Biologically active diterpenes containing a *gem*-dimethylcyclopropane subunit: an intriguing source of PKC modulators†

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The biological activities of tiglane, lathyrane, ingenane, casbane, jatrophaolane and premyrsinane diterpenoids which contain the *gem*-dimethylcyclopropyl unit are described. Particular attention is given to their anti-viral, anti-microbial and cytotoxic activities. In the main text there are 132 references. The electronic supplementary information contains tables listing 424 of these diterpenoids, their occurrence and biological activity together with the references.

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1 Introduction

The study of the biological substrate–target interactions of proteins with organic molecules of low molecular weight, including Natural Products (NPs), has led to the identification of the role of these proteins in several important biological processes. This field of research has attracted great interest in recent years because it facilitates the study of complex cellular mechanisms, many of which have led to the recognition and identification of important biological targets.¹

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† Electronic supplementary information (ESI) available: Tables listing the known natural products of these structural types, the species from which they were isolated, their biological activity and the bibliographical reference. See DOI: 10.1039/c4np00008k

The Natural Products include those containing a *gem*-dimethylcyclopropane subunit, some of which are considered to be of great interest for the discovery of new NP-based drugs due to their wide range of biological activities and structural diversity. Some of these compounds are currently under study in preclinical or clinical trials or have already been approved for the treatment of certain diseases.²

This three-membered carbocycle is found in various types of compounds, particularly terpenoids, and these have been isolated from a large variety of organisms like plants, some fungi and marine organisms such as soft corals and insects.

Natural Products with a *gem*-dimethylcyclopropane unit are mainly terpenoids and this carbocycle forms part of their basic skeleton.

Tables listing the known natural products of these structural types, the species from which they were isolated, their biological activities and references are available in the Electronic Supplementary Information (ESI).†

2 Diterpenoids with a *gem*-dimethylcyclopropyl unit

A large number of diterpenes contain a *gem*-dimethylcyclopropane ring. These diterpenes have a wide variety of carbon skeleton, derived from the cation casbane. They include tiglanes, lathyrans, ingenanes, casbanes, premyrsinanes and jatropholanes. They are mostly present in species of the Euphorbiaceae. These plants are of great interest in the search for new drugs based on Natural Products because of the wide variety of pharmacological properties they possess and the great diversity of compounds with high structural variability that they produce.^{1,3}

These polycyclic diterpenes, occurring widely in the Euphorbiaceae, can be formed by intramolecular cyclization of casbane.⁴ Despite the recent advances in the understanding of the biosynthesis of many types of natural products, the specific enzymes responsible for building this strained three membered ring have only been identified in a few cases and many mechanistic details remain unclear.⁵

María Jesús Durán-Peña was born in 1984 in Cadiz, Spain. She studied chemistry at the University of Cádiz. She carried out her PhD at Cádiz University with Professor Dr R. H. Galán and Professor Dr I. G. Collado. Her work focuses on the isolation of secondary metabolites from euphorbia species and the development of new methodologies for cyclopropanation.

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José Manuel Botubol was born in 1984 in Cadiz, Spain. He studied chemistry at the University of Cádiz. He carried out his PhD at Cádiz University with Professor Dr I. G. Collado and Dr A. J. Macías-Sánchez, where he was working on the total synthesis of polyketide natural products. His further research interests are the synthesis of biologically active molecules.

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A number of enzymes in the terpenoid synthase family that catalyze cyclopropane formation have also been biochemically and mechanistically characterized recently, especially those responsible for the production of the bicyclic plant mono-terpenes such as carene or sabinene synthase.⁵ However the reported data on the biosynthesis and enzymatic formation of the cyclopropane ring in diterpenes are sparse. At least one diterpene synthase, casbene synthase, has been shown to cyclize geranylgeranyl pyrophosphate (GGPP) into casbene, which seems to be the key biosynthetic precursor of the lathyrane skeleton, an intermediate to jatrophaolane, tiglane, or premyrsinane which retain the cyclopropane ring in their final structures.^{5–9}

This enzyme seems to follow a mechanism where cleavage of the allylic pyrophosphate moiety of GGPP, by a divalent metal ion, leads to an allylic carbocation that through alkylation and deprotonation generates the cyclopropane moiety in the casbene skeleton.^{6–9}

