Vol. 9(26), pp. 662-674, 15 July, 2015
DOI: 10.5897/AJPP2015.4361
Article Number: A6452D554320
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Incorporation of tannic acid in formulations for topical use in wound healing: A technological prospecting

Antonia de Sousa Leal[1]*, Laynne Hellen de Carvalho Leal[2], Davi da Silva[3], Livio Cesar Cunha Nunes[1] and José Arimateia Dantas Lopes[1]

[1]Postgraduate Program of Biotechnology, Doutorado em Biotecnologia (RENORBIO), Federal University of Piauí, 64049-550, Teresina, Piauí, Brazil.
[2]Department of Pharmacy, Federal University of Piauí, 64049-550, Teresina, Piauí, Brazil.
[3] Open Education Center and Distance, Federal University of Piauí, 64280-001, Teresina, Piauí, Brazil.

Received 16 May, 2015; Accepted 5 June, 2015

The tannic acid is a polyphenol with several properties that give it different applications, including leather and pharmaceutical industry. It belongs to the group of water soluble metabolites, and has the ability to complex macromolecules and metal ions, which gives it antioxidant, antimicrobial and healing activity. Therefore, such properties can be used to develop technologies related to wound healing systems. This prospective study summarizes bibliographic information about the use of tannic acid in topical formulations for healing skin wounds. The data were collected through the search tool available in patent databases (INPI, USPTO, EPO, WIPO, DERWENT) and articles (Web of Science) about the application of tannic acid in skin wound healing system. In recent decades, there has been growth in number of searches for elucidation of antimicrobial and antioxidant activities of tannic acid, and its incorporation in biomaterials in the pharmaceutical field. The United States, Japan and China stood out in inventions and publishing articles. The Brazilian biodiversity is immense, although underexplored and poorly study about extraction and properties of tannins in topical formulations, which lacks encourages to research technologies for healing system more effective and cheap.

Key words: Tannic acid, cutaneous healing system, technological prospecting.

INTRODUCTION

Natural products are raw materials of great interest for different industrial sectors, due to the fact that it presents in its composition a variety of active ingredients. The tannins, for example, have applications inecological agriculture, preparation of flocculants for water and effluent treatment, obtaining natural polymers, wine clarification, biomaterials, etc. In almost all botanical families there are species that contain tannins. When they occur in large quantities, the tannins are usually located in certain parts of the plant as the roots, bark, leaves, fruits, seeds and sap (Claus and Tyler, 1965).

Tannins belong to a group of phenolic compounds from the secondary metabolism of plants. They have a high molecular weight (500 to 3000 Da) and contain phenolic hydroxyl groups in sufficient amounts to allow crosslinking to macromolecules (Min et al., 2003). They are classified into two groups: hydrolysable tannins and condensed tannins.

The tannic acid is water-soluble tannin, comprising a central glucose molecule attached with five chains formed

*Corresponding author. E-mail: antonialeal27@gmail.com

by two esterified gallic acid molecules. In an acid medium, in mild alkaline conditions or under the action of enzymes (such as tannase), the tannic acid can undergo hydrolysis obtaining carbohydrates (glucose) and phenolic acids (gallic acid, especially) (Bruneton, 2001).

The tannic acid is considered a safe food additive (Akiyama et al., 2001). Moreover, the tannin has astringent and antibacterial properties, and it can be used as a medicament against diarrhea, hemostatic, anti-hemorrhoid formulations, in the treatment of skin ulcers, wounds and toothache (Aelenei et al., 2009). However, this compound should not be used in large quantities because it inhibits the absorption of iron in the body (Chung et al., 1998).

In previous studies, the tannic acid showed antimicrobial activity against pathogens (Chung et al., 1998; Scalbert, 1991). Research with the seed extract of *Vitis rotundifolia* species showed that tannic acid was the main chemical constituent responsible for its antimicrobial properties (Kim et al., 2008). The pure tannic acid when subjected to heat treatment, its antimicrobial activity is significantly increased (Kim et al., 2010). Among the polyphenols, the tannic acid and quercetin were considered the constituents of higher antioxidant capacity (Pulido et al., 2000).

Plants rich in tannins are used in the traditional medicine as drugs for the treatment of various organic diseases, including the healing process of wounds, burns, and inflammation (Haslam, 1996). This is explained because of its property of complexing proteins at the injury site. The tannins form complex with macromolecules (proteins and/or polysaccharides) providing a protective layer on the epithelial tissues injured; the healing process of the wound occurs naturally just below this layer (Monteiro et al., 2005).

In Brazil, there is an increasing public spending on treatment of skin lesions, especially the wounds originating from chronic diseases such as *Diabetes mellitus*, considered difficult to heal. Investigations on the pharmacological and biological activities of tannins, more specifically the tannic acid, can contribute to the technological development of cheaper and effective curative systems for skin lesions. In this context, this study aimed to perform a technological prospecting on the incorporation of tannic acid in formulations for topical use in wound healing process.

MATERIALS AND METHODS

The prospecting was conducted based on the patent applications filed at the National Institute Database of Industrial Property (INPI), European Patent Office (EPO), United States Patent and Trademark Office (USPTO), World Intellectual Property Organization (WIPO) and Derwent Innovations Index. Also, the study investigated the publication of articles on the basis of the Web of Science. The key words used in the search are listed in Table 1. In this research, were considered valid documents that submitted key words in the "title" and/or "abstract". This prospective study was conducted in March, 2015 and included the years available at the databases until now. With regard to the articles, the discussion was based on the technological field, country, year of publication and the bibliographic review.

RESULTS AND DISCUSSION

National institute of industrial property (INPI) database

The patent search in the INPI using the term "tannic acid" resulted in 15,025 patents. In the analyze of the abstracts noted that the search results generated with patents that only included the word "acid", and that did not match the tannic acid. So the study chose to use only the term "tannic" to refine the search, culminating in 18 patents. The deposit period of these patents was between the years 1991 to 2014. Brazil and the United States were the countries with the highest depositors numbers with 7 and 5 patents, respectively. Countries like Japan, Italy, Mexico, Argentina and Belgium also had depositors patents in INPI.

