

Menthol for the Treatment of Erectile Dysfunction: Generation and Technology Export

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Abstract

Erectile dysfunction (ED) is considered a public health problem with numerous risk factors, such as hypertension. Besides the existing oral treatment for ED, there are individuals that do not respond to or present numerous side effects to this therapy. Changes in the TRP channels can lead to several clinical complications, such as hypertension. More specifically, the cooling-sensing TRPM8 channel could be a novel target for the development of new drugs. In this line, menthol, a natural product TRPM8 channel agonist may be a molecule for use to treat erectile dysfunction. Then, we conducted a patent review to evaluate the application of menthol focusing on the treatment of erectile dysfunction. The search was conducted on Espacenet® associating A61K31/045 and A61K36/534 codes or using keywords, “erectile dysfunction AND menthol”. We analyzed 1,331 patents, which fourteen patents were found with the use of menthol in the genitourinary system. Although the patents had menthol in their formulations, none went directly to the development of pharmaceutical applications to treat erectile dysfunction. Taking these data into account, the use of menthol in the treatment of erectile dysfunction has been underexplored and is an opportunity for research and technological development based on a high innovation potential.

Key-words: Menthol, Topical Application, Erectile Dysfunction, Patent Review.

1. Introduction

Erectile dysfunction (ED) is defined by the National Institutes of Health Consensus Statements as the inability to achieve or maintain a penile erection suitable for sexual satisfaction (National Institutes of Health, 1993). ED is considered a public health problem affecting more than

152 million men in the world (Selvin; Burnett; Platz, 2007; Rosen *et al.*, 2005). According to the Brazilian Society of Urology (2014), the prevalence is approximately 59% in Brazilian men between 40 and 69 years of age. A number of factors, such as age, cardiovascular disease (CVD), hypertension, diabetes mellitus (DM), hyperlipidemia, smoking and others are related to the development of ED (Rosen *et al.*, 2005; Hyde *et al.*, 2012). In addition, studies have demonstrated an association between the development of ED and the hypertensive condition, in which 30% to 50% of men with systemic arterial hypertension have ED (Nunes; Labazi; Webb, 2012; Delay; Haney; Hellstrom, 2016).

The correlation between CVD and ED has been established, with endothelial dysfunction being a common risk factor (Kostis *et al.*, 2005). Studies suggest that ED can be an important marker of CVD, as this condition can present itself up to 3 years prior to a CVD event (Montorsi *et al.*, 2003). The treatment of hypertensive-associated ED is correlated with antihypertensive use (Al Khaja *et al.*, 2016). However, inhibitors of phosphodiesterase type 5 (iPDE-5) are widely accepted as the gold standard for ED treatment, commonly used via oral gastric route (Lewis *et al.*, 2001; Steers *et al.*, 2001). Despite the success of this therapy, many patients have experienced negative reactions, such as headaches, facial flushing, dyspepsia, dizziness, nasal congestion, palpitations, cardiac arrhythmia and hypersensitivity reactions (Hatzimouratidis, 2006). In addition, patients with DM have a lower risk of efficacy in treatment with iPDE-5 (Lemaire, Alexandre, 2005; Behrend, Vibe-petersen, Perrild, 2005). Therefore, it is necessary to search for additional mechanisms and therapeutic innovations promoting better efficacy in erectile dysfunction therapy associated with hypertension.

The Transient Receptor Potential (TRP) family channels is a superfamily of cationic, polymodal channels involved in several cellular processes (Minke, 2010). The mammalian TRP channels can be grouped into six subfamilies, TRPC, TRPM, TRPV, TRPA, TRPP and TRPML and a considerable number of TRP family members have been identified in the vasculature (Alonso-Carbajo *et al.*, 2017). Changes in these channels can lead to several clinical complications, such as hypertension (Nilius *et al.*, 2007). A few studies correlate the expression of TRPM8 channels in cardiovascular tissue, but it has already been shown that these channels are altered and contribute to pulmonary hypertension (Liu, Xiong, Zhu, 2014). In addition, one study showed that TRPM8 activation improved vascular function and lowered blood pressure by inhibiting RhoA/Rho-kinase-mediated calcium signaling in the vasculature (Jiao *et al.*, 2016; Mu *et al.*, 2018; Sun *et al.*, 2014).

