Euphorbia diterpenes: Isolation, structure, biological activity and synthesis (2008–2012)

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Contents

Abbreviations

ABCB1: ATB-binding cassette sub-family B member 1; CC: column chromatography; CMV: cytomegalovirus; FAR: fluorescence activity ratio; FIX: fractional inhibitory index; HJB: 17-hydroxyjolkinolide; JAK: Janus kinase; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MDR: multidrug resistance; MPP^+: 1-methyl-4-phenylpyridinium-ion; NF-κB: nuclear factor; PKC: protein kinase C; P-gp: P-glycoprotein; PTX: paclitaxel; STAT: signal transducer and activator of transcription; TLC: thin layer chromatography, TNF-α: tumor necrosis factor; TRPV1: transient receptor potential vanilloid 1; VEGF: vascular endothelial growth factor

1. Introduction

The Euphorbiaceae is one of the largest families of higher plants, comprising about 50 tribes, 300 genera and 7500 species, with probably the highest species richness in many habitats.[1] The genus *Euphorbia* is one of the 6 largest genera (*Astragalus*, *Bulbophyllum*, *Psychotria*, *Euphorbia*, *Carex*, *Begonia*) of flowering plants, with approximately 2160 species, subdivided into many subgenera and sections. Members of this genus are characterized by the production of a milky irritant latex.[2] The *Euphorbia* species are widely distributed throughout mainlands (both tropical and temperate regions) and range in morphology from small, annual or perennial herbaceous plant to woody shrubs, lianas, and trees and even large desert succulents.[3] In general, the whole plants, stems, leaves, latex, roots, and seeds of *Euphorbia* species were investigated in chemical and pharmacological studies.[1,2] The genus consists species of great economic importance, such as *Euphorbia tetragonal* and *E. triangularis* (inferior rubber), *E. antisyphylitica* (candellila wax)and *Euphorbia resinifera* ('euphorbium').[4]

Diterpenes occurring in plants of the genus *Euphorbia* are in the focus of natural product drug discovery because of the wide range of their therapeutically relevant biological activities (*e.g*. antitumor, cytotoxic, multidrug resistance-reversing, antiviral properties, various vascular effects and anti-inflammatory activity)[5] and their great structural diversity, resulting from various macrocyclic and polycyclic skeletons (*e.g*. jatrophane, ingenane, daphnane, tigliane, lathyrane, etc.) and oxygen-containing functionalities, including different aliphatic (*e.g*. acetyl, *n*-butanoyl, isobutanoyl, methylbutanoyl, tiglyl, angeloyl, isovaleroyl, etc.) and aromatic (benzoyl and nicotinoyl) acids. Diterpenes are considered to be important taxonomic markers, because of their limited occurrence; these types of diterpenes are specific to the Thymelaeaceae and Euphorbiaceae families. Over 650 diterpenoids,

incorporating more than 20 skeletal types, have been isolated from *Euphorbia* plants. In 2008, Shi et al. summarized the diterpenes isolated previously from different *Euphorbia* species.[6] The present review covers 221 new *Euphorbia* diterpenes isolated since then; the structures of the new diterpenoids are presented.

Among Euphorbia diterpenes ingenol 3-angelate (ingenol mebutate, PEP005, Picato®, LEO Pharma) attracted the greatest interest in the last years, because it was approved by the FDA in 2012, and the EMA in 2013 for the treatment of actinic keratosis, a precancerous skin condition.[7] Besides this compound, other promising diterpenes (*e.g*. some phorbol and ingenol derivatives) are under clinical investigations. In particular, prostratin is of considerable interest because of its unique ability to activate latent viral reservoirs, and preventing healthy cells from infection. These types of compounds reactivate HIV-1 latency by protein kinase C (PKC)-dependent NF-κB activation, and help to avoid the new infection of $CD4^+$ cells.[8] Resiniferatoxin, an ultrapotent capsaicin analogue belonging in the daphnane group, is currently under phase II and III clinical evaluation.[9]

In Chinese pharmacopoeias five species, *E. pekinensis*, *E. kansui*, *E. lathyris*, *E. humifusa* and *E. maculata* are official. These species are well-known poisonous plants, but in the traditional Chinese medicine they are recommended for the treatment of edema, gonorrhea, migraine and warts.[10]

2. Isolation and analytics of diterpenes

Diterpenes are generally isolated from different *Euphorbia* species by very similar protocols (Table 1). All parts of the plants may accumulate diterpenoids. The roots, leaves, stems, fruits, seeds and whole plants are equally studied. In general: extraction of the plant

materials is carried out at room temperature by maceration, and the extracts are evaporated at reduced pressure below 45 °C. As the plants commonly produce complex mixtures of esters of one or more similar diterpene nuclei, their isolation requires a multistep separation protocol.

The plant material is usually initially extracted with 95% EtOH or MeOH. Then, after removal of the solvent, the residue is dissolved in water for partition between solvents with different polarities (e.g. petroleum ether and $CHCl_3$ or CH_2Cl_2). When plant extracts are prepared from herbaceous starting material, purification of the chloroform fractions [e.g. with solid-phase extraction (SPE) on polyamide] is necessary to remove chlorophyll. In the next step, column chromatography is used, usually on silica gel with gradient elution. Repeated column chromatography (CC) separations, utilizing different adsorbents (normal- and reversed-phase silica gel and Sephadex LH-20 gel), have been applied successfully for the purification of components of complex mixtures. For final purification, preparative TLC and normal- and/or reversed-phase HPLC are used.

Table 1. Isolation methods of *Euphorbia* diterpenes

Type of diterpene	Plant	Plant part	Extraction solvent	Partitioning solvent	CC mobile phase	TLC developing systems	HPLC	Ref
Rosane	*E. ebracteolata*	root (dried)	95% EtOH	petroleum ether, $CHCl_3$	petroleum ether–Me_2CO (100:0 to 0:100)	n.d.	RP-HPLC MeOH–H_2O (95:5)	81
ent-Abietane	*E. fischeriana*	root (dried)	95% EtOH	petroleum ether, $CHCl_3$, *n*-BuOH	petroleum ether–Me_2CO	n.d.	–	68
	E. formosana	aerial parts (dried)	MeOH	$CHCl_3$	*n*-hexane–EtOAc–MeOH	n.d.	NP-HPLC *n*-hexane–EtOAc–Me_2CO–CH_2Cl_2 (25:6:4:10), *n*-hexane–Me_2CO (5:1 and 7:3)	23
	E. guyoniana	root (dried)	$CHCl_3$	n.d.	petroleum ether–EtOAc	pertroleum ether–EtOAc (85:15)	–	22
	E. neriifolia	stem (dried)	90% EtOH	petroleum ether, EtOAc, *n*-BuOH	petroleum ether–Me_2CO (9:1 to 1:9)	n.d.	–	27
	E. retusa	root (dried)	CH_2Cl_2		*n*-hexane–EtOAc (100:0 to 0:100)	n.d.	MeCN–H_2O (4:1)	21
ent-Kaurane	*E. fischeriana*	root (dried)	95% EtOH	EtOAc	petroleum ether–Me_2CO	n.d.	–	24
		root (dried)	95% EtOH	petroleum ether,	petroleum ether–EtOAc	n.d.	–	25

				$CHCl_3$, EtOAc	(100:1 to 1:2)			
	E. hirta	whole plant (dried)	95% EtOH	EtOAc	petroleum ether–Me_2CO (1:0 to 0:1)	n.d.	–	26
	E. neriifolia	stem (dried)	90% EtOH	petroleum ether, EtOAc, *n*-BuOH	petroleum ether–Me_2CO (9:1 to 1:9)	n.d.	–	27
Dimer	*E. yinshanica*	root (fresh)	85% EtOH	EtOAc	$CHCl_3$–Me_2CO (40:1 to 1:1)	n.d.	–	29
Casbane	*E. pekinensis*	root (dried)	95% EtOH	$CHCl_3$	petroleum ether–EtOAc	petroleum ether–EtOAc (98:2)	–	10
Jatrophane	*E. bungei*	aerial parts (dried)	Me_2CO	CH_2Cl_2	petroleum ether–EtOAc	n.d.	NP-HPLC petroleum ether–EtOAc (1:1)	44
	E. dendroides	aerial parts (dried)	60% EtOH	*n*-hexane	toluene–EtOAc	*n*-hexane–Me_2CO (7:3)	–	46
	E. esula	whole plant (fresh)	MeOH	CH_2Cl_2	cyclohexane–EtOAc–EtOH	cyclohexane–EtOAc–EtOH (5:5:2)	RP-HPLC MeCN–H_2O (3:2)	43
	E. guyoniana	aerial parts (dried)	CH_2Cl_2–MeOH (1:1)	n.d.	*n*-hexane–CH_2Cl_2, CH_2Cl_2–MeOH	n.d.	–	32
	E. guyoniana	aerial parts (dried)	CH_2Cl_2-MeOH (1:1)	n.d.	*n*-hexane–CH_2Cl_2 (25:75)	n.d.	RP-HPLC MeOH–H_2O (7:3)	5
	E. helioscopia	whole plant	EtOH	petroleum ether,	petroleum ether–EtOAc	n.d.	–	35

		(dried)		EtOAc				
	E. helioscopia	whole plant (dried)	95% EtOH	petroleum ether	petroleum ether–$CHCl_3$, $CHCl_3$–MeOH	n.d.	RP-HPLC MeOH–H_2O (65:35)	34
	E. kansui	root (n.d.)	95% EtOH	EtOAc	petroleum ether–EtOAc	n.d.	–	12
	E. peplus	whole plant (dried)	95% EtOH	petroleum ether	petroleum ether–Me_2CO (100:0 to 0:100)	n.d.	–	45
	E. sororia	fruit (dried)	MeOH	petroleum ether	n.d.	n.d.	–	41
	E. sororia	whole plant (dried)	MeOH	petroleum ether	n.d.	n.d.	–	42
	E. tuckeyana	whole plant (dried)	MeOH	EtOAc	*n*-hexane–EtOAc (1:0, 19:1, 4:1, 7:3, 2:3, 1:1, 2:3, 1:9, 0:1)	$CHCl_3$–MeOH (19:1), CH_2Cl_2–Me_2CO (19:1)	RP-HPLC MeOH–H_2O (13:7, 7:3, 3:2, 11:9)	33
Lathyrane	*E. aellenii*	aerial parts (dried)	MeOH	$CHCl_3$, EtOAc, *n*-BuOH	*n*-hexane–$CHCl_3$, *n*-hexane–EtOAc	$CHCl_3$–Me_2CO (97:3)	–	54
	E. bungei	aerial parts (dried)	Me_2CO	CH_2Cl_2	petroleum ether–EtOAc	n.d.	NP-HPLC petroleum ether–EtOAc (1:1)	44
	E. helioscopia	whole plant (n.d.)	30% MeOH		n.d.	n.d.	–	53
	E. kansuensis	root (dried)	85% EtOH,	$CHCl_3$	petroleum ether,	n.d.	–	48

		85ºC		petroleum ether–EtOAc (24:1 to 9:16), EtOAc			
E. lactea	latex (fresh)	EtOAc	–	*n*-hexane–EtOAc	*n*-hexane–Me_2CO (9:1)	–	56
E. lagascae	whole plant (dried)	MeOH	Et_2O	*n*-hexane–EtOAc (1: to 0:1) EtOAc–MeOH (19:1 to 1:4)	$CHCl_3$–MeOH (19:1)	RP-HPLC MeOH–H_2O (4:1, 7:3 and 13:7)	47
E. lathyris	seed (fresh)	95% EtOH	EtOAc	RP MeOH–H_2O (7:3)	n.d.	–	49
E. lathyris	seed (fresh)	95% EtOH	EtOAc	petroleum ether–EtOAc	n.d.	–	50
E. lathyris	seed (fresh)	95% EtOH	EtOAc, *n*-BuOH	petroleum ether–EtOAc	n.d.	–	51
E. laurifolia	latex (fresh)	EtOAc	–	*n*-hexane–EtOAc	*n*-hexane–Me_2CO (85:15)	–	56
E. micractina	root (dried)	95% EtOH	n.d.	n.d.	n.d.	RP-HPLC MeOH-H_2O (4:1)	55
E. neriifolia	leaves (dried)	MeOH	*n*-hexane, EtOAc, BuOH	n.d.	n.d.	RP-HPLC MeCN–H_2O (6:4)	58
E. prolifera	root (dried)	MeOH	EtOAc	petroleum ether–Me_2CO (99:1 to 6:4)	n.d.	RP-HPLC MeOH-H_2O (84:16)	57
E. royleana	aerial parts (dried)	70% MeCN	EtOAc	petroleum ether–Me_2CO (1:0 to 1:1)	n.d.	RP-HPLC MeOH-H_2O (85:15, 8:2, 76:24 and 73:27)	52

Myrsinane	*E. aellenii*	aerial parts (dried)	MeOH	$CHCl_3$, EtOAc, *n*-BuOH	*n*-hexane–$CHCl_3$ (0 to 100)	n.d.	NP-HPLC *n*-hexane–EtOAc (7:3)	60
	E. falcata	whole plant (fresh)	MeOH	$CHCl_3$	cyclohexane–EtOAc–MeOH (8:2:0 to 0:0:1)	*n*-hexane–Me_2CO (7:3), $CHCl_3$–Me_2CO (49:1)	–	66
	E. macroclada	aerial parts (dried)	EtOAc	petroleum ether, CH_2Cl_2	heptane–$CHCl_3$	n.d.	NP-HPLC pertroleum ether–EtOAc (7:3 and 6:4)	74
	E. prolifera	root (dried)	95% EtOH	petroleum ether, EtOAc	petroleum ether–Me_2CO (9:1 to 1:1)	n.d.	–	61
	E. prolifera	root (dried)	MeOH	EtOAc	petroleum ether–Me_2CN (99:1 to 3:2)	n.d.	RP-HPLC MeOH–H_2O (3:2, 3:1, 4:1)	62, 63, 64
Tigliane	*E. aellenii*	aerial parts (dried)	MeOH	$CHCl_3$, EtOAc, *n*-BuOH	*n*-hexane–$CHCl_3$ (1:0 to 0:1)	n.d.	–	71
	E. cornigera	root (dried)	Me_2CO	EtOAc, petroleum ether–MeOH–H_2O 15:10:0.5	*n*-hexane–EtOAc (19:1, 9:1, 4:1, 7:3, 1:1, 1:3)	*n*-hexane–Et_2O–EtOAc (4:3:3)	RP-HPLC H_2O–MeCN (gradient 88%→96%)	72
	E. fischeriana	root (dried)	95% EtOH	$CHCl_3$	petroleum ether–Me_2CO (50:1 to 1:1)	n.d.	–	69
	E. grandicornis	aerial parts (fresh)	MeOH	$CHCl_3$	*n*-hexane–Me_2CO (9:1 to 3:7)	*n*-hexane–Me_2CO (13:7)	RP-HPLC MeOH–H_2O (4:1)	70
	E. macroclada	aerial	EtOAc	petroleum	heptane–$CHCl_3$	n.d.	NP-HPLC	74

		parts (dried)		ether, CH_2Cl_2			petroleum ether–EtOAc (7:3 and 6:4)	
Ingenane	*E. cauducifolia*	latex (fresh)	95% MeOH	Et_2O, EtOAc	*n*-hexane–EtOAc (19:1 to 0:1)	*n*-hexane–Et_2O–EtOAc (4:3:3)	RP-HPLC MeCN–H_2O gradient	80
	E. cornigera	root (dried)	MeOH	EtOAc	EtOAc–$CHCl_3$, EtOAc–MeOH	*n*-hexane–Et_2O–EtOAc 4:3:3	RP-HPLC H_2O–MeCN and MeOH–H_2O gradient	78
	E. cornigera	shoot (dried)	MeOH	*n*-hexane, $CHCl_3$, Et_2O, EtOAc, *n*-BuOH	CH_2Cl_2–EtOAc,–MeOH (9:1:0 to 0:1:9)	CH_2Cl_2–EtOAc,–MeOH (6:3:1)	RP-HPLC MeCN–H_2O gradient	79
	E. esula	whole plant (dried)	95% EtOH	petroleum ether, EtOAc	n.d.	$CHCl_3$–EtOAc (10:1)	–	75
	E. kansui	whole plant (dried)	95% and 50% EtOH	petroleum ether–Me_2CO (*e.g.* 50:1)	n.d.	n.d.	–	11
	E. kansui	root (dried)	EtOH	*n*-hexane, EtOAc	*n*-hexane–EtOAc	$CHCl_3$–MeOH (96:4)	–	77
	E. kansui	root (dried)	95% EtOH	EtOAc	petroleum ether–EtOAc	n.d.	–	12
	E. laurifolia	latex (fresh)	EtOAc	n.d.	*n*-hexane–EtOAc	*n*-hexane–acetone (85:15)	–	56
	E. splendida	aerial parts (fresh)	MeOH	*n*-hexane, $CHCl_3$, *n*-BuOH	*n*-hexane–EtOAc	$CHCl_3$–Me_2CO	–	59
Paraliane and pepluane	*E. paralias*	n.d.	EtOAc	n.d.	n.d.	n.d.	–	82

n.d. not described

In the case of *E. kansui*, a unique extraction method has been described in the literature.[11] The toxicity of this plant has long been known; even so, it has been used in the traditional Chinese medicine for the treatment of edema, ascites and cancer. The toxicity proved to be greatly reduced by cooking the plant with rice vinegar. In the course of the investigation of the constituents of this plant, the dried herb was soaked with rice vinegar. When the rice vinegar had been completely absorbed, the material was heated in a pot over a fire, then dried and crushed. Conventional separation techniques were subsequently used. Unfortunately, in this way only one ingenane derivative was isolated from 13 kg of plant material.[11]

Zhang et al. elaborated a simple and rapid LC-DAD-ESI-MS-MS method for the separation and identification of the main diterpenes of *E. kansui* roots. In the proinflammatory fraction of the plant twelve compounds were successfully separated on a C_{18} reversed-phase column with a gradient mobile phase, and identified on the basis of spectral data.[12]

Tang et al. established a method for the simultaneous determination of ten diterpenes (prostratin, neriifolene, antiquorin, kaurane-3,16,17-triol, *ent*-atisane-3*β*,16*α*,17-triol, *ent*-16*α*,17-dihydroxyatisan-3-one, kauranoic acid, jolkinolide A and B and *ent*-16*β*-H-3-oxo-kauran-17-ol) of *E. fischeriana* by RP-HPLC using evaporative light scattering detection.[13] Four samples of the plant prepared by different extraction methods were investigated. The relationship between the proinflammatory toxicity and the content of diterpenes in different samples was also discussed. In contrast to the dried roots, the fresh roots contained a much greater quantity of prostratin, which demonstrated a higher proinflammatory effect than other diterpenes. But the authors did not discuss in detail the reason behind this phenomenon. It was also concluded that the dried roots are suitable for ordinary therapy so

as to avoid the intense stimulation of cell proliferation and NO production, while the fresh roots, containing more effective compounds (e.g. jolkinolide A and B) could be used in the antitumor therapy.[13]

