

Patentability potential of natural products for xerostomia treatment

Potencial de patenteabilidade dos produtos naturais para o tratamento de xerostomia

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ABSTRACT

Xerostomia is characterized as a symptom caused by hyposalivation, which can occur for reasons such as age, polypharmacy, radiation therapy, among others. Currently, few products are available for the treatment of xerostomia, which is a subject still underestimated by many health professionals. Thus, we searched patents applied and approved in Brazil on xerostomia, to verify the existing innovation involving natural products. We found 33 patents applied and approved in Brazil, many of them using acids derived from natural products such as sialogogue agents. This significant number of patents demonstrates the relevance of the theme and the need for more studies involving the potential use of natural products to relieve symptoms.

KEYWORDS

Xerostomia; Biological products; Patents.

RESUMO

Xerostomia se caracteriza por ser um sintoma causado pela hipossalivação, que pode ocorrer por motivos como idade, polimedicação, radioterapia, entre outros. Atualmente existe uma escassez de produtos disponíveis no mercado para o tratamento de boca seca, tema ainda subestimado por muitos profissionais da área de saúde. Assim, realizou-se uma busca das patentes depositadas e publicadas no Brasil com o tema xerostomia, com o intuito de verificar a inovação existente envolvendo produtos naturais. A xerostomia constitui-se objeto de várias pesquisas e produtos patenteados, o que demonstra a relevância do tema, assim como a necessidade de mais estudos envolvendo o potencial de utilização de produtos naturais para o alívio do sintoma.

PALAVRAS-CHAVE

Xerostomia; Produtos biológicos; Patentes

INTRODUCTION

Hyposalivation is the reduction or absence of salivary secretion occurring due to problems directly related to salivary glands or general problems, decreasing or suppressing the salivary production [1]. According to Feio, Sapeta [2], the xerostomia causes are associated with factors affecting the salivary center, such as emotions, frequent fasting, Parkinson disease,

menopause, factors altering the autonomous saliva secretion such as encephalitis, cerebral tumors, smoking, dehydration, and about 400 drugs (opioids, anti-histaminic, antidepressants, antiepileptic, anxiolytics, anticholinergics, anti-hypertensives) [3].

In the pharmaceutical field with high risk and cost of a new active molecule, it is important that protection mechanisms are established, but these mechanisms should stimulate innovation [4]. In

this context, the patent system is an instrument used for the economic and technological development[4]. New products, new uses, and new technologies to be applied in many areas, including pharmaceuticals, can be patented.

Although studies on the relief of xerostomia symptoms have been conducted, currently, no standardized treatment exists and only products for relieving the symptom are available. Accordingly, we conducted a search aiming at identifying the products already patented to be used as either salivary substitutes or stimulants, and among them, to find those of natural origin that can be treatment alternatives.

METHODS

The search for patent deposits and granting regarding xerostomia was conducted through free electronic databases of the Brazilian Institute of Industrial Property (INPI). The search period started in January, 1st, 1994 (date of the beginning of patent granting in Brazil for pharmaceutical products and processes, according to the Law Lei no. #9279/96 (LPI)[10]). We

searched the patent applications applied and approved until April, 31st, 2014. The search strategy was based on the International Patent Classification (IPC), using the following keywords in the title or abstract: dry mouth, hyposalivation, xerostomia, and natural products.

RESULTS

After the search and proper selection of the results, so that only the applications and approvals of products for xerostomia relief, we found 33 patents in Brazil.

The patented products showed different formulations and usages, including solid products; products from maternal secretions; edible films; bakery products; compounds for oral care; orabase gel; compounds containing hyaluronic acid, carbostyryl or pyridine; compounds causing formication or salivation; and artificial saliva, among others. Table 1, shows the patent number and owner. We emphasized that Table 1 displays terms as dry mouth in the applied/granted patent although scientific terms already exist.

