Trends in Food Science & Technology 49 (2016) 85–95

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: http://www.journals.elsevier.com/trends-in-food-science-and-technology

Review

The international scenario of patents concerning isoflavones

Marina Cardoso Nemitz, Débora Fretes Argenta, Letícia Scherer Koester, Valquíria Linck Bassani, Gilsane Lino von Poser, Helder Ferreira Teixeira*

Programa de Pós Graduação em Ciências Farmacêuticas, UFRGS, Av. Ipiranga, 2752, 90610-000 Porto Alegre, RS, Brazil

ARTICLE INFO

Article history:
Received 14 August 2015
Received in revised form
18 December 2015
Accepted 10 January 2016
Available online 12 January 2016

Keywords:
Cosmetics
Enriched fractions
Isoflavones
Micro and nanostructured systems
Technological indicators

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.

1. Introduction

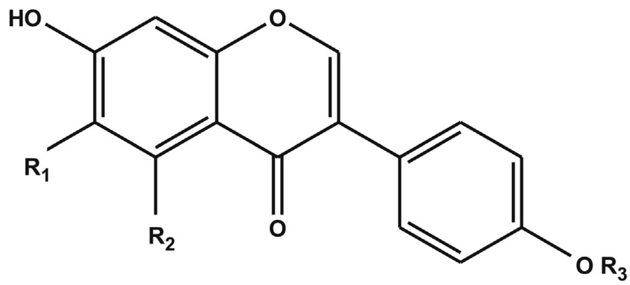
Isoflavones are a group of phytoestrogens of widespread interest in nutritional, medicinal and cosmetic fields. These compounds are chemically similar to the hormone 17-β-estradiol, conferring several beneficial effects on the organism. Among several human foods containing isoflavones, soybeans are the 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, Klejdus, 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, Gárcia-Lafuente, & Martinéz, 2009). On the other hand, red clover predominantly presents isoflavones in their aglycone forms (Tsao, 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,

* Corresponding author.
E-mail address: helder.teixeira@ufrgs.br (H.F. Teixeira).

http://dx.doi.org/10.1016/j.tifs.2016.01.008
0924-2244/



Isoflavone	R_1	R_2	R_3
Genistein	H	OH	H
Daidzein	H	H	H
Glycitein	OCH_3	H	H
Formononetin	H	H	CH_3
Biochanin A	H	OH	CH_3

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), byossintesis (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, & Carestiato, 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 clover leaves (Vacek et al., 2008). Phytoestrogens, and more specifically, the isoflavone aglycone genistein, are characterized by having various beneficial health effects, such as preventing heart disease, osteoporosis, cancer, diabetes and climacteric symptoms, besides offering beneficial effects when applied on the skin (Albertazzi & Purdie, 2002; Barnes, 1998; Chen et al., 2012; Nemitz et al., 2015; Rodrigues, Almeida, Sarmento, Amaral, & Oliveira, 2014; Rodrigues et al., 2013).

Because of these beneficial effects, both isolated isoflavones and plant extracts containing isoflavones are found in several food, dietary supplements, pharmaceutical, and cosmetic products. However, studies report that extracts containing isoflavones have higher clinical effects when compared to the individual phytoestrogens (Hsu, Bray, Helferich, Doerge, & Ho, 2010; Iovine, Iannella, Gasparri, Monfrecola, & Bevilacqua, 2011; Kim, Jeong, & Kim, 2008; Rando, Ramachandran, Rebecchi, Ciana, & Maggi, 2009). Moreover, it is important to highlight that to allow the gastrointestinal and skin absorption, the products should preferably contain the aglycone forms of isoflavones (Izumi et al., 2000; Nemitz et al., 2015).

On the other hand, isoflavone aglycones are less soluble than the conjugated forms, which often hinder the product development, especially those related to hydrophilic systems (Nemitz et al., 2015). Besides, the aglycone forms have bitterness and astringency, producing an unpleasant taste in food products and beverages (Drewnowski & Gomez-Carneros, 2000). To overcome these limitations, some technological alternatives are being proposed, such as: the development of liposome carriers, micro/nanostructures, and the formation of complexes with cyclodextrins to incorporate aglycone into hydrophilic systems or mask their disagreeable taste (Nemitz et al., 2015).

4. Products containing isoflavones – foods, dietary supplements, medicines and cosmetics

Foods that contain high amounts of isoflavones include soy, peanuts, chick peas, alfalfa, fava beans, and kudzu. Between these foods, soybeans are the most abundant source of isoflavones. Soybean products (soyfoods), reported as potential functional foods, are often associated with the reduction of menopausal symptoms (Chen et al., 2012). These products are classified as non-fermented and fermented soyfoods, and the most common are soymilk, tofu, soy sauce, miso, infant formula, natto, tempeh, among others. The soy flour is a very attractive raw-material to obtaining soy protein concentrate and bioactive fractions, such as fractions enriched in isoflavones, which normally are marked as dietary supplements.

Dietary supplements are products intended for ingestion that contains a dietary ingredient purposed to add further nutritional value to supplement the diet. According to the Food and Drug Administration (FDA) conceptions, a dietary ingredient may be one, or any combination, of the following substances: vitamins, minerals, herb and botanicals, amino acid, metabolite, constituent, or an extract. The dietary supplements may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. Some dietary supplements can help ensure an adequate dietary intake of essential nutrients; others may help to reduce risk of diseases. Whatever the form, dietary supplements are considered a special category of food and are not considered drugs (Melethil, 2006).

The differences between medicinal products (drugs) and dietary supplements are based on their regulation routes, composition, claims and presentation (Coppens, da Silva, & Pettman, 2006). The most commercialized products containing isoflavones, in USA and Europe, are the dietary supplements obtained from soybeans and red clover. These supplements are promoted worldwide for the treatment of menopausal symptoms and the maintenance of health and welfare after the menopause (Coppens et al., 2006; Eisenbrand, 2007; Melethil, 2006).

Because of the large demand for products containing isoflavones, especially by climacteric women, many studies and patents concerning the production of enriched-isoflavones products from soybeans and red clover are found in literature, as well as, many commercial products are found in the market portfolio of industries. Soy extracts are marketed as food supplements and "dietary foods for special medical purposes", whereas in most cases red clover extracts have been marketed as food supplements. These preparations are frequently market without medical prescriptions, and usually are available in pharmacies, supermarkets, and on the internet. The dosage recommended varies greatly according to the manufacture; however, it is generally between 20 and 80 mg isoflavone/day (Eisenbrand, 2007).

Cosmetic formulations containing isoflavones are market available with the appeal of anti-aging products. These formulations are supposed to reduce wrinkles and dryness, and increase skin elasticity (Kapuscinska & Nowak, 2015). According to literature and several clinical trials (Nemitz et al., 2015), the isoflavones have shown beneficial estrogenic effects on the skin, being largely attributed to the aglycone forms (Schmid & Zulli, 2002).

5. Patent survey concerning isoflavones

Owing to the diverse applications of isoflavones in food and health fields, technological mapping of patents involving this particular topic is an attractive way to assess innovation prospecting in this sector. Thus, this study conducted a data compilation of patents involving isoflavones. The method used was based on a patent search in the international databases Espacenet and Espacenet-LATIPAT, bellowing to EPO, over a period of 20 years (1994–2014). The selected title's keywords were "isoflavona", "genisteina", "daidzeina", "gliciteina", "formononetina" and "biochanina" with truncation symbol (*) used for searches in the Latin databases (lp.espacenet.com), and the words "isoflavone", "genistein", "daidzein', "glycitein", "formononetin" and "biochanin" with the truncation symbol (*) for the international database (ep.espacenet.com).