The use of natural products for empirical treatment of diseases is a common practice from ancient civilizations to the present day, as many natural compounds have their well-established

function in therapy (Eldin, Dunford, 2001; Hufford, 1997; Almeida, 1993). One such natural product recognized as a TRPM8 channel activator is menthol, a cyclic alcoholic monoterpene that is found in the essential oils of *Mentha canadensis* L. (vique) and *Mentha piperita* L. (peppermint) (Bautista *et al.*, 2007). In addition, the use of the menthol empirically in different types of preparations for use during sexual intercourse is widespread in the world, and our research group have demonstrated, for the first time, that TRPM8 channels were expressed and functional in internal pudendal artery (control 70% of vascular penile resistance (Manabe *et al.*, 2000), from both normotensive and hypertensive rats and their activation is able to relax these tissues. These results suggested that vascular TRPM8 activation can be considered as a potential strategy for the treatment of erectile dysfunction (Silva *et al.*, 2019).

Menthol is a natural product with a broad spectrum of pharmacological actions and is of interest for research and drug development. Consequently, it is widely used in several products, with various pharmaceutical applications, including for the purpose of improving performance in sexual activities. However, this use is empirical and without scientific support. Following the development of technologies, such as different pharmaceutical presentations of natural products, inventors will be able to deposit patents as a way of protecting their discoveries.

In this context, the objective of this study was to carry out a technical investigative study to evaluate the application of menthol for the treatment of erectile dysfunction, specifically through a patent review, as well as to establish which countries are the main developers of this technology.

2. Methods

The patent document search was carried out in order to provide the largest number of patents corresponding to the topic of interest, using international patent classifications or keywords, in order to allow representative research on the various uses of menthol, focused on the treatment of erectile dysfunction. Initially, searches were conducted through the patent codes. The International Patent Classification (IPC) and the Cooperative Patent Classification (CPC), enhance the investigation of patent deposits related to the subject, in the Espacenet[®], which is a worldwide access base free and covering more than ninety countries. Data collection was performed in April 2020 and no time limitation was applied. This allowed our search to map patent documents specific for menthol use in erectile dysfunction treatment.

To obtain a comprehensive search for patent deposits, the following codes were used: A61K31/045 refers to hydroxy compounds, such as alcohols; salts, alcoholates; A61K36/534 refers to

Mentha (mint); A61K9/0034 refers to the urogenital system, vagina, uterus, cervix, penis, scrotum, urethra, bladder; personal lubricants; A61K8/042 relates to Gels; A61K9/0014 relates to skin, i.e., galenic aspects of topical compositions; and A61H19/50 which refers to devices for use during intercourse. Table 1 shows the scope used to search for patent documents.

Table 1 - Number of Patents Found According to the Codes in Espacenet®

Total CPC	Total IPC	A61K31/045	A61K36/534	A61K9/0034	A61K8/042	A61K9/0014	A61H19/50
>10.000	>10.000	x					
1217	648	x	x				
24	0	x	x	x			
8.22	4.068		x				
94	0		x	x			
275	0	x	x			x	
2.245	0			x		x	
11	0		x	x		x	
10	0			x	x	x	
61	0	x		x		x	
17	0		x		x		
3	0		x	x	x		
913	0						x
3	0		x				x
3	0	x					x
4	0			x			x

Note: IPC: International Patent Classification; CPC: Cooperative Patent Classification; A61K31/045 refers to hydroxy compounds, such as alcohols; salts, alcoholates; A61K36/534 refers to Mentha (mint); A61K9/0034 refers to the urogenital system, vagina, uterus, cervix, penis, scrotum, urethra, bladder; personal lubricants; A61K8/042 relates to Gels; A61K9/0014 relates to skin, i.e., galenic aspects of topical compositions; and A61H19/50 which refers to devices for use during intercourse.

Source: Author's own table (2020).

Additionally, we performed a keyword-based search with the following terms: “erectile dysfunction”, “menthol”, “topical application”, “topical application AND menthol”, “erectile dysfunction AND menthol” and “erectile dysfunction AND menthol AND topical application”. Results are shown in table 2.

