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Review

Acmella oleracea for pain management

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ABSTRACT

Despite advances in medicine and numerous agents that counteract pain, millions of patients continue to suffer. Attention has been given to identify novel botanical interventions that produce analgesia by interacting with nociceptive-transducing channels. The aim of this review is to provide an overview of the actual knowledge of *Acmella oleracea* (L.) and its activities, particularly those that are anti-inflammatory, anti-oxidant, and painkiller. These activities are attributed to numerous bioactive compounds, such as phytosterols, phenolic compounds and N-alkylamides (spilanthol, responsible for many activities, primarily anesthetic). This review includes 99 eligible studies to consider the anti-inflammatory, anti-oxidant, and painkiller of Acmella. Studies reported in this review confirmed anti-inflammatory and anti-oxidant activities of Acmella, postulating that transcription factors of the nuclear factor-κB family (NF-κB) trigger the transcription iNOS and COX-2 and several other pro-inflammatory mediators, such as IL-6, IL-1β, and TNF-α. The antinociceptive effects has been demonstrated and have been related to different processes, including inhibition of prostaglandin synthesis, activation of opioidergic, serotoninergic and GABAergic systems, and anesthetic activity through blockage of voltage-gated Na Channels. *acmella oleracea* represents a promise for pain management, particularly in chronic degenerative diseases, where pain is a significant critical issue.

1. Introduction

Acmella is a flowering herb species in Asteraceae o Compositae's family. Its native distribution is unclear, but it is likely derived from Brazil, where it is called jambu. It is grown as an ornamental or medicinal plant and attracts fireflies when in bloom. A small, erect plant, it grows quickly and bears gold or red inflorescences. It is frost-sensitive but perennial in warmer Climates. *acmella* flower is also known as the "Toothache plant". In the Northern parts of Brazil, this flower is added to vegetables during cooking. The whole plant is used as a medicinal remedy in various parts of the world. Pain is one of the most common symptom in dentistry practice also nowadays. Many researches focused on pain and how to relieve it. Jambu, the traditional name for acmella, has been used for centuries to treat oral pain because of its analgesic properties. The leaves and inflorescence are used as household medicine in the northern region of Brazil to treat oral and throat diseases. When chewed, the leaves and flowers generate a tingling sensation to the lips and tongue. This sensation is caused by the action of spilanthol, an isobutylamide compound that promotes local anesthetic action treating the tooth ache.

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Fig. 1. Acmella oleracea.

There is some disagreement in literature over the name of the genus and species of Acmella, one of the most important plants containing spilanthol (Fig. 1).

Some call it A. oleracea [1–4] but others call it A. oleracea (L.) R. K. Jansen [2,5,6], A. oleracea Compositae [7], *S. oleracea* L. [8], *S. acmella* [5,9–15], *S. acmella* L. var. oleracea Clarke [16] and *S. acmella* Murr. (Asteraceae) [17–19].

Acmella oleracea has been classified as safe (GRAS #3783) by the Flavor and Extract Manufacturers Association FEMA, 2000 [20] and the European Food Safety Authority EFSA, 2015 [21]. It presents low toxicity [22–24] and a widespread popular use.

1.1. Active compounds of Acmella

Extensive phytochemical investigations of Acmella have been reported in many papers. Its constituents are different groups of compounds. Dias et al. [25] reported *S. acmella* to contain amino acids, triterpenoids, α and β amyrin esters, stigmasterol, myricyl alcohol and alkaloids being particularly rich in alkylamides [24]. The majority of these were lipophilic alkylamides or alkamides bearing different numbers of unsaturated hydrocarbons (alkenes and alkynes), such as spilanthol [26], which is the main compound isolated from many parts of this plant, particularly flowers.

Spilanthol is the most representative alkylamide in Acmella and due to its presence, depends the biological activities and the sensorial effect that characterizes the plant [25]. Spilanthol can be found not only in *Acmella oleracea*, but also in the other species *A. ciliate*, *A. oppositifolia*, *A. radicans*, *A. brachyglossa*, *A. paniculata*, *A. uliginosa*, *Welelia parviceps* and *Heliopsis longipes* [12,27]. Many of the works describing its presence in *H. longipes* named it affinin instead of spilanthol [28,29]. Many of the above plants are used as traditional remedies throughout the world [12,30], and they are often named toothache plants, thanks to the analgesic effect of spilanthol.