The ring strain present in the *gem*-dimethylcyclopropane moiety looks to be responsible for the biological activities of these compounds, many of them are potent alkylation agents. However, few reports about the biological relevance of this subunit have been published. For more detailed information about the biosynthesis and biological activity of this interesting subunit, the reader is directed to a recent excellent review.⁵

Tiglanes and ingenanes, together with daphnanes are referred to as phorboids and are known for being proinflammatory agents and tumor promoters which behave as protein kinase C (PKC) activators. Proof of the pharmacological relevance

of this group of compounds is the FDA's approval in January 2012 of 3-*O*-angeloylingenol (PEP-005, Picato®, Leo Pharma) for the treatment of actinic keratosis, a precancerous skin condition.¹

2.1 Tiglanes†

Protein Kinase Cs (PKCs) are involved in many physiological functions and certain NPs, such as phorbol esters, have proved to be important activators of these proteins. Certain phorbol esters can activate PKCs, but after an incubation period they decrease its regulatory activity. The activating capacity of PKCs is responsible for the wide variety of biological activities reported for this group of compounds such as platelet aggregation,¹⁰ cell differentiation,^{11,12} metabolic activity,^{13–15} irritant,¹⁶ tumor-promotion,^{17,18} anti-HIV-1,^{19,20} cytotoxicity²¹ and as a molluscicide.²²

2.1.1 Anti-HIV activity. 12-Deoxyphorbols such as prostratin (13-*O*-acetyl-12-deoxyphorbol (2)) are a subclass of PKC activators since, unlike other phorbol esters, these do not induce tumor formation. Prostratin (2) has been found in *Euphorbia* species.^{23,24} Recently, it has been shown that prostratin is a PKC activator that is potentially useful in the treatment of HIV as it affects viral reservoirs in CD4⁺ T-cells with a latent infection.²⁵ DPP (3) induces HIV-1 gene expression in latently infected cells at concentrations 20–40 times lower than prostratin.²⁶ Considering that the only structural difference between prostratin (2) and DPP (3) is the nature of the ester group bonded to the C-13 carbon, it is easy to associate the activity of the 12-deoxyphorbol skeleton with other phorbol esters such as 13-*O*-benzoyl-12-deoxyphorbol (4) which have exhibited the same type of behaviour in other studies.^{27,28} Epimers 5 and 6 are potent PKC activators.²⁹ Fischerosides A–C

(7–9), tiglanes that carry a glycoside group on the C-20 carbon, have a mild inhibitory effect on the HIV-1 virus. Fischeroside C (9) had an EC_{50} value of 0.02 μ M and a therapeutic index of 17.50, while prostratin (2) and 13,20-*O*-diacetyl-12-deoxyphorbol (10) were significantly more active.³⁰

2.1.2 Cytotoxic activity. Important protein kinase C (PKC) activators, which show great potential as HIV-1 activators, were isolated from different species of the *Euphorbia* genus. PMA (or TPA, 11) is used extensively as a molecular biological research tool. It is known to stimulate the kinase activity of PKC and antagonize HIV-1 latency efficiently.^{17,31,32} Compounds 12–19 displayed cytotoxicity on human cancer cell lines.^{33–36} Euphodendriane A (20) and pedilstatin (21) are cancer cell growth inhibitors.^{37,38}

PMA (11): $R_1 = \text{Ac}$, $R_2 = \text{CO}(\text{CH}_2)_{12}\text{CH}_3$
12: $R_1 = \text{CO}(\text{CH}_2)_8\text{CH}_3$, $R_2 = \text{Tig}$

13: $R_1 = \text{Ac}$, $R_2 = \text{Ang}$
14: $R_1 = \text{Ac}$, $R_2 = \text{A}$
15: $R_1 = \text{H}$, $R_2 = \text{B}$
16: $R_1 = \text{H}$, $R_2 = \text{OC}(\text{CH}_2)_{14}\text{Me}$
17: $R_1 = \text{decanoyl}$, $R_2 = \text{octanoyl}$
18: $R_1 = \text{decanoyl}$, $R_2 = \text{decanoyl}$
19: $R_1 = \text{decanoyl}$, $R_2 = \text{dodecanoyl}$

