Advancements in red propolis: a technological prospection for antimicrobial applications

Avanços na própolis vermelha: uma prospecção tecnológica para aplicações antimicrobianas

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ABSTRACT

The red propolis is a bee product with great biotechnological potential due to its antimicrobial and therapeutic properties. The present study used technological mapping to investigate the antimicrobial activities of red propolis in patents deposited in Brazil (INPI) and in international databases such as the European Patent Office (Espacenet) and World Intellectual Property Organization (WIPO). The results indicated that Brazil holds the highest number of patents related to red propolis, and propolis produced in Alagoas was the most cited. Class A61K was the most frequent, suggesting strong therapeutic potential, especially in dental applications. Public universities were the main patent depositors, with institutions in Alagoas standing out. The data also revealed potential for patent deposits in areas such as agriculture and new pharmaceutical applications, including the production of controlled-release devices and the synthesis of nanomaterials. Red propolis is a promising raw material for the development of products with antimicrobial activity, and the deposited patents indicate a growing interest in exploring its properties in various areas, including the pharmaceutical industry and agriculture.

Keywords: Red propolis; Technological mapping; Patents; Antimicrobial activity; Pharmaceutical Applications
RESUMO

A própolis vermelha é um produto apícola com grande potencial biotecnológico devido às suas propriedades antimicrobianas e terapêuticas. O presente estudo utilizou mapeamento tecnológico para investigar as atividades antimicrobianas da própolis vermelha em patentes depositadas no Brasil (INPI) e em bases de dados internacionais como o Escritório Europeu de Patentes (Espacenet) e Organização Mundial da Propriedade Intelectual (OMPI). Os resultados indicaram que o Brasil detém o maior número de patentes relacionadas à própolis vermelha, sendo a própolis produzida em Alagoas a mais citada. A classe A61K foi a mais frequente, sugerindo forte potencial terapêutico, principalmente em aplicações odontológicas. As universidades públicas foram as principais depositantes de patentes, com destaque para as instituições alagoanas. Os dados também revelaram potencial para depósitos de patentes em áreas como a agricultura e novas aplicações farmacêuticas, incluindo a produção de dispositivos de libertação controlada e a síntese de nanomateriais. A própolis vermelha é uma matéria-prima promissora para o desenvolvimento de produtos com atividade antimicrobiana, e as patentes depositadas indicam um interesse crescente em explorar suas propriedades em diversas áreas, incluindo a indústria farmacêutica e a agricultura.

Palavras-chave: Própolis vermelha; Mapeamento tecnológico; Patentes; Atividade antimicrobiana; Aplicações Farmacêuticas
INTRODUCTION

Currently, technological prospecting has garnered attention as a way to boost innovation (Patel et al., 2018). This type of study utilizes patent documents to identify relevant technologies, partners, competitors, innovations, and markets for potential investment (Ramalho et al., 2023). Consequently, technological prospecting plays a crucial role in acquiring the necessary information required for successfully introducing a new product to the market (Fraga et al., 2017). Patents represent the main form of intellectual property protection and serve as an excellent source of updated technological information (Kume et al., 2023). They provide data on the dynamism of innovation development in a specific field, including valuable insights into the use of natural products, assisting in predicting demands for new products and technologies (Ferreira et al., 2022).

Brazilian biodiversity, in particular, offers a vast reserve of bioactive substances for the development of therapeutic agents, such as propolis, a bee product known for its proven effectiveness in various biological actions (Rufatto et al., 2017). Obtaining patents for natural sources-derived products, such as propolis, is of great interest, necessitating meticulous attention to the requirements of novelty, inventive step, and industrial application, as stipulated by the Brazilian Industrial Property Law (Brasil, 1996).