Spilanthol, an olefinic N-alkylamide with an isobutyl side chain, (C14H23NO, 221.339 g/mol) is a bioactive compound found in many different plants used as traditional remedies [12]. Its IUPAC name is (2E,6Z,8E)-N-isobutyl-2,6,8-decatrienamide [31]. It is also known as affinin [12].

Like other alkamides, it is an amphiphilic compound with a relatively polar amide and a less polar fatty acyl. It can be extracted from plants using either methanol, ethanol, supercritical CO2 or hexane [4,16,25,26]. After being extracted, it can be purified by preparative scale TLC and/or HPLC [1,10,11,16].

Spilanthol has been demonstrated to exert a spectrum of different biological activities. With regards to pain and chronic joint inflammatory disorders the most promising ones are anti-inflammatory [32] with no adverse effects [22]; penetration enhancing effect on model drugs [33]; strong local anesthetic [34]. Few studies revealed that Acmella extracts could act as a vasorelaxant [35] with diuretic effects similar to furosemide's [36]. Compounds involved in vasorelaxant activity seem to be pentacyclic triterpenoids, oleanolic acid and erythrodiol [35].

Spilanthol has many biological activities [37], including analgesic [7,12,19,25,26,31,32,38–43], antinociceptive [28,44], antioxidant [19], anti-inflammatory [25,32,45], antiwrinkle [15,46]. Dias et al. (2012) studied the influence of different extraction methods and solvents, as well as different parts of the plant (flowers, leaves and stems) on the composition, and consequently on the bioactivity of the single extract [25]. It was observed that all factors affected the chemical composition of the extracts, both quantitatively and qualitatively. Flowers and aerial parts contain a great amount of spilanthol. Flowers and leaves are rich in phenols and their extracts may have low or even pro-inflammatory activity. Even stems contain spilanthol and other alkylamides that were easily extracted from SFE (CO2), with similar anti-inflammatory of the flowers. SFE(CO2) is the most effective extractive process for spilanthol, from all plant parts, particularly selective for the bioactive compound of the flowers [25].

Spilanthol revealed to inhibit CYP P450 enzymes, with IC50 values of 25, 16.1 and 13.5 g/ml for CYP1A1/2, CYP2D6 and CYP3A4, respectively. Spilanthol inhibits human P450 enzymes that are involved in drug metabolism, so it may interfere in this mechanism. Furthermore CYP1A1/2 inhibition could be associated with decreased carcinogenic risk. These observations were conducted in in-vitro studies; even if it's not demonstrated the same effects in vivo, a use with caution of these herbal product is advisable, especially for long term treatments [47].

N-alkylamide spilanthol and other plant constituents, have been shown to increase significantly the penetration properties of the skin towards other compounds. This may clinically influence the functionality and toxicity of these compounds. Spilanthol's skin permeation-enhancing effect of ibuprofen has been tested with three CART clustering transdermal model compounds from BDe Spiegeleer et al. (2013) Spilanthol, ranging from 0.1 to 1% concentration in the dose formulation, caffeine and testosterone demonstrated significant penetration-enhancing effects. On the contrary ibuprofen did not show any penetration enhancing effect [33].

The isolation and synthesis of the majority of compounds different from spilanthol and their bioactivities have been reported, such as: rhamnogalacturonan with gastroprotective proprieties [48]. 3-acetylaleuritolic acid had been shown to exhibit antigrowth effects against *S. aureus* and S. typhimurium [49], significant decrease on vitality of adult male worms of O. gutturosa [50], marked inhibition of DNA topoisomerase II [51]. Moreover, 3-acetylaleuritolic acid showed marked cytotoxic activity against human lung carcinoma A549 cells [51]. Vanillic acid showed to exert strong antioxidant activity [52] and relevant wound healing activity [53], as well as protective effects against DNA damage [54] and antimutagenic [55] and immunostimulating [56] activities.