The international patent classification (IPC) classifies the invention according to different technological fields to which the invention pertains. The A61K code had the highest number of patent applications (Figure 1). This IPC is related to the area of preparations for medical purposes, dental or hygienic purposes in Human Needs section. For example, the patent CI 0400241-5 (Marques, 2005) have A61K classification and describes a formulation for tattoo removal, stretch marks, scars, keloid, vitiligo, sunburn and any visible mark characterizing a skin lesion. It consists of tannic acid and water, may be present as liquid, creamy, paste or gel forms. When applied to the skin, this product causes local inflammation that causes pigments that migrate to form a scab that detached part of the dermis caring 50 to 100% of the tattoo pigment.

The PI 9811478-6 (Lener et al., 1998), invention, also A61K IPC, refers to the controlled or sustained release compositions of pharmaceutical agents that include one or more cellulosic polymers (hydroxyethyl cellulose, hydroxypropyl cellulose or hydroxypropyl methylcellulose) or proteinaceous (gelatin or collagen), and tannic acid or other tannin. The agent's field of action is topical, local or systemic. The tannic acid when combined with these polymers can make it more resistant to proteolytic enzymes, and when applied to living tissue have astringent action, which is the therapeutic application base of tannins.

Falcon (1998), in his PI 9811875-7 invention, discloses a pharmaceutical composition based in tannic acid which can be used to treat any cancer condition. The formulation is composed of tannic acid, sorbitol, castor bean oil, potassium sorbate, methylparaben and propylparaben, and can be used in the form of tablets, capsules, solutions or suspensions. Degenerative diseases such as cancer, are associated with high intercellular concentrations of reactive oxygen species or

Comment [vv1]: In references?Yes

Table 1. Terms used in the study of scientific documents in databases.

Key words	Number of patent/scientific papers					
	INPI	EPO	USPTO	WIPO	DERWENTS	Web of Science
Tannic acid	15025	2319	85	1074	2926	3460
Tannic acid and healing	0	05	0	05	31	15
Tannic acid and wound	0	17	0	03	46	26
Tannic acid and carboxymethyl cellulose	0	13	01	01	60	06

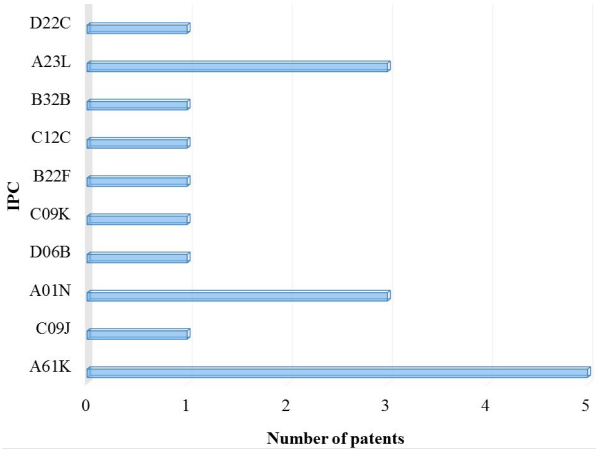

Figure 1. IPC by number of patents.

free radicals. It is then suggested that the tannic acid acts as a free radical scavenger, which intercepts the active oxygen to form stable free radicals. It has the ability of inhibiting lipid oxidation by removing free radicals (Sanchez-Moreno et al., 1999; Gulçin et al., 2010).

The A01N and A23L classifications have around 18 patent applications, which also comprise human needs. The A01N IPC comprises biocidal formulations as disinfectants, herbicides, pesticides, repellents, and plant growth regulators. The field of preparing, processing and storage of food and non-alcoholic beverages is represented by A23L IPC.

United States patent and trademark office (USPTO) database

On the databases of the USPTO were found 85 patent (Table 1) for the term "tannic acid". Among the countries of the depositors' origins, Canada stood out with 16 patents, followed by Gabon and Japan with 12 and 10 patents, respectively. The publication period included the years between 2001 to 2014 (Figure 2), in 2004 were 10 patents and in 2013, totaled 9 published patent applications.The patent application filed in 2015 included compositions to increase the selenium and lithium content in vegetables and processed products.The abstracts revealed that 62% of patents found were related to medical sciences or veterinary and hygiene.

The refined patent search using the terms "wound and healing" did not obtain any patent result that had tannic acid involved in the wound healing process. Although the two terms have not appeared in the title or abstract, some patents made use of tannic acid with dermatological purposes. Murard (2006), proposed a pharmaceutical composition for cleaning the skin to facilitate the prevention, treatment, and management of skin diseases, such as seborrheic dermatitis, psoriasis, folliculitis, rosacea, perioral dermatitis, acne and other inflammatory skin conditions, including a sufficient amount of a hydroxy acid or tannic acid, or a pharmaceutically acceptable salt thereof. Mitts et al. (2014), have formulated compositions containing polyphenol of ellagic acid and/or tannic acid for skin protection against degradation of elastic fibers by skin enzymes that act to promote total deposition of elastic fibers in skin cells. Hamtini (2004), developed a

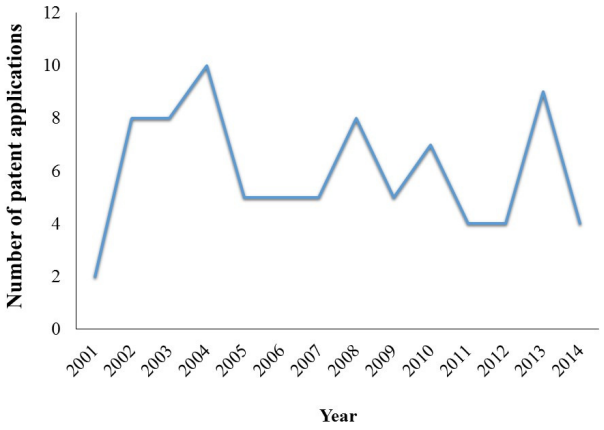

Figure 2. Evolution of patent applications period.

rash treatment product consisting of salicylic acid, boric acid, tannic acid, zinc oxide, calamine and lanolin, castor oil or cod liver oil. In this case, the exposed tissue proteins precipitate and form a antiseptic protective layer promoting the tissue regeneration.

The only patent found with a combination of tannic acid and carboxymethylcellulose terms, discoursed about an invention for the treatment of soil (Ballard, 2007). The use of organic acids have great interference in sorption/desorption processes of cations and anions, in the microbial activity, and in the metabolic disposition of carbonaceous substrate with a direct effect on soil fertility.