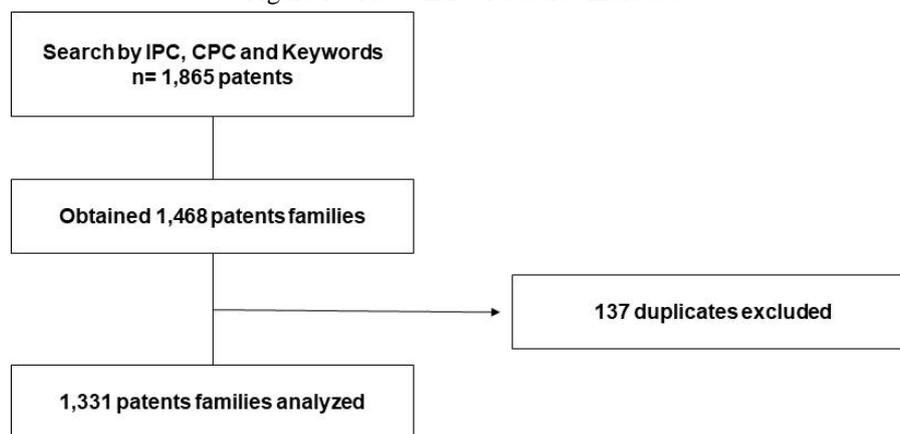
Table 2 - Number of Patents Found According to Keywords in Espacenet®

Keywords	Number of patents
Erectile dysfunction	3292
Menthol	9869
Topical application	>10.000
Topical application AND menthol	44
Erectile dysfunction AND menthol	3
Erectile dysfunction AND menthol AND topical application	0

Source: Author's own table (2020)

The first method consisted of the analysis of the patents obtained from the association between codes A61K31/045 and A61K36/534, as this association yielded the largest number of patents related to the aim of this study, both in CPC and IPC. Next, three patents obtained from the search using “erectile dysfunction AND menthol” were analyzed. A total of 1,865 patents were identified, which included 1,217 documents from CPC and 648 from IPC. Based on these searches strategies, 137 duplicate documents were excluded, leaving 1,331 families (Figure 1). The data was processed and the results were analyzed in the software Graphpad Prism 5.0®.

Figure 1 - Flowchart of Studies Included



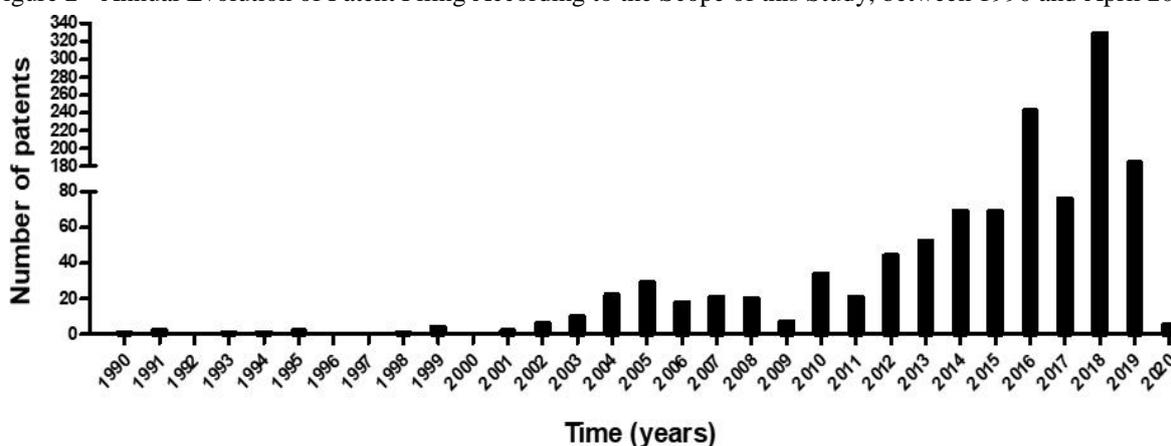
Source: Author's own figure (2020)

3. Results and Discussion

The research was carried out in the European database Espacenet® and presented a scope of 1,331 families of patents filed between the years 1979 to April 2020. The patent family represents the same patent filed in different countries, according to the individual laws of each territory. However, patent deposits obtained from this database do not provide exclusive rights to inventors in all countries, as this right is related only to the countries where the registration of the same patent

occurred. The patent analyzes enabled the identification of the annual patent deposit, as evidenced in Figure 2, where it is possible to observe patent deposits from 1990 to April 2020. Only two patent registrations were found before 1990. The year with the highest number of patents deposited was in 2018, totaling a number of 329 patents this year alone.