β-Sitostenone is a triterpenoid with significant hypoglycemic [57], antiarrhythmic [58] and pronounced antitubercular [59] activities. Scopoletin possesses vasorelaxant [60], antioxidant [61], antimicrobial [62], anti-inflammatory [63], antipyretic [64], antiplatelet aggregation [65] and antidiabetes mellitus properties [66]. Scopoletin also exerts neuroprotective [67] and hypotensive [68] properties as well as a potential treatment opportunity in various cardiovascular [66], cancer [69], cell proliferation and thyroid [70] pathologies. Ferulic acid is a natural antioxidant substance which is found in vegetables, fruits, rice bran [71], herbal medicines, beverages and supplements [72]. Ferulic acid is able to carry out many other effects: vasorelaxant [73], anti-inflammatory [72], antiviral [74] and analgesic properties [75], as well as protective effects against neurodegenerative alterations observed in

Alzheimer's disease [76], chemopreventive [77] and hypotensive effects [78].

1.2. Patended uses

Spilanthol found also an assortment of uses in cosmetic industry. There are about 30 patents describing products made from a variety of Spilanthes species [79]. Either spilanthol or extracts of plants containing it has been added to toothpaste and used as an oral analgesic and antibacterial gel (such as Buccaldol® and Indolphar®), to cream as an anti-wrinkle that can substitute for Botox in cosmetic applications [15,80] and to some anti-aging products (Gatuline®, SYN®-COLL, ChroNOlineTM).

Early humans sought to understand pain, and pain management has been the focus of centuries of research. Anatomical and physiological studies performed by Descartes (1606–1650) first confirmed the existence of nerves that are able to receive sensorial information at the periphery and transmit it to the brain. In dentistry, pain is one of the most common symptoms, and it is therefore of the utmost importance to dentists. Pain sensation can be described as acute, burning, continuous, spasm, silent or pulsating, and it varies according to human emotions. Pain control is one of the most important aspects of dentistry practice. Medication, including analgesics and anesthetics, is necessary to control pain. Anesthetic salts are formed by combining weak alkaloids and strong acids. According to the literature, a plant popularly known as Jambu or watercress from Pará (*Acmella oleracea*) is cultivated in the north of Brazil and used as an Amazonian cookery seasoning; it also has cicatrizing and analgesic properties to treat oral lesion [81,82].

The leaves and inflorescence (capitula) are used as household medicine in the northern region of the country to treat oral and throat diseases. When chewed, the leaves and flowers generate a tingling sensation to the lips and tongue. This sensation is caused by the action of spilanthol, an isobutylamide compound that promotes local anesthetic action and is used for tooth ache [82].

2. Materials and methods

The present review was made following the indications suggested by Egger et al. (2001) as follows [83]: (1) A working group was configured as follows: three operators skilled in clinical nutrition and botanical dietary supplements, one acting as a methodological operator and two participating as clinical operators. (2) The revision question on the basis of considerations made in the abstract was formulated as follows: “the state of the art on the role of Acmella in pain management”. (3) Relevant studies were identified as follows: a research strategy was planned, on PubMed (Public Medline run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of USA), as follows: (a) definition of the keywords (*Acmella oleracea*; *Spilanthes acmella*, Acmella, spilanthol, pain, inflammation), allowing the definition of the interest field of the documents to be searched, grouped in quotation marks, and used separately or in combination; (b) use of the Boolean AND operator that allows the establishment of logical relations among concepts; (c) research modalities: advanced search; (d) limits: time limits: papers published in the last 30 years; languages: English; (e) manual search performed by the senior researchers experienced in clinical nutrition through revision of reviews and individual articles on role of Acmella and its active compounds in terms of pain management in published in journals qualified in the Index Medicus. (4) The analysis was performed as a review of the data Fig. 3.

3. Results and discussion

Fig. 2 shows the study selection process. Table 1 summarizes the studies presented in the review.

