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REVIEW ON ANALGESIC POTENTIAL OF TERPENES DERIVED FROM CITRUS FRUIT

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ABSTRACT

Chronic pain is a significant health problem that has a significant influence on worldwide healthcare systems. Despite the fact that this topic has not received the same level of attention as other noncommunicable diseases, it is important to note that contemporary medicine still lacks an effective treatment for chronic pain. Essential oils have been utilised for the prevention of a variety of diseases, including pain management, in this regard. The composition of these odorous goods, which are made from botanically defined raw materials, is diverse and complex. Terpenes, commonly known as terpenoids or isoprenoids, are the biggest class of natural products, with over 55,000 structurally diverse molecules. Terpene-based medications are generated from C5 isoprene units linked in a head-to-tail form from two biosynthetic routes, and worldwide sales of terpene-based pharmaceuticals were roughly US$12 billion in 2002. Anticancer (paclitaxel) and antimalarial (artemisinin) medications are two of the most well-known terpene-based pharmaceuticals. The purpose of this review is to look at the analgesic potential of bioactive chemicals found in citrus fruits.

Keywords: Analgesic Potential, Terpenes, Citrus Fruit.

INTRODUCTION

For millennia, a diverse range of natural products originating from terrestrial plants, microbes, marine organisms, and fungi has been a valuable source of medical compounds, with applications in medicine, pharmacy, and general biology. Natural product drug development began with the isolation of early medications like penicillins and morphine, some of which are still in use today. Plants and natural sources thus constitute the foundation of modern medicine and continue to play a significant role in the commercial medicinal preparations produced today[1].

As a result, natural products continue to aid in the creation of therapeutically significant treatments for a variety of disorders. Anticancer drugs like paclitaxel, vinblastine, vincristine, and topotecan are

widely used in the treatment of HIV/AIDS, Alzheimer's disease, malaria, and cancer. Capsaicin (Qutenza), a compound isolated from chilli peppers of the genus Capsicum that produces a burning sensation on contact with tissues by binding to the sub type-1 vanilloid receptor, was approved by the FDA in November 2009 as a transdermal 8% patch for the treatment of neuropathic pain associated with post-herpetic neuralgia. As a result, it is expected that nature will continue to provide a significant source of new structural leads, and that effective drug discovery will rely on multidisciplinary collaborations involving botanical, phytochemical, biological, and molecular techniques [2].

Bioactive Compounds of Citrus Fruits

Flavonoids

Flavonoids are a type of polyphenolic secondary metabolites frequently found in plants that contribute a large amount of antioxidant components to the human diet. Flavonoids have a 15-carbon skeleton (C6-C3-C6) with two six-carbon phenyl rings connected by a heterocyclic ring that contains the embedded oxygen. Flavonoids are split into subgroups based on the substitution patterns of heterocyclic rings, such as flavones, flavonols, flavanones, flavanonols, flavanols (flavan-3-ols), isoflavones, and anthocyanins. Citrus fruits are high in flavanone-7-O-glycosides (e.g., naringin, eriocitrin, hesperidin, and narirutin), flavones (e.g., rhoifolin, vitexin, diosmin), polymethoxylated flavones (e.g., nobiletin, tangeritin, and 5-demethyl nobile (cyanidin and peonidin glucosides)[3] .

PMFs are a special type of bioactive flavonoids that have more than two methoxyl (–OCH3) groups on their chemical skeletons and are found in abundance in citrus fruits. Because of their anti-inflammatory, anti-atherosclerosis, anti-obesity, and anti-cancer capabilities, PMFs have gotten a lot of attention in recent years. Furthermore, de-methylated PMFs, which are produced by fruit metabolism, chemical processes during drying, and human metabolism, have higher anticancer and anti-inflammatory properties than their methylated counterparts[4].