Propolis is produced from resins collected from plant buds and exudates, mixed with mandibular enzymes and wax by bees. In the beehive, propolis is used for nest construction and to seal entrances and crevices in the hive, being essential in the antimicrobial control of the hive (Przybyłek et al., 2019). In Brazil, this product is classified according to its physical, chemical, and biological characteristics, with the southern, southeastern, and northeastern regions being the main producers (Salatino et al., 2021). Of the various types, green propolis, derived from the plant *Baccharis dracunculifolia* (Asteraceae) - known as "alecrim do campo" - is the most commercially traded in the country, with production mainly in Minas Gerais and São Paulo (Yuan et al., 2020).

Recently, Brazilian red propolis has gained interest from the scientific community due to its biological activities. It is produced in the states of Alagoas, Paraíba, Pernambuco, Sergipe, and Bahia, with the beach quince tree, *Dalbergia ecastaphyllum* (Fabaceae), being the main botanical source found in the mangroves of the region (Moise et al., 2020; Aldana-Mejía et al., 2021).
Additionally, the species *Symphonia globulifera* (Clusiaceae) has been indicated as a second resin source for the production of this type of propolis (Ccana-Ccapatinta et al., 2020).

An important characteristic of propolis is that its chemical composition varies according to the botanical source used by bees. Studies have indicated that red propolis produced in the Northeast region of Brazil is rich in phenolic compounds, particularly isoflavonoids and chalcones, which are attributed to the resins of *D. ecastaphyllum*, while prenylated benzophenones are associated to *S. globulifera* (Salatino et al., 2021).

Beyond Brazil, several other countries also serve as producers of red propolis. In Cuba, the species *D. ecastaphyllum* and others from the genus *Clusia* spp. are the botanical sources, while in Venezuela, species from the genus *Clusia* spp. are used. In Mexico and Nigeria, species from the genus *Dalbergia* spp. (Piccinelli et al., 2011; Moise et al., 2020; Okhale et al., 2021)

Moreover, the presence of red propolis has also been reported in Greece, although the botanical source has not yet been determined (Papachristoforou et al., 2019). Propolis is a natural product of high biotechnological value, due to its complex and varied composition. Brazilian propolis, in particular, is highly valued in the world market due to its health benefits (Santos et al., 2019). The diversity of types of propolis has been the subject of study by many researchers interested in exploring its biological properties.

In recent years, Brazilian red propolis has been investigated for its biological activities, especially its antibacterial activity against gram-positive bacteria, including *Staphylococcus aureus* and *Streptococcus mutans*, and gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*. In addition, species of fungi of the genus *Candida* have been evaluated for the antifungal activity of this propolis (Lopez et al., 2015; Silva et al., 2019)

The growing problem of bacterial resistance to traditional drugs has become a serious public health concern. The search for alternatives that can overcome this problem has led to increasing interest in the antibacterial potential of propolis, due to its complex and varied chemical composition that varies according to the location and time of collection. It is believed that this variation makes it difficult for bacterial resistance to occur, making propolis a promising source of compounds for the development of products with antibacterial action (Przybyłek et al., 2019; Serwecińska et al., 2020).
In this context, red propolis has been studied for its antimicrobial activities, especially its antibacterial action. However, despite recent advances in this area, there is still a gap in knowledge about the current technological level and trends of research related to the antimicrobial activity of red propolis. Therefore, the aim of the present study was to carry out a technological mapping of patent applications for the antimicrobial activity of red propolis, through consultation of patent databases, in order to evaluate the current state of the technology and direct future research in the area.

**METHOD**

The prospective mapping of red propolis and its potential applications in antimicrobial contexts involved a thorough examination of patent applications from various sources. Considering that Brazil is the largest producer of red propolis, the database of the National Institute of Industrial Property (INPI) was selected, along with the international databases of the European Patent Office (Espacenet or EPO) and the World Intellectual Property Organization (WIPO or WO), which were meticulously searched. To ensure comprehensive coverage, patent searches were conducted in February 2023 using a variety of strategically selected keywords.

The primary keywords employed in the search process included "propolis" and "red propolis." The search was performed using the "advanced search" option for the INPI and EPO databases (combined with the field operator defined as "=") in the EPO), while the "Search/Field Combination" option was selected for WIPO. Furthermore, the term "red propolis" was combined with the boolean operators "AND" and "OR" with "antimicrobial" and "antibacterial," used in Portuguese for the Brazilian patent database and in English for the international patent databases.

