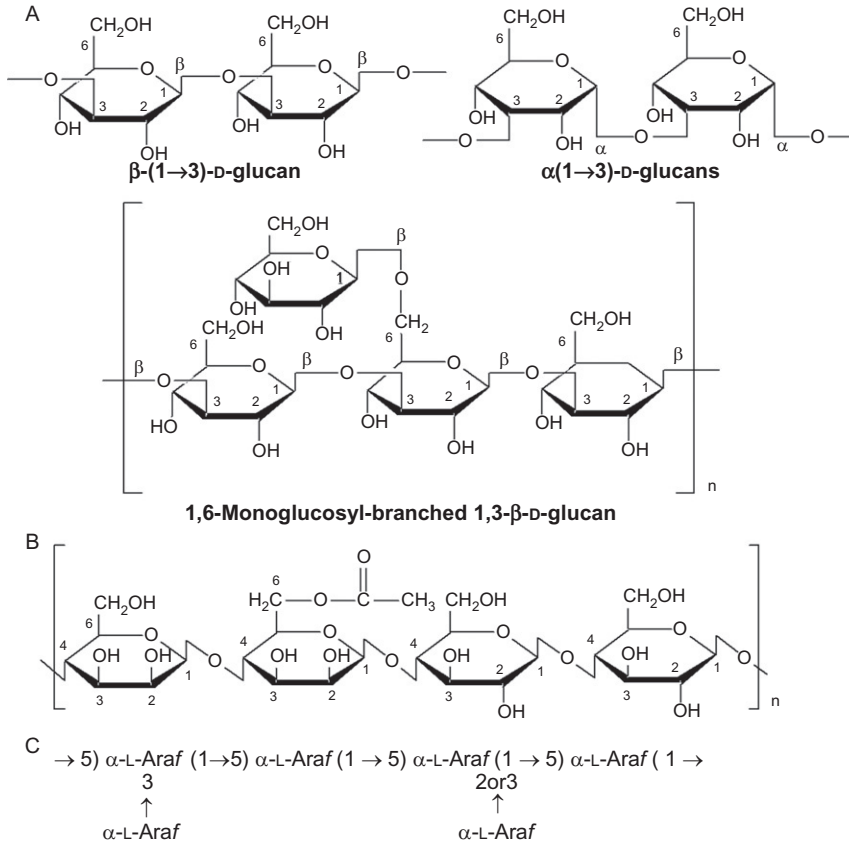



Fig. 16—cont'd

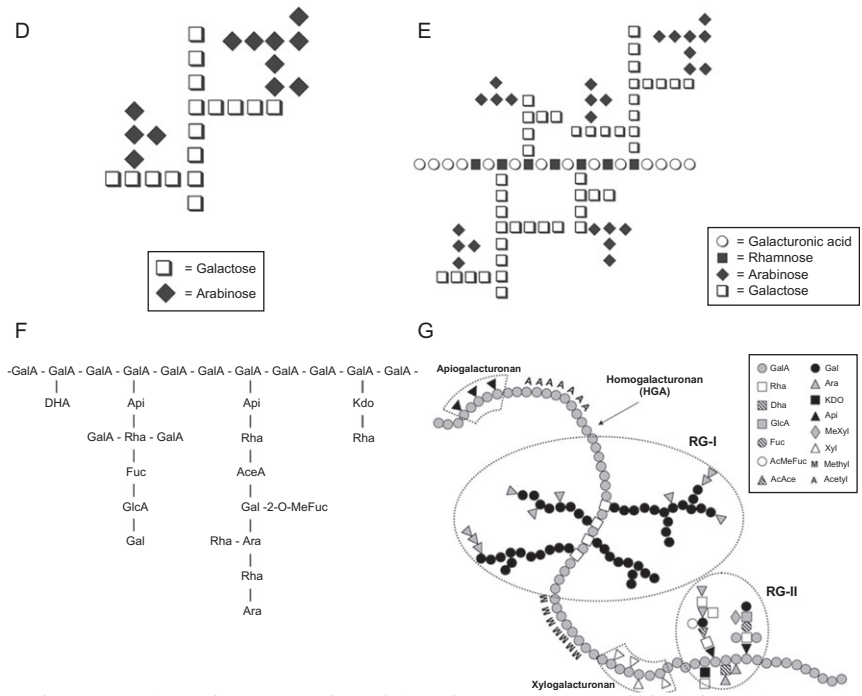



Fig. 16. Schematic presentation of the primary structure of bioactive polysaccharides. (A) and (B) from Moradali *et al.* (2007), (C) from Paulsen and Barsett (2005), (D)–(F) from Paulsen (2002), (G) from Perez *et al.* (2003).