Figure 2 - Annual Evolution of Patent Filing According to the Scope of this Study, between 1990 and April 2020



Source: Author's own figure (2020)

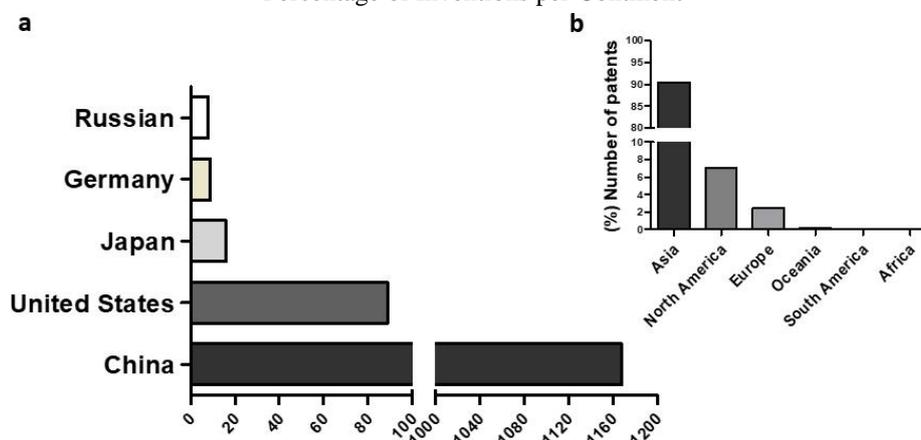
The first analyzed patent document was published on March 14, 1979 by Australia having as inventor, John Rhodes and B Evans (depositor company: Tillott JB Ltd), entitled "Carminative preparations containing essential oils or their active components". This patent provides is for the preparation of a gelatin capsule containing mint essential oils, to be administered rectally or orally for the treatment of irritable bowel syndrome and other intestinal disorders (Rhodes; Evans, 1979). Although this patent indicated that there was a pharmaceutical preparation containing menthol, it was not for topical application for ED treatment. Similarly, there was one more patent identified and filed before 1990, deposited on April 17, 1981 in France by the depositor, Yersin David, entitled: "Topical compsns. contg. arnica extract - together with camphor, menthol and surfactant for topical treatment of inflammations and infections". This patent discloses a topical preparation containing arnica, camphor, menthol, triethanolamine for the treatment of inflammation and/or infections affecting the skin, mucosa or teeth (Yersin, 1981). Again, despite its formulation and intended topical use, it was not directed to ED treatment.

When analyzing the evolution of patents since 1990 (Figure 3), there are two growth bands in patent deposits, in specific relation to the use of mint and its derivatives as components in various formulations, as well as different methods of uses and preparations. The first growth band contained 28 patents in 2005, of which China contributed the greatest number of registrations (20), followed by

the United States (5), while Japan (1), Germany (1) and Ukraine (1) presented the same number. The second growth band had a peak of 242 patents in 2016, where this growth was attributed to increased strategies to ensure an exponential growth in intellectual property in China. China represented the majority of these patents (233), followed by the United States (7), Hong Kong (1) and Russia (1). On 2018, another peak in patent deposits were observed reaching 342 patents in this year.

According to our research, the main technology priority countries, with more than seven patents, were China with a total of 1,168 patents, followed by the United States (89), Japan (16), Germany (9), Russia (8), (Figure 3A). It was possible to observe that two Asian countries, China and Japan, are among the main country inventing, summing a total of 1,184 patents.

Figure 3 - Distribution of Patent Documents by Country and Continent where based on Technology Origin (Country of Priority). In A, the Main Countries Holding the Technological Property with more than Seven Patents Invented. B, Percentage of Inventions per Continent



Source: Author's own figure (2020)