Table 1 - Year of granting, country of origin, and patented product

Nº	Year	Patent number	Country	Owner	Title
1	1994	PI 9400544-3	USA	Block Drug Company, Inc. (US)	Product and solid compound against xerostomia
2	2000	PI 9811548-0	IRL	Michael Anthony Folan (IE)	Immune maternal secretions and their use in the treatment and/or prophylaxis of body conditions
3	2001	PI 9914064-0	USA	Warner-Lambert Company LLC (US)	Edible film of fast dissolution
4	2002	PI 0012387-0	USA	Sucampo AG (CH)	Compound for treating disturbs of external secretion
5	2002	PI 0005010-5	USA	R-Tech Ueno, LTD. (JP)	Compound for treating disturbs of external secretion, except hypo lacrimation
6	2004	PI 0111390-9	USA	Soluble Systems, LLC. (US)	Compound and applicator for releasing topical substance
7	2004	PI 0300644-1	BRA	Fundação Universidade Federal de São Carlos (BR/SP)	Compounds to prepare biosilicates and resorbable bioactive biosilicates
8	2005	PI 0317196-5	FR	Laboratoires Carilene (FR)	Oil pharmaceutical compound and use of peroxidized lipids
9	2006	PI 0500039-4	USA	Pericor Science, Inc. (US)	hyaluronic acid compounds and usage methods
10	2008	PI 0514037-4	RU	Glaxo Group Limited (GB) / Glaxosmithkline Consumer Healthcare GmbH & Co. KG. (DE)	Compound for oral care and method for treating xerostomia symptoms

N°	Year	Patent number	Country	Owner	Title
11	2008	PI 0514037-4	RU	Glaxo Group Limited (GB) / Glaxosmithkline Consumer Healthcare GmbH & Co. KG. (DE)	Compound for oral care and method for treating xerostomia symptoms
12	2008	PI 0516468-0	JP	AstellasPhrama Inc. (JP)	Pharmaceutic compound for treating xerophthalmia and xerostomia
13	2008	P 10516219-0	JP	Otsuka Pharmaceutical Co., LTD (JP)	Carbostyryl compound
14	2010	PI 0611420-2	USA	Johnson & Johnson (US)	Bakery products for dry mouth treatment
15	2010	PI 0611400-8	ITL	Alfa Wassermann S.P.A. (IT)	Formulation containing xyloglucan
16	2010	PI 0805520-3	BRA	Associação Paranaense de Cultura - APC (BR/PR)	Compound of orabase gel of pilocarpine for treating xerostomia
17	2011	PI 0620285-3	RU	Novartis AG (CH)	Pyrazine derivatives
18	2011	PI 0620177-6	RU	Novartis AG (CH)	Pyrazine derivatives U extracts
19	2011	PI 0813970-9	USA	Colgate-Palmolive Company (US)	Method for treating and/or preventing dry mouth
20	2011	PI 0813093-0	USA	Colgate-Palmolive Company (US)	Dentifrice compound and methods for treating dry mouth
21	2011	PI 0814463-0	USA	Colgate-Palmolive Company (US)	Oral compound, mouthrinse, or spray for treating hyposalivation
22	2011	PI 0906452-4	USA	Colgate-Palmolive Company (US)	Compound, device for inhibiting dry mouth
23	2011	PI 0906462-1	USA	Colgate-Palmolive Company (US)	Method for treating or preventing dry mouth
24	2011	PI 0906253-0	USA	Colgate-Palmolive Company (US)	Dentifrice compound and method for treating xerostomia and/or tooth sensitivity
25	2011	PI 0908139-9	USA	Colgate-Palmolive Company (US)	Foaming agent for dentifrice compound
26	2012	PI 0613058-5	RU	Glaxo Group Limited (GB) / Glaxosmithkline Consumer Healthcare GmbH & Co. KG. (DE)	Oral care compound for oral cavity lubricant
27	2012	PI 0712006-0	SUI	Firmenich SA (CH)	Compounds that causing formication or salivation
28	2012	BR112012010455-1	USA	The Procter & Gamble Company (US)	Oral compounds for treating dry mouth
29	2012	BR112012011583-9	USA	The Procter & Gamble Company (US)	Oral compounds for treating dry mouth
30	2012	PI 011086-1	RU	Acacia Pharma Limited (GB)	Bethanechol use for treating xerostomia
31	2012	PI 1008380-4	USA	Georgia Health Sciences University Research Institute, Inc (US)	Compound for oral hygiene, method for treating or preventing xerostomia
32	2013	PI 0714755-4	FR	Unither Developpement (FR)	Salivary substitute based on egg white
33	2014	PI 0807268-0	ESP	Biocosmetics, S.L. (ES)	Compound for treating xerostomia

