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Medicinal chemistry and pharmacology of genus *Tripterygium* (Celastraceae)

Anita M. Brinker^{a,1}, Jun Ma^a, Peter E. Lipsky^b, and Ilya Raskin^{a,*}

^aBiotechnology Center for Agriculture and the Environment, Foran Hall, Cook College, Rutgers, The State University of New Jersey, 59 Dudley Road, New Brunswick, NJ 08901-8520, USA

^bAutoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Rockville Pike, Bethesda, MD 20892, USA

Abstract

Plants in the genus *Tripterygium*, such as *Tripterygium wilfordii* Hook. f., have a long history of use in traditional Chinese medicine. In recent years there has been considerable interest in the use of *Tripterygium* extracts and of the main bioactive constituent, the diterpene triepoxide triptolide (**1**), to treat a variety of autoimmune and inflammation-related conditions. The main mode of action of the *Tripterygium* extracts and triptolide (**1**) is the inhibition of expression of proinflammatory genes such as those for interleukin-2 (IL-2), inducible nitric oxide synthase (iNOS), tumor necrosis factor- α (TNF- α), cyclooxygenase-2 (COX-2) and interferon-gamma (IFN- γ). The efficacy and safety of certain types of *Tripterygium* extracts were confirmed in human clinical trials in the US and abroad. Over 300 compounds have been identified in the genus *Tripterygium*, and many of these have been evaluated for biological activity. The overall activity of the extract is based on the interaction between its components. Therefore, the safety and efficacy of the extract cannot be fully mimicked by any individual constituent. This review discusses the biochemical composition and biological and pharmacological activities of *Tripterygium* extracts, and their main bioactive components.

Keywords

Tripterygium; Celastraceae; Thunder god vine; Terpenoids; Triptolide; Inflammation; Antiinflammatory drugs; Immunosuppression

1. Introduction

Tripterygium wilfordii Hook. f. (Celastraceae) is a woody vine native to Eastern and Southern China, Korea, Japan, and Taiwan (Ma et al., 1999). In China this plant, known as lei kung teng or lei gong teng ("Thunder God Vine"), has a long history of use in traditional Chinese Medicine (TCM) for treating swelling, fever, chills, sores, joint pain, and inflammation (Tao et al., 1991; Li, 1993). Preparations of *Tripterygium* began to be used in allopathic medicine in China in the 1960s to treat rheumatoid arthritis (RA) and inflammation (Tao and Lipsky, 2000). Since then they have also been used for cancer, chronic nephritis, hepatitis, systemic lupus erythematosus, ankylosing spondylitis, and a

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*Corresponding author. Tel.: +1 732 932 8165x227; fax: +1 732 932 6535. raskin@aesop.rutgers.edu (I. Raskin).

¹Present address: Department of Nutritional Sciences, Thompson Hall, Cook College, Rutgers, The State University of New Jersey, 96 Lipman Drive, New Brunswick, NJ 08901-8525, USA.

Dedicated to Prof. David S. Seigler on the occasion of his 65th birthday.

variety of skin conditions (Juling et al., 1981; Qin et al., 1981; Xu et al., 1985; Takaishi et al., 1992a; Li, 1993). Biochemical analysis has shown that *Tripterygium* contains a vast array of natural products with strong biological activities, which may explain its multiple uses in traditional and allopathic medicine in China.

Triptolide (**1**), a diterpenoid epoxide sometimes referred to as PG490 (Fig. 1), is believed to be the major active component of *Tripterygium* extracts (Tao et al., 1995, 1998; Duan et al., 2001a). Most of the antiinflammatory and immunosuppressive activities of extracts can be attributed to triptolide (**1**). The clinical and pharmacological effects of triptolide (**1**) have been reviewed recently (Chen, 2001; Qiu and Kao, 2003; Zhu et al., 2004; Liu et al., 2005). However, several other compounds present in *Tripterygium* may contribute to the biological activity of the extracts and may substantially modify the effects of triptolide (**1**). Therefore, the efficacy of these extracts in disease treatment may be greater than that of triptolide (**1**) alone, due to additive or even synergistic effects between different compounds in the extracts, for example with triptolide (**31**). This review summarizes the pharmacology of *Tripterygium* extracts, a topic discussed in more detail elsewhere (Tao and Lipsky, 2000; Qiu and Kao, 2003; Ho and Lai, 2004), and discusses related activities exhibited by other compounds found in this genus.

2. Taxonomy of the genus *Tripterygium*

In addition to *T. wilfordii*, several other species in the genus *Tripterygium* have been described, including *T. regelii* Sprague and Takeda, native to Japan and Korea; *T. hypoglaucom* (H. Lév.) Hutch., and *T. forrestii* Loes., from China; and *T. doianum* Ohwi, also from Japan. *T. regelii*, *T. hypoglaucom* (known in Chinese as kunmiminshanhaitang (Xia et al., 1994), shan hai ton, san hai ton, or zi jin pi), and *T. forrestii* have also been used in TCM (Tao and Lipsky, 2000). Some authors consider these to be varieties of *T. wilfordii* rather than separate species, and the most recent taxonomic treatment of the genus reduced all other species to synonymy with *T. wilfordii* (Ma et al., 1999). Several taxonomic listings (GRIN, W³TROPICOS, Kew) still recognize multiple species, however, and at least one commercial nursery (Plantsman) distinguishes *T. wilfordii* and *T. regelii* based on differences in the leaves, flowers, fruit, and cold hardiness. Because of the lack of taxonomic clarity and absence of reliable botanical vouchering for the plant sources used in many studies, we prefer to refer to the source plants by the generic epithet *Tripterygium* only. Clearly more research on the taxonomy of genus *Tripterygium* is needed considering the pharmacological potential of this plant.

3. Terpenoid biosynthesis

To date, over 380 secondary metabolites have been reported from *Tripterygium* species. Of these, 95% are terpenoids. Because terpenoids dominate the medicinal chemistry of this plant, the scope of this review was limited to these compounds. *Tripterygium* chemistry in general has been reviewed by Hegnauer (1964, 1989) and by Lu et al. (1987).

The terpenoids are derived from C₅ isoprene units joined in a head-to-tail fashion. They are represented by (C₅)_n and are classified as hemiterpenes (C₅), monoterpenes (C₁₀), sesquiterpenes (C₁₅), diterpenes (C₂₀ such as triptolide (**1**) and triptolide (**31**)), sesterterpenes (C₂₅), triterpenes (C₃₀) and tetraterpenes (C₄₀) (Dewick, 1998). The active isoprene units that are synthesized into terpenoids are the diphosphate esters dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP).

In higher plants, the biosynthesis of terpenoids proceeds via two independent pathways localized in different cellular compartments. The mevalonate (MVA) pathway in the

cytoplasm is responsible for the biosynthesis of sesquiterpenes and triterpenes. Plastids contain the 1-deoxy-D-xylulose-5-phosphate (DOXP) pathway for the biosynthesis of monoterpenes, diterpenes, and tetraterpenes (Lichtenthaler, 1999).

In the cytoplasm-localized MVA pathway, three molecules of acetyl-coenzyme A are used to produce MVA (Beale and MacMillan, 1988). Two ATP react with MVA to produce mevalonate diphosphate, followed by decarboxylation and dehydration with the involvement of a third molecule of ATP to give IPP. IPP is isomerized to the other isoprene unit, DMAPP, by isopentenyl-diphosphate-D-isomerase (EC 5.3.3.2) (Dewick, 1995). IPP and DMAPP are active hemiterpene intermediates (C₅) in the pathways leading to more complicated terpenoids. DMAPP can produce the fundamental sesquiterpene precursor farnesyl diphosphate (FPP), with the successive addition of two further IPPs (Lichtenthaler, 1999). FPP can then give rise to a range of linear and cyclic sesquiterpenes (Beale, 1990). Two molecules of FPP are joined tail-to-tail to yield the precursor of triterpenes, squalene (C₃₀), from which other triterpenes arise (McGarvey and Croteau, 1995).

In the plastid-localized DOXP pathway, pyruvate reacts with glyceraldehyde-3-phosphate (GA-3P) to yield DOXP. Then DOXP can form IPP through a series of reactions (Adam and Zapp, 1998). IPP is isomerized to the other isoprene unit, DMAPP, by isopentenyl-diphosphate-D-isomerase (EC 5.3.3.2). Combination of DMAPP and IPP via the enzyme dimethylallyltransferase (EC 2.5.1.1) produces a monoterpene diphosphate (C₁₀), geranyl diphosphate (GPP) (Croteau, 1987). GPP can be isomerized to linalyl PP and neryl PP. These three compounds can produce a range of linear monoterpenes (Croteau, 1987). The linear monoterpenes can create monocyclic and bicyclic systems via cyclization reactions (Croteau, 1987). GPP can produce the fundamental diterpene precursor (C₂₀), geranylgeranyl diphosphate (GGPP), with the successive additions of a further two IPPs (Lichtenthaler, 1999). Two molecules of GGPP are joined tail-to-tail to form a tetraterpene compound phytoene (C₄₀), a precursor for other tetraterpenes (McGarvey and Croteau, 1995). The two biosynthetic pathways of terpenoids are summarized in Figs. 2 and 3.

The two terpenoid biosynthetic pathways are not totally independent. In cultured cells of the liverwort (*Heteroscyphus planus*), the cytoplasmic FPP was found to transfer into the plastid where FPP was condensed with a DOXP-derived IPP (Nabeta et al., 1995, 1997). In snapdragon (*Antirrhinum majus*) flowers, the plastidal IPP transferred into the cytoplasm (Dudareva et al., 2005).

4. Biological effects of *Tripterygium* extracts and triptolide

This review will first describe the biological activities of triptolide (**1**) and of various *Tripterygium* extracts, followed by a discussion of the activities of other terpenoids present in the plant.

Most extracts used in research and clinical studies were made from the woody roots of *Tripterygium*. However, the extracts were often prepared in different ways (e.g. with different solvents), and thus had different constituents and biological effects. Different methods of preparation included water extraction, ethyl acetate extraction, ethanol extraction or chloroform–alcohol extraction. The rodent LD₅₀ values of extracts obtained using these extraction methods were often as low as 160 mg/kg in mice (Lipsky et al., 1996). The toxicity of the extract was significantly reduced when the outer bark was removed from the roots, and the debarked roots extracted with ethanol followed by ethyl acetate partitioning. The LD₅₀ values in mice for this ethanol-ethyl acetate extract were between 860 and 1300 mg/kg (Lipsky et al., 1996). An extract prepared in this way was used in the US human clinical trials (see below).

4.1. Antiinflammatory and autoimmune conditions

Although inflammation is important in preventing disease, there are numerous autoimmune disorders that involve deleterious inflammatory responses, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, and Type 1 diabetes. The ability to suppress immune responses is also necessary for successful organ and tissue transplantation.

Extracts of *Tripterygium* have been extensively tested, both in animals and clinically, for the treatment of autoimmune diseases. These extracts showed strong activity in several standard in vivo assays for antiinflammatory activity, including the adjuvant-induced and carrageenan-induced paw edema assays, the carrageenan-induced air pouch model, and the cotton-induced granuloma assay (Chou, 1997; Su et al., 1999; Tao et al., 1999; Zhang et al., 2000a). Inhibition of antibody production in rats and mice was also observed (Lipsky et al., 1998; Hu et al., 2003). Extracts also performed well in animal models of rheumatoid arthritis (Tao and Lipsky, 2000), including collagen-induced arthritis in mice (Gu et al., 1992), adjuvant-induced arthritis in rats (Yu et al., 1994; Hu et al., 2003), and arthritis that develops spontaneously in HLA-B27 transgenic rats (Tao et al., 1996). *Tripterygium* extracts were also effective in a mouse model of graft-vs.-host disease, an immunological reaction to foreign tissue (Chen et al., 2000), and in studies with allografts, transplants of tissue from a genetically similar donor (reviewed by Chen, 2001; Qiu and Kao, 2003).

There have been numerous human clinical trials of extracts, and one that also included triptolide (**1**), for rheumatoid arthritis and other autoimmune conditions (Tao and Lipsky, 2000; Tao et al., 2001, 2002). Generally, these trials demonstrated good clinical efficacy of *Tripterygium* extracts in patients with rheumatoid arthritis. Extracts have fewer undesirable side effects than pure **1**. The potential ability of *Tripterygium* extracts to benefit transplant patients has been demonstrated in two clinical trials conducted in China. The first involved kidney transplant patients; graft function normalized more quickly in the patients treated with the *Tripterygium* extract, with fewer complications (Ao et al., 1994). In the second study (Zhang et al., 1994a), a *Tripterygium* extract prolonged the survival of islet grafts in patients with diabetes. Also, *Tripterygium* extract was found effective in a small human trial in China in patients with systemic lupus erythematosus, psoriasis and Behcet's disease (Lipsky and Tao, 1996). When given with prednisone, a corticosteroid, the extracts exhibited a steroid sparing effect.