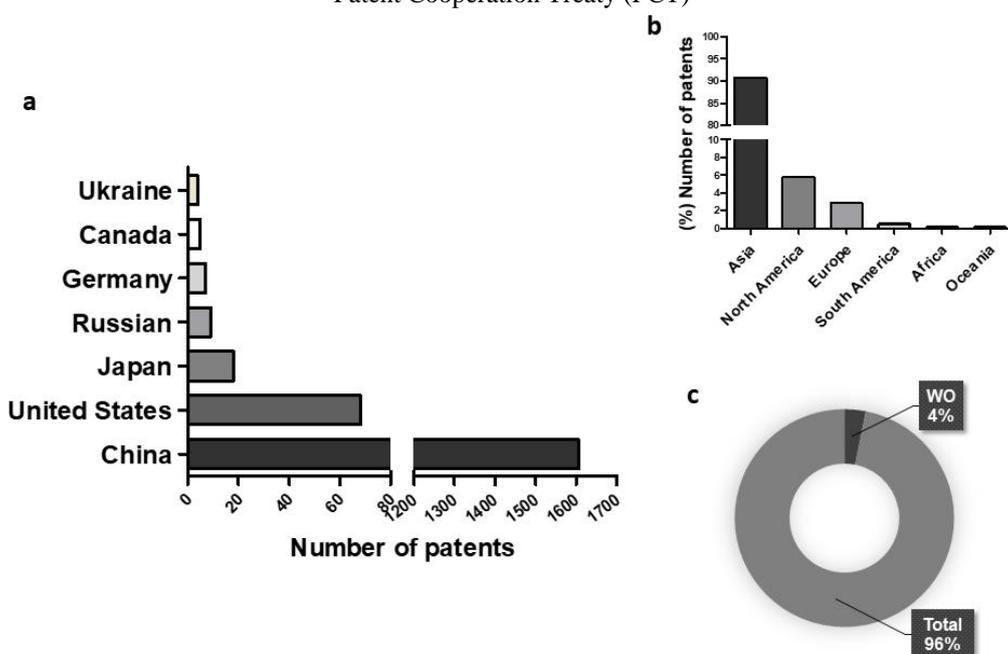
The distribution of patent priority by continent is represented in Figure 3B. The continent with the highest priority is Asia, with 90% of the patents. The high number of patents in Asia is directly related to Chinese programs aimed at the expansion, qualification and creation of patents for research and development. North America has 7% of the deposits, which United States are responsible for 89 patents. Europe represented only 2.5% of total patent deposits. Oceania had only 0.07% of the total number of records, represented by Australia (1). No invented patents were identified on the South American or African continents.

In 2010, the State Council of China launched intellectual property strategies aimed at ensuring exponential growth in the creation, protection and use of property rights, and as a result, improved the efficiency and quality of patent examinations (Kariyawasam, 2011). Additionally, this encouraged vast expansion and the ability to create patents within the scope of invention, design and utility (Yifu;

Peilin, 2003; Pacheco, 2011; Vontobel, 2011). China is the country that holds the greatest number of patent, as previously demonstrated in Figure 3. This emphasis on deposit accumulation is a reflection of its accelerated production in innovation in science and technology. Consequently, China has also stood out as the country that produces the most technological inventions, thus, it is the country with the highest number of patent registrations that may be directed to the use and development of formulations associated with the use of natural products.

The number of patent deposits by Chinese companies has grown in recent years in both the China Patent Office, the State Intellectual Property Office (SIPO) and the US Office of the United States Patent and Trademark Office (USPTO), which are requested by the Patent Cooperation Treaty (PCT). As evidenced, the main depositor countries of the patents analyzed is China, which leads all countries with a total of 1,606 documents, followed by the United States (68), Japan (18), Russia (9), Germany (7), Canada (5) and Ukraine (4), respectively. The graph in Figure 4A represents the countries that had more than three patents deposited in the study year. We note that Asia has two countries, China and Japan, among the top three countries that have deposited the most, together with 1,624 patents deposited.

Figure 4 - Distribution of Patent Documents by Country and Continent where Technologies are Deposited (Country of Deposit). In A, the Main Countries that own the Technological Property with more than Three Patents Deposited. B, Percentage of deposits per Continent. C, Percentage of Patents in search of Potential International Patent Protection by the Patent Cooperation Treaty (PCT)



Source: Author's own figure (2020)

