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Quantifying the inovation of cosmetic formulations that contains phenolic rich fruit extracts as fotoprotective bioactives

Quantificando a inovação de formulações cosméticas que contêm extratos de frutas ricas em substâncias fenólicas como bioativos fotoprotetivos

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Abstract

Introduction: *sunscreen is a cosmetic used to protect human skin from the deleterious effects of UV radiation and thus minimize the risks of developing skin cancer. Extracts produced from fruits, such as Abiu, Guava, Rambutan and Grape, have significant concentrations of chromophores and phenolic substances that have the ability to absorb UV light and neutralize free radicals. The production of cosmetics from naturally occurring substances with such activities will be of great importance for Brazilian industry and could reduce the cost of production, given the large existing biodiversity in the country.* ***Objectives:*** *carry out a patent search for formulations and cosmetic products that contains phenolic rich fruit extracts as photoprotective and antioxidant bioactives.* ***Methodology:*** *a survey of patents was carried out in the database of the National Institute of Intellectual Property (INPI) and the European Patent Office (EPO), covering a time period between 2008 and 2018, using a combination of keywords related to herbal cosmetics and sunscreens.* ***Results:*** *this research identifies a significant number of patents related to plant extract in association with sunscreen product, however, no patent filings were identified for cosmetic products containing extracts of the evaluated fruits, either alone or in combination, for photoprotective and antioxidant purposes.* ***Conclusion:*** *the Brazilian and international market for sun care products moves millions to billions of dollars annually and have a significant annual growth prospect. Considering the great biodiversity existing in the country, the production of cosmetics from naturally occurring substances with such activities will be of great importance for the Brazilian industrial sector.*

Key words: *Sunscreening Agents. Cosmetics. Radiation Effects. Sun Protection Factor. Plants. Phenolic Compounds.*

Resumo

Introdução: os filtros solares são cosméticos usados para proteger a pele humana dos efeitos deletérios da radiação UV e assim, minimizar os riscos de desenvolvimento de câncer de pele. Extratos produzidos a partir de frutos, como Abiu, Goiaba, Rambutan e Uva, têm concentrações significativas de cromóforos e substâncias fenólicas que têm a capacidade de absorver a radiação UV e neutralizar os radicais livres. A produção de cosméticos a partir de substâncias naturais com essas atividades será de grande importância para a indústria brasileira e poderá reduzir o custo de produção, dada a grande biodiversidade existente no país. **Objetivos:** realizar uma busca de registros de patentes de formulações e produtos cosméticos que contêm extratos de frutos ricos em fenólicos como bioativos fotoprotetores e antioxidantes. **Metodologia:** foi realizado um levantamento de patentes no banco de dados do Instituto Nacional de Propriedade Intelectual (INPI) e do Escritório Europeu de Patentes (EPO), abrangendo um período de tempo entre 2008 e 2018, utilizando uma combinação de palavras-chave relacionadas a cosméticos à base de plantas e protetores solares. **Resultados:** esta pesquisa identificou um número significativo de patentes relacionadas ao extrato de plantas em associação ao produto protetor solar, no entanto, não foram identificados pedidos de patente para produtos cosméticos que contenham extratos das frutas avaliadas, isoladamente ou em combinação, para fins fotoprotetores e antioxidantes. **Conclusão:** o mercado brasileiro e internacional de produtos de proteção solar movimenta milhões a bilhões de dólares anualmente e tem a perspectiva de crescimento anual significativa. Considerando a grande biodiversidade existente no país, a produção de cosméticos a partir de substâncias naturais com essas atividades será de grande importância para o setor industrial brasileiro.

Palavras-chave: Protetores solares. Cosméticos. Efeitos de radiação. Fator de proteção solar. Plantas. Compostos fenólicos.

