



## Review

## The international scenario of patents concerning isoflavones



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## ABSTRACT

**Background:** Isoflavones are a class of phytoestrogens that has been considered important raw material for healthcare products, mainly as dietary supplements for hormone replacement and active ingredients in skin care cosmetics. Because of this, many scientific reviews are found regarding the extraction, analysis methods and biological activities of these compounds. However, it is emphasized that, to date, no studies have been found concerning technological mapping of patents involving isoflavones.

**Scope and approach:** The present study aimed to map patents covering the last 20 years of technology innovation comprising isoflavones. To that, a patent survey was conducted between the years of 1994–2014 in an international patent database (*Espacenet*) using the title's keywords: isoflavones, genistein, daidzein, glycitein, biochanin A and formononetin.

**Key findings and conclusions:** The resulting data allowed the identification of the major countries, universities and companies that invest in products containing these compounds. In addition, patents were separated into interest groups. The three clusters discussed in this study were: processes for obtaining enriched isoflavone fractions from different plant materials intended to healthcare products, such as dietary supplements; the use of isoflavones in cosmetic products; and the incorporation of isoflavones in micro and nanostructured systems to mask unpleasant tastes or overcome the low water solubility of bioactive forms. In conclusion, this study, along with other literature reviews, could assist in designing strategic research and worldwide development of new products containing isoflavones.

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## 1. Introduction

Isoflavones are a group of phytoestrogens of widespread interest in nutritional, medicinal and cosmetic fields. These compounds are chemically similar to the hormone 17- $\beta$ -estradiol, conferring several beneficial effects on the organism. Among several human foods containing isoflavones, soybeans are the most abundant, presenting predominantly the aglycones genistein, daidzein, glycitein and their respective acetyl, malonyl and glucoside conjugated forms (Chen et al., 2012; Nemitz et al., 2015). Red clover is another example of enriched natural source of isoflavones, which contain the same ones of soybeans, but predominantly present the free and conjugated forms of formononetin and biochanin A (Vacek, Klejduš, Lojkova, & Kuban, 2008).

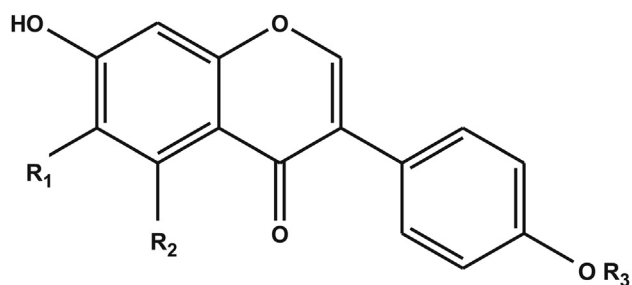
Aglycones (Fig. 1) are forms of isoflavones with a great capacity to be absorbed both in the gastrointestinal tract and skin, and have

a substantial therapeutic potential when compared to the conjugated forms (Izumi et al., 2000; Nemitz et al., 2015). These compounds can be obtained by different ways, such as purchase of the isolated and synthetic forms or by extraction from plant materials. Since soybeans predominantly present the conjugated forms of isoflavones, extraction followed by hydrolysis and purification processes has been the method most often described for obtaining isoflavone aglycones from defatted soybeans or soyfoods (Nemitz et al. 2015; Rostagno, Villares, Guillamón, García-Lafuente, & Martínéz, 2009). On the other hand, red clover predominantly presents isoflavones in their aglycone forms (Tsoo, Papadopoulos, Yang, Young, & Mcrae, 2006), so their obtainment is basically the extraction from the leaves followed by purification processes (Vacek et al., 2008).

Many patents and scientific studies can be found in the literature because of the clinical importance of isoflavones. Consequently, to facilitate the insight of the state of the art involving the use of isoflavones, several researchers have constantly written review articles. Some examples are: review on isoflavones regarding their biological activity (Albertazzi & Purdie, 2002; Andres,

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Isoflavone	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
Genistein	H	OH	H
Daidzein	H	H	H
Glycitein	OCH <sub>3</sub>	H	H
Formononetin	H	H	CH <sub>3</sub>
Biochanin A	H	OH	CH <sub>3</sub>

Fig. 1. Chemical structure of soybean isoflavone aglycones.