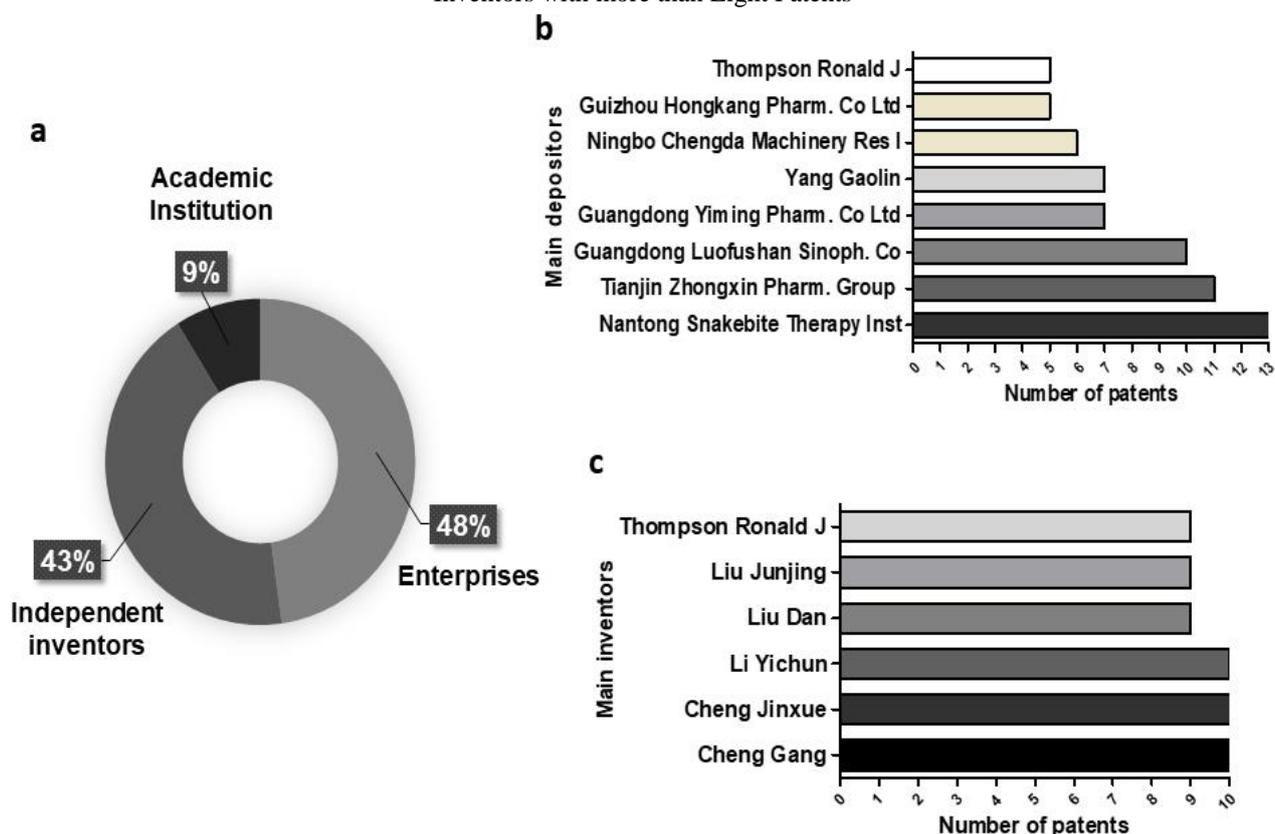
The Patent Cooperation Treaty (PCT) corresponds to a multilateral treaty, consolidated in the 1970s, and its main objective is to facilitate and reduce the initial costs in patent application procedures in member countries. This treaty facilitates the filing of the patent application for the same invention when protection is required in several countries (Lapenne, 2010; World Intellectual Property Organization, 2011). Of the total number of patents deposited, 96% are protected only in the depositor's country, however, 4% of these were classified as World Intellectual Property Organization (WIPO), as shown in Figure 4C. These 4% are the patents where the depositors sought protection of their invention in other countries through the international patent filing requested by the PCT (World Intellectual Property Organization, 2011; Ficsor, 2002).

Taken together, data from figures 3 and 4 show that patents deposited in the countries residing in South American and African continents were promoted through the PCT, since no country in these continents have priority over patents, thus patents identified in these continents come from other countries.

South America represents 0.45% of patents deposited by the PCT and within this percentage, there are three patents filed in Brazil. The first entitled "Topical Antifungal Composition", inventor Charles J. Boeglie, deposited by a American company, Oniko Labs, LLC, in 2010, develops topical antifungal medications for the treatment of conditions such as athlete's foot and onychomycosis (Boegli, 2010). In 2016, another patent was deposited describing inhalable nicotine formulations, inventors Stenzler Alex et al. (Stenzler *et al.*, 2016); and in 2017, the last one was a method for growing hybrid mint plants, inventor D Roberts Donald (Roberts, 2017). In order to protect their invention, the holders obtained the right to deposit in Brazil by the INPI through the multilateral treaty, the PCT. Therefore, it is important to note that no Brazilian patent were identified, as well as any Brazilian inventors or depositors. Once again, these patents were not intended or developed for the treatment for erectile dysfunction.

The search for patent depositors in the Espacenet® database resulted in three classifications, such as: enterprises, academic institution and independent inventor. Enterprises were the largest owners of patent warehouses with 48% of documents stored, followed by independent inventors with 43% and lastly the academic institutions with only 9% of documents deposited, as shown in Figure 5A.