Pure triptolide (**1**) has also shown significant activity in animal models including the adjuvant-induced arthritis model and allograft models (reviewed by Chen, 2001; Qiu and Kao, 2003; Zhu et al., 2004). Compounds related to **1** are currently being evaluated for use in organ transplantation (First and Fitzsimmons, 2004).

4.1.1. Proinflammatory cytokines and lymphocytes—The biochemical signaling underlying inflammation and the immune response is complex. The following discussion covers only those interactions that have been shown to be affected by compounds from *Tripterygium*; the reader is referred to other sources for more information on immunology in general (Ibelgaufts, 2003).

In rheumatoid arthritis, monocytes (a type of white blood cell) and cells in the synovial membranes of joints produce proinflammatory cytokines, including interleukin-1 (IL-1; there are α and β forms), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) (Chang et al., 1997). These small proteinaceous signaling molecules are also produced in the early stages of other inflammatory and immune reactions, and have many effects. For example, they activate T and B-cells (specialized white blood cells known collectively as lymphocytes) to proliferate and express other interleukins such as IL-2 and IL-8, and

interferon-gamma (IFN- γ). IL-1 also stimulates the expression of genes for enzymes including inducible nitric oxide synthase (iNOS, EC 1.14.13.39) and cyclooxygenase-2 (COX-2, also known as prostaglandin-endoperoxide synthase, EC 1.14.99.1) (Chen and Wei, 2003). IL-2 stimulates the proliferation of T- and B-cells, and IL-8, like TNF- α , promotes angiogenesis (the formation of new blood vessels), which is involved in rheumatoid arthritis, tumor growth, and wound healing. IFN- γ is immunomodulatory but also has some proinflammatory activity. The ultimate effects of these cytokines and enzymes include inflammation and degradation of bone and cartilage (Chen and Wei, 2003).

Numerous studies (review by Chen, 2001) indicate that extracts of *Tripterygium* suppress production of cytokines, including TNF- α (Chang et al., 1997; Luk et al., 2000a), IL-2 (Tao et al., 1991, 1995), IFN- γ (Tao et al., 1995; Lipsky et al., 1998) and IL-8 (Lee et al., 1995). IL-6 production was also inhibited, but not as strongly (Chang et al., 1997; Tao et al., 1996). Suppression of IL-2 production was due to inhibition of IL-2 mRNA expression and also promotion of IL-2 mRNA degradation (Wu et al., 1993). Expression of receptors for IL-2 was inhibited in some studies (Tao and Lipsky, 2000) but not others (Tao et al., 1991). Consistent with the effect on the proinflammatory signals, extracts strongly inhibited proliferation of T and B cells (Tao et al., 1991, 1995). Pure triptolide (**1**) also inhibited T cell proliferation and production of TNF- α , IL-1, IL-2, IL-6, and IL-8 (Tao et al., 1995; Chan et al., 1999; Qiu et al., 1999; Lin et al., 2001a; Zhou et al., 2003). The suppression of metabolic activity in T cells was not due solely to reduction in cell viability (Chan et al., 1999).

4.1.2. Proinflammatory enzymes—Nitric oxide synthase (NOS) catalyzes the production of nitric oxide (NO). Inducible nitric oxide synthase (iNOS) is expressed by vascular endothelial cells (cells that line blood vessels) and smooth muscle cells in response to cytokines, unlike the two other types of NOS, which are constitutive. NO produced by iNOS is implicated in inflammatory diseases and septic shock (Niwa et al., 1997). Because iNOS is mainly regulated at the transcriptional level, compounds that inhibit its transcription are unlikely to inhibit the beneficial constitutive NOSs and are therefore of interest for the treatment of NO mediated inflammatory conditions (Dirsch et al., 1997). Similarly, cyclooxygenase, which catalyzes the first step in the conversion of arachidonic acid to prostaglandins, has constitutive (COX-1) and inducible (COX-2) forms. The latter form is responsible for the prostaglandin synthesis that occurs as part of inflammation and potentiates its progression. COX-2 also promotes angiogenesis (Delhalle et al., 2004). Inhibition of COX-1, however, reduces blood platelet aggregation and causes gastrointestinal distress, among other effects. Therefore, specific inhibition of COX-2 but not COX-1 may provide relief from inflammation without side effects such as damage to the kidneys or gastric mucosa (Tao et al., 1998). Arachidonic acid can also be converted to leukotrienes, which are involved in asthma, by a pathway the first enzyme of which is lipoxygenase (arachidonate 5-lipoxygenase, EC 1.13.11.34). Other inflammatory enzymes include matrix metalloproteinases (MMP, EC 3.4.24 family), which cause erosion of cartilage extracellular matrix in arthritis patients.

There are several reports of the effects of *Tripterygium* extracts on inflammatory enzymes. Extracts inhibited production of COX-2 (Tao et al., 1998; Maekawa et al., 1999), iNOS (Guo et al., 2001), and MMP-3 and -13 (Sylvester et al., 2001), apparently by blocking mRNA transcription. Production of COX-1 was not affected (Tao et al., 1998). Suppression of prostaglandin E₂ (PGE₂) synthesis was observed (Chang et al., 1997; Tao et al., 1998; Maekawa et al., 1999), but the mechanism of the suppression was not determined. Inhibition of lipoxygenase was also noted (Li et al., 2003a). However, in some studies the effects varied depending on the cell line used (Tao et al., 1998). This, or differences in the methods used to prepare the plant extracts, could also account for the inconsistent results reported

concerning inhibition of COX-1 and COX-2 activity. In one study, an extract did not inhibit the activity of either enzyme (Maekawa et al., 1999); in another, an extract inhibited activity of COX-1 more strongly than that of COX-2 (Li et al., 2003a).

Similarly, triptolide (**1**) suppressed expression of COX-2 and the precursor forms of MMP-1 and -3, and inhibited production of PGE₂ and NO and activity of lipoxygenase (Tao et al., 1998; Lin et al., 2001a; Zhou et al., 2003). The inhibition of PGE₂ production was due to suppression of COX-2 (Tao et al., 1998). COX-1 expression was not affected (Lin et al., 2001a). As with the extracts, the inhibitory effects of **1** on PGE₂ production varied depending on the cell line studied (Tao et al., 1998). Inhibition of NO production was due to inhibition of transcription of the iNOS gene (Wang et al., 2004a).

4.1.3. Transcription factors and molecular mode of action—Transcription of the genes for iNOS and COX-2 is activated by the transcription factor nuclear factor-kappa B (NF-κB) (Hwang et al., 2001). NF-κB is a protein normally located in the cytoplasm in an inactive form bound to another protein, IκB. Signals (including free radicals, carcinogens, tumor promoters, and radiation as well as inflammatory factors such as TNF-α) lead to the degradation of IκB and the release of NF-κB, which then enters the nucleus and binds to DNA promoter regions, activating gene transcription (Koo et al., 2001; Aggarwal and Shishodia, 2004). Over 200 genes are induced by NF-κB (Aggarwal and Shishodia, 2004), including some that suppress apoptosis and many that encode components of the immune and inflammation responses (Schorr et al., 2002; Hwang et al., 2003). While the promoter regions of the iNOS and COX-2 genes have NF-κB binding sites, the promoter region of the COX-1 gene does not (Maekawa et al., 1999; Hwang et al., 2001). Thus, inhibitors of NF-κB are of interest as potential antiinflammatory drugs. Natural products of several types, including lignans (Hwang et al., 2003), sesquiterpene esters (Jin et al., 2002) and sesquiterpene lactones (Koo et al., 2001; Schorr et al., 2002), have been found to interfere with various steps in NF-κB release and activation of DNA transcription (Lee et al., 2002a). Genes involved in inflammation can also be activated by other transcription factors, such as activator protein-1 (AP-1), nuclear factor of activated T cells (NFAT), and Oct-1, and by the p38 mitogen-activated protein (MAP) kinase pathway (Barnes and Karin, 1997; Diehl et al., 2004; Pinna et al., 2004; Wang et al., 2004a).

A *Tripterygium* extract was found to inhibit binding of NF-κB to DNA, but did not interfere with the p38 MAP kinase pathway (Sylvester et al., 2001). Whether any components of the *Tripterygium* extract interfere with AP-1 activity remains controversial (Maekawa et al., 1999; Sylvester et al., 2001; Wang et al., 2004a). Pure triptolide (**1**) did not affect DNA binding of NF-κB; rather, it inhibited the transcription of proinflammatory genes by blocking the transactivation of NF-κB, which occurs after its binding to promoter regions of these genes (Qiu et al., 1999; Lee et al., 2002a). Triptolide (**1**) also inhibited transactivation by NFAT and upregulation of the nucleotide-binding activity of Oct-1 (Qiu et al., 1999; Wang et al., 2004a).

Activation of NF-κB and AP-1 is inhibited by activated glucocorticoid receptor (aGR), which is a glucocorticoid-receptor complex that functions as a transcription factor (Xu et al., 2001). Both an extract and **1** inhibited aGR-mediated gene activation (Lipsky et al., 1998). This effect was the result of direct binding of **1** and possibly other extract components to the glucocorticoid receptor (GR). Extract-GR complex, unlike the corticosteroid (i.e. dexamethasone)-GR complex, did not activate the genes containing glucocorticoid response elements. However, the extract-GR complex was possibly effective in inhibiting the activation of nuclear proinflammatory transcription factors, such as NF-κB. This property of *Tripterygium* extract may explain its antiinflammatory and immunosuppressive action along with the steroid-sparing effects observed in some human trials. Clinical applications of

dexamethasone and other glucocorticoids are often limited by such side effects as hyperglycemia, osteoporosis, weight gain and suppression of the pituitary-adrenal function, which are caused by transcriptional activation of many GR-responsive genes. The proposed mode of action for the *Tripterygium* extract suggests that the extract may reduce inflammation, with fewer side effects than glucocorticoids.

A recent study of the effects of triptolide (**1**) on dendritic cells (DC) showed that **1** inhibits lipopolysaccharide (LPS)-induced DC production of pro-inflammatory proteins including macrophage inflammatory proteins (MIP)-1 α , MIP-1 β , MCP-1, thymus and activation-regulated chemokines (TARC), regulated upon activation of normal T cell expressed and secreted factor (RANTES), and interferon- γ inducible protein-10 (IP-10) possibly via inhibition of NF- κ B activation and the signal transducer and activator of transcription 3 (Stat3) phosphorylation (Liu et al., 2006). However, **1** increases expression of the suppressor of cytokine signaling 1 (SOCS1), which in turn results in the reduced chemoattraction of neutrophils and T cells by **1**-treated DC.

The data on the effects of *Tripterygium* extract and its main bioactive constituent **1** on the genes involved in inflammation and immunosuppression are complex and somewhat controversial. Nevertheless, a plausible hypothesis explaining the molecular mode of action of **1** and, to a large extent, the whole *Tripterygium* extract on T cells can be formulated (Fig. 4). It is likely, however, that triptolide (**1**) also modulates the autoimmune and inflammatory pathways in other cell types, as discussed elsewhere.

4.1.4. Adhesion and surface molecules—Among the genes activated by NF- κ B are those encoding intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin, which are adhesion molecules; they attract inflammatory cells such as T cells to the site of inflammation (Barnes and Karin, 1997). *Tripterygium* extract inhibited secretion of all three of these (Chang et al., 1999) as well as production of the cell surface molecules CD18, CD11c, and CD14, which have a similar function (Luk et al., 2000a,b).

4.1.5. Apoptosis and cell proliferation—Apoptosis is a process of programmed cell death that normally is triggered in cells that are old or targets of biotic or abiotic stresses. The apoptotic process involves the activation of caspases (EC 3.4.22.36), cysteine proteases that trigger a series of reactions leading to DNA degradation (Choi et al., 2003). Defects in the apoptotic process, particularly in T cells, may be involved in autoimmune diseases (Lai et al., 2001; Ho and Lai, 2004). Induction of apoptosis in T or B cells, or inhibition of their proliferation, reduces inflammation triggered by these cells (Ho and Lai, 2004). Therefore, compounds that enhance apoptosis or inhibit T or B cell proliferation may be useful for treating inflammatory or autoimmune diseases. *Tripterygium* extracts inhibited T and B cell proliferation (Li and Weir, 1990; Tao et al., 1991) and induced apoptosis in T cells (Ho et al., 1999). Triptolide (**1**) also induced apoptosis in certain T cell types (Yang et al., 1998) and in dendritic cells, another type of immune cell (Liu et al., 2004a). Triptolide (**1**) also inhibited proliferation of T and B cells and synovial fibroblasts, which are cells that synthesize fibrous matrix proteins and that play a role in joint degradation in RA (Lipsky and Tao, 1999; Tong et al., 1999; Edwards, 2000; Kontoyiannis and Kollias, 2000).