TABLE III

*The Specific Polysaccharides Ligands and Their Target Immune Cells*

| Ligands | Immune cells | Receptors | References |
|---|---|---|---|
| Zymosan, β-1,4-glucan | Myeloid cells (monocytes, macrophages, DCs, epithelial cells, mast cells and neutrophils) | Toll-like receptors | Lu *et al.* (2011a), Graff *et al.* (2009), Han *et al.* (2003), Li *et al.* (2004) |
| Fucoidan, β-glucan | Macrophages, DCs | Scavenger receptors | Wang and Chandawarkar (2010), Means *et al.* (2009) |
| β-1,3-Glucan | Macrophages, DCs, neutrophils, eosinophils, B and T lymphocytes | β-Glucan receptor | Willment *et al.* (2005), Brown *et al.* (2002) |
| Mannan | Macrophages, DCs, hepatic endothelial cells, tracheal smooth muscle and retinal pigment epithelial cells | Mannose receptor | Linehan *et al.* (1999) |
| β-1,3-Glucan | Macrophages, neutrophils, B and T cells and natural killer cells | Complementary receptor type 3 | Hwang *et al.* (2003), Chen *et al.* (2009b) |

findings show that polysaccharides may be employed as a potent adjuvant for design and efficacy of DC-based vaccines. It has been reported that the specific extract isolated from the root of *Echinacea* contain high quantity of polysaccharides and were shown to confer strong immunostimulatory activities for activating DC maturation (Benson *et al.*, 2010). Various plant polysaccharides have also shown to affect another APC type, that is, macrophages. These activities were suggested to involve direct elimination of alien pathogens and the dying/damaged cells and the regulation of various immune effector cells (Wang *et al.*, 1992; Zhang *et al.*, 2011a). Polysaccharides can activate macrophages to secrete pro-inflammatory cytokines (e.g. IL-1, TNF-α and IFN-γ) (Zheng *et al.*, 2005), increase the production of NO (Xu *et al.*, 2011), ROS (Yang *et al.*, 2004) and myeloperoxide, enhance the activities of cytotoxicity (Choi and Hwang, 2002), phagocytosis (Zheng *et al.*, 2005) and cell proliferation (Su *et al.*, 2011b). In addition to these effects of polysaccharides on the myeloid-lineage immune cells, maintenance or skewing of the Th1/Th2 balance has been reported (Sun *et al.*, 2009a). Polysaccharides can also promote the differentiation of B cells (Han *et al.*, 2003) and the production of IgG and IgM (Nose *et al.*, 1998). We have shown that the specific extract from *D. batatas* can be used as adjuvants for DC-based vaccine (more details are described under the Section III.B (Su *et al.*, 2011b)).

## V. EMERGING APPROACHES FOR MODULATING THE COMPLEX SYSTEMS

### A. EMERGING IMMUNOMODULATORY TARGETS OF MEDICINAL HERBS FOR THERAPEUTIC INTERVENTION

Large volume of evidence shows that the use of complementary and alternative medicines is increasing in supplementing or treating various immune disorders, especially in developed countries (Boon *et al.*, 1999; Ernst and Cassileth, 1998). The use of complementary and alternative medicine has become generally acceptable by the public and becomes more and more popular in cancer patient populations of Western countries (Xu *et al.*, 2006). TCM is one of the complementary and alternative medicines that has a well-documented theoretical framework and a long-established practical history for immune-related diseases, including autoimmune diseases and cancers (Cho, 2010). From the aspect of immunomodulatory characteristics of TCM, they can be generally categorized into two major groups, that is, with pro-inflammatory activity or with anti-inflammatory activity, which are