The first set of data was carried out by sorting patents by year using the keywords "isoflavona*" and "isoflavone*" (Fig. 2a). As can be seen, the number of patent filings, as found on both Espacenet-LATIPAT and Espacenet, underwent significant growth between 1994 and 2002, signaling a potential increase in product and process innovation in a global context. Then, between 2004 and 2005, there was a steady peak in terms of innovation, with a slight decrease and constancy in the following years. Besides, Fig. 2b shows the number of patents filed using the title's keywords "genistein", "daidzein", "glycitein" "formononetin" and "biochanin" during the 20 years assessed. It is noteworthy that the greatest innovative interest occurred with the isoflavone genistein. This scenario may have arisen as a result of scientific and clinical demonstrations that this is the most bioactive compound when compared to other isoflavones (Polkowski & Mazurek, 2000; Chen et al., 2012).

In general, technologies have evolution cycles with slow onset of entering the market, followed by an ascension phase, and finally a decline when a new alternative is introduced. Cycle duration is variable because there are more stable industries in which improvements are essentially complementary or incremental, and there are more dynamic industries in which more radical technological changes are noted (Galembeck, dos Santos, Schumacher, Rippel, & Rosseto, 2007). Fig. 2a shows that current technologies involving isoflavones are in decline, meaning that product innovations and improvements in processes are needed for a new

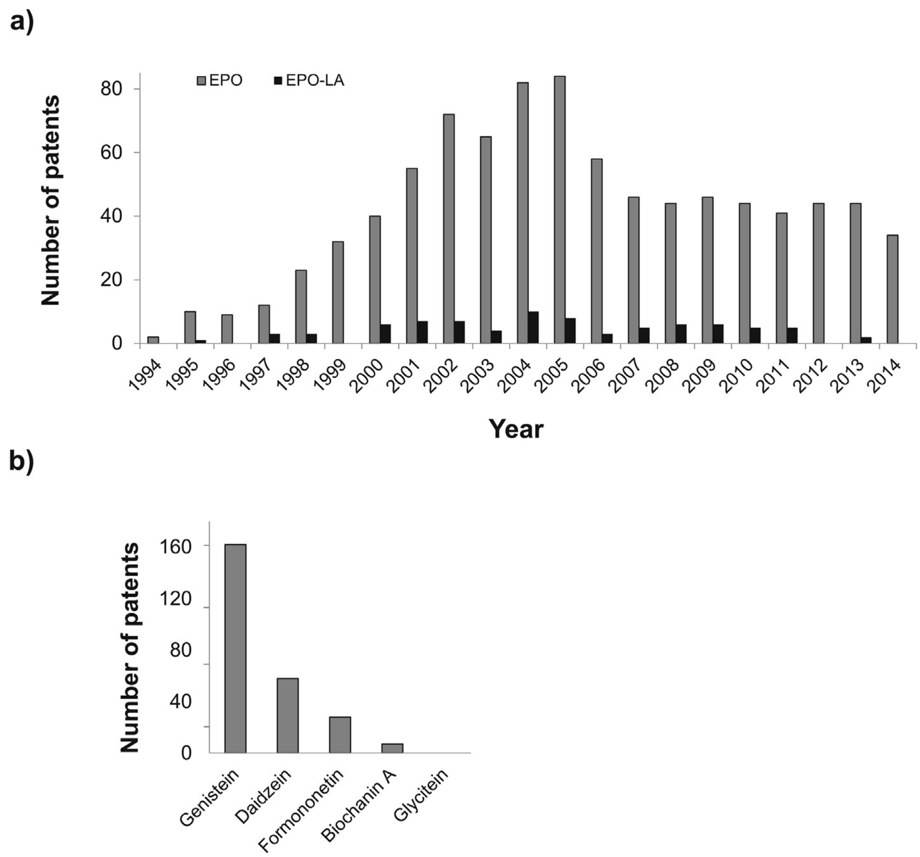


Fig. 2. Relationship of patent applications between 1994 and 2014, where: (a) annual distribution of patents with the title's keywords "isoflavona*" found in the Espacenet-LATIPAT (EPO-LA) database, and with the title's keywords "isoflavone*" found in the Espacente (EPO) database; (b) number of patents with the title's keywords "genistein*", "daidzein*", "glycitein*", "formononetin*" and "biochanin*" found in the Espacenet (EPO) database.

ascension phase in this industrial area.

In view of the potential interest that food companies can display in the production of isoflavones from natural sources for their use as dietary supplements or cosmetics, as well as taking into account a recent scientific review published by Nemitz et al. (2015), the present manuscript selected and divided the patents described in Fig. 2 into three major clusters: (1) processes for obtaining fractions enriched in isoflavones from plant materials; (2) the use of isoflavones in cosmetic products; and (3) incorporation of isoflavones into micro- and nanostructured systems designed to mask unpleasant flavors or circumvent the poor water solubility of their bioactive forms. The results of the divide-by-cluster patents from Fig. 2a and b are shown in Tables 1 and 2, respectively.

It is important to point out some peculiarities in the interpretation of the Tables 1 and 2, especially with regard to data compilation of the first cluster. Thus, it is highlighted that only the patents that describe methods of obtaining extracts, fractions, or isolated forms from plant materials and food products, resulting in a powder of isoflavones were compiled. Therefore, patents that describe obtaining food products in different forms than solid powder products, such as tofu, soy milk, cheese, cereal, noodles, soy sauce and similar products were not taken into consideration, even when the technology described ways to increase the content of isoflavones in these products. In addition, while preparing the tables, it was not taken into account, patents that describe different isoflavone synthesis routes, their by-products, analytical methods for quantification, metabolization, incorporation into classic pharmaceutical or supplement systems (e.g., capsules, tablets, and solutions), action mechanisms, types of pharmaceutical use, and changes in the culture process modifications.

Considering the total number of patents described in the three clusters in Table 1, it is important to note that the 705 patents represent a total of 346 technologies. This difference is due to the fact that some technologies were filed in more than one country. Among the protected technologies, 46 patents were filed via international application. The technology that has the highest number of patents filed via PCT is internationally entitled "*Novel isoflavone-enriched soy protein product and method for its manufacture*", first filed by the American company DuPont in 1995 under the number WO9737547 (A). This technology has been patented in over 17 countries, resulting in a total of 18 patents. However, the technology internationally entitled "*Recovery of isoflavones from soy molasses*", filed by Protein Technologies International (PTI) first and foremost in the European patent office under the number EP0812837 (A) in 1997 and granted in 2005 under the number EP0812837 (B), is the one that has the largest number of patents in different countries. This patent was not filed via PCT; however, the company filed 20 separate patents in different countries.

The patents that were reviewed and presented in Table 1 refer to obtaining isoflavones by means of extraction and purification from various plants. The different raw materials include a description of isoflavone extraction from *Glycine max* (soybeans), and their by-products or from other plant species such as *Trifolium pretense* (red clover), *Iris florentine, Astralagus membranaceous, Pueraria montana, Butea monosperma, Sophorae japonica, Pueraria thunbergiana, Belamcanda chinensis* and *Dalbergia odoriferous*, among others.

