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# Technological Prospection and Scientific Innovation of *Ilex paraguariensis* Saint-Hilaire in the Wound Healing Process

**Pedro Augusto Clemente**[1]
https://orcid.org/0000-0002-4116-076X

**Kelby Cavalheiro Mendonça**[2]
https://orcid.org/0000-0002-5687-7034

**Giovana Frazon de Andrade**[1,3,4]
https://orcid.org/0000-0002-9120-0600

**Larisse Medeiros Goncalves**[5]
https://orcid.org/0000-0002-8546-3244

**Cristiane Maria Tonetto Godoy**[3,4,6]
https://orcid.org/0000-0001-6150-9976

**Jhonatan Matheus Piaceski Rocha**[7]
https://orcid.org/0000-0002-8360-2191

**Weber Claudio Francisco Nunes da Silva**[3,4,6]
https://orcid.org/0000-0002-4688-3115

**Jéssica Brandão Reolon**[6]
https://orcid.org/0000-0001-7388-8256

**Daiane Finger Ferreira**[8]
https://orcid.org/0000-0003-2758-7860

**Maria Cristina Umpierrez Vieira**[9]
https://orcid.org/0000-0002-2173-4009

**Juliana Maria Silva**[1,3]
https://orcid.org/0000-0001-8992-2658

**Luana Mota Ferreira**[10*]
https://orcid.org/0000-0001-9951-587X

**Juliana Sartori Bonini**[3,4,6]
https://orcid.org/0000-0001-5144-2253

[1]Universidade Estadual do Centro-Oeste, Departamento de Fisioterapia, Guarapuava, Paraná, Brasil; [2]Universidade Estadual do Centro-Oeste, Programa de Pós-Graduação em Propriedade Intelectual e Transferência de Tecnologia para a Inovação, PROFNIT, Guarapuava, Paraná, Brasil; [3]Universidade Estadual do Centro-Oeste, Laboratório de Neurociências e Comportamento, Guarapuava, Paraná, Brasil; [4]Pesquisa e Assistência a Pessoas com Doença de Alzheimer, Associação de Estudos, Guarapuava, Paraná, Brasil; [5]Universidade Tecnológica Federal do Paraná, Departamento de Regionalidade e Sustentabilidade, Pato Branco, Paraná, Brasil; [6]Universidade Estadual do Centro-Oeste, Departamento de Farmácia, Guarapuava, Paraná, Brasil; [7]Universidade Estadual do Centro-Oeste, Programa de Pós-Graduação em Química Aplicada, Laboratório de Cromatografia e Produtos Naturais, Guarapuava, Paraná, Brasil; [8]Universidade Estadual do Centro-Oeste, Departamento de Química, Guarapuava, Paraná, Brasil; [9]Universidade Estadual do Centro-Oeste, Departamento de Enfermagem, Guarapuava, Paraná, Brasil; [10]Universidade Federal do Paraná, Departamento de Farmácia, Curitiba, Paraná, Brasil.

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*Correspondence: luanamota@ufpr.br; Tel.: +55 41 3360 4095 (L.M.F.).

## HIGHLIGHTS

- Current wound healing devices present limitations.
- Prospection of natural products draw attention to wound treatment.
- *Ilex paraguariensis* is promising in wound healing.
- Bioactive compounds promote antioxidant and anti-inflammatory activities.

**Abstract:** Natural compounds are possible alternatives for wound treatment, including *Ilex paraguariensis*, a plant with several pharmacological actions already reported, including anti-inflammatory, antibacterial, antioxidant, and healing activities. Therefore, this study aimed to perform a technological and scientific mapping of *Ilex paraguariensis* used for healing and/or analgesic purposes. Technological prospection was carried out in the Questel-Orbit system, while the scientific research was carried out in PubMed, Web of Science, and SCOPUS databases. The terms "*Ilex paraguariensis*", "Yerba-mate", "Painkiller", "Analgesic", "Wound", "Healing", and "Scar" were combined using Boolean operators "OR" and "AND". The technological prospection resulted in 164 patents found initially. After sorting the abstracts, five patents were read entirely, of which three were selected. Such selected patents report using *Ilex paraguariensis* for analgesics, wound healing, personal care, and pharmaceutical applications. In addition, the scientific research showed a small number of studies aimed at using *Ilex paraguariensis* for healing and/or analgesic purposes. Among the 26 articles initially found, only 5 met the inclusion requirements. Scientific studies demonstrate that *Ilex paraguariensis* is used as an extract or drink, presenting promising results regarding analgesia, inflammation, and wound healing, using *in vitro* or *in vivo* models. Despite the potential of *Ilex paraguariensis* in skin wound therapy, our study demonstrates that few patents and scientific studies explore *Ilex paraguariensis* for this purpose. This fact may be an incentive for the development of further studies employing *Ilex paraguariensis* in cutaneous wound management and the pain associated with them.

**Keywords:** Yerba mate; Natural products; Scars; Analgesia; Painkiller.

## INTRODUCTION

Cutaneous wounds are injuries to the skin's surface caused by mechanical, chemical, and thermal trauma or systemic diseases such as diabetes and leishmaniasis. After the lesion in the cutaneous tissue, the skin integrity must be promptly restored to maintain its physiological functions. Wound healing is orchestrated by a complex process that involves all cells, tissues, cytokines, chemokines, and skin growth factors. This process is divided into three main phases: inflammatory, proliferative, and remodeling [1].

