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EXPERT OPINION

Terpenes and derivatives as a new perspective for pain treatment: a patent review

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Introduction: Terpenes are natural compounds found in several organisms belonging to the animal and plant kingdoms. They constitute the largest class of natural products with > 55,000 known compounds structurally diversified. Several studies have attributed to this big family of compounds a range of pharmacological properties, such as anticancer, antimicrobial, antifungal, antiviral, antihyperglycemic, analgesic, anti-inflammatory and antiparasitic.
Areas covered: In this review, the authors summarize therapeutic patent applications concerning the employment of terpenes for pain relief, focusing on the perspective for these compounds to become candidates for new drugs intended to control painful syndromes.
Expert opinion: Over years of tremendous academic and industrial investment in the characterization of the analgesic action of terpenes, there was the development of a successful product that has been well-accepted clinically. Furthermore, there is still hope that new therapeutic options for the control of painful syndromes will be developed from terpenes, which have been shown to be great candidates for this purpose because of the range of pharmacological mechanisms in important target sites.

Keywords: analgesia, drugs, nociception, pain, terpene, terpenoid

Expert Opin. Ther. Patents (2014) 24(3):243-265

1. Introduction

A diversity of natural products derived from terrestrial plants, microorganisms, marine organisms and fungi has been an important source of medicinal products for millennia and has had its employment in the fields of medicine, pharmacy and general biology [1]. Drug development from natural products came from the isolation of early drugs, such as penicillins and morphine, of which some are still in use. Thus, plants and natural sources form the basis of today's modern medicine and continue to contribute largely to the commercial drug preparations manufactured today [2].

Thus, natural products continue to contribute to the development of clinically important agents against various diseases – HIV/AIDS, Alzheimer's disease, malaria and cancer – such as paclitaxel, vinblastine, vincristine and topotecan are important anticancer agents in widespread clinical use. The most recent example of an innovative drug obtained from natural products to treat pain is capsaicin (Qutenza®), a compound isolated from the chili peppers of the genus *Capsicum* and that which produces burning sensation on contact with tissues through binding to subtype-1 vanilloid receptor, which was approved by the FDA in November 2009, as a transdermal 8% patch for the treatment of neuropathic pain associated with post-herpetic neuralgia [3].

For this reason, it is believed that nature will continue to be a major source of new structural leads, and effective drug development depends on multidisciplinary collaborations, such as botanical, phytochemical, biological and molecular techniques [4].

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Article highlights.

- Academic research groups and pharmaceutical companies have patented analgesic properties of terpenes on different types of pain.
- Monoterpenes and sesquiterpenes are highlighted in this context and constitute the active principle of 'OTC drug' and phytomedications.
- Terpenes act through different mechanisms of conduction pathways and maintenance of pain and show satisfactory results in controlling chronic pain.
- However, further studies are still needed to enhance the viability of using these compounds for the development of new analgesic agents.
- Given the wide variety of terpenes derived from natural products and the need for new therapeutic options to control pain, there is a prospect that the terpenes continue to be the subject of research and source of new analgesics.
- The incorporation in drug delivery systems can be a useful tool to improve the chemical and pharmacological properties seeking to increase the range of clinical applications.

This box summarizes key points contained in the article.

1.1 Terpenes and their applications

Terpenes, also referred to as terpenoids or isoprenoids, constitute the largest class of natural products with > 55,000 known compounds structurally diversified [5].

These chemicals are part of the secondary metabolism of vegetal and animal species and are derived from C5 isoprene units joined in a head-to-tail fashion from two biosynthetic pathways, through the intermediates mevalonic acid or 1-deoxy-D-xylulose 5-phosphate. Typical structures contain carbon skeletons represented by (C5)n and are classified as hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30) and tetraterpenes (C40) [6].

Among the compounds from this group, many are extensively applied in the industrial sector as flavors, fragrances and spices and are also used in perfumery and cosmetic products, as well as food additives. In the pharmaceutical industry, in addition to being used as excipients to enhance skin penetration, they are also appointed as active principles of drugs. Growing interest in the clinical application of these compounds is assigned by the broad range of the biological properties of terpenoids that have been described, including cancer chemopreventive effects, antimicrobial, antifungal, antiviral, antihyperglycemic, analgesic, anti-inflammatory and antiparasitic activities [7].

The worldwide sales of terpene-based pharmaceuticals in 2002 were approximately US$12 billion. Among these pharmaceuticals, the anticancer (paclitaxel) and antimalarial (artemisinin) drugs are two of most renowned terpene-based drugs [8]. However, other terpenes are also highlighted in the pharmaceutical market, as menthol. This monoterpene is classified by the US FDA as a topical analgesic and it composes topical formulations of nonprescription analgesics or 'over-the-counter drug' (OTC), as Salonpas® (5.7% menthol, 1.12% camphor and 6.3% methyl salicylate), which are widely used in the United States and represent > $2 billion spent on each year [9].

1.2 Pain

A significant portion of the world population is affected by some kind of pain, causing loss of good quality of life [10]. Pain, recognized in some circumstances as a disease, is one of the most frequent reasons for visits to physicians, is among the most common reasons for taking medications and is also a major cause of work disability. Severe chronic pain affects physical and mental functioning, quality of life and productivity. Besides all that, it generates significant financial burden on affected individuals, as well as on their families, their employers, their friends, their communities and the nation as a whole [11].

The continued high prevalence of pain worldwide, associated to an increase in the many diseases which have pain as a symptom, drives the pharmaceutical market. Furthermore, with intensive incentive of research and development, it is expected that the analgesic drug market is going to be dynamic and commercially promising in the years ahead. Therefore, the development of treatments for pain relief has been the motivating factor behind many studies carried out by academic investigators and by the pharmaceutical industry in response to the demand for powerful analgesics, once they exhibit their pharmacological response through new mechanisms of action and with less side effects [10].

Furthermore, for the analgesic drug development to succeed, it must be a continuum from target selection to animal studies and clinical trials with relevant, approvable end points linked directly to the pathophysiology of pain and the mechanism of action of the drugs [12]. Additionally, sales and 'blockbuster potential' are threatened by the broad market, generic drugs and by patent infringement. Henceforth, development costs, standards for safety and requirements for limited side effects are factors that contribute to the pharmaceutical market to continue seeking innovative drugs with great value aggregated.

In this review, the advancing of the movements in therapeutical patents devoted to the employment of terpenes for pain relief is demonstrated, focusing on the evaluation of their potential at each development status, and current condition about a perspective of these compounds to become candidates for new drugs intended to control pain.

2. Monoterpenes (C10) and sesquiterpenes (C15)

Monoterpenes and sesquiterpenes are the important constituents of volatile oils in the essential oil of several plants. However, the most abundant terpenes in essential oils are

monoterpenes, which account for about 90% of the oils. Diterpenes can be present when the essential oils are extracted with organic solvents [6]. Several studies have shown a variety of pharmacological properties for these compounds, among which the analgesic stand out, as it has been evidenced in reviews recently published by Guimarães *et al.* [13] and De Sousa [10].

This review reports analgesic properties of monoterpenes and sesquiterpenes described in 17 patents (**Table 1**). The earliest record of filing a patent regarding the therapeutic application of monoterpenes found dates back to 1988 [14]. Such invention describes the analgesic effect of turpentine, a mixture of terpenes wherein α-pinene (**1**) is the main constituent (**Figure 1**). Evidence of the analgesic activity of this compound was obtained by describing case studies of five patients affected with cuts, burns and abrasions, which were treated topically with turpentine (α-pinene) and vitamin E solution (70:30 or 50:50). A few hours after the treatment, the symptoms were relieved, probably due to the ability of this monoterpene to facilitate healing and reduce the swelling, pain and bleeding.

After 10 years, the company Seiwa Pharmaceutical patented an analgesic comprising incarvillateine (**2**), a monoterpene alkaloid (**Figure 2**), extracted from *Incarvillea sinensis* Lam [15]. Through a preclinical study, the inventors have shown that this compound (5 or 10 mg/kg, i.p.) was able to reduce nociception in both phases of the formalin test, suggesting an analgesic and anti-inflammatory effect.

The number of patent filings reporting the analgesic effect of monoterpenes and sesquiterpenes began to increase from the twenty-first century. Center pharmaceutical chemistry (Cuba) disclosed a patent about a terpene mixture present in *Mangifera indica*, comprising two monoterpenes: the β-elemene (**3**) and hinesol (**4**); three sesquiterpenes: the α-guaiene (**5**), aromadendrene (**6**) and ledol (**7**) and two triterpenes: the mangiferonic acid (**8**) and taraxerol (**9**) (**Figures 1, 3** and **4**). That invention describes the antioxidant and analgesic effects of the referred mixture that was tested through preclinical and clinical tests. Antioxidant activity was evaluated *in vitro* by lipidic peroxidation and spontaneous autoxidation, and the terpene mixture was able to inhibit 80% of lipidic peroxidation. These compounds decrease the nociception induced by formalin and acetic acid and the paw edema induced by carrageenan. Clinical studies were conducted with 160 patients affected by different kinds of neoplasias, which were treated with 300 mg (10 – 40% of terpenoids) coated tablets or with topical cream or ointment 2.4%. After 6 months of continuous treatment, patients showed improvement in general health and increased quality of life [16].