To illustrate obtaining isoflavone fractions from plant materials

Table 1
Patents separated by clusters after examination of documents obtained in Espacenet and Espacenet-LATIPAT databases, between the years of 1994–2014, with the keywords “isoflavone*” and “isoflavona*”.

Cluster	Patent number					
Obtaining fraction containing isoflavones	US2002004458 (A) US2003104084 (A) US2003119759 (A) US2004047927 (A) US2004121059 (A) US2004126443 (A) US2004170713 (A) US2004215003 (A) US2004215003 (A) US2005085632 (A) US2005123633 (A) US2005202139 (A) US2006116510 (A) US2007179099 (A) US2008044861 (A) US2010048689 (A) US2010190844 (A) US2011305782 (A) US2012003337 (A) US2013231291 (A) US5352384 (A) US5670632 (A) US5679806 (A) US5702752 (A) US5726034 (A) US5827682 (A) US5851792 (A) US5994508 (A) US6013771 (A) US6033714 (A) US5637561 (A) US5763389 (A) US6132795 (A) US5990291 (A) US5919921 (A) US5637562 (A) US6140469 (A) US5789581 (A) US5792503 (A) US5821361 (A) US6228993 (B) US6245536 (B) US6261565 (B) US6323018 (B) US6391310 (B) US6410699 (B) US6444239 (B) US6495141 (B) US6497906 (B) US6500965 (B) US6518319 (B) US6521282 (B)	WO2004002469 (A) WO2004037020 (A) WO2004043945 (A) WO2004057983 (A) WO2005042757 (A) WO2005094604 (A) WO2005094607 (A) WO2008021699 (A) WO2008070940 (A) WO2012007978 (A) WO2014030832 (A) WO03093456 (A) WO03077904 (A) WO03000674 (A) WO03084340 (A) WO03082888 (A) WO03088907 (A) WO02056700 (A) WO02080697 (A) WO9726269 (A) WO9510512 (A) WO9510529 (A) WO9510530 (A) WO9737547 (A) WO9935138 (A) WO9849153 (A) WO0032204 (A) WO0017217 (A) WO0158262 (A) WO0234229 (A) WO0139738 (A) WO0017217 (A) KR100200182 (B) KR100361356 (B) KR100375981 (B) KR100379642 (B) KR100379642 (B) KR100380827 (B) KR100409054 (B) KR100411647 (B) KR100412116 (B) KR100412117 (B) KR100427679 (B) KR100442205 (B) KR100460697 (B) KR100475129 (B) KR100491186 (B) KR100525875 (B) KR100557006 (B) KR100613764 (B) KR100620568 (B) KR100683182 (B) KR100823896 (B) KR100847225 (B) KR100858280 (B) KR100882280 (B) KR100891165 (B) KR100996952 (B) KR101198426 (B) KR101233117 (B) KR101302376 (B) KR101393240 (B) KR20000005290 (A) KR20000055133 (A) KR20010016220 (A) KR20010027341 (A) KR20010039376 (A) KR20010073600 (A) KR20010089863 (A) KR20010091098 (A) KR20030092338 (A) KR20030095669 (A)	JP2000262244 (A) JP2000281673 (A) JP2001204486 (A) JP2001302689 (A) JP2002003487 (A) JP2004147532 (A) JP2005080655 (A) JP2005224162 (A) JP2005281251 (A) JP2005318880 (A) JP2005333973 (A) JP2005531616 (A) JP2007217367 (A) JP2007223915 (A) JP2007520192 (A) JP2008022834 (A) JP2011190245 (A) JP2013538187 (A) JP2000095792 (A) JP2004520066 (A) JPH11155592 (A) JPH11255792 (A) JPH11263786 (A) JPH08283283(A) JPH11221048 (A) JPH1067770 (A) JPH1189589 (A) JPH1099089 (A) JP4354611 (B) JP4279982 (B) JP3609273 (B) JP4031703 (B) JP3787844 (B) JP3118451 (B) JP4685202 (B) JP3777390 (B) JP3777389 (B) JP4343828 (B) JP3157168 (B) JP4090438 (B) JP4098385 (B) JP4403800 (B) JP4442422 (B) JP3118451 (B) JP4397525 (B) JP3919871 (B) JP3534844 (B) JP3239121 (B) AT192284 (T) AT201128 (T) AT222064 (T) AT241282 (T) AT282032 (T) AT302767 (T) AT312605 (T) AT361741 (T) AT415169 (T) AT437575 (T) AT460474 (T) AT460497 (T) RU2124896 (C) RU2130073 (C) RU2142957 (C) RU2151775 (C) RU2152434 (C) RU2180662 (C) RU2197095 (C) RU2197095 (C) RU2207006 (C) RU2216991 (C) RU2219785 (C) RU2273147 (C)	CN101066960 (A) CN101084978 (A) CN101104866 (A) CN101129447 (A) CN101168759 (A) CN101255150 (A) CN101278729 (A) CN101407507 (A) CN101423521 (A) CN101532039 (A) CN101928273 (A) CN101947251 (A) CN101974577 (A) CN102167688 (A) CN102174621 (A) CN102702161 (A) CN102747116 (A) CN102783647 (A) CN102885263 (A) CN102961436 (A) CN102964327 (A) CN102965184 (A) CN102994583 (A) CN102977066 (A) CN103140588 (A) CN103145675 (A) CN103146774 (A) CN103773820 (A) CN103788156 (A) CN103848804 (A) CN103755674 (A) CN103739583 (A) CN1966705 (B) CN1911924 (B) CN1813711 (B) CN101029320 (B) CN101085768 (B) CN101086002 (B) CN101200744 (B) CN101239961 (B) CN101348811 (B) CN101353340 (B) CN101357933 (B) CN101386613 (B) CN101422504 (B) CN101503469 (B) CN101559094 (B) CN101701232 (B) CN101736052 (B) CN101766673 (B) CN101775023 (B) CN101781278 (B) CN101792779 (B) CN101824019 (B) CN101921300 (B) CN102002029 (B) CN102206209 (B) CN102302539 (B) CN102424674 (B) CN102558192 (B) CN102702158 (B) CN102702160 (B) CN102838575 (B) CN102838576 (B) CN103223001 (B) CN103262941 (B) CN1321992 (C) CN1321993 (C) CN1065864 (C) CN1055931 (C) CN1055932 (C) CN1214020 (C)	CN101063158 (A) CN102319284 (A) CN102351827 (A) CN102406693 (A) CN103265614 (A) CN103342691 (A) CN103585254 (A) CN103652346 (A) CN103751260 (A) CN1111946 (A) CN1226805 (A) CN1321640 (A) CN1390946 (A) CN1422855 (A) CN1448394 (A) CN1456557 (A) CN1456558 (A) CN1456559 (A) CN1493695 (A) CN1515523 (A) CN1515524 (A) CN1537865 (A) CN1570125 (A) CN1584038 (A) CN1594307 (A) CN1757642 (A) CN1861592 (A) CN1940081 (A) CN1944634 (A) CN1986556 (A) CN100345505 (C) CN100345837 (C) CN100351388 (C) CN100356914 (C) CN100371341 (C) CN100383136 (C) CN100393710 (C) CN100405058 (C) CN100410267 (C) CN100415732 (C) CN100441555 (C) CN100454003 (C) CN100465281 (C) CN100484931 (C) CN100523210 (C) CN100577656 (C) CN100591225	EP0837139 (A) EP1038531 (A) EP1135142 (A) EP1135142 (A) EP1174144 (A) EP1197154 (A) EP1254132 (A) EP1303187 (A) EP1489918 (A) EP1491192 (A) EP1501919 (A) EP1576893 (A) EP1659118 (A) EP1659119 (A) EP1993579 (A) EP2593570 (A) EP1166643 (A) EP0647408 (B) EP0656786 (B) EP0812837 (B) EP1233747 (B) EP1359215 (B) EP1391208 (B) EP0795553 (B) EP1466609 (B) EP1450786 (B) EP0980363 (B) EP0906029 (B) EP0827698 (B) EP0804462 (B) EP0794960 (B) EP0647408 (B) EP0896795 (B) EP1377176 (B) EP1377273 (B) EP0723536 (B)

