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Neuropharmacological effects of triterpenoids

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Abstract

Triterpenes comprise one of the most interesting groups of natural products due to their diverse pharmacological activities. Triterpenes are ubiquitously present in variety of ethnomedicinal plants. The term 'triterpene' represents naturally occuring terpenes, whereas the broader expression 'triterpenoid' includes secondary metabolites. It has been estimated that 80 distinct types of both the structure and the chemical characteristics of triterpenes have been identified till today. Many such compounds can either be used directly as active compounds or modified to increase their selectivity and potency. The present article provides updates on wide range of biological activities of tetracyclic triterpenes and pentacyclic triterpenoids such as immunomodulatory, anticancer, anti-inflammatory, anti-anxiety, antidepressant, memory enhancer, antinociceptive, neuroprotective and other CNS actions. Several structural groups of triterpenes have demonstrated specificity against transcriptional factors which can be promising candidates for treating inflammation, cancer, and immune diseases.

Keywords: Ethnomedicine; Molecular signaling; Neuropharmacology; Pentacyclic triterpenoids; Tetracyclic triterpenes

Introduction

Triterpenoids are widely distributed in the plant kingdom. They are produced in plant as secondary metabolites and have varied biological activities (Hanson, 2003). The terms triterpenes and triterpenoids are often used to describe the same C_{30}-terpene compound. However, they need to be differentiated based upon their occurrence, biosynthesis and biotransformation products. The term 'triterpene' is used to describe naturally occurring terpenes whereas; the broader expression 'triterpenoid' includes natural degradation products (Eggersdofer, 2005). Triterpenes are originally synthesized by plants as metabolites, and are abundantly present in the plant kingdom in the form of free acids or aglycones (Chappell, 1995;

McGarvey Croteau, 1997). Till today, at least 80 distinct types of both the structure and the chemical characteristics of triterpenes have been shown. It is well-recognized that triterpenes have long been used as flavors, pigments, polymers, fibers, glues, and waxes. In many Asian countries, herbal products containing triterpenes are widely prescribed to prevent or treat a variety of diseases by the traditional healers (Wagner and Elmadfa, 2003; Xu et al., 2004).

Classification of triterpenes and triterpenoids

Triterpenoids are structurally diverse group of natural products that contain about 30 carbon atoms. As shown in Table 1, the triterpenoids are classified into two main groups; tetracyclic and the pentacyclic triterpenoids. Tetracyclic triterpenes such as oleandrin, euphol and cucubitacins are methylated steroids (Figure 1). The group of pentacyclic triterpenoids is by far the largest and friedelane, lupane, ursane, oleane, serratane, and taraxastane are six main groups of this category (Gunatilaka, 1986; Xu et al., 2004). Ursanes and oleananes such as oleanolic acid, ursolic acid, maslinic acid, uvaol, and erythrodiol (Figure 1) are the major triterpene skeletons present in higher plants including commonly consumed plant foods (Abe et al., 1993; Connolly and Hill, 2001). Other groups of triterpenes occur widely in edible or inedible plants (Yin M., 2012).