Papaprodromou (2001) [17] teaches about the use of a combination of natural herb oils and other ingredients for relief of pain. The invention mentioned corresponds to the topical preparations based on the essential oils of Oregano (*Origanum vulgare* L.) containing carvacrol (**10**) and thymol (**11**), oil of Laurel (*Laurus nobilis* L.), rich in 1,8-cineol (**12**) and oil of Myrtle (Myrtaceae), comprising limonene (**13**), α- and β-pinene (**1**, **14**) and cineole (**12**) (**Figure 1**). The compositions comprising oil of Oregano 90 – 95%, oil of Laurel 3 – 5% and oil of Myrtle 2% were topically applied in 17 patients with different types of pain associated with arthritis, migraine headaches, tissue injures, muscular aches, cancer and back pain. In general, the patients reported relieve of the pain and discomfort associated with their pathology.

Similarly, General Cosmetics Corp. patented other oil mixtures comprising peppermind oil 72 – 84% [menthyl acetate (**15**), menthol (**16**)], rosemary oil 5% [bornyl acetate (**17**), borneol (**18**)], eucalyptus oil 1 – 3% [1,8-cineol (**12**)], lemon oil 1 – 1.5% [citral (**19**), limonene (**13**)], orange oil 1 – 1.5% [limonene(**13**), citral (**19**), linalool (**20**)], camphor oil 0 – 3% [camphor (**21**)], aloe vera oil 5 – 15% and calendula oil 0 – 4% (**Figures 1** and **5**). After the topic application of this mixture on the abdominal region of a female with abdominal discomfort associated with premenstrual syndrome, pain relief was reported [18].

Soft gelatin capsule containing 15% of aromatic/terpenoid compounds of *Alpinia galanga* (Zingiberaceae), such as 1,8-cineol (**12**), α-pinene (**1**), β-pinene (**14**), limonene (**13**), α-terpineol (**22**), terpene-4-ol (**23**) and *trans*-β-farnesene (**24**), administered twice a day for 2 weeks, promoted alleviation of pain in five volunteer patients with osteoarthritis (**Figures 1** and **3**). Analgesic activity of this essential oil may be associated with its immunomodulatory effect, mediated by the inhibition of leukotriene C4 synthase and phosphodiesterase-IV [19].

Small [20] patented a viscous solution comprised mainly by menthol (**16**) (33.0%), α-pinene (**1**) (14.5%), 1,8-cineol (**12**) (5.6%), limonene (**13**) (1.8%), β-pinene (**14**) (1.7%), sabinene (**25**) (1.5%) and methyl salicylate (8.6%) (**Figure 1**). This preparation was tested in 210 patients affected by pain associated with several pathologies, such as osteoarthritis, metastatic cancer, injuries, tendon tears, rheumatoid arthritis, myositis, tendonitis, cervical spasm, lower back, herniated discs, spinal stenosis, osteoporotic and traumatic bone. In about 83% of those patients, the topical solution promoted pain relief, demonstrating that the composition was effective for the treatment of different modalities of pain.

Application of topical preparations containing menthol (**16**), farnesol (**26**) and vetiveryl acetate (**27**) (**Figures 1** and **3**) for use in the prophylaxis or treatment of pain was patented by Bothma *et al.* [21]. The benefits of these products were evidenced through the reporting of case studies involving nine patients with different types of pain, such as arthritis, muscle and joints pain. In general, the products tested containing those terpenes promoted on the average up to 90% improvement in pain and discomfort. In some cases, this effect was maintained for 24 h.

Another sesquiterpene that sparked interest from the pharmaceutical market was parthenolide (**28**) (**Figure 3**). This compound is presented in feverfew (*Tanacetum parthenium*) extract, and its analgesic activity was evaluated through case

Table 1. Monoterpenes and sesquiterpenes patented, their pharmacological properties, indications and development status.

Compound(s)	Inventor/company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
α-pinene	London and Gibson (USA)	USA	1988	A61L, A01N	Case studies (cuts, burns)	Treatment of cuts, burns and abrasions	Stop swelling and bleeding, and reduce pain	Turpentine (α-pinene) and vitamin E solution: 70:30 and 50:50
Incarvillateine: monoterpene alkaloid of *I. sinensis* Lam	Nakamura *et al.*, Seiwa Pharmaceutical (Japan)	EP	1998	A61K	Preclinical study: formalin test	Analgesic and anti-inflammatory	–	–
Terpenes of *M. indica*: Mangiferonic acid (15 – 30%) β-Elemene (5 – 10%) α-Guaiene (5 – 10%) Aromadendrene (5 – 10%) Hinesol (1 – 5%) Ledol (1 – 5%) Taraxerol (1 – 5%)	Nuñez Selles *et al.* Center pharmaceutical chemistry (Cuba)	WO	2000	A61K A23L	*In vitro* (antioxidant activity: lipidic peroxidation, spontaneous autoxidation) Preclinical (nociception induced by formalin and acetic acid, paw edema induced by carrageenan) Clinical (160 patients with neoplasias)	Treatment of degenerative diseases, anti-aging, pain	Stimulated NO production Inhibition of lipidic peroxidation	Topical cream and ointment 2.4% Coated tablets 300 mg of extract containing 10 – 40% of terpenoids
Oil of Oregano containing carvacrol and thymol Oil of Laurel containing 1,8-cineol Oil of Myrtle containing Limonene, pinene, cineole	Papaprodromou (Canada)	USA	2001	A61K	Case study of 17 patients with different types of pain associated with arthritis, migraine headaches, tissue injures, muscular aches, cancer and back pain	Relief of the pain and discomfort associated with arthritis, migraine headaches, tissue injures, muscular aches and back pain	–	Topic application of compositions 1: oil of Oregano 95%, oil of Laurel 3%, oil of Myrtle 2%. compositions 2: oil of Oregano 90%, oil of Laurel 5%, oil of Myrtle 2%, olive oil 3% (diluents)
Eucalyptus oil (1,8-cineol) Lemon oil (citral, limonene) Orange oil (limonene, citral, linalool)	Weise, General Cosmetics Corp. (USA)	USA	2002	A61K A01N	Case study: female with abdominal discomfort associated with premenstrual syndrome	Pain relief associated with premenstrual syndrome	–	Topic application on abdominal region of Peppermind oil 72 – 84% Aloe vera oil 5 – 15% Rosemary oil 5% Lemon oil 1 – 1.5%

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Table 1. Monoterpenes and sesquiterpenes patented, their pharmacological properties, indications and development status (continued).

Compound(s)	Inventor/company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
Peppermind oil (menthyl acetate, menthol) Rosemary oil (bornyl acetate, borneol) Aloe vera oil Camphor oil (camphor) Calendula oil								Orange oil 1 – 1.5% Eucalyptus oil 1 – 3% Camphor oil 0 – 3% Calendula oil 0 – 4%
Essential oil of *Alpinia galanga*: 1,8-cineol α- and β-pinene Limonene α-terpineol Terpene-4-ol *trans*-β-farnesene	Weidner *et al.*, Enrovita A/S Ferrosan A/S (Denmark)	USA	2003	A61K	*In vitro* studies (evaluating the inhibitory effect of leukotriene C4 synthase, 5-lipoxygenase and phosphodiesterase-IV), Case studies in five volunteers with osteoarthritis (two capsules a day for 2 weeks)	Alleviation of pain	Immunomodulation: inhibitory activity of leukotriene C4 synthase and phosphodiesterase-IV	Soft gelatin capsule containing 15% of aromatic/terpenoid compounds of *A. galanga*
Menthol α- and β-pinene Limonene 1,8-cineol Sabinene	Small R (USA)	USA	2004	A61K	Clinical study: 210 patients with pain associated with the: osteoarthritis, metastatic cancer, injuries, tendon tears, rheumatoid arthritis, myositis, tendonitis, cervical spasm, lower back, herniated discs, spinal stenosis, osteoporotic, traumatic bone	Relieve pain in human	–	Viscous solution: Acetone (25.0%) Methyl salicylate (8.6%) Menthol (33.0%) α-pinene (14.5%) 1,8-cineol (5.6%) Limonene (1.8%) β-pinene (1.7%) Sabinene (1.54%)
Farnesol Vetiveryl acetate Menthol	Bothma *et al.*, Zelpy 2549 Ltd. (South Africa)	WO	2007	A61P	Case studies of nine patients with different types of pain	Treatment of pain	–	Topical preparations containing: *Cedrus atlantica* wood oil (2 – 30%) and menthol (1%)

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Table 1. Monoterpenes and sesquiterpenes patented, their pharmacological properties, indications and development status (continued).

Compound(s)	Inventor/company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
								Zingiber officinale root oil (8%) and menthol (1%) Vetiveryl acetate (7%) Farnesol (3%) and Vetiveria zizanoids root oil *Z. officinale* root oil (8%) and trolamine salicylate (10%) Menthol (1.5%) Farnesol (4%) Menthol (1.5%) and farnesol (4%) *C. atlantica* wood oil (2 – 30%) and methyl salicylate (10%)
Sweroside	Kwak *et al.*, SK Chemicals Co., Ltd. (Republic of Korea)	USA	2008	A01K	Preclinical study: Acetic acid induced writhing test, croton oil and arachidonic acid-induced ear edema	Treatment of inflammatory and pain	–	Tablet (160 mg) Syrup (4000 mg) Injection ampoule (20, 50 or 100 mg) Ointment (5 g)
Several monoterpenes as: linalool, menthone Borneol, nerol and neral Citronellol, geraniol Myrcene, *p*-cymene Limonene, 1,8-cineole Camphor	McLellan, Origin Biomed, Inc. (Canada)	WO	2010	A61K A61P	Clinical study: Individuals with diagnosed neuropathic pain	Treatment of neuropathic pain	–	External application of a composition homeopathic containing *Hypericum perforatum* combined with essential oil mixture of lavender, pelargonium, bergamot, eucalyptus and tea tree oil.