By implementing this systematic approach, the objective was to compile an extensive collection of patent applications that encompassed the antimicrobial potential of red propolis. The choice to explore multiple databases and employ various search terms ensured a comprehensive and inclusive research process. The data were organized in a map and graphs generated in Microsoft Excel®, which present the distribution of patents by countries in the databases used in this study, as well as the evolution of patent applications in the INPI.
RESULTS AND DISCUSSION

The search results from the patent databases revealed intriguing insights regarding the distribution of patent applications across different databases and their association with specific types of propolis. Notably, a greater number of patent applications were identified in the Espacenet database, followed by WIPO, when employing the general keyword "propolis." However, a more focused analysis that specified the type of propolis (red propolis) demonstrated a notable disparity.

Within the INPI database, a total of 51 patent applications related to red propolis were found, surpassing the numbers observed in the international databases. In WIPO, 10 patent applications were registered, while Espacenet accounted for 9 applications. When the search was refined by associating the term "red propolis" with “antimicrobial” and “antibacterial” activities, once again, the INPI database exhibited the highest number of patent applications, with a total of 15, further highlighting its prominence in the field of red propolis and its antimicrobial applications. In contrast, the international databases - WIPO and Espacenet - each yielded 2 patent applications related to this specific association (Table 1).

Table 1: Number of patent applications filed by patent database

<table>
<thead>
<tr>
<th>Key words</th>
<th>INPI</th>
<th>ESPACENET</th>
<th>WIPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propolis</td>
<td>205</td>
<td>6,810</td>
<td>6,127</td>
</tr>
<tr>
<td>Red propolis</td>
<td>51</td>
<td>9</td>
<td>10*</td>
</tr>
<tr>
<td>Red propolis AND antimicrobial</td>
<td>12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Red propolis AND antibacterial</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*One duplicate patent application was excluded.
Source: Authors (2023)

The higher number of patent applications observed in the international databases, particularly in Espacenet, without specifying the type of propolis can be attributed to extensive deposit of patents from approximately 100 countries. Espacenet serves as a global repository, accommodating patent registrations from various nations. Similarly, WIPO, functioning as an international database, holds a Patent Cooperation Treaty (PCT) with numerous countries, including Brazil, facilitating a substantial number of patent registrations. It is important to note that many of the patent applications identified in the INPI database are also found in WIPO, as a result of their comprehensive registration coverage (Bandeira et al., 2021).
The data obtained from Espacenet revealed intriguing patterns. Remarkably, 98.3% of the patent applications associated with propolis originated from three Asian countries. China stood out as the primary contributor, with a staggering 5,400 patents, accounting for 79.3% of the total patents discovered. South Korea followed with 820 applications (12%), and Japan with 479 applications (7%). It is noteworthy that Brazil, despite being a significant producer of propolis, did not appear among the depositing countries in the Espacenet database (Figure 1). However, upon further examination of the 189 WIPO (World Intellectual Property Organization) applications identified in the European Patent Office (EPO), 13 applications from Brazil were identified.

**Figure 1**: Countries with the highest number of patents related to propolis in the European Patent Office (Espacenet).

![Bar chart showing the distribution of patents by country](image)

Source: Authors (2023)

According to Figure 2, the distribution of patent applications related to propolis within WIPO showcases significant contributions from China and South Korea. China held a substantial share, accounting for 59.75% of the patent applications identified, followed by South Korea at 10.77%. Furthermore, Russia and Japan emerged as significant contributors with 7% and 5.83% of the patent applications, respectively. Examining the involvement of Brazil in the patenting process, thirteen patent applications originating from Brazil were identified among the 190 records discovered in the Patent
Cooperation Treaty (PCT) category. Additionally, two patent applications from Brazil were found among the 90 records within the European Patent Office (EPO) category.