3.1. Anti-inflammatory activity

The anti-inflammatory effect of dried flowers of *Acmella oleracea* has been demonstrated on the RAW 264.7 lipopolysaccharide-activated murine macrophage model [32]. In this biological model nitric oxide (NO) is produced by macrophages to mediate inflammation with involvement of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Spilanthol inhibits production of COX-2 and iNOS and mRNAs coding for both of them. In this experimental animal model it is hypothesized that spilanthol could inactivate NF-kB, down regulating the production of proinflammatory mediators. An anti-inflammatory effect of Spilanthol has also been demonstrated on the arachidonic acid model with ED50 = 1.2 mg/ear [32] as well as a dose-dependent anti-inflammatory effect with phorbol myristate acetate model with ED50 = 1.3 mg/ear [45].

Furthermore, Bakondi et al. (2019) have reported the molecular mechanism of spilanthol linked to the inhibition of iNOS expression, NO production and the suppression of the main inflammatory transcription factors (NFkB, ATF4, FOXO1, IRF1), thus partially explaining the anti-inflammatory effect of *Acmella oleracea* reported in an intestinal mucositis model induced by 5-fluorouracil in mice [88,89].

According to these results spilanthol could be considered a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID) [32]. The anti-inflammatory activity of Acmella extract has also been studied in acute inflammation [24,85]. The results obtained in mice indicate that the aqueous extract of Camellia significantly suppresses carrageenan-induced paw edema in doses of 100, 200 and 400 mg/kg [24,85]; even though the inhibitory effect was lower than that of the standard drug, aspirin [24]. The anti-inflammatory properties of Acmella has been supported also by the observations of Barman et al. (2009) [85]. In the same acute pain animal model, Dallazen J.L. and collegauses (2018 and 2019) reported an anti-inflammatory effect of *Acmella oleracea* induced by the modulation of neutrophils infiltration and cytokines, through the significant decrease of TNF-α, IL-1β and IL-10, IL-6 levels [90,91].

Yamane et al. (2016) [84] proved the anti-inflammatory and anesthetic action of Acmella crude extract with Achyrocline satureioides's essential oil and adjuvants, in a hydroxyethyl cellulose film. This kind of administration has the advantage of avoiding first-pass metabolism. Two different dose formulations were tested against placebo by in vivo tests: wound healing activity in rats and tail-flick test in mice. Films containing the highest concentration of anesthesia are 83.6 (± 28.5) minutes longer in comparison with the positive control EMLA. Similarly, when the wound healing was tested, a significantly higher wound contraction (62.0% ± 12.1) was observed when compared to allantoin that was the positive control. The histopathological analysis showed that there was an increase in collagen synthesis and epidermal thickening. The antinociceptive activity was also dose-dependent with only 5 min time after application. Results demonstrated that these films could be used for treatment of pressure sore, skin wounds and infected surgical wounds [84].

Ferreira et al. (2004) [48] showed that rhamnogalacturonan (a polysaccharide isolated from *Acmella oleracea*) plays a gastroprotective activity against gastric lesions induced by ethanol in rats. Moreover, animals treated with rhamnogalacturonan did not show clinical alterations or weight changes of body and organs or modifications of biochemical parameters, thus demonstrating the safety of this polysaccharidic molecule Additional studies are needed to confirm the safety of rhamnogalacturonan and to evaluate complementary mechanisms of action of this substance. Further biological effects induced by rhamnogalacturonan could deal with cellular proliferation, gastric mucosecretion, antinflammatory and antioxidant properties [48].