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Table 1. Monoterpenes and sesquiterpenes patented, their pharmacological properties, indications and development status (continued).

Compound(s)	Inventor/company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
Geranium essential oil: Citronellol (19.899%) Geraniol (18.00%) β-phellandrene (12.47%) Linalool (10.23%) Citronellyl formate (8.30%) Isomenthone (7.53%) Geraniol and citronellol	McLellan *et al.* (Canada)	USA	2011	A61K	*In vitro* studies (patch clamp electrophysiological recordings), human clinical trials (64 patients with neuropathy) Case study (post-herpetic neuralgia)	Treatment of neuropathic pain	Inhibit nerve transmission in cortical nerve cells and dorsal root ganglion cells	Topical cream with 28% by volume of geranium essential oil Topical application of pure geraniol
Geranium essential oil	McLellan *et al.* (Canada)	USA	2011	A61K, A61P	*In vitro* studies (patch clamp electrophysiological recordings), Case studies (headaches, diabetic neuropathy)	Treatment of negative sensory phenomena, idiopathic neuropathy, headaches, diabetic neuropathy	Inhibition of action potential	Drops of geranium oil: Linalool (17.58%) Linalyl acetate (16.63%) 1,8-Cineole (12.26%) Terpinen-4-ol (7.60%) Citronellol (6.23%) Geraniol (4.42%) Limonene (4.66%) Citronellyl formate (2.59%) Isomenthone (2.33%)
Synthetic derivatives of geraniol	Reed *et al.* Neuroquest, INC (Canada)	WO	2012	A61K, A61P	*In vitro* studies (patch clamp electrophysiological recordings) Zebrafish anesthesia assay TRPV1 assay (calcium imaging)	Treatment of neuropathic pain	Reduce membrane currents by inhibitory effect on Na^+ channels currents in dorsal root ganglion neuron, inhibit touch response in zebrafish, effect on TRPV1	–

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Table 1. Monoterpenes and sesquiterpenes patented, their pharmacological properties, indications and development status (continued).

Compound(s)	Inventor/company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
(2-Methyl-2-(4-methyl-pent-3-en-1-yl)cyclo-propyl)methanol	McLellan *et al.* Neuroquest, INC (Canada)	WO	2013	A61K A61P C07C	Preclinical study: Na^+ channel analysis in rat DRG neurons using whole cell patch-clamp techniques, zebrafish response assay, TRPV1 assay protocol-calcium imaging	Treatment of pain and neuropathic pain	Blockade Na^+ channels, TRPV1 agonist	–
Feverfew (*Tanacetum parthenium*) extract containing Parthenolide	Mitchell *et al.* GelStat Corp. (USA)	USA	2007	A61K	Case studies: 11 patients with migraine headaches. Double-blind randomized: 48 subjects with moderate-to-severe migraine headache pain	Relieve the pain	–	Sublingual administration of a fluid with the following composition: 4 mg feverfew extract standardized to 1.2% parthenolide (0.024 mg) 1.2 mg ginger 62.5 mg L-theanine Sorbitol, Glycerin, Carrageenan, Ascorbic acid Potassium sorbate
α-humulene *Trans*-caryophyllene	Pianowski *et al.* Aché Pharmaceutical Laboratories S.A. (Brazil)	EP	2011	A61K A61P	Preclinical study: inflammatory nociception induced by carrageenan (quantification of IL-1β, TNF-α, PGE_2), edema induced by carrageenan, histamine, bradykinin, arachidonic acid, inhibition of the expression of enzymes COX-2 and iNOS	Inflammation and inflammatory pain	Inhibition of PGE_2, IL-1β and TNF-α release, COX-2 and iNOS expression	–
Huperzine A	Schachter President and Fellows of Harvard College (USA)	US	2012	A61K	Preclinical study: nociception induced by formalin	Alleviate neuropathic pain	–	–

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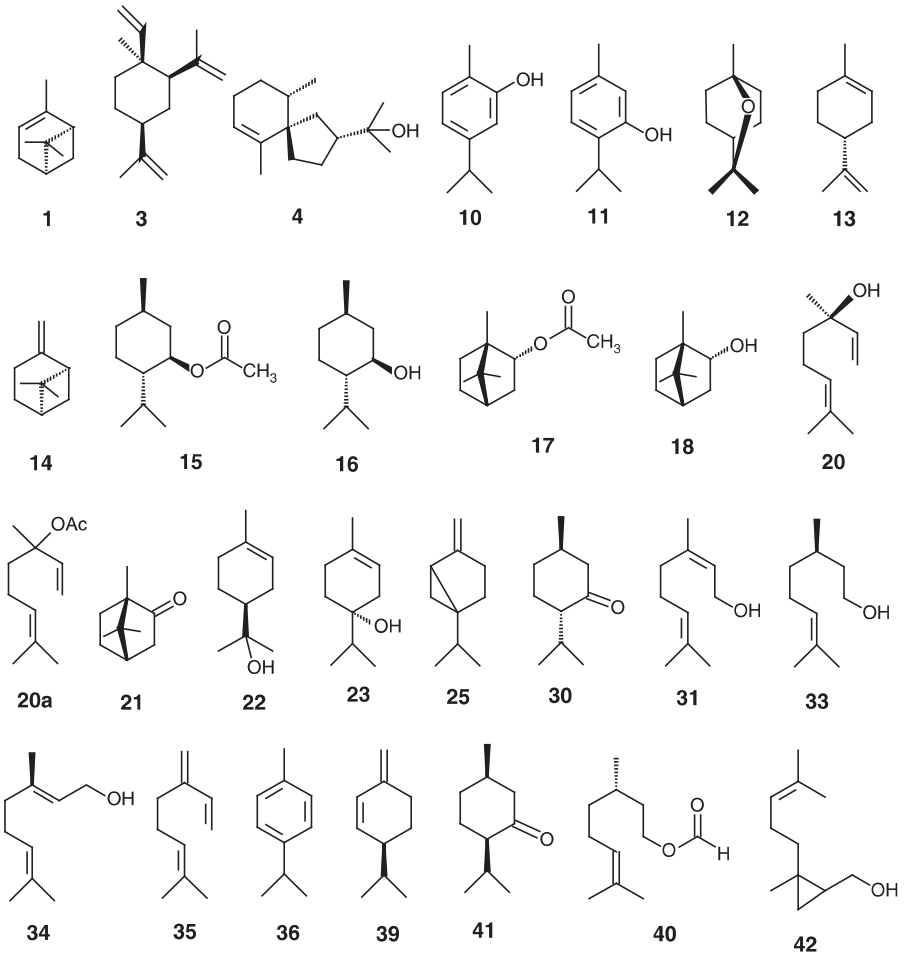


Figure 1. Chemical structures of monoterpenoids.

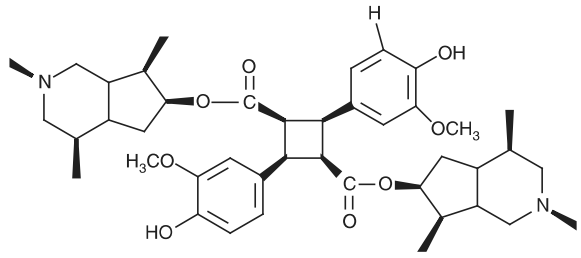


Figure 2. Chemical structure of incarvillateine, a monoterpene alkaloid (2).

studies involving 11 patients with migraine headaches, and double-blind randomized with 48 subjects with moderate-to-severe migraine headache pain. Sublingual administration of a fluid containing 4 mg feverfew extract standardized to 1.2% parthenolide (0.024 mg), 1.2 mg ginger, 62.5 mg L-theanine and other excipients promoted significant pain relief [22].

In 2008, SK Chemicals Co., Ltd. purposed formulations composed of sweroside (**29**) (**Figure 6**), a monoterpene iridoid, as anti-inflammatory and analgesic drugs [23]. In this finding, the analgesic effect was observed through a preclinical study. Sweroside reduced nociception induced by acetic acid and decreased the edema induced by croton oil and arachidonic acid. From these results, pharmaceutical formulations have been suggested as tablet (160 mg), syrup (4000 mg), injection ampoule (20, 50 or 100 mg) and ointment (5 g), which present as active agent of the monoterpene referred.

