



Review

Spilanthol-containing products: A patent review (1996–2016)

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ABSTRACT

Background: Spilanthol is a bioactive alkamide widespread in Asteraceae and Piperaceae plant species. The species from Asteraceae are famous because of their sensorial anesthetic and spicy properties. One of these plants is *Acmella oleracea*, popularly known as jambu, is widely used as a spice in Brazilian cuisine and as a folk remedy. Many scientific papers can be found in the literature regarding the biological importance of spilanthol and its methods of extraction. However, to date, none of the studies has presented a technological mapping of patents involving this natural product.

Scope and approach: The present study aimed to compile data relating the state of the art on patents filed or granted between 1996 and 2016 involving spilanthol. To that end, a patent research was performed in the international patent database Patentscope, in a period of 20 years (1996–2016), using the keyword spilanthol.

Key findings: Patents were separated into four groups of interest, according to the technological use of spilanthol: a) pharmacological properties; b) use in cosmetics; c) methods for obtaining and d) sensorial effects. Only 91 patents were found regarding the first three groups, which showed that there is a scope for the development of new technologies. The sensorial properties of spilanthol are widely used in oral care compositions, personal products, cleaning products, foodstuffs and beverages.

Conclusions: This study presents different technological approaches to apply spilanthol, which helps to visualize opportunities and to boost innovation for new products.

1. Introduction

Alkamides (alkylamides) are a group of secondary metabolites found in more than 25 plant families (Boonen et al., 2012), including Aristolochiaceae, Asteraceae, Brassicaceae, Euphorbiaceae, Menispermaceae, Piperaceae, Poaceae and Rutaceae. Over 300 alkamides have been identified from those eight plant families. These metabolites form a distinct class of natural products in which different amino acids are combined with unsaturated fatty acids via peptide bonding. The interest of investigating this class of substances comes from their unique tingling and pungency effects, which are usually accompanied by salivation and anesthesia (Greger, 2015).

Spilanthol, (2*E*,6*Z*,8*E*)-*N*-isobutyl-2,6,8-decatrienamide, also known as affinin (Fig. 1) is a well-known bioactive alkamide that is found in different plant species belonging to Asteraceae family which is one of the major alkamides responsible for the sensorial effects (pungency, tingling, numbing and mouth-watering) that characterizes these plants. Industrial interest has increased these last few decades around this food ingredient (Greger, 2015). One of these plants are *Acmella oleracea*, popularly known as jambu, which is widely used in the cuisine of the North and Northeast of Brazil, as well as popular medicine for the

treatment of toothaches, due to the anesthetic effect caused when its aerial parts are chewed. Also, several plants in which spilanthol is obtained are frequently used as traditional medicine for toothache, thanks to spilanthol analgesic effect (Rios, Guadarrama, & Gutiérrez, 2007; Wu et al., 2008; Abeysiri, Dharmadasa, Abeysinghe, & Samarasinghe, 2013; Prachayasittikul, Prachayasittikul, Ruchirawat, & Prachayasittikul, 2013). In accordance with the European Food Safety Authority, the use of spilanthol as flavoring in the European industry corresponds to an intake of 24 mg/capita/day on the basis of this Maximized Survey-derived Daily Intake approach (EFSA, 2015). Furthermore, it is able to penetrate the skin after topical administration, to pass the endothelial gut and also to cross the oral mucosa as well as the blood-brain barrier (Verysse et al., 2014). Additional studies can be found in the literature concerning the biological importance of this metabolite, such as anti-nociceptive (Rios, Guadarrama, & Gutiérrez, 2007, Déciga-Campos, Arriaga-Alba, Ventura-Martínez, Aguilar-Guadarrama, & Rios, 2012), anti-inflammatory (Wu et al., 2008; Dias et al., 2012), antimutagenic (Arriaga-Alba, Rios, & Déciga-Campos, 2013), antifungal and antimicrobial (Molina-Torres, Salazar-Cabrera, Armenta-Salinas, & Ramírez-Chávez, 2004, Dubey, Maity, Singh, Saraf, & Saha, 2013, Cruz, Cheetham, Arnason, Yack, & Smith, 2014, insecticidal (Moreno,

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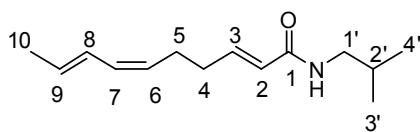


Fig. 1. Chemical structure of (2E,6Z,8E)-N-isobutyl-2,6,8-decatrienamide (spilanthol).

Carvalho, Picanc, Morais, & Pereira, 2012; Sharma & Kumar, 2013), antiplasmodial (Silveira et al., 2016), larvicidal against *Aedes aegypti* e *Anopheles albimanus* (Simas et al., 2013; Hernández-Morales et al., 2015) e anti-wrinkle (Veryser et al., 2014). Despite of the large number its potential bioactive properties and applications, to the best of our knowledge there are only a few spilanthol-based commercial products available for pharmacological purpose: buccal gels (Buccaldol[®], from Alphamega, France) and (Indolphar[®], from ID Phar, Belgium) presenting analgesic and anti-inflammatory activities) and tinctures for topical treatment of infections (Vogel spilanthol tincture containing 65% ethanol, from Biohorma, Belgium).