4.2. Cancer

Substances that induce apoptosis or inhibit cell proliferation could also be of interest for the treatment of cancer, because apoptosis is blocked in cancer cells. Many existing anticancer drugs, including cisplatin and paclitaxel, act by inducing apoptosis (Chan et al., 2001). Although TNF- α induces apoptosis, it also activates NF- κ B, which inhibits apoptosis;

therefore inhibitors of NF- κ B may enhance the apoptotic activity of TNF- α (Lee et al., 1999). In addition, induction of proinflammatory cytokines via activation of NF- κ B has been linked to tumor promotion (Suganuma et al., 2002), suggesting a further benefit of blocking NF- κ B.

Several other possible approaches to the treatment of cancer are currently being studied. Inhibitors of angiogenesis are of interest because the development of new capillaries is important for the growth of tumors. New capillaries are formed by vascular endothelial cells, which migrate, proliferate, and organize into tubes that mature into new vessels. The migration is assisted by the activity of MMPs. Inhibitors of endothelial cell proliferation and of MMPs are among substances being tested as anticancer drugs (National Cancer Institute, 2005). DNA polymerase β (DNA-directed DNA polymerase, EC 2.7.7.7) repairs DNA damage, and therefore reduces the efficacy of drugs that act by damaging DNA in dividing cells. Administration of a DNA polymerase β inhibitor in combination with a DNA-damaging drug might enhance the drug's effectiveness and allow a lower dose to be given (Sun et al., 1999). Topoisomerase II (EC 5.99.1.3) relieves strain in DNA by breaking and religating double-stranded DNA; several anticancer drugs are topoisomerase II inhibitors (Furbacher and Gunatilaka, 2001). Aromatase (cytochrome p450 subfamily 19) converts androgens to estrogens and is present at elevated levels in breast tumors; aromatase inhibitors may be beneficial in the treatment of hormone-dependent breast cancer and benign prostatic hyperplasia (Ganßer and Spittler, 1995; Jeong et al., 2000).

A preparation from *Tripterygium* induced apoptosis of HL-60 leukemia cells (Wang and Hidenori, 2000; Zhuang et al., 2004). An extract given to cancer patients produced a substantial improvement within 5 weeks, and was patented as a treatment for human melanomas (Debiopharm, 1994). Triptolide (**1**) has shown antiproliferative and apoptotic effects in several tumor lines in vitro (Kutney et al., 1997; Tengchaisri et al., 1998; Lee et al., 1999; Kiviharju et al., 2002; Yang et al., 2002; Choi et al., 2003) and restricted tumor growth, or shrank tumors, in animals (Tengchaisri et al., 1998; Yang et al., 2002). By suppressing activation of NF- κ B, **1** made tumor cells more sensitive to TNF- α -induced apoptosis (Lee et al., 1999, 2002a). Triptolide (**1**) also showed synergistic effects with other chemotherapeutic agents (Chang et al., 2001; Fidler et al., 2003). A derivative known as PG490-88 has been approved for Phase I clinical trials for solid tumors (Kiviharju et al., 2002; Fidler et al., 2003).

4.3. Neurodegenerative diseases

Inflammation also plays a role in neurodegenerative diseases including Alzheimer's and Parkinson's. When microglial cells (a type of immune cell found in neural tissue) in the brain are stimulated by factors such as neurotoxins, they release inflammatory cytokines, NO, and other reactive oxygen species (Li et al., 2004a). Free radicals are also generated in Alzheimer's patients by aggregations of β -amyloid protein (Brinton and Yamazaki, 1998). Reactive oxygen species produce oxidative stress (a shift in the oxidant-antioxidant balance in favor of the former) that causes damage to which neurons are particularly sensitive (Shaw and Bains, 2002). The proinflammatory cytokines TNF- α and IL-1 β can also trigger damage or improper function in neurons (Zhou et al., 2003). Triptolide (**1**) scavenged free radicals (Ren et al., 1997) and inhibited release of inflammatory factors from microglia (Zhou et al., 2003; Li et al., 2004a).

4.4. Antifertility

Among the side effects noted in patients treated with *Tripterygium* extracts was reversible sterility in men. This proved to be due to lack of sperm and/or weakly active sperm in patients administered the extract (Tao and Lipsky, 2000). Inhibition of Ca²⁺ channels in

spermatogenic cells may be the cause (Bai and Shi, 2002; Bai et al., 2003). Triptolide (**1**) had antifertility activity in adult rats (Lue et al., 1998). These observations led to interest in developing extracts or compounds from *Tripterygium* as male contraceptives.

4.5. Insecticidal activity

T. wilfordii was also used traditionally in China as an insecticide, and it was this property that caused it to be brought to the U.S. in 1935 by scientists with the U.S. Department of Agriculture's Division of Plant Exploration and Introduction (Swingle et al., 1941). Much of the early chemical work on *Tripterygium* was undertaken by USDA scientists attempting to identify the insecticidal compounds (Acree and Haller, 1950; Beroza, 1953 and papers cited therein). Triptolide (**1**) has shown both antifeedant activity and contact toxicity to larvae of *Mythimna separata* Walker (Oriental armyworm) (Luo et al., 2004).

4.6. Recent clinical studies

Clinical studies of *Tripterygium* extracts that demonstrated their efficacy have been reviewed by Tao and Lipsky (2000). Since that review, the results of several studies in China and the US have been published. In most of these studies, the preparation used was that known as multiglycoside or polyglucoside, also known as T2 or T_{II} (Zhu, 1998), frequently in combination with other treatments. For instance, in rheumatoid arthritis (RA) patients, the multiglycoside preparation combined with low doses of methotrexate, a standard RA drug, produced better symptom reduction with fewer side effects than did higher doses of methotrexate alone (Wu et al., 2001). The multiglycoside preparation was as effective as prednisone in the treatment of Graves' ophthalmopathy (Wang et al., 2004b) and, in two small studies, gave substantial improvement in the symptoms of refractory pyoderma gangrenosum (Li, 2000) and anaphylactoid purpura nephritis (Zhang et al., 2004a). It has also been used as a control treatment in some trials; it improved the symptoms of patients with RA (Zhou et al., 2004a) and childhood Henoch-Schonlein purpura nephritis (Zhou et al., 2004b), though not as well as some other treatments.

The multiglycoside preparation gave improvements in the in vivo levels of cytokines and other disease markers in several studies. It significantly decreased the levels of IL-6 and peripheral B lymphocytes in patients with myasthenia gravis (Li et al., 2002), IL-5 and CD4⁺ T lymphocytes in asthma patients (Wang and Zhang, 2001), and serum IL-2 and TNF- α in patients with acute anterior uveitis (Huang et al., 2002). Multiglycoside also lowered IL-6 levels and improved symptoms in Guillain-Barre syndrome patients more effectively than adrenal corticosteroid (Zhang et al., 2000b).

A few studies of other *Tripterygium* extracts have been undertaken. In a study involving nearly 600 RA patients, a *T. wilfordii* preparation gave better relief of symptoms than indomethacin/ibuprofen (both commercial nonsteroidal antiinflammatory drugs), though about 30% of the *Tripterygium* group reported adverse effects (Yao and Nian, 2004). Treatment with *Tripterygium* also decreased the size of uterine leiomyomas (uterine fibroids) (Gao and Chen, 2000).

Two studies compared different *Tripterygium* preparations. The multiglycoside preparation was more effective than a *T. hypoglaucom* root preparation in treating grade 1 erosive oral lichen planus, but there was no significant difference between treatments in grade 2 patients (Lin and Qi, 2005). A preparation from *T. wilfordii* leaves was just as effective as a root preparation at alleviating the symptoms of RA, with no significant difference in the occurrence of side effects (Du et al., 1998).

Triptolide (**1**) has also been tested in recent clinical trials. It produced improvement in 75% of psoriasis vulgaris patients in an uncontrolled study (Wu and Guo, 2005). It also decreased levels of urinary monocyte chemoattractant protein-1, a marker of kidney inflammation, in patients with diabetic nephropathy (Song et al., 2005) and has shown efficacy in treating nephrotic syndrome and in suppressing rejection of kidney transplants (Peng et al., 2005).

Two clinical trials of an ethanol/ethyl acetate extract of *Tripterygium* in the treatment of RA have been undertaken in the US. The first was an open label dose escalation Phase I study that found that dosages up to 570 mg/day (the highest dose used) appeared to be safe and that 6 of 10 patients treated with 180 mg/day showed disease improvement. Eight out of the 9 patients who received a dose over 360 mg/day showed improvement in both clinical manifestations and laboratory findings (Tao et al., 2001). In the second trial, a double-blind, placebo-controlled study that compared two dose levels with a placebo, 80% of the highdose patients (360 mg/day) and 40% of the low-dose patients (180 mg/day), but none of the patients receiving a placebo, experienced symptom improvement (Tao et al., 2002). Both doses were well tolerated. In both trials, over 80% of the patients taking the higher doses met the American College of Rheumatology (ACR) 20% improvement criteria.

5. Biological activity of *Tripterygium* terpenoids other than triptolide

5.1. Sesquiterpenes

To date, 124 sesquiterpene derivatives have been reported from *Tripterygium*. Most of these compounds are either dihydroagarofurans or alkaloids composed of a dihydroagarofuran esterified to a pyridine dicarboxylic acid.

5.1.1. Dihydroagarofurans—These compounds (Fig. 5 and subsequent figures include only the biologically active ones) are characteristic of plants in the Celastraceae, to which *Tripterygium* belongs. Although the biological activities of many dihydroagarofurans have been studied, relatively few compounds found in *Tripterygium* have been tested. In addition to the effects described below, compounds of this class have shown immunosuppressive activity, including inhibition of NF- κ B activation and iNOS production in vitro, and the ability to reverse multidrug resistance, a mechanism some cancer cells have for removing toxic substances (Kim et al., 1999; González et al., 2000a; Jin et al., 2002). Several compounds of this type have shown at least weak insect antifeedant activity (González et al., 1992).

5.1.1.1. Antiinflammatory and autoimmune conditions: Five sesquiterpenes from *T. wilfordii* significantly inhibited lymphocyte transformation, an early stage in the immune response (Wang et al., 2005a). The compounds were 1 β -furanoyl-2 β ,3 α ,7 α ,8 β ,11-pentaacetoxy-4 α ,5 α -dihydroxy-dihydroagarofuran (**10**), 1 β ,2 β ,3 α ,5 α ,7 β ,8 β ,11-heptaacetoxy-dihydroagarofuran (**11**), 1b-furanoyl-2b,3 α ,7 α ,8b, 11-pentaacetoxy-5 α -hydroxy-dihydroagarofuran (**12**), 1 β ,7 β , 8 α -triaceoxy-2 β -furanoyl-4 α -hydroxy-11-isobutyryloxydihydroagarofuran (**13**), and 1 β -nicotinoyl-2 β ,5 α ,7 β -triaceoxy-4 α -hydroxy-11-isobutyryloxy-8 α -furanoyl-dihydroagarofuran (**14**).

5.1.1.2. Cancer: The ability of compounds to inhibit 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein–Barr virus early antigen activation (EBV-EA) is used as an indicator of antitumor-promoting activity. Of the 29 dihydroagarofurans from *T. wilfordii* var. *regelii* screened in this assay, triptofordin F-2 (**5**) and triptogelin A-1 (**6**) were particularly active (Takaishi et al., 1992a). The latter compound was also tested in mice and reduced the number of papillomas that formed (Ujita et al., 1993). Triptogelin C-1 (**8**) showed only weak

cytotoxicity to KB-3-1 human oral epidermal cancer cells, but good multidrug resistance-reversing activity in the corresponding multidrug resistant cell line (Kim et al., 1999).

5.1.1.3. Insecticidal activity: Triptogelin G-1 (**9**) had moderate antifeedant activity and significant insecticidal activity against *Pieris rapae* (Tu and Wu, 1992). Triptofordin D-2 (**2**) had antifeedant activity against *Spodoptera littoralis*, and triptofordin E (**3**) and compound **8** (**4**) had insecticidal activity (González et al., 1993, 1997). Angulatueoid G (apparently identical to triptogelin A-3 (**7**)) had antifeedant activity against *Aulacophora femoralis* and *Plutella xylostella* (Wu et al., 1992).

5.1.2. Sesquiterpene alkaloids—The sesquiterpene alkaloids from *Tripterygium* (Figs. 6 and 7) have been reviewed recently (Cao, 2003; Shu et al., 2003), and the biological activities of alkaloids of this class from plants in the families Celastraceae and Hippocrateaceae have been described (González et al., 2000b). The reported activities are similar to those for the dihydroagarofurans.