3. Isolated diterpenoids

3.1. Higher diterpenoids

Among the diterpene constituents of the family Euphorbiaceae, the nonspecific 'higher diterpenes' may be mentioned. The skeletons of these compounds involve the classical 'concertina-like' cyclization of the precursor to form the variously cyclized hydrocarbon structures of many diterpenoids, triterpenoids and steroids.[14] Higher diterpenes, such as the bicyclic labdane and clerodane, the tricyclic abietane, and the tetracyclic atisane, kaurane, and bayerane types are not specific compounds of Euphorbiaceae species, these occur in many other plant families, too (Figure 1).[15]

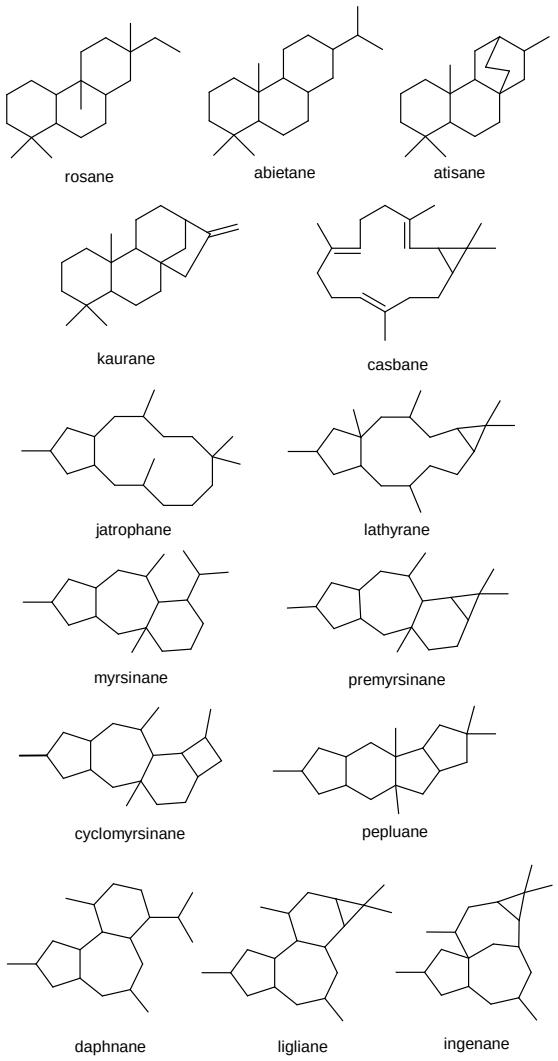


Figure 1. Skeletal types of *Euphorbia* diterpenes

3.1.1. Rosanes, ent-abietanes, atisanes and ent-kauranes

The tricyclic rosanes, which arise from migration of the C-10 methyl group of pimaranes to C-9, occur predominantly in higher plants.[16] Abietane diterpenoids of the Euphorbiaceae family are usually substituted with an α,β-unsaturated γ-lactone ring connected in position C-12 and C-13. Some carbons of these diterpenes, especially C-8, C-14, C-11 and C-12, usually form double bonds or are substituted with hydroxy or keto groups.[17] Kauranes and atisanes are important groups of tetracyclic diterpenes; their structures

comprise a perhydrophenanthrene unit (A, B and C rings) fused with a cyclopentane (in kauranes) or cyclohexane (in atisanes) unit (D ring) formed by a bridge of two carbons between C-8 and C-13 (in kauranes) or between C-8 and C-12 (in atisanes) (Table 2).[18]

The new rosane-type diterpenoid (**1**) isolated from *E. ebracteolata* by Deng et al.[19] differs from 18-hydroxyhugorosenone, isolated previously from *Hugonia casteneifolia* (Linaceae), only in its stereochemistry.[20]

Six *ent*-abietane-type diterpenes (retusolide A–F, **5**–**10**) were reported from *E. retusa*, among them retusolide F (**10**) was identified as the first example of a rearranged *ent*-abietane lactone of plant origin.[21] Haba et al. isolated two new *ent*-abietane diterpenoids (**11** and **12**) from the roots of *E. guyoniana*.[22] From the chloroform fraction of the aerial parts of *E. formosana*, two new (**3**, and the *seco*-helioscopinolide **4**) and four known [helioscopinolide A–C and *ent*-(5*β*,8*α*,9*β*,10*α*,12*α*)-12-hydroxyatis-16-ene-3,14-dione] diterpenoids were isolated by Yu et al.[23]

Qi-Cheng et al. obtained eight known diterpenoids (jolkinolide A and B, prostratin, *ent*-kaurane-3-oxo-16*α*,17-diol, antiquorin, neriifolene, *ent*-atisane-3*β*,16*α*,17-triol and kauranoic acid) from the roots of *E. fischeriana*,[24] and four known diterpenoids (jolkinolide B, 12-deoxyphorbol 13-(9*Z*)-octadecanoate 20-acetate and 17-hydroxyjolkinolide A and B) were later isolated from this plant by Geng et al.[25]

A phytochemical study of the ethanol extract of *E. hirta* led to the isolation of one new (**18**) and two known (2*β*,16*α*-dihydroxy-*ent*-kaurane and 16*α*,19-dihydroxy-*ent*-kaurane) *ent*-kaurane diterpenoids.[26] Liu et al. isolated nine diterpenoids (eight of them were new compounds) including two *ent*-3,4-*seco*-kaurane-type diterpenoids (**19** and **20**), three atisane derivatives (**13**–**15**), two 3,4-*seco*-atisane-type diterpenoids (**16** and **17**) and one *ent*-

abietane-type (**2**) diterpene from the stems of *E. neriifolia*. The absolute configurations of **19** and **20** were determined by X-ray crystallography.[27]

Wu et al. investigated the constituents of *E. fischeriana* and isolated *ent*-kaurane-3-oxo-16α,17-diol, antiquorin, neriifolene, *ent*-atisane-3β,16α,17-triol and kaurenoic acid for the first time from the roots of the plant.[28]

3.1.2. Dimeric higher diterpenes

In 2012, Zhang et al. investigated the secondary metabolites of *E. yinshanica*, a plant used in traditional Tibetan medicine for the treatment of exanthema, furuncles and cutaneous anthrax, and as a purgative agent. From the EtOAc extract of the fresh roots of the plant, two novel diterpene dimers [bisyinshanic acids A (**21**) and B (**22**)] with a bismagdalenic acid skeleton were isolated.[29]

3.2. Lower diterpenoids

The macrocyclic diterpenes and their cyclization products can be classified as 'lower terpenes' ('Euphorbiaceae diterpenes'), derived from a geranylgeranyl pyrophosphate precursor through a 'head-to-tail' cyclization.[30] The functionalization of diterpenes presumably proceeds after cyclization. The cembrene cation is a very reactive intermediate containing a 14-membered ring, which is stabilized through the formation of cembranoids.[31] Lower diterpenoids are characteristic compounds of Euphorbiaceae and Thymelaeaceae and are of chemotaxonomic relevance.

3.2.1. Casbanes

Casbanes are macrocyclic diterpenes containing a 14-membered and a cyclopropane ring. They have been considered to be precursors of a number of macrocyclic diterpenes. Liang et al. isolated a new casbane diterpenoid (pekinenal, **23**) from *E. pekinensis*. Its absolute configuration was determined by X-ray crystallography.[10]

3.2.2. Jatrophanes

Jatrophane diterpenes occur exclusively in the Euphorbiaceae family, in general in form of polyesters. These macrocyclic compounds are based on a bicyclo[10.3.0]pentadecane skeleton, without the presence of a cyclopropane ring. Their great structural variability stems from the number and positions of the double bonds, the nature and number of the oxygen functions, and the configuration of the diterpene core. The oxygen functions can be hydroxy, keto, epoxy, ether and ester groups. Natural jatrophane diterpenes are mainly polyacylated derivatives, the number of ester moieties ranging between three [guyonianin E (**46**)] and eight [esulatin H (**54**)]. The acyl residues are most frequently acetyl, benzoyl, isobutanoyl, 2-methylbutanoyl or nicotinoyl, and rarely propionyl, butanoyl, angeloyl, tigloyl or cinnamoyl. The most heterogeneously esterified molecules are euphopeplin A (**26**), **32** and **34**, containing four different acyl groups. Depending on their substitution, jatrophanes may have 5–10 chiral centers. Jatrophane diterpenes do not form a stereochemically homogeneous series, because the configurations of the carbons are variable.

El-Bassuony isolated two new jatrophane-type diterpenes, guyonianin C (**29**) and D (**31**), from the aerial parts of *E. guyoniana*.[5] Later, Hegazy et al. also investigated the chemical constituents of this species and isolated two new [guyonianins E (**46**) and F (**47**)] and one known jatrophane diterpenes from the aerial parts of the plant. *E. guyoniana* is used traditionally in Algeria for curing the venomous bites of scorpions and for removing warts.[32]

From the methanol extract of *E. tuckeyana*, Duarte et al. isolated three new jatrophane-type diterpenes: tuckeyanol A (**44**) and B (**45**), and euphotuckeyanol (**30**).[33] In the same year, Tao et al. isolated one new (euphornin L, **24**) and seven known jatrophane-type macrocyclic diterpenes from *E. helioscopia*. This plant has been used to treat malaria, bacillary dysentery, osteomyelitis and tumors in Chinese folk medicine.[34] Later, Geng et al. also isolated jatrophane diterpenes [euphornin L (**24**) and N (**25**)] from this plant.[35] Such diterpenes (with a 5*E*,11*E*-diene structure) have previously been isolated only from four *Euphorbia* species (*E. serrulata*, *E. platyphyllos*, *E. helioscopia* and *E. pubescens*).[36–39]

A new macrocyclic diterpenoid, kansuinine J (**53**), was isolated from the roots of *E. kansui* by Guo et al. This is the first jatrophane type diterpene reported in the literature, esterified with an isopentenoyl group.[40]

From the fruits of *E. sororia*, six new jatrophane diterpenes esterified with six or seven acyl groups (**27**, **28**, **37**–**40**) were isolated by Huang et al. The seeds of this plant have been used in traditional Chinese medicine for the treatment of abdominal pain and distention, skin disease and paralysis. It has also been administered to improve intelligence and appetite.[41] Phytochemical investigations of the whole plant resulted in three new bishomojatrophane diterpenoids, sororianolides A–C (**55**–**57**).[42]

Phytochemical studies of the whole, undried plant of *E. esula* led to the isolation of six new jatrophane diterpene polyesters, esulatins H–M (**41**–**43**, **48**, **49** and **54**), together with three known compounds.[43] Shokoohinia et al. isolated two new (**50** and **51**) and one known jatrophane diterpenoids from the acetone extract of the aerial parts of *E. bungei*.[44] Phytochemical investigation of *E. peplus* led to the isolation of a new jatrophane diterpenoid, euphopeplin A (**26**), in addition to two known jatrophanes.[45] Aljancic et al. isolated six new compounds (euphodendrophanes A–F, **32**–**36** and **52**) from *E. dendroides*, a small tree located in the Mediterranean region.[46]

3.2.3. Lathyranes

One of the largest groups of tricyclic diterpenes with a 5/11/3-membered ring system is the lathyrane group. The hydrocarbon nucleus of casbene and its saturated analog, casbane, may be considered to be the biogenetic precursor of these diterpenes. They can contain an epoxy function between C-4 and C-15, or C-5 and C-6, and double bonds between C-5 and C-6 and/or C-12 and C-13. The configurations of the fusion of rings A and B are usually *trans*, while those of rings B and C have the *cis* configuration.

Duarte et al. investigated the diterpene constituents of *E. lagascae* and isolated three new (latilagascenes D–F, **76**–**78**) and one known (jolkinol B) lathyrane diterpenes. Latilagascene D and E (and A–C, isolated previously from the plant) were the first macrocyclic lathyrane diterpenes that displayed oxidation at C-16. Latilagascene F differs from jolkinol B in only one substituent: it contains a benzoyloxy group instead of cinnamoyloxy group at C-15.[47] Wang et al. isolated two lathyrane diterpenes (**61** and **62**) from the ethanol extract of the roots of *E. kansuensis*. The roots of this plant have been used

in Tibetian medicine, as a cholagog and purgative and in cases of pyretolysis and apocenosis.[48]

Jiao et al. isolated a new lathyrane diterpenoid (Euphorbia factor L_8, **58**) from the seeds of *E. lathyris*. Its absolute configuration was determined by single-crystal X-ray diffraction.[49] This research group later isolated six lathyrane diterpenes from the seeds of *E. lathyris*: two of them new, [Euphorbia factor L_{7a} (**75**) and L_{7b} (**63**)], with jolkinol, isolathyrol, 7-hydroxylathyrol and lathyrol. The ^{13}C NMR and X-ray diffraction data of Euphorbia factor L_{7a} (**75**) and L_{7b} (**63**) were analyzed for the first time.[50] In 2011, Zhang et al. isolated Euphorbia factor L_3 (**60**) from the ethanol extract of the seeds of this plant.[51]

Li et al. isolated 10 ingols (4,15-epoxylathyrane-type diterpenes) (**90**–**99**) from the aerial parts of *E. royleana*. This plant, which is a common thorny succulent occurring in south-western mainland China, is known in the traditional Chinese medicine as a fencing plant.[52]

Feng et al. isolated a new lathyrane diterpene glucoside (**105**) from *E. helioscopia*. This was the first isolation of a glycosylated *Euphorbia* diterpene. To date, more than 30 diterpenoids have been isolated from this plant.[53]

A new lathyrane diterpene (**89**) was isolated from *E. bungei* by Shokoohinia et al.,[44] while Ayatollahi et al. isolated two new esters of 6(17)-epoxylathyrol (**101** and **102**) from the aerial parts of *E. aellenii*. This plant has been used in Iranian ethnopharmacology as a strong laxative, in the therapy of gout and for curing sores.[54] Tian et al. isolated 17 new (**59**, **64**–**68**, **71**–**74**, **78**, **80**–**85**) and 2 known (15*β*-*O*-benzoyl-5*α*-hydroxyisolathyrol and jolkinol A) lathyrane diterpenes from the ethanol extract of the roots of *E. micractina*.[55] Avila et al. isolated two new diterpenes (**69** and **70**) from the ethyl acetate extract of the latex of *E. laurifolia*.[56] In 2012, Xu et al. recently isolated 4 lathyrane diterpenes from *E. prolifera*,

including one new compound (**103**), and presented previously unreported spectroscopic data on another [(12*E*,2*S*,3*S*,4*R*,5*R*,6*S*,9*S*,11*S*,15*R*)-3-propionyloxy-5,15-diacetoxy-6,17-epoxylathyra-12-en-14-one, **104**].[57] Finally, Toume et al. isolated an ingol diterpene (**100**) from the leaves of *E. neriifolia*, a perennial shrub whose leaves are used in traditional medicine as an aphrodisiac, diuretic and antitussive.[58]

3.2.4. Myrsinanes, premyrsinanes and cyclomyrsinanes

Myrsinane diterpenes are based on a 5/7/6-tricyclic ring system. The configurations of the fusion of rings A and B and rings B and C are *trans*. Ester groups are located mainly at C-3, C-5, C-7 and C-15, with a double bond between C-8 and C-9. Premyrsinanes have a 5/7/6/3-tetracyclic, and cyclomyrsinanes a 5/7/6/4-tetracyclic carbon framework. In both cases, a hemiacetal ring or a 13/17-epoxy ring can be present.

In 2009, Ayatollahi et al. isolated a myrsinane diterpene (decipinone, **121**) from the aerial parts of *E. splendida*, found in the west of Iran.[59] In the same year, they isolated two new 14-desoxo-10,18-dihydromyrsinols (**106** and **107**) from the cytotoxic chloroform fraction of *E. aellenii*. This type of diterpenoids is very rare in nature, and previously found only in *E. prolifera*.[60] Li et al. isolated four new (proliferins A–D, **110–112** and **144**) and four known (euphorprolitherin B and D, SPr5 and 14-desoxo-3-*O*-propionyl-5,15-di-*O*-acetyl-7-*O*-nicotinoylmyrsinol 14*β*-acetate) myrsinol diterpenes from the ethanol extract of the roots of *E. prolifera*.[61] Xu et al. isolated 10 new myrsinol diterpenoids (euphorbiaproliferins A–J, **125**, **126**, **113**, **114**, **118–120**, **140**, **141** and **145**) from the roots of *E. prolifera*. The structure of euphorbiaproliferin A was confirmed by X-ray crystallography.[62] Later, Xu et al. isolated 10 new compounds (euphorbialoids A–J, **122**, **123**, **108**, **109**, **131–134**, **146**, and **147**) from the

methanol extract of the roots of the plant. The absolute configurations of two compounds (**108** and **131**) were determined by X-ray crystallography.[63] Seven further compounds, euphorbialoids K–N (**124**, **138**, **139** and **142**) and **115–117** were also isolated from this plant.[64,65]

In 2010, Shokoohinia et al. isolated four premyrsinane diterpenoids (**127–130**) from the aerial parts of *E. macroclada*.[74] Sulyok et al. isolated four premyrsinane-type diterpenes (**135–137** and **143**) and two new (**148** and **149**) and one known (SPr4) cyclomyrsinane derivatives from the methanol extract of *E. falcata*.[66,67] Compound **143** contains a rare hemiacetal moiety. Cyclomyrsinanes are hexa- and heptaesters of diterpene polyols, esterified with acetic, propanoic, 2-methylbutanoic or benzoic acids.