McLellan has reported a series of potent analgesics. In 2010, McLellan [24] developed a homeopathic formulation containing *Hypericum perforatum* combined with essential oil mixture of lavender, pelargonium, bergamot, eucalyptus and tea tree oil for the treatment of neuropathic pain. In two double-blind randomized clinical trials with 14 and 60 subjects diagnosed with neuropathic pain, the treatment with the homeopathic/essential oil composition in topic spray resulted in a statistically significant reduction in spontaneous pain which was in effect within 30 min and lasted ~ 8 h. There is a case study involving a patient with diabetic

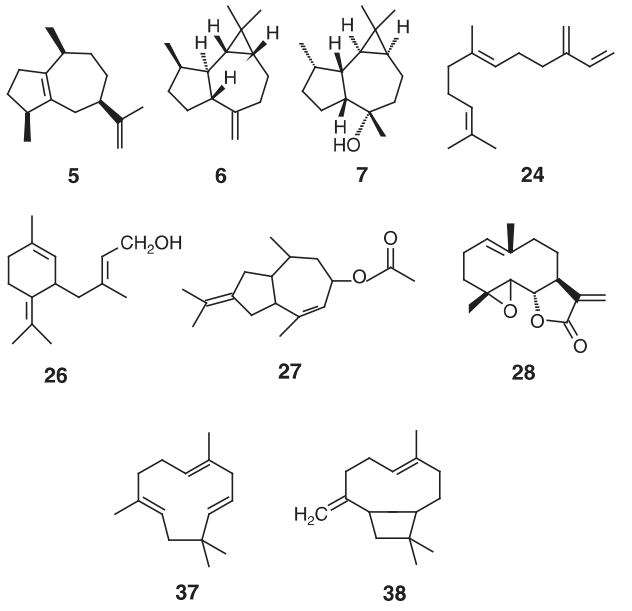


Figure 3. Chemical structures of sesquiterpenes.

neuropathy on the left foot, treated with a thin film of a cream consisting of 1% homeopathic ingredients (equal parts of *H. perforatum*, *Aconitum napellus*, *Secale cornutum*, *Rhus toxicodendron*, *Lycopodium* and phosphorus all at 12C potency) prepared in a non-medicinal cream base. Her right foot was treated with a thin film of the same 1% homeopathic ingredients prepared in a base consisting of an essential oil mixture of 28.29% v/v lavender, 28.29% v/v *Pelargonium graveolens*, 14.14% v/v *Citrus bergamia*, 14.4% v/v *Eucalyptus globulus* and 14.14% v/v *Melaleuca alternifolia*. The patient experienced a greater relief of pain in the right limb. A similar effect was observed in a patient with post-herpetic neuralgia who reported a greater pain relief with the preparation containing monoterpenes as linalool (**20**), menthone (**30**), borneol (**18**), nerol (**31**) and neral (**32**), citronellol (**33**), geraniol (**34**), myrcene (**35**), *p*-cymene (**36**), limonene (**13**), 1,8-cineol (**12**) and camphor (**21**) (**Figures 1** and **5**).

In patent application of Pianowski *et al.* [25] α-caryophyllene (**37**) and β-caryophyllene (**38**) are cited in the control of inflammation and pain inflammatory (**Figure 3**). Aché Pharmaceutical Laboratories S.A (Brazil) evaluated caryophyllenes effects on preclinical study and demonstrated that α-caryophyllene (**37**), also known as α-humulene, was able to reduce inflammatory nociception induced by carrageenan and edema induced by carrageenan, histamine, bradykinin and arachidonic acid, even when applied topically. Caryophyllenes also inhibited the production of proinflammatory cytokines, such as IL-1β, TNF-α, the growth of PGE_2 levels, and the COX-2 and iNOS expression.

In 2011, McLellan and Greenway patented a therapeutic application of geranium essential oil, extracted from *P. graveolens*, for the treatment of neuropathic pain, negative sensory phenomena and headaches [26,27]. Geranium oil is composed mainly by of citronellol (**33**), geraniol (**34**), terpinen-4-ol (**23**), linalool (**20**), linalyl acetate (**20a**), phellandrene (**39**), 1,8-cineole (**12**), limonene (**13**), citronellyl formate (**40**) and, isomenthone (**41**) (**Figure 1**). The pharmacological effect of this oil was evaluated through a topical cream with 28% volume of geranium essential oil or pure geraniol in human clinical trials with 64 patients with neuropathy and cases studies involving patients with post-herpetic neuralgia, headaches or diabetic neuropathy. By means of *in vitro* studies (patch clamp electrophysiological recordings), the authors verified that geranium oil and some of their compounds isolated, as geraniol (**34**) and citronellol (**33**) (**Figure 1**), inhibited nerve transmission in cortical nerve cells and dorsal root ganglion cells.

The analgesic effect of geranium oil has already been patented in the US patent by Frome [28] from National Pain Institute (USA). They demonstrated that topical application of geranium oil promoted 80 – 100% reduction in pain, in a clinical study performed with 200 patients exhibiting neuropathic pain.

From geraniol (**34**), Reed *et al.* [29] and McLellan *et al.* [30] produced several synthetic derivatives for treatment of neuropathic pain. Through *in vitro* studies, they assessed the analgesic effect of these compounds, which reduce membrane currents through an inhibitory effect on sodium channel currents in dorsal root ganglion neuron, inhibit touch response in zebrafish and have demonstrated agonist or antagonist effect of transient receptor potential vanilloid type 1 channel (TRPV1). The compound (2-methyl-2-(4-methylpent-3-en-1-yl)cyclopropyl)methanol (**42**) demonstrated TRPV1 agonist effect and greater effectiveness in reduced touch response and spontaneous coiling in zebrafish, which are correlated with analgesic activity (**Figure 1**).

An academic group at Harvard College has protected patent on analgesic activity of huperzine A (**43**) (**Figure 7**), a sesquiterpene alkaloid [31]. Through preclinical study, it was possible to verify that this compound significantly decreased nociception induced by formalin, in phases mediated by central and inflammatory mechanisms.

3. Diterpenes (C20)

Diterpenes represent a large group of terpenoids with a wide range of biological activities, isolated from a variety of organisms [8]. Among the most important clinical diterpenes stands paclitaxel (Taxol®), an important anticancer agent, with a broad spectrum of activity against some cancers that do not respond to other agents [6].

In this review, three patents on diterpenes application for the treatment of pain are discussed (**Table 2**). The oldest patent found in the search concerning the use of diterpenes for pain control was performed by an academic group at University of California (USA). In 1989, Jacobs and Fenical [32] demonstrated through a preclinical study that pseudopterosin

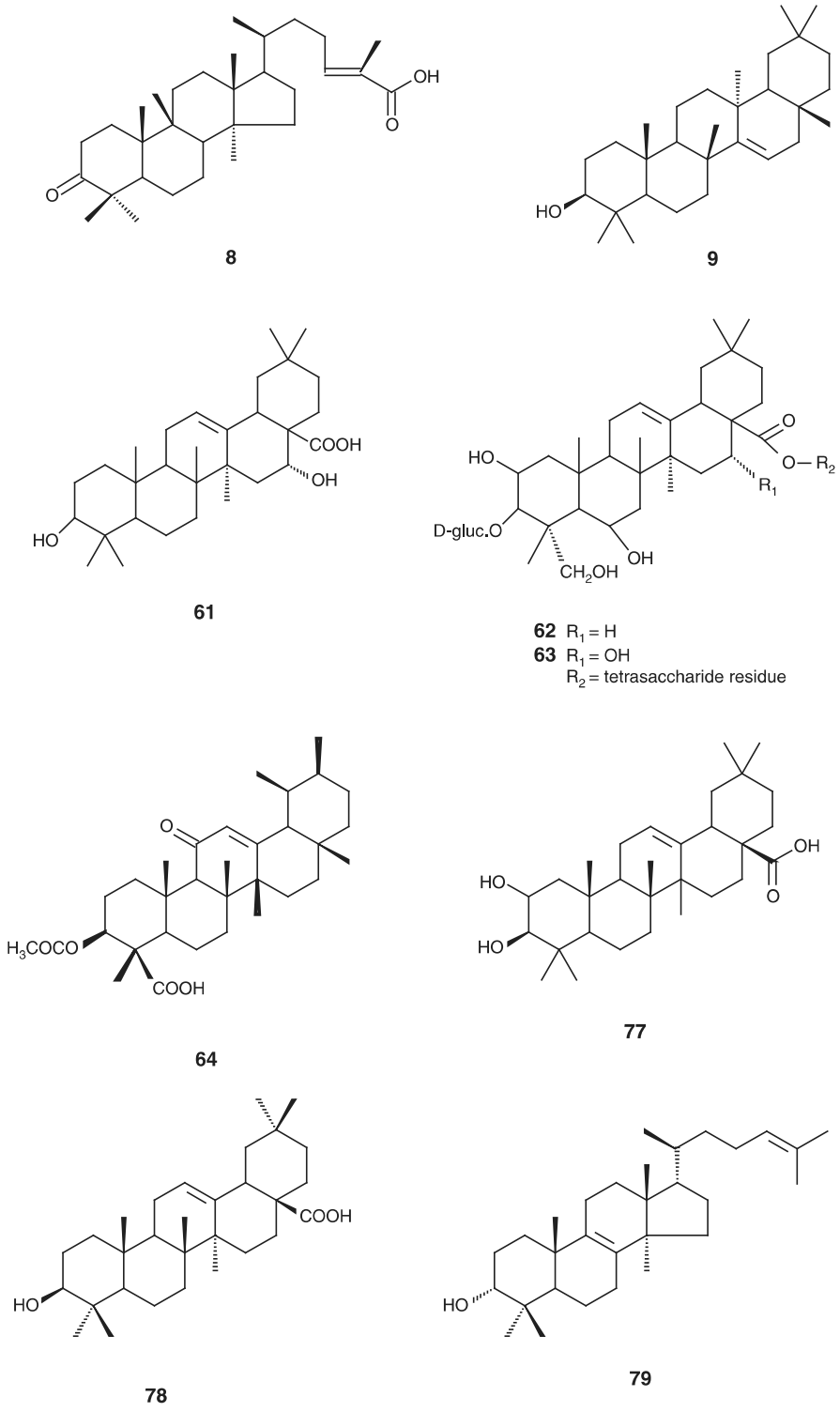
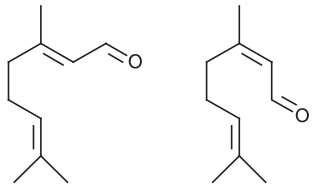


Figure 4. Chemical structures of triterpenes.