2.1.3 Inhibitory activity on the mitochondrial respiratory chain. Compounds 22–25 were active when evaluated for their inhibition of NADH oxidase activity in submitochondrial particles from beef heart. All of them are described as NADH oxidase inhibitors, 22 being the strongest inhibitor of NADH oxidase activity with an IC_{50} value of 2.60 mM.³⁹

22: $\beta\text{-H}$, $R = \text{H}$
23: $\beta\text{-H}$, $R = \text{OAc}$
24: $\alpha\text{-H}$, $R = \text{OH}$
25: $\beta\text{-H}$, $R = \text{OH}$

2.1.4 Toxic activity. It is known that ingestion of certain members of the Euphorbiaceae by animals reduces their performance, contaminates milk, decreases reproduction and can even cause death.⁴⁰ This toxicity is associated with phorbol esters such as PMA (11). The phorbols 26–33 are known to be toxic and are also powerful irritants.⁴¹ Jatrophol-I (34) was highly toxic to silkworm larvae,^{42,43} moreover compounds 35–51 acted as irritants.^{44–50} On the other hand, compounds 52–59 exhibit

26: $R = \text{iBu}$
43: $R = \text{COCHMe}_2$

27: $R_1 = \text{H}$, $R_2 = \alpha\text{-MeBu}$
28: $R_1 = \text{H}$, $R_2 = \text{heptanoyl}$
29: $R_1 = \text{H}$, $R_2 = \text{lauroyl}$
40: $R_1 = \text{Ac}$, $R_2 = \alpha\text{-MeBu}$
41: $R_1 = \text{Ac}$, $R_2 = \text{lauroyl}$
52: $R_1 = \text{Ang}$, $R_2 = \text{Ac}$
53: $R_1 = \text{Ac}$, $R_2 = \text{D}$
54: $R_1 = \text{Bz}$, $R_2 = \text{Bz}$
55: $R_1 = \text{Ang}$, $R_2 = \text{Ang}$
56: $R_1 = \text{D}$, $R_2 = \text{Ang}$
57: $R_1 = \text{D}$, $R_2 = \text{Tig}$
58: $R_1 = \text{D}$, $R_2 = \text{Bz}$
59: $R_1 = \text{D}$, $R_2 = \text{hexanoyl}$

sapatoxin A (30): $R = \text{OH}$, $R_1 = \text{H}$
sapatoxin B (31): $R = R_1 = \text{OH}$
sapatoxin C (32): $R = \text{H}$, $R_1 = \text{OH}$

stillingia factor S8 (33)

molluscicidal activity against the snail, *Biomphalaria glabrata*. This snail is the major intermediate host for *Schistosoma mansoni*, one of the important schistosomes infecting man.^{21,51}

jatrophol-I
(34)

35: α -H, R = COCHMe₂
36: β -H, R = COC₆H₅
37: α -H, R = COC₆H₅

38

39

42

44: R = Ac
45: R = COEt
46: R = COCHMe₂

sapintoxin A (47): R=R₁= H, R₂= OH
sapintoxin B (48): R= H, R₁=R₂= OH
sapintoxin C (49): R=R₂= H, R₁= OH
sapintoxin D (50): R=R₂= OH, R₁= H

milliamine H (51)

2.1.5 Tumor promotion activity. PMA (11) is a known protein kinase C activator that promotes tumors.^{52–54} The esters, 35–39 also display tumor-promoting activity.⁴⁷ Phorbol esters do not induce tumors on their own but rather promote their growth by continuous exposure to certain levels of these esters.³⁸

In contrast to this ability to activate tumor growth, many malignant cells have been observed entering apoptosis in response to PKC activation by phorbol esters. PKC activity displacement is attributed to its role in the activation of different metabolic pathways, its cellular localization, phosphorylation, interaction with other molecules and accessibility to various substrates.^{55,56}

2.1.6 Other activities. Prostratin (2) exhibited analgesic and sedative effects in preliminary pharmacological assays carried out with mice.²² Fischeroside B (8) provided significant protection against the oxidative stress caused by *tert*-butylhydroperoxide by inhibiting the generation of reactive oxygen species and increasing glutathione levels in HepG2 cells.⁵⁷ Trigowiin A (60) exhibited antiviral activity against the Chikungunya virus.⁵⁸

trigowiin A
(60)

2.2 Lathyranes†

2.2.1 Antimicrobial activity. Diterpenes 61–63 exhibited antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*.^{59–61}