3.2.5. Daphnanes

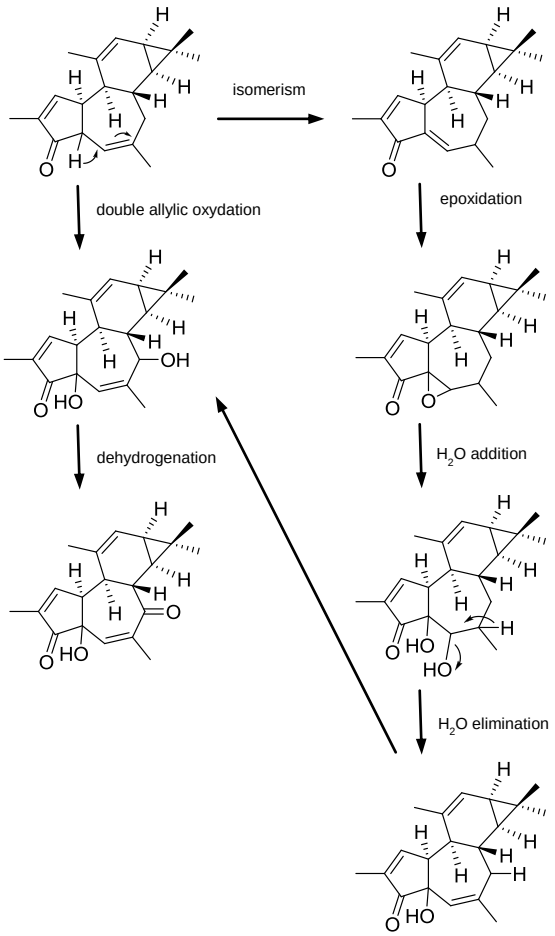
Daphnane diterpenoids are based on a 5/7/6-tricyclic skeleton. The configurations of the fusions of rings A and B and rings B and C are *trans*. Most daphnane diterpenoids are polyhydroxy derivatives substituted at C-4, C-9 and C-20.[17] C-3 forms a carbonyl group, and double bonds can be found in positions C-1/C-2 and C-6/C-7.[17]

Wang et al. isolated a daphnane diterpenoid (**150**) from *E. fischeriana*.[69] Yan et al. investigated the roots of *E. fischeriana* and isolated 17-acetoxyjolkinolide B, together with six known daphnanes. This herb has been used in traditional medicine for the treatment of cancer, edema and ascites.[68]

3.2.6. Tiglianes

Tigliane diterpenoids have a 5/7/6/3-tetracyclic ring system. The configurations of the fusions of rings A and B are usually *trans*, while those of rings B and C are *trans*, and those of rings C and D have the *cis* configuration. Most tigliane diterpenoids contain hydroxy groups in C-4, C-9, C-13 and C-20 positions. C-3 forms a carbonyl group, and olefin bonds can be found between C-1 and C-2 and between C-6 and C-7.[17]

A new tigliane diterpenoid (**176**) was described from the roots of *E. fischeriana* by Wang et al., and three known compounds were obtained for the first time from this plant, too.[69] A phytochemical investigation of *E. grandicornis* herb resulted in the isolation of two new tigliane diterpenes (**174** and **175**). Their structures are rare, since the molecule contains a 5-en-7-one or 5-en-7-ol functionality instead of the usual 6,7-olefin group. The proposed biosynthesis of the compounds was also discussed (Scheme 1).[70]



Scheme 1. Proposed biogenesis of unusual tigliane diterpenes[70]

Ghanadian et al. isolated two new diterpenoids (**171** and **172**) from the cytotoxic chloroform extract of *E. aellenii*,[71] and Aljancic et al. isolated a new compound (euphodendriane A, **173**) from *E. dendroides*.[46]

E. cornigera is considered to be one of the most toxic species of the Euphorbiaceae family. On the other hand its shoots, roots, leaves and fruits are used for the treatment of various ailments in Pakistan. Baloch et al. studied the components of the roots of the plant and isolated nine new compounds (**159–167**), all of them were diesters of 13,20-*O*-diacyl -12-deoxyphorbol.[72] Later, the same group isolated eight new deoxyphorbol esters (**151–158**) from the fresh latex of *E. cauducifolia*, five of them substituted with the rare *N*-(2-aminobenzoyl)anthraniloyl moiety.[73]

From *E. macroclada*, three 4,12-dideoxy-(4αH)-phorbol analogs (**168–170**), differing only in the esterification pattern, and one A-*seco*-phorboid (**177**) were isolated by Shokoohinia et al.; A-*seco*-tigliane **177** is an unprecedented type of natural diterpenoids.[74]

3.2.7. Ingenanes

Ingenane diterpenoids have a 5/7/7/3-tetracyclic ring system including a ketone bridge between C-8 and C-10. A double bond can be found in ring A between C-1/C-2, and another between C-6/C-7 in ring B. Moreover, a *β*-hydroxy group is linked to C-4, and rings A and B are *trans*-fused.[17] There may be an oxygen functionality (hydroxy, acetyl, benzoyl or long-chain alkyl ester) at some positions, *e.g.* C-3, C-5, C-13, C-17 and C-20.

In 2008, Lu et al. isolated 16 new ingenane diterpenoids (**180**–**195**) from the ethanol extract of *E. esula*.[75] Later, Wang et al. isolated one new (**179**) and two known ingenanes from this plant.[76] Li et al. investigated the compounds of *E. kansui*. The toxicity of this plant, which has long been known, could be greatly reduced by heating the plant with rice vinegar. Processed *E. kansui* was studied with the aim to survay its chemical constituents and a new diterpene (4-*O*-acetyl-5-*O*-benzoyl-3*β*-hydroxy-20-deoxyingenol, **178**) was isolated.[11] In the same year, Shi et al. isolated two new ingenanes (**216** and **217**) from the roots of this plant.[77]

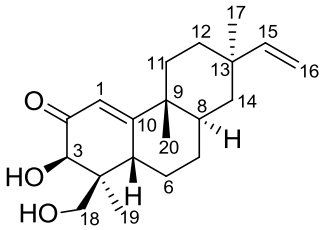
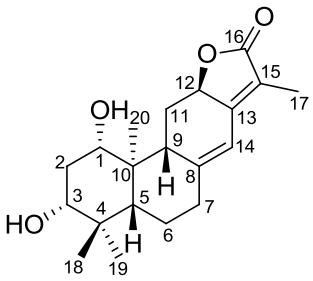
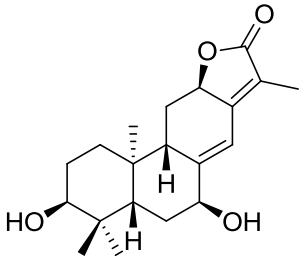
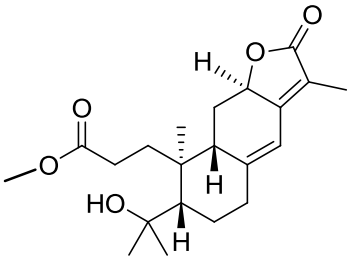
Baloch et al. isolated eight new ingenol derivatives (**206**–**213**) from the acetone extract of *E. cornigera* roots. Five of the compounds are esterified with the rare anthraniloyl group.[78] They later isolated two new (**214** and **215**) and two known [3-*O*-(2,3-dimethylbutanoyl)-13-*O*-dodecanoyl-20-*O*-hexadecanylingenol and 13-*O*-dodecanoyl-20-*O*-hexanoylingenol] diterpenoids from the shoots of the plant.[79]

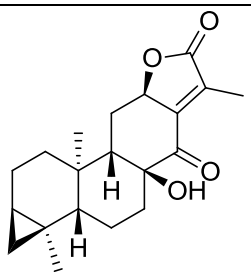
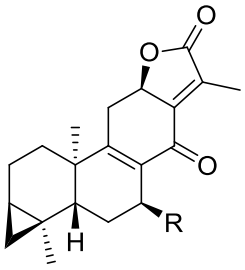
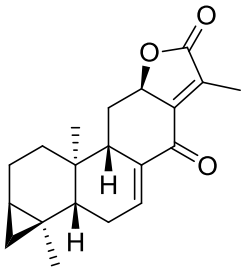
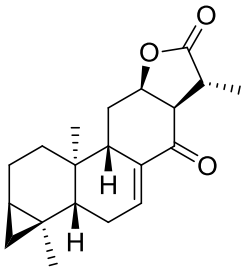
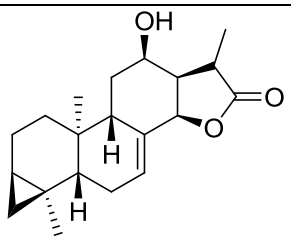
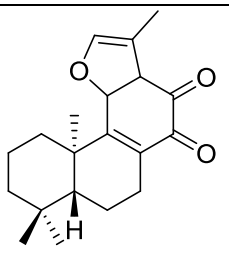
In 2010, Baloch et al. isolated 10 new ingenane-type esters (**196**–**205**) from the latex of *E. cauducifolia* (syn. *E. nerifolia*). The diterpenes are substituted with acetyl, angeloyl, palmitoyl, tetradecatrienoyl or benzoyl groups.[80] In the same year, Deng et al. isolated the known ingenol 3-myristate and ingenol 3-palmitate from *E. ebracteolata*. This plant is one of the sources of raw material for *Langdu*, which is commonly used in traditional Chinese medicine. The highly toxic roots of *E. ebracteolata* are often used to treat pulmonary tuberculosis, psoriasis, neuropathic dermatitis and chronic bronchitis.[19] Moreover, Deng et al. isolated two known (ingenol 3-myristate and ingenol-3 palmitate) and two new ingenane diterpenes (**218** and **219**) from the roots of *E. ebracteolata*.[19,81]

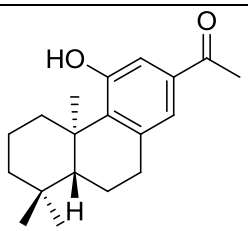
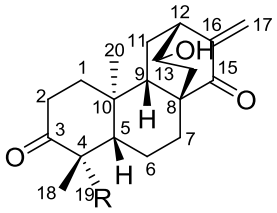
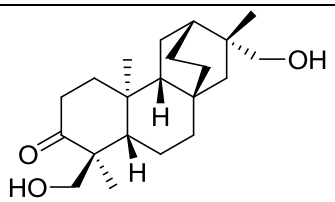
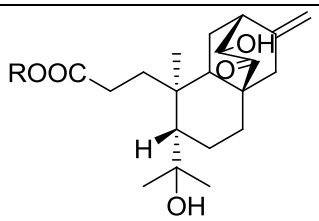
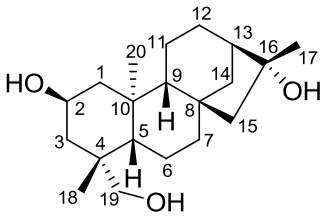
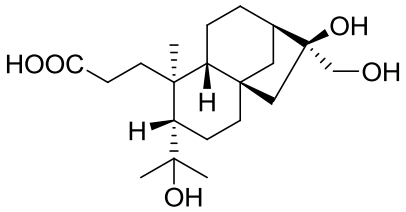
3.2.8. Paralianes and pepluanes

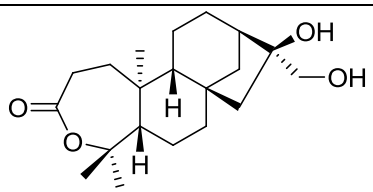
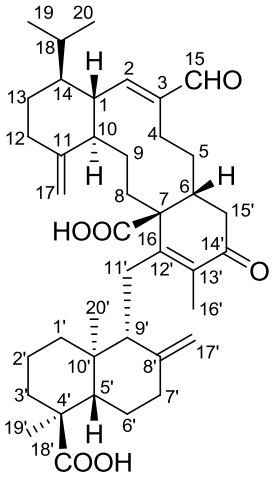
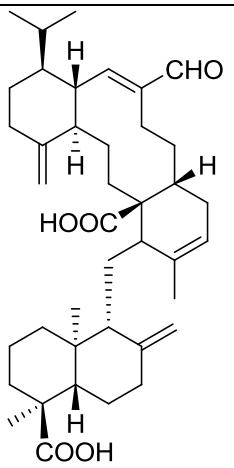
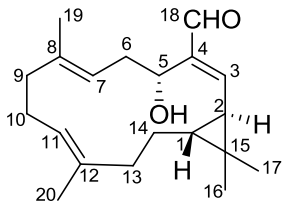
In 2007, two new (paralianone **220** and pepluene **221**) and two known diterpenes were isolated by Barile et al. from *E. paralias*.[82] Their structures demonstrated close analogy to that of pepluanone, isolated previously from *E. peplus*.[83]

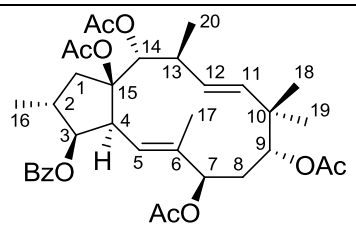
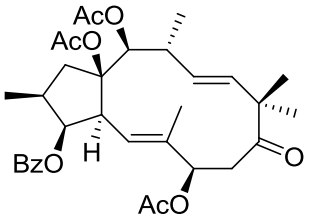
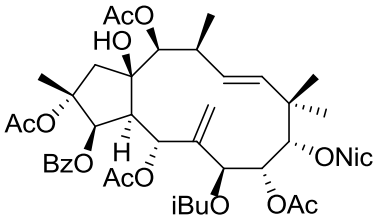
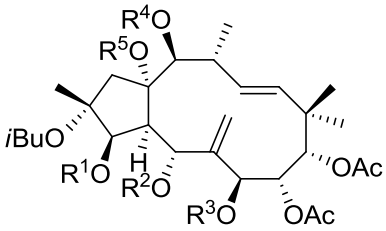
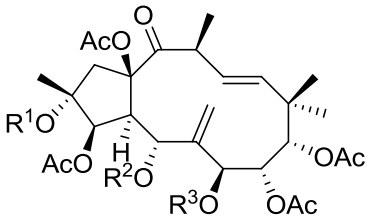
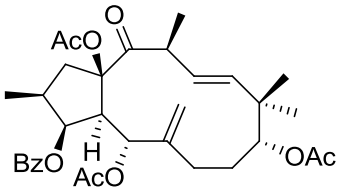
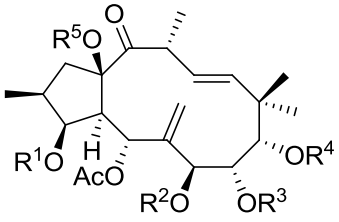
Table 2. Isolated compounds

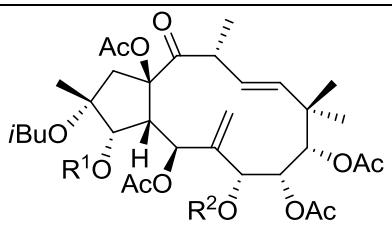
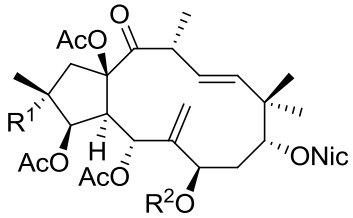
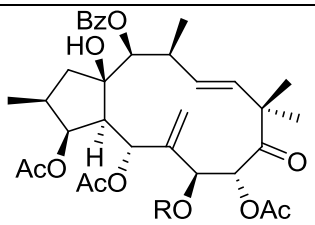
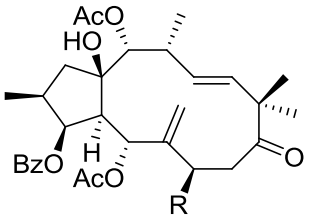
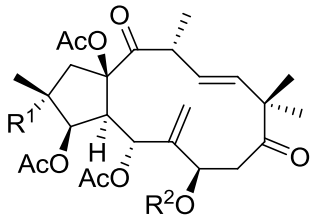
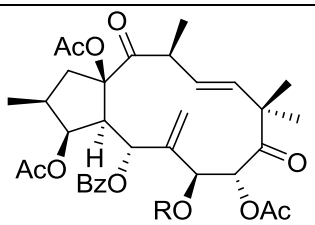
Compound	R (common names)	Plant	Ref.
Rosane			
	**1.**	*E. ebracteolata*	81
***ent*-Abietanes**			
	**2.**	*E. neriifolia*	27
	**3.**	*E. formosana*	23
	**4.**	*E. formosana*	23

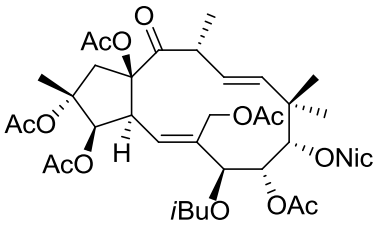
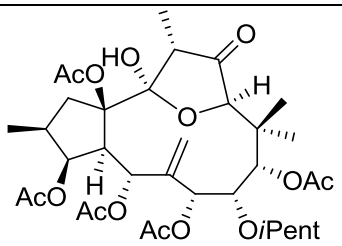
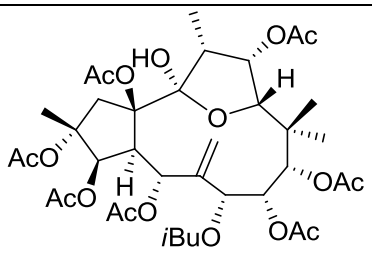
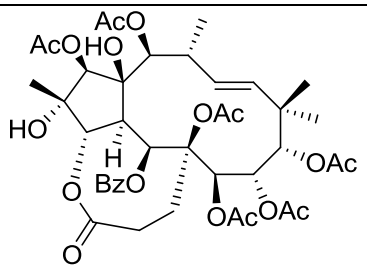
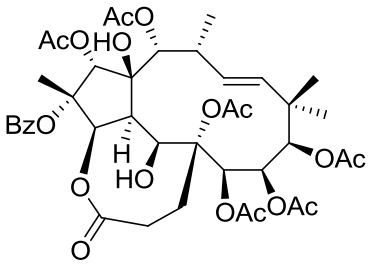
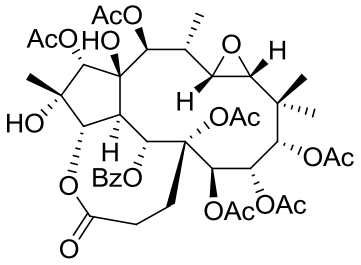
	**5.** retusolide A	*E. retusa*	21
	**6.** R=H retusolide B **7.** R=OH retusolide D	*E. retusa*	21
	**8.** retusolide C	*E. retusa*	21
	**9.** retusolide E	*E. retusa*	21
	**10.** retusolide F	*E. retusa*	21
	**11.**	*E. guyoniana*	22

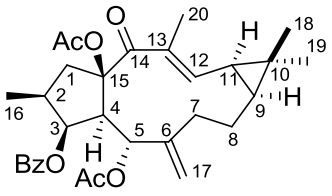
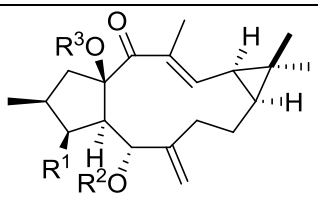
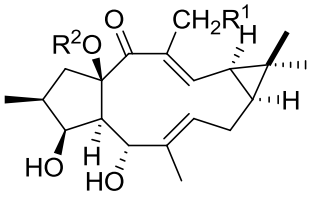
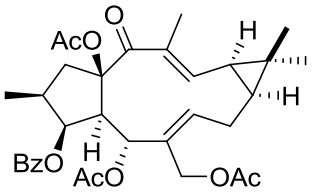
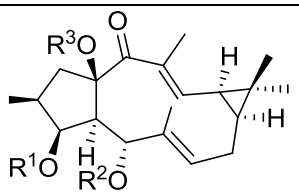
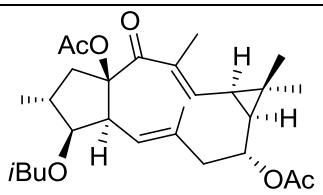
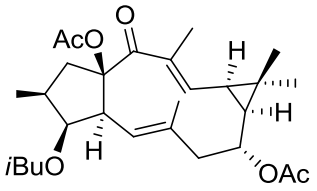
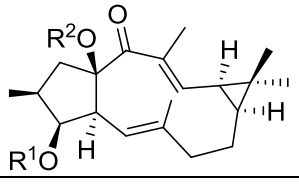
	**12.**	*E. guyoniana*	22
Atisanes and *seco*-atisanes			
	**13.** R=CH_2OH **14.** R=CH_3	*E. neriifolia*	27
	**15.**	*E. neriifolia*	27
	**16.** R=H **17.** R=CH_3	*E. neriifolia*	27
***ent*-Kauranes and *ent-seco*-kauranes**			
	**18.**	*E. hirta*	26
	**19.**	*E. neriifolia*	27