Dengetal[5] identified 11 flavonoids from (cv. Shatianyu) pulp, with the highest oxygen radical absorbance capacity (ORAC) activity being naringin and rhoifolin. In flavonoid extracts, however, melitidin, bergamjuicin, and naringin were the primary contributions to ORAC activity. Flavonoids accounted for 89.34 percent of polyphenolic fractions in the albedo (inner layer) of ancient Mediterranean citrus fruit, with flavanones eriocitrin and hesperidin as significant components, accounting for 52.81 percent and 31.31 percent of total flavonoids, respectively. Citrus fruits contain the highest amount of flavonoids during the middle stages (60–80 days after pollination (DAP)) of development, and a decrease during complete maturation, probably due to the high expression of Chalcone synthase-1(CHS 1) and chal cone isomerase, the rate-limiting enzymes in flavonoid biosynthesis [6].

In the juice sacs of lemon (cv. Akraga), on the other hand, hesperidin surged at the last developmental stage. Furthermore, the flavedo (outside layer) and albedo of citrus fruits contain more flavonoids than the juice sacs. The highest levels of PMFs, particularly OCH3-PMFs (nobiletin and tangeritin), were found in loose-skin mandarins (including mandarins and tangerines) and their hybrids, followed by tangelo (C. reticulataC. paradisi), sweet orange, junos, Rangpur lime, sour orange, and grape fruit, among the 116 citrus accessions screened. Surprisingly, the levels of nobiletin, 5-demethylnobiletin, and tangeritin increased during maturation, peaked at 60 DAP, and then dropped (60–210 DAP).

Carotenoids and Apocarotenoids

Carotenoids are isoprenoid pigments that play a role in photosynthesis and signalling [7]. Carotenoids are split into two classes based on their chemical structure: (a) carotenes—hydrocarbon carotenoids like - and -carotene, as well as lycopene; (b) xanthophylls—oxygenated carotenoids like neoxanthin, vio laxanthin, lutein, and -cryptoxanthin[8].

Xanthophylls' oxygenated functional groups can be esterified with fatty acids, resulting in free or fatty acid esterified forms, but carotenes are only found in free form due to their simple hydrocarbon structure (no esterification possible due to the absence of oxygenated functional groups). Caprate (C10:0), laurate (C12:0), myristate (C14:0), palmitate (C16:0), stearate (C18:0), palmitoleate (C16:1), and oleate (C18:1) acyl moieties are widely acylated with saturated and unsaturated fatty acids in citrus fruits[9].

A group of carotenoids called apocarotenoids exists in addition to carotenes and xanthophylls. The cleavage of carotenoids by carotenoid cleavage dioxygenases (CCDs)/9-cis-epoxycarotenoid dioxygenase (NCED) results in ecologically and nutritionally significant apocarotenoids[10]. CCD4b1/CitCCD4-catalyzed asymmetric cleavage (at either position 7, 8 or 70, 80) of -cryptoxanthin or zeaxanthin produces -citraurin in citrus[11].

Essential Oil (Terpenes and Limonoids)

Due to the presence of terpenes and limonoids, as well as other bioactive components such as flavonoids, carotenoids, and coumarins, essential oil obtained mostly from the flavedo of citrus fruits is an economically important product with beneficial health activities[12]. Because of their natural fruity scents, citrus essential oils are frequently employed in the pharmaceutical, cosmetics, perfumery, and food industries[13]. Citrus essential oils also have antimicrobial, antioxidant, analgesic, anxiolytic, neuroprotective, and antibacterial properties[14].

Citrus essential oil bioactive chemicals, in particular, are widely known for their potential antibacterial effects, as they degrade the bacterial cell wall, cause intracellular ingredient leakage, and, as a result,

cell death. Citrus essential oil has garnered a lot of attention in recent years as a preservation agent for fruits, vegetables, meat, and processed foods because of its significant antibacterial properties.

Terpenes and their applications

Terpenes, commonly known as terpenoids or isoprenoids, are the biggest class of natural products, with over 55,000 structurally diverse molecules. These compounds are generated from C5 isoprene units connected in a head-to-tail form from two biosynthetic routes, via the intermediates mevalonic acid or 1-deoxy-D-xylulose 5-phosphate. They are found in the secondary metabolism of both vegetal and animal species. Hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C30) are examples of typical structures with carbon skeletons represented by (C5)n (C40)[15].