61: R₁= OH, R₂= Me
62: R₁= Me, R₂= OH

japodagrins (63)

2.2.2 Antiviral activity. Latilagascenes A–C (64–66), E (67) and jolkinol B (68) decreased immediate-early (IE) antigen expression of the human cytomegalovirus (CMV). These antiviral compounds also act as anti-tumour compounds towards certain forms of cancers that are associated with human CMV.⁶² On the other hand, the HIV/AIDS field is gaining momentum with the goal of finding a functional cure for HIV infection by utilizing strategies that specifically reactivate the latent viral reservoir in combination with the Highly Active Antiretroviral Therapy (HAART). The virus HIV can be destroyed by HAART when it is active.⁶³ Compounds 69 and 70 were able to reactivate HIV-1 latency. Results with 69 strongly suggest that it reactivates

64: R₁= OAc, R₂= R₃= H
65: R₁= OH, R₂= R₃= H
66: R₁= OAc, R₂= Ac, R₃= H
67: R₁= OBz, R₂= H, R₃= OH
jolkinol B (68): R₁= R₂= R₃= H

69: R₁= Ac, R₂= H, R₃= Tig
70: R₁= Bz, R₂= Ac, R₃= Me

HIV-1 through a PKC-dependent pathway.³⁰ Compound **70** induced cell-cycle arrest and HIV-1-LTR promoter activation and could be a novel lead compound for the development of therapies against HIV-1 latency.⁶⁴

2.2.3 Cytotoxic activity. Latilagascene B (**65**) showed anti-tumour activity against gastric carcinoma cells.⁶⁵ The diterpenoid esters **71–80** exhibited important cytotoxic activity.^{66,67} Euphorbia factors L₁ (**81**), L₃ (**82**) and japodagrol (**83**) exhibited *in vitro* anticancer activity.^{68,69}

- 71: R₁ = 2-MeBu, R₂ = R₃ = R₄ = Ac
 72: R₁ = R₃ = R₄ = Ac, R₂ = 2-MeBu
 73: R₁ = R₂ = R₄ = Ac, R₃ = 2-MeBu
 74: R₁ = R₂ = R₃ = Ac, R₄ = 2-MeBu
 75: R₁ = 2-MeBu, R₂ = R₄ = Ac, R₃ = Me
 76: R₁ = R₄ = Ac, R₂ = 2-MeBu, R₃ = Me
 77: R₁ = R₂ = Ac, R₃ = Me, R₄ = 2-MeBu
 78: R₁ = R₄ = Ac, R₂ = Ang, R₃ = Me
 79: R₁ = H, R₂ = Ang, R₃ = Me, R₄ = Ac
 80: R₁ = R₄ = Ac, R₂ = H, R₃ = Me

2.2.4 Modulation of multidrug resistance. P-Glycoprotein (P-gp) is a multidrug transporter which is overexpressed in cancer cell plasma membranes as an efflux pump conferring cellular resistance to anticancer chemotherapy. Latilagascene B (**65**) was found to be an effective P-gp inhibitor and it is an inhibitor of multidrug resistance by tumor cells. It proved highly efficient in inhibiting rhodamine 123 efflux of the human MDR1 gene from transfected mouse lymphoma cells when compared to the untreated cells or the positive control verapamil.^{70,71} Euphorbia factor L₁₀ (**84**) also inhibited the transport activity of this protein, exhibiting a higher level of activity than that of the specific and potent P-gp inhibitor cyclosporin A.⁷²

2.2.5 Other activities. Latilagascenes A–C (**64–66**) and jolkinol B (**68**) are antitumor promoters and diminished the IE antigen expression of cytomegalovirus (CMV).⁶⁰ Besides, latilagascenes C (**66**) and D (**85**) exhibited high antineoplastic activity.⁶³ Lathyrane **69** has recently been patented as a promoter of stem cell proliferation in mouse brain.⁷³ Lathyrane **79** was particularly active as a prostaglandin E₂ inhibitor⁷⁴ and lathyrane **86** is a potent active ingredient in rabbit basilar and carotid arteries at resting tension.⁷⁵ Finally, lathyrans **87–91** showed significant vascular-relaxing activity.⁷⁶

- 85: R₁ = H, R₂ = Cinn, R₃ = OBz
 87: R₁ = R₂ = Bz, R₃ = H
 88: R₁ = Bz, R₂ = R₃ = H