Figure 5 - Main Patent Depositors, their Social Distribution and main Inventors. In A, Distribution of Patents Depositors by Type of Institution. B, Number of Patents by main Depositors of major Relevance with more than Four Patents. C, main Inventors with more than Eight Patents



Source: Author's own figure (2020)

The Nantong Snakebite Therapy Institute deposited the largest number of patents, as evidenced in Figure 5B, followed by Tianjin Zhong Xin Pharmaceutical Group CO. (Zhong Xin Pharmaceutical) founded in 1992, which is an investment holding company that produces and sells traditional Chinese medicines, Western medicines and health products, mainly in the China Popular Republic. This company is also engaged in the manufacturing and sale of organic products, biochemical pharmaceutical products, products for daily use, hospital operation and drug processing. The Tianjin Zhong Xin Pharmaceutical company has filed a total of 11 patents filed, which describe a Chinese medicinal composition called, Indigo Naturalis, based on natural products, containing menthol as one of its active principles, used for detoxification and throat cleansing. In addition, they describe their methods with various forms of pharmaceutical presentations as aerosol, oral liquid, tablet, capsule, controlled release tablet, pellets and emulsion.

Other companies that stood out with more than four patents were the Guangdong Luofushan Sinoph. Co with a total of 10 inventions referring to the curative effect of the formulation on eczema, itching, nasal congestion and pain relief. A Guangdong Yiming Pharm. Co Ltd. with 7 patents

describing the use and preparation of Radix Trichosanthis gel for itch dissipation and pain relief; and Guizhou Hongkang Pharm. Co Ltd holding 5 patents deposited. Although these patents included use of menthol in their technologies, none were directed with the intent of pharmaceutical applications to treat erectile dysfunction.

Among the academic institutions, despite the main depositor, Ningbo Chengda Machinery Res Inst., holds a total of 6 patents, described the use of a formulation containing *Salvia officinalis* for the treatment of inflammation and infections from bacteria. These patents relate to the use and preparation of an ointment used to treat herpes labialis and a cooling oil to reduce inflammation, containing camphor and menthol as main cooling substances.

The independent inventors with the largest number of patent deposits were Yang Gaolin, with 7 documents referring to the composition of traditional Chinese medicine tablets to treat chronic pharyngitis and its method of preparation, followed by Thompson Ronald J. with 5 patents filed, disclosing the method of using a menthol-containing compound and L-arginine as the absorption promoter for the treatment of sexual dysfunction. The vast majority of patents are represented by Chinese inventors followed by US inventors, supporting the fact that China has deposited 1,606 and the United States 68 patent documents. Among the inventors with the most patents, Cheng Gang (14); Cheng Jinxue (14); Li Yichun (10); Liu Dan (9); Liu Junjing (9) and Thompson Ronald J. (9) as demonstrated in Figure 5C.

Patents found on search by keywords were not focusing on use of menthol to treat ED. These patents contained menthol in their preparations, but it was used like an agent to enhance penetration of the main compound to the tissue. In 1995, a Korean group formulated a patch composition to treat ED using an erectile-inducing agent as a main compound and, among other penetration enhancers, menthol was included (Hun-han; Jung-woong; Jae-Seung, 1997). In 2005 a Russian group developed a sublingual preparation to treat ED using as an active compound an iPDE-5 (Kiselev; Mikhelashvili; Kiselev, 2005). Also, in 2008 a Chinese group developed a gargle preparation to treat ED with menthol as the solvent in this preparation (Hong, 2008). Therefore, although menthol is present in these patents, any used menthol as the main compound to treat ED, reinforcing the importance of developing new preparations using menthol focusing on treatment of ED.

The United States hold the deposited patents of the greatest relevance to the study (Table 3). These patents are directed primarily to the topical administration of a formulation that promotes the absorption of drugs into the genitourinary system for the treatment of sexual dysfunction and also for enhancement of sexual pleasure.

Table 3 - Most Relevant Patent Documents through April 2020 on the use of Menthol in Formulations to Improve Sexual Intercourse