INTRODUCTION

The American Cancer Society (ACS) estimates that by 2019, about 96,480 new skin cancers will emerge in the United States alone, predicting more than 7,000 deaths directly related to these cases[1]. The World Health Orga-

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nization (WHO) estimates that by the year 2020 there will be almost 280,000 new cases of melanomas around the world[2]. This is a problem that directly affects Brazil because it is a geographically tropical and highly ethnically diverse country. The individual characteristics respond differently to the intensity, frequency and time of exposure to UV light[3]. This fact is aggravated because, in Brazil, there are large areas of beaches and people have an idea of beauty associated with tanned skin, which stimulates an excessive exposure to the sun's rays[4]. Such an excessive exposure can cause skin tissue oxidative stress, which is the appearance of reactive oxygen species (ROS). This can cause DNA damage with also multiple effects on the immune system. For these reasons, it is imperative the use of proper protective product against the effects of UV light.

Ultraviolet (UV) radiation is of fundamental importance to life on Earth, playing key role for vitamin D_3 biosynthesis in humans, but overexposure can lead to important skin changes such as sunburn, ocular damage, inflammation, immune suppression, photoaging and skin cancer, because its mutagenic and non-specific damaging effects[5,6]. Depending on wavelengths, UV radiation is divided into three bands, UV-A (between 400-315nm), UV-B (between 315-280nm) and UV-C (between 280-100nm). Among these ranges, UV-B is more related to the cellular changes that initiate skin cancer. Only about one tenth of UV-B radiation reaches the earth's surface, but due to its higher energy, it promotes more significant changes in cell structures. Almost all UV-A radiation reaches the Earth's surface, being related to immediate effects related to skin pigmentation, but it has cumulative and long-term effect and can also contribute to significant cellular changes, promoting skin aging. UV-C radiation has little effect on human health as it has low penetration into the Earth's surface as it is completely absorbed by the atmospheric ozone layer[7].

Cosmetic products kwon as sunscreen are frequently used to prevent skin damage promoted by UV radiation[8]. The active ingredients of these products are called UV filters and are substances capable of absorbing, scattering or reflecting solar radiation. Two categories of filters, depending on their chemical characteristics and their mechanism of action, are used in sunscreen formulations; Inorganic filters are particulate and act by reflecting and scattering radiation; Organic filters are usually aromatic, lipophilic substances that absorb UV radiation and turn it into thermal energy[9]. Regulatory agencies, like Food and Drug Administration (FDA), in USA, and European Commission, in Europe, set the maximum allowed concentration of specific actives in cosmetic formulations, including sunscreens, as well as the list of agents that should not be present in these products[9-11].

The first commercially available sunscreens appeared in 1928, but it was in the 1970s that such product was widely available[12]. Its formulations were based on the observation of mitigating effects provided by substances that prevented the penetration of solar rays into the dermis, thus avoiding skin burns (erythema). Nowadays, there is also the interest that the protective substances have further therapeutic properties such as that stimulates the skin hydration. For this reason, the use of these substances are considered as one of the most effective measures for the prevention of cutaneous neoplasia and early aging[13].

The search for safer, less irritating and more skin-compatible cosmetic bioactives has been the focus of the cosmetic industry in recent years. This trend has led to the development of research on herbal products that, in addition to producing less adverse reactions, adds value to the final product by incorporating complementary cosmetic actions such as skin moisturizing, antioxidant and nutritive[14].

Plants extracts have significant concentrations of chromophores and phenolic substances that have the ability to absorb UV light and neutralize free radicals. Thus, several cosmetics products are being marketed using such plant extracts. However, although there are several commercial products that are supplemented with plant substances, the diversity of flora available can still stimulate an innovative revolution in this sector. In addition, the consumers are seeking product with substances that have a sustainable, organic origin and cause no side effects during prolonged use[15].

Fruits of yellow, red, orange and dark green coloration are rich in antioxidants of the carotenoid family, a group of substances recognized as UV light protectors. It is also common to find in the fruits phenolic substances such as ferulic acid, tannic, protocatechic, vanillic and others that are natural antioxidants and UV light absorbers[16,17]. Due to the presence of conjugated bonds in the chemical structure of these substances, they are capable of absorbing electromagnetic radiation at different wavelengths, including UV radiation, and this absorption can minimize skin exposure[18,19].