World intellectual property organization (WIPO) database

In the WIPO database, 1074 patents were found with the use of the "tannic acid" term in the title and/or abstract. China is the country with the largest number of applications filed (287), followed by Japan (214) and United States (205) (Figure 3). The inventions stood out in the category of human needs with the A61K, A61P and A23L IPC (Figure 4). As mentioned before, the rating A61K covers the sub-area of medical science or dental and hygiene; A61P is the sub-area of specific therapeutic activity of chemical compounds or medicinal preparations, and A23L refers to processes, treating and storage of food products and non-alcoholic beverages. The publication period was between the years 1990 to 2014. The largest number of patent applications occurred in the years 2014 and 2008 with 68 cases, followed by 2000, 2007 and 2009 with 67, 58 and 54 patents, in that order. It was observed in the last two decades an increasing in research that explore the physical, chemical, biological and pharmacological properties of tannic acid. Its application versatility can be attributed to three general characteristics of tannins: complexation with metal ions, oxidant activity and scavenging of free radicals, and the ability to form complexes with macromolecules (Bruneton, 2001). The search resulted in 3 patents with combination of the words "tannic acid and wound" in which contemplated formulations for: wound healing in horses, second degree burns and hemorrhoids treatment. Using the term "healing", 5 patents were obtained as a result of the search. The inventions have applications in wound healing in the form of ointment, chewing gum (oral ulcer) and the biomaterial (membrane) made by other chemical constituents, and tannic acid. The use of the term "carboxymethylcellulose" resulted in a patent, and that one is the same as the patent found in the USPTO database, that described the use of tannic acid in the treatment of soil.

European patent office (EPO) database

The patent informations in the EPO were obtained using the ESPACENET search tool, taking the Worldwide collection of patents as a reference. The search resulted in 2319 patents using the term "tannic acid" (Table 1). The five patents found with the combination of the term "tannic acid" and "healing" are the same ones available in WIPO database. This is because the World wide database provides access to applications from more than 90 countries. Using the words "tannic acid" and "wound" the study got a number of 17 patents. Among these, nine patents were related to the human needs and hygiene. For example, the preparation of a biomaterial (in the form

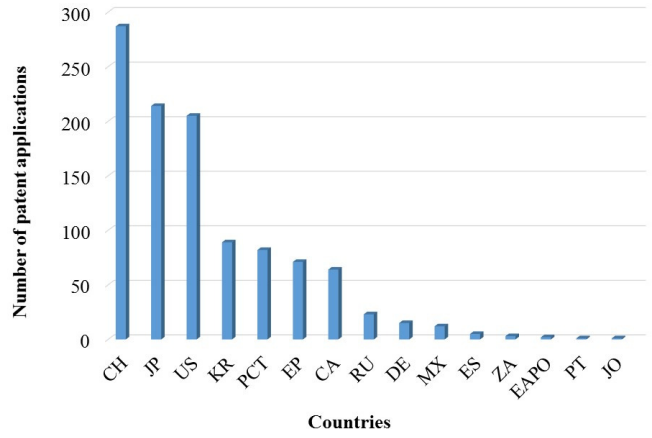

Figure 3. Number of patents per countries.

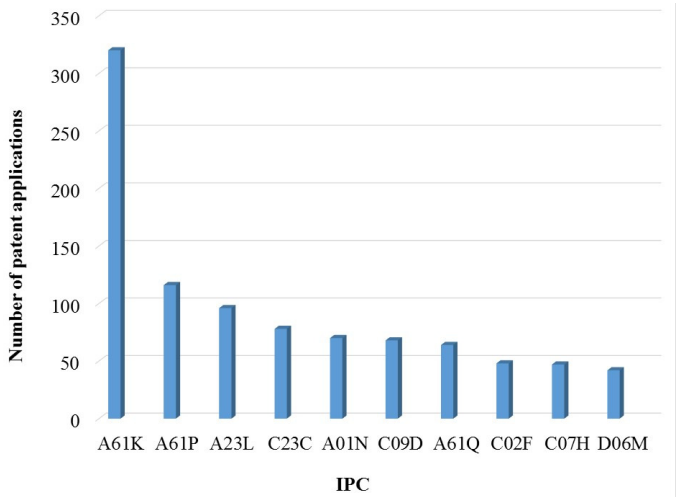

Figure 4. Number of patents per IPC.

of powder or film) for wound treatment (George, 1970). The term "wound" was used in the abstract of four patents with no topical wound healing purposes. These patents included inventions related to textile and paper industry. The search for tannic acid and carboxymethylcellulose compositions resulted in 13 patents with different application areas, like anti-rust coating, hair dye, explosives, cigarette filter and drug entrainment.

DERWENTS database

In this database, 2926 patents were found using only the term "tannic acid" (Table 1). In addition to A61K classification, the C09D IPC also exceeded in number of

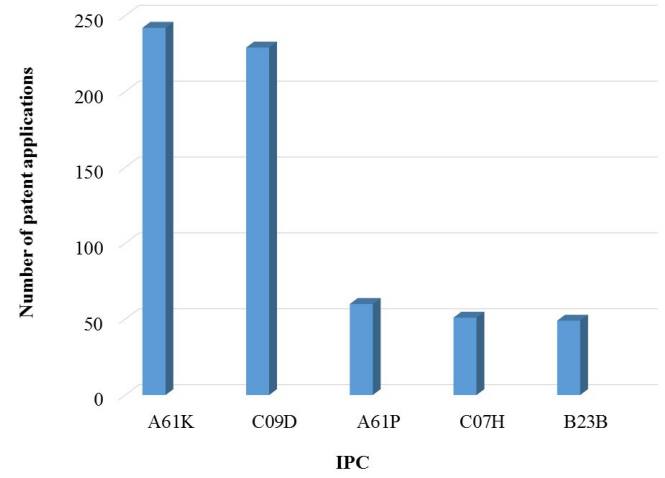

Figure 5. Number of patents per IPC.