**Figure 2:** Main patent depositors related to propolis identified in the World Intellectual Property Organization (WIPO)

![Figure 2](image.png)

The considerable number of patents filed by Chinese inventors can be attributed to several factors. In recent years, China has experienced significant growth in research and development activities, contributing to a surge in patent applications across various fields, including propolis. Furthermore, the increase in foreign direct investment, favorable changes in Chinese patent law that support patent holders, and property reform initiatives clarifying property rights allocation have all contributed to a higher propensity for Chinese companies to seek patent protection (Hu et al., 2017).

On the other hand, Brazil's incipient performance in patent applications can be attributed to specific factors. These include the slow return on investment in the biotechnology industry and a lower proportion of researchers working within companies (Cota et al., 2016). Additionally, it is worth noting that developing countries like Brazil often have locally relevant technological activities that may not reach significant at the international levels, resulting in patents primarily at the national level (Albuquerque et al., 2000).

Despite these challenges, Brazil holds a prominent position as one of the world's largest producers of propolis, with an annual production of approximately 160 tons (Migliore et al., 2022). Changes in dietary habits the expanding applications of propolis
in the food industry have contributed to the increased consumption and demand for propolis globally (Seibert et al., 2019). Moreover, the distinct types of propolis produced in Brazil are highly valued in the global market due to their well-documented biological activity (Marcucci et al., 2021).

In contrast, the international databases, EPO and WIPO, recorded only 9 and 10 patent applications, respectively. Among the Brazilian records, three were filed by the Federal University of Alagoas (UFAL).

In comparison to a previous prospective study conducted by Fraga et al. (2017) which identified only 14 patent records related to red propolis, a significant increase in patent filings has been observed in the Brazilian National Institute of Industrial Property (INPI) database. This suggests a growing interest in red propolis patent protection within Brazil. Interestingly, when the type of propolis is not specified, Asian countries, particularly China, stand out as major contributors in patent filings. However, when specifically focusing on red propolis, Brazil emerges as the country with the highest number of patent filings (Figure 3).

**Figure 3:** Main patent holders of red propolis in the National Institute of Industrial Property, European Patent Office, and World Intellectual Property Organization.

Within the WIPO and EPO databases, two noteworthy patent filings were identified concerning the antimicrobial and antibacterial actions of red propolis. The first patent, titled "Functional Food and Drink", was filed by a Japanese company in 2004. Interestingly, Japan is not a producer of red propolis. This patent pertains to a protective agent against hepatic dysfunction, utilizing red propolis as the active ingredient for the
production of functional foods and beverages that safeguard liver functions. The patent claims various effects, including antibacterial, antioxidant, antiallergic, and antitumor properties. The second patent filing was made by a Brazilian university (UFAL) and is titled “Red propolis microcapsules, method for producing microcapsules, pharmaceutical compositions containing same, method for producing pharmaceutical compositions and uses thereof”. This patent elucidates the production of red propolis microcapsules and their utilization in gastro-resistant pharmaceutical compositions with antimicrobial action. Both of these patent filings are currently archived.

Brazil, being a significant producer of red propolis, made its first deposit in 2008 with the title “Extratos de própolis vermelha, frações ativas dos extratos, composições farmacêuticas e seu uso”. The number of patent applications pertaining to red propolis reached its peak in 2020, with 11 registrations (Figure 4). Furthermore, the latest registration identified in our search was in August 2021 (Marcucci et al., 2021). It is worth noting that there may be additional applications that have been filed but are currently unavailable due to the secrecy period stipulated by the Brazilian Industrial Property Law. This law establishes an 18-month period of confidentiality from the date of filing or from the earliest priority date (Brasil, 1996).

**Figure 4:** Evolution of patent applications with red propolis at the Brazilian National Institute of Industrial Property (INPI).