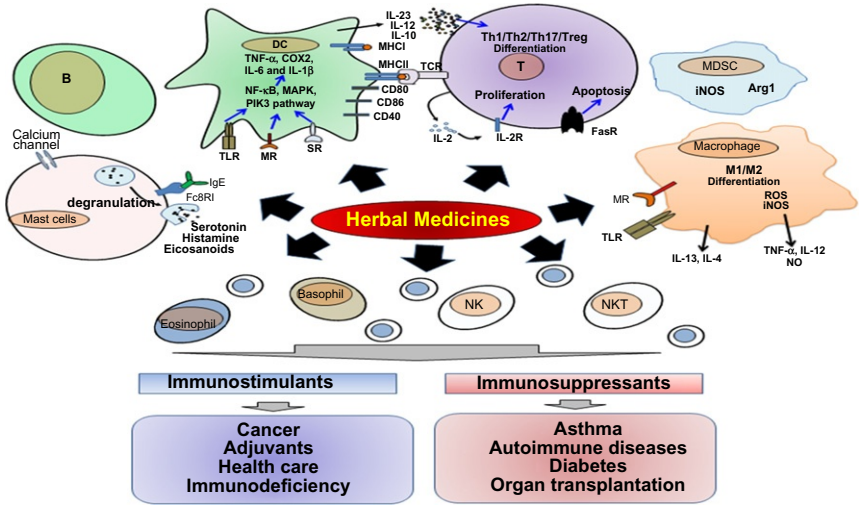



Fig. 17. Possible mechanisms of herbal medicines in immune systems. A number of possible cellular and/or molecular mechanisms of herbal medicines involved in regulation of various immune cells are depicted (black arrow) as follows. The different immunomodulatory activities of specific or defined herbal medicines may be employed for the potential in future/current clinical application of immunotherapies for immune disorders (black box). Abbreviations: NK, natural killer cells; DC, dendritic cells; TLR, toll-like receptor; MR, mannose receptor; SR, scavenger receptor; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase.

being investigated for potential therapeutic application to adjuvant treatment for cancer or autoimmune diseases, respectively. The possible cellular and/or molecular mechanisms of herbal medicines and their potential applications for future/current clinical immune-therapies of immune disorders are shown in Fig. 17. The following section summarizes in brief published reports, supporting the usage of various TCM in combination with cancer chemotherapy or clinical immune modulators for supportive measures in cancer care and autoimmune disorders.

### B. DEVELOPING MEDICINAL HERBS AS ADJUVANT FOR CANCER THERAPY

As a major global public health problem, cancer has become the major leading cause of death for most developed countries. Chemotherapy is the main stream of current therapeutic approaches; however, it has several drawbacks: (1) serious side effects and complications, (2) poor immune functions for the host and (3) frequent recurrence and poor survival rate

(Qi *et al.*, 2010). The effect of chemotherapy in suppressing the host immune function may in fact worsen the tolerogenic tumour microenvironment orchestrated by tumour-associated macrophages, myeloid-derived suppressor cells (MDSCs) and T regulatory cells (Tregs), which can lead to the escaping of tumour cells form immunosurveillance of host. Therefore, how to effectively break down the invasion and metastasis of tumour microenvironment and to restore the immune functions of cancer patients is one of the most challenging issues we are facing in cancer research today. Growing evidence revealed that TCM may effectively support and enhance the efficacy of cancer chemotherapy via improving certain specific cellular immune functions and diminishing the side effects and complications resulting from conventional cancer therapy (Xu *et al.*, 2006).

MDSCs, identified by the myeloid cell lineage cell antigens-Gr-1 and CD11b (Pan *et al.*, 2008b), is a critical immune cell type involved in maintenance of tolerogenic tumour microenvironment. MDSCs can produce several immunosuppressive factors (e.g. Arginase 1, iNOS and ROS) and specific cytokines (TGF-β and IL-10), leading to the development of Treg (Huang *et al.*, 2006). They can inhibit both the innate and adoptive immunities, subvert immunosurveillance (Pan *et al.*, 2008a) and create a significant impediment in elimination of malignant cells. Curcumin was shown to inhibit tumourigenicity, tumour growth, the expansion of MDSCs and the activation of Stat3 and NF-κB in MDSCs, and to reduce IL-6 levels in a human gastric cancer xenograft model and a mouse colon cancer allograft model (Tu *et al.*, 2011). Curcumin treatment polarized MDSCs towards a M1-like phenotype with an increased expression of CCR7 and decreased expression of dectin-1, *in vivo* and *in vitro* (Tu *et al.*, 2011). The extracts of two Chinese medicinal herbs, namely, *Astragalus membranaceus* and *Ligustrum lucidum*, can exert significant anti-tumour activity via abolition of tumour-associated macrophage suppression (Rittenhouse *et al.*, 1991). Icariin, the major active ingredient of *Herba epimedii*, has been demonstrated to confer anti-inflammatory effect in murine innate immune cells and activated human PBMCs (Zhou *et al.*, 2011). It has been reported that administration of icariin can significantly reduce the percentage of MDSCs with a concomitant activity for differentiation into DCs and macrophages, leading to a downregulation of IL-10, IL-6 and TNF-α production, which may result from decreased expression of S100A8/9 and inhibition of the activation of STAT3 and AKT (Zhou *et al.*, 2011).