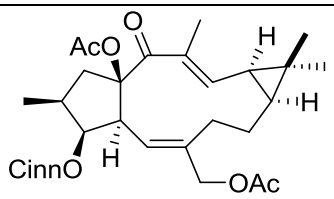
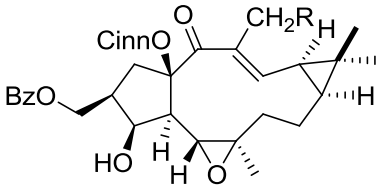
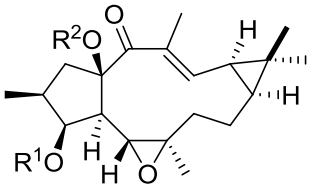
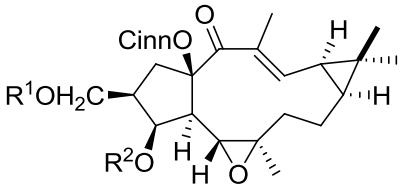
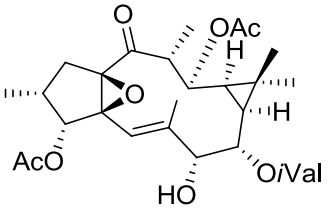
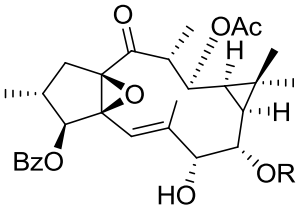
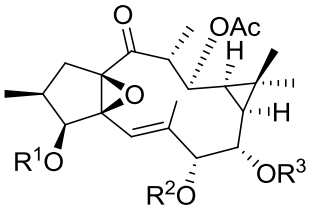
	**20.**	*E. neriifolia*	27
Dimeric higher diterpenoids			
	**21.** bisyinshanic acid A	*E. yinshanica*	29
	**22.** bisyinshanic acid B	*E. yinshanica*	29
Casbane			
	**23.** pekinenal	*E. pekinensis*	10
Jatrophanes			

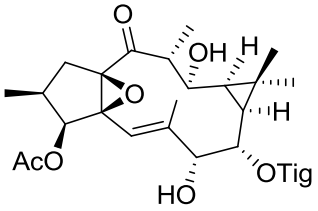
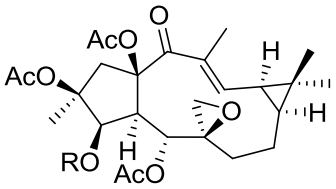
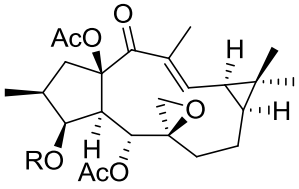
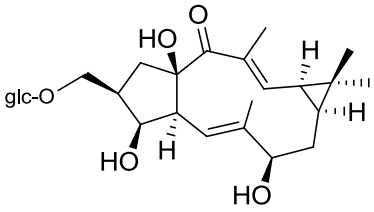
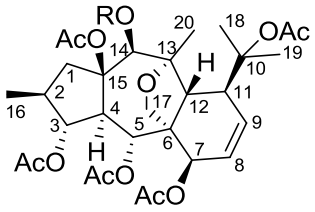
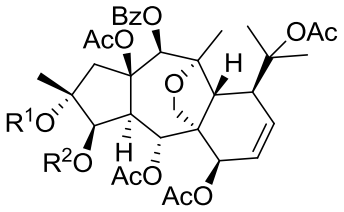
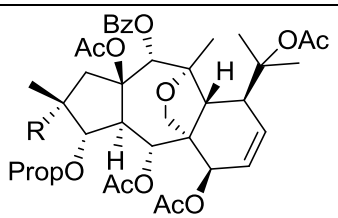
	**24.** euphornin L	*E. helioscopia*	34
	**25.** euphornin N	*E. helioscopia*	35
	**26.** euphopeplin A	*E. peplus*	45
	**27.** R^1=Bz, R^2=H, R^3=Ac, R^4=H, R^5=Ac **28.** R^1=Ac, R^2=Ac, R^3=*i*Bu, R^4=Bz, R^5=H	*E. sororia*	41
	**29.** R^1=Nic, R^2=Bz, R^3=Ac, guyonianin C **30.** R^1=Bz, R^2=Ac, R^3=Bz, euphotuckeyanol	*E. guyoniana* *E. tuckeyana*	5 33
	**31.** guyonianin D	*E. guyoniana*	5
	**32.** R^1=Prop, R^2=*i*Bu, R^3=Ac, R^4=Nic, R^5=H, euphodendrophane A **33.** R^1=*i*Bu, R^2=*i*Bu, R^3=Ac, R^4=Nic, R^5=H, euphodendrophane B **34.** R^1=Prop, R^2=*i*Bu, R^3=Ac, R^4=Nic, R^5=Ac,	*E. dendroides*	46

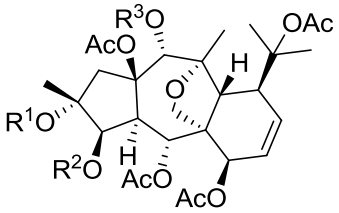
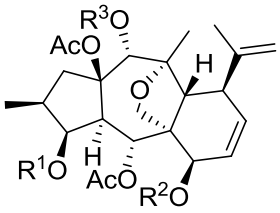
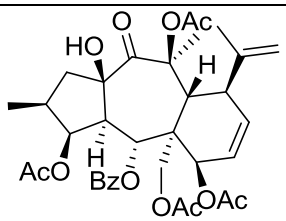
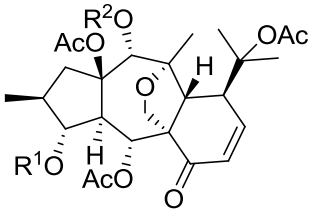
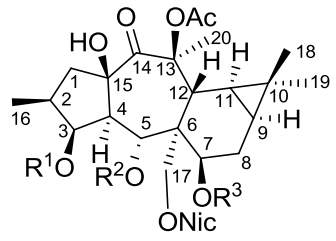
	euphodendrophane C **35.** R^1=*i*Bu, R^2=Ac, R^3=Bz, R^4=Ac, R^5=H, euphodendrophane D **36.** R^1=Prop, R^2=*i*Bu, R^3=Bz, R^4=Ac, R^5=H, euphodendrophane E		
	**37.** R^1=Nic, R^2=Ac **38.** R^1=Nic, R^2=*i*Bu **39.** R^1=Bz, R^2=*i*Bu **40.** R^1=Bz, R^2=Ac	*E. sororia*	41
	**41.** R^1=ONic, R^2=Ac, esulatin K **42.** R^1=OAc, R^2=*i*Bu, esulatin L **43.** R^1=H, R^2=*i*Bu, esulatin M	*E. esula*	43
	**44.** R=MeBu, tuckeyanol A **45.** R=iBu, tuckeyanol B	*E. tuckeyana*	33
	**46.** R=H, guyonianin E **47.** R=OAc, guyonianin F	*E. guyoniana*	32
	**48.** R^1=OBz, R^2=Ac, esulatin I **49.** R^1=H, R^2=*i*Bu, esulatin J	*E. esula*	43
	**50.** R=Ac **51.** R=Bz	*E. bungei*	44

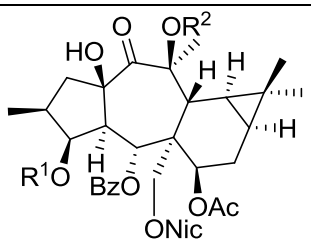
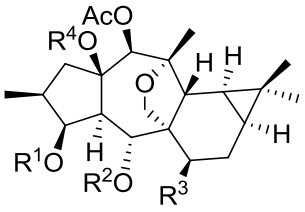
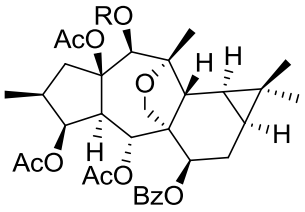
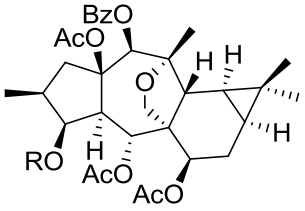
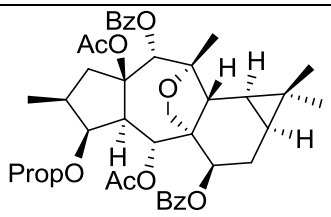
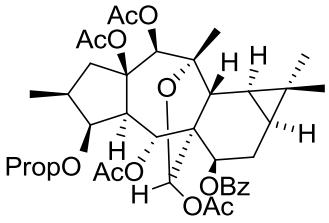
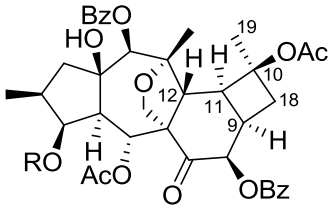
	**52.** euphodendrophane F	*E. dendroides*	46
	**53.** kansuinine J	*E. kansui*	40
	**54.** esulatin H	*E. esula*	43
	**55.** sororianolide A	*E. sororia*	42
	**56.** sororianolide C	*E. sororia*	42
	**57.** sororianolide B	*E. sororia*	42
Lathyranes			

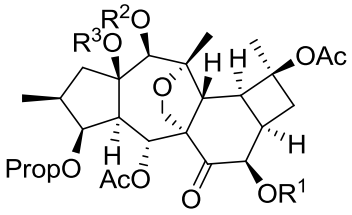
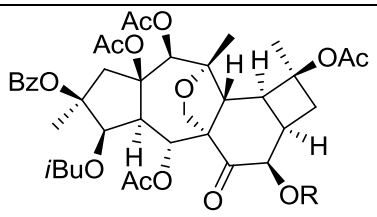
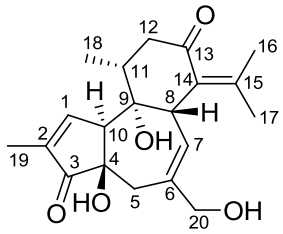
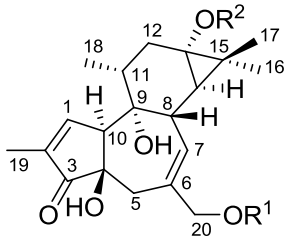
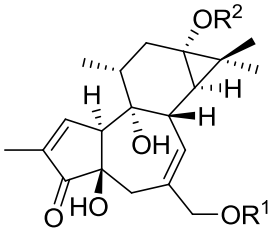
	**58.** Euphorbia factor L_8	*E. lathyris*	49
	**59.** R^1=CH_3, R^2=H, R^3=Cinn **60.** R^1=OBz, R^2=Ac, R^3=Ac, Euphorbia factor L_3	*E. micractina* *E. lathyris*	55 51
	**61.** R^1=H, R^2=Cinn **62.** R^1=OH, R^2=Cinn	*E. kansuensis*	48
	**63.** Euphorbia factor L_{7b}	*E. lathyris*	50
	**64.** R^1=Cinn, R^2=H, R^3=H **65.** R^1=H, R^2=H, R^3=Cinn **66.** R^1=Ac, R^2=H, R^3=Bz **67.** R^1=H, R^2=Ac, R^3=Bz **68.** R^1=*i*propilidene, R^2=*i*propilidene, R^3=Bz	*E. micractina*	55
	**69.**	*E. laurifolia*	56
	**70.**	*E. laurifolia*	56
	**71.** R^1=Ac, R^2=Ac **72.** R^1=Cinn, R^2=H **73.** R^1=H, R^2=Cinn **74.** R^1=H, R^2=Bz	*E. micractina*	55

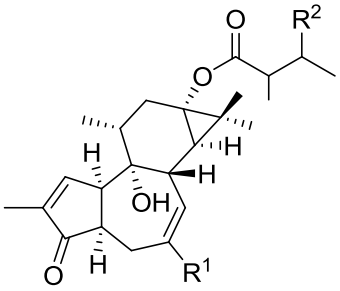
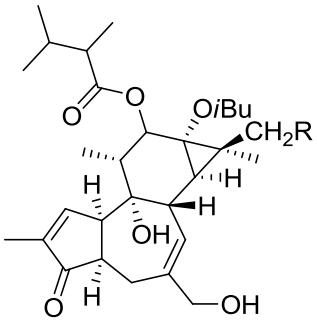
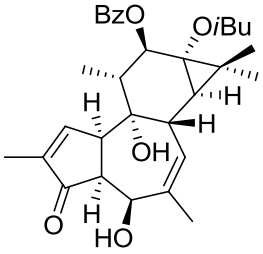
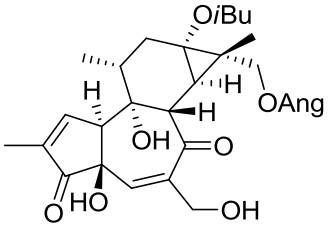
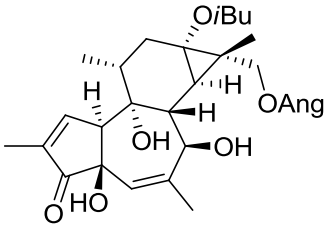
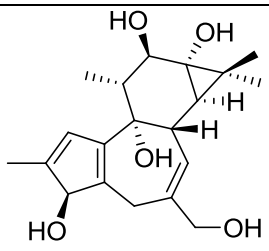
	**75.** Euphorbia factor L_{7a}	*E. lathyris*	50
	**76.** R=H, latilagascene D **77.** R=OH, latilagascene E	*E. lagasce*	47
	**78.** R^1=H, R^2=Bz, latilagascene F **79.** R^1=Ac, R^2=Ac **80.** R^1=Ac, R^2=H **81.** R^1=H, R^2=Ac **82.** R^1=Cinn, R^2=H **83.** R^1=Bz, R^2=Bz **84.** R^1=Bz, R^2=H **85.** R^1=Ac, R^2=Bz	*E. lagasce* *E. micractina*	47 55
	**86.** R^1=Bz, R^2=Ac, latilagascene G **87.** R^1=Prop, R^2=Prop, latilagascene H **88.** R^1=Bu, R^2=Bu, latilagascene I	*E. lagasce*	47
	**89.**	*E. bungei*	44
	**90.** R=Bz **91.** R=Tig	*E. royleana*	52
	**92.** R^1=Tig, R^2=H, R^3=Tig **93.** R^1=Tig, R^2=Tig, R^3=Ac **94.** R^1=Tig, R^2=Bz, R^3=Tig **95.** R^1=Bz, R^2=Bz, R^3=Ac **96.** R^1=Ac, R^2=Bz, R^3=Ac **97.** R^1=Tig, R^2=H, R^3=Bz	*E. royleana*	52

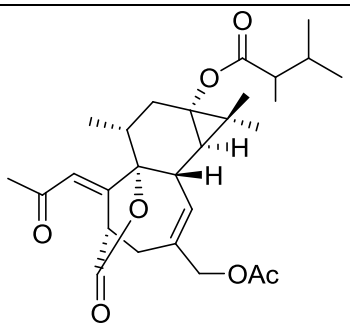
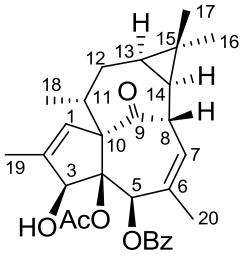
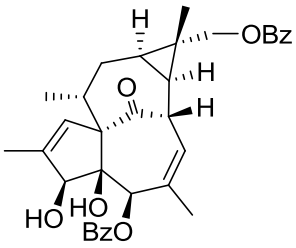
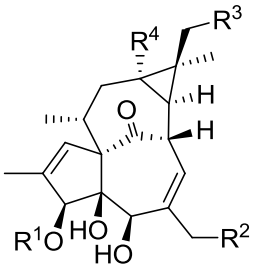
	98. R^1=Bz, R^2=H, R^3=Bz **99.** R^1=Bz, R^2=H, R^3=Tig		
	**100.**	*E. neriifolia*	58
	**101.** R=Nic **102.** R=Ac	*E. aellenii*	54
	**103.** R=Bu **104.** R=Prop	*E. prolifera*	57
	**105.**	*E. helioscopia*	53
Myrsinanes			
	**106.** R=Bz **107.** R=Bu	*E. aellenii*	60
	**108.** R^1=Nic, R^2=Prop, euphorbialoid I **109.** R^1=*i*Bu, R^2=Nic, euphorbialoid J	*E. prolifera*	63
	**110.** R=2-MeProp, proliferin A **111.** R=OBz, proliferin B **112.** R=H, proliferin C	*E. prolifera*	61

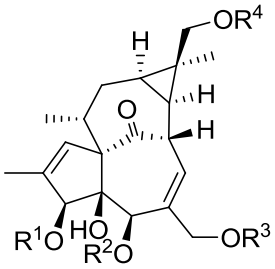
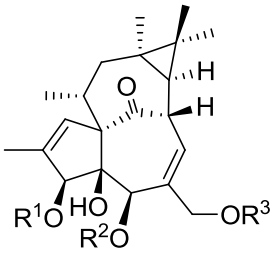
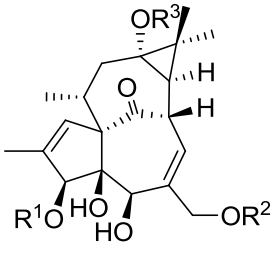
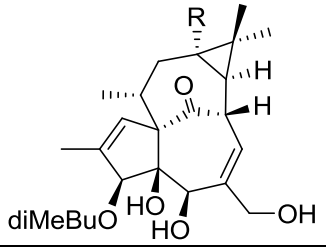
	**113.** R^1=*i*Bu, R^2=Prop, R^3=*i*Bu, euphorbiaproliferin A **114.** R^1=Bz, R^2=Bu, R^3=Bz, euphorbiaproliferin B **115.** R^1=*i*Bu, R^2=Ac, R^3=Bz **116.** R^1=Bz, R^2=Ac, R^3=Bz **117.** R^1=*i*Bu, R^2=Prop, R^3=H	*E. prolifera*	62 65
	**118.** R^1=Prop, R^2=Ac, R^3=Bz, euphorbiaproliferin F **119.** R^1=Prop, R^2=Ac, R^3=Ac, euphorbiaproliferin G **120.** R^1=Ac, R^2=Bz, R^3=Bz, euphorbiaproliferin H	*E. prolifera*	62
	**121.** decipinone	*E. splendida*	59
	**122.** R^1=Nic, R^2=Ac, euphorbialoid E **123.** R^1=Prop, R^2=Nic, euphorbialoid F **124.** R^1=Ac, R^2=Nic, euphorbialoid N **125.** R^1=*i*Bu, R^2=Ac, euphorbiaproliferin C **126.** R^1=Prop, R^2=Bz, euphorbiaproliferin D	*E. prolifera*	63 63 64 62 62
Premyrsinanes			
	**127.** R^1=Bu, R^2=Tig, R^3=H **128.** R^1=Prop, R^2=Tig, R^3=H **129.** R^1=*i*Bu, R^2=Tig, R^3=Ac **130.** R^1=Bu, R^2=MeBu, R^3=Ac	*E. macroclada*	74