5.1.2.1. Antiinflammatory and autoimmune conditions: Twenty-one sesquiterpene alkaloids from *T. wilfordii* were screened for inhibition of cytokine production from human peripheral mononuclear cells, which include B- and T-cells among other types (Duan et al., 2001b). Two compounds – ebenifoline E-II (**27**) and cangorinine E-1 (**25**) – showed at least 80% inhibition of IL-2, IL-8, and IFN- γ . Compounds showing greater than 70% inhibition of particular cytokines included **27** and wilforine (**16**) for TNF- α , and eunone (=wilforine) (**21**) for IFN- γ . On the other hand, **27** and mayteine (**26**) induced IL-6 and, weakly, TNF- α in human peripheral blood mononuclear cells (Nakagawa et al., 2004); this could have antitumor but also proinflammatory effects. The alkaloids wilfordsine (**24**), wilfordconine (**28**), and wilforine (**20**) were reported to be immunosuppressive (Deng et al., 1987a; Lin et al., 1995, 2001b), and wilfortrine (**15**), eunone (**21**), and wilforine (**16**) inhibited the humoral immune response (antibody-mediated responses) in animals (Zheng et al., 1989; Xia and Chen, 1990). Wilfortrine (**15**) also depressed the graft-vs.-host reaction (Zheng et al., 1989). Wilforine (**16**) was effective in treating idiopathic pulmonary fibrosis (an inflammatory lung condition) in rats, and arthritis (Dai et al., 1998; Xia and Chen, 1990). Wilfordine (**19**) inhibited the functioning of B cells from lupus patients as well as proliferation of peripheral blood mononuclear cells (Yu et al., 1999).

5.1.2.2. Cancer: Wilfortrine (**15**) inhibited growth of murine leukemia cells in vivo (Deng et al., 1987b). Euonymine (**23**) had some inhibitory effect on TPA-induced EBV-EA, though it was not as active as the non-alkaloidal dihydroagarofurans tested at the same time (González et al., 2000a).

5.1.2.3. Insecticidal activity: The insecticidal properties of *Tripterygium* appear to be due mainly to compounds of this class, some of which are present in patented insecticidal formulations (Wu et al., 1994; Liu and Yang, 2001). Two early reports from China mention insecticidal alkaloids from root bark of *T. forrestii* (Chiu et al., 1945) and *T. wilfordii* (“tripterygine”) (Hwang, 1940). Wilforgine (**18**) and wilfortrine (**15**) were toxic to young European corn borer larvae (Beroza, 1952). Wilforine (**16**) had antifeedant activity that was greater against *Pieris rapae* and *Locusta migratoria* than against more polyphagous feeders (Delle Monache et al., 1984). Wilfordine (**17**), alatusinine (**22**), and eunone (**21**) showed good antifeedant activity against the lepidopteran *Spodoptera littoralis* (Núñez et al., 2004). Eunone (**21**) had no contact activity against larvae of *Mythimna separata* (Oriental armyworm), but good activity in antifeedant and ingested toxicity assays, with activity levels higher than that of the commercially available limonoid toosendanin (Luo et al.,

2004). Ebenifoline E-II (**27**) (called euoverrine A by the authors) also was toxic to *M. separata* (Zhu et al., 2002).

5.1.3. Dinorsesquiterpene—Wilforonide (**29**), a C₁₃ compound (Fig. 8), inhibited T cell proliferation and IL-2 production from T cells (Lipsky et al., 1998).

5.2. Diterpenes

The majority of the 116 reported diterpenes in *Tripterygium* are abietanes. Of these, about two-thirds have a benzenoid ring as part of the structure; 36 have a lactone ring.

5.2.1. Triptolide derivatives—A number of diterpenoid epoxides structurally similar to triptolide (**1**) have been found in *Tripterygium* (Figs. 9 and 10). Several of these compounds are referred to by codes in some papers. Tripchlorolide (**36**) is also known as T₄, triptonide (**30**) as T₇, triptiolide (**31**) as T₈, triptolidenol (**32**) as T₉, triptolide (**1**) as T₁₀, triptriolide (**34**) as T₁₁, and 16-hydroxytriptolide (**33**) as L₂ (Zheng et al., 1991a; Li, 1993). Tripchlorolide (**36**) may be an artifact of isolation and can spontaneously reconvert to **1** (Matlin et al., 1993), which suggests that the biological activity reported for this compound may actually be due to **1**.

5.2.1.1. Antiinflammatory and autoimmune conditions: Diterpene epoxides other than triptolide (**1**) have, like **1**, exhibited considerable antiinflammatory activity. Five triptolide derivatives – triptonide (**30**), triptiolide (**31**), triptolidenol (**32**), 16-hydroxytriptolide (**33**), and tripchlorolide (**36**) – were active in both the croton oil-induced mouse ear edema assay and the hemolysin-antibody formation model of immunosuppressive activity (Zheng et al., 1991a). These compounds and triptriolide (**34**) inhibited proliferation of mouse T and B cells (Zheng et al., 1994). Triptolidenol (**32**) was also active in the carrageenin-induced rat paw and cotton-induced granuloma assays, and lowered plasma levels of PGE₂ (Gu et al., 1994). Triptriolide (**34**) and 12-epitriptriolide (**35**) were antiinflammatory in the croton oil-induced mouse ear edema assay (**34** only weakly) but were not immunosuppressive (Ma et al., 1991a; Zheng et al., 1991a; Ma and Yang, 1993). Triptonide (**30**) inhibited proliferation of lymph cells (Zhang et al., 1986a) and mouse splenocytes, and suppressed mixed lymphocyte culture, which indicates immunosuppressive activity (Pei et al., 1993). Triptiolide (**31**) was also immunosuppressive in the mixed lymphocyte reaction (Gu et al., 1995) and inhibited production of IL-1 β , IL-2, IL-8, TNF- α , and IFN- γ as well as T cell DNA synthesis (Tao et al., 1995; Duan et al., 2001a). Like **1**, it inhibited glucocorticoid receptor-induced gene activation (Lipsky et al., 1998). Triptonide (**30**) also inhibited IL-2 production and DNA synthesis by T cells, but less strongly than **31** (Tao et al., 1995).

Tripchlorolide (**36**) has been especially well studied. In addition to the activity mentioned, it inhibited production of the cytokines TNF- α , IL-1, IL-2, IL-6, IL-8, and IFN- γ (Yao and Zhang, 1994a; Zhang et al., 1994b; Zeng and Zhang, 1996, 1997; Qiu et al., 2000; Duan et al., 2001a), though in one study it had no effect on IL-6 production by IL-1 stimulated fibroblasts (Guo et al., 2000). It also inhibited production of NO (Qiu et al., 2000) and PGE₂ (Yao and Zhang, 1994b), and DNA synthesis in and expression of the IL-2 receptor on T cells (Tao et al., 1995; Fan et al., 1996). Proliferation of several cell types was inhibited, including peripheral blood mononuclear cells (Yao and Zhang, 1994c), synovial fibroblasts (Guo et al., 2000) and mesangial cells (present in the kidney and possibly involved in immune responses) (Zhang et al., 1994b). Tripchlorolide (**36**) also prolonged functioning of transplanted hearts in rats (Li et al., 1994).

5.2.1.2. Cancer: Triptiolide (**31**) was cytotoxic to KB cancer cells (Kupchan and Schubert, 1974) and was more effective against leukemia cell lines than against solid tumors (Wood,

1979). In tests using six human cancer cell lines, it appeared to inhibit cell growth without killing the cells (Kutney et al., 1997). Triptonide (**30**) was also cytotoxic to KB cells (Kupchan and Schubert, 1974) and to five of the six lines tested in another study (Ning et al., 2003). Tripchlorolide (**36**) inhibited proliferation of endothelial cells (Yao and Zhang, 1994a), suggesting it may have antiangiogenesis activity. Triptonide (**30**), triptolidenol (**32**), and tripchlorolide (**36**) did not produce DNA damage in male rats (Wang and Xie, 1999; Zhang et al., 2002).

5.2.1.3. Neurodegenerative diseases: Tripchlorolide (**36**) showed neuroprotective effects both in vitro and in vivo, possibly by suppressing cytokine production. It also increased the expression of mRNA for brain-derived neurotrophic factor, a protein that supports neuron survival (Cheng et al., 2002; Li et al., 2003b).

5.2.1.4. Antifertility: Studies of triptolide (**1**) derivatives for antifertility activity in male rats and mice indicated that five compounds – triptonide (**30**), triptolide (**31**), triptolidenol (**32**), 16-hydroxytriptolide (**33**) and tripchlorolide (**36**) – were active (Ma et al., 1991b; Zheng et al., 1991b; Zhang et al., 1993); **36** also showed reversible antifertility activity in rhesus monkeys (Lin et al., 2000). Compounds **30–32** significantly reduced sperm counts and sperm motility in rats (Matlin et al., 1993; Zhang et al., 1993; Wang et al., 2000). Several microscopic studies on rats fed **36** showed deformed sperm and possibly also negative effects on the epididymis (Ye et al., 1991, 1994; Feng et al., 1993; Dang et al., 1995; Wang et al., 1999). Tripchlorolide (**36**) appears to inhibit Ca^{2+} influx into sperm (Wu and Sha, 1996).

5.2.1.5. Insecticidal activity: Triptonide (**30**) had antifeedant activity and contact toxicity to larvae of *Mythimna separata* Walker (Oriental armyworm) (Luo et al., 2004).

5.2.2. Abietanes with benzenoid and lactone rings—Triptophenolide (=hypolide) (**37**) (Fig. 11) has been found to have several immunosuppressive and antiinflammatory effects such as inhibition of edema (Yang et al., 1995). It inhibited IL-2 production and DNA synthesis by T cells, though considerably less strongly than the triptolide derivatives (Tao et al., 1995). It also inhibited glucocorticoid receptor-induced gene activation (Lipsky et al., 1998). Triptophenolide (**37**) was moderately active against tumor cell replication in two human cell lines (Tanaka et al., 2004).

5.2.3. Abietanes with benzenoid rings (Fig. 12)—Dehydroabietane (=abietatriene) (**41**) and dehydroabietic acid (**38**) have been reported only from cell cultures of *Tripterygium* (Kutney et al., 1981a, 1992; Kutney and Han, 1996). Both compounds are constituents of several conifers; **41** is found in the essential oil of numerous species. Dehydroabietic acid (**38**) is also a major constituent of the effluent from pulp and paper processing. As such, it is of concern because of its detrimental effects on fish, including liver dysfunction, hemolysis of red blood cells, organ and tissue lesions, and genotoxic and neurotoxic effects (Zheng and Nicholson, 1998; Rabergh et al., 1999; Pacheco and Santos, 2002; Teles et al., 2004). It seems to be less toxic than most other resin acids (Peng and Roberts, 2000; Rigol et al., 2004). Beier et al. (2000) summarize the biological effects of this compound.

5.2.3.1. Antiinflammatory and autoimmune conditions: Hinokiol (**45**) was active in rats and mice in carrageenan-induced inflammation assays (El-Sayed, 1998; Du et al., 2001). Triptobenzene J (**44**) showed greater than 70% inhibition of IL-2 and IL-8 production (Duan et al., 2001a). Triptobenzene H (=hypoglic acid) (**39**), triptenin B (**43**), and triptoditerpenic acid B (=triptinin A) (**40**) had competitive antagonistic activity towards leukotriene D_4 (Xu et al., 1997).

5.2.3.2. Cancer: Dehydroabiatic acid (**38**) and abieta-8,11,13-trien-7-one (**42**) had antitumor-promoting activity in the TPA-induced EBV-EA assay (Kinouchi et al., 2000; Minami et al., 2002).

5.2.3.3. Insecticidal activity: Dehydroabiatic acid (**38**) deterred feeding by gypsy moth (*Lymantria dispar*) larvae (Powell and Raffa, 1999) and by three sawfly species, *Neodiprion dubiosus*, *N. rugifrons*, and *N. lecontei* (Schuh and Benjamin, 1984). It also inhibited larval growth of *Pectinophora gossypiella* (Elliger et al., 1976) and *Peridroma saucia* (Xie et al., 1993). Its inhibitory activity against *Pristiphora erichsonii* was apparently due to reduction in efficiency of food use rather than feeding deterrence (Wagner et al., 1983).

5.2.4. Diterpene quinoids (Figs. 13 and 14)—Benzoquinones in general were found to inhibit NF- κ B activation, possibly by interfering with one or more of the redox systems involved in activation (Niwa et al., 1997). Triptoquinones A–F (**47–52**) reduced release of IL-1 α and IL-1 β (Takaishi et al., 1992b; Shishido et al., 1994). Triptoquinone A (=triptoquinonoic acid A) (**47**) inhibited NO formation by two types of NO synthases in rat thoracic aorta (Kida et al., 1998). Suppression of NO formation was due to inhibition of induction of the mRNA for iNOS rather than to inhibition of iNOS activity (Niwa et al., 1996). Triptoquinone A (**47**) appears to be a competitive antagonist of leukotriene D₄ (Xu et al., 1997) and was effective in the adjuvant-induced arthritic rat model (Takaishi et al., 1992b; Shishido et al., 1994). Also, **47** and triptoquinone B (**48**) inhibited growth of P-388 leukemia cells in vitro (Zhou, 1991; Shen and Zhou, 1992a). Three compounds, quinone 21 (=triptoquinonide) (**46**), **48**, and triptoquinone H (**53**), moderately inhibited replication in two human tumor cell lines (Tanaka et al., 2004).