(*continued on next page*)

Table 1 (*continued*)

Cluster	Patent number					
	US6562380 (B) US6579561 (B) US6664382 (B) US6703051 (B) US6703051 (B) US6706292 (B) US6818246 (B) US6987098 (B) US7045155 (B) US7060470 (B) US7208594 (B) US7524526 (B) US7553505 (B) US7618671 (B) US6395279 (B) US5858449 (B) US6320028 (B) US6369200 (B) US6391308 (B) US6391309 (B) US6399072 (B) US6479054 (B) US6517840 (B) US6818246 (B) US7083819 (B) US7084263 (B) US7112573 (B) US7306821 (B) US7354765 (B) US7378114 (B) US7560131 (B) BRPI0502309 (A) BRPI0903222 (A) BR0002609 (A) BR0001876 (A) BR0004237 (A) BR0208798 (A) BR1101092 (A) BR1101108 (A) BR9404054 (A) BR9407792 (A) BR9407820 (A) BR9407822 (A) BR9703526 (A) BR9704589 (A) BR9705019 (A) BR9705428 (A) BR9705428 (A) BR9708545 (A) BR9708545 (A)	KR20040038481 (A) KR20040009971 (A) KR20050065486 (A) KR20040048225 (A) KR20040098612 (A) KR20070106255 (A) KR20070111655 (A) KR20100035786 (A) KR20100035840 (A) KR20120059198 (A) KR20140026725 (A) BR9805069 (A) BR9809316 (A) BR9809316 (A) BR9815832 (B) BR9815832 (B) BR9915896 (A) BR9915896 (A) AU718810 (B) AU748832 (B) AU717144 (B) AU720462 (B) AU742569 (B) AU764493 (B) AU720838 (B) AU680554 (B) AU732423 (B) AU696553 (B) AU696574 (B) AU738774 (B)	RU2309603 (C) HK1024918 (A) HK1071512 (A) US7595080 (B) TWI260205 (B) TWI377254 (B) TW574225 (B) TWI241893 (B) TWI245603 (B) AU4099897 (A) AU5956699 (A) AU3690601 (A) AU1847097 (A) AU1243402 (A) AU1704601 (A) AU2475600 (A) AU777632 (B) AU674437 (B) AU2003285804 (A) AU2002210886 (A) AU2003231985 (A) AU2003231977 (A) AU2003223644 (A) AU2003284189 (A) AU2002328824 (A) AU2003291446 (A) AU2002254573 (B) AU2003227617 (B) AU2003296185 (B) CL31972002 (A)	CN103965154 (A) CN103623048 (A) CN103598579 (A) ITRM20100378 (A) RU2013105731(A) KR101451298 (B) ZA200307700 (A) DE69430314 (T) DE69429931 (T) DE69429673 (T) DE69422124 (T) DE69709472 (T) DE69908219 (T) DE69921778 (T) DE69714734 (T) DE69704861 (T) DE69701842 (T) DE69734042 (T) ZA9808962 (A) TW474930 (B) TW491688 (B) TW491851 (B) TW491852 (B) TW491895 (B) TW493002 (B) TW526081 (B) GB2339429 (B) FR2817866 (B) FR2815539 (B) IL158569 (A)	(C) CN1095468 (C) CN1107065 (C) CN1109682 (C) CN1114351 (C) CN1069903 (C) CN1120163 (C) CN1132830 (C) CN1137629 (C) CN1158273 (C) CN1163150 (C) CN1176084 (C) CN1193683 (C) CN1216151 (C) CN1233639 (C) CN1237896 (C) CN1257899 (C) CN1261586 (C) CN1300135 (C) CN1314678 (C) CN1241922 (C) CN1305869 (C) CN1328274 (C) CN1282650 (C) CN1273609 (C) CN1210407 (C) CN1305392 (C) CN1309716 (C) CN1094044 (C) CN1127495 (C) CN1195750 (C) DK0827698 (T) DK0906029 (T) DK0943245 (T) DK1450786 (T) HU0002624 (A) NZ500715 (A) ZA9702978 (A) NZ331691 (A) NZ506701 (A) IL120409 (A) IL140953 (A) NO984695 (A) NO325456 (B) ES2147660 (T) ES2160895 (T) ES2160895 (T) ES2180979 (T) ES2180979 (T) ES2199523 (T) ES2232107 (T) ES2247617 (T) ES2254725 (T) ES2315332 (T) ES2333304 (T) IL158263 (A)	EP0656786 (B) EP1054008 (B) EP0943245 (B) PT9800305 (A) PT827698 (E) PT906029 (E) CA2443383 (C) CA2218236 (C) CA2214665 (C) CA2207360 (C) CA2643973 (A) CA2249366 (C) CA2249501 (C) CA2307064 (C) CA2290004 (C) CA2484258 (A) CA2173743 (A) CA2448513 (A) CA2133382 (C) CA2173999 (C) CA2307061 (C) CA2403584 (C) CA2288321 (C) CA2174120 (A) CA2803322 (A) CA2240795 (C) CA2217649 (C) CN2666177 (Y) NO20045212 (A) NO325127 (B) AR016141 (A) SG43879 (A) US6146668 (A) US7033621 (B)
Use of isoflavones in cosmetics	US2002106388 (A) US2002107282 (A) US2002160064 (A) US2004170655 (A) US2005256061 (A) US6017893 (A)	WO2004002435 (A) WO2005030157 (A) WO2007000192 (A) WO02074278 (A) WO02076409 (A) WO02089757 (A) WO0234229 (A) WO0139738 (A) WO0152840 (A) WO0164177 (A) EP1361854 (B)	DE202005012206 (U) DE102004020712 (A) DE102004006829 (A) KR20040091178 (A) CN101212965 (A) CN101732180 (A) CN102113977 (A) CN102525850 (A) CN102631362 (B) DE10009424 (A) DE10114305 (A)	MXPA05000073 (A) AU2003264673 (A) ITMI20060392 (A) TW201021843 (A) KR100500641 (B) KR100530199 (B) KR100868904 (B) KR101195970 (B) KR101229511 (B) KR101314689 (B) BRPI0612705 (A)	EP1158975 (A) EP1205179 (A) EP1259221 (A) EP1377254 (A) EP1667641 (A) EP1896009 (A) EP1233747 (B) EP1234572 (B) FR2841470 (B) HK1074404 (A) ES2311730 (T)	

Table 1 (*continued*)