The first invention applied and approved in Brazil to treat xerostomia is of 1994 (Table 1, patent #1), defined as a solid product containing a lubricant polymer of polyethylene oxide and sialologue, as citric acid, malic acid, ascorbic acid,

or fumaric acid, in a vehicle pharmacologically acceptable and non-cariogenic. All sialologue agents can be possibly obtained from a natural product, as simply demonstrated in Table 2.

Table 2 - Acids assialologue potential, extracted from natural products

Acid	Source	Scientific name	Reference
Citric	Passion fruit	<i>Passiflora edulis</i>	Chan et al, [8]
	Acai berry	<i>Euterpe oleracea</i>	Scherer et al., [9]
	Jack fruit	<i>Artocarpus integrifolia</i>	Jagtap&Bapat, [10]
	Lemon	<i>Citruslimon</i>	Couto&Canniatti-Brazaca, [11]
	Orange	<i>Citrussinensis</i>	Couto&e Canniatti-Brazaca, [11]
Malic	Passion fruit	<i>Passiflora edulis</i>	Chan et al., [8]
	Apple	<i>Malus domestica</i>	Rodrigues-Saonaet al, [12]
	Jack fruit	<i>Artocarpus integrifolia</i>	Jagtap&Bapat, [10]
	Acerola cherry	<i>Malpighiapunicifolia</i>	Scherer et al., [9]
	Acai berry	<i>Euterpeoleracea</i>	Scherer et al., [9]
	Pear	<i>Pyruscomunis</i>	Rodrigues-Saonaet al., [12]
Fumaric	Pineapple	<i>Ananascomosus</i>	Pinheiro et al., [13]
	Cocoa	<i>Theobromacacao</i>	Santos et al., [14]
	Guava fruit	<i>Psidiumguajava</i>	Santos et al., [14]
	Umbufruit	<i>Spondias tuberosa</i>	Santos et al., [14]
Ascorbic	Pineapple	<i>Ananascomosus</i>	Pinheiroet al., [13]
	Cashew apple	<i>Annacardiumocidentale</i>	Scherer et al., [14]
	Tangerine	<i>Citrusreticulata</i>	Couto&Canniatti-Brazaca, [11]
	Orange	<i>Citrussinensis</i>	Couto&Canniatti-Brazaca, [11]
	Acerolacherry	<i>Malpighiapunicifolia</i>	Scherer et al., [9]

In 2000, a patent containing medicines formed from an immune maternal secretion with biological activity characteristic of the human saliva and/or mucous secretion. Among the secretions is included egg fluid or milk from domestic animal or their replicas. The medicines have particular application in the treatment and/or prophylaxis of oral infection, dental caries, inflammation conditions of the mouth, xerostomia, and halitosis (Table 1, patent#2).

The invention containing edible films of fast dissolution of oral route was patented in the year of 2001. This is a film of fast dissolution in oral route which is used for releasing the agents of breath deodorizing, antimicrobial agents, and salivary stimulants. The inventions is a film especially adapted to adhere and dissolve rapidly in mouth, composed preferentially by pullulan, essential oils, deodorizing agents, antimicrobials, and water. The stimulant agents of saliva may also be added to the films for oral care, according to this invention (Table 1, patent #3).

In 2002, two patents containing the subject xerostomia was approved. The first was about

an invention comprising as active ingredients derivative from fatty acid as omega-3 (linolenic acid) and omega-6 (linoleic acid). Omega-3 is mainly found in fish and fish oil, and omega-6 in vegetal oils (sunflower, corn, soybean, cotton). The invention compound is useful for treating at least one symptom related to external secretions as hypo lacrimation and hyposalivation (Table 1, patent#4). The other invention is a compound to treat disturbs of external secretion, except hypo lacrimation, with active ingredient of aldose reductase inhibitor (Table 1, patent#5).