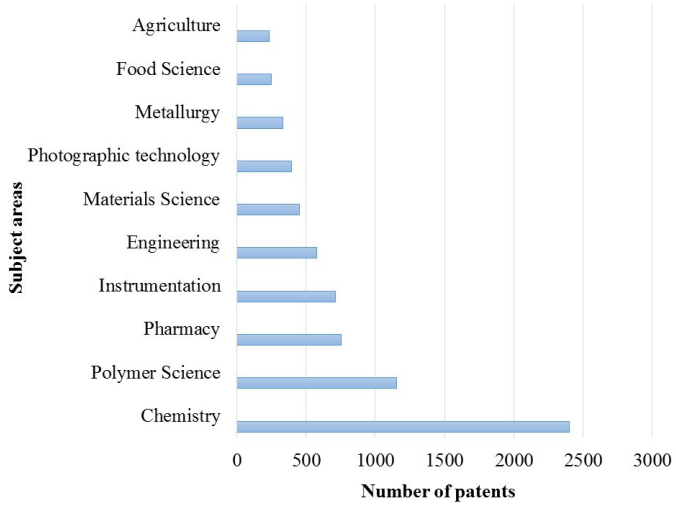

Figure 6. Number of patents for subject areas.

patents (Figure 5). The C09D category belongs to the Chemistry and Metallurgy section, but specifically, to the class of coatings, inks, dyes and removers. The chemical field, showed the greatest number of patents, followed by Polymer Sciences and Pharmacy (Figure 6). After analyzing the patent abstracts with the key words "tannic acid and healing", it was found that four patents used the term healing as a cure synonymous, causing results of curing agents, known as hardeners and used in Chemical, Polymer and Material Science sectors. Thus, only 27 patents were directly related to wound healing. Chen and Zhou (2014), proposed a formulation based on

Comment [vv2]: In references?Yes.

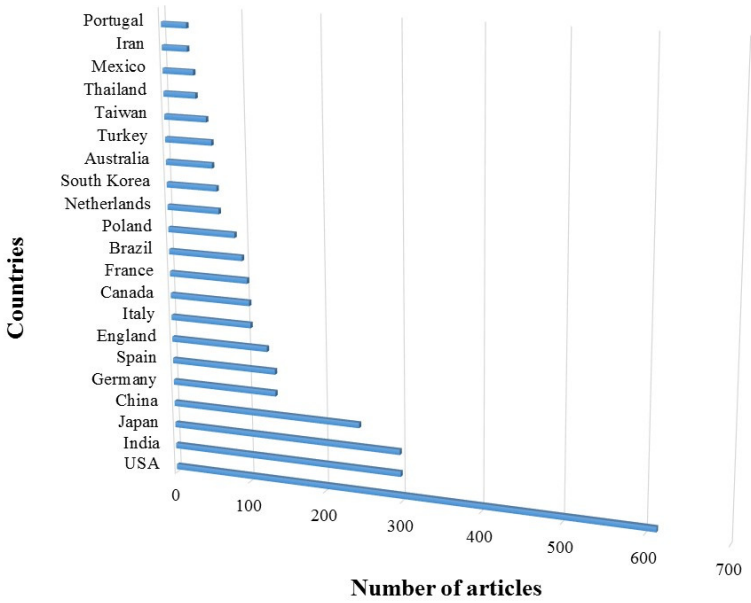

Figure 7. Number of articles per country.

protease enzyme isolated from the terrestrial fungus Aspergillus and tannic acid, for the treatment of wounds originating from burns, chronic ulcers and diabetic foot. Mcclure (2001), has developed a pharmaceutical mixture which included sulfur, zinc oxide, tannic acid and olive oil to heal horses' wounds. According to the author, the product can be used in dogs, human beings, cows and administered topically as an ointment. The combination of the terms "tannic acid" and "carboxymethyl cellulose" resulted in 60 patents with different applications, as in the paint sector and drug delivery systems. Among the patents related to wound healing, there was a composition to treat burns which included menthol, thymol, camphor, vitamin E, tannic acid, niacin, *Salvia* extract and other constituents (Li and Zhang, 2014). Zhao (2013), developed a product constituted by seed extracts, fruit or bark, alcohol, glycerol, Carbopol, tannic acid, carboxymethyl cellulose and others. The paste obtained was indicated for the treatment of exudative ulcers, burns, eczema, bedsores and haemorrhoids.

Web of science database

The main collection of web of science is a tool that lets you search for various types of scientific papers (articles, patents, book chapters, etc.). The search resulted in on included 3460 documents that had "tannic acid" as a keyword, among which, 3080 were articles and two were book chapters. The United States was the country that had the largest number of research results developed with tannic acid (614 published articles), followed by India, Japan and China with 299, 298 and 246 articles, in that order (Figure 7). Brazil appears on the list with 97 publications, representing a significant number compared with patent applications. The publication period comprised the years 1960 (two posts) and 2014 (190 articles). Until the research data, it has published 35 articles in 2015. There is increasing interest in research that include to unravel the tannic acid properties aimed at different technological applications. Figure 8 shows the evolution of the number of publications per year. The chemical field presented the greatest number of publications with 595 articles (Figure 9). Among these articles, there is a study of processing and characterization of chitosan nanocomposites reinforced with chitin, using tannic acid as a crosslinking agent. The addition of chitin improved mechanical properties of the chitosan film and, tannic acid reduced the moisture content and solubility in water of these nanocomposites (Rubentheren et al., 2015).

The search for data with the combination of the terms "tannic acid" and "healing" resulted in 15 documents. Among these are 11 articles, six of which publications

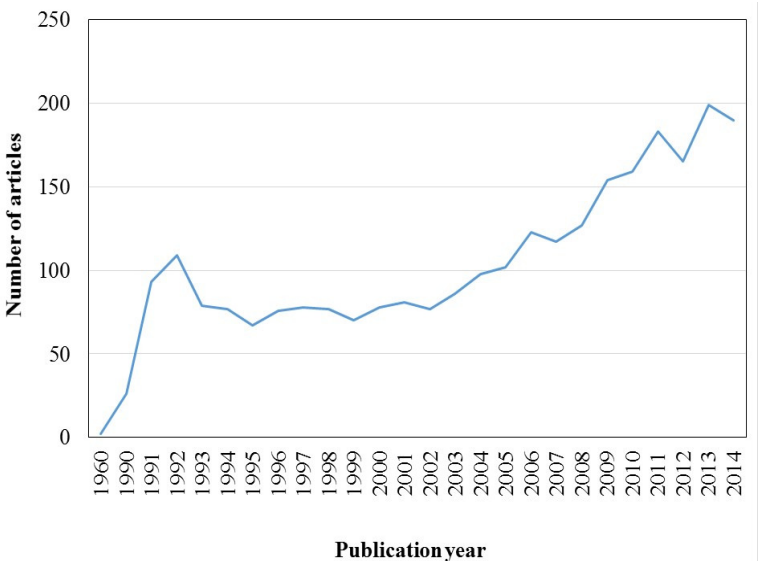

Figure 8. Number of articles per publication year.