Many of the compounds in this group are widely utilised as tastes, perfumes, and spices in the industrial sector, as well as in perfumery and cosmetic products and as food additives. They are also utilised as active principles of medications in the pharmaceutical industry, in addition to being used as excipients to improve skin penetration. The broad range of biological properties of terpenoids that have been described, including cancer chemopreventive effects, antimicrobial, antifungal, antiviral, antihyperglycemic, analgesic, anti-inflammatory, and antiparasitic activities, has sparked increased interest in their clinical application[16].

In 2002, the global sales of terpene-based medications were estimated to be around $12 billion. Anticancer (paclitaxel) and antimalarial (artemisinin) medications are two of the most well-known terpene-based pharmaceuticals[17]. Other terpenes, such as menthol, are also promoted in the pharmaceutical industry. The US FDA classifies this monoterpene as a topical analgesic, and it is found in topical formulations of nonprescription analgesics or 'over-the-counter drugs,' such as Salonpas (5.7 percent menthol, 1.12 percent camphor, and 6.3 percent methyl salicylate), which are widely used in the US and account for over $2 billion in annual spending [18].

Pain

Pain affects a large section of the world's population, resulting in a loss of high quality of life[19]. Pain, which is classified as an illness in some cases, is one of the most common reasons for seeing a doctor, one of the most common reasons for taking medications, and a major cause of work incapacity. Physical and mental functioning, as well as quality of life and productivity, are all impacted by severe chronic pain. Aside from that, it places a substantial financial strain on those who are affected, as well as their families, employers, friends, communities, and the country as a whole[20].

The pharmaceutical market is driven by the continuous high prevalence of pain worldwide, which is linked to a growth in the number of diseases with pain as a symptom. Furthermore, with a strong

emphasis on research and development, the analgesic drug industry is likely to be dynamic and commercially promising in the next years. As a result, many studies conducted by academic investigators and the pharmaceutical industry in response to the demand for powerful analgesics, once they exhibit their pharmacological response through new mechanisms of action and with fewer side effects, have been motivated by the development of pain relief treatments.

Furthermore, for analgesic medication development to be successful, it must be a continuous process that includes everything from target identification through animal research and clinical trials with relevant, approving end points that are directly linked to pain pathophysiology and drug mechanism of action. Furthermore, the large market, generic medications, and patent infringement all threaten sales and 'blockbuster potential.' As a result, development expenses, safety standards, and the need for minimal side effects are all elements that contribute to the pharmaceutical market's continued search for breakthrough drugs with high aggregated value[21].

The progress of therapeutical patents devoted to the use of terpenes for pain relief is demonstrated in this review, with a focus on the evaluation of their potential at each development stage, as well as the current state of knowledge about the potential of these compounds to become candidates for new pain-controlling drugs.

Monoterpenes (C10) and sesquiterpenes (C15)

Monoterpenes, which make up approximately 90% of the oils. When essential oils are extracted with organic solvents, diterpenes may be found. Several studies have revealed that these compounds have a variety of pharmacological effects, with the analgesic standing out, as evidenced by reviews recently published by Guimara et al.[22]. The analgesic actions of monoterpenes and sesquiterpenes are detailed in 17 patents in this review. The oldest record of submitting a patent for the therapeutic use of monoterpenes was discovered in 1988[23]. The analgesic effect of turpentine, a combination of terpenes in which a-pinene (1) is the predominant ingredient, is described in this invention. Case studies of five patients with wounds, burns, and abrasions who were treated topically with turpentine (a-pinene) and vitamin E solution provided evidence of this compound's analgesic efficacy (70:30 or 50:50). The symptoms were reduced a few hours after the therapy, most likely due to this monoterpene's capacity to aid healing and minimise swelling, discomfort, and bleeding. Seiwa Pharmaceutical patented an analgesic containing incarvillateine (2), a monoterpene alkaloid derived from Incarvillea sinensis Lam[24], after ten years of research.