A polymerized hydrogel compound and an applicator for hydrating surface was a patent approved in the year of 2004. The compound is a mixture of two polymerizable materials, a redox catalyzer system and two-part polymerization medium. The applicator includes a thermoplastic central section and two reservoir sections, each one with a reservoir to retain humidity and/or medicines. According to the invention, the applicator is projected to insert in the human mouth after hydration and is used to xerostomia (Table 1, patent #6). Still in 2004,

it was approved the description of a process of bioactive, resorbable particulate biosilicates from glass plates. The process is the one- or two-step thermal treatment of glass plates, at controlled temperatures and times, followed by grinding the crystallized glass to obtain the desired powder of crystalline, bioactive, resorbable biosilicate product, free of cutting surfaces, which in contact of body fluids results in a layer of restorative hydroxycarbonateapatite of teeth that is gradually replaced by dental tissue and resorbed (Table 1, patent #7).

In the year of 2004, a patent was approved regarding an oil pharmaceutical compound based on peroxidized lipids and silica. In this compound, the peroxidized lipids are preferentially obtained by peroxidation of natural vegetal oil, e.g. sunflower oil; and preferentially colloidal silica. The products of the invention are indicated for treating xerostomia (Table 1, patent #8).

The patent approved in 2005 shows the use of fatty acids to aid in xerostomia symptoms (Table 1, patent #8). Some studies on patients with Sjogren syndrome show the fatty action in the stimulus of cell proliferation of [15]. This same patent uses green tea polyphenols (extract of *Cameliasinensis*) to stimulate the saliva production. This sialogogue property of green tea is already much known in Chinese medicine [16].

In the year of 2006, hyaluronic acid compounds for treating xerostomia were patented. The invention is about compounds and methods for relieving symptoms associated with dryness benefiting from the use of hyaluronic acid, including, but not limited to xerostomia or xerophthalmia. The invention provides an alternative to the continuous and frequent application of therapeutic agents for xerophthalmia, xerostomia, and other conditions associated with dryness. The invention is based, partly, in discovering the efficacy of hyaluronic acid can be improved by covalently linking the hyaluronic acid to the tissue or body surface, such as, mucous surface (e.g., mouth or cornea),

endothelial surface, or external surface (e.g., hair or nail) using a reaction mediated by transglutaminase. The hyaluronic acid is found in connective tissues of humans and animals, with an important function in cushioning and lubrication of the body, normally abundant in eyes, joints, and heart valves. Additional to the presence in animal organisms, some hyaluronic sources are present in nature, e.g.: *Streptococcus* strains, cells of umbilical cord and rooster combs [16].

In the year of 2008, a compound for oral care was described for treating or relieving the symptoms of xerostomia containing polyvinylpyrrolidone (PVP) or a derivative, a mucous-adhesive anionic polymer and an excipient or acceptable pharmacological vehicle. Still in this year, an invention has two aims: to provide a therapeutic agent for xerophthalmia and xerostomia free of undesirable effects, and as a medium to solve problems. The invention proposes the administration of a compound A, from which the saliva and tear secretion was increased without perspiration, and through controlled releasing of this same substance increased the multiplication of the cells of lacrimal and salivary glands (Table 1, patents #10, #11, and #12).

Still in the year of 2008, an invention was patented providing a carbostyryl compound capable of inducing the production of TFF (Trefoil Factor), and this mode can be used to treat and/or prevent disturbances as alimentary disease, oral diseases, respiratory disease, ophthalmic disease, cancer, and injuries. The owners extensively conducted a research to develop a new compound capable of upregulating the endogenous TFF, and as a result, the owners found that carbostyryl compounds can do it (particularly TFF2). The carbostyryl compounds can be used as a prophylactic and/or therapeutic agent in a disturbance in which the TFF upregulation has this effect, as ulcer induced by drug, peptic gastric ulcer, ulcerative colitis, Crohn's disease, enteritis induced by drug, ischemic colitis,

irritable bowel syndrome, developed developed ulcers after endoscopic flaking, acute gastritis, chronic gastritis, reflux esophagitis, esophageal ulcer, Barrett esophagus, gastrointestinal mucositis, hemorrhoidal diseases, stomatitis, Sjogren syndrome, xerostomia, rhinitis, pharyngitis, bronchial asthma, chronic obstructive lung disease, dry eye or keratoconjunctivitis (Table 1, patent #13).