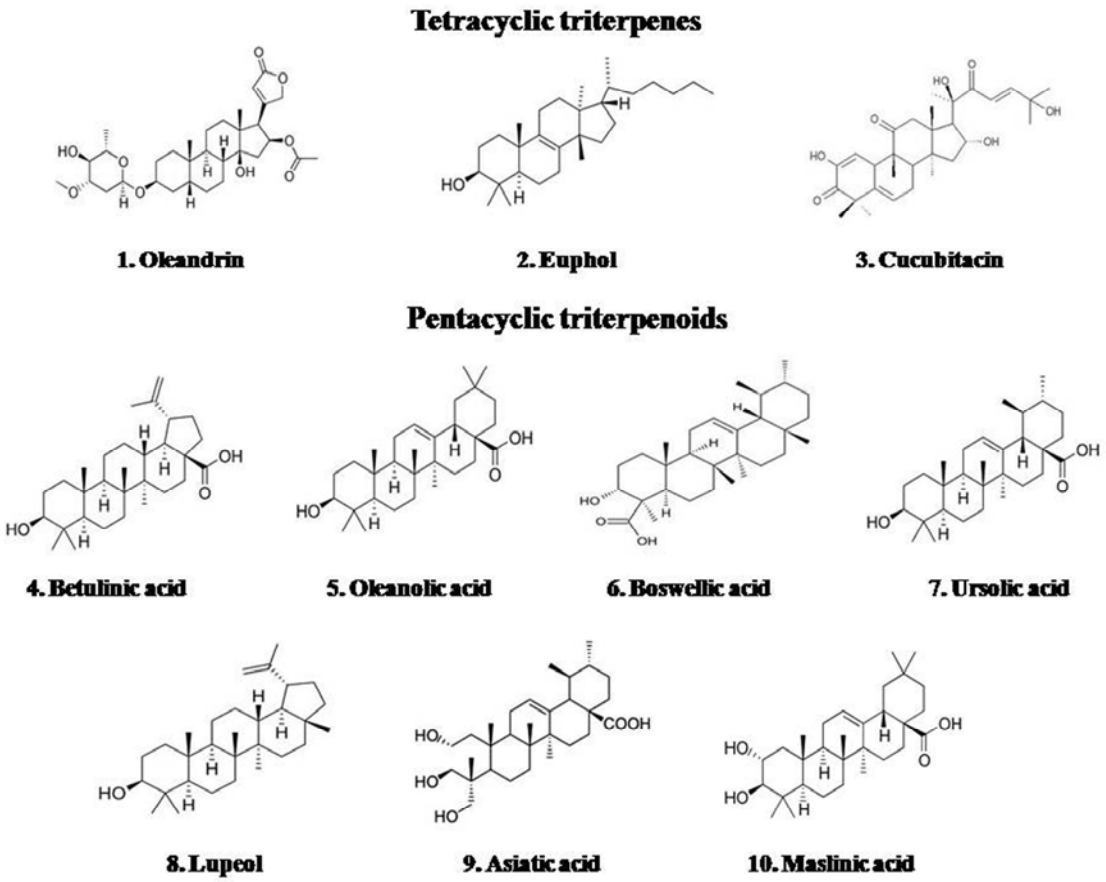

Figure 1. Chemical structures of tetracyclic triterpenes and pentacyclic triterpenoids.

Table 1. Classification of triterpenoids and their derivatives.

Triterpenoid Family	Triterpene	R_1	R_2
Ursane	Ursolic acid	COOH	
	Uvaol	CH_2OH	
	α-amyrin	CH_3	
Oleanane	Erythrodiol	CH_2OH	H
	β-amyrin	CH_3	H
	Oleanolic acid	COOH	H
	Maslinic acid	COOH	OH
Lupane	Betulin	CH_2OH	
	Lupeol	CH_3	
	Betulinic acid	COOH	

The majority of triterpenoids are 6-6-6-5 tetracycles, 6-6-6-6-5 pentacycles, or 6-6-6-6-6 pentacycles types. However, acyclic, monocyclic, bicyclic, tricyclic, and hexacyclic triterpenoids have also been isolated from natural sources. These triterpenoids have a common origin and their structures is said to be derived from squalene, an important intermediate in biogenesis of various plant metabolites (Buckingham, 2002).

Occurrence in plant kingdom

Although terpenes are widely distributed in the plant kingdom, most of the bioactive terpenes have been found in higher plants. Mono- and sesquiterpenes are chiefly present in plants possessing volatile oil whereas, higher terpenes, such as triterpenes are chiefly discovered in balsams and resins (Gildemeister and Hoffmann, 1960; Sandermann, 1960). They are also present in prokaryotic as well as eukaryotic organisms. An excellent review on bacterial triterpenoids with specific focus on triterpenoid occurrence and their functions in bacteria has been described by Tylor (1984). The triterpenes content of different plants varies depending on parameters such as species, season and soil. Table 2 depicts widespread occurrence of triterpenes and triterpenoids in the plant kingdom.

Table 2. Occurrence of triterpenes and triterpenoids in the plant kingdom.

Chemical compound	Botanical name	Family
Tetracyclic triterpenoid		
Cucurbitacin	*Bryonia alba*	Curcutibaceae
Ganoderic acid	*Ganoderma lucidum*	Ganodermataceae
Oleandrin	*Nerium oleander*	Apocynaceae
Pentacyclic triterpenoid		
Amyrin	*Diospyros kaki*	Ebenaceae
Asiatic acid	*Centella asiatica*	Mackinlayaceae
Avicin	*Acacia victoriae*	Fabaceae
Betulinic acid	*Ziziphus mauritiana*	Rahmnaceae
	Anemone raddeana	Ranunculaceae
	Lycopodium cernuum	Lycopodiaceae
	Syzygium claviflorum	Myrtaceae
Boswellic acid	*Boswellia serrata*	Burseraceae
	Boswellia carteri	Burseraceae
Lupeol	*Mangifera indica*	Anacardiaceae
	Crataeva nurvala	Capparidaceae