For instance, the fruits of Abiu (Pouteria caimito), Guava (Psidium guajava), Rambutan (Nephelium lappaceum) and Grape (Vitis sp) are easily grown on Brazilian Northeast soil and have indicators of high concentrations of such substances. Phenolic compounds, such as flavonoids, found in these fruits, are responsible for the plant protection against the deleterious effects of UV radiation[20]. Literature data show that the total phenolic content in these fruits is 1,132.43 mg 100 g^{-1} (abiu), 1,047.55 to 1,462.86 mg 100 g^{-1} (guava), 244.00 mg 100 g^{-1} (rambutan) and 121.00 to 335.00 mg 100 g^{-1} (grape). These data indicate the potential of these fruits as a source of such bioactives[21-24], suggesting that they are species of great interest in conducting future research to develop products based on them.

The introduction in the market of bioactive ingredients derived from plants with antioxidant or photoprotective characteristics, which seek to prevent or retard cellular aging, represents another tool to be used by the cosmetic and pharmaceutical industries, representing a major scientific and economic impact. The production of cosmetics from naturally occurring substances with such activities

will be of great importance for Brazilian industry and could reduce the cost of production, given the large existing biodiversity in the country. This cost reduction may be related to the high number of viable sources of obtaining renewable active raw materials, to the reduction of time and inputs needed to obtain these bioactives, contrary to the various steps involved and reagents employed in obtaining and purifying synthetic materials. The use of these assets in sunscreens can further reduce the concentration of synthetic organic filters used in their composition, reducing toxicity associated with these filters, as well as the enhancement of their sun protection factor.

Some synthetic UV filters suffers photodegradation after exposure to artificial UV light. The antioxidant properties of kappacism bioactive ingredients derived from plants may also contribute to stabilize the organic synthetic UV filters, minimizing their photodegradation and improving the UV protection effect[25,26].

Due to their chemical characteristics, substantial systemic absorption and distribution of organic UV filters in humans, and excretion of their metabolites in urine, after topic sunscreen application have been reported in many experimental studies[27]. Also, UV filters can reach humans by environmental exposure, like drinking contaminated water or absorption through oral and dermal route[28]. Despite the beneficial effects of these filters in minimizing exposure to UV radiation, they have toxicity, with some adverse effects, such as various types of dermatitis (allergic and irritant) and neurotoxic effects[28,29]. Another current concern is the introduction of UV filters into the environment, either directly (through skin and clothing removal during recreational activities) or indirectly (through industrial waste from sunscreen production and household uses), posing a risk to both aquatic life and humans[30,31].

The aim of this article is to carry out a patent search for formulations and cosmetic products that contains phenolic rich fruit extracts as photoprotective and antioxidant bioactives, especially of the species P. caimito, P. guajava, N. lappaceum and Vitis sp due to the ease of cultivation in different regions of Brazil.

METHODOLOGY

A survey of patents was carried out in order to measure the plant sun cream product impact in the pharmaceutical market. The search comprised a time period between 2008 and 2018. The research was carried out in the database of the National Institute of Intellectual Property (INPI)[32], which contains patent documents deposited in Brazil, and the Espacenet database, which is maintained by the European Patent Office (EPO)[33] and contains more than 90 million patent documents from different countries.

The search of patents was carried out using the keywords shown in Table 1. A combination of English and Portuguese words was carefully chosen first based on previously selected patents directly related to the objectives of this work. Combinations and logical operators ("And" for required characteristics; "Or" for synonyms or words with similar meanings and "" for words with the same radical and their plurals) to obtain different results from the most general product characteristics, even those more specific or similar to the intended product. In both databases, Advanced Search was used and the keyword searches were done in the titles and summaries of the documents. The keywords and desired results are described in Table 1.*

Table 1 – *Keywords used in patent search in the INPI (B) and Espacenet (I) databases and intended results.*