In the inflammatory phase, a large influx of neutrophils and macrophages stimulates the reactive species production, triggering an oxidative stress environment [2]. When cells are healthy, the inflammatory phase is well orchestrated, lasting only a few days, followed by wound re-epithelialization, granulation tissue formation, wound contraction, and scar formation. However, when cells are dysfunctional, the inflammatory process is prolonged, skin integrity is not restored, and pathological ulcer or fibrosis occurs. In addition, pain is a factor that is often present in skin lesions and, if neglected, can impair the healing process, causing discomfort to the patient [3].

Wound management becomes challenging, mainly in chronic lesions that do not progress through an orderly and timely process in promoting anatomical and functional integrity [4,5]. Multiple mechanisms cause chronic wounds, including hyperglycemia, neuropathy, impaired vascular status, and the risk of developing a chronic wound is higher in diabetic, early, and obese patients [4,5]. Chronic wounds are susceptible to infection, significantly burdening the healthcare system. Managing chronic wound infections is complex, and several conditions contribute to the delayed healing process, such as comorbidities and concomitant systemic and local factors [5,6]. The current treatment options for infected wounds have been unsuccessful in healing because of biofilm formation and drug resistance. In addition, topical corticosteroids are commonly used; however, these drugs have poor skin permeation and need repeated administration, causing patient discomforts and adverse effects, such as rosacea, stretch markers, and immunological changes [7].

The complex healing process and failures of conventional treatments lead to the rationale for seeking a new therapeutic approach to wound management. The unique ability of natural molecules to interact with different biomolecules has demonstrated the potential of plants as a promising alternative in searching for new products with economic, social, and environmental value. Natural compounds have been studied for wound healing. The exudate may contain multiple bacteria resistant to conventional drugs, free radicals forming during the inflammatory phase, and factors interfering with wound repair [6,8]. Among natural products, *Ilex paraguariensis* Saint-Hilaire (*I. paraguariensis*) draws attention due to its composition, which is rich in bioactive compounds and can be used for wound healing therapy in multiple targets [9,10].

*Ilex paraguariensis*, popularly known as yerba mate, is an arboreal, umbrophilous, and endemic plant; it is an important specie of the Aquifoliaceae family, native to southern Brazil, Paraguay, and northeastern Argentina. The specie distribution coincides mainly with the subtropical Araucaria Forest, covering approximately 540,000 $km^2$ [11–13]. Before being classified by Saint-Hilaire, the plant was already known and used by indigenous people, mainly by the Guaranis in Brazil, with reports since the pre-colonial period

[14]. Yerba mate consumption is expanding worldwide, mainly as mate tea extraction, a typical drink from the south of Brazil, which is part of the habits and customs of people in South America [12,15–17].

Although the consuming advantages of *I. paraguariensis* are not fully established, studies have demonstrated its potential as a functional food product [18]. Among the main bioactive compounds found in the plant leaves and branches are chlorogenic acid, xanthines (caffeine and theobromine), caffeic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinoic acid, quercetin, kaempferol, rutin, amino acids, minerals, and vitamins [16]. A composition rich in biocompounds results in several therapeutic properties already described, including anti-inflammatory, antibacterial [19,20], antidiabetic [21], healing [10,22], antioxidant [23], neuroprotective [15], anxiolytic [12], and antifungal [24] as well as a protective effect on liver cells, central nervous system stimulation, and beneficial effect on the cardiovascular system [12,25].

Considering the wound healing process limitations, the constant search for new therapeutic products for treating such disorders, and the *I. paraguariensis* therapeutic potential, this study aimed to present a technological prospection and scientific innovation using *I. paraguariensis* for healing and/or analgesic purposes. Thus, we will present the main pharmacological aspects of *I. paraguariensis*, extracting data from patents and scientific articles, which will then be discussed to elucidate the effects on the wound healing process and pain management.

## RESEARCH STRATEGY

This technological and scientific prospection is exploratory and documentary research of a quali/quantitative nature. It sought to elucidate the number of patents and scientific articles within the study scope and qualify the documents' content, with subsequent description and discussion of the data found. The "state of the art search" was used for the technological prospection, in which patent documents were surveyed based on Patent Families, between June and August 2022, in the Orbit-Questel database. This platform hosts patents and has comprehensive coverage. The search was carried out by combining the terms "*Ilex paraguariensis*", "Painkiller", "Analgesic", "Wound", "Healing", "Scar", using Boolean operators. No filter was applied in the patent year. The inclusion criteria were patents demonstrating the use of *Ilex paraguariensis* for analgesic effects and application in wound healing. Innovations that did not involve these pharmacological activities were excluded.

The research of scientific articles was performed in the PubMed, Scopus, and Web of Science databases from November to December 2022, following the PRISMA guideline [26]. The terms related to *I. paraguariensis* and healing/analgesic effects are described in Supplementary Material Table S1, which presents the database search strategy. Likewise, no filter was applied in the publication year. Each database result was exported to the Rayyan online platform, where each article was first evaluated by reading the title and abstract. Two independent reviewers analyzed the papers, and a third reviewer was consulted in case of discrepancies. Duplicate items or items not within the review area of interest were excluded. After the preliminary selection, the articles were read in full to assess whether they met the eligibility criteria. Research articles that demonstrate the activity of *I. Paraguariensis* in wound healing or acting as an analgesic agent were included. Publications that did not respect the delimitated theme and the study objective, opinion or reflection articles, editorials, and book chapters were excluded.

Next, the relevant data were extracted from the patents and selected articles. Quantitative data were revealed regarding patents, such as protections by country and technological domain, followed by a content description of each selected patent. The following data were extracted from the articles: type of plant extract and pharmacological model used.