Following, in the year of 2010, a patent of orally ingested compounds (also known as candies) was approved for application of agents stimulating saliva and/or replacing saliva in mouth and throat (Table 1, patent #14). The candies include a core and a shell surrounding the core. The composition of the core and the shell makes the candy uniquely suited for the application of targeted stimulating agents of saliva and / or saliva replacement in the mouth and throat. The compositions of the invention relate to orally ingestible products for the delivery of at least one active agent for the prevention, reduction or alleviation of the symptoms of mouth dryness, among the acids listed in Table 2.

Formulations containing xyloglucan and muco-adhesive useful in medical devices and pharmaceutical compositions were patented in 2010 (Table 1, patent #15). The object of the invention are muco-adhesive and controlled release formulations consisting of aqueous solutions containing the purified natural polymer having xyloglucans structure and 10% to 70% by weight of glycerol. These formulations are suitable for application to human mucous membranes (nasal, oral and vaginal mucous membranes), or as wetting agents and softeners, or as pharmaceutical release system. Because xyloglucans are obtained from the plant wall of several dicotyledonous present in flora, their collection and use become facilitated. Still in 2010, it was described a patent of orabase pilocarpine-based gel composition (substance obtained from the *Pilocarpus jaborandi*) for the treatment of xerostomia, to be administered

as topical gel on the oral mucosa of patients who require an effective control of xerostomia, particularly when caused by psychotropic and similar drugs (Table 1, patent #16).

In 2011, two patents containing pyridine derivatives have been approved, owing to its action in blocking epithelial sodium channels (Table 1, patents #17 and #18). Diseases mediated by blockade of epithelial sodium channel also include diseases associated with the regulation of fluid volumes of epithelial membranes, including respiratory diseases associated with abnormal fluid regulation by the epithelium, xerostomia and keratoconjunctivitis sicca. The agents of the invention may be administered by any appropriate route, for example orally in the form of a tablet or capsule; parenterally; intravenously; by inhalation in the treatment of an obstructive airway disease; intranasally, in the treatment of allergic rhinitis; topically to the skin; or rectally.

Also in 2011, oral compositions comprising silicone polyols are described for lubricating and hydrating the oral cavity and are effective in relieving the symptoms of xerostomia (Table 1, patent #26). In this same year, several patents were internationally approved, waiting for the Brazilian publication phase, including the patent of the use of bethanechol for xerostomia (Table 1, patent #30).

In early 2012, it was applied a patent containing compositions that cause tingling and salivation, to provide compositions that combine the ability to overcome dry mouth problems. An organoleptic composition comprises a salivary component, a fumigating agent and an aroma component. Salivary component is formed of at least a mixture of citric, malic and succinic acid or its salts. Fumigating component is formed by an ingredient selected from the group consisting of oleoresin from jambu, spilanthol, any extract containing either or both and mixtures. The inventors have established that in preparing a composition involving a salivary component,

a flavor and fumigator that provide improved salivary effects can be obtained. Furthermore, jambu (*Acmellaoleracea*), a typical grass of the northern region of Brazil, has diuretic and sialagogue properties already recognized (Table 1, patent #27).

The purpose of the invention patented in 2013 was the production of a saliva substitute from egg white to introduce chemical, rheological and physiological properties similar to those of natural human saliva (Table 1, patent #32). The egg white is a natural protein compound that meets almost all of saliva components in an equivalent balance. It also has a similar covering power and a similar viscosity, allowing the coexistence of the different components together. Also, egg white is a naturally aseptic environment which composition stability is well known. The saliva substitute according to the invention comprises at least one egg. Natural saliva consists of high molecular weight proteins that gives its viscosity, its covering power of the mucous membranes and teeth, as well as ensures the exchange and establishment of minerals on the tooth enamel. These proteins are mainly mucins, immunoglobulins, and acid glycoproteins. The egg white proteins are similar to the constituent proteins, molecular weight and structure of natural saliva.