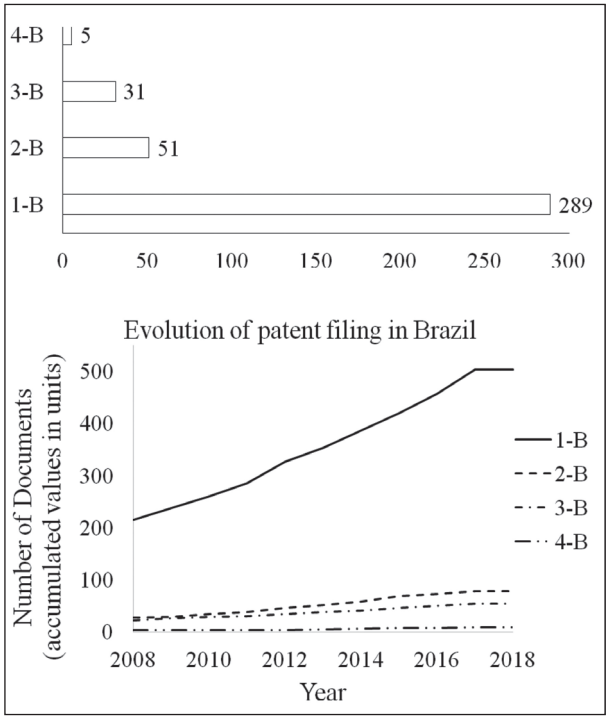
Search Number	Keywords		Expected results
	Brazilian Database (B)	International Database (I)	
1	*Cosmétic* AND (Extrat* OR Vegeta*)	Cosmetic* AND Herb*	Cosmetic or phytocosmetic products containing one or more types of plant extracts or derivatives in their compositions, and / or cosmetic applications of these plant extracts or derivatives
2	*Cosmétic* AND (Extrat* OR Vegeta*) AND (Antioxida* OR Anti-Oxida*)	Cosmetic* AND Herb* AND Antioxidant*	Cosmetic or phytocosmetic products containing one or more types of plant extracts or derivatives in their compositions and with antioxidant action and / or application, and / or cosmetic applications of these plant extracts or derivatives
3	(Fotoprote* OR (Filtro* AND Solar*) OR (Prote* And Solar*)) AND (Extrat* OR Vegeta*)	Sunscreen* AND Herb*	Cosmetic products containing one or more types of plant extracts or derivatives, in their compositions and with photoprotective action and / or application
4	(Fotoprote* OR (Filtro* AND Solar*) OR (Prote* AND Solar*)) AND (Extrat* OR Vegeta*) AND (Antioxida* OR Anti-Oxida*)	Sunscreen* AND Herb* AND Antioxidant*	Cosmetic products containing one or more types of plant extracts or derivatives, in their compositions, having a photoprotective action and / or complementary antioxidant

Source: The author (2019).

RESULTS AND DISCUSSION

It is important to note that in 2018 this search did not find any mention to patents related to the object of this study and, for search 4-B (Table 1) specifically, there were only few patent found between 2013, 2014, 2015 and 2017. Figure 1 shows the quantitative of this search.

Figure 1 – *Number of documents found in the INPI database between 2008 and 2018 and evolution of brazilian patent filing in the period. Group of keywords used in searches (Table 1) organizes data.*



** 1-B: Products containing one or more types of plant extracts or derivatives in their compositions, and / or cosmetic applications of these plant extracts or derivatives; 2-B: Products containing one or more types of plant extracts or derivatives in their compositions and with antioxidant action and / or application, and / or cosmetic applications of these plant extracts or derivatives; 3-B: Products containing one or more types of plant extracts or derivatives, in their compositions and with photoprotective action and / or application; 4-B: Products containing one or more types of plant extracts or derivatives, in their compositions, having a photoprotective action and / or complementary antioxidant.*