Helicobacter pylori infection and NSAIDs (nonsteroidal anti-inflammatory drugs) are the most common causes of gastric an d duodenal ulcers in humans [92]. H2 receptor antagonists and proton pump inhibitors constitute effective treatments of gastric and duodenal ulcers, but the long term use of these drugs is associated to negative side effects

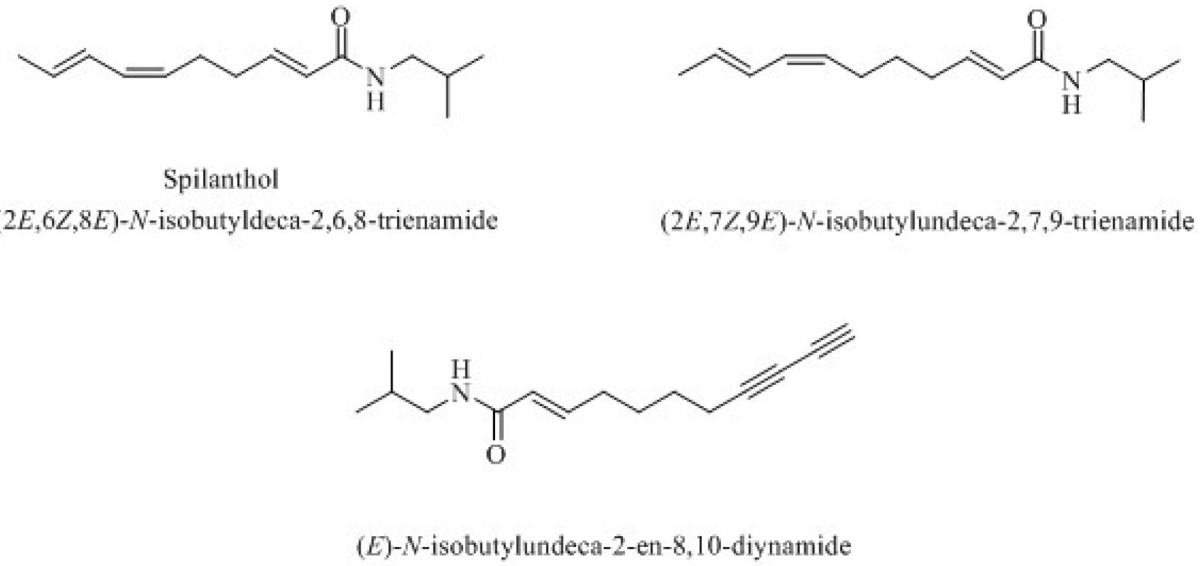

Fig. 2. Chemical structures of the main active alkilammides of *Acmella oleracea*.

and drug interactions [93]. Therefore, new and efficacious therapeutic opportunities, characterized by lower risk of side effects, are to favor ulcer prevention and healing as well as the reduction of ulcer relapse.

Spiegeleer et al. (2013) showed in their experiments that Spilanthol increases the permeability of some mycotoxins. Therefore, care should be taken if dangerous contaminants such as mycotoxins are present in plant formulations applied at the dermal level [33].

3.2. Antioxidant property

Many research groups demonstrated the potential role of the Acmella extracts to produce pharmaceutical drugs, cosmetic products, supplements and healthy food. Wu et al. (2008) [32] studied the antioxidant activity of Acmella and demonstrated that the extract of Acmella flower EtOAc (ethanolic followed by liquid partition ethyl acetate) was associated with the highest DPPH and ABTS radical scavenging activity when compared to the other tested extracts. Spilanthol, obtained from chloroform extracts, reduced the availability of various va mediators of inflammation such as IL-1β, IL-6, and TNF-α and down regulated the expression of and iNOS and COX-2, probably by means of the decreased activation of NF-κB. Previous studies have suggested that transcription factors of the nuclear factor-κB family (NF-κB) activate various proinflammatory mediators such as iNOS, COX-2, IL-6, IL-1β, and TNF-α [94,95].

The study of Wu et al. indicates that spilanthol attenuates the LPS-induced inflammatory responses in murine RAW 264.7 macrophages. To a certain extent this could be related to the inactivation of NF-κB, which negatively regulates the production of proinflammatory mediators. Actually, the reduced levels of LPS-induced response diminishe iNOS, COX.2 mRNA and protein expression suggesting that spilanthol inhibits the production of various mediators of inflammation at the transcriptional and translational levels. In addition, spilanthol reduces the LPS-stimulated, IL-1β, IL-6 and TNF-α productions in a dose-dependent way [32].