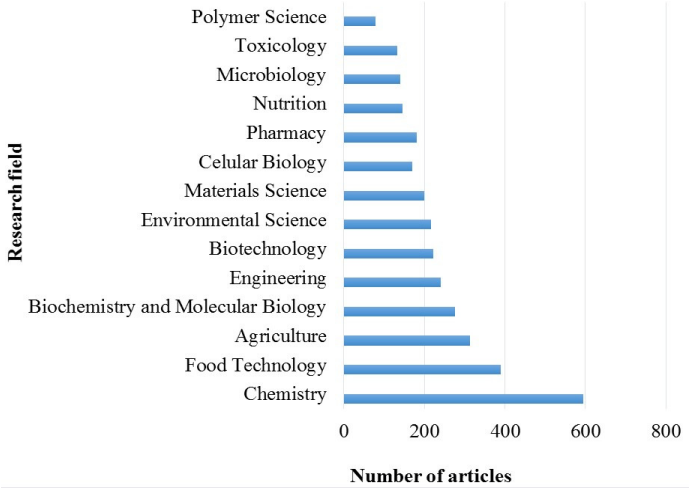

Figure 9. Number of articles perresearch field

belong to the areas of Pharmacy and Chemistry, with three items each. Japan stood out with three published articles Table 2. One of these articles had a study of calcium phosphates composts which included tannic acid in the composition. The material was intended to repair bone defects (Yoshikawa and Toda, 2000). The tannic

Table 2. Published articles about the tannic acid incorporation in the healing process of skin wounds (Web of Science).

Periodic	Authors	Title	Innovation
Biomaterials	Heijmen et al. (1997)	Cross-linking of dermal sheep collagen with tannic acid	Characterization of biomaterials developed from the dermal sheep collagen matrix, tannic acid and metallic ions with possible application as a therapeutic agent in the burn treatment.
Journal of Biomedical Materials Research	Yoshikawa and Toda (2000)	Reconstruction of alveolar bone defect by calcium phosphate compounds.	Use of tannic acid in the cement liquid phase calcium phosphate based in bone alveolar reconstruction process.
Wounds-A Compendium of Clinical Research and Practice	Halkes et al. (2001)	The use of tannic acid in the local treatment of burn wounds: Intriguing old and new perspectives	Review study of the tannic acid use in the burn treatment. A critical appraisal of the literature showed that liver toxicity is not exclusively related to the use of tannic acid. Furthermore, in the studies reported adverse effects, tannic acid preparations used in high concentrations, or impurities. The survey showed the use of this tannin with potential in treating burns in safe dosages.
Free Radical Biology and Medicine	Khanna et al. (2002)	Dermal wound healing properties of redox-active grape seed proanthocyanindins	The tannin extract use obtained from the grape seed for topical application in dermal healing *in vivo* processes.
Burns	Halkes et al. (2002)	Transaminase and alkaline phosphatase activity in the serum of burn patients treated with highly purified tannic acid	Treatment of burns with highly purified tannic acid. The tests indicate that tannic acid does not cause hepatotoxicity when applied by at least 10% of the total body surface area.
Bioorganic and Medicinal Chemistry Letters	Halkes et al. (2002)	Synthesis and biological activity of polygalloyl-dendrimers as stable tannic acid mimics	Synthesis of dendrimer derivatives of tannic acid with stability, antioxidant activity and collagen crosslinking capacity improved. These compounds showed potential application in the burn treatment.
Journal of Materials Science: Materials in Medicine	Silva et al. (2003)	In vitro degradation and cytocompatibility evaluation of novel soy and sodium caseinate-based membrane biomaterials	Biomaterials consisting of crosslinked casein with tannic acid did not exert cytotoxic effects on cells and promoted their proliferation. The membranes demonstrated potential application in drug delivery system and astopicals curatives.
Revista de Chimie	Albu et al. (2009)	Spectral Characteristics and Antioxidant Properties of Tannic Acid Immobilized on Collagen Drug-Delivery Systems	Obtaining biomaterials compounds with antioxidant activity made up of collagen and tannic acid for use in both topical formulations as biativos systems in the wound healing process.
Molecular crystals and liquid crystals	Albu et al. (2010)	Doxycycline Delivery From Collagen Matrices Crosslinked With Tannic Acid	Collagen matrices containing doxycycline and tannic acid showed activity against gram-positive and gram-negative bacteria, fungi or yeasts. The material may be suitable for wound treatment.

Table 2. Contd.

Letters in Applied Microbiology	Chusrin and Voravuthikunchai (2011)	Damage of staphylococcal cytoplasmic membrane by *Quercus infectoria* G. Olivier and its componentes	Establishment of the mechanism of action of thr ethanol extract of *Q. infectoria*, as well asits major constituent chemicals for their application in skin infections and wounds. The study provides scientific information to support its traditional use, suggesting antibacterial mechanisms.
International Wound Journal	Hemmati et al. (2011).	Topical grape (*Vitis vinifera*) seed extract promotes repair of full thickness wound in rabbit	Evaluation of healing activity of hydroalcoholic extracts of grape seed in rabbits. The results demonstrated that the topical use of the extracts promoted wound healing.
Surgery Today	Hachiro et al. (2011)	Aluminum potassium sulfate and tannic acid (ALTA) injection as the mainstay of treatment for internal hemorrhoids	The therapy for symptomatic hemorrhoids with the use of potassium sulphate and aluminum and tannic acid. The therapy proved to be simple and safe, with few complications.
Digest Journal of Nanomaterials and Biostructures	Jinga et al. (2013)	Silver green synthesis on bacterial celulose membranes using tannic acid	Silver nanoparticles were added to the bacterial cellulose membrane using tannic acid as crosslinking agent. The films showed good antibacterial activity against *E. coli* K12 MG1655, and can be used as wound curative.
Journal of Biomedical Materials Research Part B-Applied Biomaterials.	Natarajan et al. (2013)	Preparation and properties of tannic acid cross-linked collagen scaffold and its application in wound healing.	Development of cross-linked collagen films with tannic acid. The material has potential for use as a curative on skin lesions.
Digest Journal of Nanomaterials and Biostructures	Popa et al. (2013)	Hysteresis of contact angle. Dynamic wettability studies of collagen and doxycycline porous matrices crosslinked with tannic acid	Porous membranes of collagen crosslinked with doxycycline and tannic acid showed good wetting properties and hydrophobicity for use in drug delivery systems.
Chemical Communications	Krogsgaa et al. (2014)	Gels and threads: mussel-inspired one-pot route to advanced responsive materials	Obtaining hydrogels for biomedical use from the reaction with tannic acid, trivalent metal ions and polyallyamine.
International Pharmacology	Upadhyay et al. (2014)	A review on the pharmacological aspects of *Terminalia chebula*.	A review study of the pharmacological effects of Terminalia chebula and the relation of isolated chemical constituents in its biological activities.
Journal of Bioactive and Compatible Polymers: Biomedical Applications	Xu et al. (2014)	Large-scale production of a ternary composite nanofiber membrane for wound dressing applications	The development of membranes from chitosan, tannic acid and polyvinyl alcohol. The membranes showed potential for use as wound curative with antimicrobial activity against E. coli, adhesion and development of fibroblast cells.
Diseases of the colon and rectum	Abe et al. (2014)	Combined aluminum potassium sulfate and tannic acid sclerosing therapy and anal encirclement using an elastic artificial ligament for rectal prolapse	Evaluation of clinical data and recurrence rates in patients with rectal prolapse treatment based on the potassium sulfate, tannic acid and aluminum. The procedure is easy to perform, inexpensive, low recurrence rate and appears to be a reasonable alternative to rectal prolapse in elderly patients, debilitated and high risk.