A (**44**), a diterpene isolated from *Caribbean gorgonians* of the genus *Pseudopterogorgia*, and synthetic analogs (**45 – 50**), reduced nociception caused by phenylquinone and ear edema induced by phorbol myristate acetate. After 13 years, the same group protected the application of novel pseudopterosins, seco-pseudopterosins, diterpene aglycones and tricyclic diterpene derived from *Pseudopterogorgia elisabethae*, as pseudopterosin M (**51**), N (**52**) and O (**53**), seco-pseudopterosin



19a 32

Figure 5. Chemical structure of citral (19), a mixture of geranial (*trans*-citral) (19a) and neral (*cis*-citral) (32).

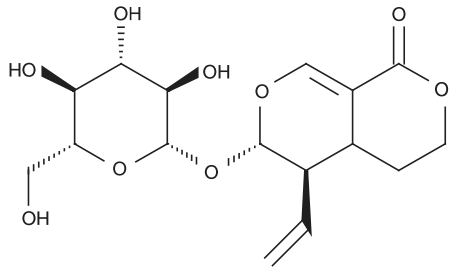


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Figure 6. Chemical structure of sweroside, a monoterpene iridoid (29).

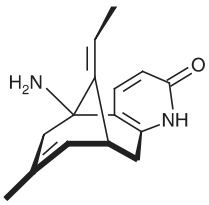

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Figure 7. Chemical structure of huperzine A, a sesquiterpene alkaloid (43).

E (54), F (55) and G (56), elisabethadione (57) and elisabethadiol (58) (**Figure 8**). These diterpenes showed analgesic and anti-inflammatory effects on preclinical studies performed on rodents [33].

Analgesic and anti-inflammatory properties of diterpene glycosides (59, 60) isolated from the fruit of the genus *Capsicum* were protected by BMB Patent Holding Corp. (USA) (**Figure 9**). This report describes analgesic and anti-inflammatory effects of these compounds on hypernociception induced by capsaicin and mouse air pouch assay [34].

4. Triterpenes (C30)

A wide range of pharmacological activities of triterpenes have been reported in literature and were recently reviewed by Parmar *et al.* [35], including its application on control pain. Among the various therapeutic applications of these terpenes stand out the pain control and treatment. In the search performed on the banks of patents, it was possible to find nine patents on the analgesic properties of triterpenes (**Table 3**).

The oldest record found dates back to 1979 [36], which matches a report on analgesic and anti-inflammatory effects of an extract rich in triterpenic constituents and that contains a glycoside of echinocystic acid (61) as major component (**Figure 4**). Laboratories Sarget (France) verified that these triterpenes reduced nociceptive responses in writhing induced by phenyl *p*-benzoquinone and hot plate test; all these testes are screening protocols. Besides, the extract also inhibited the inflammatory response induced by carrageenan and croton oil.

After 10 years, a second deposit was made by Sigma-Tau pharmaceutical industry [37]. Analgesic and anti-inflammatory effects of triterpene saponins isolated from roots and back of *Crossopteryx febrifuga*, as crossoptine A (62) and crossoptine B (63), was observed in a preclinical study using phenylguinone writhing and carrageenan edema test (**Figure 4**). This report also proposes the development of pharmaceuticals formulations, such as ointment and tablets containing 1% and 20 mg of triterpenes, respectively.

In 2008, Gokaraju *et al.* [38] patented an enriched extract containing 3-*O*-acetyl-11-keto-β-boswellic acid (AKBA, 64), a triterpene from *Boswellia serrata*, and its use for treatment of pain associated with inflammatory disease (**Figure 4**). The extract reduces inflammatory pain and edema induced by Freund's complete adjuvant (CFA), inhibits nitrite and IL-1β release and 5-LOX activity. From these data, the inventors suggested the use of dietary supplement enriched with AKBA extract, curcuminoids in different proportions for the treatment of inflammatory diseases and joint pain.

Application of pulchinenoside (65) and synthetic derivatives DA021 (66) and DA034 (67) (**Figure 10**) against pain and inflammation was patented by Biotechnology Research Corp. (China) [39]. Preclinical study *in vitro* and *in vivo* demonstrated that these triterpenes have antagonist effect of *N*-methyl-D-aspartate receptor (NMDA), melanocortin and PGE_2 receptors, contributing to pain and inflammation control.

An academic group at Hong Kong Baptist University (China) patented the use of triterpene glycosides from the root of *Ilex paraguariensis* for treatment of inflammation and pain [40]. Triterpene glycosides fraction reduces nociception induced by chemistry and thermal stimuli and decreases edema induced by carrageenan and histamine. After the isolation of major triterpenes, a pharmaceutical composition was proposed, comprising chikusetsusaponin-IVa (20 – 42%) (68), ilexsaponin B2 (18 – 28%) (69), ilexsaponin B3 (16 – 20%) (70), ilexsaponin A1 (13 – 17%) (71), pubescenoside C (10 – 20%) (72) and pubescenoside D (1 – 4%) (73) (**Figure 11**).

Griffith University in partnership with Jarlmadangah Buru Aboriginal Corp. (Australia) filed a patent related to the analgesic effect of barringtogenol C (74), a triterpene obtained from plants of the barringtoside species, and its synthetic

Table 2. Diterpenes patented, their pharmacological properties, indications and development status.

Compound(s)	Inventor/ company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
Pseudopterosin A and analogs	Jacobs and Fenical, University of California (USA)	USA	1989	A61K, C07H	Preclinical study: Mouse ear anti-inflammatory assay, phenylquinone assay for analgesia	Alleviation of pain	–	–
Pseudopterosin M, N and O Seco-pseudopterosin E, F and G Elisabethadione Elisabethadiol	Jacobs and Keer, University of California (USA)	WO	2002	C07H	Preclinical study: Phenylquinone assay for analgesia, mouse ear anti-inflammatory assay	Treatment of pain and inflammation	–	–
Diterpenes monoglycosides and diglycosides isolated from the fruit of the genus *Capsicum*	Belgorod BMB Patent Holding Corp. (USA)	WO	2008	A61K A61P	Preclinical study: hypernociception induced by capsaicin; mouse air pouch assay	Treatment of pain and inflammation	–	–

A61K: Preparations for medical purposes, dental or hygienic; A61P: Therapeutic activity specific chemicals or preparations medical; C07H: Sugar and their derivatives; nucleoside; nucleotides; nucleic acids and derivatives; IPC: International Patent Classification; WO: World Intellectual Property Organization.

derivatives I (75) and II (76) (**Figure 12**). These triterpenes were able to reduce the inflammatory pain induced by CFA, which was evaluated through paw pressure test. Besides, such compounds also decreased paw volume [41].

Analgesic and anti-inflammatory activities of maslinic acid (77) and oleanolic acid (78) were protected by Prados *et al.* [42] from Granada University (Spain) (**Figure 4**). These triterpenes inhibit PGE_2 and IL-6 production, COX-2 activity. Furthermore, two pharmaceuticals formulations were proposed, a cream and a lotion for topical use containing 0.5 – 2.5% of maslinic and oleanolic acids, which relieved pain and increased the flexibility of cartilage in 43 patients with arthrosis, fibromyalgia and other musculoskeletal syndromes.

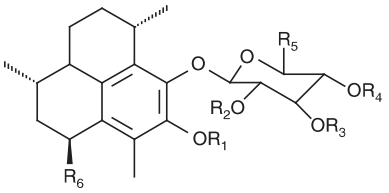
A more recent patent reports the antinociceptive effect of maslinic acid (77) in rodents (**Figure 4**). Nieto López *et al.* [43] also from the Granada University (Spain) verified that maslinic acid decreases the nociception induced by acetic acid, hot plate and the mechanic allodynia induced by capsaicin. Moreover, a formulation of hydrogel maslinic acid 1% was suggested which, after topic application, reduced the nociception induced by formalin in 47% of patients. Thus, this study corroborates with the results protected by Prados *et al.* [42], demonstrating the benefit of maslinic acid for the management of inflammatory or neurogenic pain.

Recently, Amazonia Fitomedicamentos LTDA (Brazil) patented an invention related to the pharmaceutical use of lanosta-8,24-dien-3-ol (79), a tetracyclic terpene obtained from Euphorbiaceae plants or through chemical synthesis, as anti-inflammatory, analgesic and anticancer agent (**Figure 12**). This terpene was able to reduce inflammatory nociception induced by carrageenan, CFA and the neuropathic pain induced by partial sciatic nerve constriction, suggesting the use of this compound for chronic pain treatment [44].

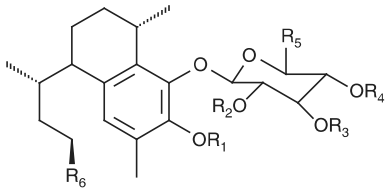
5. Terpenophenolics: cannabinoids (C21)

These special terpenes are found in herbs of Indian hemp, the *Cannabis sativa* (Cannabaceae) also popularly known as hashish or marijuana and have been used for centuries for the pleasurable sensations and mild euphoria experienced after its consumption, usually by smoking. Cannabinoids are metabolites of mixed origins and their structure contains a monoterpene unit (C10 – mevalonic origin) attached to a phenolic ring (C6) that carries a C5 alkyl chain (polyketide origin), being classified as terpenophenolics [6].