- 90: R₁ = Cinn, R₂ = R₃ = H
 91: R₁ = R₃ = H, R₂ = Cinn

- PEP-008 (**92**): R₁ = Ang, R₂ = H, R₃ = Ac
 euphorbia factor L₅ (**93**): R₁ = CO(CH₂)₁₄CH₃, R₂ = R₃ = H
 kansuiphorin A (**94**): R₁ = 2,3-dimethylbutanoyl,
 R₂ = dodecanoyloxy, R₃ = hexadecanoyl
 98: R₁ = CO(CH=CH)(CH=CH)(CH₂)₄CH₃, R₂ = R₃ = H
 (E) (Z)
 99: R₁ = R₂ = Bz, R₃ = H
 100: R₁ = 2,3-dimethylbutanoyl, R₂ = dodecanoyl, R₃ = H
 101: R₁ = Bz, R₂ = octanoyl, R₃ = H
 102: R₁ = 2,3-dimethylbutanoyl, R₂ = octanoyl, R₃ = H

kansuiphorin B (**95**)

kansuiphorin C (**96**): R₁ = Ac, R₂ = Bz
 kansuiphorin D (**97**): R₁ = Bz, R₂ = Ac

2.3 Ingenanes†

2.3.1 Cytotoxic activity. PEP-005 (**1**) is a PKC activator exhibiting topical antitumor activity against human cancer cell lines in mice and against actinic keratosis in humans. PEP-005 also appears to have antileukemic effects, inducing apoptosis in leukemia cell lines and primary acute myeloid leukemia blasts.⁷⁷ The related compound PEP-008 (**92**) is a novel PKC-activating drug that arrests growth with senescence characteristics in solid cell lines derived from a variety of tissue types. This compound may therefore have therapeutic potential in a subset of breast cancer, colon cancer and melanoma tumors.⁷⁸ Euphorbia factor L₅ (**93**) acts as a cocarcinogen on the back skin in mice.⁷⁹ Kansuiphorin A–D (**94–97**) and **98–102** were cytotoxic against various cancer cell lines.^{34,35,80,83}

2.3.2 Effects on cell division. Results showed that esters **98** and **103–112** significantly inhibited cell division (0.5 µg ml^{−1} of each compound led to a reduction in cell division above 75%). Amongst these, **110** and **111** significantly prevented cell cleavage. It should be noted that inhibitory activity was weaker in compounds with an acyl residue at position 13. Besides, compound **113** was tested and showed some activity (10 µg ml^{−1} of this compound led to a 60% reduction in cell division).^{84,85}

- 103: R₁ = CO(CH=CH)^(E)(CH=CH)^(Z)(CH₂)₄CH₃, R₂ = H, R₃ = OAc
 104: R₁ = H, R₂ = H, R₃ = OCO(CH=CH)^(E)(CH=CH)^(E)(CH₂)₄Me
 105: R₁ = H, R₂ = H, R₃ = OCO(CH=CH)^(E)(CH=CH)^(Z)(CH₂)₄Me
 106: R₁ = CO(CH=CH)^(E)(CH=CH)^(Z)(CH₂)₄Me, R₂ = COMe, R₃ = OH
 107: R₁ = CO(CH=CH)^(E)(CH=CH)^(E)(CH₂)₄Me, R₂ = H, R₃ = OAc
 108: R₁ = H, R₂ = H, R₃ = OCO(CH₂)₈Me
 109: R₁ = H, R₂ = CO(CH=CH)^(E)(CH=CH)^(E)(CH₂)₄Me, R₃ = OH
 110: R₁ = CO(CH=CH)^(E)(CH=CH)^(E)(CH₂)₄CH₃, R₂ = H, R₃ = H
 111: R₁ = CO(CH=CH)^(E)(CH=CH)^(Z)(CH₂)₄CH₃, R₂ = H, R₃ = H
 112: R₁ = CO(CH=CH)^(E)(CH=CH)^(Z)(CH₂)₄CH₃, R₂ = H, R₃ = OH

113: R₁ = Bz, R₂ = OH

2.3.3 Irritant activity. PEP-005 (**1**), euphorbia factor L₅ (**93**) and compounds **114–118** exhibit irritant activity.^{86–90}