Acmella extracts also perform a vasorelaxant activity. Wongsawatkul et al. (2008) [35] proved this effect looking at the phenylephrine-induced contraction of rat thoracic aorta after stimulation with *Spilanthes acmella* Murr. Extracts. This result could be due to the reduced production of peroxynitrite after the reaction of NO (as superoxide scavenger) with O2– with a dose dependent increase of vasorelaxation induced by NO.

Probably this is not the only mechanism that is involved. Also, the ethyl acetate extract demonstrates marked vasorelaxation in nanogram amounts and appears to be the most active antioxidant in the DPPH assay. Both the DPPH and SOD assays were used to confirm the antioxidant activity of *Spilanthes acmella* Murr. Extracts. *acmella*'s extracts showed antioxidant activity at 200 μg/mL. The polar ethyl acetate and methanol extracts were associated with the highest antioxidant activity in a DPPH test, while the chloroform extract demonstrated the highest SOD activity. The results showed that all the tested extracts exhibited antioxidative activity. In DPPH assay at 200 μg/mL, the ethyl acetate and methanol extracts showed similar effects with the highest radical scavenging activity (47.90 and 47.76%) with IC50 216 and 223 μg/mL, while α-tocopherol (a positive control) showed antioxidant activity with IC50 6.67 μg/mL. The chloroform extract exhibited 29.82% radical scavenging activity [32].

3.3. Anesthetic activity

Spilanthol's anesthetic activity has been studied in animal models through intracutaneous wheal in guinea pigs and plexus anesthesia in frogs with 2% xylocaine as the standard drug. *S. acmella* aerial aqueous extract showed a relevant effect that could be attributed to the presence of alkamides. Xylocaine showed a faster onset of action when compared with spilanthol. Spilanthol in concentrations of 10% and 20% produced 70,36% and 87,02% anesthesia respectively, while the effect of 2% xylocaine was 97,22%. The blockage of voltage-gated Na + channels constitutes the main local anesthetic mechanism of action [34].

The spilanthol's activity at CNS (central nervous system) level are not well known and different N-alkylamide containing plants could show different CNS pharmacological effects. In an in vivo rat tail flick experiment, Chakraborty et al. (2004), and Barman et al. (2009) demonstrated a central analgesic activity of a subcutaneous *Spilanthes acmella* extract [24,85].

The tail-flick test has been demonstrated to be useful to evaluate the antinociceptive effect of various topical and mucoadhesive products [96–98]. Chakraborty et al. (2004) [24], demonstrated also the analgesic activity after intraperitoneal administration of Acmella aqueous extract in albino rats at doses of 100, 200, and 400 mg/kg. Barman et al. (2009) [85] showed the analgesic effect of an ethanolic extract of Acmella after subcutaneous administration to albino rats at a dose of 100 mg/kg. The onset of action was very quick because the antinociceptive effect was evidenced after two minutes since the beginning of the topical treatment. The concentration of spilanthol in the

Table 1
Summary of Acmella reviewed activities.

Pharmacological activity	Species	Parts of plant used	Type of extract	Experimental models animals used	References
Anti-inflammatory	Acmella	Aerial parts	Ethanol	Lipopolysaccharide-activated murine macrophage model in cell line RAW 264.7	[32]
Anti-inflammatory	Acmella	Aerial parts	Ethanol	Wound Healing activity in male Wistar rats and Tail-Flick test in male Swiss mice	[84]
Anti-inflammatory	Acmella	Leaves	Ethanol	Acute gastric lesions induced in female Wistar rats	[48]
Anti-inflammatory	Acmella	Aerial parts	Aqueous	Carragenan-induced paw edema in rats	[24,85]
Anesthetic	Acmella	Aerial parts	Aqueous	Intracutaneous wheal in guinea pigs and plexus anasthesia in frog	[34]
Anesthetic	Acmella	Aerial parts	Aqueous	Acetic acid-induced writhing response in albino mice and tail flick method in albino rats.	[24]
Anesthetic	Acmella	Leaves	Ethanol	tail flick in albino rats	[85]
Anesthetic	Acmella	NA	Ethanol	Franz diffusion cell experiments using porcine buccal mucosa	[86]
Anesthetic	Acmella	Aerial parts	Ethanol,	In vitro permeation franz diffusion cell experiments pig esophagus epithelium	[87]
Antioxidant Activity	Acmella	Aerial parts	Ethanol, hexane, chloroform, ethyl acetate	In vitro DPPH	[32]
Antioxidant Activity	Acmella	Aerial parts	Methanol, chloroform, ethyl acetate, hexane	In vitro DPPH and SOD Assay	[35]