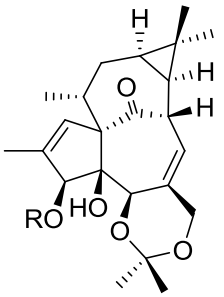
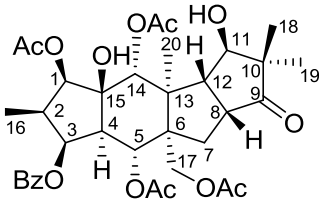
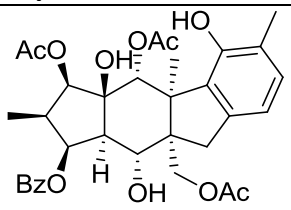
	**131.** R^1=Prop, R^2=H, euphorbialoid A **132.** R^1=Ac, R^2=H, euphorbialoid B **133.** R^1=Prop, R^2=Ac, euphorbialoid C **134.** R^1=Bu, R^2=Ac, euphorbialoid D	*E. prolifera*	63
	**135.** R^1=Hex, R^2=H, R^3=H, R^4=H **136.** R^1=Prop, R^2=Ac, R^3=OBz, R^4=Ac **137.** R^1=*i*Bu, R^2=H, R^3=OBz, R^4=Ac	*E. falcata*	66
	**138.** R=Ac, euphorbialoid K **139.** R=Nic, euphorbialoid M	*E. prolifera*	64
	**140.** R=Prop, euphorbiaproliferin I **141.** R=Bu, euphorbiaproliferin J	*E. prolifera*	62
	**142.** euphorbialoid L	*E. prolifera*	64
	**143.**	*E. falcata*	66
Cyclomyrsinanes			
	**144.** R=Prop, proliferin D **145.** R=Ac, euphorbiaproliferin E	*E. prolifera*	61 62

	**146.** R^1=Nic, R^2=Ac, R^3=H, euphorbialoid G **147.** R^1=Bz, R^2=Nic, R^3=Ac, euphorbialoid H	*E. prolifera*	63
	**148.** R=MeBu **149.** R=*i*Bu	*E. falcata*	67
Daphnane			
	**150.**	*E. fischeriana*	69
Tiglianes and *seco*-tiglianes			
	**151.** R^1=Ang, R^2=Ac **152.** R^1=Ac, R^2=Anth **153.** R^1=Bz, R^2=Bz **154.** R^1=Ang, R^2=Ang **155.** R^1=Anth, R^2=Ang **156.** R^1=Anth, R^2=Tig **157.** R^1=Anth, R^2=Bz **158.** R^1=Anth, R^2=Hex	*E. cauducifolia*	73
	**159.** R^1=Ac, R^2=Bz **160.** R^1=Ac, R^2=*p*-methoxyBz **161.** R^1=Dec, R^2=Ang **162.** R^1=Dec, R^2=Tig **163.** R^1=Ac, R^2=Dec **164.** R^1=Bu, R^2=Dec **165.** R^1=Hex, R^2=Dec **166.** R^1=Oct, R^2=Dec **167.** R^1=Dodec, R^2=Dec	*E. cornigera*	72

	**168.** R^1=CH_2OAc, R^2=CH_3 **169.** R^1=CH_2OAc, R^2=H **170.** R^1=CHO, R^2=CH_3	*E. macroclada*	74
	**171.** R=H **172.** R=OH	*E. aellenii*	71
	**173.** euphodendriane A	*E. dendroides*	46
	**174.**	*E. grandicornis*	70
	**175.**	*E. grandicornis*	70
	**176.**	*E. fischeriana*	69

	**177.**	*E. macroclada*	74
Ingenanes			
	**178.**	*E. kansui*	11
	**179.**	*E. esula*	76
	**180.** R^1=A, R^2=H, R^3=OBz, R^4=H **181.** R^1=A, R^2=H, R^3=OBz, R^4=OA **182.** R^1=A, R^2=OH, R^3=OBz, R^4=OA **183.** R^1=H, R^2=OA, R^3=OBz, R^4=OA **184.** R^1=H, R^2=OH, R^3=OBz, R^4=OOct **185.** R^1=Bz, R^2=OH, R^3=OBz, R^4=OOct **186.** R^1=H, R^2=OBz, R^3=OBz, R^4=OOct **187.** R^1=Bz, R^2=H, R^3=OBz, R^4=OOct **188.** R^1=A, R^2=OH, R^3=OBz, R^4=OOct **189.** R^1=H, R^2=OA, R^3=OBz, R^4=OOct **190.** R^1=Bz, R^2=OH, R^3=OBz, R^4=OBz **191.** R^1=A, R^2=OH, R^3=OBz, R^4=OBz **192.** R^1=Bz, R^2=OH, R^3=OBz, R^4=OA	*E. esula*	75

	193. R^1=A, R^2=H, R^3=OBz, R^4=OBz **194.** R^1=Bz, R^2=OH, R^3=H, R^4=OBz **195.** R^1=A, R^2=OH, R^3=H, R^4=OOct		
	**196.** R^1=Ang, R^2=H, R^3=H, R^4=Palm **197.** R^1=Palm, R^2=Ang, R^3=H, R^4=H **198.** R^1=H, R^2=Ang, R^3=H, R^4=Palm **199.** R^1=Ang, R^2=Palm, R^3=H, R^4=H **200.** R^1=H, R^2=H, R^3=Palm, R^4=Tetradec **201.** R^1=H, R^2=Ang, R^3=H, R^4=Bz **202.** R^1=H, R^2=Ang, R^3=Ac, R^4=Ac **203.** R^1=Ang, R^2=H, R^3=Ac, R^4=Bz **204.** R^1=Ac, R^2=Ang, R^3=H, R^4=Bz **205.** R^1=Ac, R^2=Ang, R^3=Ac, R^4=Ac	*E. cauducifolia*	80
	**206.** R^1=*N*-(2-aminobenzoyl)anth, R^2=Ac, R^3=Ang **207.** R^1=*N*-(2-aminobenzoyl)anth, R^2=Ang, R^3=Ac **208.** R^1=Ac, R^2=*N*-(2-aminobenzoyl)anth, R^3=Ang **209.** R^1=Ac, R^2=Ang, R^3=*N*-(2-aminobenzoyl)anth **210.** R^1=Ang, R^2=Ac, R^3=*N*-(2-aminobenzoyl)anth **211.** R^1=Ang, R^2=*N*-(2-aminobenzoyl)anth, R^3=Ac **212.** R^1=Ac, R^2=*N*-(2-aminobenzoyl)anth, R^3=Ac **213.** R^1=*N*-(2-aminobenzoyl)anth, R^2=Ac, R^3=Ac	*E. cornigera*	78
	**214.** R^1=Bu, R^2=Tet, R^3=Dodec **215.** R^1=Dec, R^2=Hex, R^3=H	*E. cornigera*	79
	**216.** R=Dodec **217.** R=Dec	*E. kansui*	77

	**218.** R=Palm **219.** R=Tetradec	*E. ebracteolata*	81
Paraliane			
	**220.** paralianone	*E. paralias*	82
Pepluane			
	**221.** pepluene	*E. paralias*	82

Ester groups: Ac = acetyl, Bz = benzoyl, *p*-methoxyBz = *p*-methoxybenzoyl, Nic = nicotinoyl, Cinn = cinnamoyl, Anth = anthraniloyl, Tig = tigloyl, Prop = propanoyl, Bu = butanoyl, *i*Bu = isobutanoyl, MeBu = 2-methylbutanoyl, A = 2,3-dimethylbutanoyl, *i*Pent = isopentanoyl, *i*Val = isovaleroyl, Hex = hexanoyl, Ang = angeloyl, Oct = octanoyl, Dodec = dodecanoyl, Dec = decanoyl, Myr = myristoyl, Palm = palmitoyl, Tetradec = tetradecanoyl

4. Occurrence of Euphorbia diterpenoids

To date, diterpenes have been isolated from 78 *Euphorbia* species (Table 3). In the last 5 years, the newly investigated plants were *E. aellenii*, *E. bungei*, *E. falcata*, *E. formosana*, *E. grandicornis*, *E. hirta*, *E. laurifolia*, *E. macroclada*, *E. neriifolia*, *E. pekinensis*, *E. retusa*, *E. royleana*, *E. sororia*, *E. splendida*, *E. tuckeyana* and *E. yinshanica*. Most of the diterpenes isolated from them are of the jatrophane type. Some species (*E. caudicifolia*, *E. ebracteolata*, *E. fischeriana*, *E. guyoniana*, *E. helioscopia*, *E. neriifolia*, *E. portulacoides*, *E. pubescens*, *E. quinquecostata*, *E. segetalis*, *E. seguieriana*, *E. semiperfoliata*, *E. terracina* and *E. wallichii*) contain both higher and lower diterpenes, while *E. acaulis*, *E. calyptrata*, *E. characias*, *E. fidjiana*, *E. formosana*, *E. hirta*, *E. retusa*, *E. sessiliflora*, *E. sieboldiana* and *E. yinshanica* synthesize only higher diterpenoids. The very high numbers of diterpenes isolated from *E. prolifera* (*n*=39), *E. esula* (*n*=36), *E. kansui* (*n*=32), *E. cornigera* (*n*=29) and *E. cauducifolia* (*n*=26) reflect the complexity of the mixtures of diterpenes that occur in plants of the Euphorbiaceae. There are some species (e.g. *E. angulata*, *E. dentata*, *E. lucida*, *E. maculata*, *E. chamaesyce* subsp. *chamaesyce* and *E. davidii*) in which the investigations have not revealed diterpenes, and the chemical screening of others (e.g. *E. hirta*, *E. amygdaloides*, *E. epithymoides*, *E. palustris*, *E. pannonica*, *E. virgata*, *E. abyssinica* and *E. grandidens*) has indicated only low quantities of diterpenes.[7]

Table 3. Occurrence of diterpenes in Euphorbiaceae species

Species	Types of diterpenes*	Ref.
E. acaulis	*ent*-abietane (n=1)	6
E. acrurensis	lathyrane (n=9), ingenane (n=2)	6
E. aellenii	lathyrane (**101**, **102**), myrsinane (**106**, **107**), tigliane (**171**, **172**)	54, 60, 71
E. aleppica	premyrsinane (n=4)	6
E. altotibetic	jatrophane (n=4)	6
E. amygdaloides	jatrophane (n=12)	6
E. boetica	premyrsinane (n=1)	6
E. bungei	jatrophane (**50**, **51**), lathyrane (**89**)	44
E. canariensis	ingenane (n=3)	6
E. caudicifolia	*ent*-abietane (n=1), tigliane (**151–158)**, ingenane (n=7) (**196–205**)	6, 73, 80
E. calyptrata	*ent*-abietane (n=2)	6
E. characias	*ent*-abietane (n=4), *ent*-atisane (n=3), *ent*-kaurane (n=1), *ent*-pimarane (n=3)	6
E. cheiradenia	myrsinane (n=3)	6
E. cornigera	tigliane (n=10) (**159–167**), ingenane (**206–215**)	6, 72, 78, 79
E. cyparissias	ingenane (n=2)	6
E. decipiens	myrsinane (n=20), premyrsinane (n=4)	6
E. dendroides	jatrophane (n=21) (**32–36**, **52**), tigliane (**173**)	6, 46
E. ebracteolata	*ent*-abietane (n=3), rosane (**1**), casbane (n=2), ingenane (**218**, **219**)	6, 81
E. esula	jatrophane (n=5) (**41–43**, **48**, **49**, **54**), ingenane (n=16), (**179–195**)	6, 43, 75, 76
E. falcata	premyrsinane (**135–137**, **143**), cyclomyrsinane (**148**, **149149**)	66, 67
E. fidjiana	*ent*-abietane (n=1), *ent*-atisane (n=6)	6
E. fischeriana	*ent*-abietane (n=9), *ent*-pimarane (n=1), dimer (n=2), other higher diterpenoids (n=1), daphnane (n=1) (**150**), tigliane (n=5) (**176**)	6, 69
E. formosana	*ent*-abietane (**3**, **4**)	23
E. grandicornis	tigliane (**174**, **175**)	70
E. guyoniana	rosane (**12**), *ent*-abietane (**11**), jatrophane (**29**, **31**, **46**, **47**), tigliane (n=1)	22, 5, 32, 6
E. helioscopia	*ent*-abietane (n=5), jatrophane (n=5) (**24**, **25**), lathyrane (**105**)	6, 34, 35, 53
E. hermentiana	lathyrane (n=2), ingenane (n=1)	6
E. hirta	*ent*-kaurane (**18**)	26
E. hyberna	jatrophane (n=1), lathyrane (n=2)	6
E. hyberna subsp. *insularis*	jatrophane (n=1)	6
E. ingens	lathyrane (n=1)	6

E. kamerunica	lathyrane (n=1)	6
E. kansuensis	lathyrane (n=2) (**61**, **62**)	6, 48
E. kansui	jatrophane (n=8) (**53**), ingenane (n=20) (**178**, **216**, **217**)	6, 40, 11, 77
E. lactea	lathyrane (n=1)	6
E. lagasce	jatropholane (n=2), lathyrane (**76**–**78**, **86**–**88**)	6, 47
E. lathyris	lathyrane (n=10) (**58**, **60**, **63**, **75**), ingenane (n=4)	6, 49, 50, 51
E. laurifolia	lathyrane (**69**, **70**)	56
E. leuconeura	ingenane (n=1)	6
E. macroclada	premyrsinane (**127**–**130**), tigliane (**168**–**170**, **177**)	74
E. micractina	lathyrane (**59**, **64**–**68**, **71**–**74**, **78**, **80**–**85**), euphoractine (n=5)	6, 55
E. mongolica	jatrophane (n=3)	6
E. myrsinites	myrsinane (n=4)	6
E. neriifolia	*ent*-abietane (**2**), *ent*-atisane (**13**–**17**), *ent*-kaurane (**19**, **20**), lathyrane (**100**)	27, 58
E. nivulia	lathyrane (n=8)	6
E. obtusifolia	jatrophane (n=7), tigliane (n=6)	6
E. officinarum	lathyrane (n=3)	6
E. paralias	jatrophane (n=7), ingenane (n=2), segetane (n=12), paraliane (n=2) (**220**), pepluane (**221**)	6, 82
E. pekinensis	casbane (**23**)	10
E. peplus	jatrophane (n=12) (**26**), ingenane (n=2), pepluane (n=3)	6, 45
E. pithyusa subsp. *cupanii*	lathyrane (n=2), premyrsinane (n=7), tigliane (n=3)	6
E. platyphyllos	jatrophane (n=4)	6
E. poisonii	lathyrane (n=3), daphnane (n=2), tigliane (n=4)	6
E. portlandica	segetane (n=1)	6
E. portulacoides	*ent*-abietane (n=5), *ent*-kaurane (n=2), lathyrane (n=4), ingenane (n=1)	6
E. prolifera	lathyrane (**103**, **104**), myrsinane (n=4) (**108**–**126**), premyrsinane (**131**–**134**, **138**–**142**) cyclomyrsinane (n=2) (**144**–**147**)	6, 57, 61, 62, 63, 64
E. pubescens	*ent*-abietane (n=2), jatrophane (n=5)	6
E. quinquecostata	*ent*-atisane (n=2), *ent*-isopimarane (n=1), ingenane (n=2)	6
E. resinifera	daphnane (n=1), tigliane (n=2), ingenane (n=1)	6
E. retusa	*ent*-atisane (**5**–**10**)	21
E. royleana	lathyrane (**90**–**99**)	52
E. salicifolia	jatrophane (n=6)	6
E. segetalis	other higher diterpene (n=1), jatrophane (n=15), lathyrane (n=1), ingenane (n=4), segetane (n=4), paraliane (n=4), pepluane (n=1)	6
E. seguieriana	*ent*-abietane (n=4), jatrophane (n=1), myrsinane (n=7), cyclomyrsinane (n=2), premyrsinane (n=1)	6

E. semiperfoliata	*ent*-abietane (n=3), jatrophane (n=18), tigliane (n=2)	6
E. serrulata	jatrophane (n=13)	6
E. sessiliflora	*ent*-abietane (n=3)	6
E. sieboldiana	*ent*-kaurane (n=1)	6
E. sororia	jatrophane (**27**, **28**, **37**–**40**, **55**–**57**)	41, 42
E. splendida	myrsinane (**121**)	59
E. teheranica	cyclomyrsinane (n=2)	6
E. terracina	*ent*-abietane (n=1), jatrophane (n=25)	6
E. tirucally	lathyrane (n=1)	6
E. tuckeyana	jatrophane (**44**, **45**)	33
E. turzaninowii	jatrophane (n=6)	6
E. villosa	lathyrane (n=1), euphoractine (n=3)	6
E. wallichii	*ent*-trachylobane (n=3), *ent*-kaurane (n=1), ingenane (n=2)	6
E. yinshanica	dimeric higher diterpenoid (**21**, **22**)	29

*n=number of previously reviewed compounds; or compounds according to the numbering in the present review

5. Biological acitivities

Compounds isolated from different *Euphorbia* species exert many different activities, including antiproliferative, MDR-reversing, antimicrobial, vasoactive, immunomodulatory and anti-inflammatory effects.

5.1. Antitumor activity

In the past few years, many investigations have been performed on the antitumor activity of *Euphorbia* diterpenes. Compounds with different skeletal types (*e.g.* casbane, abietane, ingenane, tigliane, lathyrane, myrsinane and jatrophane) proved to have moderate or strong antiproliferative effects on different human cancer cell lines (*e.g.* chronic myeloid leukaemia, nasopharyngeal, gastric, pancreatic, lung, ovarian and colon carcinomas). Some

of them were reported to have cytotoxic activity, others inducing apoptosis. The mechanisms of actions were also investigated in some cases, and it was observed that diterpenes could be cytotoxic via inhibition of the activity of topoisomerase II and/or DNA synthesis or protein kinase C (PKC) modulation or the induction of apoptosis through either the inhibition of IL-6-induced and STAT3 activation or inhibition of the NF-*κ*B signalling pathway.