Madecassic acid	*Centella asiatica*	Mackinlayaceae
Momordin	*Kochia scoparia*	Amaranthaceae
Oleanolic acid	*Arctostaphyllos uva-ursi*	Ericaceae
	Calluna vulgaris	Ericaceae
	Crataeva nurvala	Capparidaceae
	Ganoderma lucidum	Ganodermataceae
	Sambucus chinensis	Adoxaceae
	Solanum incanum	Salanaceae
Platycodon D	*Platycodon grandiflorum*	Campunulaceae
Pristimerin	*Maytenus ilicifolia*	Celastraceae
	Celastrus hypoleucus	Celastraceae
	Tripterygium wilfordii	Celastraceae
Ursolic acid	*Ocimum sanctum* L.	Lamiaceae
	Thymus vulgaris L.	Lamiaceae
	Lavandula augustifolia	Lamiaceae
	Nepeta sibthorpii	Lamiaceae
	Mentha piperita L.	Lamiaceae

Biosynthesis

Plants biosynthesize diverse group of triterpenoids. As described in Figure 2, the terpenes biosynthesis can be divided into four distinct stages. Initial or the first stage involves the formation of isopentenyl diphosphate that is basic building block for isoprenoids (Gershenzon and Kreis, 1999). Secondly, these units associate to form the $(C_5H_8)_n$ isoprenoid backbone of the terpene families. Thirdly, there is generation of the carbon skeletons as a result of the cyclization of these units. Finally, various chemical reactions such as hydroxylations and oxidations lead to the formation of individual terpenoids. Most of the triterpenes are derived from squalene, which is synthesized from the reductive coupling of two molecules of farnesyl pyrophosphate by the enzyme squalene synthase. The enzyme squalene epoxidase then oxidize squalene to generate 2, 3-oxidosqualene. Furthermore, these oxidized squalene moiety is cyclized by oxidosqualene cyclases (OSCs) to form intermediate cations. These cations then undergo structural changes by various enzymes to produce triterpene alcohols or aldehydes including α- and β-amyrin and lupeol (Haralampidis et al., 2002; Phillips et al., 2006).

It is well-established that different plants possess genomic machineries for multiple OSC enzymes that facilitate triterpenoid biosynthesis. These OSCs confers the structural diversity to the triterpenoids by their unique role on cyclization of 2,3-oxidosqualene (Mangas et al., 2006). Cyclization of 2,3-oxidosqualene through a protosteryl cation intermediate generates lanosterol and cycloartenol which are structural precursors for all the steroids, whereas cyclization through a baccharenyl, dammarenyl and lupenyl cation intermediates produces lupeol and α/β-amyrin (Jenner et al., 2005). The cyclization of 2,3-oxidosqualene by α/β-amyrin synthase enzymes results into the formation of dammarenyl cation which undergo further ring expansion and a few rearrangements before deprotonation to α-amyrin and β-amyrin, respectively.

Following cyclization, further diversity in structure is conferred by modification of the products by oxidation, hydroxylation, glycosylation and other substitutions mediated by cytochrome P450-dependent monooxygenases, glycosyl transferases and other enzymes. The enzymes employed for these chemical elaborations of triterpenes and triterpenoids have not been well documented.