Table 2. Contd.

RSC Adv.	Zhou et al. (2014)	Vacuum-assisted layer-by-layer electrospun membranes: antibacterial and antioxidative applications	The LBL type of film prepared with tannic acid and AGNPS-Lis showed antioxidant and antibacterial activity and potential for application in food packaging, wound healing and tissue engineering.
Carbohydrate Polymer	Xu et al. (2015)	Development of tannic acid/chitosan/pullulan composite nanofibers from aqueous solution for potential applications as wound dressing	Development of curative systems for wounds from nanocomposites of tannic acid/chitosan/pullulan. The material showed antibacterial properties and promoted the regeneration of skin on wound healing assays.
European Journal of Medicinal Chemistry	Moulaoui et al. (2015)	Identification and nanoentrapment of polyphenolic phytocomplex from *Fraxinus angustifolia*: In vitro and in vivo wound healing potencial	The quercetin, rutin, catechin and tannic acid were identified in the extracts of the leaves and bark of Fraxinus angustifolia species. The application of the extracts in wound healing promoted the cure of the wounds.
Journal of Applied Polymer Science	Sahiner et al. (2015)	p(AAm/TA)-based IPN hydrogel films with antimicrobial and antioxidant properties for biomedical applications	Crosslinked polyacrylamide hydrogel preparation with tannic acid and evaluation of antibacterial and antioxidant properties. The hydrogel has the potential for application in the biomedical field.

acid can be applied in the dentistry field for the complex dentin-pulp protection.

In the area of wound healing, the development of tannic acid/chitosan/pullulan composite showed potential applications as a curative, with antibacterial properties against Gram-negative bacteria (*Escherichia coli*), and favor the attachment of fibroblast cells and intercalary growth on the membrane, regenerating the skin (Xuet al., 2015). The healing properties of tannins is attributed to its astringent action, promoting the elimination of water into cells, leading to contraction of the fibers by decreasing hemorrhage and facilitating healing.

Akiyama et al. (2001), investigated the tannins antibacterial action against *Staphylococcus aureus* and the effect of standard chemotherapy in combination with tannic acid. The results indicate that tannic acid can be a useful adjunctive agent for treating skin infections caused by *S. aureus*, becausethis tannin seems to act on the cell membranes of *S. aureus*. The β-lactam antibiotics had their antistaphylococcal activity enhanced by the presence of tannic acid.

Park et al. (2006) and Jung et al. (2010), examined the effect of tannic acid on skin inflammation with a cell line of human keratinocytes (HaCaT). Topical application of tannins in mouse skin treated with UVB irradiation demonstrated inhibition of erythema formation. The results showed that the tannic acid presented significant anti-inflammatory activity in response induced by UVB radiation on the skin and can be a natural candidate compound for regulating skin inflammation.

The combination of the words "tannic acid" and "wound" were found in 26 documents, including 23 articles. The United States published five articles, followed by Romania with 4 articles. Four of the 23 articles belong to the dermatological field, one of which evaluated the effects of burn treatment with highly purified tannic acid. The results indicate that purified tannic acid can provide a valuable tool for improving wound healin (Halkes et al., 2002). In another study, tannic acid promoted the stabilization of the collagen matrix against collagenolytic degradation, achieving significant results on wound healing in rats. The collagen-based material and tannic acid were considered biodegradable, and may have applications in tissue engineering and drug entrainment (Natarajanet al., 2013). The tannic acid has important properties that gives it a variety of technological applications, especially in the Pharmaceutical field as curative in the wound healing process.

Using the "carboxymethylcellulose" and "tannic acid" terms, six articles were obtained of which covered different areas, such as quantification of heavy metals in water (Sui et al., 2013), substrates for isolated yeasts from the rotten wood (Middelhoven, 2006), wax additives (Tascioglu and Akar, 2003) and reduced astringency of phenolic compounds (Troszynska et al., 2010). Two articles have dealt with the use of tannic acid and carboxymethylcellulose as biomaterials in the medical

field. Shutava et al. (2009), research involved the development of nanocapsules with polyelectrolyte polymer for entrainment of natural polyphenols, in order to assess its anti-cancer potential. The second article encompassed the studies by Aeleneiet al. (2009), which reviewed the addition of tannic acid in biodegradable polyelectrolyte complex for medical and pharmaceutical applications. The results confirmed the possibility of adding tannic acid in microparticles based on chitosan, sodium alginate and carboxymethylcellulose. These complexes have shown potential for use in the treatment of dental pain and skin lesions. Table 2 includes the searches with tannic acid, pure or extract, in the development of biomaterials for the treatment of dermal healing.

Conclusion

In pure form or in extracts, the tannic acid introduced itself as a versatile material with applications in different industrial sectors. Regarding the healing subject, the United States, Japan and China are the countries that invested the most in the elucidation of mechanisms and inventions that contemplated the different properties of tannic acid in wound healing, burns and inflammations. Tannins are found in nearly all plant families, and Brazil has a large plant diversity, which makes it a potential field to develop biomaterials with extracts rich in tannic acid. The public spending on curative for skin ulcers is growing, which requires urgent researches to develop more effective healing systems at lower cost. Within this scenario, the tannic acid appears with potential application in topical formulations, although there are controversial ideas about its cytotoxic effects. Also, in Brazil the development of this economic sector is still lacking in research and technology.