The inventors demonstrated that this chemical (5 or 10 mg/kg, i.p.) reduced nociception in both phases of the formalin test in a preclinical trial, implying an analgesic and anti-inflammatory activity. Since the twenty-first century, the number of patent filings describing the analgesic effects of monoterpenes

and sesquiterpenes has increased. Two monoterpenes, b-elemene and hinesol, three sesquiterpenes, a-guaiene, aromadendrene, and ledol, and two triterpenes, mangiferonic acid and taraxerol, were discovered in Mangifera indica, according to a patent filed by the Center Pharmaceutical Chemistry (Cuba). That patent describes the antioxidant and analgesic properties of the referenced mixture, which were studied in preclinical and clinical trials. 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[25]. Papaprodromou (2001)[26] explains how to relieve pain using a combination of natural herb oils and other medicines. The above-mentioned invention relates to topical compositions based on Oregano (Origanum vulgare L.) essential oils comprising carvacrol and thymol, as well as Laurel oil (Laurus nobilis L.)

Limonene, a- and b-pinene, and cineole are all found in myrtle (Myrtaceae). 17 patients with various types of pain related with arthritis, migraine headaches, tissue injuries, muscular aches, cancer, and back pain were given topically applied compositions containing 90–95 percent oil of oregano, 3–5% oil of Laurel, and 2% oil of Myrtle. Patients reported relief from pain and discomfort caused by their condition in general. Other oil mixtures patented by General Cosmetics Corp. include peppermint oil 72-84 percent [menthyl acetate, menthol], rosemary oil 5 percent [bornyl acetate, borneol], eucalyptus oil 1 — 3 percent [1,8-cineol], lemon oil 1 — 1.5 percent [citral, limonene], orange oil 1 — 1.5 percent [limonene, citral, linalool], camphor oil. 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 [27].

A soft gelatin capsule containing 15% of aromatic/terpenoid chemicals from Alpinia galanga (Zingiberaceae), such as 1,8-cineol, a-pinene, b-pinene, limonene, a-terpineol, terpene-4-ol, and trans-b-farnesene, was given twice a day for two weeks to five volunteer osteoarthritis patients.

This essential oil's analgesic action may be due to its immunomodulatory impact, which is mediated via suppression of leukotriene C4 synthase and phosphodiesterase-IV. Small patented a viscous solution containing menthol (33.3%), a-pinene (14.5%), 1,8-cineol (5.6%), limonene (1.8%), b-pinene (1.7%), sabinene (1.5%), and methyl salicylate (8.6%). This formulation was studied in 210 patients who suffered from pain caused by osteoarthritis, metastatic cancer, injuries, tendon rips, rheumatoid

arthritis, myositis, tendonitis, cervical spasm, lower back, herniated discs, spinal stenosis, osteoporotic and traumatic bone. The topical solution relieved pain in roughly 83 percent of those individuals, indicating that the formulation was effective for treating a variety of pain modes. Bothma et al. [28] patented the use of menthol, farnesol, and vetiveryl acetate in topical formulations for pain prophylaxis and therapy. Case studies involving nine individuals with various types of pain, such as arthritis, muscular, and joint pain, were used to demonstrate the benefits of these items. In general, the products tested that contained those terpenes improved pain and discomfort by up to 90% on average. This impact lasted for up to 24 hours in some circumstances. Parthenolide was another sesquiterpene that piqued the pharmaceutical industry's interest. This chemical is found in feverfew (Tanacetum parthenium) extract, and its analgesic effectiveness was tested in case studies with 11 migraine patients and double-blind randomised trials with 48 migraine patients with moderate-to-severe pain [29].

SK Chemicals Co., Ltd. developed anti-inflammatory and analgesic formulations including sweroside, a monoterpene iridoid, in 2008 [30]. A preclinical investigation revealed the analgesic efficacy in this discovery. Sweroside lowered edoema caused by croton oil and arachidonic acid and reduced nociception caused by acetic acid.