Recently, Barbosa et al. have published a review on spilanthol (Barbosa, Carvalho, Smith, & Sabaa-Srur, 2016), however, to date, none of the review studies has presented a technological mapping of the patents involving this natural product.

Due to its amphiphilic structure, spilanthol can be extracted from plants using either polar solvents (e.g. methanol and ethanol) (Boonen, Baert, Roche, Burvenich, & De Spiegleer, 2010, Abeyisiri et al., 2013, Silveira et al., 2016) or less polar solvents such as hexane (Costa, Arumugam, Garipey, Rocha, & Raghavan, 2013; Nakatani & Nagashima, 1992) and supercritical CO₂ (Dias et al., 2012). It also can be commercially obtained for U\$ 125.00/5 mg (ChromaDex[®], USA, 2017).

It is remarkable that searching on patent documents is a very important source of technological information, as it allows accessing the state of the art of the knowledge on protected technologies and can help to avoid duplication of research into a particular subject. Moreover, the increase of a country economy and competitiveness is linked to the development of technological innovation measured by the number of the patents requested (Cockburn & Long, 2015, Pereira, Silva, & Porto, 2015).

Given the background, this review was based on a data compilation of the state of the art on patents involving spilanthol between 1996 and 2016.

2. The importance of patents

Technological innovation is widely recognized as a key element of economic and public health progress (Grabowski, DiMasi, & Long, 2015). According to the World Intellectual Property Organization (WIPO) a patent is a legal document in the public domain that ensures an exclusive right for an invention, which is a product or a process that provides, in general, a new solution to a technical problem. In return, the inventors agree to disclose all the technical information about the invention to the public in a patent application. A patent can last up to 20 years, but the patent holder has to pay fees throughout the period for the patent remain valid. In general, the exclusive rights have a legal effect only in the country in which the patent is granted. On the other hand, WIPO administers the Patent Cooperation Treaty (PCT) that is an international patent application valid in 152 different countries designed to make the process easier and less costly (WIPO, 2015).

Patent analysis is a useful analytical tool for summarizing the innovation profile of a specific subject (Lee, Kang, & Shin, 2015). Analyzing patents is essentially advantageous to manage the complexity of searching and inter-relating patent information. These analyses are performed strategically on key points, such as patents trends, forecasting technological developments and strategic technology planning. The patent mapping is an instrument widely used to visualize the

scenario of a specific technology, therefore the correct choice of research variables, such as the selection of keywords and database, is very important (Lee et al., 2015; Nemitz et al., 2016). Data acquisition can be done by searching national offices and international databases. Patentscope is a free database provided by WIPO that allows access to PCT applications (administered by WIPO) and a wide range of other countries including the European Patent Office (EPO), United States Patent and Trademark Office (USPTO) and Japan Patent Office (JPO) in full text format on the day of publication, as well as to patent documents of participating national and regional patent offices. Patent documents contain vast information on patented invention, including technological area of the invention, the inventor, the organization to which the invention is assigned (assignee or proprietor) and their geographical location. That is why, patent information is a very useful tool to understand industrial developments, revealing all about the most recent and commercially feasible technologies.

3. Patents containing spilanthol

Considering the number and relevance of scientific papers about spilanthol, a data compilation of patents involving this subject is an interesting path to evaluate novelty in this area.

The qualitative and quantitative analyses were conducted based on a search in the international database Patentscope (patentscope.wipo.int), following to WIPO, over a period of 20 years (1996–2016). The selected keywords were “spilanthol” and “affinin” and the search was made in the title, abstract and full text. For all documents the following aspects were observed: Number and date of deposit; title; abstract; assignee country and technological focus. After the analysis, the patents were categorized in groups according to the technological use of spilanthol.

This search provided 1444 records. It is important to highlight that often the same technology is patented in more than one country, which makes the number of records higher than the number of patented technologies. The documents are identified by two letters at the beginning, indicating the country where it was deposited and a letter at the end, showing the current situation (letter A, for application and letters B, C or T for grant). Patents starting with “WO” are temporary PCT, which is an international treaty that officializes a system for the filing of patent applications and allows obtaining patents in several countries from a single application for 18 months.

After duplicate data has been removed, 497 (360 applications and 137 concessions) documents were grouped in four categories according to the technological use of spilanthol: a) pharmacological properties (30); b) use in cosmetics (30); c) methods for obtaining (31) and d) sensorial effects (406), representing a total of 95 different technologies. Among them, the technology entitled “Flavor release from multilayer film during brushing”, first filed by the American company Colgate Palmolive, in 2010 and published in 2012 under the number WO2012002946 (A), is the one that has the largest number of patents in different countries (12).

Fig. 2 shows the number of patents filed and granted between 1996 and 2016. From 1996 to 2000, only the patent “Extended release of additives in comestible products” was published. The number of applications started to increase in 2005, peaking in 2007, signaling a potential increase in product and process innovation in a global context. Then a slight decrease and constancy was observed in the following years. 2014 was the year with the highest number of patents granted.

Among 32 published documents involving the pharmacological properties of spilanthol (Table 1), the technology entitled “Herbal composition for improving oral hygiene, for providing local anesthesia, for use as an oral sensate, flavor enhancer and potentiator, and methods of using same”, filed by the Philippine company Phytos, refers to obtain a composition from *Heliopsis longipes*, a traditional Mexican plant with higher content of spilanthol. The patent highlighted that a spilanthol standard has been produced for the first time, enabling quantitative

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