Cluster	Patent number					
	US8685456 (B) AU1243402 (A) AU1704601 (A) AU3555101 (A) FR2803747 (B) FR2815539 (B) FR2816502 (B) FR2820974 (B) FR2822068 (B)	EP1515696 (B) EP1834628 (B) DE4432947(C) JP3271840 (B)	DE10122342 (A) DE10344531 (A) DE60219432 (T) AU4647101 (A)	JP2002193726 (A) CN1460465 (A) CN1671354 (A) CN1205915 (C)	AT493109 (T) JP5129130 (B) CA2491150 (A)	
Micro and nanotechnology systems containing isoflavones	US2002160064 (A) US2005220949 (A) US2009035336 (A) US2012121654 (A) US2013189320 (A) US2013190392 (A) WO2007000192 (A) WO2007000193 (A) WO2012068140 (A) KR100482355 (B)	BRPI0612705 (A) BRPI0612848 (A) CN103961716(A) WO0113890 (A) US5847108 (A) US8551530 (B) US8685456 (B) US6890561 (B) CA2382218 (A) CA2852410 (A)	KR20000030509 (A) KR20000030512 (A) KR100504379 (B) KR101242851 (B) KR101314689 (B) CN1861058 (A) AU6591400 (A) ES2369928 (T) AR044000 (A) AT520396 (T)	JP2003183166 (A) JP2013545752 (A) JP2002155072 (A) JPH09309902 (A) JPH10298175 (A) JP5129130 (B) JP5134535 (B) EP1210066 (A) EP1896009 (A) IL131508 (A)	CN101757640 (B) CN102652736 (B) CN201657748 (U) CN101212964 (A) CN101212965 (A) CN101947251 (A) CN103099798 (A) CN103211750 (A) CN103211769 (A) CN1660075 (A)	EP2640188 (A) EP1234572 (B) EP1904053 (B)

for use as dietary supplement, it can be cited US6146668 (A) filed in the United States in 1997 by the American company Novogen, that posterior assistance of in the creation of the patent US6599536 (B), filed by the same company. These technologies refers to obtaining a fraction enriched in isoflavones from plant material (preferably red clover, *Trifolium pratense*), and the oral administration of tablets containing the fraction, respectively. These patents have given rise to Promensil®, Rimostil® and Trinovin®, supplements recommended for the treatment of climacteric symptoms in menopausal women, bone health, and to maintain prostate health and urinary function in men, respectively (Booth et al., 2006). The dietary supplement protected by the second technology was also protected in several countries or regions, such as South Africa (ZA200005070 A), Turquia (TR200002770 T), Portugal (PT1063990 E), Norway (NO325456 B), Japan (JP2002507568 A), Israel (IL138129 A), Spain (ES2281169 T), Europe (EP 1063990 B), Denmark (DK1063990 T), Germany (DE69934877 T), Canada (CA2325631 A), and Brazil (BR9909105 A).

Another example of successful marketing of a food product from protected technology, comprising an innovative way to obtain fractions containing isoflavones, is Novasoy®, a supplement belonging to the American company ADM (Ray, 2004). This product was launched in 1998 and consists of concentrated isoflavones, commercially sold as a raw material for nutritional supplements, medicine, or cosmetics with a composition of 40% genistin, daidzin, and glycitin and their aglycone forms in a ratio of 1.3: 1.0: 0.3. As an example of its use in the medicinal products, it is cited the technology filed in the United States under number US2003175345 (A), in Europe (EP1463515 A), Canada (CA2484528 A), and Australia (AU20023666380 A), which describes the use of this supplement in the production of controlled-release tablets for oral use. In the cosmetics field, an example of using Novasoy® technology is a patent filed by L'oreal under number FR2818148 (A) in 2002, granted in 2005, and also filed in Europe (EP1343459 B), Japan (JP2004515516 A), United States (US6852326 B), Spain (ES2278680 T), Germany (DE60125823 T), Australia (AU2080302 A) and Austria (AT350111 T).

With regard to patents shown in the cosmetic cluster, those filed by German company Biersdorf, represented by the Nivea brand, are of particular interest since this brand has a strong global presence in the cosmetics sector (Chen & Liang, 2013). Technologies filed by the company include WO02076409 (A), WO02089757 (A) filed in 2002 and WO2005030157 (A), DE102004020712 (A), DE102004006829 (A) filed in 2005, and describe formulations containing isoflavones among the products' active ingredients, which are suitable for different cosmetic actions, such as a reduction of sebum, antiperspirant and anti-aging actions, and a decrease in sensitive skin irritation. In the cosmetics cluster, it is also interesting to mention the patent WO0234229 (A) filed by the French company Silab in 2002. This technology describes obtaining a fraction enriched in isoflavone aglycones from rhizomes of plants belonging to the genus *Florentine* with subsequent incorporation into gels and creams suitable for anti-aging skin action.

In the nanotechnology cluster, some patents describe product innovations containing isoflavones for dietary supplements or cosmetic use. The patent WO2007000193 (A) describes the production of genistein powder with nano-sized particles resulting from the substance's self-aggregation, but without being incorporated into a nanocarrier. Subsequently, the patent WO2007000192 (A) describes the use of this nano-sized particle in cosmetic products. The patents JPH09309902 (A), US5847108 (A), JPH10298175 (A), JP2002155072 (A) describe the combination of cyclodextrins with isoflavone aglycones, particularly aimed at reducing their bitterness and astringency or increasing their water solubility. The patent CN1660075 (A) uses the combination of isoflavones and cyclodextrin to manufacture various kinds of medicinal products. The patents KR20000030509 (A) and KR20000030512 (A) describe the production of microcapsules with sugars and emulsifiers to increase the isoflavone's water solubility. The patent WO0113890 (A) describes the production of modified release microcapsules for oral administration, and patent KR100482355 (B) describes the production of liposomes and nanoemulsions containing soy isoflavones and dipalmitoyl hydroxyproline for incorporation into cosmetics. Finally, the United State patent US2002160064 (A)

Table 2
Patents separated by clusters after examination of documents obtained in Espacenet and Espacenet-LATIPAT databases, between the years of 1994–2014 with interested keywords.