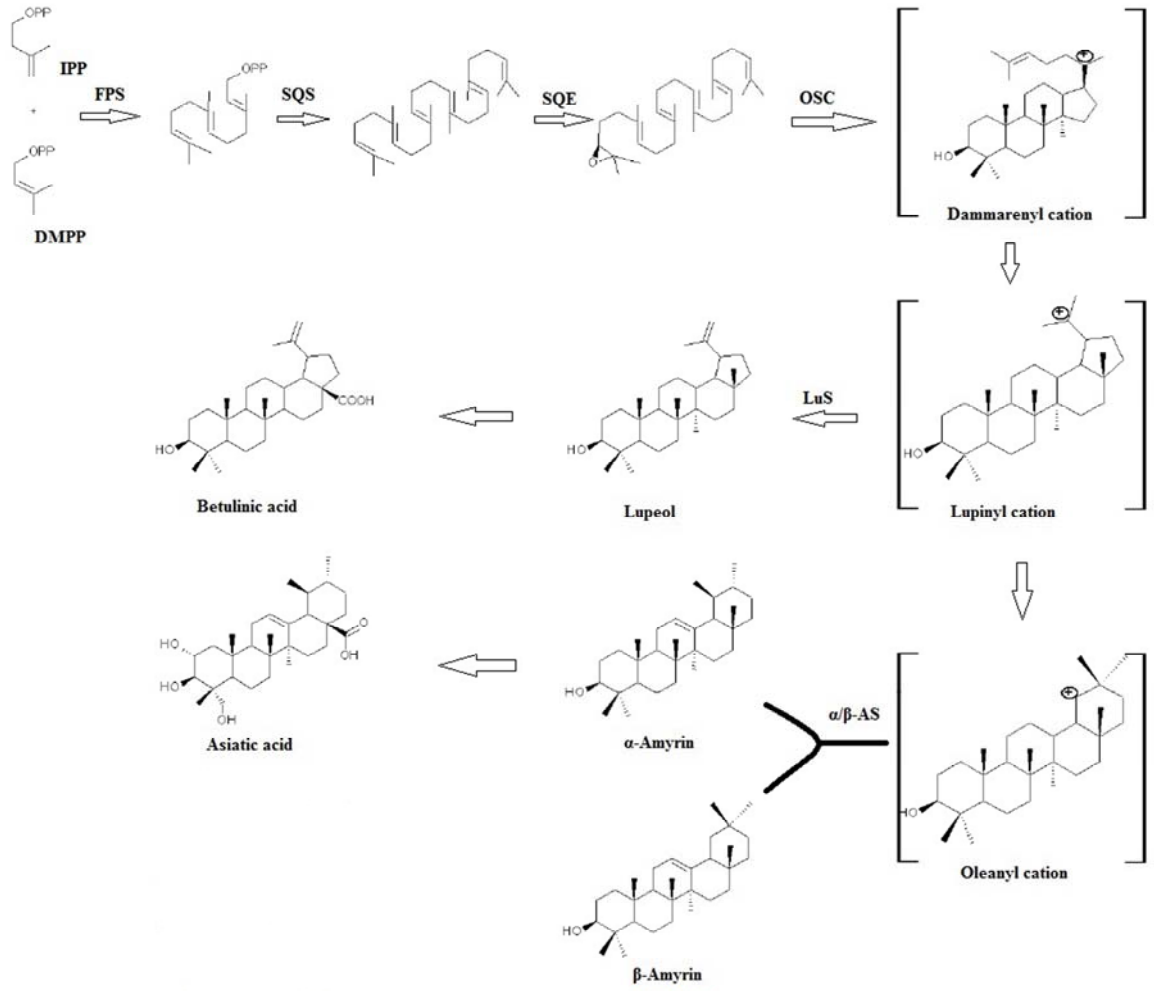

Figure 2. A simplified scheme of triterpenoid biosynthesis. Isomerization of isopentyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) by farnesyl diphosphate synthase (FPS) leads to farnesyl diphosphate (FPP), which is then converted to squalene by the enzyme squalene synthase (SQS). Subsequently, squalene epoxidase (SQE) oxidises squalene to 2,3-oxidosqualene. This is followed by enzymatic ciclyzation of 2,3-oxidosqualene by oxidosqualene cyclase (OSC) to produce intermediate dammarenyl cation. Further, the ring expansion of dammarenyl cation produce lupinyl or oleanyl cations. Finally, enzymes α/β-amyrin synthases (α/β-AS) and lupeol synthase converts oleanyl and lupinyl cations to form the α/β-amyrin and lupeol, respectively.

Effects of triterpenoids on molecular and cellular signaling

Biological activities

A wide range of biological activities of triterpenoids have been reported. Some of these activities along with molecular signalling of important tetracyclic and pentacyclic triterpenoids are discussed here. Ursolic acid, a pentacyclic triterpenoid, has been shown to possess immunomodulatory (Jang et al., 2009; Raphael and Kuttan, 2003), antioxidative (Ramachandran and Prasad, 2008), anti-HIV (Lee et al., 2008a), bone anabolic activities (Lee et al., 2008b), hypolipidemic (Min et al., 2008; Somova et al., 2003), antibacterial (Fonranay et al., 2008), anti-mutagenic (Resende et al., 2006), antitumor (Hsu et al., 2004; Ma et al., 2005), antidysrhythmic (Somova et al., 2004), and hepatoprotective (Saraswat et al., 2000). Apop-

tosis inducing activity of betulinic acid have been studied thoroughly in neuroblastoma and glioblastoma cells, which is believed to be mediated by the activation of the mitochondrial pathway (Fulda et al., 1997; Jeremias et al., 2004; Tan et al., 2003).

Table 3. Molecular targets of tetracyclic triterpenes and pentacyclic triterpenoids for antitumor and anti-inflammatory actions.