mucoadhesive films (10% JB: 2.37 mg; 20% JB: 5.13 mg; 10% JBC: 3.14 mg) was lower than the concentration of lidocaine/prilocaine (EMLA1: 7.5 mg) used in the control group.

Acmella is used since long time by traditional medicine for toothache pain treatment. Boonen et al. (2010) proved that spilanthol permeates buccal mucosa of pigs using a vertical Franz diffusion cells method. They compared the permeation effect of two formulations of oral gel (Indolphar® and Buccaldol®) with a pure Acmella ethanolic extract with propylene glycol, using a porcine buccal mucosa of pig (426 ± 10 μm). A different local or systemic effect has been obtained when different formulations were used. The purely aqueous permeation coefficient Kp,aq (± SEM) was found to be 11.3 (± 0.403) 10–3 cm/h. An N-alkylamide profiling from a 65% ethanolic *S. acmella* extract was done using HPLC/ESI-MS. Eleven N-alkylamides were identified and also systemic effects were observed after topical administration on porcine buccal mucosa [86].

De Freitas-Blanco et al. (2016), [87] confirmed the permeation effects observed by Boonen et al., utilizing different concentrations of spilanthol and different films composition (2010) as well as a different permeation barrier: the pig esophageal mucosa. The permeation flux rates observed in this study were high when compared with those found by Boonen et al., (2010) [86]. This different finding could be due to the different thickness of the barrier used (buccal mucosa versus esophageal mucosa) as well as to the 10 times greater spilanthol concentration used in the experiment of De Freitas-Blanco et al. (2016), [87], with higher flux of the active component, in agreement with Fick's first law of diffusion. Also, the duration of the analgesic effect was correlated to the flux rate and this could be due to the greater amount of spilanthol reaching the specific receptors. This observation is in line with a previous study of Franz-Montan et al. (2013) [99] who found a marked correlation between the flux of benzocaine across pig esophageal epithelium and anesthetic efficacy in volunteers. The analgesic effect was observed after only two minutes of application thus confirming what found in previous studies [24,85]. As a consequence, an N-alkylamide formulation applied on the buccal mucosa could be an interesting route to reach the systemic level.

Rios et al. showed that a Heliopsis longipes extract, in which spilanthol was the main active compound, induced cortical GABA (gamma-aminobutyric acid) release in an ex vivo in vitro mice brain-tissue study [28]. In order to exert these CNS effects, these compounds must be able to cross several physiological barriers in the human body. Using in vitro Franz diffusion cell experiments, it has already been shown that the N-alkylamide spilanthol can permeate the human skin and pig oral mucosa, reaching the systemic circulation after topical application [33,86].

Alkylamides modify immune cell activity, as well as cannabinoids: this could represent a great opportunity to treat various neuroinflammatory diseases [99,100].

As already described, *Spilanthes acmella* possesses strong anti-inflammatory effects [24,32] and this could be one of the biological mechanisms that favor the analgesic effect of Acmella extracts. The analgesic effect of genus Spilanthes has been correlated to multiple mechanisms: inhibition of prostaglandins synthesis [36], activation of opioidergic [101], serotoninergic and GABAergic systems [102] and anesthetic activity through blockage of voltage-gated Na channels [34]. In an acute pain mouse model, *Acmella oleracea* has been reported to have antiallodynic and anti-oedematogenic activities due to alkylammides and in particular spilanthol [90]. The molecular mechanism was already described for spilanthol demonstrated to act as modulator of TRPA1 receptors and as TRPV1 antagonist, thus promoting analgesic effects [91].