- euphorbia factor L₆ (**114**): R₁ = CO(CH₂)₁₃Me, R₂ = OH
 ingenol (**115**): R₁ = H, R₂ = OH
 116: R₁ = COC(Me)=CHMe, R₂ = H
 117: R₁ = H, R₂ = octanoyloxy
 milliamine C (**118**): R₁ = E, R₂ = OH

2.3.4 Pesticidal activity. Ingenol esters **112** and **119–122** exhibited antinematodal activity against the pine-wood nematode *Bursaphelenchus xylophilus*. This nematode is the causal agent of pine wilt disease, one of the most damaging pest problems found in forests.^{83,91–94}

- 119: R₁ = CO(CH=CH)^(E)(CH=CH)^(Z)(CH₂)₄CH₃, R₂ = H, R₃ = Ac
 120: R₁ = H, R₂ = CO(CH=CH)^(E)(CH=CH)^(Z)(CH₂)₄CH₃, R₃ = Ac

- 121: R₁ = 2,3-dimethylbutanoyl,
 R₂ = dodecanoyloxy, R₃ = OH
 DBDI (**122**): R₁ = 2,3-dimethylbutanoyl,
 R₂ = decanoyloxy, R₃ = OH

Compounds **123–131** exhibited molluscicidal activity. Amongst these, milliamine L (**131**) proved to be one of the most potent molluscicidal substances discovered to date under laboratory conditions.^{95–97}

Compounds **98** and **100** showed insecticidal activity.⁹⁸ Results suggest that both compounds could be used directly as natural pesticides or as lead ingredients for the control of

yuexiandajisu A
(142)

10-hydroxydepressin
(143)

144

brown plant hopper and two-spotted spider mite.⁸¹ Ingenol-3,20-diester 132–138 showed weak piscicidal activity.⁹⁹

- 132: R₁=COEt, R₂=H, R₃=2-MeBu
 133: R₁=H, R₂=H, R₃=COCHMe₂
 134: R₁=COEt, R₂=H, R₃=COCHMe₂
 135: R₁=COCHMe₂, R₂=H, R₃=COCHMe₂
 136: R₁=Ac, R₂=Ac, R₃=Ac
 137: R₁=H, R₂=H, R₃=2-MeBu
 138: R₁=COEt, R₂=COEt, R₃=COCHMe₂
 139: R₁=Ac, R₂=H, R₃=Ang
 140: R₁=Ang, R₂=H, R₃=Ac
 141: R₁=Ang, R₂=OAc, R₃=OAc

2.3.5 Tumor-promoting activity. Biological investigations revealed that euphorbia factor L₅ (93) and compounds 139 and 140 are tumor promoters.^{100,101}

2.3.6 Other activities. Kansuiphorin A (94) showed antiviral activity and it is suggested that this compound prevents viral pneumonia in mice.¹⁰² DBDI (122) inhibits degranulation in rat basophilic leukemia cells and results suggest that DBDI may have therapeutic potential for allergic diseases¹⁰³ and finally, compound 141 exhibits anti-angiogenic activity.¹⁰⁴

2.4 Casbanes†

Diterpenes with casbane skeletons are rarely found in plants. However, some have been isolated from plants of the *Euphorbia* genus.^{105–109}

2.4.1 Antimicrobial activity. Yuexiandajisu A (142) and 10-hydroxydepressin (143) exhibited antibacterial activity.¹¹⁰ Additionally, casbene 144 had an antimicrobial effect on planktonic forms and the biofilm arising from some bacteria and yeasts.¹¹¹

2.4.2 Cytotoxic activity. 10-Hydroxydepressin (143) and casbanes 145–154 were cytotoxic against cancer cell lines.^{106,109,112–115}

pekinenal (145): R=OH
 pekinenin F (146): R=H

microclavatin (147)

148: R=O
 agrostistachin (149): R=β-OH

agroskerin
(150)

pekinenin A (151): R=CH₂OH
 pekinenin C (152): R=CHO

pekinenin D (153): R=CHO
 pekinenin E (154): R=COOH

2.4.3 Other activities. Yuexiandajisu B (155) inhibited the proliferation of B lymphocytes.¹⁰⁸

2.5 Jatropholanes†

2.5.1 Antimicrobial activity. Sikkimenoid (156) demonstrated inhibitory activity against the microorganisms *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus epidermidis*.¹¹⁶