Keywords	Patent number			
	Cluster 1		Cluster 2	Cluster 3
Genistein	KR20040005113 (A)	WO9706273 (A)	JP2000511907 (A)	CN102319438 (A)
Genisteína	KR100858280 (B)	US5554519 (A)	US2012083524 (A)	CN103271892 (A)
	KR100849145 (B)	US5726034 (A)	US2009286872 (A)	CN103301090 (A)
	KR100412116 (B)	US5851792 (A)	US5824702 (A)	CN103446055 (A)
	CN103773820 (A)	CA2218236 (C)	CA2257579 (C)	
	CN101760488 (A)	CA2214665 (C)	DK0918504 (T)	
	CN101619338 (A)	BR0304014 (A)	DE69719994 (T)	
	CN102351828 (A)	BR9705428 (A)	WO9746208 (A)	
	CN101544626 (B)	BR9704589 (A)	PT918504 (E)	
	CN101497594 (B)	DK0827698 (T)	AT234599 (T)	
	CN101709057 (B)	AU4099897 (A)	AU716131 (B)	
	CN100523210 (C)	AU6716196 (A)	KR20070014672 (A)	
	CN101781278 (B)	AU718810 (B)	WO2007116052 (A)	
	CN102491965 (B)	EP0827698 (B)	KR100500641 (B)	
	CN101210058 (B)	ES2147660 (T)	CN102488210 (B)	
	MX9706806 (A)	ES2160895 (T)	ES2188963 (T)	
	DE69701842 (T)	PT827698 (E)	EP0918504 (B)	
	DE69704861 (T)	AT201128 (T)	EP2004161 (B)	
	CN1210407 (C)	AT192284 (T)		
	CN1269810 (C)	TW574225 (B)		
	CN1352896 (A)	JPH11155592 (A) JPH1099089 (A)		
	CN1216878 (C)	JP3078694 (B)		
	RU2152434 (C)	JP3482558 (B)		
	RU2309603 (C) NZ252051 (A)			
Daidzein	AU718810 (B)	US5851792 (A)	KR20070014672 (A)	CN101204392 (A)
Daidzeína	AT192284 (T)	US5726034 (A)		CN102008454 (B)
	AT201128 (T)	EP0827698 (B)		CN102058528 (B)
	TW574225 (B)	ES2160895 (T)		CN102060870 (B)
	CN1210407 (C)	ES2147660 (T)		CN102258475 (B)
	JPH1099089 (A)	CA2214665 (C)		CN102274202 (B)
	DE69704861 (T)	CA2218236 (C)		CN102552208 (B)
	DE69701842 (T)	BR0304014 (A)		CN102727482 (B)
	JPH11155592 (A)	BR9705428 (A)		CN100487032 (C)
	CN100523210 (C)	BR9704589 (A)		
	JP2007223915 (A)	DK0827698 (T)		
	KR100412116 (B)	RU2309603 (C)		
	KR100855741 (B)	RU2152434 (C)		
	CN102911978 (A)	AU4099897 (A)		
	CN103059008 (A)	MX9706806 (A)		
	CN101210058 (B)	PT827698 (E)		
	KR20040009971 (A)	NZ252051 (A)		
Glycitein	No patents			
Gliciteína				
Formononetin	CN102532083	NZ252051 (A)		
Formononetina	KR20080075343			
	CN101775418			
Biochanina A	CN103773820 (A)			
Biochanin A	CN102373248 (A)			
	NZ252051 (A)			

Cluster 1: Obtaining fraction containing isoflavones; Cluster 2: Use of isoflavones in cosmetics; Cluster 3: Micro and nanotechnology systems containing isoflavones.

describes the production of liposomes, preferably containing genistein and daidzein, for incorporation into cosmetics. This patent was subsequently licensed to Mibelle for the production of a marketable product known as Lipobelle Soyaglycone®.

To better visualize the most prominent countries in technological innovation involving isoflavones, the technologies shown in Table 1 were organized by countries in which patents were filed. Thus, the most prominent countries for the cluster related to obtaining isoflavone fractions are China, USA, Korea and Japan, with 132, 63, 44 and 28 protected technologies, respectively. The most prominent countries in the cosmetic cluster are France, Germany, China, and Korea with 08, 07, 05 and 05 protected technologies, respectively. The most prominent countries in the nanotechnology cluster are China, Japan, and Korea with 10, 04, and 04 protected technologies, respectively. The total number of patented technologies is a valuable indicator of the degree of innovative development of the countries. However, it is noteworthy that this indicator is considered controversial when the objective is the comparison of aggregated value, for example, estimates of economic, technological, social, and strategic value in different countries, since some companies may file patents without subsequently launching marketable products involving the patented technology, or there are institutions such as universities filing patents that end up not being licensed afterwards (Frietsch et al., 2010).

To better visualize the types of patent applicants involving isoflavones, the technologies presented in Table 1 were organized by type of holder, which was broken down into three categories: independent, company, or university. The proportion of patents filed independently, by companies, and by universities within each cluster can be seen in Fig. 3. For the cluster related to obtaining

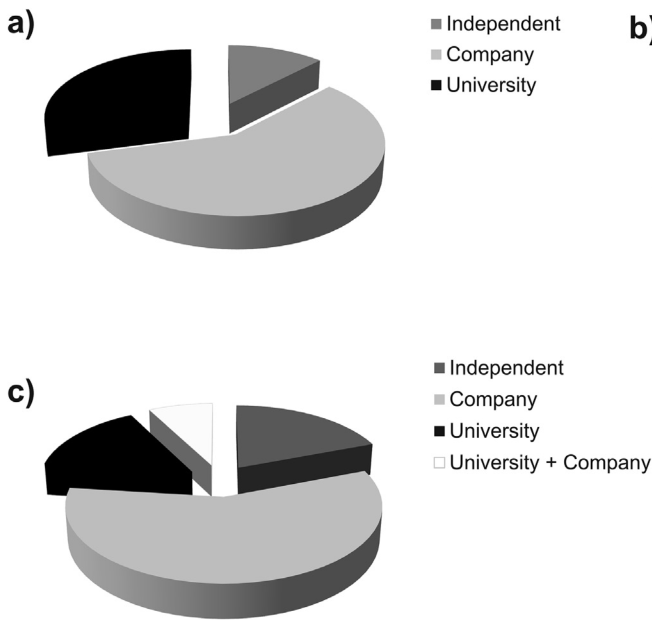


Fig. 3. Types of patent applicants according to technologies filed for each cluster, where: (a) obtaining fraction containing isoflavones; (b) use of isoflavones in cosmetics; (c) micro and nanotechnology systems containing isoflavones.

fractions (Fig. 3a), 168 technologies represent filings made by companies, 83 technologies by universities, and 35 independent filers. With regard to the cosmetic cluster (Fig. 3b), 24 technologies represent filings made by companies, 01 technology by a university, and 07 by independent filers. For the cluster related to nanotechnology systems (Fig. 3c), 15 technologies represent filings made by companies, 04 by universities, 02 by partnerships between universities and companies, and 05 by independent filers. Among the patents filed by universities, China is the country that most protects its technologies, and when it comes to obtaining fractions, the educational institutions with more patent applications are Northeast Agricultural University, Zhejiang University, and the Institute of Jilin of Chemical Technology, with 06, 05, and 03 protected technologies, respectively.

To better visualize the most outstanding companies in products containing isoflavones, the technologies in Table 1 were organized by filing companies. These data prove to be important, especially when the interest is in seeking potential partners, competitors, or markets for future innovations and business strategies. Thus, in the area of obtaining isoflavone fractions, the most prominent companies are the American's DuPont (34 technologies), ADM (07 technologies), Novogen (06 technologies), the Japan's Kokkoman (04 technologies), Fuji Oil (04 technologies), and the South Korea's Eugenbio (05 technologies) and Rexgene (04 technologies). In the cosmetics area, the most prominent companies that invest in products containing isoflavones are the German Biersdorf (05 technologies), the French Pharmascience (03 technologies), Korean Amorepacific (02 technologies), and Kolmar (02 technologies). In the area involving isoflavones and the complexation of cyclodextrins or incorporation into nanostructures, the leading companies in terms of protected technologies are the Japanese Fuji Tsuko (03 technologies), the Chinese Nano and Advanced Materials Institute Ltd (02 technologies), and the Netherlands' DSM (02 technologies).

To get a better understanding of the history of companies that innovate in products containing isoflavones, especially those of the first cluster, a search was made of the literature and websites of the most prominent companies in the field. Protein Technologies International (PTI), founded in 1958 in the United States, was bought in 1997 by DuPont and Bunge. Up until 2002, PTI was the leader in the protection of new technologies involving obtaining isoflavones from plant materials, especially soybeans. In 2003, PTI changed its name to Solae LLC and, in 2012, DuPont became its majority shareholder. According to data reported by Shurtleff and Aoyagi (2013), the biggest competitor of DuPont is the American company Archer Daniels Midland (ADM). This company, founded in 1902, has a consolidated trade in the food market. However, according to the results here expressed, DuPont, through its subsidiaries PTI and Solae LLC, is the one that has the most protected technologies involving obtaining fractions that contain isoflavones.