Miyata et al. investigated the effects of ingenol diterpenes isolated from the roots of *E. kansui* on the proliferation activity of *Xenopus* embryo cells. Eight of the 20 investigated diterpenes [20-*O*-(2'*E*,4'*E*)-ingenol, 20-*O*-(2'*E*,4'*Z*)-ingenol, 3-*O*-(2'*E*,4'*Z*)-ingenol, 3-*O*-(2'*E*,4'*E*)-ingenol, 20-*O*-(decanoyl)-ingenol, 5-*O*-(2'*E*,4'*E*)-ingenol, 5-*O*-benzoyl-20-deoxyingenol and 3-*O*-(2'*E*,4'*E*-decadienoyl)-20-deoxyingenol] induced significant inhibition of cellular proliferation at low concentration. Further, it was stated that most of the diterpenes that inhibited cellular proliferation also inhibited topoisomerase II activity, since the high potency on topoisomerase II were measured.[84] Later, Yoshida et al. studied the mechanism of inhibition of topoisomerase II activity and effects on the cell proliferation through DNA damage or the blockade of topoisomerase II by 20-*O*-(2'*E*,4'*Z*-decadienoyl)-ingenol and 3-*O*-(2'*E*,4'*Z*-decadienoyl)-ingenol. The conclusion was drawn that 20-*O*-(2'*E*,4'*Z*-decadienoyl)-ingenol is a catalytic inhibitor of topoisomerase II. It brought about the growth arrest of mouse mammary tumor (MMT) cells in the G2/M phase of the cell cycle, without inducing *γ*-H2AX by DNA breaks.[85]

Luo et al. tested the cytotoxicity of jolkinolide B in human chronic myeloid leukaemia (K562), and observed that this compound displayed high activity against K562 cells, with an IC_{50} of 12.1 *μ*g/mL.[86] Later, Wang et al. investigated the molecular mechanism of the antitumor effect of jolkinolide B.[87] It was found that jolkinolide B treatment resulted in the

activation of caspase-3 and -9. Moreover, the compound reduced cell viability and induced apoptosis in a dose- and time-dependent manner in human leukaemic cells (U937). The induction of apoptosis was accompained by the downregulation of PI3K/Akt and the inhibition of apoptosis of protein family.[88]

The *in vitro* antiproliferative activities of helioscopinolide E and B, isolated from *E. tuckeyana*, were investigated by Duarte et al. against human gastrointestinal cancer cell lines: gastric (EPG85-257), pancreatic (EPP85-181) and colon (HT-29) carcinomas. These compounds were inactive (IC_{50} = 108 ± 3 μM in case of helioscopinolide E and IC_{50} = 102 ± 3 μM in case of helioscopinolide B) against the colon carcinoma cell line (HT-29) and showed moderate growth inhibitory activity on the gastric (EPG85-257) (IC_{50} = 45 ± 4 μM in case of helioscopinolide E and IC_{50} = 38 ± 2 μM in case of helioscopinolide B) and pancreatic (EPP85-181) (IC_{50} = 45 ± 4 μM for helioscopinolide E and IC_{50} = 38 ± 2 μM for helioscopinolide B) tumor cells.[33]

The antitumor activities of 12-deoxyphorbol esters isolated from *E. cornigera* were investigated by Baloch et al. Three compounds (**166**, **167** and 13,20-didecanoylphorbol) were cytotoxic, and displayed IC_{50} values of 0.8, 0.5 and 1.0 μg/mL, respectively. The mechanisms of their action in the inhibition of DNA synthesis were also investigated and a significant correlation was found between the cytotoxicity and DNA cross-link and DNA strand-break formation.[72] The levels of *in vitro* cytotoxicity of 4 ingenol derivatives (**214**, **215**, 3-*O*-(2,3-dimethylbutanoyl)-13-*O*-dodecanoyl-20-*O*-hexadecanoylingenol and 13-*O*-dodecanoyl-20-*O*-hexanoylingenol) isolated from *E. cornigera* were evaluated against RAW (mouse macrophage cells) and HT-29 (a colon cancer cell line) by the same group, using the MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Compound **214** displayed noteworthy cytotoxicity, with IC_{50} = 5.0 μM (RAW) and 2.90 μM (HT-29). It was 5- and 1.5-

fold more effective against RAW and HT-29 cancer cell lines than the positive control amrubicin hydrochloride [IC_{50} = 25.0 μM (RAW) and 4.36 µM (HT-29)]. Compound **215** showed moderate cytotoxic activity against both cell lines [IC_{50} = 10.0 μM (RAW) and 10.0 µM (HT-29)].[79]

It is well-known that most chemotherapeutic agents exert their anticancer activity by inducing apoptosis or programmed cell death.[47] Resistance to apoptosis may be a major factor for the ineffectiveness of cancer treatment. Investigation of the apoptosis-inducing mechanism of 17-hydroxyjolkinolide B (HJB) revealed that HJB strongly inhibits IL-6-induced and constitutive STAT3 (signal transducer and activator of transcription) activation. Furthermore, HJB directly targets the JAK (Janus kinase) family kinases, JAK1, JAK2, and TYK2, by inducing dimerization of the JAKs via cross-linking. HJB has no activity on the platelet-derived and epidermal growth factor, or insulin-like growth factor 1 signalling pathways, therefore its effect is highly specific.[89]

Yan et al. investigated the antitumor effects of 17-acetoxyjolkinolide B and 6 analogues, isolated from *E. fischeriana*. It was concluded that these compounds irreversibly inhibit the NF-κB signalling pathway by interacting directly with inhibitory kappa B kinases (IKK-β). Moreover, 17-acetoxyjolkinolide B induces apoptosis of tumor cells and acts synergistically with anticancer drugs such as doxorubicin.[68]

Serova et al. investigated the effects of PKC modulation by ingenol 3-angelate (PEP005, ingenol mebutate) on mitogen-activated protein kinase and phosphatidylinositol 3-kinase signalling in cancer cells, and concluded that both the AKT (also known as protein kinase B) and Ras/Raf/MAPK pathways in Colo205 colon cancer cells are differentially modulated by ingenol 3-angelate, and that only the latter is mediated by PKC isozymes.[90] Ersvaer et al. later evaluated the balance between the efficacy and toxicity of ingenol 3-

angelate in the treatment of human cancer. This hydrophobic diterpene ester is a selective activator of PKC 10–100 at concentrations of ng/mL, but strongly cytotoxic at high concentration (100 μg/mL).[91,92] Ingenol 3-angelate has both anticancer and proinflammatory effects, which is an advantage in topical skin application, but it can be dangerous in the event of systemic therapy. In conclusion, the authors established that extensive *in vivo* experimental models and carefully designed clinical studies can clarify whether the systemic use of this compound will be acceptable with regard to the risk of toxicity.[93]

Tao et al. investigated the cytotoxic activity of jatrophane diterpenes, isolated from *E. helioscopia*, on HL-60 cells by the MTT method and on A-549 cells by the SRB (sulphorhodamine B) method. Two compounds [euphornin L (**24**) and euphoscopin F] exhibited cytotoxicity against HL-60, with IC_{50} values of 2.7 and 9.0 μM, respectively, while the other compounds were inactive.[34] Guyonianins E (**46**) and F (**47**) and 5,7,14-triacetoxy-3-benzoyloxy-15-hydroxy-9-oxojatropha-6(17),11*E*-diene isolated from *E. guyoniana* were investigated for cytotoxic activity by Hegazy et al. 5,7,14-Triacetoxy-3-benzoyloxy-15-hydroxy-9-oxojatropha-6(17),11*E*-diene exhibited significant activity (IC_{50} = 35 μM), and guyonianins E (**46**) and F (**47**) showed moderate activity (IC_{50} = 70 and 100 μM, respectively) against human embryonic kidney 293 (HEK293) cells.[32] Investigation of the anticancer characteristics of euphodendrophane A (**32**) and B (**33**) on a sensitive non-small cell lung cancer cell line (NCI-H460) and its resistant counterpart (NCI-H460/R) demonstrated that these compounds inhibited the growth of these cancer cells (IC_{50} ≈ 20 µM for **33** and IC_{50} ≈ 50 µM for euphodendrophane **32**, on both cell lines) and were non-toxic for peripheral blood mononuclear cells (PBMS). The effects of these compounds in combination with paclitaxel (PTX) were also examined.[94] Jatrophanes overcome PTX resistance in concentration-dependent manner in multidrug resistant cancer cells (the strongest decrease

was observed in combination of 5 µM euphodendrophane A/B + 40 nM PTX), as these compounds induce cell killing and modify cell cycle distribution leading to G2/M arrest. The most pronounced effect was obtained with euphodendrophane B + PTX (40.4%). In addition, jatrophanes acts as anti-angiogenic agents by decreasing the vascular endothelial growth factor (VEGF) secretion (combination of euphodendrophane A with PTX exerted the strongest inhibition of VEGF secretion: 370 µg/mL).[94]

Jatrophane diterpenes (**41–43**, **48**, **49**, **54**, 2*α*,3*β*,5*α*,7*β*,15*β*-pentaacetoxy-9*α*-nicotinoyloxyjatropha-6(17),11-dien-14-one, salicinolide and euphosalicin) isolated from *E. esula* were investigated for their antiproliferative activities by Vasas et al.[43] It was demonstrated that the diterpenes possess tumor cell growth-inhibitory activities on HeLa (cervix adenocarcinoma), Ishikawa (endometrial adenocarcinoma), and MCF7 (breast epithelial adenocarcinoma) cells. Esulatins J (**49**), A, and E exhibited the highest activities against all three cell lines; especially esulatin J (**49**) displayed high antiproliferative effect on Ishikawa (98.4%) and MCF7 (81.4%) cells at the tested concentration 30 *µ*g/mL.[43]

The cytotoxic activity of pekinenal (**23**) was investigated against 4 human cancer cell lines, NCI-H460 (lung), KB (nasopharyngeal), SGC7901 (gastric) and HO-8910 (ovarian), by the MTT assay. The compound exhibited cytotoxic activity, with IC_{50} values of 10.05, 8.52, 13.82, and 14.16 *µ*g/mL, respectively.[10] Wang et al. evaluated the cytotoxicities of 6 tigliane-type diterpenes (**150**, **176** and four known ones) isolated from *E. fischeriana* against human cancer cell lines, MDA-MB-231 and HepG2, and a human immortalized cell line (HEK293). Only 12-deoxyphorbol 13-hexadecanoate was found to be cytotoxic against MDA-MB-231 cells (IC_{50} = 6.694 *µ*M).[69] In the following year, Zhang et al. investigated the antiproliferative activity of euphorbia factor L_3 (**60**) against a lung cancer cell line (A549) *in vitro*. It was stated that this compound has high cytotoxic effect and induce apoptosis via the mitochondrial

pathway in A549 cells, with involvement of the loss of mitochondrial potential and the release of cytochrome C.[51] The cytotoxicities of proliferins A (**110**), B (**111**) and D (**144**), isolated from *E. prolifera*, were evaluated against various cancer cells (HCT-8, Bel-7402, BGC-823, A549 and A2780). Only proliferin A (**110**) proved to be cytotoxic against A2780 human ovarian cancer cells (IC_{50} = 7.7 μM).[61]

The antiproliferative activity of premyrsinane (**135**–**137**, **143**) and cyclomyrsinane (**148**, **149** and SPr4) diterpenes isolated from *E. falcata* were tested on HeLa, Ishikawa, and MCF7 cells, and for their ability to modulate resistance to doxorubicin in L5178 mouse lymphoma cells that over-express the MDR1 efflux pump.[67] All compounds exhibited weak or moderate antiproliferative activities against all of the tested cell lines, only compound **137** showed significant activity at the higher tested concentration (30 μg/mL). However all premyrsinane and cyclomyrsinane diterpenes proved to have a mild to a very strong synergism with doxorubicin against the MDR mouse lymphoma cell line.[67]

Human cytomegalovirus (CMV) promotes tumor cell survival by inhibiting apoptosis, interfering with both the intrinsic and the extrinsic cellular apoptosis pathways CMV immediate-early (IE) antigen, accumulating in tumor tissues, and may provoke tumor promotion and progression.[95] The development of strategies intended to inhibit the human CMV IE antigen expression and/or function is an important goal as concerns the prevention and treatment of certain forms of cancers associated with human CMV. Pusztai et al. investigated the effects of the lathyrane-type latilagascenes A, B, C, D (**76**) and E (**77**) and jolkinol B on CMV IE antigen expression in lung cancer cells. It was concluded that latilagascene E (**77**) demonstrated the highest activity, while latilagascene D (**76**) was inactive.[95]

5.2. Multidrug-resistance reversing activity

The most common tumors are resistant to available drugs. One of the reasons of this is the multidrug resistance (MDR) of cancer cells which can be evolve by multiple mechanisms, *e.g*. with the expression of P-glycoprotein (P-gp, an efflux protein belonging to the ABC transporter superfamily) which transports anticancer drugs out of the cells. Therefore, inhibition of P-gp represents a promising approach for overcoming MDR. Compounds with a broad structural diversity can reverse P-gp mediated MDR.[47] One group of them is the diterpenes, isolated from different *Euphorbia* species. Unfortunately, the knowledge on the mechanism of action, on a molecular basis, is still missing. The structure-activity relationship studies concerning MDR reversing activity confirmed that hydrophobicity and the presence of hydrogen bond-acceptor groups in the molecules are important features for the interaction of the modulator with P-gp.[96] Some P-gp modulators, such as verapamil and cyclosporine, also inhibit drug efflux in a competitive manner, whereas recent studies suggested an allosteric mode of action for several compounds.[97]

Jiao et al. investigated the MDR activities of six related lathyrane diterpenes (among them the new **63** and **75**) isolated from *E. lathyris* on MCR7/ADM cell lines *in vitro*.[50] The compounds contain jokinol, isolathyrol, 7-hydroxylathyrol, epoxylathyrol and lathyrol skeleton. The most active compounds were Euphorbia factor L_{7a} (**75**) (reversal fold, RF = 10.33) and Euphorbia factor L_2 (RF = 12.84) in comparison with the standard verapamil (RF = 2.95). It was established that the position of the double bond between C-6 and C-7, and substitution on C-7 are important factors relating to the capability of inhibition. The approximate sequence of various skeletons as MDR modulators was 7-hydroxylathyrol,

jokinol > lathyrol > epoxylathyrol > isolathyrol. None of the compounds showed significant cytotoxicity on MCF-7 cells.[50]

Duarte et al. derivatized latilagascene B, previously isolated from *E. lagasce*, to yield 3 new lathyrane esters: latilagascene G (**86**), H (**87**) and I (**88**)[98]. Their MDR-inhibitory activities were investigated together with those of tuckeyanols A and B, euphotuckeyanol, latilagascene A–F and jolkinol B. Structure–activity relationship studies were also carried out. It was stated that the most active lathyrane derivatives [**86**—**88**, fluorescence activity ratio (FAR) = 68.9, 61.6 and 62.4 at 4 μg/mL] has an aromatic ring at C-16, while replacement of the aromatic ring by an acetyl group at this position resulted in a decrease of activity (FAR = 13.0 and 12.2 for latilagascene A and C at 4 μg/mL). Moreover, **86** has a much lower FAR value than found for latilagascene D (**76**, FAR = 168.5 at 4.0 μg/mL) differing the two compounds only in the presence of a free hydroxyl group at C-3 in **76**. In case of jatrophane polyesters euphotuckeyanol proved to be the most active (FAR = 81.0 at 4 μg/mL). This compound, with seven ester groups has the highest molecular weight (818), log*P* values (6.7), and the number of hydrogen bond acceptor groups is 15, all of them considered as important requirements to P-gp modulation. They investigated the antiproliferative effects of lathyranes and jatrophanes in combination with epirubicine on human MDR1 gene-transfected mouse lymphoma cells, and found that all the tested diterpenes have a synergistic interaction with epirubicine on the studied cell line, the most effective were **87** and euphotuckeyanol [fractional inhibitory index (FIX) = 0.07 (**87**) and 0.08 (euphotuckeyanol), respectively].[98] Later, the MDR-reversing and apoptosis-inducing activities of latilagascenes A–F [D (**76**) E (**77**) and F (**78**)] and jolkinol isolated from *E. lagascae* were evaluated. All the tested compounds exhibited drug retention enhancing activity by inhibiting the P-gp-mediated efflux-pump activity. Latilagascene E (**77**) displayed

the highest effect (FAR = 216.8, at 4 μg/mL). Moreover, the anti-MDR effect of latilagascene B in combination with doxorubicin on human MDR1 gene-transfected mouse lymphoma cells was also investigated *in vitro*. A synergistic interaction was observed between the two compounds (fractional inhibitory index (FIX) = 0.292). In the case of apoptosis induction, it was found that latilagascene B was the most active at the highest concentration.[47] Lage et al. also investigated macrocyclic diterpenes [latilagascenes B, C and D (**76**), jolkinol B, *ent*-16α-hydroxyatisane-3-one and *ent*-16α,17-dihydroxykauran-3-one] isolated from *E. lagasce*, and helioscopinolides A, B, D and E from *E. tuckeyana*, an acetylation reaction product of helioscopinolide B[99] and acetylation products of *ent*-16α-hydroxatisane-3-one and *ent*-16α,17-dihydroxykauran-3-one[100]) for their potential antineoplastic activity on gastric (EPG85-257), pancreatic (EPP85-181) and colon (HT-29) human carcinoma cell lines. Furthermore, the effects of these diterpenes on different multidrug-resistant variants of these cancer cell lines over-expressing MDR1/P-gp or without MDR1/P-gp expression were also evaluated. The most active compounds were the lathyrane diterpenes latilagascenes C (IC_{50} = 1.5 µM) and D (**76**) (IC_{50} = 2.7 µM), and the diterpene lactones helioscopinolide B (IC_{50} = 5.7 µM), 3β-acetoxyhelioscopinolide B (IC_{50} = 4.6 µM) and helioscopinolide E (IC_{50} = 4.4 µM), which exhibited high antineoplastic activities against the drug-resistant EPG85-257 cell line (etoposide was the positive control with IC_{50} = 6.2 µM).[100]

In the search for MDR-reversing compounds from natural sources, a series (*n* = 32) of *Euphorbia* diterpenes were tested by Molnár et al. on mouse lymphoma cells, using the rhodamine 123 exclusion test. The diterpenes investigated represented various skeletal types, *e.g.* jatrophanes, lathyranes and 'euphoractine-type' compounds. The results showed that structurally different diterpene polyesters may display significant MDR-reversal effects.[101] In another screening programme, Corea et al. investigated the MDR-modulatory

activities of 62 diterpenes isolated previously from *Euphorbia* species (*E. dendroides*, *E. characias*, *E. peplus*, *E. paralias* and *E. helioscopia*). Since these compounds were based on a structurally homogeneous skeleton, with differences only in the substitution pattern, a structure–activity relationship study was possible. Among others, it was concluded that the presence of hydroxy groups on C-3 and C-15, acetyl groups on C-8 and C-9 and a keto group on C-14 in jatrophanes increased the anti-MDR activity, while the presence of a hydroxy group on C-2, an acetyl group on C-14, and nicotinoyl groups on C-5 and C-9 reduced the inhibitory potency of the compounds.[102] Jatrophane polyesters isolated from *E. esula* were assayed for their anti-MDR activity on L5178 mouse lymphoma cells. It was observed that the diterpenes differ significantly in the inhibition of the efflux pump activity of P-gp in tumor cells. Esulatin J (**49**) (FAR = 52.5 at 40 μg/mL) and esulatin M (**43**) (FAR = 119.9 at 40 μg/mL) were found to be the most effective inhibitors of efflux pump acitivity.[43]

In 2011, Zhang et al. investigated the MDR-reversing potency and the detailed mechanisms of actions of Euphorbia factor L_1. It was concluded that this compound potentiated the sensitivity of the ABCB1 (ATP-binding cassette sub-family B member 1) substrates investigated and increased the accumulation of doxorubicin and rhodamine 123 in ABCB1-mediated MDR KBv200 and MCF7/adr cells. Moreover, Euphorbia factor L_1 did not downregulate the expression of ABCB1 at either an mRNA or a protein level.[103]

The MMP-2 and -9 (matrix metalloprotein)-modulating activities of diterpenes isolated from *E. formosana* on human fibrosarcoma cell line HT1080 were investigated by Yu et al. Among them, 3-hydroxy-*ent*-abietane compounds [helioscopinolide A–C and *ent*-(5β,8α,9β,10α,12α)-12-hydroxyatis-16-ene-3,14-dione)] significantly up-regulated the expressions of MMP-2 and -9 at concentrations of 10 and 50 μM.[23]