## RESULTS AND DISCUSSION

### *Ilex paraguariensis*: general aspects

Skin wounds represent a public health problem considering the psychological, social, and economic impact on the patient and the high and increasing costs for the health system [27]. In recent years, investigating natural products with biological activities has been proven to be a promising strategy for numerous disease treatments, mainly due to the significant structural diversity, specific stereochemistry, and interaction with active protein sites [28]. *Ilex paraguariensis* has already demonstrated different therapeutic potentials, including healing, antioxidant, anti-inflammatory, and antimicrobial potential, which are significant in treating cutaneous wounds, especially those presenting disorders in the inflammatory phase of healing [2].

Regarding medicinal properties, *I. paraguariensis* natural matrix has a variety of bioactive compounds which provide several therapeutic benefits. Among the constituents (Supplementary Material Figure S1. Structure of steroid saponins, triterpene saponins, and ursolic acid saponins) are polyphenols, xanthines,

alkaloids, saponins, and vitamins, such as vitamins B3 and B5 [16]. Polyphenols are substances characterized by hydroxyl groups attached to benzene rings. The high content of polyphenols in yerba mate is directly associated with antioxidant [29,30] and anti-inflammatory [31] properties. Saponins are responsible for anti-inflammatory [32], anti-cholesterol [33], anti-obesity [34], and some have antiparasitic properties [35]. Matesaponins 1, 2, 3, 4, and 5 are some of the main saponins identified in *I. paraguariensis*, all containing ursolic acid (Supplementary Material Figure S2. Chemical structure of major compounds presents in *I. paraguariensis*) as a hydrophobic part [36,37]. Derivatives containing oleanolic acid were also identified [38].

In the phytochemical profile, bioactive compounds such as caffeine, theobromine, theophylline, quinic acid, chlorogenic acid, caffeic acid, quercetin, and kaempferol stand out (Supplementary Material Figure S2. Chemical structure of major compounds presents in *I. paraguariensis*), which give the plant a series of pharmacological actions. The chemical composition present in yerba mate and the pharmacological properties already reported lead us to believe that *I. paraguariensis* can have great potential as a natural activity in wound therapy, acting in healing and pain control.

## Technological prospecting

Technological prospecting is the first step in the long journey of the strategy to add value to new knowledge and technologies through the legal protection of intellectual property to convert innovation. To materialize a promising idea and transform it into innovation, the first step is the revelation, followed by prospection. Essentially, it is necessary to have complied with the indispensable requirements for the protection of intellectual property and to receive transactional value as an intangible asset to be a financial investment object and technological capital. Finally, reaching the market and producing wealth and well-being, increasing productivity, competitiveness, and life quality for the benefit of society [39].

Technological prospecting qualifies research to verify the limits where knowledge of a specific area is found at a given time [40]. Prospective studies allow for obtaining a broad family patent analysis, knowing potential technologies, forecasting new products or services, and mapping technologies. For this, the data herein present compose a report showing the deposits number evolution, countries where the technology is protected, and the evolution of deposits by country, among others [41].

The search on Orbit-Questel found that the term "*Ilex paraguariensis*" generated 615 results. Regarding the application for healing purposes and/or analgesics in wounds, the terms *Ilex paraguariensis*, analgesic, healing, wound, and scar were combined, as seen in Table 1.

**Table 1.** Combination of terms used in Orbit-Questel.

| Combination of terms | Results |
|---|---|
| *Ilex paraguariensis* | 651 |
| *Ilex paraguariensis* and painkiller | 3 |
| *Ilex paraguariensis* and analgesic | 164 |
| *Ilex paraguariensis* and painkiller or analgesic | 164 |
| *Ilex paraguariensis* and wound and healing | 149 |
| *Ilex paraguariensis* and scar | 55 |
| *Ilex paraguariensis* and wound and healing or scar | 152 |
| *Ilex paraguariensis* and painkiller or analgesic or wound and healing or scar | 164 |

Regarding the prospection of patents that use yerba mate for healing purposes and/or analgesics, 164 patents were obtained (Figure 1).