5.2.5. Kauranes (Figs. 15 and 16)

5.2.5.1. Antiinflammatory and autoimmune conditions: Tripterifordin (=hypodiolide A, antriptolactone) (**54**) inhibited by at least 70% the production of several cytokines including IL-1 β , IL-2, IL-8, IFN- γ , and TNF- α (Duan et al., 1999). Three other compounds, 16 α -hydroxy-19,20-epoxy-19*R*-ethoxy-kaurane (**55**), 16 α -hydroxy-19,20-epoxy-20*R*-ethoxy-kaurane (**56**), and 16 α -(—)-kauran-17,19-dioic acid (**60**), showed greater than 70% inhibition of IL-2 production (Duan et al., 2001a). Antiinflammatory activity was reported for 17-hydroxy-16 α -kauran-19-oic acid (**59**) (Han et al., 1975). Kaurenes similar to some found in *Tripterygium* inhibited NF- κ B-inducing kinase (Castrillo et al., 2001), a site of action different from that of triptolide (**1**) (Lee et al., 2002b). This suggests the possibility that *Tripterygium* extracts might act on the same system at multiple sites.

5.2.5.2. Cancer: (—)-16 α -Hydroxykauran-19-oic acid (**58**) was cytotoxic to five cancer cell lines with some selectivity and also inhibited crown gall tumors on potato disks, an assay indicative of antileukemic activity (Hui et al., 1990). Doianoterpene A (**57**) was moderately inhibitory of tumor cell replication in two human cell lines (Tanaka et al., 2004). Of 10 kauranes tested, *ent*-19-hydroxy-kaur-16-en (=ent-kaurenol) (**61**) showed the best antiproliferative activity against a leukemia cell line; 17-hydroxy-16 α -kauran-19-oic acid (**59**) was less active (Han et al., 2004).

5.2.6. Other diterpenoids—Two manoyl oxide derivatives and one labdane, labd-13(E)-ene-8 α ,15-diol (**62**) (Fig. 17), have been reported from *Tripterygium*. 13-Epi-manoyl oxide-18-oic acid (**63**) (Fig. 18) gave nearly complete inhibition of the production of IL-2 and IFN- γ (Duan et al., 1999). Labd-13(E)-ene-8 α ,15-diol (**62**) was cytotoxic to human T and pre-B cell lines (Demetzos et al., 1994). This compound had growth inhibitory and cytotoxic effects against numerous human and one mouse cancer cell lines, though this activity was weak in many cases (Chinou et al., 1994; Demetzos et al., 1994, 2001; Dimas et

al., 1998). It was found to reduce DNA synthesis (Dimas et al., 1998). 13-*Epi*-manoyl oxide-18-oic acid (**63**) inhibited larval growth of *Pectinophora gossypiella* (Elliger et al., 1976), whereas **62** stimulated oviposition by *Heliothis virescens* (tobacco budworm moth) (Jackson et al., 1991).

5.3. Triterpenes

The 123 triterpenes reported from *Tripterygium* fall into three main groups: 38 oleananes, 22 ursanes, and 57 friedelanes/friedooleananes (including 7 quinone methides). There are also 5 steroids and one hopane, zeorin (**107**). Pentacyclic triterpenes in general are known to have antioxidant, antiinflammatory, antitumor, and antibacterial effects, among others (Oliveira et al., 2004). Triterpenes with a carboxy group at C28 are generally cytotoxic (Chiang et al., 2005).

5.3.1. Quinone methides—These nortriterpenoids (Fig. 19) are characteristic of the Celastraceae and the closely related Hippocrateaceae. Studies of plants in the Celastraceae found that the quinone methides were located in root bark (as is the case with *Tripterygium*) but not in leaves, and that the friedelanes had the opposite distribution (Corsino et al., 2000). The best studied quinone methide is celastrol (**65**), sometimes called “tripterine” or “tripterin” in the literature; the compound was isolated and named by separate groups in the late 1930s – early 1940s (Yang, 1941).

5.3.1.1. Antiinflammatory and autoimmune conditions: Celastrol (**65**) was effective in several rodent models of arthritis and other inflammatory diseases. It reduced joint swelling and damage in the streptococcal cell wall-induced (Huang et al., 1998) and collagen-induced (Li et al., 1997) arthritic rat models. It also reduced granuloma growth in the cotton pellet-induced granuloma assay in rats (Zhang et al., 1990). Celastrol (**65**) inhibited airway inflammation in asthmatic mice; it lowered the level of inflammatory cells in lung tissue (Liu et al., 2004b). This compound also showed activity against several markers in two mouse lupus models: it lowered production of serum autoantibodies to single- and double-stranded DNA and histone, reduced levels of immunoglobulin G and NO in serum and albumin in urine, decreased IL-10 production by peritoneal macrophages, and reduced severity of glomerular lesions (Xu et al., 2003; Li et al., 2005). Pristimerin (**64**) showed antiinflammatory activity in mice in the croton oil-induced ear edema, carrageenan-induced paw swelling, and acetic acid-induced capillary permeability assays (Hui et al., 2003). Tripterygone (**68**) also showed antiinflammatory activity (Zhang et al., 1991). Focal segmental glomerulosclerosis is a kidney disease that is sometimes treated with antiinflammatory agents. Celastrol (**65**) protected isolated kidney glomeruli (structures composed of small blood vessels) from the effects of serum from patients with the disease (Sharma et al., 1999), suggesting it might be a useful treatment after kidney transplants in such patients.

5.3.1.1.1. Proinflammatory cytokines and lymphocytes: Celastrol (**65**) has been found to reduce levels of cytokines including IL-1 α and IL-1 β (Lei and Li, 1991; Li et al., 1997; Takaishi et al., 1997; Huang et al., 1998), IL-2 (Lei and Li, 1991; Xu et al., 1991; Li et al., 1997), IL-6, IL-8 (He et al., 1998; Pinna et al., 2004), and TNF- α (Allison et al., 2001; Pinna et al., 2004). It also reduced antibody formation in mice (Lei and Li, 1991). However, **65** did not lower IL-2 levels in one study (Pinna et al., 2004). There are conflicting reports as to whether **65** reduces cytokine production by inhibiting synthesis, or by inhibiting post-translational processing/secretion (Huang et al., 1998; Pinna et al., 2004). Tingenone (=tingenin A, maytenin) (**66**), 22 β -hydroxytingenone (=tingenin B) (**67**), and **64** also inhibited IL-1 β production; **67** inhibited synthesis of IL-1 α as well (Takaishi et al., 1997; Huang et al., 1998).

5.3.1.1.2. Proinflammatory enzymes: Celastrol (**65**) lowered production of both PGE₂ (Xu et al., 1991) and induced NO (Allison et al., 2001; Jin et al., 2002). However, in a mouse model of lupus, **65** increased levels of matrix metalloproteases-1 and -2 (Xu and Wu, 2002; Xu et al., 2002). Pristimerin (**64**) did not inhibit activity of iNOS, but did reduce levels of mRNA for the enzyme (Dirsch et al., 1997).

5.3.1.1.3. Transcription factors and molecular mode of action: Celastrol (**65**) inhibited transfer of NF- κ B to the nuclei and also decreased levels of phosphorylated p38 in LPS-activated monocytes. It thus blocked both major pathways regulating TNF- α expression, the NF- κ B and p38 MAP kinase pathways. It did not act via the glucocorticoid receptor-dependent pathway (Pinna et al., 2004). Although pristimerin (**64**) reduced NF- κ B binding activity, it did not reduce levels of COX-2 mRNA (Dirsch et al., 1997).

5.3.1.2. Cancer: Compounds in this class showed good cytotoxicity in in vitro assays with tumor cell lines. Celastrol (**65**) was toxic to several human cancer cell lines (Kutney et al., 1981a; Figueiredo et al., 1998; González et al., 1998; Ankli et al., 2000; Zhou et al., 2002; Lee et al., 2004) and inhibited TPA-induced EBV-EA (Takaishi et al., 1997). Pristimerin (**64**) and tingenone (**66**) were also toxic to numerous cancer cell lines (Gonzalez et al., 1977; Kutney et al., 1981a,b; Itokawa et al., 1991; Ngassapa et al., 1994; Shirota et al., 1994; Figueiredo et al., 1998; González et al., 1998; Setzer et al., 1998, 2001; Lee et al., 2004). 22 β -Hydroxy-tingenone (**67**) was about as cytotoxic as **64** and **66** (Kutney et al., 1981b; Bavovada et al., 1990; Itokawa et al., 1991; Shirota et al., 1994; Sattar et al., 1998; Lee et al., 2004), which were generally more toxic than **65** (Ngassapa et al., 1994; Ankli et al., 2000; Chang et al., 2003).

A few in vivo studies of these compounds have been carried out. Celastrol (**65**) and **64** inhibited tumor growth in the hamster cheekpouch model (Schwenk, 1962), and **65** inhibited angiogenesis in a mouse model (Huang et al., 2003a). Tingenone (**66**) has been tested on a few skin cancer cases in humans; it showed some activity and low irritation (Melo et al., 1974).

The quinone methides are able to exert antitumor effects in multiple ways. Celastrol (**65**) has been shown to induce apoptosis, which may be due at least partly to the compound's ability to inhibit topoisomerase II (Nagase et al., 2003). Tingenone (**66**) also showed weak topoisomerase II inhibitory activity (Furbacher and Gunatilaka, 2001). Celastrol (**65**) also affected expression of several cancer-related genes. It inhibited transcription of the oncogene *c-myc*, which is overexpressed in many human cancers (Chen et al., 1998; Gardner et al., 2002). It increased expression of the pro-apoptotic proteins Bax and ICE and decreased expression of the antiapoptosis protein Bcl-2 (Bao et al., 2001; Zhou et al., 2002), though one study found that expression of the mRNA for Bax was downregulated (Bao et al., 2001). Another possible mode of action for these compounds involves DNA binding; several antitumor drugs are believed to act via quinone methide intermediates that bind covalently to DNA (Lewis et al., 1996). Based on molecular orbital calculations, **66** was postulated to have a DNA intercalator-like mode of action, possibly intercalation followed by alkylation of DNA bases (Campanelli et al., 1980; Setzer et al., 2001).

5.3.1.3. Neurodegenerative diseases: Celastrol (**65**) had antioxidant effects and suppressed production of TNF- α , IL-1 β , and class II major histocompatibility antigens, which are also produced by activated microglia. The compound produced some improvement in indicators of learning and memory in rats. These results suggested that **65** might be useful as a treatment for Alzheimer's (Allison et al., 2001).

The development of Huntington's disease is associated with a mutant version of a protein called huntingtin. Abnormal protein aggregates have been observed in neurons of Huntington's patients, and it is thought that these aggregates result from aggregation of mutant huntingtin. Also, in a mouse model of Huntington's, the mutant huntingtin tends to accumulate in the nuclei of neurons, rather than being distributed throughout the nuclei and cytoplasm. Celastrol (**65**) was found to inhibit aggregation of a fragment of mutant huntingtin with an IC₅₀ value of 3.55 μ M. It also reversed the tendency of mutant huntingtin to accumulate in nuclei in a cell-based assay (Wang et al., 2005b). Celastrol (**65**) also showed activity in other assays related to protein aggregation and neurotoxicity (Westerheide et al., 2004; Wang et al., 2005b).

5.3.1.4. Antifertility: Celastrol (**65**) inhibited sperm motility and several components of the process by which a sperm fertilizes an egg cell (Yuan et al., 1995). Celastrol's (**65**) ability to inhibit Ca²⁺ channels in spermatogenic cells may also produce an antifertility effect (Bai and Shi, 2002; Bai et al., 2003).

5.3.1.5. Insecticidal activity: Pristimerin (**64**) showed some toxic, molt suppression, and antifeedant activity towards codling moth (*Cydia pomonella*) larvae; tingenone (**66**) had weaker antifeedant and molt suppression activity and no significant mortality activity (Avilla et al., 2000). Pristimerin (**64**) also had significant antifeedant activity towards *Sitophilus zeamais*, on a par with rotenone, but low mortality activity (Reyes-Chilpa et al., 2003).

5.3.2. Friedelanes, friedooleananes (saturated rings) (Figs. 20 and 21)

5.3.2.1. Antiinflammatory and autoimmune conditions: 3-Oxo-friedelan-28-oic acid (**70**) showed moderate (32%) inhibition of edema in the carrageenan-induced rat paw edema test and good inhibition of TPA-induced rat ear edema (Arciniegas et al., 2004). Polpunoic acid (=polpunoic acid, maytenoic acid, maytenonic acid) (**69**) inhibited IL-2 release, and wilforic acid B (**72**) inhibited production of IL-2, IL-8, and TNF- α (Duan et al., 2000). Orthosphenic acid (**75**) had antiinflammatory activity (Zhang et al., 1989a).