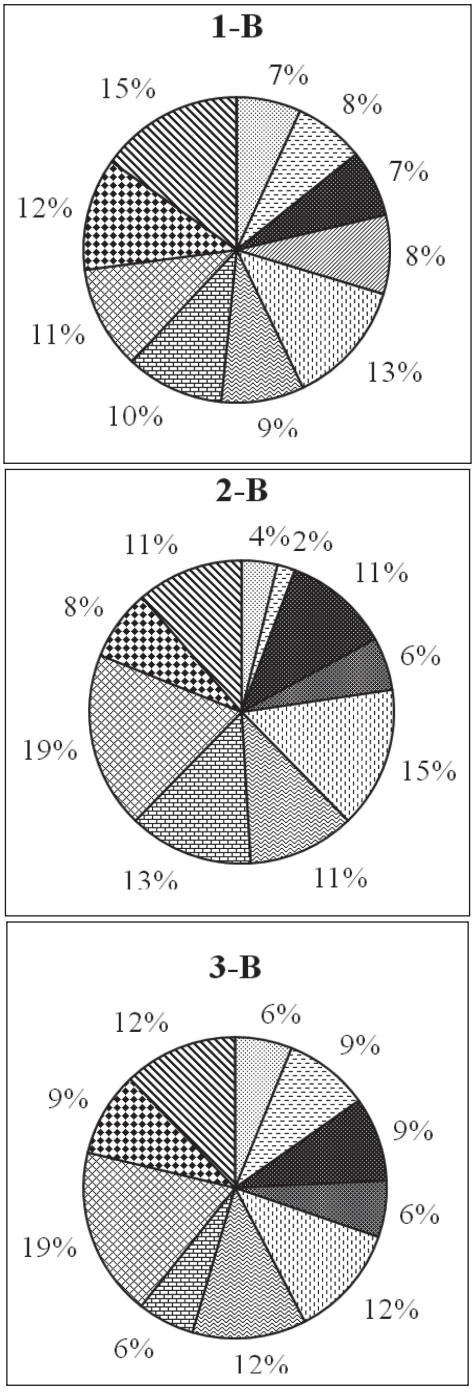
Source: Research data.

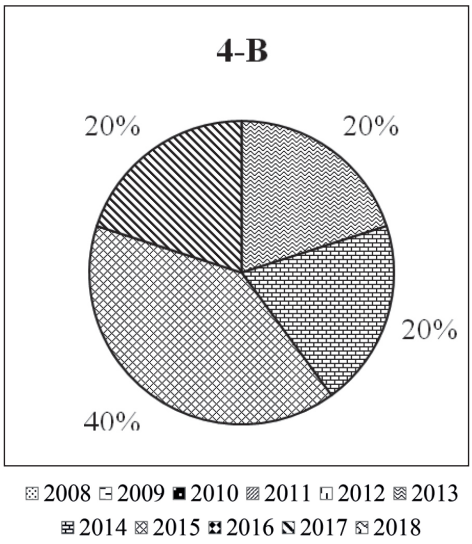
The search shows that keywords with higher specificity selected only 5 documents describing the manufacture of cosmetic products containing one or more types of plant extracts with photoprotective action and / or complementary antioxidant application. Furthermore, none of the identified patents mentioned the use of Abiu (Pouteria caimito), Guava (Psidium guajava), Rambutan (Nephelium lappaceum) or Grape (Vitis sp).

Figure 1, which shows data from accumulated values before 2008, shows that the overall number of patent applications for cosmetic products containing some kind of plant derivative more than tripled between 2008 to 2018. This clearly reflects the importance and interest of researchers and pharmaceuticals in the development of cosmetic formulations based on plants bioactive. For products containing some plant derivative and with photoprotective and / or antioxidant action, the growth was not so pronounced, but it is possible to notice that it has been increasing gradually over the years.

Figure 2 shows that more deposits were made from 2012 to 2017. Therefore, keyword combinations 1-B (Table 1) account for more than 70% of the total documents found in the aforementioned period. The highest number of patent filings for the 1-B keyword combination was observed in 2018, and for the 4-B keyword combination was in 2015 (Figure 2).

Figure 2 – *Prospecting of patents filed in the INPI from 2008 to 2018. There were 4 separate searches, as described in Table 1, organized by the keywords highlighted in each Pie chart. Data are organized by year showing the percentage of the total of 11 years.*





** 1-B: Products containing one or more types of plant extracts or derivatives in their compositions, and / or cosmetic applications of these plant extracts or derivatives; 2-B: Products containing one or more types of plant extracts or derivatives in their compositions and with antioxidant action and / or application, and / or cosmetic applications of these plant extracts or derivatives; 3-B: Products containing one or more types of plant extracts or derivatives, in their compositions and with photoprotective action and / or application; 4-B: Products containing one or more types of plant extracts or derivatives, in their compositions, having a photoprotective action and / or complementary antioxidant.*

Source: Research data.