Based on these findings, pharmaceutical formulations such as tablet (160 mg), syrup (4000 mg), injection ampoule (20, 50, or 100 mg), and ointment (5 g) have been proposed, with the monoterpene referred to as the active ingredient. McLellan has discovered a number of powerful analgesics. For the treatment of neuropathic pain, McLellan[31] devised a homoeopathic formulation of Hypericum perforatum coupled with an essential oil blend of lavender, pelargonium, bergamot, eucalyptus, and tea tree oil. 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 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 , menthone, borneol , nerol and neral, citronellol , geraniol , myrcene , p-

cymene , limonene , 1,8-cineol and camphor . In patent application of Pianowski et al. [32] a-caryophyllene and b-caryophyllene are cited in the control of inflammation and pain inflammatory .

Ache ´ Pharmaceutical Laboratories S.A (Brazil) evaluated caryophyllenes effects on preclinical study and demonstrated that a-caryophyllene , also known as a-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-1b, TNF-a, the growth of PGE2 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 [33]. Geranium oil is composed mainly by of citronellol , geraniol , terpinen-4-ol , linalool , linalyl acetate , phellandrene , 1,8-cineole , limonene , citronellyl formate and, isomenthone .

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 and citronellol , 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[34] 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 , Reed et al.[35] and McLellan et al. [36] 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-en1-yl) cyclopropyl) methanol demonstrated TRPV1 agonist effect and greater effectiveness in reduced touch response and spontaneous coiling in zebrafish, which are correlated with analgesic activity. An academic group at Harvard College has protected patent on analgesic activity of huperzine A, a sesquiterpene alkaloid [37]. 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.

Diterpenes (C20)

Diterpenes represent a large group of terpenoids with a wide range of biological activities, isolated from a variety of organisms . 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 . In this review, three patents on diterpenes application for the treatment of pain are discussed . 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 [38] demonstrated through a preclinical study that pseudopterosin. A, a diterpene isolated from Caribbean gorgonians of the genus Pseudopterogorgia, and synthetic analogs , 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 and O , seco-pseudopterosin

Triterpenes (C30)

A wide range of pharmacological activities of triterpenes have been reported in literature and were recently reviewed by Parmar et al. [39], 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 . The oldest record found dates back to 1979 [40], 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 as major component . 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 [41].

Analgesic and anti-inflammatory effects of triterpene saponins isolated from roots and back of Crossopteryx febrifuga, as crossoptine A and crossoptine B, was observed in a preclinical study using phenylguinone writhing and carrageenan edema test . 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. [42] patented an enriched extract containing 3-O-acetyl-11-keto-b-boswellic acid (AKBA, a triterpene from Boswellia serrata, and its use for treatment of pain associated with inflammatory disease . The extract reduces inflammatory pain and edema induced by Freund's

complete adjuvant (CFA), inhibits nitrite and IL-1b 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 and synthetic derivatives DA021 and DA034 against pain and inflammation was patented by Biotechnology Research Corp. (China) . Preclinical study in vitro and in vivo demonstrated that these triterpenes have antagonist effect of N-methyl-D-aspartate receptor (NMDA), melanocortin and PGE2 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.

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%), ilexsaponin B2 (18 -- 28%) , ilexsaponin B3 (16 -- 20%) , ilexsaponin A1 (13 -- 17%), pubescenoside C (10 -- 20%) and pubescenoside D (1 -- 4%). Griffith University in partnership with Jarlmadangah Buru Aboriginal Corp. (Australia) filed a patent related to the analgesic effect of barringtogenol C , a triterpene obtained from plants of the barringtoside species, and its synthetic derivatives I and II . 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 [43].

Analgesic and anti-inflammatory activities of maslinic acid and oleanolic acid were protected by Prados et al. [44] from Granada University . These triterpenes inhibit PGE2 and IL-6 production, COX-2 activity. Further more, 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 in rodents. Nieto Lo ´pez et al. [45] 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.

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 [46].

CONCLUSION

Pain is a prominent and complex symptom of many underlying diseases and disorders. Although scientists have made considerable efforts and progress in recent years to clarify and better understand cellular-, signaling- and network-level mechanisms of pain, which have suggested new and alternative targets for pain management, these results have not yet yielded improved pain therapies and approaches. Present review gives the significance of bioactive Compounds present in citrus fruits and there pharmacological effect.

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