Taking account all the patents described in Table 2, the 122 patents represent, in real, a total of 56 technologies. In the cluster of obtaining fractions, the sum of technologies that describe obtaining individuals or mixtures of genistein, daidzein, formononetin and biochanin A is 37, in which: 19 filed by companies, 15 by universities, and 03 by independent filers. Six technologies were found in the cosmetic cluster involving genistein and/or daidzein: 03 filed by companies, 02 by universities, and 01 by independent filer. Thirteen technologies were found in the nanotechnology cluster involving genistein and/or daidzein: 10 filed by universities, 02 independent, and 01 by a company.

A literature review was recently conducted by Nemitz et al. (2015), which took into account papers published in scientific journals addressing the same clusters of interest described herein. Thus, the set of previously published scientific data and the technological data described in this paper may help researchers from universities and the private sector look for ideas and input for new product innovations containing isoflavone aglycones, especially with regard to the use of these substances in dietary supplements and skin care products.

6. Conclusions

Owing to the importance of technological prospecting for the development of new projects and research, this paper has presented a technological mapping related to isoflavones, specifically their use in cosmetics, their incorporation into different delivery systems, and the processes for obtaining enriched fractions from plant materials. The results presented herein refer to patents filed over a period of 20 years (1994–2014), showing the current scenario by country and type of filers. With the present data, it is possible to see the state of the art of technologies applied to food (extracts for dietary supplements) and cosmetic fields. However, the results should be interpreted with caution when considering society's social, economic, and political aspects or the field of knowledge involved. This study contributes to the food sciences, once it helps to visualize opportunities for future decision-making and expansion in research concerning new routes of obtaining isoflavones from natural sources, and impulses the innovation for development of new products intended mainly for the area of dietary supplements and cosmetic products.

Acknowledgments

This work was supported by the Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES) – Rede Nanobiotec-Brasil (grant agreement nº 902/2009) and State Foundation for Research Support (FAPERGS) – PRONEM (grant agreement nº11/2206-7). M.C.N. wishes to thank CAPES for her scholarship. H.F.T., G.V.P., and V.L.B are recipients of CNPq research fellowship.