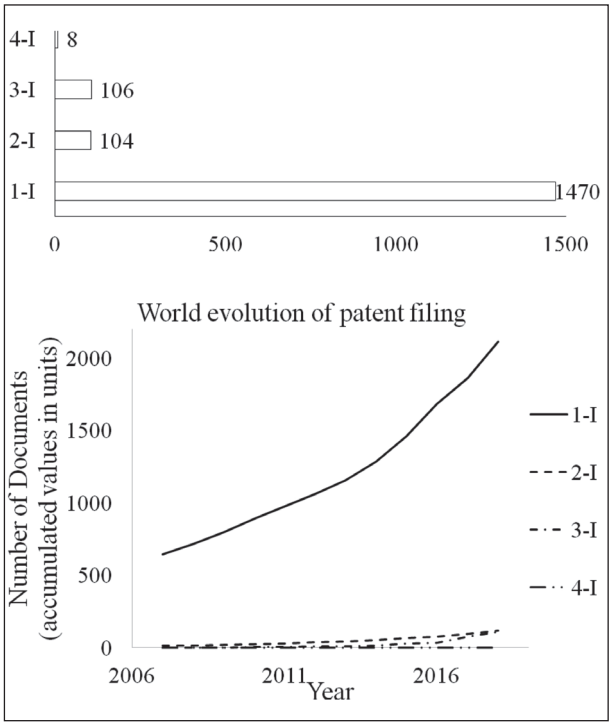
The combination of terms used in search 1-B (Table 1) with the keywords "Nephellium Or Rambut", as well as "Guava or Guajava", could not find any positive match. A single patent was identified in 2008 using the combination of the keywords "(Pouteria Or Lucuma Or Abiu)" with this search. Pouteria sp is cited in the patent, but its use in the cosmetic compositions was not clarified[34]. Using the association of "Vitis Or Grapes", a patent was also found in 2015. The document reports a synergistic blend of four plant extracts for hair treatment of gray hair[35].*

The results from the searches containing one or more keywords using plant extracts with photoprotective and antioxidant action showed that no document was found reporting the four plant species researched here. Two documents report the use of red propolis, which composition is associated with the nature of the plant that bees feed on, as a photoprotector[36,37]. Another patent describes a chitosan-based microparticulate system containing a multifunctional cosmetic using natural plant active ingredient[38]. Regarding the other two patents, one refers to animal extracts and the other to plant extracts without specifying the plant species[39,40].

The search for patents based only on photoprotective action, excluding complementary antioxidant action, also did not find results containing the species researched here. The identified patents describe the formulation of products containing photoprotectors extracted from plant species like Passiflora cincinnata[41], Croton tricolor Klotzsch ex Baill[42], and Anacardium occidentale[43]. Some patents mention the additional or complementary use of Ginkgo biloba extract and Porphyra umbilicalis[44].

The total number of documents found in the international Espacenet database, containing some kind of plant extract or derivative, for each keyword group (Figure 3) was higher than that obtained in the INPI database search. Although the number of results is lower for the national base, the value found for search 1-B corresponds to almost 20.0% of that found for the same type of product in the international database. This can be explained by the great biodiversity of the country, which can be an incentive factor for research and development and patenting of products containing these plant derivatives. If the searches with the keywords 4-B and 4-I are compared, the results found in the national database correspond to 62.5% of those found in the international database.