The last patent to be approved was in 2014, with a composition based on olive oil, dimethylglycine, and xylitol for treating xerostomia. Studies on this formulation proved a synergistic effect with an increase of nearly 200% of the salivary flow (Table 1, patent#33).

Of patents filed and granted in Brazil, for the relief of xerostomia in the period 1994-2014, one can observe a wide variety of mechanisms for obtaining sialagogue effect. Currently on the market, there are some products that attempt to replace the effect of saliva, but all these products are far from rheological complexity, mucous protector effect, and biological activity of natural saliva. They have a composition and different behaviors, which does not allow them

to offer such a complex equivalent functionality, not participating in the oral homeostasis. Added to this is the fact that patients often do not want to use artificial saliva due to its own consistency, which can cause discomfort. Thus, the patented egg white based salivary substitute explained that its composition (due to proteins and properties of egg white components) can indeed be a suitable replacement, in addition to foam property as in contact with the air, similar to human saliva. The negative factor is the fact that it requires use at every 1 hour.

Drugs with sialagogue activity are drugs that increase salivary secretion by stimulation of the autonomic nervous system, both sympathetic and parasympathetic. Each drug acts on a specific site of the autonomic nervous system, causing consequently different responses, allowing the professional to select the one that best meets the patient's needs. They act by stimulating exocrine system, generally comprising the ophthalmic glands, sweat glands, vaginal secretions, skin hydration, increased sputum, and urinary system, among others. The main parasympathomimetic drugs are pilocarpine and bethanechol. However, its secretagogue action in salivary, sweat, lacrimal, and gastric glands are some limiting factors for clinical use by the systemic route since it lead discomforts to the patient user of these drugs. Among the classic adverse effects reported in the literature associated with the use of pilocarpine, are worth mentioning facial flushing, excessive sweating, nausea, vomiting, gastrointestinal disorders, headache, increased urinary frequency, cardiac, vascular changes, smooth muscle, among others. Due to this the presence of an orabase gel containing pilocarpine is extremely important to avoid the occurrence of the above-mentioned event; however, it is a product that requires consistent application.

The derivatives of pyridine, which promotes the blocking of epithelial sodium channel, may be important allies in the relief of xerostomia. However, derivatives of pyridine can also promote

the blocking of different sodium channels in other body systems, which will cause an increase of intra-corporeal fluids, which is not desirable for a patient complaining only of xerostomia. Furthermore, a blockage of the sodium channels in the kidney epithelium increases diuresis, which can cause the onset of hypotension.

Figure 1 shows the relationship between the percentages of patents published versus the number of papers related to xerostomia versus the number of products obtained from plants. The number of papers on xerostomia is still small when we compare the number of patents registered, showing that most of these developed products are confidential. The number of products developed from natural products is still very small when considering the number of patents registered. Thus, studies related to the

potential use of plants in the field of xerostomia can lead to an increase in the number of patents in Brazil, considering the existing flora.

Formulations containing xyloglucan (mucous-adhesive) and hyaluronic acid are extremely useful in the case of natural products. Many different plant extracts can be added to these formulations, which may have a complementary action in the moistening of tissues. Moreover, the presence of these compounds in the mucosa may be beneficial not only in cases of xerostomia, but also in other body mucosae where there is loss of moisture.