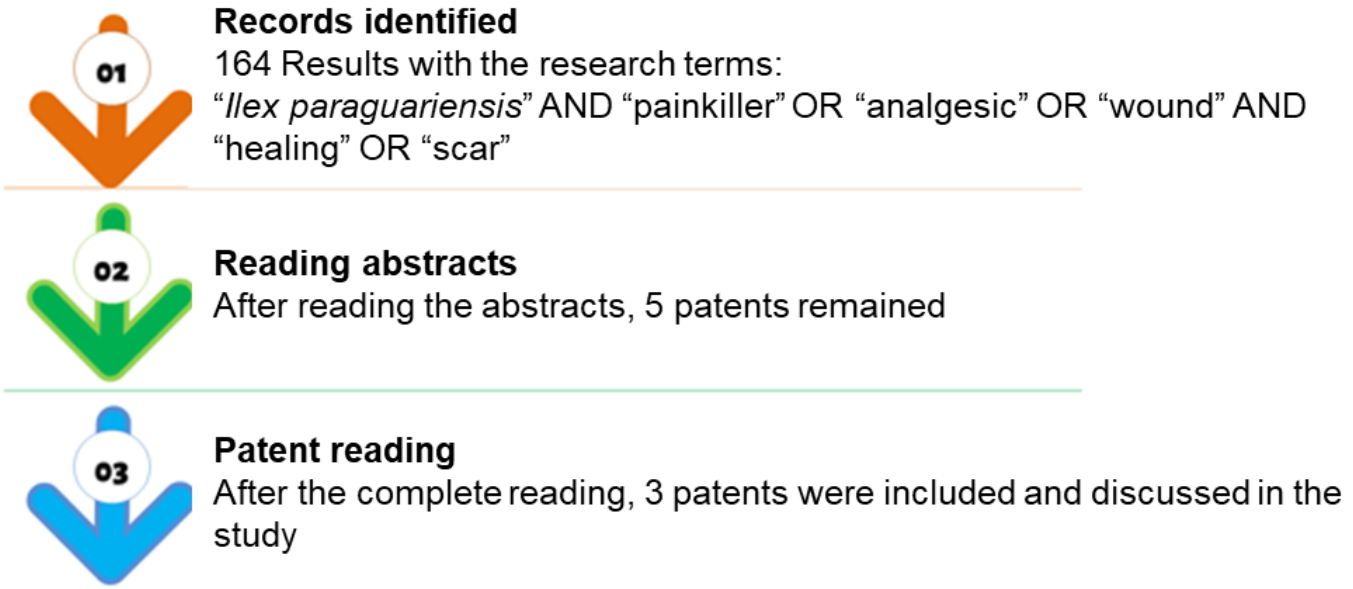


**Figure 1.** Systematic patent search flowchart.

After reading the patent summaries, 5 patents were selected, and with the complete reading of the patents contained in the previous step, only 3 were chosen for discussion (Table 2). Two of them were deposited in 2015 and one in 2018.

**Table 2.** Patent search results.

| Sequence | Publication number | Title |
|---|---|---|
| 01 | KR101500485 | Compositions to relieve, prevent or treat pain comprising extracts of *Ilex paraguariensis* as active ingredients. |
| 02 | EP3126011 | Fermentation extract of a bacterial strain for increasing adiponectin levels. |
| 03 | EP3371238 | Thermoformable dual lattice hydrogel compositions. |

Source: Orbit (2022).

Regarding patent protection by countries, the markets with the most protection are the United States (95), the European Patent Office (82), France (52), China (51), Germany (50), Japan (50), United Kingdom (49), Republic of Korea (42) and Canada (41) (Figure 2A). The first South American country in the ranking is Brazil, which is in 11th position. This information demonstrates which markets are most attractive for depositors to protect their technologies and maximize profits. In addition, to providing knowledge about which markets are little explored and which technologies are not protected, the research allows us to take advantage of the moment to register such patents, considering that they follow the principle of territoriality. Regarding the area of depositors, represented in Figure 2B, four companies stand out, namely: CHENANGO ZERO (21), SEDERNA (19), JOHNSON & JOHN CONSUMER (14), and SYMRISE (11).