Terpenoids	Targets	References
Tetracyclic triterpenes		
Cucurbitacin	Cyclin B1, cyclin D1, Mcl-1, cdc25C, STAT3, p53	Chan et al., 2010; Lui et al., 2009
Ganoderic acid	NF-κB, AP-1, NFATc1, cdk4, uPA, MMP2, MMP9	Chen et al., 2008; Jiang et al., 2008
Oleandrin	NF-κB, AP-1, Fas, ERK, FGF-1	Afaq et al., 2004; Manna et al., 2000
Pentacyclic triterpenoid		
Amyrin	NF-κB, IL-1β, COX-2, CREB, ERK, PKC, P38 MAPK	Medeiros et al., 2007; Vitor et al., 2009
Asiatic acid	NF-κB, caspases-2, -3, -8 and -9, PARP, Bcl-2	Tang et al., 2009; Park et al., 2007
Avicin	NF-κB, Fas, STAT3, caspase-8, Bcl-2, Bcl-xL	Haridas et al., 2009; Zhang et al., 2008
Betulinic acid	NF-κB, STAT3, Bax, Bcl-2, Bcl-xL, FAK	Chen et al., 2008; Chintharlapalli et al., 2007
Boswellic acid	NF-κB, STAT3, AR, p21, DR5, caspase-3 and -8	Kunnumakkara et al., 2009; Syrovets et al., 2005
Celastrol	NF-κB, IAP1, IAP2, Bcl-2, Bcl-xL, c-FLIP, COX-2, survivin, cyclin D1, MMP9, VEGF, iNOS, Hsp90, cdc37, VEGFR	Jung et al., 2007; Kim et al., 2009
Escin	NF-κB, STAT3, JAK2, cyclin D1, Bcl-2, Bcl-xL, survivin, Mcl-1, VEGF, COX-2, MMP9	Harikumar et al., 2010; Tan et al., 2010
Lupeol	NF-κB, cFLIP, survivin, Bax, caspase-3, caspase-9	Murtaza et al., 2009; Lee et al., 2007
Madecassic acid	iNOS, COX-2, TNF-α, IL-1, IL-6	Won et al., 2010
Momordin	NF-κB, AP-1, Bcl-2, Bax, caspase-3, PARP	Hwang., 2005; Kim et al., 2002
Oleanolic acid	NF-κB, mTOR, caspases-3, -8, and -9, ICAM-1, VEGF, PARP, Akt	Chu et al., 2010; Deeb et al., 2008
Pristimerin	NF-κB, PARP-1, JNK, Bax, p27, Bcl-2, Bcl-xL	Tiedemann et al., 2009; Wu et al., 2005
Ursolic acid	NF-κB, STAT3, Bcl-2, Bax, ICAM-1, p53, PKC	Manu et al., 2008; Shishodia et al., 2003

AIF, apoptosis inducing factor; AMPK, 5' AMP-activated protein kinase; AP-1, activator protein-1; Apaf1, apoptotic protease activating factor 1; AR, androgen receptor; Bax, BCL2-associated X protein; Bfl-1/A1, BCL2-related protein A1; cdc, cell division cycle; cdk, cyclin-dependent kinase; cFLIP, cellular FLICE inhibitory protein; COX-2, cyclooxygenase-2; CREB, cAMP response element binding protein; DR, death receptor; EGFR, epidermal growth factor receptor; Egr-1, earyl growth response factor-1; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FasL, Fas-ligand; FGF-1, fibroblast growth factor-1; GSK3β, glycogen synthase kinase-3 β; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; Hsp, heat shock protein; IAP, inhibitor of apoptosis protein; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; Mcl-1, myeloid cell leukemia-1; MCP, monocyte chemotactic protein; MEK, MAPK/ERK kinase, MIP-2, macrophage-inflammatory protein-2; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF-AT, nuclear factor of activated T-cells; NF-κB, nuclear factor-kappa B; PARP, poly (ADP-ribose) polymerase; PI3K, phosphoinositide-3 kinase; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; Sp1, specificity protein 1; STAT3, signal transducer and activator of transcription 3; TF, tissue factor; TLR2, Toll-like receptor-2; TNF-α, tumor necrosis factor-α; TRAF1, TNF receptor-associated factor-1; uPA, urokinase-type plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Table 3 depicts different molecular targets for tetracyclic and pentacyclic triterpenoids. It can be observed that triterpenoids act on wide range of chemokines and apo-ptotic factors and play major role in tumor suppression, inflammatory response, and immune response.