Conflict of Interest

The authors have not declared any conflict of interest.

REFERENCES

Abe T, Hachiro Y, Kunimoto (2014). Combined aluminum potassium sulfate and tannic acid sclerosing therapy and anal encirclement using an elastic artificial ligament for rectal prolapse. Dis. Colon Rectum. 57(5):653-657

Aelenei N, Popa MI, Novac O, Lisa G, Balaita L (2009). Tannic acid incorporation in chitosan-based microparticles and in vitro controlled release.J. Mater. Sci. Mater. Med. 20(5):1095-1102.

Akiyama H, Fuji K, Yamasaki O, Oono T, Iwatsuki K (2001).Antibacterial action of several tannins against *Staphylococcus aureus*. J. Antimicrob. Chemother. 48(4):487-491.

Albu MG, Ghica MV, Leca M, Popa L, Borlescu C, Cremenescu E, Giurginca M, Trandafir V (2010). Doxycycline delivery from collagen matrices crosslinked with tannic acid. Mol. Cryst. Liq. Cryst. 523(1):97-105.

Albu MG, Ghica MV, Giurginca M, Trandarfir V, Popa L, Cotrut C (2009). Spectral characteristics and antioxidant properties of tannic acid immobilized on collagen drug-delivery systems. Rev. Chim. (Bucharest). 60(7):666-672.

Ballard D (2007). Aqueous gels for well bore strengthening. US 20070249504 A1.

Bruneton J (2001). Farmacognosia, fitoquímica, plantasmedicinales. 2. Edición Zaragoza: Acribia P. 366.

Chen H, Zhu C (2014). Application of *Aspergillus terricola* protease in preparing medicine for cleaning wound and accelerating healing of wound.CN 103977398-A1.

Chung KT, Lu Z, Chou MW (1998). Mechanism of inhibition of tannic acid and related compounds on the growth of intestinal bacteria. Food Chem. Toxicol. 36 (12):1053-1060.

Chusri S, Voravuthikunchai SP (2011). Damage of staphylococcal cytoplasmic membrane by *Quercus infectoria* G. Olivier and its componentes. Lett. Appl. Microbiol. 52(6):565-572.

Claus EP, Tyler VE (1965). Farmacognosia. 5. Edición. Buenos Aires: El Ateneo p.135.

Falcon J (1998). Composição e processo de tratamento de câncer com ácidotânico e complexostanino.VPI 9811875-7.

George GJ (1970). Process and agente for topical treatment. GB1273308-A.

Gulçin I, Huyut Z, Elmastas M, Aboul-Enein HY (2010). Radical scavenging and antioxidant activity of tannic acid.Arabian J. Chem. 3(1):43-53.

Hachiro Y, Kunimoto M, Abe T, Kitada M, Ebisawa Y (2011). Aluminum potassium sulfate and tannic acid (ALTA) injection as the mainstay of treatment for internal hemorrhoids.Surg.Today. 41(6):806-809.

Halkes SBA, Hoekstra MJ, du Pont JS, Kreis RW (2001). The use of tannic acid in the local treatment of burn wounds: Intriguing old and new perspectives. Wounds. 13(4):144-158.

Halkes SBA, van den Berg AJJ, Hoekstra MJ, du Pont JS, KreisRW (2002a). Transaminase and alkaline phosphatase activity in the serum of burn patients treated with highly purified tannic acid. Burns. 28 (5):449-45.

Halkes SBA, Vrasidas I, Rooijer GR, van der Berg AJJ, Liskamp RMJ, Pieters RJ (2002b).Synthesis and biological activity of polygalloyl-drendrimers as stable tannic acid mimics.Bioorg. Med. Chem. Lett. 12(12):1567-1570.

Hamtini SI (2004). Topical medicationfor treating nappy rash.US 20040022863-A1.

Haslam E (1996). Natural polyphenols (vegetable tannins) as drugs and medicines: possible modes of action. J. Nat. Prod. 59(2):205-215

Heijmen FH, du Pont JS, Middelkoop E, Kreis RW, Hoekstra MJ (1997). Cross-linking of dermal sheep collagen with tannic acid. Biomaterials.18(10):749-754.

Hemmati AA, Aghel N, Rashidi I, Gholampur-Aghdami A (2011). Topical grape (*Vitisvinífera*) seed extract promotes repair of full thickness wound in rabbit.Int. Wound J. 8(5):514-520.

Jinga SI, Isopencu G, Stoica-Guzun A, Stroescu M, Ferdes M, Ohreac B (2013). Silver green synthesis on bacterial celulose membranes using tannic acid.Dig. J. Nanomater. Bios. 8(4):1711-1717.

Jung MK, Hur DY, Song SB, Park Y, Kim TS, Bang SI, Kim S, Song HK, Park H, Cho DH (2010). Tannic acid and quercetin display a therapeutic effect in atopic dermatitis via suppression of angiogenesis and TARC expression in Nc/Nga mice. J. Invest. Dermatol. 130:1459-1463.

Khanna S, Venojarvi M, Roy S, Sharma N, Trikha P, Bagchi D, Bagchi M, Sen CK(2002). Dermal wound healing properties of redox-active grape seed proanthocyanindins.Free Radical Biol. Med. 33(8):1089-1096.

Kim TJ, Silva JL, Kim MK, Jung YS (2010).Enhanced antioxidant capacity and antimicrobial activity of tannic acid by thermal processing. Food Chem. 118(3):740-746.

Kim TJ, Weng WL, Stojanovic J, LU K, Jung YS, Silva JL (2008). Antimicrobial effect of water-soluble muscadine seed extracts on *Escherichia coli O157:H7*. J. Food Prot. 71(7):1465-1468.

Krogsgaard M, Andersen A, Birkedal H (2014). Gels and threads: mussel-inspired one-pot route to advanced responsive materials. Chem. Commun. 50(87):13278-13281.

Lener EI, Rosenberger V, Flasner M (1998). Composições de polímero-ácidotânicoparaliberaçãocontrolada de agentesfarmacêuticosparticularmentenacavidade oral. International

Comment [vv5]: chronological order

Comment [vv3]: References are not as per journal format. Capitals are to be removed. Full stops are to be added to abbreviated journals name. commas are to be removed.

Comment [vv6]: Chronological order?