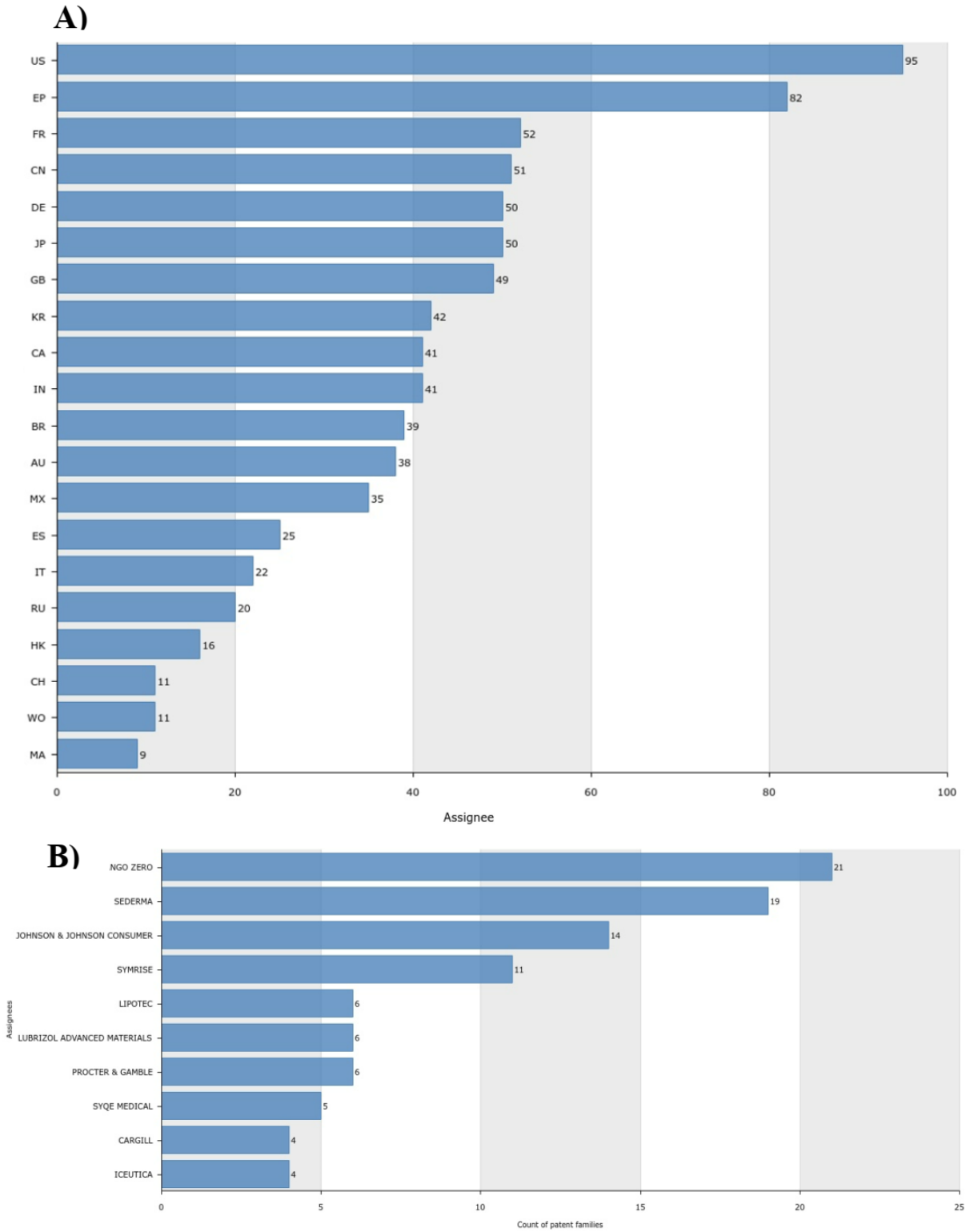


**Figure 2.** A) Patent Deposit by Market–Bars; B) The Top 10 Depositors of Patent Families. Source: Orbit (2022).

Although yerba mate is native to southern Brazil, Paraguay, and northeastern Argentina, there is a more significant number of patents distributed in North America, especially in the USA, which stands out in the world context with 95 patents protected in its territory (Figure 3). In Latin America, this may be related to the impact of the colonial period, where the first patents in the post-colonial period were rudimentary, providing weak legal security, patent rights with little use, little commercial value, and serving foreign interests [42].

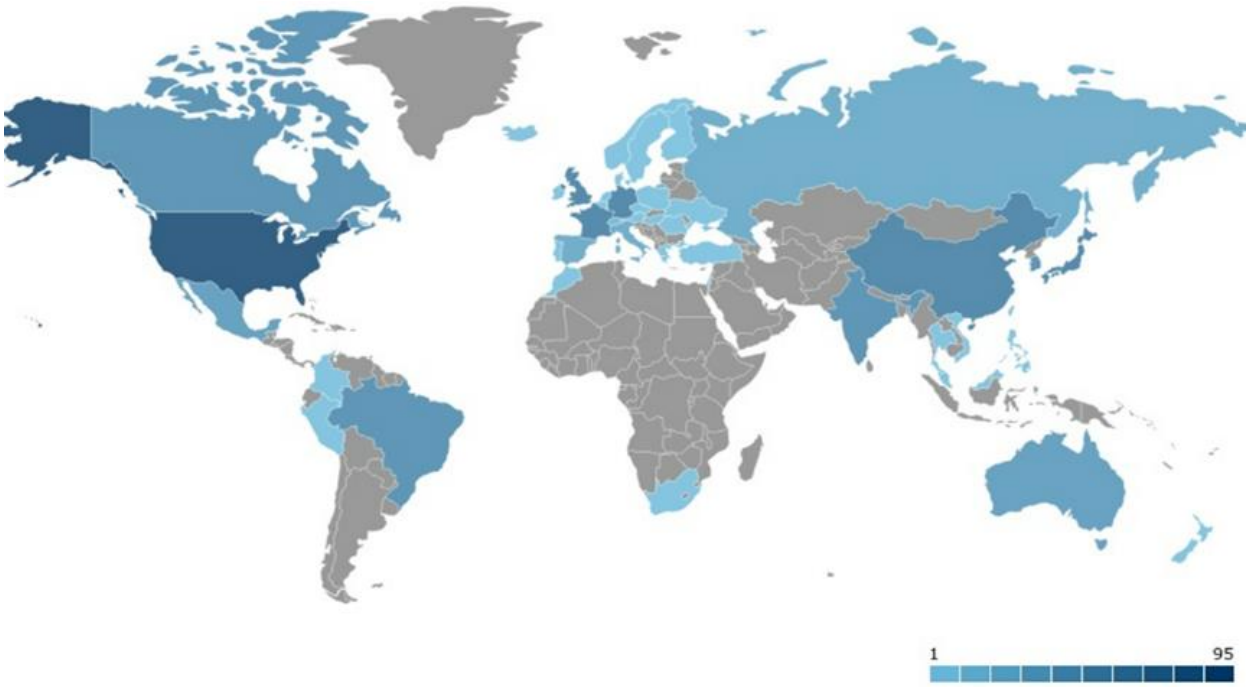


**Figure 3.** Patent Protection by Market – World Map. Source: Orbit (2022).

Another important fact is that 88.4% of patents involving *I. paraguariensis* remain valid, and 11.6% of patents lost protection, demonstrating that most inventions were created recently. Most of the technological domains are located in the areas of Fine Organic Chemistry (94) and Pharmaceuticals (93) (Figure 4), demonstrating the interest of large applicants in protecting their technologies in these domains.