The purpose of the work of Ferreira et al. was to define an improved pharmacophore that combines the structural features of macrocycle diterpenes with the majority of compounds known to possess MDR inhibitory effect.[104] In the course of the study a database containing 272 molecules with the ability to modulate the P-gp was used. It was stated that the mode of interaction with the transporter is principally hydrophobic, where the aromatic acceptor or donor groups are responsible for the increased affinity. The proposed 4-point pharmacophore comprised one hydrogen bond and three hydrophobic acceptor points.[104]

Barile et al. performed structure-activity relationship studies on over sixty jatrophane, modified jatrophane, segetane, pepluane and paraliane diterpenoids isolated previously from *Euphorbia dendroides*, *E. characias*, *E. peplus*, *E. amygdaloides* and *E. paralias*. They focused on the anti-MDR and anti-inflammatory activities of the compounds.[105] It was concluded that in case of euphodendroidins a free OH group at C-3, together with the negative effect of this group at C-2 were needed for the anti-MDR activity. Moreover, substitution at C-5 with an aromatic group (e.g. nicotinoyl) decreased the activity. The pharmacological evaluation of terracinolides and abeojatrophanes demonstrated the effect of substitution at positions C-3, C-6, and C-15, and the significance of the relative configuration of the free OH group, quite apart from its position. Euphocharacin derivatives are highlighting the positive roles of benzoyl and propyl groups at C-9 and C-3, respectively, and confirming the positive effect of hydroxyl group at C-15 and the negative role of the same group at C-2. Finally, in case of pepluane series investigated, pepluanin A with acetyl group at C-8 and nicotinoyl group at C-9 was found to be the most potent inhibitor of P-gp.[105]

5.3. Immunomodulatory activity

The immunomodulatory effect of 14-desoxo-3*β*,5*α*,7*β*,10,15*β*-*O*-pentaacetyl-14*α*-*O*-benzoyl-10,18-dihydromyrsinol (**106**) isolated from *E. aellenii* was investigated on the oxidative burst activity of whole-blood phagocytes and the proliferation of human peripheral blood lymphocytes. In concentrations of 0.5, 5 and 50 μg/mL, **106** exhibited in the dose-dependent suppression of T-cell proliferation by 39 ± 5.0%, 68 ± 2.0%, and 72 ± 1.6%, respectively.[60] Later, the immunomodulating potentials of tigliane diterpenes (**171** and **172**) isolated from *E. aellenii* were tested by Ghanadian et al., using neutrophils of human whole blood. It was concluded that 4-deoxy-4*α*H-phorbol-12 (2,3-dimethyl)butyrate 13-isobutyrate (**171**) exhibited moderate inhibitory activity against both T-cell proliferation and reactive oxygen species production, with IC_{50} = 14 and 44.1 μg/mL, respectively.[71]

The *in vitro* anti-inflammatory activities of jolkinolides (jolkinolide A and B, and 17-hydroxy-jolkinolide A and B) in lipopolysaccharide-stimulated RAW264 macrophages were investigated by Uto et al. Among them, 17-hydroxyjolkinolide B (HJB) was found to be the most powerful inhibitor of the LPS-induced production of inflammatory mediators such as NO, PGE_2, and pro-inflammatory cytokines TNF-*α* and IL-6. These inhibitory effects were induced by the suppression of MAPK (mitogen-activated protein kinase) phosphorylation and NF-*κ*B activation. Moreover, HJB was found to be a strong inducer of heme oxygenase-1 protein and mRNA expression.[106]

5.4. Anti-inflammatory activity

Pepluanone, a diterpene component of *E. peplus*, possesses a high anti-inflammatory effect *in vivo*.[107] *In vitro* assays of the compound on LPS-stimulated J774 murine

macrophages revealed that it decreased the production of PGE_2, NO and TNF-α by decreasing the expression of iNOS, COX-2 and TNF-α mRNA, respectively.[107] Barile et al. tested the anti-inflammatory activities of compounds (**220** and **221**) with pepluane and paraliane skeletons, isolated from *E. paralias*. In this assay, one of the isolated compounds showed high activity, comparable to that found for pepluanone.[82] Moreover, they investigated the anti-inflammatory activity of six compounds with pepluane and paraliane skeletons. The results showed that all compounds have NO_2^- production inhibitory activity in LPS-stimulated J774 macrophages by iNOS. They demonstrated the crucial role of a carbonyl on the D-ring and the negative effects when the D-ring is either hydroxylated or aromatic, suggesting the possible involvement of the D-ring structure in the inhibition of NF-κB activation.[105]

Nunomura et al. investigated the effects of 3-*O*-(2,3-dimethylbutanoyl)-13-*O*-decanoylingenol (DBDI), isolated previously from the roots of *E. kansui*,[108] on the activation of intracellular signalling pathways and the release of inflammatory chemical mediators in bone marrow-derived mouse mast cells (BMMCs) upon FcεRI stimulation. It was revealed that DBDI significantly inhibits the $[Ca^{2+}]_i$ increase, the β-hexosaminidase release and the synthesis of PGD_2, PGE_2 and LTC_4 in BMMCs stimulated with IgE and multivalent antigen complex. Moreover, they demonstrated that DBDI inhibits the activation of intracellular signalling molecules, including Syk, PLC-γ2 and ERKI/2.[109]

In 2010, Chang et al. reported that IL-6-induced Stat3 activation was inhibited by kansuinine A and B in HepG2 cells. Moreover, they established that ERK1/2 activation by these compounds play an important role in the downregulation of IL-6-induced Stat3 activation.[110]

5.5. Antimicrobial activity

Antiviral activity: The main problem of virus eradication in patients treated with highly active antiretroviral therapy is the persistence of latent HIV-infected cellular reservoirs.[8] Prostratin and other non-tumorigenic PKC agonists have the ability to reactivate HIV-1 latency *in vitro* by activating NF-*κ*B through a PKC-dependent pathway.[56] Avila et al. investigated the effects of extracts and fractions from the latex of *E. laurifolia* and *E. lactea* on HIV-1 reactivation in Jurkat-LAT-GFP cells. Moreover, the bioactivity of the isolated diterpenes (**69** and **70**) was also investigated.[56] 3,12-Di-*O*-acetyl-8-*O*-tigloylingol, obtained from *E. lactea*, showed HIV-1 latency reactivating activity in a concentration-dependent manner with an EC_{50} of 0.5 μg/mL and reaching maximal GFP induction at 5 μg/mL (84.3%). Other investigated compounds were significantly less active [33% (**69**) and 0% (**70**) at 25 μg/mL]. Due to the structural similarity between 3,12-di-*O*-acetyl-8-*O*-tigloylingol and phorbol esters such as PMA and prostratin, the role of PKC in 3,12-di-*O*-acetyl-8-*O*-tigloylingol-induced HIV-1 reactivation was studied. It was concluded that 3,12-di-*O*-acetyl-8-*O*-tigloylingol reactivates HIV-1 through a PKC-dependent pathway. Moreover, the conformational relation of cyclopentyl and the parent skeleton and the stereochemistry of the side-chain are responsible for this pharmacological effect.[56]

Bedoya et al. investigated the antiviral activity of a series of previously isolated jatrophane diterpenes. It was confirmed that one of the compounds, SJ23B, exerted remarkable antiviral effect through the downregulation of HIV receptors and the induction of viral reactivation. In this investigation, the activity of SJ23B was 10-fold more potent than that of prostratin. Moreover, this jatrophane diterpene was able to activate PKC and cells where HIV is hidden as a latent provirus.[111]

Tian et al. investigated the antiviral activities of lathyrane diterpenoids (**59**, **64**–**68**, **71**–**74**, **78**, **80**–**85**), isolated from *E. micractina*. It was established that 15-cinnamoyloxylathyra-5,12-dien-3-ol-14-one (**73**) exhibited activity against HIV-1 replication (IC_{50} = 8.2 μM) *in vitro.* [55]

Antibacterial activity: Screening of the *in vitro* antibacterial activities of guyonianin C (**29**) and D (**31**) by El-Bassouny on Gram-positive (*Bacillus cereus* and *Staphylococcus aureus*) and Gram-negative (*Serratia* sp. and *Pseudomonas* sp.) bacteria, demonstrated that guyonianin C (**29**) possesses activity against *B. cereus*.[5]

5.6. Vascular relaxing activity

Lathyrane diterpenoids (**64**–**68**, **71**–**74**, **78**, **80**–**85**) isolated from *E. micractina* displayed substantial vascular-relaxing activities on phenylephrine-induced vasoconstriction model, with relaxation rates of 41–53%; the positive control verapamil exhibited a 44% relaxation at the same concentration.[55]

Xu et al. investigated the inhibitory activities of lathyrane diterpenes isolated from *E. prolifera* on LPS-induced NO production in murine microglial BV-2 cells. Compounds **103** and 15-*O*-acetyl-17-hydroxyjolkinol showed dose-dependent inhibition with IC_{50} values of 14.56 and 82.56 μM, respectively. (12*E*,2*S*,3*S*,4*R*,5*R*,6*S*,9*S*,11*S*,15*R*)-3-benzoyloxy-5,15-diacetoxy-6,17-epoxylathyra-12-en-14-one showed weak inhibitory effect (IC_{50} 113.5 μM), and (12*E*,2*S*,3*S*,4*R*,5*R*,6*S*,9*S*,11*S*,15*R*)-3-propionyloxy-5,15-diacetoxy-6,17-epoxylathyra-12-en-14-one was inactive. Neither of the tested compounds possessed remarkable cytotoxic effect on the BV-2 cells at their effective concentrations.[57]

5.7. Neuroprotective effect

Xu et al. investigated the neuroprotective effect of 19 myrsinol type diterpenes (**113**, **114**, **118–120**, **125**, **126**, **140**, **141**, **145**, 14-deoxo-3-*O*-propionyl-5,15-di-*O*-acetyl-7-*O*-benzoylmyrsinol 14*β*-acetate, euphorprolitherin C, 14-deoxo-3-*O*-propionyl-5,15-di-*O*-acetyl-7-*O*-benzoylmyrsinol 4*β*-nicotinoate, proliferin A–C, euphorprolitherin B, SPr5 and premyrsinol-3-propanoate-5-benzoate-7,13,17-triacetate) isolated from *E. prolifera*. The activities were tested against MPP^+ (1-methyl-4-phenylpyridinium ion)-induced neuronal cell death in SH-SY5Y cells using MTT assay at concentrations 3, 10 and 30 μM, and guanosine as a standard. All the compounds revealed to have neuroprotective effects. The active compounds neither modified the cell viability nor exhibited any cytotoxicity.[62] Later, the same group investigated the neuroprotective effect of three myrsinol (**115–117**) diterpenes. Compounds **115** and **117** exhibited neuroprotective activities.[65]

5.8. Proinflammatory activity

Shu et al. investigated the proinflammatory constituents of *E. kansui*. The results showed that kansuinines A and B and 3-*O*-(2'*E*,4'*Z*-decadienoyl)-20-*O*-acetylingenol markedly facilitated proliferation of the splenic lymphocytes of exoteric mice and NO production by rat peritoneal macrophages at the used concentrations (from 0.78 to 12.50 μg/mL). The three compounds are therefore held to be the compounds responsible for the proinflammatory activity of the roots of *E. kansui*.[112] It was also observed that kansuinines A

and B displayed anticancer and antiviral activities,[113,114] so these diterpenes are belived as the main bioactive and toxic compounds of the plant.

Ingenane-type diterpenes (**196**–**205**) isolated from *E. cauducifolia* showed ID_{50} = 2.5–4.4 μg/mL, indicated moderate irritant activity of the compounds compared to TPA. Compound **197** was the most irritant in the series, other esters showed less irritant activity. None of the tested ingenanes showed tumor promoting effect up to a dose of 40 nM/application after 48 weeks, compared to the standard TPA.[80]

5.9. Pesticidal activity

The MeOH extract of the roots of *E. kansui* exerted pesticidal activity against the brown plant hopper (*Nilaparvatal ugens* Stal) and the two-spotted spider mite (*Tetranychus urticae* Koch). Bioassay-directed separations led to the isolation of 3-*O*-(2,3-dimethylbutanoyl)-13-*O*-dodecanoylingenol and 3-*O*-(2'*E*,4'*Z*-decadienoyl)-ingenol. The two diterpenes showed greater activity against the brown plant hopper as compared with anise oil and eugenol. The calculated LD_{50} doses were 0.139 μg/insect for 3-*O*-(2,3-dimethylbutanoyl)-13-*O*-dodecanoylingenol and 0.111 μg/insect for 3-*O*-(2'*E*,4'*Z*-decadienoyl)-ingenol.[115]

Geng et al. investigated the feeding deterrent activities of diterpenes isolated from *E. fischeriana*. Significant feeding deterrent activity was found in case of jolkinolide B and hydroxyjolkinolide B against *Sitophilus zeamais* (EC_{50} = 342.1 and 543.9 ppm, respectively) and *Tribolium castaneum* adults (EC_{50} = 361.4 and 551.5 ppm, respectively).[25]

5.10. Molluscicidal activity

Baloch et al. investigated the molluscicidal activities of extracts (CCl_4, Et_2O, $CHCl_3$, Me_2CO, EtOAc, EtOH and MeOH) of the roots of *E. cornigera*, on the freshwater snail *Biomphalaria glabrata*, an intermediate host of *Schistosoma mamsoni*.[78] Bayluscide was used as positive control. The Me_2CO extract displayed significant activity (IC_{50} = 15.5 μg/mL). Further purification of this extract resulted in the isolation of ten ingenol-type diterpene polyesters. Eight of the isolated compounds [**206**–**209**, **212**, **213**, 3-*O*-[*N*-(2-aminobenzoyl)]anthraniloyl-20-*O*-acetylingenol and 20-*O*-[*N*-(2-aminobenzoyl)]anthraniloyl-3-*O*-acetylingenol] exhibited relatively high activity (1.3-2.2 times more toxic than bayluscide) against the intermediate snails. It was observed that these components were responsible for this activity.[78]

Later, Baloch et al. investigated the molluscicidal effects of 8 phorbol derivatives (**151**–**158**) isolated from *E. cauducifolia* against *B. glabrata* snails. Two compounds, with an acetyl (**151**) or an *N*-(2-aminobenzoyl)anthraniloyloxy (**152**) moiety at C-13, had higher activities than that of bayluscide, while other compounds showed the same potency than that of the control niclosamide. The compounds probably provoke osmosnailic instability and surface vesiculation, causing the death of the snails.[73]

Using a bioassay-guided fractionation of methanol extract of *E. aellenii*, two lathyrane diterpenoids (**101** and **102**) were isolated by Ayatollahi et al. The cytotoxicity of fractions was tested *in vitro* on brine shrimp (*Artemia saline*).[54]

6. Clinical studies

There is only one compound, ingenol mebutate (ingenol 3-angelate, formerly PEP005), isolated from *Euphorbia peplus*,[116] which has been used in clinical practice. Numerous clinical studies have been performed with this compound. Siller et al. evaluated the safety of two applications of ingenol mebutate gel in a randomized, double-blind, vehicle-controlled, phase IIa study. Preselected lesions were treated with 0.0025%, 0.01% or 0.05% ingenol mebutate gel or vehicle gel, on days 1 and 2 or 1 and 8. No substantial differences in efficacy or tolerability were detected between the two applications, and the treatment was well tolerated.[117] Ingenol mebutate gel was later investigated as topical application for superficial basal cell carcinoma in 60 patients, and it was observed that the treatment of 0.05% ingenol mebutate gel was effective and safe.[118]

In a randomized, double-blind, double-dummy, vehicle-controlled, sequential cohort dose-finding study, Anderson et al. evaluated the efficacy, tolerability and safety of ingenol mebutate gel as topical therapy for actinic keratosis. In the phase IIb study, 0.025% ingenol mebutate gel was used once daily for 3 days, or 0.05% was applied once daily on 2 or 3 consecutive days, to a continuous area of skin containing actinic keratosis lesions. It was concluded that the application of ingenol mebutate gel either for 2 or 3 days produced a statistically significant, greater lesion clearance by all measures of efficacy and at each of the dosing regimens studied as compared with the vehicle gel.[119] Phase III data are also available, in connection with the use of ingenol mebutate on the scalp, face, arm, back of the hand, and chest.[120]

Resiniferatoxin (RTX), like capsaicin, is an ultrapotent vanilloid receptor agonist, isolated from the latex of *Euphorbia resinifera*. RTX activates the transient receptor potential vanilloid 1 (TRPV1), a Ca^{2+} permeant non-selective cation channel expressed in a subpopulation of primary afferent sensory neurons (involved in nociception).[121] RTX is

therefore promising lead molecule for the therapy of long-lasting analgesia. It has also been investigated in clinical trials for bladder hyperreflexia, diabetic neuropathy and cancer pain.[122–124]

7. Synthesis of Euphorbia diterpenes

In 2007, a diastereoselective synthesis of polyoxygenated atisane-type diterpenes was elaborated by Abad et al. (*S*)-(+)-Carvone served as starting material.[125] In the course of the preparation an intramolecular Diels–Alder reaction, intramolecular diazoketone cyclopropanation of an unsaturated ketone and a endocyclic regioselective cleavage of a cyclopropyl carbinyl radical were applied. 18-Hydroxy-16-atisene-3,14-dione, isolated previously from *E. fidjiana*, has also been synthesized.[125]

In 1989, the total synthesis of (±)-jolkinolides A, B and E from 10-(methoxycarbonyl)-*β*-ionone was performed by Katsumura et al. The synthetic route contained approximately 20 reaction steps.[126] Later, Shi et al. modified this total synthesis, using easily available and low-cost stevioside as starting material, and prepared in 13 steps jolkinolide A and 19-hydroxyjolkinolide E in an overall yield of 7.8%. Some related derivatives have also been synthetized.[127] Suenaga et al. achieved the first total synthesis of the enantiomer of jolkinolide D from abietic acid.[128]

Naturally occurring jatrophane polyesters, which contain many stereocenters and ester groups, such as with acetyl, nicotinoyl or benzoyl groups, have been isolated in several *Euphorbia* species.[129] Previously different biological activities have been published for jatrophane diterpenes, *e.g*. multidrug resistance-modulating activity, and inhibition of P-gp, cytotoxicity against various human cancer cell lines, and immunomodulatory, antiviral, and

antiplasmodial activities. These findings, together with the unique structure of the jatrophane skeleton, have prompted synthetic experiments by many groups.[129] The first total synthesis of a jatrophane type diterpene, named normethyljatrophone was carried out by Smith et al., in 1981.[130] Later, Stille et al. elaborated another synthetic route. The key step in their experiment was the palladium-catalyzed intramolecular carbonylative coupling of vinyl stannane with vinyl triflate.[131] Mulzer et al. and Hiersemann et al. also reported synthetic studies targeting jatrophanes. The key reactions were a Claisen–Eschenmoser rearrangement, and thereafter hydroxy-lactonization, intramolecular *trans*-lactonization, Davis hydroxylation and regioselective enoltriflate formation.[132–135] In 2007, Shimokawa et al. subsequently described a short and striking synthesis of the cyclopentane fragment of kansuinine A using SmI2-mediated cyclization of the δ-iodoester as a key step,[129] and Helmboldt et al. reported the enantioselective synthesis of a jatrophane-type diterpene, (+)-17-norcharaciol.[136]