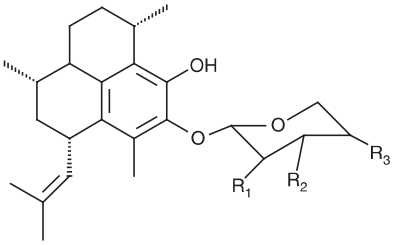
In the search performed, we found a patent describing the application of a topical preparation containing cannabinoids for pain relief and reduced inflammation (**Table 4**). A topical composition containing about 0.5% – 2.5% of a synergistic cannabinoid mixture extracted from the female plant *C. sativa* L., including in combination: 9-tetrahydrocannabinol (9-THC; **80**), 9-THC propyl analog (**81**), cannabidiol (**82**), cannabidiol propyl analog (**83**), cannabinol (**84**), cannabichromene (**85**), cannabichromene propyl analog (**86**), cannabigerol (**87**), terpenoids and flavonoids (the latter were not



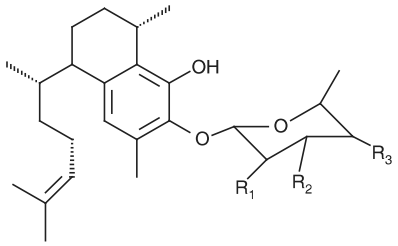
44 R_1-R_5 = H; R_6 = 2-methyl-1-propene
45 R_1, R_3, R_4, R_5 = H; R_2 = acetate; R_6 = 2-methyl-1-propene
46 R_1-R_4 = acetate; R_5 = H; R_6 = 2-methyl-1-propene
47 R_1-R_5 = H; R_6 = 2-methyl-1-propenemoxide
48 R_1-R_5 = H; R_6 = 2-methylpropane



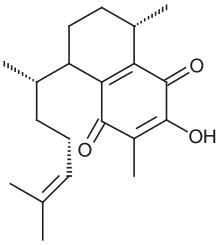
49 R_1, R_3, R_4, R_5 = H; R_4 = acetate; R_6 = 2-methyl-1-propene
50 R_1-R_5 = H; R_6 = 2-methyl-1-propene



51 R_1 = AcO; R_2 and R_3 = OH
52 R_1 = OH; R_2 = AcO; R_3 = OH
53 R_1 and R_2 = OH; R_3 = AcO



54 R_1 = AcO; R_2 and R_3 = OH
55 R_1 = OH; R_2 = AcO; R_3 = OH
56 R_1 and R_2 = OH; R_3 = AcO



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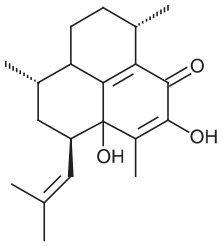

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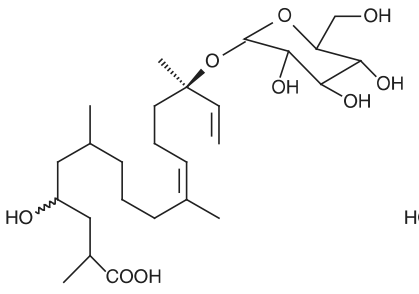
Figure 8. Chemical structures of diterpenes.



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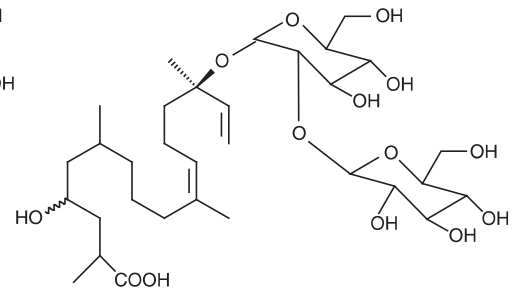

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Figure 9. Chemical structures of diterpenes monoglycoside (59) and diglycosides (60) isolated from the fruit of the genus *Capsicum*.

Table 3. Triterpenes patented, their pharmacological properties, indications and development status.

Compound(s)	Inventor/company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
Extract rich in triterpenic constituents and contains as major a glycoside of echinocystic acid	Fauran *et al.*, Laboratories Sarget (France)	USA	1979	A61K	Preclinical study: Writhing induced by phenyl *p*-benzoquinone; hot plate test; paw edema induced by carrageenan; ear edema induced by croton oil	Treatment of pain and inflammation	_	_
Triterpene saponins of *C. febrifuga*: Crossoptine A Crossoptine B	Foresta *et al.* Sigma-Tau pharmaceutical industry (Italy)	USA	1989	A61k	Preclinical study: Carrageenan edema test Phenylguinone writhing test	Anti-inflammatory, analgesic and mucolytic activities	–	Ointment 1% Tablets containing 20 mg
Enriched extract with AKBA	Gokaraju *et al.* (India)	WO	2008	A61K A23L	Preclinical study (*in vitro* and *in vivo*): 5-LOX inhibitory activity, inflammatory pain induced by CFA (nitrite, IL-1β, and paw volume)	Treatment of inflammatory disease	5-LOX inhibition	Dietary supplement containing enriched extract with AKBA, curcuminoids in different proportions
Pulchinenoside and derivatives (DA021 and DA034)	Ip *et al.*, Biotechnology Research Corp. (China)	USA	2011	A61K A61P C07C	Preclinical study (*in vitro* and *in vivo*): LPS-induced cytokine production; oxazolone-induced ear edema; hippocampal/cortical survival assay against NMDA, glutamate and kainite excitotoxicity; experimental autoimmune encephalomyelitis (quantification of cytokine levels)	Against pain and inflammation	NMDA, melanocortin and PGE_2 receptors antagonists	_
Triterpene saponins from the root of Ilex paraguariensis	Liu *et al.* Hong Kong Baptist University (China)	USA	2009	A61K	Preclinical study: Acetic acid-induced writhing, tail flick, carrageenan- and histamine-induced paw edema	Treatment of inflammation and pain	_	Pharmaceutical composition comprising: Chikusetsusaponin-IVa (20 – 42%) Ilexsaponin B2 (18 – 28%) Ilexsaponin B3 (16 – 20%) Ilexsaponin A1 (13 – 17%) Pubescenoside C (10 – 20%) Pubescenoside D (1 – 4%)

A61K: Preparations for medical purposes, dental or hygienic; A61P: Therapeutic activity specific chemicals or preparations medical; C07C: compound or acyclic carbocyclic; C07H: sugar and their derivatives; nucleoside; nucleotides; nucleic acids and derivatives; CFA: Freund's Complete Adjuvant; IL-1β: Interleukin-1 beta; IL-6: Interleukin 6; IPC: International Patent Classification; LPS: Lipopolysaccharide; MX: México; NMDA: *N*-methyl-D-aspartate receptor; PGE_2: Prostaglandin E2; USA: United States of America; WO: World Intellectual Property Organization.

Table 3. Triterpenes patented, their pharmacological properties, indications and development status (continued).

Compound(s)	Inventor/company (country)	Country of protection	Year	IPC	Development status	Indication	Action mechanism	Formulation
Barringtogenol C derivatives I and II	Quinn and Mills Griffith University, Jarlmadangah Buru Aboriginal Corp. (Australia)	USA	2009	A61K A61P C07H	Inflammatory pain induced by CFA (paw pressure test and paw volume)	Treatment and control of pain	–	–
Maslinic acid Oleanolic acid	Prados *et al.* Granada University, Biomaslinic S.I. (Spain)	WO	2009	-	Preclinical study: LPS-induced PGE_2 and COX-2 production IL-1-induced PGE_2 and IL-6 Clinical study: 43 patients with artrose, fibromialgia and others diseases	Treatment of disorders associated with COX-2 activation	Inhibition of PGE2, IL-6 production, COX-2 activity	Cream and lotion to topical use containing 0.5 – 2.5% of maslinic and oleanolic acids
Maslinic acid	Nieto López *et al.* Granada University (Spain)	WO	2011	-	Preclinical study: Nociception induced by formalin and acetic acid, hot plate test, mechanic allodynia induced by capsaicin, Rota rod test	Treatment of inflammatory or neurogenic pain	–	Hydrogel maslinic acid 1%
Lanosta-8,24-dien-3-ol	Pianowski Amazon Phytomedicine LTDA (Brazil)	MX	2011	A61K A61P	Preclinical study: inflammatory nociception induced by carrageenan, CFA, neuropathic pain induced by partial sciatic nerve constriction	Treatment of pain	–	–

A61K: Preparations for medical purposes, dental or hygienic; A61P: Therapeutic activity specific chemicals or preparations medical; C07C: compound or acyclic carbocyclic; C07H: sugar and their derivatives; nucleoside; nucleotides; nucleic acids and derivatives; CFA: Freund's Complete Adjuvant; IL-1β: Interleukin-1 beta; IL-6: Interleukin 6; IPC: International Patent Classification; LPS: Lipopolysaccharide; MX: México; NMDA: *N*-methyl-D-aspartate receptor; PGE_2: Prostaglandin E2; USA: United States of America; WO: World Intellectual Property Organization.

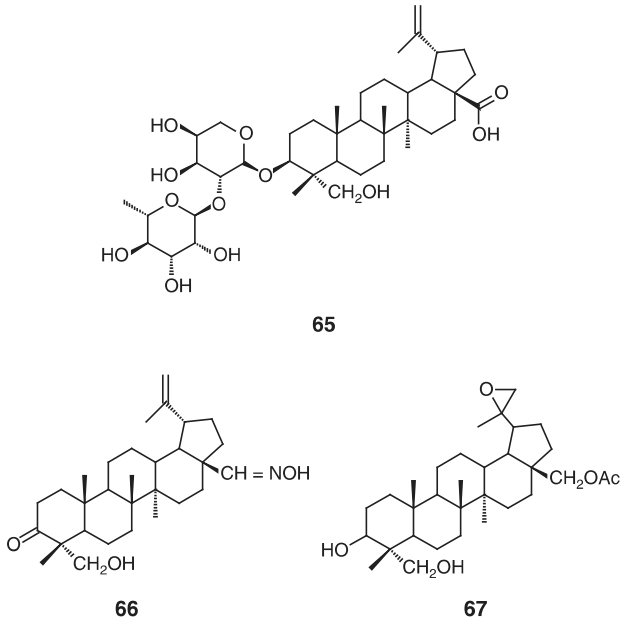

Figure 10. Chemical structures of pulchinenoside (65) and derivatives (66 and 67).

specified) (**Figure 13**). Case studies were conducted with middle-aged persons and senior citizens who volunteered to test the liniment compositions and reported pain relief and improvement in their physical condition after a few days to about 3 months of continued use on a daily basis [45]. It is worth mentioning that there are other patents reporting the analgesic effects of cannabinoids which were not found in this search.