In addition to MDSCs, the development of Treg cells in tumour microenvironment is another important determinant for the efficacy of certain cancer immunotherapies. *Radix glycyrrhizae* polysaccharides can reduce Treg population and Foxp3 expression in Treg cells and upregulate Th1/Th2 cytokine

ratio (decreased level of IL-10 and TGF-β and increased level of IL-2 and IL-12p70) in sera of H22 hepatocarcinoma-bearing mice (He *et al*., 2011). Recently, *R. glycyrrhizae* has also been shown to regulate the cellular immunity of tumour-bearing mice by decreasing the proportion of Treg cells and by increasing the spleen lymphocyte transformation ratio (Li *et al*., 2010b). In addition, glycyrrhizin isolated from *R. glycyrrhizae* was shown to reduce the generation of suppressor macrophages and enhance the efficacy of adoptive transfer therapy of allospecific CTLs (Suzuki *et al*., 1992). A sulphated polysaccharide-protein complex from Gekko swinhonis Guenther, for a TCM, has been found to confer strong bioactivities for restoring the defective biorheological characteristics of DCs via decreasing the secretion of IL-10 of DCs and thus modifying the tumour microenvironment (Chen *et al*., 2011). The *Lycium barbarum* polysaccharides was shown to confer anti-tumour activity through increasing the numbers of $CD4^+$ and $CD8^+$ T cells in tumour infiltrated lymphocytes to relieve the immunosuppressive responses and enhance the anti-tumour function of the immune system (He *et al*., 2005). Bushen Gubiao Recipe, a traditional Chinese herbal medicine, was shown to improve the innate immune function by upregulation of the TLR/NFκB signalling pathway and adjustment of the immune imbalance of T-helper cell (Th) 1/Th2, through reducing the activity of $CD4^+CD25^+Foxp3^+$ Tregs and enhancing the Th1 immune response (Zhou *et al*., 2010). Radix Astragali (*Astragalus propinquus*, Huangqi) has long been used to modulate the function of the lung and gastrointestinal system, promote healing and reduce fatigue. Currently, a number of immunomodulatory properties of *Astragalus* have been detected, including an increase in expression of interferon and TNF, and the activation of lymphocytes, NK cell and macrophages (Nalbantsoy *et al*., 2011; Song and Hu, 2009). The polypeptide extract from *Scorpion venom* was shown to inhibit the angiogenesis activity of *Lewis* lung cancer, which may be due to the decreased level of angiogenic factors—factor VIII, α-SMA, Dll4 and Notch1 in test tumour microenvironment (Sun *et al*., 2011).

In addition to the single herb plants mentioned above, the mixtures of multiple plants and formulated TCM preparations were also shown to confer immunostimulatory activities. Such multiple plant formulations were repeatedly documented in traditional Chinese medicine books. Knowledge and experience presented in such formulations also may provide new and alternative therapy approaches in combination with chemotherapy treatment. A recent interesting example is the successful development of the PHY906 formula for TCM reported by Dr. Y. C. Cheng (Ye *et al*., 2007). PHY906 is a Chinese medicine formulation composed of four medicinal herbs (Yen *et al*., 2009; Zhang and Ma, 2010): Huang Qin (dried roots of *Scutellaria baicalensis*