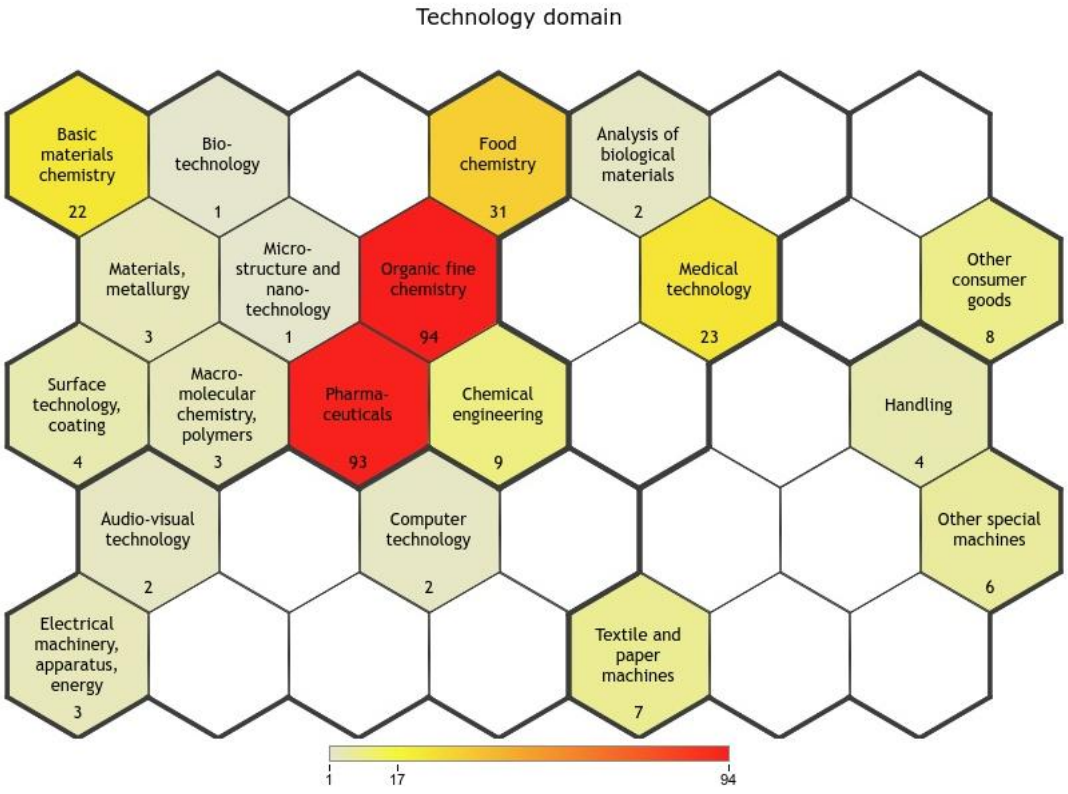


**Figure 4.** Depositors by Technological Domain. Source: Orbit (2022).

The first patent to be described is KR101500485, protected in South Korea, filed by KOREA FOOD RESEARCH INSTITUTE and published on March 10, 2015. The invention relates to a composition for relieving, preventing, or treating pain, comprising a yerba mate extract as an active ingredient. The design of the present invention not only has mitigating and treating effects on pre-generated pain but also exhibits a preventing effect when administered to an individual before

the occurrence of pain. The composition of the present invention shows a remarkable pain-relieving impact even by oral administration and is highly applicable to food products. The inventors investigated examples to develop patient-safe materials, particularly plant-derived materials, capable of effectively alleviating pain. As a result, herbs conventionally used as raw materials for tea are very effective in relieving, preventing, or treating pain, thus completing the present invention.

Next, patent EP3126011, protected by the European Patent Office, filed by LUBRIZOL ADVANCED MATERIALS, was published on March 30, 2015. The disclosed technology refers to a fermented extract of bacterial origin, which increases adiponectin levels. Said yeast extract is secreted by a strain of the *Bacillus pumilus* species. This invention also relates to cosmetic or dermo pharmaceutical compositions containing said yeast extract. Provide a solution to increase adiponectin level in adipocytes and mitochondrial activity in muscle by a fermented extract of a strain of Bacillus pumilus species with LMG deposit number P-28202 containing peptide and glycidic material with molecular weight less than 7000 Da. In particular, it can be used for muscle strength, wound healing, and skin firming.

Finally, patent EP3371238, protected by the European Patent Office, filed by LUBRIZOL ADVANCED MATERIALS, was published on September 12, 2018. The invention relates to a hydrogel composed of a poly(acrylic acid) microgel, pH-sensitive, and water-soluble thermoplastic polyurethane. The hydrogels of the invention resist deformation at room temperature but are thermoformable and water and electrolyte resistant at room and body temperature. The hydrogel can be used in personal care, healthcare, and pharmaceutical applications where smooth adhesion, high conformability, and a high aqueous environment are beneficial, such as controlled drug delivery devices, microfluidic devices, biosensors, and for dermal, mucosal, and transdermal delivery of chemically and physiologically active ingredients.

It was demonstrated that few patents use *I. paraguariensis* with healing/analgesic function, and none presented the combination of both functions, being a niche to be explored. The herb demonstrated, by patent KR101500485, relevant analgesic effects, including in the preventive treatment against pain. Patents with analgesic effects were search targets, as it is suggested that pro-inflammatory cytokines are biomarkers of pain related to the healing process [43]. As there is no treatment available to help obese patients who suffer severely from delayed wound healing [44], patent EP3126011 describes the use of the plant to increase adiponectin levels in adipose tissues and thus should have its effects evaluated in wound healing of obese populations, considering that trimeric adiponectin as a specific isoform is reduced in the abdominal adipose tissues of obese women with delayed wound healing, demonstrating a role for the trimeric form in the wound healing process in humans [44]. Puangpraphant & Mejia (2009) observed that combining matesaponins with quercetin showed synergistic inhibition properties of some specific markers with pro-inflammatory action. The combined phytochemicals were superior to the yerba mate tea extract [32]. Souza and coauthors (2015) also evaluated the anti-inflammatory properties by comparing methanolic extracts (MeOH/$H_2O$ 80:20, v/v) of leaves and bark of *I. paraguariensis*, where the bark showed superior anti-inflammatory power in inhibiting nitric oxide producers and prostaglandin 2 when compared with the leaf extract, which showed antioxidant power and higher polyphenol content, leading to the conclusion that compounds other than phenolics may be associated with anti-inflammatory action [45]. The patents demonstrated that *I. paraguariensis* is little explored for pharmacological purposes in wound healing. Even so, *I. paraguariensis* extracts have a wide variety of phytochemical compounds that have anti-inflammatory and antioxidant actions that should be better studied in the future, including primary metabolites such as polysaccharides, amino acids, minerals and vitamins, and secondary metabolites [16,24,46]. Polyphenols such as hydroxycinnamic acid, caffeic acid, chlorogenic acid, gallic acid, syringic acid, ferulic acid, feruloylquinic acid, 5-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, 3-O-caffeoylquinic acid, quinic acid, citric acid, quercetin glycoside, kaempferol glycoside, and rutin may play an essential role in the plant activities [47–49]. In addition to phenolic compounds, methylxanthines such as caffeine, theophylline, and theobromine are also found in large amounts [12,48].