6. Expert opinion

A patent review was carried in specialized search databases (WIPO, ESPACENET, DERWENT and USPTO) in January 2013 and included patents deposited over a period of 34 years (January 1979 to January 2013). The patent selection was based on inclusion criteria such as patents published in English or Spanish containing the keywords as terpene(s) or terpenoid(s) and pain and its several synonyms (analgesia, analgesic, analgesics, hyperalgesia, hypernociception, nociception, nociceptive pain, antinociceptive, antinociception), in the title, abstract or full text.

In this search, 30 patents were selected concerning terpene application on control pain. These reports describe the analgesic effect of 87 terpene compounds, through preclinical and clinical studies. As in this review, we selected patents written only in English or Spanish, it is possible that there are many other patents relating to the application of terpenes in pain control. However, although this inclusion criterion was a limiting factor of this review, the results presented herein are sufficient to understand the importance of this class of compounds as a source of new chemical entities for use in the relief of pain.

From the data collected, it was observed that most of the selected patents (60%) describe the analgesic profile of monoterpenes and sesquiterpenes, alone or in mixtures such as essential oils extracted from medicinal plants. Thus, it is suggested that, in this line of research, this class presents the most innovative and promising compounds for pain relief. This statement can be proposed by the number of analgesics marketed that contain in their formula these terpenes as active ingredients, such as Sativex® (THC and cannabidiol), Salonpas® (menthol), Acheflan® (caryophyllenes) and Vimang® (terpenes of *M. indica* L.), all considered best sellers in their respective markets. Other terpenes are employed by the pharmaceutical industry as active ingredients of medicament for treatment of diseases such as cancer (paclitaxel), malaria (artemisinin) or as synthetic precursors (hecogenin and diosgenin) of oral contraceptives and hormone drugs, thus strengthening the use of terpenoids in industry and pharmaceutical market.

Further, the studies of more clinical evidence were conducted with monoterpenes and sesquiterpenes. Analgesic effect of most terpenes was evaluated in patients with different types of pain, mostly chronic such as neuropathies, migraine, osteoarthritis; types of painful disorders which are difficult to treat and with a lack of selective drugs. The incessant search for new therapeutic options for chronic pain control is based on the fact that it is most prevalent human health problem, affecting over one-quarter of the world's population [11]. Besides, the incidence of the number of people with chronic pain is rising as the population ages and arise other chronic disorders such as cancer, whereas therapeutic resources for this purpose are limited.

The several clinical trials with terpenes application for relieving pain have demonstrated that cannabinoids, essential oils and other terpene mixtures present beneficial effect on the control of pain and are well tolerated, with generally non-serious adverse effects, as demonstrated in this review and in articles recently published by Aggarwal [46], Ou *et al.* [47], Garrido-Suárez *et al.* [48] and Sengupta *et al.* [49]. All these studies support the clinical evidence required for validation of the use of medicinal plants and their derivatives for the treatment of painful conditions by providing information about the adverse effects and safety of use of this alternative therapy.

From the records of patents about preclinical *in vitro* and *in vivo* studies, we can observe that terpenes generally promote pain relief by inhibition of inflammatory cascade. Pronounced effect on the reduction of inflammatory cytokines (IL, TNF-α) and PGE_2 levels, besides the decrease in COX-2, iNOS and 5-LOX expression were the targets of greatest relevance. On the other hand, these compounds may also inhibit the conduction pathways of nociceptive stimulus, through the blockade of Na^+ channels, NMDA and TRPV1 receptors.

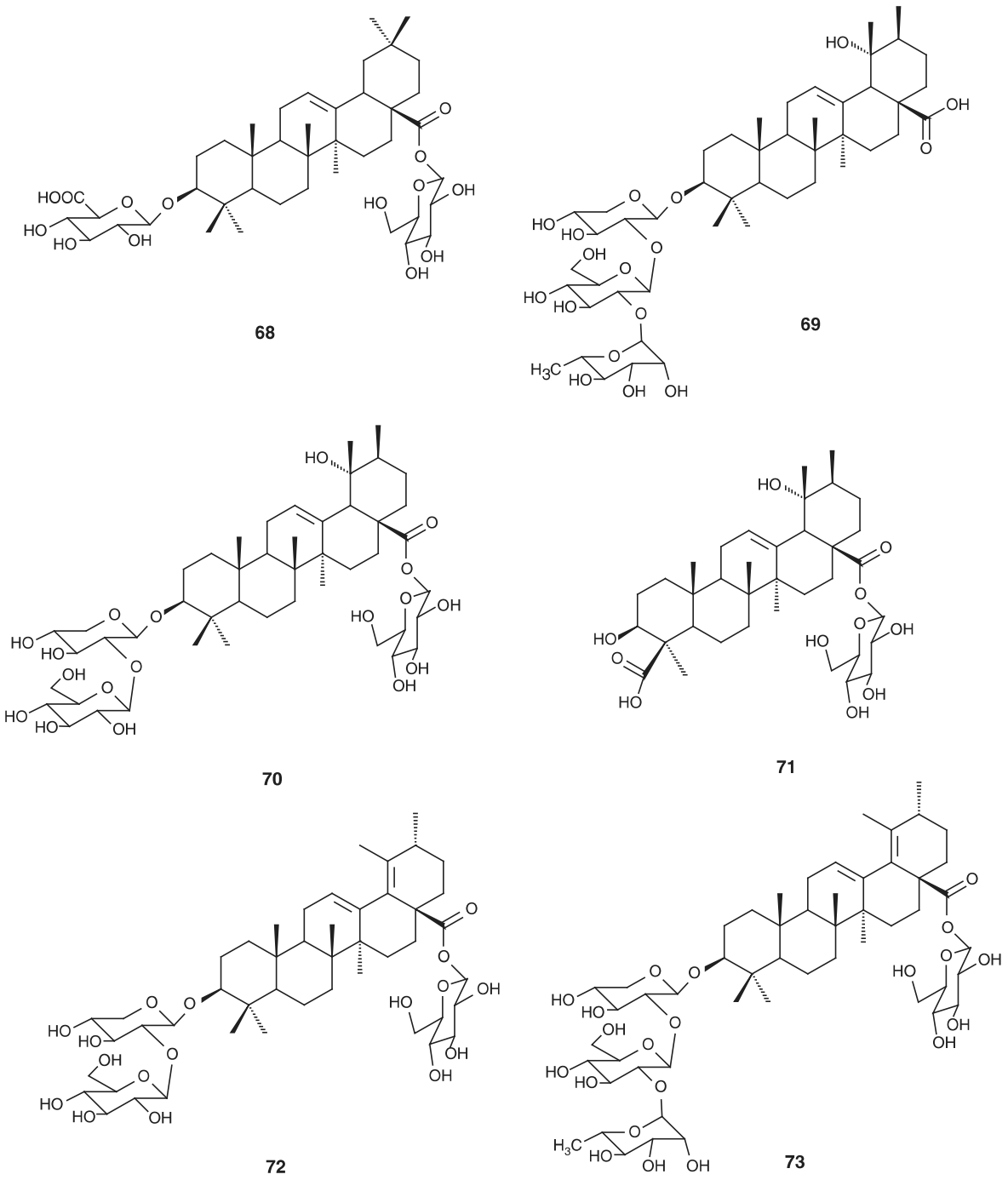

Figure 11. Chemical structures of triterpenes saponin (68 – 73).

In general, these compounds can inhibit the sensitization of primary afferent fibers of pain through their anti-inflammatory effect, or block nerve conduction of painful stimuli featuring peripheral and central action drugs, respectively. Generally, it is perceived that terpenes are compounds endowed with the ability to modulate several mechanisms that contribute to the relief and control of pain. Many of these cellular and molecular mechanisms have been described as novel molecular targets in acute and persistent pain control [50,51], generating great prospects for the development of new analgesic drugs composed of terpenes.