Figure 3 – *Number of documents found in the international database between 2008 and 2018 and evolution of patent filing in the period. Group of keywords used in searches (Table 1) organizes data.*



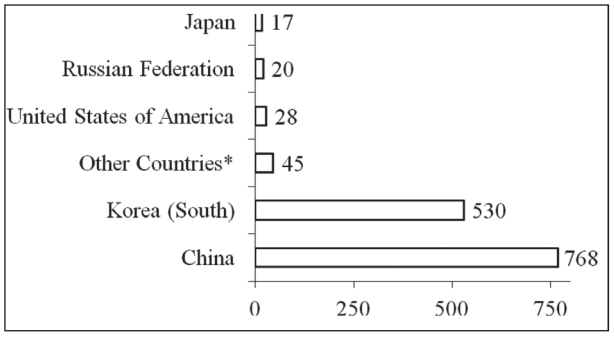
** 1-I: Products containing one or more types of plant extracts or derivatives in their compositions, and / or cosmetic applications of these plant extracts or derivatives; 2-I: Products containing one or more types of plant extracts or derivatives in their compositions and with antioxidant action and / or application, and / or cosmetic applications of these plant extracts or derivatives; 3-I: Products containing one or more types of plant extracts or derivatives, in their compositions and with photoprotective action and / or application; 4-I: Products containing one or more types of plant extracts or derivatives, in their compositions, having a photoprotective action and / or complementary antioxidant.*

Source: Research data.

In Figure 3 it is possible to observe the evolution of the accumulated number of submitted patents between 2008 to 2018. It is possible to observe through the graph a considerable growth of patent applications of cosmetic products using some kind of vegetable derivative in its composition. For the photoprotective and / or antioxidant products, the number of orders is still small and with no expressive growth in the period. Prospecting using the search terms combined with the names of the species surveyed in this work, either individually or in combination, did not yield any results in the surveyed period.

The assessment of the number of documents filed per country (Figure 4) shows that China has a considerable number of deposits compared to other countries, representing more than 52% of the total documents filed in the period, followed by South Korea with about 36% of patent filing.

Figure 4 – *Number of documents published by country between 2008 and 2018 (herbal cosmetics).*

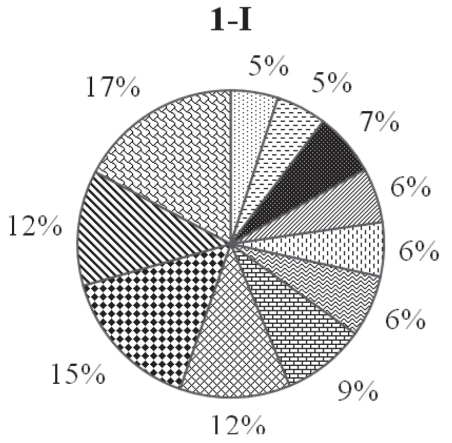


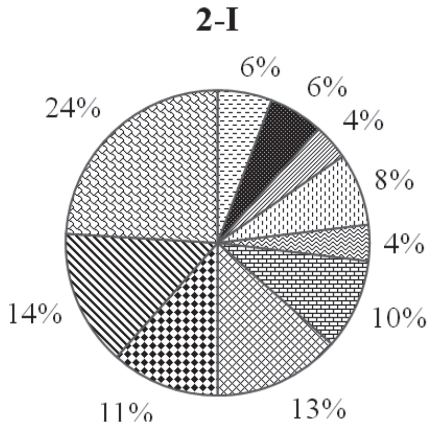
*** Other** *Countries = France (8); Ukraine (5); Bulgaria (4); Taiwan (4); Canada (3); Germany (3); Slovakia (3); Australia (2); United Kingdom (2); Mexico (2); Poland (2); Austria (1); Greece (1); Croatia (1); India (1); Malaysia (1); New Zealand (1); Philippines (1).*

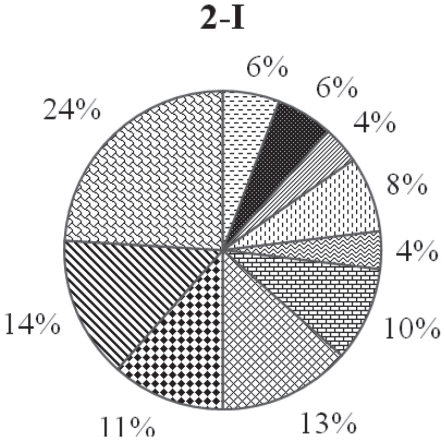
Source: Research data.

