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Revision Article

From fibers electrospun with honey to the healing of wounds: a review

De las fibras electrohiladas con miel a la curación de heridas: una revisión

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Abstract

In order to take advantage of the antiseptic and healing properties of honey, the preparation of polymeric micro and nanofibers with honey from bees has been investigated in many parts of the world, in order to enhance their use in the development of biomedical products such as dressings, bandages and other elements that favors wound closure and tissue restoration. To contribute to this line of research, a background review is presented here on the application of the electrospinning technique in the preparation of micro and nanofiber membranes with honey, focusing on experimental methodology including the use of polymers, solvents, therapeutic agents, active principles or drugs loaded in apitherapeutic fibers. Electrospinning techniques and parameters, tests and material characterization methods have been compiled, presenting the effect of these variables on the compositional, morphological, mechanical and physicochemical properties of the fibrous meshes. A compendium of biological tests evaluated in vitro and in vivo was made in order to analyze the functionality and potential of the application of fibers in tissue engineering, as well as in the construction of devices for clinical diagnosis and in general for the development of advanced materials for wound treatment. This review sees the establishment of the methodological foundations for the design of new materials based on honey and plant extracts not yet explored, and which could be developed into compounds of high scientific and industrial interest.

Resumen

Con el fin de aprovechar las propiedades antisépticas y cicatrizantes de la miel, en muchas partes del mundo se ha investigado la preparación de micro y nanofibras poliméricas con miel de abejas, con el fin de potenciar su uso en el desarrollo de productos biomédicos como apósitos , vendajes y otros elementos que favorezcan el cierre de la herida y la restauración del tejido. Para contribuir a esta línea de investigación, se presenta una revisión de antecedentes sobre la aplicación de la técnica de electrohilado en la preparación de membranas de micro y nanofibras con miel, enfocándose en la metodología experimental que incluye el uso de polímeros, solventes, agentes terapéuticos, principios activos o fármacos cargados en fibras apiterapéuticas. Se han recopilado técnicas y parámetros de electrohilado, ensayos y métodos de caracterización de materiales, presentando el efecto de estas variables sobre las propiedades composicionales, morfológicas, mecánicas y fisicoquímicas de las mallas fibrosas. Se realizó un compendio de pruebas biológicas evaluadas in vitro e in vivo con el fin de analizar la funcionalidad y potencial de la aplicación de fibras en ingeniería de tejidos, así como en la construcción de dispositivos para diagnóstico clínico y en general para el desarrollo de materiales avanzados. para el tratamiento de heridas. Esta revisión prevé el establecimiento de las bases metodológicas para el diseño de nuevos materiales basados en miel y extractos de plantas aún no explorados, y que podrían desarrollarse en compuestos de alto interés científico e industrial.

Keywords: electrospinning, honey, nanofibers, wound microenvironment, dressings, tissue regeneration.

Palabras clave: electrohilado, miel, nanofibras, microambiente de heridas, apósitos, regeneración de tejidos.

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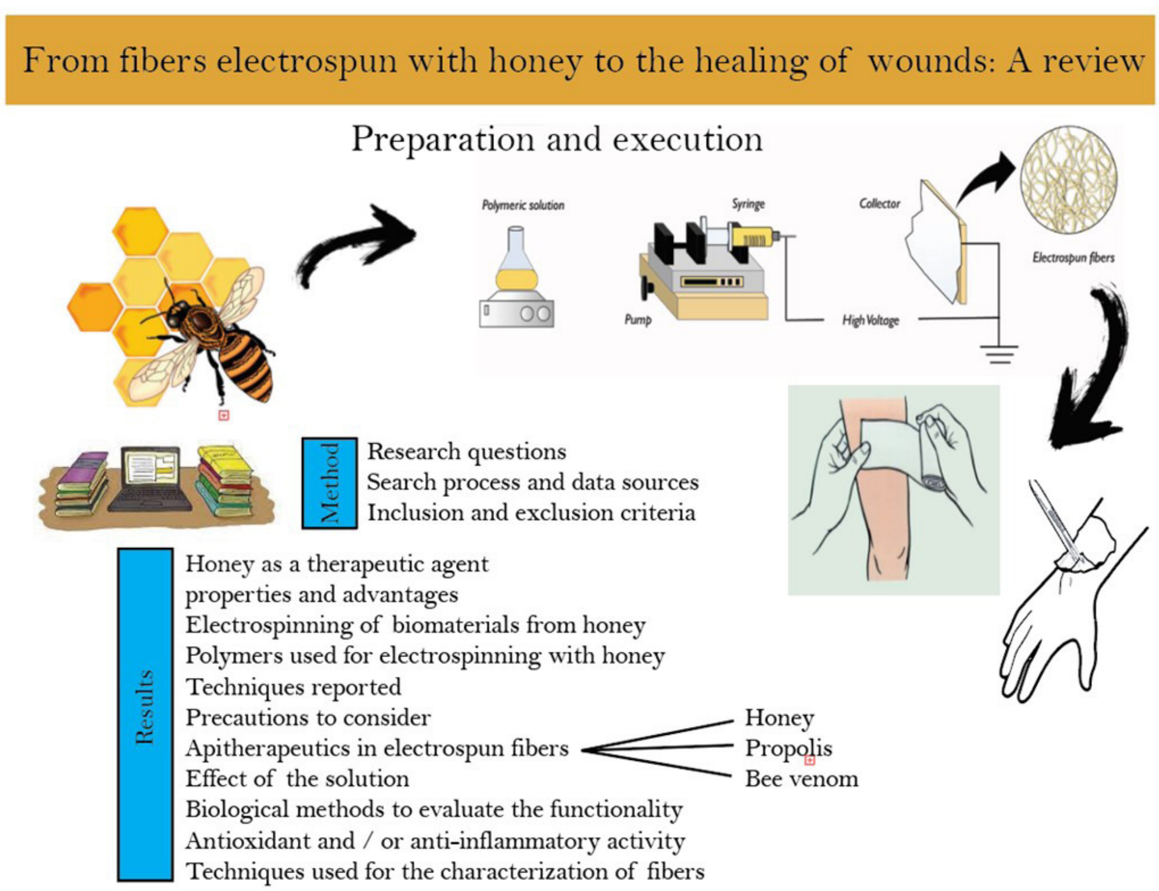
Why was it carried out?
The research was carried out with the aim of providing a comprehensive and updated view on the development of membranes from honey using the electrospinning technique. This research arose from the need to address questions, knowledge gaps and controversies existing in the field, with the purpose of consolidating and synthesizing the available information, as well as analyzing and critically evaluating previous studies. The primary objective was to contribute to the advancement of knowledge in the area, offering an informed and rigorous perspective that could serve as a reference for both researchers and professionals interested in the topic.