Behavioral and psychopharmacological effects

Biological effects of pentacyclic triterpenoids

Memory and dementia

Nasira et al. (2011) have investigated the effects of acute administration of asiatic acid isolated from *Centella asiatica* on memory and learning using active and passive avoidance models in experimental animals and concluded that administration of asiatic acid facilitated passive avoidance on memory and learning but had no effect on active avoidance on memory. In another study, ursolic acid has been reported to possess antioxidant activity. Furthermore, the protective effect of ursolic acid against the D-galactose-induced neurotoxicity and learning and memory impairment has been demonstrated. The study also postulated molecular mechanism and concluded that the cerebroprotective action of ursolic acid against D-galactose-induced neurotoxicity might be caused, at least in part, by the restoration of antioxidant enzyme levels such as super oxide dismutase, catalase, glutathione peroxidase and glutathione reductase with a marked reduction in lipid peroxidation. Additionally, ursolic acid might have increased the level of growth-associated protein GAP43 in the brain of D-galactose -treated mice (Lu et al., 2007).

Depression

The α/β-amyrin, a triterpene isomeric mixture from *Protium heptaphyllum*, has been shown to decrease the immobility time in the behavior despair test in mice (Yildiz et al., 2002). In another study, β-amyrin palmitate showed tonic inhibitory action on depression. Further, it was suggested that the release of norepinephrine from newly synthesized pools might account for the antidepressant actions of β-amyrin palmitate (Chen et al., 2003; Subarnas et al., 1993).

Convulsions

The distinct $GABA_A$-receptor related properties of lupane type triterpenoids such as betulin, betulinic acid and lupeol have been reported *in vivo* and *in vitro*. Muceniece et al. (2008) has showed that betulin competed with [3H]GABA for binding to the corresponding sites on the $GABA_A$ receptor, whereas betulinic acid and lupeol did not show any binding affinity. Further, antagonistic action of betulin against bicuculline, a convulsant drug, following central and peripheral administration of betulin has been reveled by this study.

Pain and nociception

Various triterpenoids such as lupeol, tormentic acid, betulin, betulinic acid and *epi*betulin have been reported to produce significant antinociceptive and/or anti-inflammatory

activities by different mechanisms such as inhibition of cyclo and lipoxygenase pathways (Calixto et al., 2000, Moroney et al., 1988). Tormentic acid, a naturally occurring pentacyclic triterpenoid found in a variety of plants, has been shown to possess anti-allodynic action in two different models of chronic pain in mice: neuropathic pain caused by partial constriction of the sciatic nerve and inflammatory pain caused by plantar injection of complete Freund's adjuvant (Bortalanza et al., 2002).

Anti-nociceptive effect of lupeol isolated from *Zanthoxylum rhoifolium* in models of acute pain in rodents has been evaluated. In this study, lupeol reduced the glutamate-evoked nociceptive response and ameliorated the neurogenic nociception induced by intraplantar injection of capsaicin that stimulated nerve endings causing intense thermal and nociceptive pain (Sakurada et al., 1992, Santos and Calixto, 1997).

The lupane triterpenoids such as betulin, 28-acetoxy-betulin, *epi*betulin, *epi*betulinic acid, and betulonic acid have been shown to possess potent anti-inflammatory activity through inhibition of nitric oxide and prostaglandin E_2 production in mouse macrophages stimulated with bacterial endotoxin (Misko et al,1993, Moroney et al.,1988). Luiz et al. (2007) has evaluated the ethanolic extract from roots of *Humirianthera ampla* against neurogenic and inflammatory models of nociception in experimental animals and concluded that the nociceptive activity might be attributed to di- and triterpenoids, the chief constituents of *H. ampla*.

Oleanolic acid, the anti-inflammatory pentacyclic triterpenoid, produced tonic inhibitory effects on capsaicin-evoked acute nociception due to mechanisms possibly involving endogenous opioids, nitric oxide, and potassium-ATP-channel opening (Maia et al., 2006) in experimental animals. The anti-inflammatory mechanisms of the ursane type pentacyclic triterpenoid, β-boswellic acid and its derivatives have been studied by Giner et al. (2000). The study concluded that β-boswellic acid and its derivatives produced anti-inflammatory action through inhibition of 5-lipoxygenase.

Anxiety

The oral and intraperitoneal administration of betulinic acid produced anti-anxiety activity in animals. Further, a pharmaceutical composition containing betulinic acid has been patented as a means for prevention or treatment of anxiety (Durst et al., 2002).

The anxiolytic effects of the mixture of α/β-amyrin, the pentacyclic triterpenoids isolated from the stem bark resin of *Protium heptaphyllum*, has been demonstrated by different animal models. The results of this study showed that α/β-amyrin significantly decreased the number of crossings, grooming, rearing and the time of permanence and the number of entrances in the close arms whereas, increased the time of permanence and the number of entrances in the open arms (Dias et al., 2005; Herrera-Ruiz et al., 2006; Morris et al., 2006).