In Mexico, the root of *H. longipes* is used as a condiment and to treat tooth and muscular pain in traditional medicine. Cilia-Lopez et al. (2010) in male albino mice studies confirmed that both affinin (1 mg/kg), synonymous of spilanthol, and its ethanol extract (10 mg/kg) showed analgesic effect similar to ketorolac (6 mg/kg) [38]. The

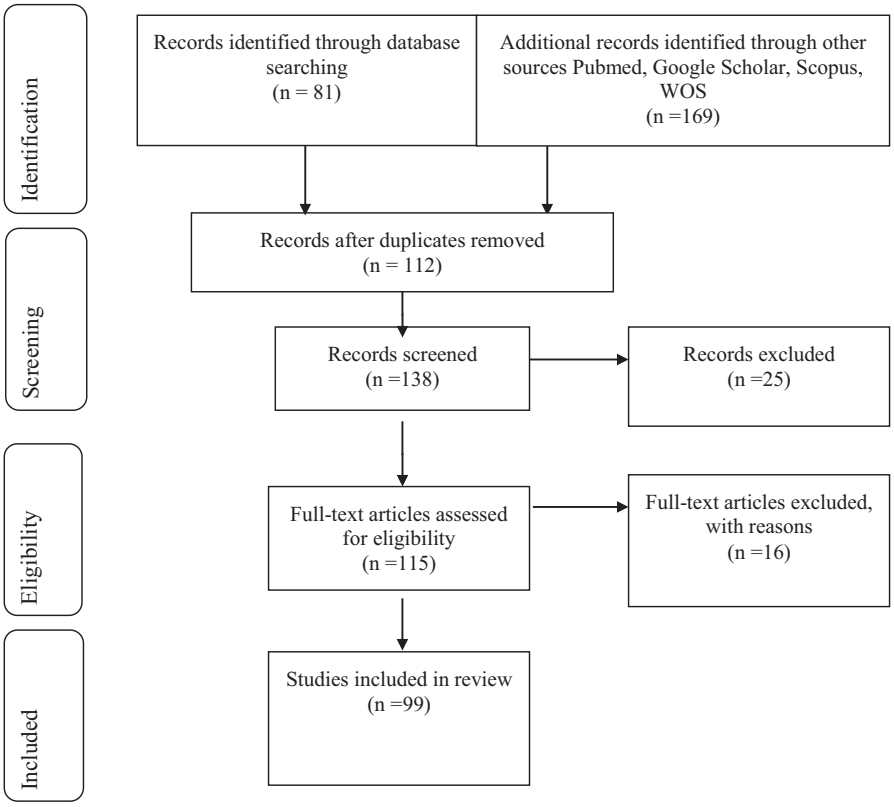

Fig. 3. Flow diagram of the review process. WOS, web of science.

antinociceptive effect of *H. longipes* was evaluated with the acetic acid and hot-plate tests, which are used to detect narcotic and non-narcotic analgesia, respectively. Since the acetic acid test is used to evaluate peripheral analgesic effects of drugs, this study gives evidence that affinin and its ethanol extract have analgesic action by significantly reducing the nociceptive reactions. Given that the abdominal contraction relates to the sensitization of prostaglandin-nociceptive receptors and of sympathetic nervous system mediators, it is likely that affinin and its ethanol extract inhibit either their synthesis or the contact with their receptors, thereby producing the analgesic effect [38].

4. Conclusions

Studies reported in this review confirm anti-inflammatory and antioxidant activities of Acmella, postulating that transcription factors of the nuclear factor-κB family (NF-κB) trigger the transcription iNOS and COX-2 and several other pro-inflammatory mediators, such as IL-6, IL-1β, and TNF-α. The antinociceptive effects has been demonstrated and have been related to different processes, including inhibition of prostaglandin synthesis, activation of opioidergic, serotoninergic and GABAergic systems, and anesthetic activity through blockage of voltage-gated Na channels.

This review showed that *Acmella oleracea* represents a promise for pain management and that human studies must be conducted, particularly in chronic degenerative diseases, where pain is a significant critical issue.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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None.

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