5.3.2.2. Cancer: Polpunoic acid (**69**) and 3-oxofriedelan-28-oic acid (**70**) were weakly to moderately cytotoxic to cancer cell lines; 3 β ,29-dihydroxy-D:B-friedoolean-5-en (**71**) and 29-hydroxy-friedelan-3-one (=D:A-friedooleanan-29-ol-3-one) (**74**) were less active (Nozaki et al., 1990; Itokawa et al., 1991; Chiang et al., 2005). Salaspermic acid (**76**) weakly stimulated proapoptotic cytokines, suggesting the possibility of antitumor activity (Nakagawa et al., 2004). Regeol B (**73**) inhibited TPA-induced EBV-EA (Takaishi et al., 1997).

5.3.3. Friedooleananes (benzenoid ring) (Fig. 22)

5.3.3.1. Antiinflammatory and autoimmune conditions: Demethylzeylasteral (**77**) (sometimes called TZ-93) inhibited the mixed lymphocyte reaction and carrageenan-induced mouse paw swelling, and prolonged the survival time of rats with kidney transplants, although it did not greatly suppress IL-2 production (Tamaki et al., 1997; Lin et al., 2003). It also inhibited proliferation of peripheral blood mononuclear cells without being cytotoxic, and suppressed levels of CD4, a glycoprotein found on the surface of T-cells and other cell types that is involved in immune responses, and CD25, which is part of the IL-2 receptor (Wu and Qin, 1997). 2,3-Dihydroxy-1,3,5(10),7-tetraene-6 α -(1'-hydroxyethyl)-24-nor-D:A-friedooleane-29-oic acid (**82**) was a good inhibitor of cytokine production; 10 μ g/ml gave complete inhibition of IL-2, TNF- α and IFN- γ and greater than 80% inhibition of IL-1 β and IL-8 (Duan et al., 2001a). Wilforic acid A (**79**) also showed greater than 70% inhibition of IL-1 β , IL-2 and IFN- γ (Duan et al., 2001a).

5.3.3.2. Cancer: Demethylzeylasterone (**78**) and 3-methyl-22 β ,23-diol-6-oxotingenol (**81**) were cytotoxic to tumor cell lines (Shirota et al., 1994; Furbacher and Gunatilaka, 2001).

Demethylzeylasteral (**77**) inhibited proliferation and migration of vascular endothelial cells, and tumor growth in vivo (Ushiro et al., 1997). Triptohypol C (**80**) and **78** inhibited topoisomerase II (Furbacher and Gunatilaka, 2001; Nagase et al., 2003). The latter compound apparently prevents topoisomerase II from binding to DNA, but is not a DNA intercalator.

5.3.3.3. Antifertility: Demethylzeylasteral (**77**) inhibited the Ca²⁺ current in spermatogenic cells and the sperm acrosome reaction, which allows a sperm to inject its DNA into an egg cell (Bai and Shi, 2002; Bai et al., 2003).

5.3.3.4. Insecticidal activity: Demethylzeylasterone (**78**) showed weak ecdysteroid antagonist activity in a *Drosophila* cell-based assay (Dinan et al., 2001).

5.3.4. Oleananes—Compounds from this class reported from *Tripterygium* (Figs. 23 and 24) include two that are widespread in nature: oleanolic acid (**83**) and β -amyrin (**88**). The former compound has been the subject of numerous studies in recent years and its pharmacology has been reviewed (Liu, 1995; Tian et al., 2002; Ovesna et al., 2004a). It has been reported to have hepatoprotective, antiinflammatory, antihyperglucemic, antimutagenic, antitumor, antifungal, antioxidant, antiulcer, antifertility, and anticariogenic effects (Liu, 1995).

5.3.4.1. Antiinflammatory and autoimmune conditions: Oleanolic acid (**83**), 3-acetoxy-oleanolic acid (**84**), triptotriterpenic acid A (=maytenfolic acid, abrusgenic acid) (**85**), and triptotriterpenic acid B (**87**) had antiinflammatory activity (Zhang et al., 1984, 1986b, 1989a; Zhou and Meng, 1992). Oleanolic acid (**83**) exhibited activity in the adjuvant- and formaldehyde-induced arthritis assays (Singh et al., 1992; Liu, 1995) and in several rodent edema models, including carrageenan-, dextran-, and phospholipase A₂-induced paw edema (Singh et al., 1992; Liu, 1995; Recio et al., 1995; Giner-Larza et al., 2001) and croton oil- and TPA-induced ear edema assays (Recio et al., 1995; Ismaili et al., 2001; Banno et al., 2004). In the last of these it was more active than indomethacin (Banno et al., 2004). It was not active in the cotton pellet assay, however (Singh et al., 1992). Oleanolic acid (**83**) also suppressed exudation of white blood cells (leukocytes) in inflamed areas in vivo (Singh et al., 1992) and inhibited allergic responses (Liu, 1995). Regelide (=wilforlide A, abruslactone A) (triptotriterpenic) inhibited carrageenin-induced rat paw swelling (Ding et al., 1992). β -Amyrin (**88**) inhibited TPA-induced ear edema in mice (Recio et al., 1995; Yasukawa et al., 2000). A 2:1 mixture of α -amyrin (**99**) and **88** significantly inhibited mouse paw edema (Oliveira et al., 2004).

5.3.4.1.1. Proinflammatory cytokines and lymphocytes: At low concentrations (up to 3 μ M), oleanolic acid (**83**) inhibited release of TNF- α , IL-1 β , and IL-6 (Wu et al., 2004). 3-Epikatononic acid (**86**) inhibited production of IL-2, IL-8, and TNF- α ; triptotriterpenonic acid A (**89**) and 2 α ,3 β -dihydroxy-olean-12-ene-22,29-lactone (**95**) inhibited IL-2 production (Duan et al., 2000, 2001a).

5.3.4.1.2. Proinflammatory enzymes: The complement system is another major mediator of the inflammatory response (Kapil and Sharma, 1994). Oleanolic acid (**83**) inhibited the classic pathway of complement activation in vitro (Kapil and Sharma, 1994; Assefa et al., 1999) but did not inhibit the alternate pathway (Kapil and Sharma, 1994). The inhibition of

the classic pathway by **83** was mainly due to inhibition of C₃-convertase (EC 3.4.21.43), a serine protease in the pathway (Kapil and Sharma, 1994).

Hydrolysis of elastin in blood vessels by human leukocyte elastase (EC 3.4.21.37) promotes inflammation by enhancing migration of proinflammatory cells. Oleanolic acid (**83**) inhibited human leukocyte elastase (Facino et al., 1995; Safayhi and Sailer, 1997). It also inhibited COX-2, and COX-1 in one study (Ringborn et al., 1998) but not in another (Zhang et al., 2004b). Oleanolic acid (**83**) is a good inhibitor of adenosine deaminase (EC 3.5.4.4) (Koch et al., 1994), one isoform of which is increased in many cancers and immune diseases. This compound also inhibited production of NO and PGE₂ (Wu et al., 2004). Wilforol C (**91**) has been patented as a leukotriene antagonist (Morota et al., 1997).

5.3.4.1.3. Transcription factors and molecular mode of action: Oleanolic acid (**83**) blocked NF-κB-mediated gene activation (Wu et al., 2004). At higher concentrations, however, it activated NF-κB, increased binding of NF-κB to DNA, and stimulated expression of iNOS and TNF-α by increasing levels of the mRNAs for these proteins (Choi et al., 2001); these are proinflammatory effects.

5.3.4.1.4. Adhesion and surface molecules: Oleanolic acid (**83**) was moderately inhibitory of ICAM-1 induction (Fu et al., 2005).

5.3.4.1.5. Apoptosis and cell proliferation: At 40 lg/ml, the highest concentration tested, oleanolic acid (**83**) weakly inhibited proliferation of human peripheral blood mononuclear cells (Chiang et al., 2003a). 3-Epikatononic acid (**86**) inhibited lymphocyte proliferation (Tanaka et al., 2001).

5.3.4.2. Cancer: Several oleananes have shown activity in vitro that suggests they may have anticancer properties. Oleanolic acid (**83**), 3-acetoxy-oleanolic acid (**84**), and katononic acid (**90**) all inhibited TPA-induced EBV-EA (Ohigashi et al., 1986; Konoshima et al., 1987; Taniguchi et al., 2002; Ismail et al., 2003; Banno et al., 2004); **84** was more active than **83**, and **90** was less active. Oleanolic acid (**83**) was a good inhibitor of the mutagenicity of benzo[a]pyrene in a bacterial assay (Niikawa et al., 1993). Several oleananes, including triptotriterpenic acids A (**85**) and B (**87**), 3-epikatononic acid (**86**), triptocallic acid D (**92**), regelide (**93**), and wilforlide B (**94**), showed some ability to induce IL-6 in human peripheral blood mononuclear cells. Regelide (**93**) also had weak IL-12 and TNF-α induction activity. These activities may have antitumor effects (Nakagawa et al., 2004).

Oleanolic acid (**83**) was cytotoxic to numerous cancer cell lines, including a vincristine-resistant cell line (Fernandes et al., 2003). Although its activity was relatively weak in several studies (Njoku et al., 1997; Kim et al., 2000; Chiang et al., 2003b; Fu et al., 2005), it did show some selectivity (Taniguchi et al., 2002). In vitro studies into **83**'s effects indicated that it acted by inducing apoptosis (Fernandes et al., 2003; Huang et al., 2003b; Urech et al., 2005), but it also had other effects: it inhibited the invasive, adhesive, and migration abilities of lung cancer cells (Huang et al., 2003b); showed antiangiogenic activity, possibly by inhibiting proliferation of vascular endothelial cells (Sohn et al., 1995); and induced differentiation, which does not proceed normally in some cancer types (Umehara et al., 1992). 3-Acetoxy-oleanolic acid (**84**), β-amyrin (**88**), and katononic acid (**90**) also showed varying degrees of cytotoxicity to cancer cells (Kaneda et al., 1992; Topcu et al., 2003; Ono et al., 2004), and **84** had some differentiation-inducing activity (Umehara et al., 1992).

Oleananes have shown the ability to inhibit enzymes involved in cancer development. Topoisomerase II and aromatase have been mentioned above. DNA polymerase β plays a role in the repair of damaged DNA, as mentioned earlier. Oleanolic acid (**83**) inhibited all

three of these enzymes, albeit weakly in the case of aromatase, and **90** was an effective DNA polymerase β inhibitor (Ganßer and Spiteller, 1995; Sun et al., 1999; Deng et al., 1999, 2000; Hecht, 2003; Mizushima et al., 2003).

Oleanolic acid (**83**) has also shown anticancer activity in vivo. In mice, it decreased tumors and inhibited tumor promotion with activity comparable to that of retinoic acid, a known tumor promotion inhibitor (Tokuda et al., 1986; Hsu et al., 1997). Oleanolic acid (**83**) significantly reduced the numbers of aberrant crypt foci (possible biomarkers for colon cancer) and levels of silver-stained nucleolar organizer region protein and colonic mucosal ornithine decarboxylase activity (both biomarkers of cell proliferation) in carcinogen-treated rats (Kawamori et al., 1995). Pretreatment with **83** increased leukocyte levels in irradiated mice, suggesting that this compound could have a protective effect on the bone marrow of patients undergoing radiation therapy (Hsu et al., 1997). Triptotriterpenic acid A (**85**) also showed antileukemic effects in mice (Nozaki et al., 1986).

5.3.4.3. Neurodegenerative diseases: Oleanolic acid (**83**) enhanced nerve growth factor (NGF)-stimulated neurite (neural cell projections including axons and dendrites) outgrowth in PC12D cells to a greater extent than most of the other natural products tested (Li et al., 2003c; Li and Ohizumi, 2004). NGF promotes the development and survival of neurons; enhancement of its activity may be beneficial in the treatment of neurodegenerative disorders including various dementias (Li and Ohizumi, 2004).

5.3.4.4. Antifertility: The possibility of using oleanolic acid (**83**) as an antifertility agent has been mentioned (Ghosh and Bhattacharya, 2002). Male rats treated with **83** were less fertile, spermatogenesis was reduced, and sperm motility was reversibly affected (Rajasekaran et al., 1988; Mdhluli and van der Horst, 2002). It was speculated that **83** might have triggered events including Ca^{2+} influx and cAMP increase, producing premature hyperactivation of sperm (Mdhluli and van der Horst, 2002). 3-Epikatonol acid (**86**) was also reported to be spermicidal (Shen and Zhou, 1992b).

5.3.4.5. Insecticidal activity: Oleanolic acid (**83**) was toxic to larvae of *Aedes aegypti*, the yellow fever mosquito (Njoku et al., 1997); the aphid *Rhopalosiphum padi* (Schmeda-Hirschmann et al., 1995); and *Rhodnius prolixus*, a vector of Chagas' disease (Kelecom et al., 2002). It also showed strong antimoiting activity against the last of these. Oleanolic acid (**83**) had some antifeedant activity against *Spodoptera litura* (Mallavadhani et al., 2003), and 3-acetoxy-oleanolic acid (**84**) showed antifeedant activity against *Leptinotarsa decemlineata* (the Colorado potato beetle) (Hua et al., 1991).