References

Albertazzi, P., & Purdie, D. W. (2002). The nature and utility of the phytoestrogens: a review of the evidence. *Maturitas, 42*, 173–185.
Anderson, J. W., Johnstone, B. M., & Cook-Newell, M. E. (1995). Meta-analysis of the effects of soy protein intake on serum lipids. *The New England Journal of Medicine, 333*, 276–282.
Andres, A., Donovan, S. M., & Kuhlenschmidt, M. S. (2009). Soy isoflavones and virus infections. *Journal of Nutritional Biochemistry, 20*, 563–569.
Auerbach, J. I. (2006). *Patent law principles & strategies*. http://euro.ecom.cmu.edu/program/law/08-732/Patents/PatentLawPrinciples.pdf Accessed April 2015.
Aura, A. M. (2008). Microbial metabolism of dietary phenolic compounds in the colon. *Phytochemistry Reviews, 7*, 407–429.
Barnes, S. (1998). Evolution of the health benefits of soy isoflavones. *Proceedings of the Society for Experimental Biology and Medicine, 217*, 386–396.
Barnes, S. (2010). The biochemistry, chemistry and physiology of the isoflavones in soybeans and their food products. *Lymphatic Research and Biology, 8*, 89–98.
Basberg, B. L. (1987). Patents and the measurement of technological change: a survey of the literature. *Research Policy, 16*, 131–141.
Booth, N. L., Piersen, C. E., Banuvar, S., Geller, S. E., Shulman, L. P., & Farnsworth, N. (2006). Clinical studies of red clover (*Trifolium pratense*) dietary supplements in menopause: a literature review. *Menopause, 13*, 251–264.
Carvalho, D. S., Winter, E., Mothé, C. G., & Carestiato, T. (2011). Technological monitoring applied to survey-based on Brazilian patent applications about PEMFC. *Journal of Technology Management & Innovation, 6*, 146–160.
Chen, K. I., Erh, M. H., Su, N. W., Liu, W. H., Chou, C. C., & Cheng, K. C. (2012). Soyfoods and soybean products: from traditional use to modern applications. *Applied Microbiology and Biotechnology, 96*, 9–22.
Chen, R., & Liang, C. (2013). The strategy tool: the trademark map of best 100 brands in the world. *Journal of Management and Strategy, 4*, 21–31.
Coppens, P., da Silva, M. F., & Pettman, S. (2006). European regulations on nutraceuticals, dietary supplements and functional foods: a framework based on safety. *Toxicology, 221*, 59–74.
Drewnowski, A., & Gomez-Carneros, C. (2000). Bitter taste, phytonutrients, and the consumer: a review. *The American Journal of Clinical Nutrition, 72*, 1424–1435.
Eisenbrand, G. (2007). Isoflavones as phytoestrogens in food supplements and dietary foods for special medical purposes. Opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG)-(shortened version). *Molecular Nutrition & Food Research, 51*, 1305–1312.
Ernst, H. (2003). Patent information for strategic technology management. *World Patent Information, 25*, 233–242.
Frietsch, R., Schmoch, U., van Looy, B., Walsh, J. P., Devroede, R., du Plessis, M., et al. (2010). *The value and indicator function of patents*. http://www.e-fi.de/fileadmin/Studien/Studien_2010/15_2010_Patent_Value.pdf.
Fritz, H., Seely, D., Flower, G., Skidmore, B., Fernandes, R., Vadeboncoeur, S., et al. (2013). Soy, red clover, and isoflavones and breast cancer: a systematic review. *PLOS One, 8*, 1–18.
Galembeck, F., dos Santos, Á. C. M., Schumacher, H. C., Rippel, M. M., & Rosseto, R. (2007). Chemical industry: recent developments, problems and opportunities. *Quimica Nova, 30*, 1413–1419.
Gartoulla, P., & Han, M. M. (2014). Red clover extract for alleviating hot flushes in postmenopausal women: a meta-analysis. *Maturitas, 79*, 58–64.
Heinonen, S. M., Wähälä, K., & Adlercreutz, H. (2002). Metabolism of isoflavones in human subjects. *Phytochemistry Reviews, 1*, 175–182.
Hsu, A., Bray, T. M., Helferich, W. G., Doerge, D. R., & Ho, E. (2010). Differential effects of whole soy extract and soy isoflavones on apoptosis in prostate cancer cells. *Experimental Biology and Medicine, 235*, 90–97.
Idris, K. (2003). *Intellectual property a power tool for economic growth*. http://www.wipo.int/edocs/pubdocs/en/intproperty/888/wipo_pub_888_1.pdf.
Iovine, B., Iannella, M. L., Gasparri, F., Monfrecola, G., & Bevilacqua, M. A. (2011). Synergic effect of genistein and daidzein on UVB-induced DNA damage: an effective photoprotective combination. *Journal of Biomedicine and Biotechnology, 2011*, 1–8.
Izumi, T., Piskula, M. K., Osawa, S., Obata, A., Tobe, K., Saito, M., et al. (2000). Soy isoflavone aglycones are absorbed faster and in higher amounts than their glucosides in humans. *The Journal of Nutrition, 130*, 1695–1699.
Kapuscinska, A., & Nowak, I. (2015). The use of phytoestrogens in anti-ageing cosmetics. *Chemik Science, 69*, 154–159.
Kim, H. A., Jeong, K. S., & Kim, Y. K. (2008). Soy extract is more potent than genistein on tumor growth inhibition. *Anticancer Research, 28*, 2837–2842.
Kolodziejczyk-Czepas, J. (2012). *Trifolium* species-derived substances and extracts—biological activity and prospects for medicinal applications. *Journal of Ethnopharmacology, 143*, 14–23.
Lee, C., Kang, B., & Shin, J. (2015). Novelty-focused patent mapping for technology opportunity analysis. *Technological Forecasting & Social Change, 90*, 355–365.
Leyden, J. M. D., & Wallo, W. M. S. (2011). The mechanism of action and clinical benefits of soy for the treatment of hyperpigmentation. *International Journal of Dermatology, 50*, 470–477.
Luthria, D. L., & Natarajan, S. S. (2009). Influence of sample preparation on the assay of isoflavones. *Planta Medica, 75*, 704–710.
Melethil, S. (2006). Proposed rule: current good manufacturing practice in manufacturing, packing, or holding dietary ingredients and dietary supplements. *Life Sciences, 78*, 2049–2053.
Mortensen, A., Kulling, S. E., Schwartz, H., Rowland, I., Ruefer, C. E., Rimbach, G., et al. (2009). Analytical and compositional aspects of isoflavones in food and their biological effects. *Molecular Nutrition & Food Research, 53*, S266–S309.
Nemitz, M. C., Moraes, R. C., Koester, L. S., Bassani, V. L., von Poser, G. L., & Teixeira, H. F. (2015). Bioactive soy isoflavones: extraction and purification procedures, potential dermal use and nanotechnology-based delivery systems. *Phytochemistry Reviews, 14*, 849–869.
Noh, H., Jo, Y., & Lee, S. (2015). Keyword selection and processing strategy for applying text mining to patent analysis. *Expert Systems with Applications, 42*, 4348–4360.
Okubo, Y. (1997). *Bibliometric indicators and analysis of research systems: Methods and examples*. http://dx.doi.org/10.1787/208277770603.
Polkowski, K., & Mazurek, A. P. (2000). Biological properties of genistein. A review of in vitro and in vivo data. *Acta Poloniae Pharmaceutica, 57*, 135–155.
Raju, K. S. R., Kadian, N., Taneja, I., & Wahajuddin, M. (2015). Phytochemical analysis of isoflavonoids using liquid chromatography coupled with tandem mass spectrometry. *Phytochemistry Reviews, 14*, 469–498.
Rando, G., Ramachandran, B., Rebecchi, M., Ciana, P., & Maggi, A. (2009). Differential effect of pure isoflavones and soymilk on estrogen receptor activity in mice. *Toxicology and Applied Pharmacology, 237*, 288–297.
Ray, K. (2004). *A strategic analysis for new product entry into the nutraceuticals, functional foods, and vitamins and supplements markets*. Doctoral dissertation. Simon Fraser University.
Rodrigues, F., Almeida, I., Sarmento, B., Amaral, M. H., & Oliveira, M. B. P. (2014). Study of the isoflavone content of different extracts of *Medicago* spp. as potential active ingredient. *Industrial Crops and Products, 57*, 110–115.
Rodrigues, F., Palmeira-de-Oliveira, A., das Neves, J., Sarmento, B., Amaral, M. H., & Oliveira, M. B. (2013). *Medicago* spp. extracts as promising ingredients for skin care products. *Industrial Crops and Products, 49*, 634–644.
Rostagno, M. A., Villares, A., Guillamón, E., Gárcia-Lafuente, A., & Martinéz, J. A. (2009). Sample preparation for the analysis of isoflavones from soybeans and soy foods. *Journal of Chromatography A, 1216*, 2–29.
Schmid, D., & Zulli, F. (2002). Topically applied soy isoflavones increase skin thickness. *Cosmet Toiletries, 117*, 45–50.
Setchell, K. D. R. (1998). Phytoestrogens: the biochemistry, physiology, and implications for human health of soy isoflavones. *The American Journal of Clinical Nutrition, 68*, 1333S–1343S.
Shurtleff, W., & Aoyagi, A. (2013). *History of soy flour, grits and flakes (510 CE to 2013): Extensively annotated bibliography and sourcebook*. http://www.soyinfocenter.com/pdf/171/Flou.pdf.
Speziali, M. G., Guimarães, P. P. G., & Sinisterra, R. D. (2012). Desmystifying patent protection in universities. *Quimica Nova, 35*, 1700–1705.
Taku, K., Melby, M. K., Kurzer, M. S., Mizuno, S., Watanabe, S., & Ishimi, Y. (2010). Effects of soy isoflavone supplements on bone turnover markers in menopausal women: systematic review and meta-analysis of randomized controlled trials. *Bone, 47*, 413–423.
Tian, L., Pang, Y., & Dixon, R. A. (2008). Biosynthesis and genetic engineering of proanthocyanidins and (iso)flavonoids. *Phytochemistry Reviews, 7*, 445–465.
Tsao, R., Papadopoulos, Y., Yang, R., Young, J. C., & Mcrae, K. (2006). Isoflavone profiles of red clovers and their distribution in different parts harvested at different growing stages. *Journal of Agricultural and Food Chemistry, 54*, 5797–5805.
Vacek, J., Klejdus, B., Lojkova, L., & Kuban, V. (2008). Current trends in isolation,

separation, determination and identification of isoflavones: a review. *Journal of Separation Science, 31*, 2054–2067.

Wang, C. C., Prasain, J. K., & Barnes, S. (2002). Review of the methods used in the determination of phytoestrogens. *Journal of Chromatography B, 777*, 3–28.

Wei, H., Saladari, R., Lu, Y., Wang, Y., Palep, S. R., Moore, J., et al. (2003). Isoflavone genistein: photoprotection and clinical implications in dermatology. *The Journal of Nutrition, 133*, 3811S–3819S.

WIPO - Word International Patent Organization. (2015). *Guide to technology database*. http://www.wipo.int/edocs/pubdocs/en/patents/434/wipo_pub_l434_11.pdf Accessed August 2015.

Wuttke, W., Jarry, H., & Seidlova-Wuttke, D. (2007). Isoflavones—safe food additives or dangerous drugs? *Ageing Research Reviews, 6*, 150–188.

Yang, B., Chen, Y., Xu, T., Yu, Y., Huang, T., Hu, X., et al. (2011). Systematic review and meta-analysis of soy products consumption in patients with type 2 diabetes mellitus. *Asia Pacific Journal of Clinical Nutrition, 20*, 593–602.

Yoon, B. U., Yoon, C. B., & Park, Y. T. (2002). On the development and application of self-organizing feature map-based patent map. *R&D Management, 32*, 291–300.

Yuan, J. P., Wang, J. H., & Liu, X. (2007). Metabolism of dietary soy isoflavones to equol by human intestinal microflora – implications for health. *Molecular Nutrition & Food Research, 51*, 765–781.

Zhan, S., & Ho, S. C. (2005). Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *The American Journal of Clinical Nutrition, 81*, 397–408.