Donovan, & Kuhlenschmidt, 2009; Barnes, 1998; Chen et al., 2012; Fritz et al., 2013; Kolodziejczyk-Czepas, 2012; Mortensen et al., 2009; Setchell, 1998; Wuttke, Jarry, & Seidlova-Wuttke, 2007), metabolism (Aura, 2008; Barnes, 2010; Heinonen, Wähälä, & Adlercreutz, 2002; Setchell, 1998; Yuan, Wang, & Liu, 2007), biosynthesis (Tian, Pang, & Dixon, 2008), meta-analysis of preclinical and clinical studies (Anderson, Johnstone, & Cook-Newell, 1995; Gartoulla & Han, 2014; Taku et al., 2010; Yang et al., 2011; Zhan & Ho, 2005), description of the different ways of obtaining them (Chen et al., 2012; Nemitz et al., 2015; Rostagno et al., 2009), analytic methods for their quantitative measurement (Luthria & Natarajan, 2009; Mortensen et al., 2009; Raju, Kadian, Taneja, & Wahajuddin, 2015; Vacek et al., 2008; Wang, Prasain, & Barnes, 2002), their topical use (Leyden & Wallo, 2011; Nemitz et al., 2015; Wei et al., 2003), the unpleasant taste that these compounds cause in foods (Drewnowski & Gomez-Carneros, 2000), or a description of technological alternatives to circumvent solubility challenges during the production of topical products (Nemitz et al., 2015). However, to date, none of the review studies has presented a technological mapping of patents involving isoflavones.

It is noteworthy that to assess the state of the art of a particular subject, not only the scientific literature should be evaluated, but also the technologies protected by patents (Okubo, 1997). The reviews of patents are important tools for measuring the rates of production and dissemination of knowledge, and assist in making decisions about new research projects to be undertaken either by universities or private sectors. Bibliometric indicators related to the patent also serve as a tool for assessing the degree of a country's technological development, in addition to identifying potential partners or market competitors (Frietsch et al., 2010).

In this context, considering both the importance and originality of the subject, this study aimed to conduct a search of the state of the art on patents within a 20-year timeframe involving the main isoflavones and their isolated forms: genistein, daidzein, glycitein, formononetin and biochanin A. The justification for undertaking the study was to help make new decisions concerning studies involving isoflavones, especially when it comes to risk management and technological innovations, improving the technological competitiveness, reducing investment uncertainty, and supporting new decision-making in research and development (R&D) of new products containing isoflavones.

## 2. The importance of patents

Technological innovations are recognized as strategic elements of growth and development for all types of industries (Frietsch et al., 2010; Idris, 2003). An important way to induce innovation is the intellectual property (IP), since IP rights protect inventors and companies for a determined period from having their creations and innovations exploited in an unauthorized manner by third parties (Idris, 2003).

One way to ensure IP rights is by patenting a product or process (Frietsch et al., 2010; Idris, 2003). A patent is a legal document in the public domain aimed at ensuring the inventor of the right to economically exploit his invention or utility model, either individually or in the form of a license, for a determinate period of time, generally 20 years from the filing date of the application. In return, the inventor is obliged to provide technical information about the invention so as to allow for technological diffusion of innovations covered by patents (Auerbach, 2006). Furthermore, patents are territorial rights. In general, the exclusive rights are only applicable in the country or region in which a patent has been filed and granted. However, to ensure the exploitation in different countries, the applicant can also submit an international patent application under the Patent Cooperation Treaty (PCT) which is administered by the World Intellectual Property Organization (WIPO).

Some assessment ways for summarizing the innovation profile of a specific region or segment are the prospecting studies through technological mapping (Ernst, 2003; Lee, Kang, & Shin, 2015). That way, data and analyses based on technology indicators are typically used, and the number of patent applications is an important industrial development indicator (Basberg, 1987; Yoon, Yoon, & Park, 2002). This indicator is normally used to mirror the profile of technological innovations as well as assists in future research and development activities (Frietsch et al., 2010). In addition, all of the information derived from patent surveys can assist in strategic planning for institutions, developing public policies, and industrial management (Ernst, 2003; Lee et al., 2015; Speziali, Guimarães, & Sinisterra, 2012).

During the technological mapping, the correct searching of information is essential. While exhaustive searches can be difficult to conduct, the correct choice of research variables, such as the selection of keywords and database, is critical to determining the scenario to be evaluated (Noh, Jo, & Lee, 2015).

The technological monitoring of patents in different countries can be made by means of national office databases or commercial databases. National or regional offices strive to maintain free access to documents. Some examples are the Brazilian National Institute of Intellectual Property (INPI), the U.S. Patent and Trademark Office (USPTO), the Japan Patent Office (JPO), and the State Intellectual Property Office of the People's Republic of China (SIPO). The Espacenet database is another free website, part of the European Patent Office (EPO), characterized by the fact that it can locate patents filed in over 70 countries. Nonetheless, it is interesting to note that there are widely-specialized patent files, such as the Derwent Innovations Index (IBD), Questel Orbit, and Micropatent, but they are commercial databases and, therefore, access to their files is done by prepayment (Carvalho, Winter, Mothé, & Carestiatto, 2011; WIPO, 2015).

## 3. Clinical importance of isoflavones and technological challenges

Isoflavones are plant compounds belonging to the group of polyphenols, known for their considerable estrogenic activity. In general, these compounds are found in the Leguminosae family, being predominantly present in soybeans, alfalfa sprouts, and red

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