What were the most relevant results?
The most relevant results of the research likely include:
Experimental Methodology: The review likely outlines various experimental methodologies used in the preparation of micro and nanofiber membranes with honey. This may include details on the choice of polymers, solvents, therapeutic agents, and other materials involved in the electrospinning process.
Characterization of Fibers: The research likely presents findings on the compositional, morphological, mechanical, and physicochemical properties of the fibrous meshes produced through electrospinning with honey. This could involve insights into how different variables such as electrospinning techniques and parameters affect the properties of the fibers.
Biological Tests: The review likely compiles information on the results of biological tests conducted both in vitro and in vivo to evaluate the functionality and potential of honey-infused fibers in tissue engineering and wound treatment. This may include data on the efficacy of these fibers in promoting tissue regeneration and wound healing.

What do these results provide?
These results provide valuable insights into the feasibility and effectiveness of utilizing honey-infused fibers in biomedical applications. By understanding the properties and performance of these fibers, researchers can potentially design improved wound dressings and other medical materials that offer enhanced therapeutic benefits. Additionally, the research may pave the way for the exploration of novel materials based on honey and plant extracts, opening up new avenues for scientific and industrial advancements in wound treatment and tissue engineering.to it, Giant Geotextiles bags, having a geotechnical and hydraulic design according to the project, is considered as a reliable alternative and infrastructure solution.

Graphical Abstract



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Introduction

This article focuses on the narrative review of scientific literature regarding the preparation by electrospinning of micro and nanofibers with honey, a natural compound that has been an interesting focus of research given its therapeutic properties as an antibacterial, antibiotic, antioxidant and anti-inflammatory agent(1–5). It is an aromatic organic compound used as a medical treatment since ancient times(6,7), that has the ability to maintain a moist wound healing environment without allowing bacterial growth and infection development (8,9). Due to its acidic nature, honey favors the growth and activity of fibroblasts, connective tissue cells that have a structural function and are an aid in wound healing (10). This review was carried out in order to give added value to a type of regional honey not yet used in the design of advanced materials of biological interest and medicinal treatment. This honey is differential because it comes from the activity of bees fed with the nectar of regional plants recognized as medicinal. These therapeutic attributes are transferred to the polymeric fibers through the incorporation of honey by electrospinning. Statistical information was collected on the number of publications per year related to electrospinning of fibers with honey, as presented in Figure 1**.** As it can be seen, 2019 saw a great increase in electrospinning of fibers with honey by researchers. In this review, through technological surveillance, questions related to electrospinning of honey were answered: What was the objective, need and / or problem that motivated the investigation in each work reviewed? (Table 3), What polymers and synthetic or natural

solvents have been used?, WIn what concentration has the honey been supplied?, What are the applied electrospinning parameter values?, How have researchers supplemented honey to make fibers?, What results have been impressive enough to be taken as a basis for future research?, What has been the potential application of the fibers from honey? The objective of this review is to understand the most suitable electrospinning parameters for the experimental design of polymeric micro and nanofibers from honey from regional apiaries, initially as a model and subsequently with a view to extend it into future studies; it also aims to identify the potential applications of these biomaterials.

Method

To collect information, scientific databases such as ScienceDirect, PubMed and Embase were consulted, under the search criteria presented in Table 1 and they were selected Figure 1 based on the inclusion criteria of Table 2. Additionally, Google Patents was also used to search for related patents. The scientific publications referring to the electrospinning of fibers with honey are presented in Table 3 and through the review, the results related to these investigations are discussed. With the search, selection and analysis of this topic, the antecedents related to electrospinning of honey fibers were recognized, compared and summarized, in order to answer the main question: What research antecedents are important to be taken as the basis for the electrospinning of fibers with regional honey?