## Scientific innovation

Since the patent finds were restricted, we sought to assess the evidence at the level of scientific innovation regarding *I. paraguariensis* employed in wound healing therapy. We opted for databases relevant to the health area, which presents a broad search spectrum, including several indexed journals. After searching the databases, 26 articles were found, 6 in PubMed, 11 in Scopus, and 9 in the Web of Science database (Figure 5). With the application of the eligibility criteria, 5 scientific articles were selected to be characterized and discussed in this research, which addressed an analgesic or healing effect of *I. paraguariensis* (Table 3). Two of the selected articles were published in the year 2015 (40%), one in the year 2016 (20%), one in 2020 (20%), and the most recent work in 2021 (20%). The herb was used in different

ways, two studies with the aqueous extract (40%), one with hydroalcoholic extract (20%), and two works where the herb was used as a drink (40%).

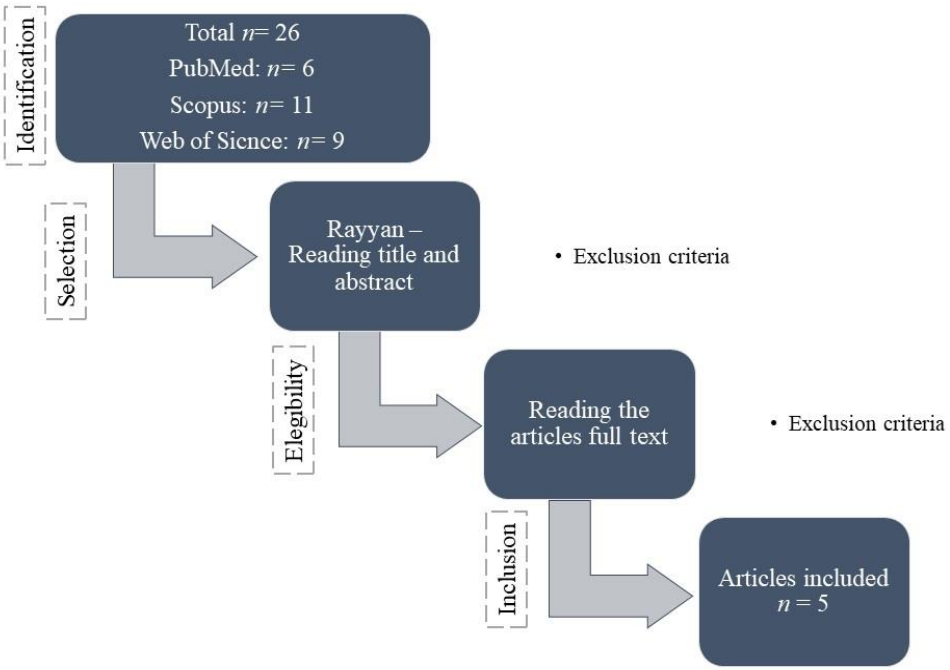


**Figure 5.** Systematic flowchart of the search strategy and publications selection.

**Table 3.** Description of studies found in the search for scientific innovation.

| **Reference** | ***Ilex paraguaniensis*** | ***In vitro/ In vivo* evaluation (dosage)** |
|---|---|---|
| Lim et al., 2015 | Hydroalcoholic extract | Analgesic (100 mg/kg and 300 mg/kg; oral route) |
| Romana-Souza et al., 2015 | Roasted mate tea beverage | Excisional wound model (0.03 mg/day for 14 days; oral route) |
| Carvalho et al., 2016 | Mate drink obtained by infusion | Analgesic and antiinflamatory (262,0–778,0 mg/kg; oral route) |
| Aliabadi et al., 2020 | Aqueous extract | Wound Scratch Assay (5 mg/mL and 25 mg/mL) |
| Nowacki et al., 2021 | Aqueous extract | Analgesic (250, 500, 1.000, 2.000 mg/kg; oral route) |

The first report found refers to the analgesic (antinociceptive) activity of a hydroethanolic extract of *I. paraguariensis* leaves, evaluated in a plantar incision model of postoperative pain and a model of nerve injury simulating neuropathic pain. This study provides essential information for this research since many wounds are caused by surgical procedures in which pain is often present. In this study, Lim and coauthors (2015) [50] evaluated the phytochemical profile of the extract obtained using the high-performance liquid chromatography technique, which demonstrated the presence of 3,5-dicaffeoylquinic acid, chlorogenic acid, and neochlorogenic acid as the main constituents. This composition gave the extract the ability to significantly attenuate mechanical hyperalgesia after oral administration of *I. paraguariensis* extract (100 and 300 mg/kg). In neuropathic pain evaluation, in addition to the extract, the activity of chlorogenic acid, one of the main actives of the plant, was also evaluated.

Interestingly, both the extract and the phenolic compound reduced hyperalgesia in the surgical lesion model, indicating that this activity could have a significant contribution to the analgesic action of the herb [50]. Pro-inflammatory cytokines, such as IL-6 and TNF-α, stimulate neuropathic pain while inhibiting pro-

inflammatory cytokines or administration of anti-inflammatory cytokines, such as IL-10, reduce pain in animal models of neuropathic pain. The hydroalcoholic extract of *I. paraguariensis* showed significantly lower IL-6, IL-2, and IFN-γ levels, suggesting an anti-inflammatory role in pain management. This result also makes us think that the herb has great potential in wound healing, especially in the inflammatory phase [50].