Item	Publication number	Title	Country	Application date	Reference
1	KR970025609	Pharmaceutical composition for treatment of erectile dysfunction and device for transdermal administration of formulation	KR	24/11/1995	Stenzler <i>et al.</i> , 2016
2	US2001029268	Clitoral sensitizing arrangement using compound of menthol and L-arginine	US	11/10/2001	Kiselev; Mikhelashvili; Kiselev, 2005
3	US2004258774	Method of using a compound of menthol and L-arginine as a preparation for the topical delivery of a 5-phosphodiesterase inhibitor for the treatment of female sexual dysfunction	US	23/12/2004	Hong, 2008
4	US2005069597	Method of using a compound of menthol and L-arginine as a preparation for the topical delivery of alprostadil for the treatment of female sexual dysfunction	US	31/03/2005	Thompson, 2001
5	US2005100618	Method of using a compound of menthol and L-arginine as a preparation for the topical delivery of Icariin, a herbal product produced from the Epimedium genus of the Berberidaceal family of plants, for the treatment of sexual dysfunction	US	12/05/2005	Thompson; FRYE, 2006
6	US2005186294	Method of using a compound of menthol and L-arginine as a preparation for the topical delivery of vardenafil for the treatment of female sexual dysfunction	US	25/08/2005	Thompson R; Thompson J, 2004
7	RU2005130337	Method of treating erectile dysfunction in men and drug for treating erectile dysfunction in men	RU	30/09/2005	ROBERTS, 2017
8	US2005244520	Topical menthol, or a related cooling compound, to induce lubrication	US	03/11/2005	Thompson; Thompson; Thompson, 2005a
9	US2005245494	Methods to treat one or all of the defined etiologies of female sexual dysfunction	US	03/11/2005	Thompson; Thompson; Thompson, 2005b
10	US2004170708	Arrangement to enhance a woman's sexual sensitivity by a combination of phytoestrogens, L-arginine and menthol	US	24/01/2006	Thompson <i>et al.</i> , 2005
11	CN101269212	Gargle capable of being swallowed	CN	30/04/2008	Hun-Han; Jung-Woong; Jae-Seung, 1997
12	US2008213407	Topical application of L-arginine and menthol to increase penis size	US	04/09/2008	Thompson; Thompson; Thompson, 2005c
13	US2019134138	Skin sensitizer delivery system	US	30/08/2018	Thompson; Thompson; Thompson, 2005d
14	CN109200115	A kind of essential oil and preparation method thereof and application method	CN	13/09/2018	Thompson <i>et al.</i> , 2008

Note: CN: China; KR: Korea; RU: Russia; US: United States.

Source: Author's own table (2020)

It should be noted that from the fourteen patents of greatest relevance, nine are credited to the inventor, Thompson Ronald J, the individual with the largest number of patents (figure 5C), and eight of these are related to the female reproductive system. One of the most relevant patents is dedicated to the preparation composed of L-arginine and menthol for topical application to non-keratinized epithelium in the female reproductive organ (Thompson, 2001). Another patent shows a formulation to induce regrowth of the urothelial sensory nerve in the female vulva containing menthol, L-arginine and a phytoestrogen (Thompson; Frye, 2006). Additionally, there are patents of topical combination for sensitization of the clitoris constituted by L-arginine, menthol and a iPDE-5 (Thompson; Thompson, 2004); Alprostadil (Thompson; Thompson; Thompson, 2005a); Vardenafil (Thompson; Thompson; Thompson, 2005b) and Icariin, an herbal product produced from the genus *Epimedium* of the Berberidaceal family (Thompson *et al.*, 2005). In addition, there is a patent for a new formulation composed of menthol or any related cooling compound, applied topically to the clitoris for treatment of atrophic vaginitis (Thompson; Thompson; Thompson, 2005c). This topical formulation contains L-arginine, menthol and Vardenafil for the treatment of female sexual dysfunction (Thompson; Thompson; Thompson, 2005d). A single formulation patent for increasing the size, thickness, diameter and volume of the penis composed of L-arginine and menthol or menthol derivative or menthol analogue, wherein the combination is applicable manually to the penis (Thompson *et al.*, 2008), however its design and use is not intended for the treatment of erectile dysfunction. Interestingly, a skin-sensitizer formulation that may include an essential mint oil or TRPM8 activator among others constituents, proposed for enhances sexual pleasure (Grosso-piacentino, 2018). The most recent patent describes an essential oil applied to temple, skull top and ears rear to prolong sexual action time (Zhang, 2018). Finally, any of these patents dealt with the use of menthol as the main constituent for the treatment of erectile dysfunction.

4. Final Considerations

This patent review provides a more complete understanding of the technological developments deposited in the Espacenet® database by different countries over forty years. It was possible to verify the strong growth in the generation of technologies regarding the deposit of patents by countries like China and the United States. In addition, the use of menthol in the genitourinary system is still poorly explored. Some patents identified in this study aimed for the topical treatment of ED, but none used menthol as the main compound. Thus, the development of a topical application of

menthol for the treatment of erectile dysfunction remains an innovative and highly potential target formulation.

Conflict of Interests

The authors declare no conflicts of interest.

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