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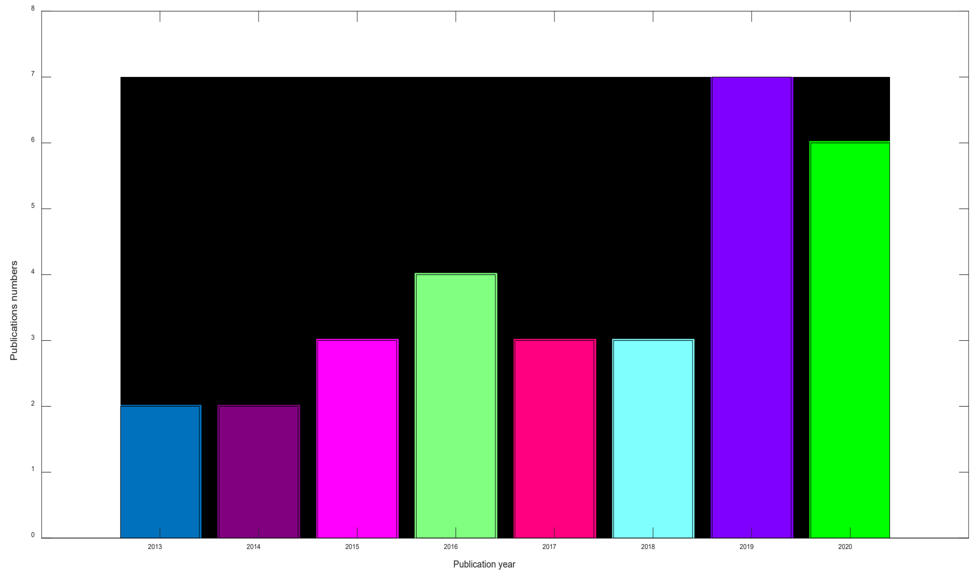

Figure 1. Annual frequency of electrospinning publications with honey

Table 1. Search criteria for publications related to electrospinning of fibers with honey.

Search criteria	Filter
Key words	Electrospinning, Honey, Nanofibers
Language	English
Publication Type	Original article, patent, abstract conference and poster summary

Table 2. Inclusion criteria for publications

Inclusion Criteria	Filter
Fiber obtention technique	Electrospinning
Principal component	Honey
Material Characterization technique	Yes/No

First of all, this review presents a description of the functionality of products generated by the activity of bees, which have been used in different scientific studies for the electrospinning of fibers. These apitherapeutics are: honey, propolis and apitoxin (bee venom). Next, this review describes the importance of honey in wound healing, highlighting the factors that allow electrospun fibers with honey to provide an effective environment

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for the restoration of damaged skin. In addition, several investigations are looked where the authors potentiated the medicinal functions of honey by using plant or fruit extracts alongside different synthetic or natural electrospun polymers; in turn, the characteristics of each polymer used are presented, such as concentration, presentation, molecular weight, degree of polymerization and hydrolysis degree. ; Next, the electrospinning techniques by which fibers with honey have been obtained, the process parameters and the results obtained with each system are listed. Reference is also made to the interesting fact that honey has not only been used in electrospinning, but in other nanofunctionalization techniques such as layer-by-layer (LbL) assembly, for the administration of bioactive molecules in the treatment of skin infections. On the other hand, the precautions that the researchers have to be taken into account for the electrospinning of fibers with honey are also presented, in order to avoid errors and failures in the process of obtaining them.

Furthermore, the review includes techniques used for the characterization of the apitherapeutic material in terms of its composition, size and porosity, morphology, and mechanical and thermal properties; it also includes the effects of the concentration of active principles on the size of the fiber from honey, as well as the effects of the parameters of the electrospun solution on the characteristics of the fibers.

Finally, it specifies and describes the results obtained by researchers when applying in vitro and in vivo biological methods using honey fibers are in order to evaluate their effectiveness at a biological and medicinal level, by analyzing

their antibacterial, antioxidant and / or anti-inflammatory potential, and as such, whether they allow cell viability, are cytocompatible and therefore have the capacity to help in the tissue regeneration process.

Apitherapeutics in electrospun fibers

Different by-products of beekeeping have been used for the design and electrospinning of fibers for wound healing.

Honey

It is said to be the oldest wound dressing. It is an aromatic hydrocarbon with a prominent organic composition, used as a medical treatment since ancient times due to its high biocompatibility(2). It is also a complex mixture made up of macrocomponents and microcomponents, the main ones being water, lipids and sugars such as glucose, fructose and sucrose; Within the minority components are amino acids, vitamins, mineral salts and enzymes (11,12), and chemical species have been reported that have specific functions and are responsible for the biological functionality of honey..

Flavonoids: phenolic compounds that act directly against bacteria, by inhibiting their energy metabolism, the function of the cytoplasmic membrane and the action of DNA gyrase (9).
Tetracycline antibiotics: they contribute to the aseptic state of the wound (13).
Hydrogen peroxide: antimicrobial produced by the enzyme glucose oxidase, which provides an antioxidant environment by inhibiting the production of inflammation causing free radicals (14).
Defensin-1: cysteine-rich peptide with antibiotic function against bacteria, fungi and viruses (15).