Malaria is one of the most common parasitic infections worldwide. *Plasmodium falciparum*, a protozoan parasite, is the most prevalent strain in Africa and also the most fatal.¹¹⁷ Jatropholone A (157) and compound 158 showed antiplasmodial activity against *Plasmodium falciparum*.¹¹⁸

2.5.2 Cytotoxic activity. Jatropholones A (157) and B (159) exhibited antitumor activity.^{119,120} Compound 160 was mildly cytotoxic against Vero cells.¹²¹ Moreover, falodone (161) strongly inhibited the proliferation of the A-549 human cancer cell line.¹²²

2.5.3 Gastroprotective activity. Jatropholones A (157) and B (159) showed biological activity as gastroprotectors. Compound 157 was less active than compound 159 in preventing the appearance of gastric ulcers but both reduced gastric lesions.¹¹⁸

2.6 Premyrsinanes†

2.6.1 Modulation of multidrug resistance. Premyrsinanes 162–165, isolated from *Euphorbia falcata*, act with a mild to very strong synergy with doxorubicin against the MDR mouse lymphoma cell line.^{123,124}

2.6.2 Neuroprotective activity. Euphorbiaproliferins I (166) and J (167) exhibited neuroprotective effects.¹²⁵

2.7 Euphoractine group†

Euphoractines are Natural Products that contain the rare 5-6-7-3 fused diterpene core obtained from a lathyrane skeleton by chemical cyclization.¹²⁶ The listed euphoractines showed no biological activities.^{127–130}

2.8 Other diterpenes†

Other compounds with a *gem*-dimethylcyclopropane in the structures have been isolated from many different sources. However, their structures do not belong to the above groups and were therefore placed together in this sub-group.

2.8.1 Antimicrobial activity. Rioloatrione (168) acts as an antibiotic against *Staphylococcus aureus*.¹³¹

2.8.2 Cytotoxic activity. The cytotoxicity of multifidone (169) was measured against the cancerous cell lines TPH-1, HL-60, A-375 and A-549.¹³²

3 Conclusions and future outlook

In summary, this comprehensive review covered the isolation of diterpenes containing this *gem*-dimethylcyclopropane and whose biological activities are enhanced. The *gem*-dimethylcyclopropane

ring remains intact in the biogenetic route leading to a large variety of secondary metabolites in many organisms. In fact, in these natural products the dimethylcyclopropyl unit remains as opposed to an isopropyl unit. This suggests the vital importance of this subunit in nature. Biological research on these *gem*-dimethylcyclopropane derivatives has lent credence to the use of some plants in traditional medicine. Furthermore, the secondary metabolism of these plants and of a group of micro-organisms, fungi or soft corals, revealed new activities for those compounds.

The study of the structure–activity relationships of these compounds has gained momentum in recent years, especially with the study of interactions with proteins kinase C and it is to be expected that this trend will continue in the years to come.

On the other hand, the massive genome sequencing projects of different types of organisms will lead to the discovery and identification of new cyclopropane-ring containing natural products and their biosynthetic gene clusters, which will help to unveil new terpene synthases and additional mechanisms for *gem*-dimethylcyclopropane ring formation.

We anticipate that this substantial number of diterpenoids containing the *gem*-dimethylcyclopropane ring could be used in the study of *in vivo* protein–NP interactions with the aim of designing new drugs. A deeper study of these biological interactions will reveal the role of this intriguing ring in the pathway of the modulation of diverse proteins kinase C and it will allow to modulate them. The occurrence of a wide range of diterpenoids with this feature or even derivatized products that have resulted in biological activities supports the biological potential of these structures. This is the main reason why they should deserve more attention. Therefore, these metabolites and those that will be isolated in the future as well as related compounds offer scope for development as potential therapeutic agents.

4 Abbreviations

2-MeBu	2-Methylbutanoyl
Ang	Angelate
Anth	Anthranoyl
Bz	Benzoyl
Cinn	Cinnamoyl
EBV	Epstein–Barr virus
HIV-1-	Human Immunodeficiency Virus-1-Long Terminal
LTR	Repeats
PKC	Protein Kinase C
PMA	Phorbol Myristate Acetate
Tig	Tiglate
TPA	Tetradecanoyl Phorbol Acetate

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