Comment [vv4]: delete

Patent WO/1999/004764
Li D, Zhang K (2014). Medicinal insole used for preventing frostbite, comprises camphor, thymol, menthol, vitamin E, boric acid, tannic acid, niacina, *Salvia* extract, Tween 80, purified water, liquid and binder. CN103720133-A.
Marques MR (2005). Substânciaquímicapararemoção de tatuagens, estrias, cicatrizes, queloides, vitiligo, queimadura e qualqueroutramarcavisívelquecaracterizeumalesãocutânea. CI 0400241-5.
Mcclure RL (2001). Pharmaceutical blend useful for healing wounds such as harness chaffing on horses comprises súlfur, zinc oxide, tannic acid and olive oil. CA 2302446-A1.
Middelhoven WJ (2006). Polysaccharides and phenolic compounds as substrate for yeasts isolated from rotten wood and description of *Cryptococcus fagi sp*.A. vanLeeuw. J. Microb. 90(1):57-67.
Min BR, Barry TN, Attwood GT, McNabb WC (2003). The effect of condensed tannins on the nutrition and health of ruminants fed fresh temperate forages: a review. Anim. Feed. Sci. Technol. 106(1-4):13-19.
Mitts T, Jimenez F, Hinek A (2014). Elastin protective polyphenolics and methods of using the same. US 20140155335-A1.
Monteiro JM, Albuquerque UP, Araújo EL, Amorim ELC (2005). Taninos: umaabordagem da química à ecologia. Quím. Nova, 28(5):892-896.
Moulaoui K, Caddeo C, Letizia MM, Castangia I, Valenti D, Escribano E, Atmani D, Fadda AM, Maconi M (2015). Identification and nanoentrapment of polyphenolicphytocomplex from *Fraxinus angustifolia*: *In vitro* and *in vivo* wound healing potencial. Eur. J. Med. Chem. 89(7):179-188.
Murad H (2006). Pharmaceutical compositions and methods for managing skin conditions. U.S. Patent No. 6,673,374.
Natarajan V, Krithica N, Madhan B, Sehgal PK (2013). Preparation and properties of tannic acid cross-linked collagen scaffold and its application in wound healing. J. Biomed. Mater. Res. B Appl. Biomater. 101(4):560-567.
Park HJ, Kim HJ, Kwon HJ, Lee JY, Cho BK, Lee WJ, Yang Y, ChoDH (2006). UVB-induced interleukin-18 production is downregulated by tannic acids in human HaCaT keratinocytes. Exp. Dermatol. 15(8):589-595.
Popa L, Ghica MV, Albu MG, Ortan A, Dinu-Pirvu CE (2013). Hysteresis of contact angle. Dynamic wettability studies of collagen and doxycycline porous matrices crosslinked with tannic acid. Dig. J. Nanomater. Bios. 8(3):937-943.
Pulido R, Bravo L, Saura-Calixto F (2000).Antioxidant activity of dietary polyphenols as determined by a modified ferric reducing/antioxidant power assay. J. Agric. Food Chem. 48(8):3396–3402.
Rubentheren V, Ward TA, Chee CY, Tang CK (2015).Processing and analysis of chitosan nanocomposites reinforced with chitin whiskers and tannic acid as a crosslinker. Carbohyd. Polym.115(22):379-387.
Sahiner M, Sagbas S, Bitlisli BO (2015). p(AAm/TA)-based IPN hydrogel films with antimicrobial and antioxidant properties for biomedical applications. J. Appl. Polym. Sci. 132(16):41876-41888.
Sanchez-Moreno C, Larrauri AJ, Saura-Calixto F (1999). Free radical scavenging capacity and inhibition of lipid oxidation of wines, grape juices and related polyphenolic constituents. Food Res. Int. 32(6):407-412.
Scalbert A (1991). Antimicrobial properties of tannin. Phytochemistry 0(12):3875-3883.
Shutava TG, Balkundi SS, Vangala P, Steffan JJ, Bigelow RL, Cardelli JA, O'neal DP, Lvov YM (2009). Layer-by-Layer-Coated gelatin nanoparticles as a vehicle for delivery of natural polyphenols. ACS NANO. 3(7):1877-1885.
Silva GA, Vaz CM, Coutinho OP, Cunha AM, Reis RL(2003). *In vitro* degradation and cytocompatibility evaluation of novel soy and sodium caseinate-based membrane biomaterials. J. Mater. Sci. Mater. Med. 14(12):1055-1066.
Sui DP, Li J, Zhang G, Liu JX, Fan HT, Sun T (2013). New diffusive gradients in thin-films device for quantitative measurement of heavy metals in water.Chem. J. Chinese. U. 34(5):1132-1138.
Tascioglu S, Akar N (2003). Conversion of an investment casting sprue wax to a pattern wax by chemical agentes. Mater. Manuf. Process. 18(5):753-768.
Troszynska A, Narolewska O, Robredo S, Estrella I, Hernandez T, Lamparski G, Amarowicz R(2010). The effect of polysaccharides on the adstringency induced by phenolic compounds. Food Quality. Prefer. 21(5):463-469.
Upadhyay A, Agrahari P, Singh DK (2014). A review on the pharmacological aspects of *Terminaliachebula*. Int. J. Pharmacol. 10(6):289-298.
Xu F, Weng B, Materon LA, Gilkerson R, Lozano K (2014). Large-scale production of a ternary composite nanofiber membrane for wound dressing applications. J. Bioact. Compat. Pol. 29:646-660.
Xu F, Weng B, Gilkerson R, Materon LA, Lozano K (2015). Development of tannic acid/chitosan/pullulan composite nanofibers from aqueous solution for potential applications as wound dressing. Carbohyd. Polym. 115(22):16-24.
Yoshikawa M, Toda T (2000).Reconstruction of alveolar bone defect by calcium phosphate compounds. J. Biomed. Mater. Res. 53(4):430-437.
Zhao J (2013). Firewood seed tannin care paste useful for treating exudative ulcer, burns and scalds, eczema, bedsore and hemorrhoids comprises extract, glycerol and water soluble matrix. CN 103142660-A.
Zhou B, Jim X, Li J, Xu W, Liu S, Li Y, Li B (2014). Vacuum-assisted layer-by-layer electrospun membranes: antibacterial and antioxidative applications. RSC Adv. 4:54517-54524.

Comment [vv10]: delete

Comment [vv7]: delete

Comment [vv8]: delete

Comment [vv9]: delete