For electrospinning of fibers with apitherapeutics, Manuka honey is often used, which is produced in New Zealand from the nectar of the Leptospermum scoparium bush, (16–18). It differs from other types of honey by the presence of methylglyoxal (MGO), component that

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reinforces antibacterial activity, with respect to hydrogen peroxide commonly present in honey types (19). It has a broad spectrum of antibacterial action fighting aerobic, anaerobic, gram-positive and gram-negative bacteria (20). As well as honey, other bee products have also been used to treat different human diseases. This practice is called apitherapy (21).

Propolis

It is a resinous and highly viscous product, made by bees from the secretion that they collect from different types of trees and herbaceous plants. Similar to honey, propolis is used medicinally against infections generally caused by microorganisms, due to the properties conferred by phenolic compounds such as those that are antibacterial / bactericidal, antioxidant, antifungal and anti-inflammatory(22). It is also cytostatic for the treatment of tumors, it is astringent, spasmolytic, anesthetic, antiulcer and immunomodulatory, which makes it a special agent for healing wounds(23,24). The effectiveness of propolis and the polyphenolic content depends on the geographical area and the plant environment where the bees develop (22). In practice, the research by Ullah et al., A (9). demonstrated the utility of propolis when impregnated in cellulose acetate nanofibers and CA / PCL polycaprolactone. These bee fibers showed high antioxidant activity and effective antibacterial activity against gram-negative and gram-positive bacteria.

Bee venom

Also called apitoxin, it has a great therapeutic potential in relieving pathological symptoms such as pain, severe inflammation, rheumatic arthritis, skin diseases and tumors (19). It acts as an analgesic, antiviral, antioxidant and antimicrobial, which makes it a favorable agent for wound healing (21). the antibacterial capacity of bee venom was demonstrated in the work of Abou et al.S. and collaborators (19). who Iincorporated PVA scaffolds were manufactured with different combinations between pomegranate extract, honey and bee venom. Scaffolds loaded with bee venom were effective against gram-positive bacteria, but showed no activity against gram-negative bacteria. In contrast, propolis has been shown to be fully effective against gram-positive and gram-negative bacteria; with the scaffolds composed of honey and bee venom, better tissue repair was obtained in rats wounds (19). Thus, despite the fact that apitoxin does not present a complete antibacterial activity against all types of bacteria, its other therapeutic properties provide an improved microenvironment for wound healing. Not only must the antibacterial activity of a substance be taken into account, but its properties as a whole can contribute synergistically to the treatment of wounds.

Honey as a therapeutic agent in wound healing

True wound healing requires that the entire physiological process of normal healing be accomplished in all its stages. In this way, with the presence of a wound, the immune system triggers a healing cascade composed of phases such as: inflammation, production of granulation tissue, re-epithelialization or deposition of collagen fibers (13). It has been reported that honey as a therapeutic agent contributes to the development of healing stages by fighting inflammation, causing autolytic debridement, that is, moderate separation between necrotic and healthy tissue, by enzymatic action. In addition, honey, due to its acidic nature, provides an environment with reduced pH, which favors the growth and activity of cells involved in the repair of tissues such as: fibroblasts, keratinocytes, lymphocytes, neutrophils and monocytes (25–27). Skin tissues they regenerate and the size of the collagen fibers and the epidermis increases, reducing inflammation and the risk of a recurrent opening of the wound (1). In oxygen-hemoglobin dissociation, honey as an apitherapeutic intervenes by increasing the release of oxygen. It allows the elimination

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of abnormal collagen and the synthesis of normal collagen with its maturation (28) and promotes the emergence of blood vessels (29–32).

Dressings need to provide a moist environment to the wound while not allowing the growth of bacteria. Honey gives these characteristics to the polymeric matrices, in addition to constituting an interface between the wound and the external environment, which added to the protection barrier allows the non-adherence of the material to the skin, so that when the the scaffold is removed, does not damage the new tissue (10). Honey stimulates the activity of macrophages, leukocytes to produce cytosines that fight against infection and decreases the toxicity of substances produced by bacteria such as ammonia (19). It also counteracts resistant bacteria that put health at risk with a possible systemic infection (21).

Fibers electrospun with honey: properties and advantages

Nanofibers are considered fibers with diameters of less than 100 nm (33) which, due to their morphology and spatial arrangement, offer different advantages as materials for dressings. If the polymeric fibers are hydrophilic and even so their hydrophilicity is increased with the incorporation of honey, they will provide good exudate management (17). Furthermore, nanofibers with a small pore size will hinder the development of bacteria and infection, they will help the flow of nutrients, waste elimination and gas exchange, fundamental characteristics to providing an optimal environment for tissue renewal (25). The decrease in size of the materials provides differential properties with respect to conventional ones, such as a high surface / volume ratio that allows the excessive liquid to be filtered and retained through the small fissures of the fibers, thereby maintaining a humid environment (10,25). Honey nanofibers have great therapeutic and clinical potential to be applied in biotechnology, biomedicine, controlled release of active ingredients, local regeneration of skin affected by wounds, design of cell scaffolds / dressings (34) and for biosensor devices (16). The fibers with honey have been developed to be used mainly in medical treatments and at the same time to replace the common use of raw honey, while innovating how the apitherapy is administered (13). A great advantage of nanofibers is that due to their 3D morphology and their small-scale size, they can mimic the structure of the extracellular matrix, favoring the development and proliferation of cells, as happens in their natural environment (32).