Between 2015 and 2021, a total of 15 patent applications related to the antimicrobial and/or antibacterial use of red propolis were filed at the Brazilian National Institute of Industrial Property (INPI). These applications were submitted by various Brazilian educational institutions and private companies. Among them, the Federal
University of Alagoas (UFAL) filed the highest number of applications, with six in total. The Federal University of Ceará (UFC) followed with three applications, while São Paulo State University (Unesp), Federal University of Campina Grande (UFCG), and Federal University of Paraíba (UFPB) each filed one application. Additionally, the Jayme de Altavila Educational Foundation (FEJAL) and the Technology and Research Institute (ITP) in collaboration with the Tiradentes University (UNIT) jointly filed three applications (Table 2).

Brazilian public universities have a crucial role in the technological innovation system, experiencing a significant increase in patent applications after the approval of the industrial property law in the country. Additionally, these universities are responsible for the majority of scientific publications produced in Brazil, playing an important role in human resource development and providing technological knowledge (Ferreira et al., 2022).

The patent applications are assigned an international patent classification (IPC) based on the purpose of the invention, with the technological field divided into sections A to H. In this classification, class A is specifically related to human necessities (Ferreira et al., 2022). The patent records associated with red propolis at INPI are categorized under section A, which pertains to the pharmacological use of the compound. Among these records, subclass A61K (Preparations for medical, dental, or hygienic purposes), indicating therapeutic use, was the most prevalent, comprising nine applications (81.8%). These records also encompassed classes such as A61P, which relates to specific therapeutic activities of chemical compounds or medicinal preparations, A61Q, which is specific to cosmetics or the preparation of hygiene items, and A61F, which includes prostheses, dressings, and other related topics. However, two applications (18.18%) fell under class A01N, which signifies the agricultural use, plant preservation, and their respective parts (Table 2).

<table>
<thead>
<tr>
<th>Filing year</th>
<th>Subclass</th>
<th>IPC</th>
<th>Title</th>
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<td>2021</td>
<td>A61K35/644; A61K 6/52; A61P 1/02</td>
<td>Gel mucoadesivo à base de natrosol com própolis vermelha de Alagoas para aplicação tópica intrabucal por irrigação subgengival intrasulcular e outros usos</td>
<td>UFAL/AL</td>
<td></td>
</tr>
<tr>
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<td>Descrição</td>
<td>Instituição(s)</td>
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</tr>
<tr>
<td>2020</td>
<td>A61K 35/644; A61K 9/107; A61K 8/98; A61P 1/00; A61Q 11/00</td>
<td>Saliva artificial carregadas com nanopartículas micelares de própolis vermelha e usos clínicos</td>
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<tr>
<td>2020</td>
<td>A61K 6/20; A61K 6/54; A61K 8/98; A61Q 11/00</td>
<td>Adesivo dental fotopolimerizável à base de metacrilatos com nanopartículas de prata biosintetizadas com própolis vermelha de Alagoas</td>
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<td>2020</td>
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<td>2020</td>
<td>A61K 6/20; A61K 6/40; A61K 6/50</td>
<td>Adesivo dentinário fotopolimerizável contendo polifenóis e própolis vermelha de Alagoas</td>
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<td>2020</td>
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<td>Adesivo dental fotopolimerizável à base de metacrilatos com própolis vermelha de Alagoas, quercetina e resveratrol</td>
<td>UFAL/AL</td>
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<td>2018</td>
<td>A61K 35/644; A61P 17/02; A61P 17/18; A61P 31/04; A61P 29/00; A61F 13/00</td>
<td>Curativo contendo própolis vermelha, processo de obtenção, composição farmacêutica, aplicação na prevenção e tratamento de feridas</td>
<td>UFAL/AL</td>
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<td>2018</td>
<td>A61K 35/644; A61P 31/04</td>
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<td>2017</td>
<td>A61K 8/98; A61Q 19/00</td>
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<td>2017</td>
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<td>Desenvolvimento de dentífricos incorporados com própolis vermelha brasileira associados a arginina, flúor e hidroxiapatita para controle de microrganismos orais</td>
<td>UFC/CE</td>
<td></td>
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<tr>
<td>2016</td>
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<td>Desenvolvimento de verniz dentário de própolis vermelha para controle de cárie dentária</td>
<td>UFC/CE</td>
<td></td>
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<tr>
<td>2015</td>
<td>A01N63/04; A01N59/00; A01N63/02; A01P1/00</td>
<td>Formulação filmogênica para revestimento de sementes contra fitopatogênicos</td>
<td>ITP/SE, UNIT/SE</td>
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</table>
The field of dentistry has shown promising applications of red propolis. Numerous patents have been registered exploring the antimicrobial, anti-inflammatory, and healing properties of red propolis in dental products. These patents evaluate its effectiveness against various microorganisms such as *Streptococcus mutans*, *Streptococcus mitis*, *Streptococcus sanguis*, *Streptococcus oralis*, *Streptococcus salivarius* and *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*.