Sedation and hypnotics

α/β-amyrin has also been evaluated for their sedative effects in mice (Petty, 1995). Subarnas et al. (1993) have investigated hypnotic potential of β-amyrin palmitate in pentoba-

rbitone-induced narcosis in mice and concluded that administration of β-amyrin palmitate potentiated the pentobarbitone-provoked narcosis in experimental animals.

Biological role of tetracyclic triterpenes

Pain and nociception

A number of studies indicate that tetracyclic triterpenes play a central role in the manageeement of pain. Scott et al. (2004) have investigated the anti-nociceptive activity of euphol against nociceptive response induced by ligation of the sciatic nerve and injection of complete Freund's adjuvant in rat paw and spinal cord. The results showed significant effect of euphol in preventing the mechanical nociception induced by sciatic nerve ligation and also ameliorated the levels and mRNA of cytokines in both paw and spinal cord tissues following injection of complete Freund's adjuvant. An interesting finding of this study was that even in higher doses, euphol did not cause any relevant action in the central nervous system. Recently, Dutra et al. (2011 & 2012) evaluated the molecular mechanism of anti-nociceptive properties of euphol and found that anti-nociception effect of euphol was related with its ability to inhibit the activation and/or release of various inflammatory mediators such as IL-1β, IL-6 and TNF-α, as well as due to the blockade of neutrophils influx in the rat paw and spinal cord tissue, respectively.

The analgesic effects of the extract of roots and tubers of *Wilbrandia ebracteata* has been studied by Peters et al. (1997). In this study, it was suggested that cucurbitacins, the chief constituents of the *W. ebracteata* extracts, might be responsible for the analgesic activity by inhibition of PGE2 production. Similarly, Bralley et al. (2007) have evaluated topical application of tirucallol, a tetracyclic triterpene from *Euphorbia lacteal* latex, against mouse model of ear oedema. The results from this study showed that tirucallol improved ear oedema and inhibited the influx of polymorphonuclear cells to inflammed area of mouse ear. In another study, the effect of tirucallol on some macrophage functions has been analyzed *in vitro* (Carlson et al. 1989). It was postulated that non-toxic concentrations of tirucallol inhibited nitrite production in lipopolysaccharide-stimulated macrophages. Anti-nociceptive and anti-inflammatory effects of (-)-cassine, a tetracyclic triterpene from *Senna spectabilis*, has been evaluated using pharmacological, behavioural and biochemical approaches in experimental animals. The study indicated that pretreatment with (-)-cassine reduced carrageenan-induced mechanical and thermal nociception, and prostaglandin E2-, Freund's complete adjuvant-, (IL)-1b-, (IL)-6- and keratinocyte-derived chemokine-provoked hyperalgesia (Kathryn et al., 2012). De Souza et al. (2009) have reported potent antinociceptive property of filicene, a triterpene from *Adiantum cuneatum* leaves, in acetic acid-induced writhing, capsaicin and glutamate-induced nociception models in mice. Li et al. (2012) has investigated the antinociceptive effects of escin against formalin-induced activation of c-Fos and phosphorylated p38 MAPK in the rat spinal cord. In this study, escin decreased pain-related behaviours, c-Fos and phosphorylated p38 MAPK expressions. In another study, the molecular mechanisms underlying antinociceptive effect of the 3β, 6β, 16β-trihydroxylup-20(29)-ene (TTHL), a triterpene, in mice was evaluated. The findings of this study suggested that TTHL produced antinociceptive effect that was dependent on opioid and serotonergic systems, Gi/o protein activation and the opening of specific K+ channels (Longhi-Balbinot et al., 2009).

Anxiety

An infusion prepared with aerial parts from *Galphimia glauca* has been widely used in Mexican traditional medicine as a remedy for nervous excitement. The sedative activity of a methanolic extract from this plant has been demonstrated by neuropharmacological tests such as elevated plus-maze, light-dark test and the forced swimming models. The effect was attributed to the nor-secotriterpene named galphimine B (Herrera-Ruiz et al., 2006). Similarly, galphimine-B has been investigated for anxiolytic effect by means of a double blind clinical trial. It was demonstrated that galphimine-B could be a promising therapeutic candidates for the patients with generalized anxiety (Jiménez-Ferrer et al., 2011).