Electrospinning of biomaterials from honey and plant extracts

The effectiveness of honey-loaded polymeric fibers for wound healing has been reported; however, it has also been shown that enriching the fibers with natural extracts improves their therapeutic effect and increases their potential as biomaterials for tissue repair. In this way, the wound healing process is dynamized, with fibers that act as vehicles that allow the free or controlled release of medicinal agents on the affected area (9) (Table 4).

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Table 3. Publications related to obtaining fibers with honey by electrospinning: objective and application.

Original title	Objective/Application	Referencia
In vivo evaluation of the wound healing properties of bio-nanofiber chitosan/ polyvinyl alcohol incorporating honey and Nepeta dschuparensis	To design bio-nanofibers of PVA, chitosan, Nepeta dschuparensis and honey, to evaluate their application as a potential scaffold in the treatment of burns.	(35)
Manuka honey incorporated cellulose acetate nanofibrous mats: Fabrication and in vitro evaluation as a potential wound dressing	Manufacture honey loaded cellulose acetate nanofibrous mats by electrospinning in order to evaluate their antibacterial activity and cytocompatibility.	(36)
Honey-based PET or PET/ chitosan fibrous wound dressings: Effect of honey on electrospinning process	Electrospinning solutions of polyethylene terephthalate, chitosan and honey to obtain possible wound dressing materials.	(36)
Fabrication and hemocompatibility assessment of novel polyurethane-based bio-nanofibrous dressing loaded with honey and Carica papaya	To determine the physicochemical and hemocompatibility properties of a new bio-nanofibrous dressing by electrospinning, based on polyurethane loaded with honey and Carica papaya fruit extract, to aid in the management of burn injuries.	(37)
Fabrication and characterization of nanofibers of honey/ poly (1,4-cyclohexane dimethylene isosorbide trephthalate) by electrospinning	Manufacture new nanofibers using natural honey incorporated in poly (1,4-cyclohexane dimethylene isosorbide trephthalate) for possible application as a wound dressing.	(38)
Electrospinning for wound healing and tissue engineering*	Obtain coaxial nanofibers with a shell of PVA / PEO polymers and honey core, with silver or magnetic iron nanoparticles with antibacterial action and biofilm control, as possible materials for wound healing and tissue engineering.	(39)

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Hybrid electrospun PHBV/ Aloe vera and PHBV/Honey nanofibers are scaffolds for rat dorsal root ganglion neurite outgrowth and guidance as well as for the regeneration of mouse skin after wounding**	Check the in vivo effect of skin regeneration and neurogenesis caused by aligned and non-aligned electrospun matrices of pure PHBV [Poly (3-hydroxybutyrate-co-3-hydroxyvalerate)] and its combinations with aloe vera and honey.	(40)
A Novel Honey-Based Nanofibrous Scaffold for Wound Dressing Application	Manufacture an electrospun nanofibrous dressing from mixtures of PVA and honey with incorporated Dexamethasone (Dex-P) to reduce inflammation in the wound.	(41)
Potential of Manuka Honey as a Natural Polyelectrolyte to Develop Biomimetic Nanostructured Meshes With Antimicrobial Properties	To develop a novel antibacterial system, based on honey-loaded biomimetic meshes for the treatment of soft tissue infections.	(42)
Manuka Honey Reduces NETosis on an Electrospun Template Within a Therapeutic Window	To examine the effect on neutrophil NETosis response and wound preconditioning of electrospun templates with honey.	(43)
Pine honey–loaded electrospun poly (vinyl alcohol)/gelatin nanofibers with antioxidant properties	Obtain bioactive fibers from PVA, gelatin and pine honey with potential application in biomedicine and active food packaging.	(44)
Comparison of silk fibroin electrospun scaffolds with poloxamer and honey additives for burn wound applications	Build an inexpensive and biodegradable dermal regeneration template from silk fibroin with additives such as poloxamer 407 and honey for burn wounds.	(45)
Impedimetric aptamer based determination of the tumor marker MUC1 by using electrospun core-shell nanofibers	To develop a new and improved method for the diagnosis of breast cancer, by manufacturing a sensitive biosensor with honey nanofibers for the detection of the protein marker for breast cancer MUC1.	(46)

doi: 10.25100/iyc.v26i1.12811

An Impedimetric Immunosensor modified with electrospun core-shell nanofibers for the determination of carcinoma embryonic antigen	To manufacture a novel electrochemical immunosensor based on core-shell nanofibers based on honey, gold nanoparticles and carbon nanotubes, for the determination of the tumor biomarker: carcinoma-embryonic antigen (CEA) and the clinical diagnosis of cancer.	(47)