Georgi), Baishao (dried roots of *Paeonia lactiflora* Pall), Gan Cao (dried and honey-fried roots and rhizomes of *Glycyrrhiza uralensis* Fisch, *Glycyrrhiza inflata* Bat or *Glycyrrhiza glabra* L.) and Da Zao (dried fruits of *Ziziphus jujuba* Mill). This formulation was shown as efficacious for use as adjuvant treatment cancer chemotherapy approaches (Ye *et al.*, 2007). It has been found to reduce the chemotherapy-induced gastrointestinal toxicity (Lam *et al.*, 2010) and can be used as an adjuvant therapy for chemotherapy using capecitabine (Yen *et al.*, 2009), irinotecan, 5-fluorouracil and leucovorin (Wang *et al.*, 2011a) in advanced colorectal cancer (Kummar *et al.*, 2011) and pancreatic and other gastrointestinal malignancies (Kummar *et al.*, 2011; Saif *et al.*, 2010; Yen *et al.*, 2009). Further, Juzen-taiho-to (TJ-48) is an extract prepared from a mixture of 10 species of medicinal plants, including *Angelica sinensis*, *P. lactiflora*, *Atractylodes macrocephala*, *Poria cocos*, *Cinnamomum cassia*, *A. membranaceus*, *Liqusticum wallichii*, *G. inflata* and *Rehmannia glutinosa* (Saiki, 2000). This prescription has long been traditionally used against anaemia, anorexia, extreme exhaustion and fatigue (Saiki, 2000). TJ-48 was shown to augment antibody production, the mitogenic activity in splenocytes and B cells, and anti-complementary activity, and to activate macrophages, by oral administration of TJ-48 (Yamada, 1989). TJ-41 (Bu-Zhong-Yi-Qi-Tang) is another traditional herbal formulation, containing *Pinellia tuber*, *S. baicalensis*, *Zingiberis rhizoma*, *Zizyphi fructus*, *Coptidis rhizoma*, *G. radix* and *P. ginseng* (Yang *et al.*, 2010). TJ-41 has been reported to enhance concomitant immunity against tumour development and restore the anti-tumour response of effector T cell in tumour-bearing mice (Li *et al.*, 1999).

Immunogenic chemotherapy has recently emerged as an interesting approach, based on the ability of a cytotoxic compound to induce immunogenic tumour cell death, which are characterized by the changes of danger-associated molecular pattern, including heat shock protein, calreticulin, glucose-related protein and high-mobility group protein box 1 (Garg *et al.*, 2010). This new compelling anti-cancer strategy may offer good therapeutic potential in providing not only a direct tumour-killing effect but also a restoration of tumour-specific immune responses for prevention of tumour recurrence (Ullrich *et al.*, 2008). Unfortunately, there are currently very limited chemotherapeutic drugs that are shown to confer such pharmacological characteristics. Effective reutilization of TCMs as well as its phytochemicals may offer great value in drug discovery, and one of their potentials may be in the area for development of immunogenic chemotherapy. Our laboratory has also identified and tested several phytochemicals, including shikonin and its derivatives and synthetic compounds (Wen *et al.*, 2011), aiming to make use of the immunogenic cell death activity.

### C. DEVELOPING MEDICINAL HERBS FOR USE AGAINST AUTOIMMUNE DISEASES

Autoimmune diseases are a group of illnesses that often involve multiple organs. For clinical applications, autoimmune diseases appear to be either systemic (as in the case of systemic lupus erythematosus) or organ specific (as in the case of type 1 diabetes mellitus). Both the activation and the defective apoptosis of immune effector cells, such as T and B lymphocytes and macrophages, can play critical roles in the pathogenesis of autoimmune disorders (Liu *et al*., 2011). Current therapy for autoimmune diseases often recommends a combination of several disease-modifying antirheumatic drugs (DMARDs) that are designed to preserve different immunomodulatory mechanisms. Because of the limited success in prevention of RA joint destruction for currently available DMARDs, the development of more effective and less toxic DMARDs is in urgent need.

Two commonly prescribed Chinese antirheumatic herbs, namely, TWHF (as mentioned above in Section III.D) and tetrandrine, were shown to preserve both anti-inflammatory and immunosuppressive effects. Tetrandrine, purified from a creeper *Stephania tetrandra* S Moore, is a bisbenzylisoquinoline alkaloid and has been used as a drug in China for decades (Ho and Lai, 2004; Lai, 2002). The immunosuppressive effect of tetrandrine may be synergistic with current DMARDs, highlighting that tetrandrine is a potential candidate of DMARDs for treatment of autoimmune diseases, especially RA (Lai, 2002). For centuries, *Ganoderma*, a fungus (also named as Ling Zhi in Chinese), has been regarded as a premium remedy for a number of diseases. The extracts of *Ganoderma* have been reported to improve the survival rate of lupus mice, decreased the amount of proteinuria, decreased serum levels of anti-dsDNA autoantibody and showed evidence of decreased perivascular and parenchyma mononuclear cell infiltration in vital organs (Lai *et al*., 2001). The extract of *Acanthopanax gracilistylus* markedly suppressed the proliferative activities of human peripheral blood lymphocytes stimulated with mitogens concanavalin A and *Staphylococcus aureus* Cowan I. The mechanism of AGE-induced suppression of lymphocytes was shown to involve cell cycle arrest at the G0/G1 stage without a direct cytotoxic effect. AGE also suppressed the alloantigen-specific CTL response (Shan *et al*., 1999). The ethanol extract of *Celastrus aculeatus Merr.* (*Celastrus*), another Chinese herb, can downmodulate the severity of adjuvant arthritis and reduce the levels of NO (Tong and Moudgil, 2007).