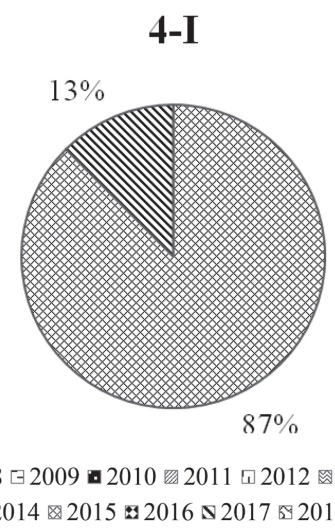
The evaluation of the number of documents per year of filing (Figure 5) shows a higher number of deposits in 2016 and 2018, for the keywords used in the search 1-I, totaling more than 32% of the total documents in the 11 years. For the keywords used in search 2-I, 2018 alone amounted to 24% of the total documents deposited in the period. Search 3-I only generated results in 2010 and from 2012 to 2018, and the years 2017 and 2018 represent 70% of all documents filed in the surveyed period.

Figure 5 – *Prospecting of patents filed in the international database from 2008 to 2018. There were 4 separate searches, as described in Table 1, organized by the keywords highlighted in each Pie chart. Data are organized by year showing the percentage of the total of 11 years.*









** 1-I: Products containing one or more types of plant extracts or derivatives in their compositions, and / or cosmetic applications of these plant extracts or derivatives; 2-I: Products containing one or more types of plant extracts or derivatives in their compositions and with antioxidant action and / or application, and / or cosmetic applications of these plant extracts or derivatives; 3-I: Products containing one or more types of plant extracts or derivatives, in their compositions and with photoprotective action and / or application; 4-I: Products containing one or more types of plant extracts or derivatives, in their compositions, having a photoprotective action and / or complementary antioxidant.*

Source: Research data.

Among the patents that matched the keywords used, 106 reported a sunscreen application citing one or more types of plant extracts or derivatives, none of which deals with fruit extracts of Abiu (Pouteria caimito), Guava (Psidium guajava), Rambutan (Nephelium lappaceum) or Grape (Vitis sp), and with different application claims. In these patents, the use of plant extracts is associated not with the photoprotective effect. Most of these patents use traditional Chinese herbs or relate the use of the plant as a skin lightening agent and anti-signs, such as a sunscreen composition with seeds extracts of Raphanus sativus L. (radish), Cinidium officinale Makino and Angelica gigas Nakai[45]. The patent does not claim a synthetic interaction for photoprotection. Another example is a photoprotective and depigmenting product composition containing cellulose nanoparticles and extracts of Angelica, lemon and others[46].

This research identifies a significant number of patents related to plant extract in association with sunscreen product. On the other hand, such plant extract is used with distinct goals, which may or may not include photoprotective activity.

The evolution of the accumulated number of these types of patents filed has been growing at an average of 9.0%, nationally, and 11.4% per year, worldwide, during the surveyed period. This expressive growth can be explained by the growing demand of the consumer market for cosmetics that incorporate assets of natural origin, especially those of plant origin, which leads to a constant search for the development of new products with these characteristics.

The Brazilian and international market for sun care products moves millions to billions of dollars annually and have an annual growth prospect of 11.05% and 6.37%, respectively. If the projections are confirmed, it is possible that the sector will move about US$ 932.5 million for the Brazilian market and US$ 21.5 billion for the international market by 2020[47].

CONCLUSION

Patent search revealed no patent filings for cosmetic products containing extracts of abiu, rambutan, guava or grape, either alone or in combination with each other or with other active substances, for photoprotective and antioxidant purposes, either in the Brazilian or international database. However, several studies published in the literature already indicate that there is potential for these products to have this application.

The production of cosmetics from naturally occurring substances with such activities will be of great importance for the Brazilian industrial sector, being able to reduce the cost of production, considering the great biodiversity existing in the country, representing a great scientific and economic impact.

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