*Poster summary **Conference-summit

Original title	Objective / application	Reference
Electrospun polyvinyl alcohol-honey nanofibers	Manufacture polyvinyl alcohol (PVA) and honey nanofibers by electrospinning to obtain fibrous meshes with excellent mechanical properties	(48)
Repositing electrospun nanofiber membranes with incorporated honey to provide anti-oxidant, anti-bacterial and anti-inflammatory microenvironment for wound regeneration	To develop a wound dressing system with antioxidant, anti-biofilm and anti-inflammatory properties, from a nanofibrous matrix loaded with little honey, for the clinical treatment of the wound microenvironment	(49)
Fabrication of pomegranate/ honey nanofibers for use as antibacterial wound dressings	Develop a new nanofibrous dressing with pomegranate peel extract, bee venom, honey and PVA, for use as antibacterial wound dressings	(50)
Honey/Chitosan Nanofiber Wound Dressing Enriched with Allium sativum and Cleome droserifolia: Enhanced Antimicrobial and Wound Healing	Develop new electrospun nanofiber dressings based on high concentrations of honey, chitosan and PVA, enriched with natural extracts to improve antibacterial activity and wound healing	(51)
Honey loaded alginate/PVA nanofibrous membrane as potential bioactive wound dressing	Manufacture a nanofibrous membrane of honey, alginate and PVA using electrospinning as a dressing for wound recovery	(52)
Apitherapeutics and phage-loaded nanofibers as wound dressings with enhanced wound healing and antibacterial activity	To develop ecological dressings based on nanofibers of honey, PVA and chitosan, which exhibit a high capacity for wound healing and powerful antibacterial effects	(53)

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Microbicidal nano- and meso-polymer fibers produced from polymers and honey, for textile applications Patent number: WO2008049251⁺	Obtain, by means of extrusion, antimicrobial electrospun fibers of polymers and honey (in solution or microcapsules) for the control of infections at the physiological site and the application of fibers for sportswear	(54)
Hybrid aloe vera nanofibers: Hybrid nanofibers of honey and synthetic polymer Patent number: WO2017153619A1⁺	Manufacture nanofibers with honey to allow the regeneration of nervous tissue, return the sensitivity of the organ or system where this tissue is present; design nanofibers for the construction of bandages and dressings in the healing of injured skin and for the manufacture of tubular nerve reconnection prostheses.	(55)

⁺Patent

In the study by Naeimi, A. et al. (1) Nepeta dschuparensis extract was added to chitosan fibers, PVA and honey. This biocomposite facilitated cell attachment and proliferation, characteristics of a material applicable as a dressing for tissue engineering. Fibrous meshes loaded with Nepeta dschuparensis presented an improved capacity to induce a higher percentage of wound closure, compared to clean polymeric fibers loaded with honey or with medicated cream, silver sulfadiazine. The work of Naeimi, A. et al. (1) demonstrates that the addition of the plant extract promotes great advantages for the renewal of skin tissues, due to the total strengthening of the antibiotic and antibacterial properties with natural agents. In a similar investigation by Arunpandian, B. et al. (10), extract of Carica papaya was incorporated into the electrospinning of polyurethane (PU) fibers and honey, demonstrating that the addition of fruit extract influenced a smaller fiber diameter, due to its effect on the physical properties of the solution being electrospun. The thin nanofibers facilitated the proliferation and spread of skin cells, such as fibroblasts and keratinocytes (10). As such, the trend of designing functional materials based on synthetic polymers and natural agents has spread (6), in order to maximize their wound healing power.

In the study by Abou, S. et al.(33), a new fibrous wound dressing was developed based on honey and powdered pomegranate peel extract. Pomegranate peel residues were used for electrospinning because they are a major source of polyphenols compared to the fruit juice. The abundance of polyphenols is responsible for the therapeutic effect of the materials designed with these extracts. Additionally, the use of residual biomass is interesting to reduce waste at the environmental level and its use in scalable research processes.

For the design of electrospun dressings for the treatment of wounds, the high potential of plants is being exploited as alternatives for the treatment of diseases. As part of the materials research, an analysis of the phytochemical profile of each species is carried out and the raw materials with the highest content of therapeutically active biomolecules are used. Likewise, the medicinal properties of garlic (Allium sativum) and the plant species Cleome droserifolia have been used for the design of nanofibrous dressings. Garlic is known for its potential for treating infections due to its broad antibacterial activity against gram-

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positive, gram-negative and resistant bacteria. Garlic's antiseptic activity is attributed to the content of sulfur compounds soluble in both water and oil (56). Cleome droserifolia on the other hand, contains compounds such as phenols, flavonoids, terpenoids and alkaloids, used as anti-inflammatories, antioxidants and antibacterials; therefore, they are good wound healing agents (20). Fibers were made with natural extracts of garlic and Cleome in order to enhance the antibacterial activity of the PVA honey and Chitosan HPCS nanofibers. In general, the addition of plant extracts to the honey fibers increased their antibacterial activity, resulting in better results compared to the commercial dressing AquacelAg®.

Table 4. Natural extracts and other functional agents used for the design of fibers with honey for biomedical applications.