## VI. CHALLENGES, CONCLUSION AND FUTURE PERSPECTIVES

The high value of traditional herbal medicines, specific medicinal plants and the derived phytochemicals for medicinal chemistry study and applications was recently addressed by Dr. Y. Y. Tu in *Nature Medicine* 2011 (Tu, 2011). Her wonderful experience in the discovery of artemisinin from *A. annua* plants and for its use in treatment of malaria very appropriately won her the 2011 Lasker Award in medical research. As elegantly addressed in her article, the wisdom of traditional medicines may need to be re-recognized for the development of future medicines. Within the same context, the recent study on a ''multiple formulation'' of TCM, consisting of four different medicinal plant species, instead of a single phytochemical, for potential use as a ''botanical drug'' for cancer treatment was elegantly demonstrated by the group of Y. C. Cheng (Lam *et al.*, 2010) as recently reported in *Science Translational Medicine*. Here, high-quality experimental results were obtained on metabolite profiling, anti-tumour and anti-inflammatory molecular mechanisms and related clinical studies. The above two reports in combination have exemplified the high interest and importance worldwide on research into medicinal plants and phytomedicines.

Our renewed interests in herbal medicines and phytochemistry should not be blindfolded by the complexity, challenge and difficulty in redefining or readdressing the empirical and anecdotal features of a number of traditional medicines, including TCM and Ayurveda. For instance, even though our own laboratory and others have employed the functional genomics, proteomics and limited metabolomics approaches and attempts to define the immune-modulatory activities of *E. purpurea plants extracts* (Hou *et al.*, 2010; Wang *et al.*, 2008a) or other medicinal plants, our new findings, although helpful in exploring possible molecular mechanisms of the action mode on key immune cell type(s), these results are still not able to allow us to demonstrate the ''efficacy'' or exact function of a spectrum of *E. purpurea* herbal products as the commercial products. Careful and redefined clinical (trail) studies using bioactivity and chemical profiling-defined phytoextracts or phytochemical mixtures may be helpful or required in such future efforts.

The experimental systems and tools for systems biology/omics studies are increasingly available and applicable to research into medicinal plants and their effects on mammalian bioactivities. These research approaches and strategies, however, do not necessarily provide additional or beneficial information on how to improve the use of phytomedicines, due to the complexity

of the disease, disorder and our body's normal physiology systems; we therefore should avoid categorically becoming over-optimistic and unrealistic about the future prospect of the science and technology for developing herbal medicines. The same or similar problems are also being recognized for the current development of new chemical drugs from pharmaceutical industry.

Repeated findings on the "readily detectable" antioxidant, anti-inflammation and "anti-tumour" effects of a broad spectrum of herbal medicines may not always serve as a good indication for the effectiveness or "efficacy" of test herbal remedies or phytochemicals. Since a modest level in these bioactivities may simply represent the "reductant" activities of a big spectrum of plant primary and secondary metabolites in common. As a result, there may often be a lack of "true specificity" in detected bioactivities in tested phytoextracts or phytochemicals. Overly simplified or casual claims of "potent anti-inflammatory or anti-tumour activities" may be viewed as hypes and can be very harmful to our research activities in general, and hence they need to be carefully avoided.

The nature or/and appearance of multiple molecular targets for traditional herbal medicines or phytochemicals may be true, but it may not be a unique feature for herbal medicines only, as many single chemical compounds are well known to exhibit their effects via interaction with multiple molecular targets. With the same token, multiple plant formulations, as often prescribed in TCM practice, may not always be accurately viewed as "aiming at multiple cellular/molecular targets". As the key rationales behind the multiple plants in a TCM formulation often reflect the benefit of a king (primary) drug, minister (secondary) drug, the adjuvant and the bioavailability/delivery (carrier) in combination. Therefore, it could be quite specific towards some specific "target(s)".

In conclusion, we are observing a big change in phytomedicine research, with new concepts, tools and approaches becoming increasingly available. What we may need now are systems build-up, networking, integration of collaboration and the data and database sharing at the global level.

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