These findings lead to the application of medicinal plant derivatives to develop the standardized phytomedicines (phytotherapics or herbal medicine) with proved efficacy (assessed by both preclinical and clinical studies), safety and high

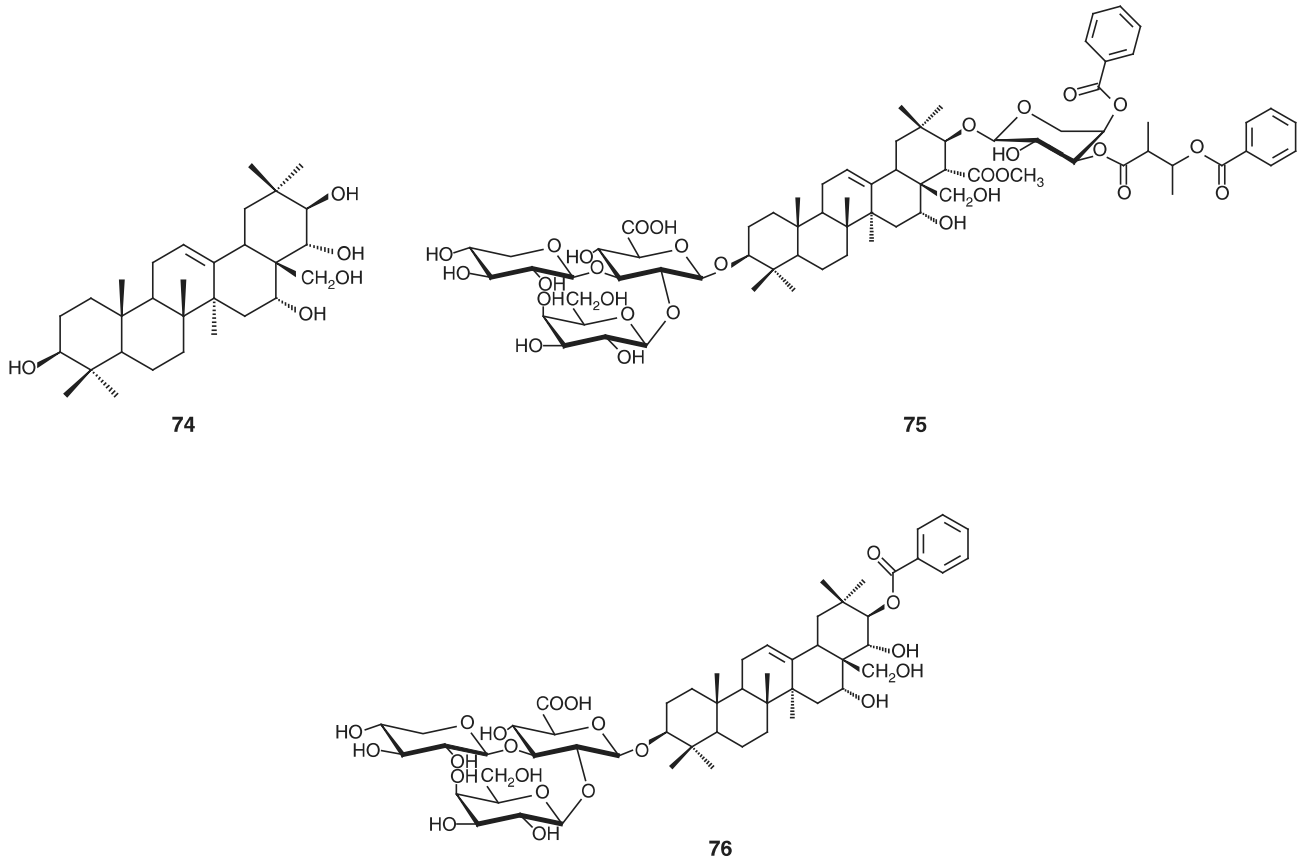

Figure 12. Chemical structures of triterpenes barringtogenol (74) derivatives (75 and 76).

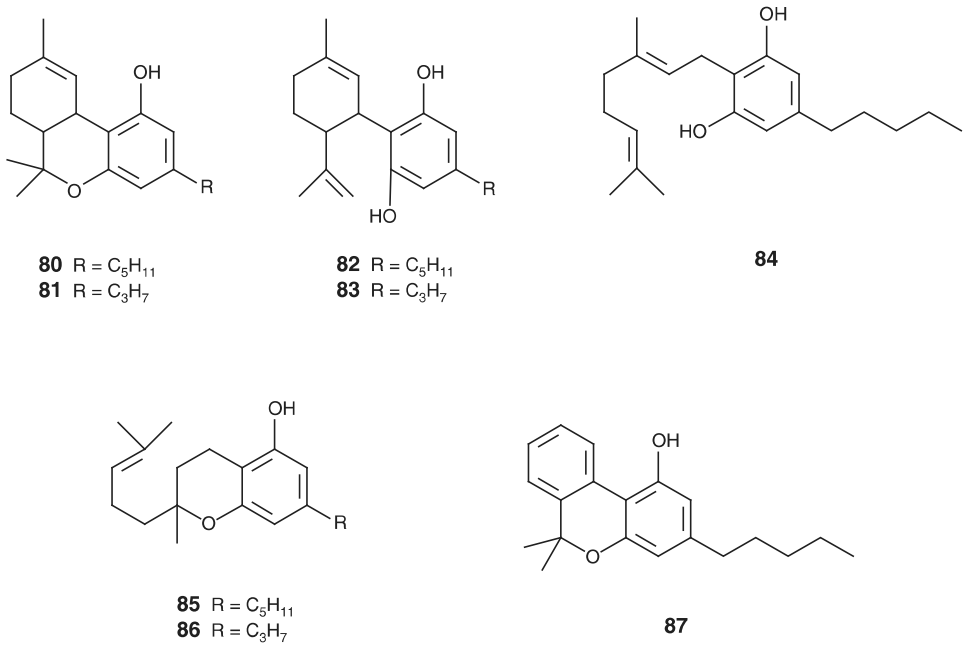

Figure 13. Chemical structures of terpenophenolics (cannabinoids: 80 – 87).

Table 4. Terpenophenolics (cannabinoids) patented, their pharmacological properties, indications and development status.

Compound (s)	Inventor/ company (country)	Country of protection	Year	IPC	Development s tatus	Indication	Action mechanism	Formulation
Cannabinoid mixture from *C. sativa* L: 9-tetrahydrocannabinol, 9-THC propyl analog, Cannabidiol, Cannabidiol propyl analog, Cannabinol, Cannabichromene, Cannabichromene propyl analog, Cannabigerol, and other terpenoids	Wallace W.H. (USA)	USA	2005	A61K	Case studies: patients with joint pain, herniated disc and degenerative disc disease or bipolar rubbery concentric subareolar tissue under the breast	Relieving analgesia and reducing inflammation	–	Topical liniment composition containing: 97.5 – 99.5% by weight a 70% monohydric alcohol solution 0.5 – 2.5% by weight of cannabinoid mixture extracted from the female plant *C. sativa* L.

A61K: preparations for medical purposes, dental or hygienic; IPC: International Patent Classification; USA: United States of America.

quality [52]. It is for this reason that natural product-based drugs constitute a substantial proportion of the pharmaceutical market, particularly in the therapeutic areas of infectious diseases and oncology, besides pain and inflammation [53].

Brazil, for instance, has increased its investment in research and development and had the first phytomedicine approved by the local authority ANVISA (Brazilian FDA-like agency) at the end of 2004, which was launched in the market in 2005. Acheflan is a phytomedicine fully developed in Brazil produced with essential oils from *Cordia verbenaceae*, a native species used in Brazilian traditional medicine to treat inflammations [52]. This oil is rich in caryophyllenes and formulations containing these compounds have been used by population for pain inflammatory treatment and after 8 years on the market, the product has excellent acceptance of medical grade being the leading prescription in this segment, with market share exceeding 40% from the end of 2007. Similarly, standardized aqueous extract of *M. indica* L. rich in terpenes, named Vimang have been used in Cuba as immunomodulatory, antioxidant, analgesic and anti-inflammatory medicine, which is safe and is well tolerated by humans [54].

Other terpenes that have been gaining attention in the scientific field and pharmaceutical industry are cannabinoids that act in cannabinoid receptors CB_1 and CB_2 found in the brain and that can be used for treating pain, muscle spasms, nausea and vomiting. Different types of cannabinoid medicines as Sativex, Cesamet® (nabilone, a synthetic cannabinoid) and others are available in various countries, such United States and/or Canada. Beyond, phytocannabinoid–terpenoid interactions could act synergistically on the treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections [46,55,56].

Terpenes, besides being direct sources of biologically active compounds, are also used as raw material for innovative drug synthesis. In this review, 20% of the patent reported the analgesic effect of terpene compounds synthesized. Conducting synthesis reactions from terpenes is favored by the chemical diversity of this compound, which provides the skeleton for future drugs, besides the fact that it enables the improvement of efficacy/safety profile of new chemical entities [57,58].

However, there is a long path between the pharmacological characterization of a class of compounds and their clinical application since the development of a new drug, depending on the regulatory requirements of the country, can take 10 to 15 years of research and higher investment. To achieve the ultimate goal, it is necessary to know the toxicity and pharmacokinetic characteristics of these compounds, which is an arduous process but essential to be certain of safety and effectiveness of this candidate new drug. Without a doubt, this is the great challenge, to overcome barriers between the laboratory benches and clinical application, so that new drugs are discovered to provide more effective control of different pain syndromes.

Recently, seeking a light at the end of the tunnel for greater clinical applicability of the less studied terpenes, some research

groups have also sought to improve the pharmacological properties of this compound family through the inclusion of cyclodextrins, a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides) [59-61]. Thus, the dose escalation, security levels, bioavailability and especially water solubility have been improved for increasing the chance of terpenes already used in the clinic, as well as the use of new compounds which are still in wide preclinical studies. We believe that the encapsulation (or nanoencapsulation) in controlled drug release systems can be a new frontier to be further explored for these compound class, after all, this approach has been successful in nutraceuticals [61].

Summing up, one can realize a significant advancement in this field of research over the years, demonstrating the growing interest of academic and industrial groups in the analgesic potential of terpenes, with development of successful products clinically well accepted. Thus, these compounds are already great candidates for new analgesics development, and probably, will have an important role in the pharmacotherapy of pain, because of the range of pharmacological mechanisms in target sites to the control of disorders and painful syndromes.

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Declaration of interest

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