Currently, there is no standard treatment for hyposalivation. There are popular practices that are widespread, and some alternatives in the pharmaceutical market, such as artificial

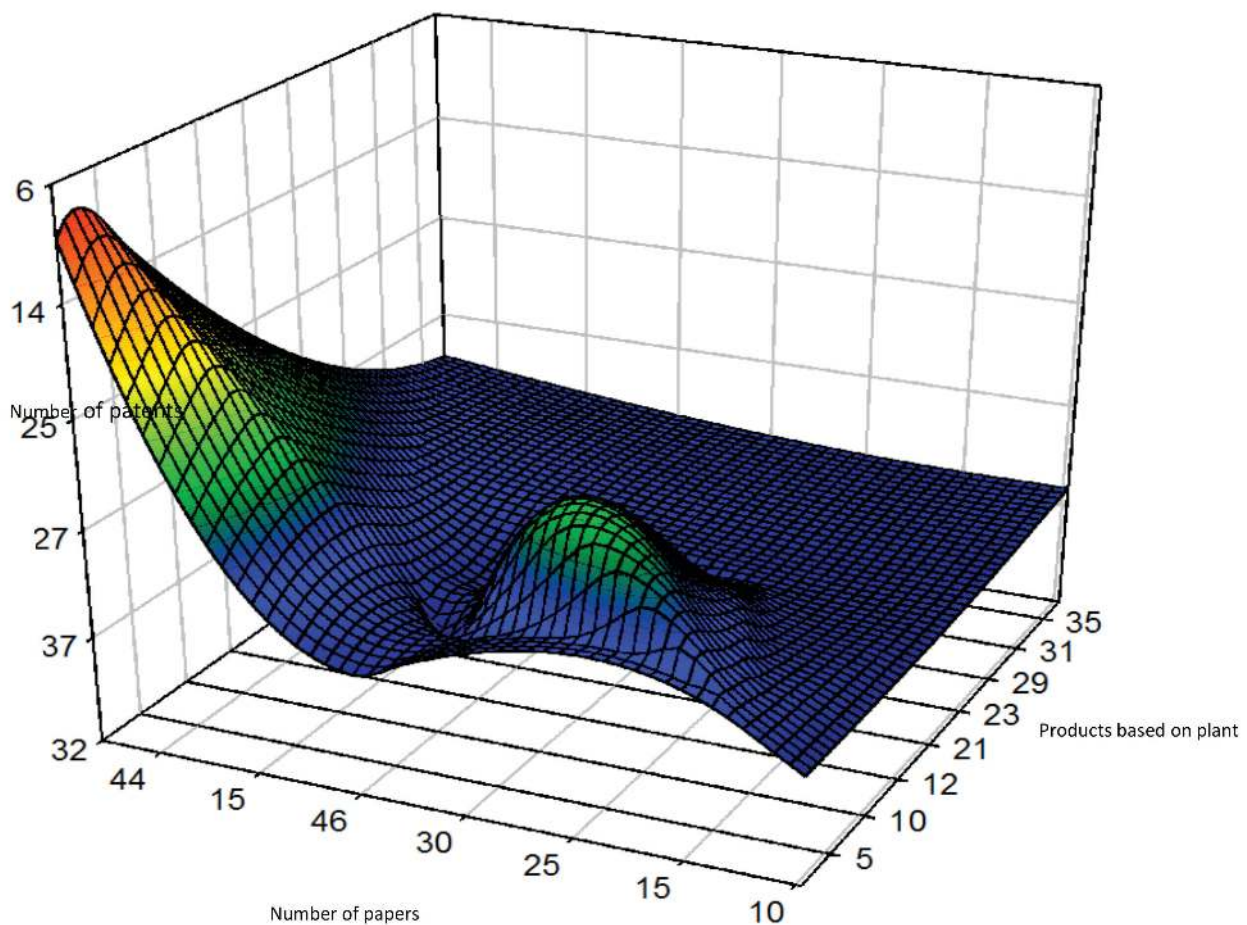


Figure 1 - Relationship between the numbers of patents versus papers versus products based on plant described in patent databases and literature.

saliva, and some products based on cemiveline and pilocarpine. This demonstrates the growing need for study and implementation of new techniques or improved techniques and products already standardized, so that both the professional and the patient easy have a treatment with proven action, which especially is of low cost and easy handling.

There are gaps in the development of new drugs for the relief of xerostomia, this subject is an open field to expand research, especially using natural products, which are many and have several mechanisms. Thus, it becomes necessary a better understanding and knowledge of the epidemiology of incidents and contributing factors, and the impact on health caused by xerostomia. Brazil still lacks on encouraging innovation on the xerostomia and natural products.

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