5.3.5. Ursanes (Fig. 25)—Ursolic acid, which is widespread in plants, has not been reported from *Tripterygium*, but the 3 β -acetoxy (**103**) and 2 α -hydroxy (**104**) derivatives have, as has α -amyrin (**99**).

5.3.5.1. Antiinflammatory and autoimmune conditions: Antiinflammatory activity has been reported for triptotriterpenic acid C (=tripterygic acid A) (**98**) (Zhang et al., 1989a,b) and 2 α -hydroxy-ursolic acid (=corosolic acid, colosolic acid) (**104**) (El-Hawary et al., 2003). The latter compound was active in vivo against TPA-induced inflammation in mice, with an ID₅₀ value lower than that of indomethacin (Banno et al., 2004). In vitro, **104** inhibited production of NO from LPS-stimulated macrophages (Ryu et al., 2000). α -Amyrin (**99**) inhibited carrageenan-induced paw edema in rats and mice, and TPA-induced mouse ear edema (Agnihotri et al., 1987; Recio et al., 1995). Dulcioic acid (**101**) inhibited production of IL-1 β , IL-2, IL-8, IFN- γ , and TNF- α from human peripheral mononuclear

cells (Duan et al., 2000); demethylregelin (**102**) showed some inhibition of IL-2 production (Duan et al., 2001a).

5.3.5.2. Cancer: Several ursanes were active against cancer cell lines in vitro, including regelin (**96**), regelinol (**97**) (Hori et al., 1987), 3 β -acetoxy-ursolic acid (**103**) (Lee et al., 1988; Chiang et al., 2005), and α -amyrin (**99**) (weakly) (Fu et al., 2005). 3 β -Acetoxy-ursolic acid (**103**) was also antimutagenic in the *umu* test (Miyazawa et al., 2005) and had antitumor activity in vivo (Dominic and Subbaiyan, 1993) and some aromatase-inhibiting activity in vitro (Jeong et al., 2000). Although 2 α -hydroxy-ursolic acid (**104**) inhibited TPA-induced EBV-EA (Banno et al., 2004) and showed good cytotoxicity to several cancer cell lines, seeming to be particularly effective against solid tumors (Yamagishi et al., 1988; Numata et al., 1989; Ahn et al., 1998; El-Hossary et al., 2000; Kim et al., 2000), in one study it was as cytotoxic to normal human fibroblasts as to two tumor cell lines (Taniguchi et al., 2002). The cytotoxicity seems to be related to the compound's ability to inhibit protein kinase C (EC 2.7.11.13) (Ahn et al., 1998). It also inhibited DNA topoisomerase II (Mizushima et al., 2003) and weakly inhibited the lyase activity of DNA polymerase β (Chaturvedula et al., 2004). Triptocallin acid A's (**100**) ability to induce IL-6 suggests it may have antitumor effects (Nakagawa et al., 2004).

5.3.5.3. Neurodegenerative diseases: 2 α -Hydroxy-ursolic acid (**104**) showed some ability to enhance NGF-stimulated neurite outgrowth in PC12D cells, though it was not as active as oleanolic acid (**83**) (Li and Ohizumi, 2004).

5.3.5.4. Insecticidal activity: α -Amyrin (**99**) caused molting in *Spodoptera littoralis* (Khafagy et al., 1981).

5.3.6. Steroids—Of the five steroids reported from *Tripterygium*, two, β -sitosterol (**105**) and daucosterol (= β -sitosterol- β -D-glucoside) (**106**) (Fig. 26) are widespread; **105** is the main phytosterol in most higher plants (Villaseñor et al., 2002). The cholesterol-lowering effects of phytosterols, including **105**, are well-known and have been reviewed (Ling and Jones, 1995). Other therapeutic effects of phytosterols include anticarcinogenic, antiinflammatory, antipyretic, antiulcer, anticomplement, insulin-releasing, and estrogenic activities (Ling and Jones, 1995; Bouic et al., 1996).

5.3.6.1. Antiinflammatory and autoimmune conditions: Both β -sitosterol (**105**) and daucosterol (**106**) had antiinflammatory activity in rodent paw edema assays (Salama et al., 1987; Delporte et al., 1998; Juan Hikawczuk et al., 1998) and, in the case of **106**, in the TPA-induced mouse ear edema assay (Yasukawa et al., 2000). Both compounds were weak COX-2 inhibitors and did not inhibit COX-1 (Zhang et al., 2004b); **105** was also a weak inhibitor of lipoxygenase (Ali and Houghton, 1999). Daucosterol (**106**) was much more effective than **105** at inhibiting human leucocyte elastase (Mitaine-Offer et al., 2002).

In allergic conditions, some autoimmune diseases, and chronic viral infections including HIV infection, the balance between cellular (high cytotoxic T cell activity) and humoral (high antibody activity) immune responses is shifted in favor of the humoral response. A 100:1 **105:106** mixture enhanced the cellular response. It also inhibited release of IL-6 and TNF- α (Bouic, 2002). In clinical studies, this mixture produced improvements in the symptoms of patients with allergic rhinitis. It also improved several markers of disease severity, and decreased the need for pain medication, in rheumatoid arthritis patients (Bouic, 2002). In other studies, this mixture was more active than the separate components at equivalent concentrations, suggesting that there may be a synergistic effect between the compounds (Bouic et al., 1996).

5.3.6.2. Cancer: β -Sitosterol (**105**) had inhibitory activity at several stages of tumor development (Ling and Jones, 1995; Ovesna et al., 2004b). It inhibited tumor promotion, specifically the transformation of preneoplastic cells into neoplastic (abnormally growing) cells (Gao et al., 2003), and was antimutagenic (Villaseñor et al., 2002). Its cytotoxic activity to cancer cells in vitro was mild (Chang et al., 2003), but a mixture of this compound with the anticancer drug bleomycin was considerably more toxic than either compound alone (Li et al., 2004b).

Daucosterol (**106**) inhibited TPA-induced EBV-EA without significant cytotoxicity (Guevara et al., 1999). Though its inhibitory activity against cancer cell lines was moderate at best (Ratnayake et al., 1992; Chang et al., 2003; Ono et al., 2004), it showed antileukemic effects in mice (Nozaki et al., 1986).

Both compounds inhibited the lyase activity of DNA polymerase β (Li et al., 2004b). Daucosterol (**106**) also inhibited DNA methyltransferase (EC 2.1.1.37), another target for anticancer drugs (Nagao et al., 1998). On the other hand, both compounds, particularly β -sitosterol (**105**), showed angiogenic activity; **105** stimulated migration of endothelial cells, though not their proliferation (Moon et al., 1999).

5.3.6.3. Neurodegenerative diseases: Daucosterol (**106**) inhibited prolyl endopeptidase (EC 3.4.21.26) (Lee et al., 1998), which has been linked to psychiatric disorders, memory loss, and conditions such as Parkinson's (Amor et al., 2004), and xanthine oxidase (EC 1.17.3.2), which may generate free radicals that lead to inflammation and other conditions (Chiang and Chen, 1993). Daucosterol (**106**) showed neurotoxic properties, however, although β -sitosterol (**105**) did not (Khabazian et al., 2002; Shaw and Bains, 2002). The neurotoxicity was apparently at least partly due to stimulation of glutamate release, which can trigger cell death via multiple mechanisms (Shaw and Bains, 2002).

5.3.6.4. Antifertility: Reversible antifertility effects such as reduced sperm levels were observed in rats given high doses of β -sitosterol (**105**) (Malini and Vanithakumari, 1991).

5.3.7. Hopanoids—Zeorin (107**),** the only hopane reported from *Tripterygium* to date (Fig. 27), showed significant cytotoxicity against P-388 cancer cells (Wong et al., 1986).

6. Conclusions

Many studies have demonstrated the potential of *Tripterygium* extracts to reduce inflammation and autoimmune responses. Triptolide (**1**) is one of the most bioactive components of *Tripterygium* extract, probably followed by triptidiolide (**31**). These compounds are responsible for the majority of the pharmacological effects of the *Tripterygium* extract. However, other extract components described in this review may, to some degree, augment the pharmacological effects of the extract and modify its pharmacokinetics, bioavailability and toxicological properties. Such potentiating and interfering effects were demonstrated for other multi-component botanical extracts (Raskin and Ripoll, 2004; Lila and Raskin, 2005).

On the molecular level, some of the pharmacological effects of **1** can be explained by the observations that it strongly inhibits the transcription of TNF- α and blocks the activation of NF- κ B and other transcription factors, resulting in the inhibition of transcription of inflammation- and immune-related genes. In addition, **1** was shown to bind to the glucocorticoid receptor. The glucocorticoid receptor-**1** complex cannot activate glucocorticoid-responsive genes and may suppress the transcriptional activity of NF- κ B and AP-1, producing a combination of antiinflammatory and steroid sparing effects. The effect

of the glucocorticoid receptor-1 complex on NF- κ B and AP-1 has not been experimentally documented and remains hypothetical.

Further studies are needed to understand the exact molecular modes of action of *Tripterygium* extract and its components. These studies are particularly complex, since the methodologies of investigating pleiotropic effects of multi-component mixtures are not well developed. Nevertheless, the powerful antiinflammatory and immunosuppressive action of *Tripterygium* extract may be useful for treating inflammatory and autoimmune diseases. In addition, the antineoplastic properties of the extract warrant further investigation and clinical validation.

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Biographies

Anita M. Brinker is currently a Laboratory Researcher in the Department of Nutritional Sciences at Rutgers University. Her interests are in the identification and applications of bioactive natural products, particularly from plants. She obtained a B.S. from the University of Michigan, an M.S. from Cornell University, and a Ph.D. from the University of Illinois under the supervision of Prof. David Seigler. She has worked in industry and for the U.S. Department of Agriculture, studying herbicidal compounds and natural products for skin care. She also conducted enzymological research in Germany as an Alexander von Humboldt Research Fellow. Before her current position, she worked with Prof. Ilya Raskin at Rutgers University on the development of *Tripterygium* extract as a botanical drug.

Jun Ma is a Postdoctoral Associate at the Biotech Center of Rutgers University. He received his B.S. in Botany from Shandong University (China), M.S. in Genetics from Shandong Agricultural University (China), and Ph.D. in Phytochemistry from The City University of New York (CUNY). His Ph.D. research was focused on antioxidant constituents from tropical fruits and vegetables. Now, he is working on developing a novel

botanical drug for the treatment of rheumatoid arthritis from Chinese traditional herb *Tripterygium wilfordii* (having completed a Phase II clinical trial with positive results).

Peter E. Lipsky, MD, Chief, Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases. Dr. Lipsky was a Professor of Internal Medicine and Microbiology at the University of Texas Southwestern Medical Center at Dallas and the Harold C. Simmons Professor of Arthritis Research and the Director of the Simmons Arthritis Research Center until assuming his current position in October 1999. He was previously on the Board of Directors of the American College of Rheumatology and President of the Clinical Immunology Society. He is the previous Editor-in-Chief of the *Journal of Immunology*, current editor of *Arthritis Research and Therapy* and *Nature Clinical Practice Rheumatology*, a past President of the Clinical Immunology Society, and a member of the American Society for Clinical Investigation and the Association of American Physicians. Dr. Lipsky is an author of more than 500 scholarly publications. His research activities have focused on the immunologic basis of autoimmune and inflammatory rheumatic diseases.

Dr. Lipsky received his AB degree at Cornell University and his MD degree at New York University School of Medicine. He subsequently was a resident in Internal Medicine at the University of Rochester/Strong Memorial Hospital and completed fellowship training at the NIH. He is Board certified in Internal Medicine and Rheumatology. He is the recipient of the Howley Prize, the ACR Distinguished Investigator Award, and the Carol Nachman Prize.

Ilya Raskin is a Professor II at the Biotech Center of Rutgers University. He graduated with B.S. degree from Brandeis University and received a Ph.D. in 1984 from Michigan State University. Following graduation, Dr. Raskin spent 5 years working for Shell Agricultural Chemical Company and DuPont Co. and moved back to academia in 1989 as an Associate Professor at Rutgers University. Early in his career Dr. Raskin worked on the role of ethylene in plant development and on salicylic acid as a signal in plant thermogenesis and disease resistance. Subsequently, he played a role in the development of phytoremediation, the use of green plants to extract contaminants from soil and water.

Dr. Raskin's current research concentrates on reconnecting plants and human health through plant biochemistry, biotechnology and genetic engineering. He is particularly interested in discovering, studying and developing pharmaceuticals from plants. Several botanical therapeutics developed in Dr. Raskin's laboratory are currently in human clinical trials funded by industry and government. In addition to his academic career, Dr. Raskin is the Director and founder of Phytomedics Inc., a biopharmaceutical spin-off company of Rutgers University that commercializes botanical therapeutics. He has published more than 130 papers and is one of 108 most cited researchers in Plant and Animal Science according to the Institute of Scientific Information (ISI).