Formulations incorporating red propolis have been developed for dental use, including mucoadhesive gels based on natrosol, micellar nanoparticles, and nanoencapsulated formulations. These formulations offer the advantage of a slow and sustained release of the active compounds of red propolis in the oral cavity, maximizing its therapeutic effects.

Furthermore, the application of red propolis in dental adhesives has been investigated. Dental adhesives combined with antioxidant and anti-inflammatory polyphenols, such as quercetin and resveratrol, have been studied to enhance dental repair capacity and reduce postoperative sensitivity. The use of dental adhesives in conjunction with silver nanoparticles synthesized with red propolis has also been explored for the prevention of secondary caries, increasing the longevity of adhesive restorations and minimizing the need for replacements. Another patent application focuses on a dental varnish, a topical application material used to protect and treat teeth against caries and other dental problems.

Although the potential of red propolis in dentistry has been recognized, challenges remain, such as the lack of standardization of commercial products containing propolis. However, prospective studies, such as the one conducted by Furtado Junior et al. (2018), support the promising applications of red propolis in the dental field.
Beyond dentistry, other applications of red propolis have also been identified. These include the production of gels for the treatment of musculoskeletal disorders using ultrasound (phonophoresis), the development of healing and antimicrobial membranes for wound treatment, and the formulation of a gel for acne treatment. In the agricultural field, red propolis extract has been explored as an additive for food preservation and as a seed coating against phytopathogens. Additionally, a patent related to the process of obtaining red propolis extracts with a high concentration of formononetin, one of the chemical markers of Brazilian red propolis, for use in dietary supplements, herbal compositions, and as an antimicrobial agent was identified.

It is worth noting that most of the patent applications in Brazil focus on red propolis produced in Alagoas. This is due to the identification of biological activities and the presence of isoflavonoids as chemical markers and indicators of its botanical origin, allowing for quality control of the propolis. As a result, red propolis from Alagoas has received geographical indication registration and has been included in the Local Productive Arrangement Program, which promotes its production and commercialization (Silva et al., 2016; Silva et al., 2016; Almeida et al., 2018; Brasil, 2019).

While patents serve to protect intellectual property rights and can be registered before products undergo clinical trials, further investigations are necessary to confirm the efficacy and safety of red propolis for human or veterinary use, despite the use of natural products being considered generally safe.

CONCLUSION

The technological prospecting analysis highlights that red propolis has primarily been used for pharmacological purposes due to its notable antimicrobial activity. However, its applications have expanded to include its use as a dressing, in cosmetics, in nanomaterial synthesis, and in agriculture. While patent registrations are predominantly concentrated in Asian countries, Brazil has emerged as the country with the highest number of patent filings related to red propolis.

These patent deposits in Brazil primarily utilize red propolis from Alagoas and focus on applications in the prevention and treatment of cavities, gingivitis, and periodontitis. Public universities have played a significant role as the main depositors of these patents. This indicates that red propolis has the potential to become an important resource for various industries, offering innovative solutions in the fields of health, nutrition, and the environment.
The technological prospecting analysis provides valuable insights into the current trends and potential future applications of red propolis, demonstrating its versatility and promising prospects for commercial and industrial utilization.

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