Others

Neuroprotective activities

Asiatic acid has been studied for its neuroprotective effects *in vitro* and *in vivo*. Vogel et al. (1990) showed that asiatic acid produced neuroprotection through reduction in apoptotic cell death, neutralization of reactive oxygen species and stabilizing the mitochondrial membrane potential. The study also showed that oral administration of asiatic acid markedly improved Morris water maze test experience, reduced lipid peroxidation levels and normalized glutathione and SOD levels in the rat brain. *Ganoderma lucidum*, the rich source of triterpenoids, is one of the most popular medicinal fungi with a long history of use in Asian countries (Sanodiya et al., 2009). Chen et al. (2012) has investigated cerebroprotective activity of *G. lucidum* against mitochondrial toxins in mouse model of Huntington's disease and suggested that the effect could be attributed to the triterpenoids from this plant. Similarly, ursolic acid, oleanolic acid, 3-*epi*ursolic, 3-*epi*oleanolic acid and derivatives of ursolic acid and oleanolic acid are abundantly present in *Verbena officinalis* (Deepak and Handa, 1998). The study of Lai et al. (2006) indicated that triterpenoids could play a central role in the effects of *V. officinalis* on β-amyloid peptide-induced cytotoxicity.

Diverse efforts have been made to discover anti-Alzheimer's agents from natural sources. Various group of chemicals like ginsenosides, gingkolides, and canabinoids as potential anti- Alzheimer's disease agents have been studied. These compounds exhibit promising *in vitro* and *in vivo* biological activities, but are still to be tested clinically. Other compounds such as cornel iridoid glycoside, oleanolic acid, tenuifolin, cryptotanshinone and ursolic acid have outstanding neuroprotective effects in in vitro assays. These compounds can exert beneficial effects on central nervous system directly or indirectly by acting on peripheral targets (Yoo and Park, 2012). Ginsenosides enjoy a special attention among triterpenoids when it comes to pharmacological activities. Ginsenosides have been research targets over the last three decades to explain ginseng actions and a wealth of literature has been presented reporting on ginsenosides' effects on the human body. Recently, there is increasing evidence on beneficial effects of ginsenosides to the central nervous system. Using a wide range of *in vitro* and *in vivo* models, researchers have attributed these effects to specific pharmacological actions of ginsenosides on cerebral metabolism, oxidative stress and radical formation, neurotransmitter imbalance and membrane stabilizing effects, and even antiapoptotic effects. Modulating these particular mechanisms by ginsenosides has thus been reported to exert either general stimulatory effects on the brain functions or protecting the CNS against various dis-

ease conditions (Radad et al., 2011). Another study reported that maslinic acid exerts anti-apoptotic as well as neuroprotective effect through inhibition of inducible nitic oxide synthase and normalization of caspase expression/activation against oxygen-glucose deprivation-induced neuron damage (Qian et al., 2011). Considerable evidence has been accumulated demonstrating an important role for inflammation in ischemic brain injury and its contribution to greater cerebral damage after ischemia. Blocking the inflammatory reaction promotes neuroprotection and shows therapeutic potential for clinical treatment of ischemic brain injury (Brea et al., 2009; Dos-Anjos et al., 2009). Moreover, celastrol a pentacyclic triterpenoid has been showed to possess anti-ischemic action against ischemia-reperfusion-induced cerebral injury through downregulation of the expression of p-JNK, p-c-Jun and NF-κB (Lia et al., 2012). This ameliorating effect of celastrol on the expression of p-JNK, p-c-Jun and NF-κB is evidenced by the another set of experiments where celastrol has been showed to possess anti-inflammatory and anti-apoptotic activities by inhibition of NF-κB activation and MAPK inactivation including JNK (Kannaiyan et al., 2011a, 2011b; Kim et al., 2009). Ursolic acid, a natural pentacyclic triterpenoid acid, a well-known anti-oxidative and anti-inflammatory reagent, protects the brain against ischemic injury by promoting the activation of nuclear factor-erythroid 2-related factor 2 pathway and downregulation of the expression of TLR4 and NF-κB (Li et al., 2012). Escin, a natural mixture of triterpenoid saponin has been showed to improve learning and memory recovery and reduce hippocampal damage in the cerebral ischemic mice (Zhang et al., 2010). This study reported that anti-ischemic action conferred by escin was by downregulation of certain inflammatory gene expression and upregulating the expression of granulocyte-macrophage colony-stimulating factor in experimental animals.

In conclusion, triterpenes comprise one of the most interesting groups of natural products due to their high potential as pharmacological agents. Triterpenes are ubiquitously present in plants of ethnomedicinal use. Many such compounds can either be used directly as active compounds or modified to increase their selectivity and potency. Although they have generally been examined for their anti-inflammatory and antiviral properties, their possible use as immunosuppressant drugs should be considered for future research. In addition, new paths of investigation should be pursued, including studies on their effects on transcriptional pathways as well as their implication in immune responses. Several structural groups of triterpenes have demonstrated specificity against transcriptional factors which could be of particular interest in treating inflammation, cancer, and immune diseases.

Conflict of interest

None of the authors have any conflict of interest to declare.

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