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Fig. 1.
Structure of triptolide (1).

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Fig. 3.
The outline of terpenoid biosynthesis via DOXP pathway in the plastid.

Fig. 4.

Proposed action of triptolide (1) on the genes involved in the inflammation and immunosuppressive cascade in T cells. The glucocorticoid receptor-1 complex cannot activate glucocorticoid-responsive genes (1), while potentially suppressing the levels of NF- κ B and AP-1 (2, not documented) producing a combination of antiinflammatory and steroid sparing effects. Triptolide (1) also inhibits the transcription of TNF- α (3) and blocks the activation of NF- κ B (4), resulting in the inhibition of transcription of the inflammation-related genes.

	Compound name	R 1	R 2	R 3	R 4	R 5	R 6	R 7	R 8
2	triptofordin D-2	Cin	H	H	OH	OAc	β-OAc	β-OBz	OAc
3	triptofordin E	Bz	OAc	H	OH	OAc	O (keto)	β-OBz	OAc
4	compound 8	Ac	OAc	H	OH	OAc	O (keto)	β-OBz	OAc
5	triptofordin F-2	Ac	OAc	H	OH	OH	α-OBz	β-OBz	OAc
6	triptogelin A-1	Bz	OBz	H	H	OAc	β-OBz	β-OBz	H
7	triptogelin A-3	H	OH	H	H	OAc	β-OBz	β-OBz	H
8	triptogelin C-1	Ac	OAc	H	H	OAc	H	α-OBz	H
9	triptogelin G-1	Ac	H	H	H	H	H	α-OCin	H
10	1β-furanoyl-2β, 3α, 7α, 8β, 11-pentaacetoxo-4α,5α-dihydroxy-dihydroagarofuran	Fur	OAc	OAc	OH	OH	α-OAc	β-OAc	OAc
11	1β,2β, 3α, 5α, 7β, 8β, 11-heptaacetoxo-dihydroagarofuran	Ac	OAc	OAc	H	OAc	β-OAc	β-OAc	OAc
12	1β-furanoyl-2β, 3α, 7α, 8β, 11-pentaacetoxo-5α-hydroxy-dihydroagarofuran	Fur	OAc	OAc	H	OH	α-OAc	β-OAc	OAc
13	1β, 7β, 8α-triacetoxo-2β-furanoyl-4α-hydroxy-11-isobutyryloxy-dihydroagarofuran	Ac	OFur	H	OH	OAc	β-OAc	α-OAc	OCOCH(Me)2
14	1β-nicotinoyl-2β, 5α, 7β-triacetoxo-4α-hydroxy-11-isobutyryloxy-8α-furanoyl-dihydroagarofuran	Nic	OAc	H	OH	OAc	β-OAc	α-OFur	OCOCH(Me)2

Fig. 5.
Bioactive dihydroagarofurans in *Tripterygium*. Ac = acetate, Cin = cinnamoyl, Bz = benzoyl, Fur = furanoyl, Nic = nicotinoyl.

Compound name	R 1	R 2	R 3	
15 wilfortrine	Fur	OH	Ac	
16 wilforine	Bz	H	Ac	
17 wilfordine	Bz	OH	Ac	
18 wilforgine	Fur	H	Ac	
19 wilforidine	H	OH	Ac	
20 wilformine (= 2-debenzoyl-2-nicotinoyl-wilforine)	Nic	H	Ac	
21 euonine (= wilformine)	Ac	H	Ac	
22 alatusinine	Ac	OH	Ac	

Fig. 6. Wilforine-type active sesquiterpene alkaloids in *Tripterygium*. Ac = acetate, Bz = benzoyl, Fur = furanoyl, Nic = nicotinoyl.

	Compound name	R 1	R 2	R 3	R 4	R 5
23	euonymine	Ac	Ac	H	Ac	OAc
24	wilfordsine (N at pos. 3)	Ac	Bz	OH	Ac	OAc
25	cangorinine E-1	Ac	Ac	H	Bz	OAc
26	mayteine	Bz	Ac	H	Ac	OAc
27	ebenifoline E-II	Bz	Ac	H	Bz	OAc
28	wilfordconine (N at pos. 3)	Ac	H	OH	Ac	OFur

Fig. 7.
Euonymine-type active sesquiterpene alkaloids in *Tripterygium*.

Fig. 8.
Structure of wilforonide (**29**).

	Compound name	R 1	R 2	R 3	R 4
30	triptonide	H	H	H	O (keto)
31	tripdiolide	OH	H	H	OH
32	triptolidenol	H	OH	H	OH
33	16-hydroxytriptolide	H	H	OH	OH

Fig. 9.
Bioactive triptolide derivatives in *Tripterygium*.

	Compound name	R 1	R 2
34	triptriolide	OH	H
35	12-epitriptriolide	H	OH
36	tripchlorolide	Cl	H

Fig. 10.
Diterpene diepoxides in *Tripterygium* with biological activity.

Fig. 11.
Structure of triptophenolide (**37**).

	Compound name	R 1	R 2	R 3	R 4	R 5	R 6	R 7
38	dehydroabietic acid	H	H	H	H	Me	COOH	H
39	triptobenzene H (dbl bond C3-4) (= hypoglic acid)	OH	H	OMe	H	Me	none	COOH
40	triptoditerpenic acid B (dbl bond C3-4) (= triptinin-A)	H	H	OMe	H	Me	none	COOH
41	(+)-dehydroabietane (= abietatriene)	H	H	H	H	Me	Me	H
42	abieta-8,11,13-trien-7-one	H	H	H	O (keto)	Me	Me	H
43	triptenin B (dbl bond C3-4) (= triptinin-B)	H	H	OH	H	Me	none	COOH
44	triptobenzene J	H	H	OH	H	CH ₂ OH	Me	OH
45	hinokiol	H	OH	H	H	Me	Me	OH

Fig. 12.
Bioactive benzenoid abietanes from *Tripterygium*.

Fig. 13.
Structure of quinone 21 (**46**).

	Compound name	R 1	R 2
47	triptoquinone A (dbl bond C3-4) (= triptoquinonoic acid A)	none	COOH
48	triptoquinone B	CH ₂ OH	O (keto)
49	triptoquinone C (=triptoquinondiol)	CH ₂ OH	OH
50	triptoquinone D (= triptoquinonol)	CH ₂ OH	H
51	triptoquinone E (= triptoquinonal)	CHO	H
52	triptoquinone F (= triptoquinonoic acid B)	COOH	H
53	triptoquinone H	Me	O (keto)

Fig. 14.
Bioactive diterpene quinoids from *Tripterygium*.

	Compound name	R1	R2	R3
54	tripterifordin(= hypodiolide A, antriptolactone)	HO	HO	(keto)
55	16 α -hydroxy-19,20-epoxy-19R-ethoxy-kaurane	H	OH	OEt
56	16 α -hydroxy-19,20-epoxy-20R-ethoxy-kaurane	OEt	OH	H
57	doianoterpene A (dbl bond C15-16)	O (keto)	none	H

Fig. 15.
Bioactive five-ring kauranes from *Tripterygium*.

	Compound name	R1	R2	R3
58	(-)-16 α -hydroxy-kauran-19-oic acid	Me	OH	COOH
59	(-)-17-hydroxy-16 α -kauran-19-oic acid	CH ₂ OH	H	COOH
60	16 α -(-)-kauran-17,19-dioic acid	H	COOH	COOH
61	<i>ent</i> -19-hydroxy-kaur-16-en (= <i>ent</i> -kaurenol)	vinyl		CH ₂ OH

Fig. 16.
Bioactive four-ring kauranes from *Tripterygium*.

Fig. 17.
Structure of labd-13(*E*)-ene-8 α , 15-diol (**62**).

Fig. 18.
Structure of 13-*epi*-manoyl oxide-18-oic acid (**63**).

	Compound name	R1	R2	R3	R4
64	pristimerin	COOCH3	H	H	Me
65	celastrol (= tripterin)	COOH	H	H	Me
66	tingenone (= tingenin A, maitenin, maytenin)	H	O (keto)	H	Me
67	22 β -hydroxy-tingenone (= tingenin B)	H	O (keto)	OH	Me
68	tripterygone (no dbl bonds C5-6 and 7-8; β -Me at C5)	COOH	H	H	H

Fig. 19.
Bioactive quinone methides from *Tripterygium*.

	Compound name	R1	R2	R3	R4	R5	R6	R7
69	polpunonic acid (= maytenoic acid, maytenonic acid)	COOH	Me	H	Me	H	O (keto)	H
70	3-oxo-friedelan-28-oic acid	Me	COOH	H	Me	H	O (keto)	H
71	3 β , 29-dihydroxy-D:B-friedoolean-5-en (dbl bond C5-6)	CH ₂ OH	Me	H	none	Me	OH	H
72	wilforic acid B (dbl bond C4-5)	COOH	Me	H	none	none	O (keto)	β -OH
73	regeol B (dbl bond C4-5)	COOH	Me	OH	none	none	O (keto)	α -OH
74	29-hydroxy-friedelan-3-one (= D:A-friedooleanan-29-ol-3-one)	CH ₂ OH	Me	H	Me	H	O (keto)	H

Fig. 20.
Bioactive five-ring friedelanes/friedooleananes with saturated rings from *Tripterygium*.

	Compound name	R1
75	orthosphenic acid	OH
76	salaspermic acid	H

Fig. 21.
Bioactive six-ring friedelanes/friedooleananes with saturated rings from *Tripterygium*.

	Compound name	R1	R2	R3	R4	R5	R6
77	demethylzeylasteral	COOH	H	H	O (keto)	CHO	H
78	demethylzeylasterone	COOH	H	H	O (keto)	COOH	H
79	wilforic acid A (no dbl bond at C7-8)	COOH	H	H	H	Me	H
80	triptohypol C	COOH	H	H	H	Me	H
81	3-methyl-22β, 23-diol-6-oxotingenol	H	O (keto)	OH	O (keto)	CH2OH	Me
82	2,3-dihydroxy-1,3,5(10),7-tetraene-6α(1'-hydroxyethyl)-24-nor-D:A-friedooleane-29-oic acid	COOH	H	H	CH(OH)-Me	Me	H

Fig. 22.

Bioactive friedooleananes with a benzenoid ring from *Tripterygium*.

	Compound name	R1	R2	R3	R4	R5
83	oleanolic acid	Me	H	COOH	Me	β -OH
84	3-acetoxy-oleanolic acid	Me	H	COOH	Me	β -OAc
85	triptotriterpenic acid A (= abrusgenic acid, maytenfolic acid)	COOH	α -OH	Me	Me	β -OH
86	3-epikatonic acid	COOH	H	Me	Me	β -OH
87	triptotriterpenic acid B	COOH	β -OH	Me	Me	β -OH
88	β -amyrin	Me	H	Me	Me	β -OH
89	triptotriterpenonic acid A (= 22 α -hydroxy-3-oxo-olean-12-en-29-oic acid)	COOH	α -OH	Me	Me	O (keto)
90	katononic acid	COOH	H	Me	Me	O (keto)
91	wilforol C	Me	H	COOH	CH ₂ OH	α -OH
92	triptocallic acid D	COOH	α -OH	Me	Me	α -OH

Fig. 23.
Bioactive five-ring oleananes from *Tripterygium*.

	Compound name	R1
93	regelide (= wilforlide A, abruslactone A)	OH
94	wilforlide B	O (keto)
95	2 α ,3 β -dihydroxy-olean-12-ene-22,29-lactone	OH

Fig. 24.
Bioactive six-ring oleananes from *Tripterygium*.

	Compound name	R1	R2	R3	R4	R5	R6
96	regelin	COOMe	OH	Me	Me	O (keto)	H
97	regelinol	COOMe	OH	Me	CH ₂ OH	O (keto)	H
98	triptotriterpenic acid C (= tripterygic acid A)	COOH	OH	Me	Me	β-OH	H
99	α-amyrin	Me	H	Me	Me	β-OH	H
100	triptocallic acid A	COOH	OH	Me	Me	α-OH	H
101	dulcioic acid	COOH	H	Me	Me	β-OH	H
102	demethylregelin	COOH	OH	Me	Me	O (keto)	H
103	3β-acetoxy-ursolic acid (= acetyl ursolic acid)	Me	H	COOH	Me	β-OAc	H
104	2α-hydroxy-ursolic acid (= corosolic acid, colosolic acid)	Me	H	COOH	Me	β-OH	OH

Fig. 25.
Bioactive ursanes from *Tripterygium*.

Compound name	R1
105 β -sitosterol	OH
106 daucosterol	O- β -D-glucopyranose

Fig. 26.
Bioactive steroids from *Tripterygium*.

Fig. 27.
Structure of zeorin (**107**).