The enantioselective total synthesis of the jatrophane (−)-15-*O*-acetyl-3-*O*-propionylcharaciol was carried out by Schnabel et al.[137] Starting from a cyclopentane, a *β*-alkyl Suzuki−Miyaura cross-coupling and carbonyl addition were carried out to construct a fully functionalized triene, and a ring-closing metathesis was then applied to produce the 12-membered ring (Figures 2a, 2b and 2c).[137,138]

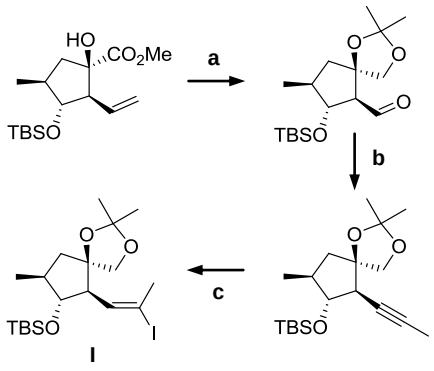


Figure 2a. Synthetic route toward the production of a jatrophane diterpene structural fragment[137] **a**) *i*: $LiAlH_4$, THF, rt (90%); *ii*: $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt (85%); *iii*: O_3, CH_2Cl_2, MeOH, –78 °C, PPh_3 (90%); **b**) *i*: CBr_4, PPh_3, CH_2Cl_2, –78 °C; *ii*: MeLi, THF, –78 °C; MeI, –78 °C to rt (78%); **c**) $Cp_2Zr(H)Cl$, THF, 40 °C, 1.5 h then I_2, CH_2Cl_2, (80%)

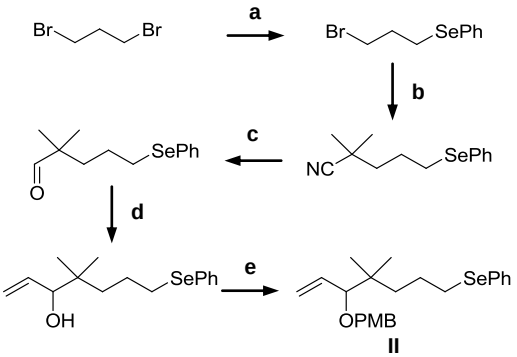


Figure 2b. Synthetic route toward the production of a jatrophane diterpene structural fragment[137] **a**) $(PhSe)_2$, $NaBH_4$, MeOH, 0 °C, 30 min, to rt (91%); **b**) LiN*i*-Pr_2, *i*-PrCN, Et_2O, 0 °C to rt (93%); **c**) *i*-Bu_2AlH, toluene, –78 °C, 1h (81%); **d**) $BrMgCH{=}CH_2$, THF, –78 °C, 45 min (76%); **e**) NAH, PMBCl, *n*-Bu_4NI, THF, DMSO (90%)

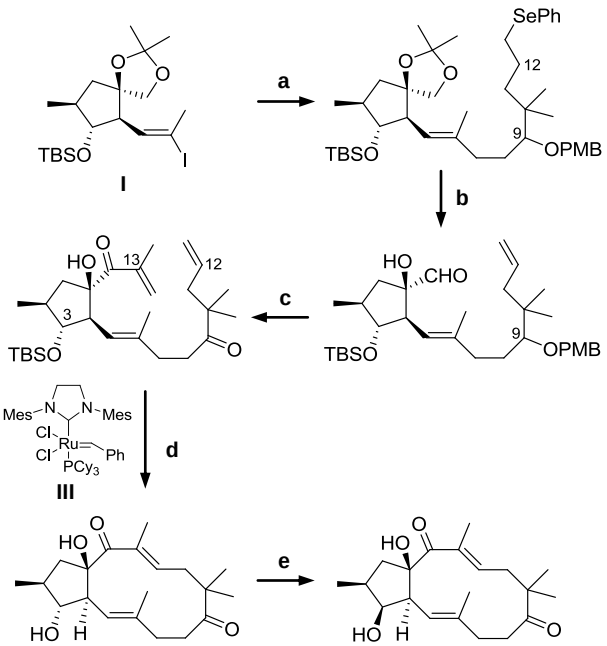


Figure 2c. Total synthesis of a jatrophane diterpene[137] **a**) 9-BBN, THF, 40 °C, 24 h, + **II** (100 mol %), $(dppf)PdCl_2$ (7 mol %), Ph_3As (20 mol %), Cs_2CO_3 (270 mol %), THF, DMF, H_2O

(14/2/1), 80 °C, 8 h (86%); **b**) *i*: H_2O_2, $NaHCO_3$, H_2O, THF, rt (68%); *ii*: $La(NO_3)_3 \cdot 6H_2O$, MeCN, 50 °C (54%); *iii*: IBX, CH_2Cl_2, DMSO (1/1), rt (81%); **c**) *i*: $H_2C=C(Me)Br$, *t*-BuLi, THF, –78 °C, 15 min (91%); *ii*: DDQ, CH_2Cl_2, aq. pH 7 buffer, rt, 2.5 h; *iii*: IBX, CH_2Cl_2, DMSO (1/1), rt, 6 h (75%); **d**) *i*: **III** (10 mol %), toluene (c = 1.3×10-3 mol/L), 110 °C, 2 h; *ii*: HF·Py, THF, 0 °C, 3 h; **e**) *i*: PPh_3, DIAC, *p*-Br-C_6H_4COOH, THF, 0 °C (87%); *ii*: MeOH, K_2CO_3, rt, 5 h (91%)

Later, Schnabel and co-workers reported the total synthetic routes toward natural and non-natural jatropha-5,12-dienes, applying a *β*-alkyl Suzuki–Miyaura cross-coupling for the construction of the C-5/C-6 olefin bond, and a ring-closing metathesis for the formation of the double bond between C-12 and C-13.[139] In 2012, Mohan et al. applied a thermal intramolecular carbonyl-ene reaction to accomplish the highly substituted cyclopentane part of the molecule.[140]

Duarte et al. derivatized latilagascene B, previously isolated from *E. lagasce*, with acylating reagents (benzoyl chloride, propionic anhydride and butyric anhydride) to yield three new lathyrane esters: latilagascene G, H and I.[98]

Appendino et al. demonstrated that macrocyclic diterpenoids (*e.g*. the lathyrane type Euphorbia factors L_1 and L_3) can be conversed to densely functionalized diterpenoids with unnatural framework. The utilized starting compounds are easily available from the seeds of the caper spurge (*E. lathyris*) and have a pronounced potential to generate rigid polycyclic skeletons.[141]

Ingenol has also been of great interest not only because of its unusual structure containing an “inside-outside” bridged BC ring, but also because of a broad spectrum of pharmacological activities. The synthesis of the highly strained ingenane framework required special approaches, and strategically distinct methods.[142–144] The first total synthesis of ingenol was performed by Winkler with the use of an intramolecular de Mayo reaction.[145]

Other successful synthetic approaches (Winkler, Wood and Tanino/Kuwajima) and promising partial syntheses have since been reported and reviewed (Figure 3).[146–153] In 1997, Nakamura et al. carried out an efficient method for the synthesis of ingenane by application of a tandem cyclization–rearrangement involving the complete C and D ring structure of ingenol, although the methoxy group at position C-4 was not sufficient to serve as an anchor for incorporation of the hydroxy groups and the double bonds of the A and B rings.[154] Later, they described the total synthesis of ingenol on the basis of another strategy from a commercially available compound. A rearrangement of an epoxy alcohol afforded the key intermediate, which is substituted with two oxygen functions (at C-1 and C-6).[151] In 2002, Rigby et al. elaborated a facile entry into the ingenane core by developing a Lewis acid-catalyzed intramolecular [6+4] cycloaddition.[155] The main challenges concerning the synthesis stems from the strained 'in-out' [4.4.1]-bicycloundecane ring and the highly oxygenated and densely functionalized southern part of the molecule.

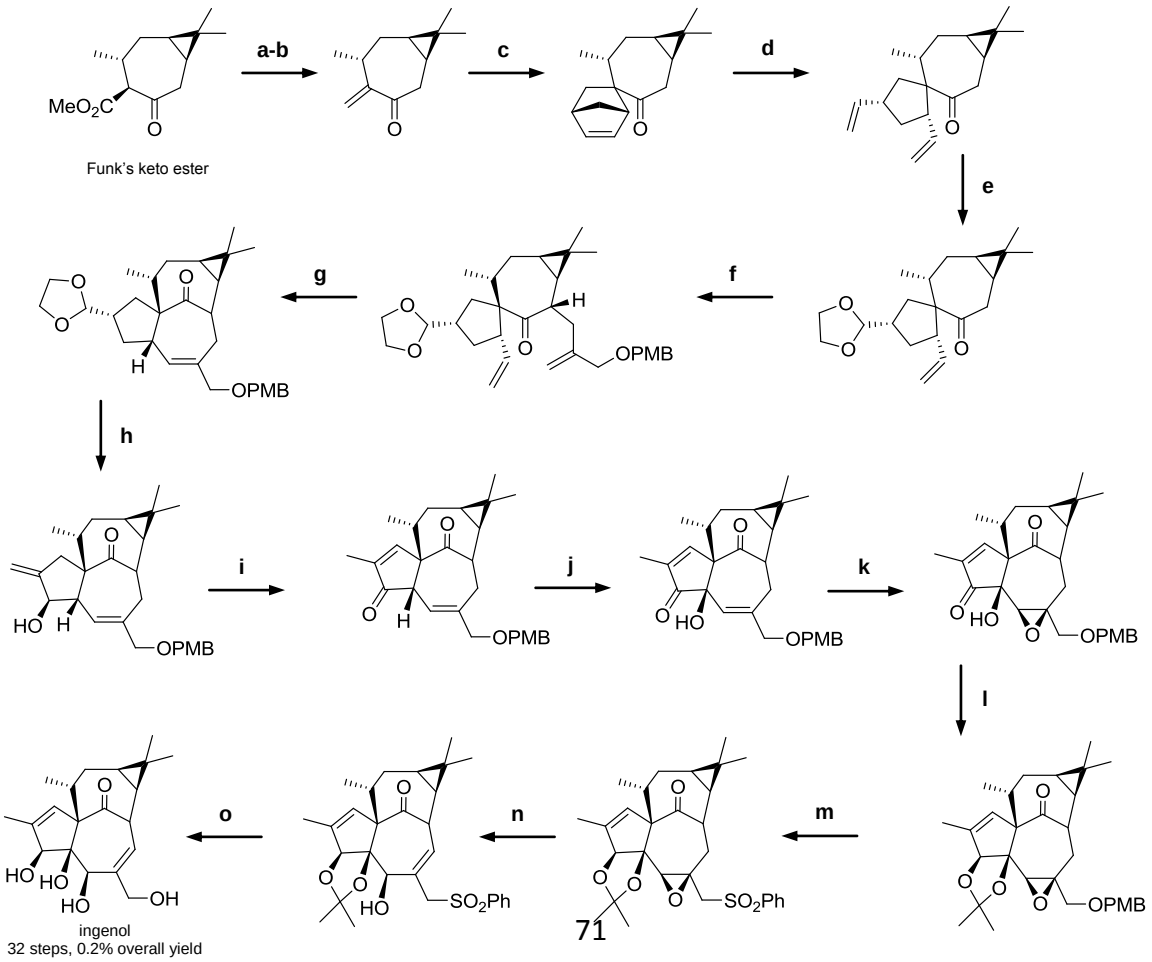


Figure 3. Wood's total synthesis of ingenol[152] **a**) *i*: $(HOCH_2)_2$, pTsOH, C_6H_6, Δ, 96%, dr= 43:23:18:16; *ii*: $LiAlH_4$, Et_2O; *iii*: HCl, acetone, H_2O, 95% (2 steps); **b**) *i*: Ac_2O, pyridine, DMAP, 96%; *ii*: DBU, C_6H_6, Δ, 80%; **c**) cyclopentadiene, $BF_3{\cdot}OEt_2$, $PhCH_3$, –78 °C, 59%; **d**) Grubbs-I, ethylene, CH_2Cl_2, 98%; **e**) *i*: OsO_4, NMO, THF–H_2O 4:1; *ii*: $NaIO_4$, MeOH–THF 4:1; *iii*. $(HOCH_2)_2$, ^{p}TsOH, C_6H_6, Δ, 73% (3 steps); **f**) $ClCH_2C(=CH_2)CH_2OPMB$, KH, THF, Δ, 98%; **g**) RCM, $PhCH_3$, Δ, 76%; **h**) *i*: HCl, THF–H_2O, Δ; *ii*: $NaBH_4$, EtOH–THF, 0 °C, 77% (2 steps); *iii*: I_2, PPh_3, imidazole, THF, 0 °C; *iv*: KO^{t}Bu, THF–DMSO, 94% (2 steps); **i**) *i*: SeO_2, ^{t}BuOOH, CH_2Cl_2–H_2O–HOAc, 0 °C, rt, 68% brsm; *ii*: Dess-Martin periodinane (DMP), CH_2Cl_2, –40 → 10 °C, 74%; *iii*: $RhCl_3$, EtOH, 115 °C, 74%; **j**) KO^{t}Bu, O_2, $P(OMe)_3$, THF, ^{t}BuOH 4:1, –40 °C, 94%; **k**) $VO(acac)_2$, ^{t}BuOOH, C_6H_6, 10 °C to rt, 73%; **l**) *i*: TMSOTf, Net_3, CH_2Cl_2, –10 °C to –5 °C, 72%; *ii*: $NaBH_4$, MeOH; *iii*: 2.2-DMP, PPTS, CH_2Cl_2, Δ, 86% (2 steps); **m**) *i*: DDQ, CH_2Cl_2, 90%; *ii*: MsCl, Net_3, CH_2Cl_2, –78 °C, 96%; *iii*: PhSH, Li_2CO_3, DMF, 55 °C, 76%; *iv*: $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 97%; **n**) DBU, C_6H_6, Δ, 47%; **o**) *i*: Na–Hg, Na_2HPO_4, MeOH, –20 → –10 °C, 76%; *ii*: HCl, THF–H_2O, 92%; *iii*: SeO_2/SiO_2, THF, 80 °C, 85% brsm.

The structurally related phorbol and its analogs were synthetized by Wender et al. in 1990. The interesting feature of this process was an unprecedented silicon transfer-induced oxidopyrilium cycloaddition and transition metal-mediated synthesis of ring A.[156]

8. Conclusions

In the past few years, more than 200 novel diterpenes with rosane, *ent*-abietane, *ent*-atisane, *ent*-kaurane, casbane, jatrophane, lathyrane, myrsinane, premyrsinane, cyclomyrsinane, daphnane, tigliane, ingenane, paraliane or pepluane skeletons have been

isolated from different *Euphorbia* species. Many of the investigated species contain constituents with two or more different cores. Some *Euphorbia* species (*E. prolifera*, *E. esula*, *E. kansui*, *E. cornigera* and *E. cauducifolia*) are especially rich in diterpenes. Diterpenes are considered to be important taxonomic markers of the Euphorbiaceae family, because of their limited occurrence and structural diversity.

Dimeric and glycosylated diterpenes in *Euphorbia* species are very rare. The first dimeric diterpenoids were langduin C and D, isolated from *E. fischeriana* in 2003 by ZHOU *et al*.[157] In 2012, Zhang *et al*. obtained two other dimers (bisyinshanic acids A and B) from *E. yinshanica*.[29] Only one glycosylated Euphorbia diterpene is known, discovered in *E. helioscopia* in 2010.[53]

In some cases, the diterpenes of given *Euphorbia* species of different origins have been found to be different, *e.g*. in the case of *E. esula*. Samples from different locations (China, Hungary, and North America) contained different diterpenes (jatrophanes, ingenanes).[158–166] In the diterpene series obtained from the Hungarian collection, the aromatic acyl residues were missing and the alcohol core of the compounds was different from that isolated from North American and Chinese samples. As concerns the diterpene composition, *E. esula* displays many similarities with *E. salicifolia*. These species contain the same main diterpene components (esulatin A, salicinolide and euphosalicine), and other jatrophanes differing only in the esterification pattern (number and position of ester groups).[167,168] In case of *E. peplus*, different investigations jatrophane, ingenane and pepluane diterpenes have been reported. The diterpenes of the samples originating from Chile, Germany and Hungary were found to be similar, while from an Italian sample, different compounds were isolated.[45,83,169,170] These facts indicated that in case of *E. peplus* chemovarietas must presumably be exist.

All *Euphorbia* species produce a white milky sap (latex), which is exuded when they are injured. The common name of the Euphorbiaceae family is the spurge family. This is derived from the Medieval French “epurger,” which means “to purge”.[171] The sap of many herbaceous *Euphorbia* species has traditionally been used as a purgative, or laxative. Moreover, several *Euphorbia* species have been applied in traditional medicine against various tumors.[172] However, their application in modern therapy is impossible because of the irritant and tumor-promoting activities of certain diterpenes occurring in the latex. The toxic constituents of *Euphorbia* species are the ‘phorboids’, which comprise ingenane, daphnane and tigliane diterpenes.[173]

Biologically active compounds of traditional medicinal plants are frequently utilized in the pharmaceutical industry either as active agents of medicines or as lead compounds in drug development. Almost 70% of modern drugs had a natural product origin.[174] The importance of this type of natural products may be demonstrated primarily by the approval of ingenol mebutate (Picato®) by the FDA and EMA for the treatment of actinic keratosis a pre-cancerous skin condition. This compound isolated from *E. peplus* for the first time by Hohmann et al.[170] It has been a considerable time since a natural product without structural modification has been introduced into clinical practice. Some other ingenol and phorbol derivatives (*e.g*. prostratin), have become of considerable interest in HIV therapy. In combination with other antiretroviral drugs they can activate viral reservoirs and overwhelm the pool of latent HIV infection. Resiniferatoxin which acts by destroying nerves that transmit pain information is at present undergoing evaluation in phase II and III clinical trials.[175]

Recent pharmacological experiments encompassed the assessment of antiproliferative, cytotoxic, MDR inhibitory, anti-inflammatory, immunomodulatory,

antimicrobial, vascular relaxing, neuroprotective, pesticidal and molluscicidal activities. These results open up new opportunities primarily in the design and development of drugs against tumors and to overcome the multidrug resistance of human cancers.

Investigation of the diterpenoids of *Euphorbias* is very promising. The hit probability of the search for new natural compounds is noteworthy: the *Euphorbia* species produce a great number of previously undiscovered compounds (almost 70% of the isolated compounds are new). Approximately 100 *Euphorbia* species have so far been investigated for diterpene content, i.e. only less than 5% of the species belonging in this genus. Moreover, the analytical (primarily HPLC) studies of constituents as biomarkers and correlations of biological and/or toxic effects of *Euphorbias* may be helpful in discovering the mechanisms of their bioactivity, and for guiding safer application of these species in the clinic.[13]

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