Chronic stress stimulates the production of oxidants and oxidative damage that compromise skin wound healing. Thus, Romana-Souza, Pires, and Monte-Alto-Costa (2015) evaluated mate tea as an alternative for managing oxidative disorders. The study aimed to investigate the effect of dietary supplementation with mate tea on skin wound healing in chronically stressed mice. Psychological stress, generated by environmental and emotional factors, seems to be involved in delaying the wound healing process. This happens due to the activation of the medullary sympathetic-adrenal and hypothalamic-pituitary-adrenal axes, which stimulate the release of catecholamines from the adrenal medulla and glucocorticoids from the adrenal cortex. With the release of stress hormones, there is an impairment of the inflammatory response, wound contraction, and dermal reconstruction, hindering the closure of the cutaneous wound. In skin lesions, stress-induced high epinephrine levels promote oxidative damage to lipids and proteins, directly contributing to delayed wound closure in mice [30].

Mate tea produced from the roasted *I. paraguariensis* herb is one of the most consumed beverages in several countries in South America, as mentioned earlier. The study cited above prepared the roasted mate tea drink by dissolving mate tea powder in water, followed by homogenization. The drink (1 mg/kg of body weight) was administered to the animals by gavage over 14 days, starting the second day after the stress protocol. A rotational stress model was used, compromising the animals' housing due to spatial disorientation leading to anxiety. After three days of stress, an excisional wound was made on the back of the animals, which had its healing evaluated at predetermined intervals [30]. Supplementation with mate tea attenuated the increase in plasma levels of normetanephrine induced by chronic stress and reduced levels of carbolated protein at the wound site. From the histopathological analysis, it is evident that chronic stress reduces re-epithelialization in the wound area, while in animals treated with mate tea, there was an increase in wound contraction and skin re-epithelialization. Due to the rich composition of polyphenols, yerba mate exhibits high antioxidant activity and can reduce the damage caused by oxidative stress in different pathologies. Such action may be related to increased production of endogenous antioxidants such as the enzyme glutathione peroxidase and reduced levels of catecholamines in plasma, thus reducing oxidative damage to lipids and proteins.

*Ilex paraguariensis* has also been evaluated in the form of a hot infusion, the famous “chimarrão” [51]. The study developed by Carvalho and coauthors (2016) aimed to determine the pharmacological activity of *I. paraguariensis* infusion on formalin-induced orofacial nociception and its possible mechanism of action. The authors simulated the effect of yerba mate at the same concentrations humans consume by mate ingestion. The analysis of the phytochemical composition showed high levels of chlorogenic acid and methylxanthines (caffeine and theobromine). To evaluate the antinociceptive activity, abdominal writhing tests induced by acetic acid, formalin test in the paw and orofacial, and paw edema induced by carrageenan were used. The infusion reduced the number of writhing at all tested doses, whereas it was unable to reduce pain at any stage of the formalin paw test nor carrageenan-induced paw edema. Acute administration of *I. paraguariensis* inhibited both phases of the orofacial formalin test at all doses tested. This difference can be explained due to the difference in the innervation of the two regions. According to the authors, the modulation of noradrenergic pathways seems to be involved in the mechanism of action, mainly due to methylxanthines, such as caffeine [51].

In a more innovative approach, Aliabdi and coauthors (2020) investigated the effect of an aqueous extract of yerba mate incorporated into microfibrillated cellulose films in an in vitro wound healing model [9]. In the in vitro assay, a wound caused by scratching plates containing cells is simulated. After achieving proper confluence, a mechanical scratch wound is created by gently scraping the cell layer with the tip of a micropipette. After a certain time, the ability of cells to migrate is evaluated, simulating wound healing. The films containing yerba mate increased the rate of cell regeneration by the in vitro test. The films were also evaluated for antimicrobial activity, where the growth of common pathogens, such as E. coli and S. aureus, was inhibited in the flask shaking method, probably due to polyphenols. Polymeric films are advantageous pharmaceutical forms for wound healing, mainly due to their ability to maintain a humid environment and incorporate compounds with antioxidant, anti-inflammatory, and antibacterial properties, as is the case of *I. paraguariensis*. Finally, Nowacki and coauthors (2021) also demonstrated that the aqueous extract of *I. paraguariensis* has analgesic properties in orofacial pain, similar to some drugs such as dexamethasone, and present two hypotheses for this. The first is that its effects occur through an immediate stimulation of the opioid system, and the second is that it acts similarly to carbamazepine, stabilizing the overexcited nerve

membrane, inhibiting repetitive neuronal firings, and reducing the propagation of excitatory synaptic impulses. The authors indicated that the antinociceptive action of the extract is probably associated with polyphenolic compounds and flavonoids capable of inhibiting substances related to inflammatory action released during pain phases. Still, more studies are needed investigating the analgesic activity and the production of histopathological and inflammatory markers to understand the mechanisms involved [31].

## CONCLUSION

Technological prospecting and the search for scientific innovation revealed few patents and studies involving *I. paraguariensis* with healing purposes. Studies involving such patents are needed to assess their effectiveness in different populations with delayed healing. The patents found can also inspire the development of projects and new patents with *I. paraguariensis*, aiming at the sustainable use of biodiversity, as well as guaranteeing the rational research of natural products with pharmacological potential and of interest to the pharmaceutical industry. Still, despite studies demonstrating that yerba mate has promising potential to be used in the wound healing process, few studies can support this hypothesis. Thus, more studies still need to be carried out, mainly in incorporating yerba mate in pharmaceutical forms for cutaneous application to restore the skin's integrity after injuries.

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