Type of honey/ Therapeutic agent	Other functional agents	Reference
Extract Nepeta dschuparensis	None	(35)
Regional honey	Dex-P	(41)
Indian Dabur honey (commercial)	Ningunone	(49)
-Lyophilized multifloral honey Pomegranate Peel -Extract Powder	Bee venom	(50)
Manuka honey(MH)	Poloxámer 407	(45)
-Clover honey -Extracts of bee venom and propolis	Bacteriophage Myoviridae Stock Solution	(53)
-Manuka honey -Carica papaya fruit extract	None	(37)
Aloe vera	None	(40)
MH	None	(43)
Pine honey	Gelatine	(44)

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-Reginal honey -Gold nanoparticles -Multiple-walled Carbon nanotubes	Biomarker for breast cancer, MUC1	(46)*
(MWCNT)	Carcinoma embryonal antigen	(47)*
Acacia honey	None	(48)
Clover honey	Extracts: -Allium sativum -Cleome droserifolia	(51)
Acacia honey	None	(52)

* In these investigations, fibers with honey were not used as materials for dressings, but for the manufacture of biosensors for the clinical diagnosis of cancer.

Polymers used for electrospinning with honey

Different polymers of both synthetic and natural origin have been used for electrospinning of fibers with honey (Table 5 and 6). The polymers mostly mentioned by the authors are described for their versatility for electrospinning with honey.

Polyvinyl alcohol (PVA): it is a polymer of synthetic origin, biocompatible, biodegradable, soluble in water; by Naeimi, A. et al.(1) its hydrophilic nature makes it suitable for electrospinning of fibers in aqueous solution and with hydrophilic agents such as honey, while promoting a humid environment in the wound (10). It is a polymer approved by the FDA for the development of medical materials such as dressings, due to its swelling capacity, its null toxicity and high elasticity, which allow the obtaining of uniform fibers without defects.

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Table 5. Characteristics of the polymers and solvents used to obtain fibers with honey.

Polymer		Solvent	References
PVA Chitosan	Average M_w 400 KDa	Aqueous extract of Nepeta dschuparensis	(35)
Chitosan PET	Average M_w; ADD: 85% MW: 49,500 g/mol	Trifluoroacetic acid (TFA)	(36)
	Medical grade	-N,N	(37)
PICT	99.8% with 70% mol isosorbide (99.8%)	99.9% TFA: Chloroform (1:3)	(38)
PCL	M_w: 82 KDa	Chloroform solution: formic acid (70:30 v/v)	(42)
Silk fibroin (Bombyx mori)	Cocoons		(45)
	-		(43)
PVA	M_w: 72,000 g/mol 99% hydrolyzed	DMF	(46)
-Chitosan -PVA	-M_w: 240 KDa; 84% ADD -M_w: 85 KDa	Aqueous glacial acetic acid solution (99-100%)	(51)

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-Alginate -PVA	M_w: 99% 80.000- 120.000 98-99% hydrolyzed	Distilled water	(52)
-PVA -Chitosan	- M_w: 85 KDa -M_w: 240 KDa	1% acetic acid	(53)
Cellulose acetate	Content in weight: ~ 40% M_w 30.000	99.5%Acetone 99.8%DMF	(57)
PVA	M_w: 195,000; 4300; 98% hydrolyzed -M_w: 72.000 g/mol -In particles (1750 ± 50) -M_w: 89–98 KDa; 99% hydrolyzed ~1,250,000 Mowiol 20–98	Distilled water	(41,47–50)
PVA y gelatine	-	80% acetic acid and wáter 7:3 v/v ratio	(44)

Chitosan: It is a natural polymer obtained from chitin present in the exoskeleton of crustaceans (4,8). Chitosan has been used for electrospinning of fibers with honey due to its high biocompatibility, biodegradability, its antimicrobial and healing properties and the ease with which it promotes cell growth and regulation (1,17).

The polycationic nature of chitosan contributes to the antibacterial effect, by affecting the surface membranes of bacteria, causing leakage and cell death (19). Electrospinning this polymer with honey has been shown to lead to increased fiber diameter and hinders its conversion to fibers. Therefore, to improve fiber morphology, it is necessary to add surfactants and combine chitosan with other polymers such as PVA (13,17,58).

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Table 6. Polymers and solvents used in patents for electrospinning of fibers with honey.

Polymers	Solvents	References
PHBV, PLLA, PDS, Biodegradable thermoplastic polyurethanes, PLGA, PHAs, PPC, among others	Hexafluoride-2-propanol (HFIP), PVA, 1% acetic acid, TFA	(59)
polyesters, polyolefins, polycarbonates, polyurethanes, natural rubber, polycarboxylic acids, polyethylene oxides, poly-N-vinyl pyrrolidone, hydroxymethylcelluloses, among others[26]	Water and suitable organic solvents depending on the nature of the polymer	(26)

Sodium alginate: it is a natural polymer present in the cell walls of brown marine algae and to a lesser extent, produced by biotechnology. It is a biocompatible and biodegradable anionic polysaccharide. Electrospinning of alginate with honey has been possible, as long as it is accompanied with another polymer, given the deficiency in chain entanglements which hinder its mechanical resistance, in addition to its high surface tension and high conductivity. Like PVA, it is a hydrophilic compound that facilitates humid conditions to absorb exudates from wounds(60).

Techniques reported for production of nanofibres with honey

Honey fibers have been obtained by different electrospinning techniques, among them electrospinning by needle, by centrifuge and coaxial. In Table 7 the parameters used by the various authors for different electrospinning techniques are presented. The system basically consists of subjecting a solution of synthetic and / or natural polymers to high voltage so it can be molded and collected in the form of fibrous strands. Thus fibrous nonwoven matrices are obtained with large ratio area / volume, significant permeability and high porosity (20). The technique offers the ability to predict and design in advance the morphology, composition and applicability of the fibers, to fit the needs of the investigation, while also allowing the control of fiber size to nanometric or micrometric scale by via the elecrospinning parameters (61). In most studies, the polymer fibers with honey were obtained by electrospinning needle. Table 8 showsare the parameters used in this technique by different investigators to obtain fibers with honey.

Other researchers have manufactured core-shell fibers by coaxial electrospinning, where honey has become part of the core and polymers as the shell or covering of the fibers (33). In this technique, a dual nozzle is used to connect two tubular conduits, one inside another, so that the honey flows internally while the crust of the nanofiber is formed towards the outside. The fibers give the possibility of releasing their content by diffusion through small pores or holes in the polymeric wall. Therefore, fibers with honey have been obtained by different electrospinning techniques such as: horizontal and vertical needle electrospinning, centrifugal electrospinning and coaxial electrospinning.

Core-shell fibers have a wide application in biomedicine for the controlled release of different therapeutic agents such as, but not limited to, drugs, antibiotics, growth factors, among others (15,27).

doi: 10.25100/iyc.v26i1.12811

It is interesting to highlight the wide application of honey in another nanomaterial manufacturing technology, which was related to the electrospinning technique. In the work of Mancuso, E.,2019 (15) they reported the design of a multilayer nanocoating with honey, by layer-by-layer (LbL) electrostatic assembly, as a nanofabrication technique that functionalizes molecules on surfaces.

Mancuso E. et al (15) exposed poly (ε-caprolactone) meshes to alternating electrostatic interaction between honey as polyanion and poly (allylamine hydrochloride) as polycation to form the layered structure. The result was functionalized biomimetic meshes for the administration of natural antibiotics derived from honey, in the treatment of soft tissue infections (15). Poly (ε-caprolactone) fibers were manufactured by centrifuge electrospinning (Table 7), a technique that allows the manufacture of nanofibers at large volumes in a short time for possible industrial application. This technique depends on process components such as the electric field and the centrifugal force (62). Different results and interesting applications are recorded as antecedents in the manufacture of polymeric fibers with honey. These advances are presented in Table 9; however, reserchers have voiced certain precautions on the subject, and these must be taken into account in order to successfully obtain fibers with honey by means of electrospinning.

Precautions to consider when obtaining electrospun fibers with honey

Honey fibers are highly soluble in water and much more so when the concentration of honey increments (58). As such, upon contact with aqueous media, they tend to degrade and lose their fibrous structure and stability. It is therefore very important that the scaffold is resistant, remains for a certain time without degradation in the wound, and in general that mechanical and therapeutic properties are retained. Reticulation or crisscrossing of fibers immediately after electrospinning not only prevents degradation of the honey fibers upon contact with aqueous media or ambient moisture, but also preserves the potential clinical scaffolding, facilitating the implementation of biological testing and analysis necessary to assess the applicability of the fibers. To prevent such degradation, researchers subjected the fibrous matrices to contact with agents that cause crosslinking of fibers and reduce its solubility. For example, in the work by Kadakia P. et al. (20), the scaffolds were completely wetted in methanol for 30 min, which allowed the randomly arranged primary silk fibroin chains to regain their secondary structure β, and the material lost its solubility in water. Besides methanol, it glutaraldehyde (GAH) has also been employed as another crosslinking agent. Sarkar R. et al. (28) subjected their electrospun fibers to contact with GHA vapors for 24 h.

In another study (19), fibers with vapors of the same compound led to meshes that were highly resistant to instant dissolution when in contact with saline aqueous media or with the wound itself. There was also a moderated release of the loaded active ingredient and the scaffold maintained its functionality until the completion of the healing process. This result is very important for further research because it also highlighted that the non-crosslinked scaffolds dissolved very quickly in the medium and did not contribute optimally to wound closure and total healing. Furthermore, crosslinking of fibers has been applied in more studies(19,60) all in order to improve the scaffold’s ability to handle exudate, facilitate the constant release of active principles and provide a compact fibrous structure. However, this procedure must be practiced with caution and in a balanced way, since evidence shows that an increased degree of polymer crosslinking interferes with the movement of the bioactive molecules, which are trapped in the entangled chains within the fibers, limiting its functionality (19). Moreover, care must be taken in establishing the concentration of honey in fibers for its application as dressings in tissue regeneration.

doi: 10.25100/iyc.v26i1.12811

In the study carried out by Kadakia P. et al.(20) it was indicated that by means of in vitro tests, Manuka honey at 5% v/v or more caused cell death, possibly due to the acidity that honey gives to the medium.

Table 7. Electrospinning techniques and parameters to obtain fibers with honey.

Technique	Polymers electrospun with honey	Electrospinning parameters				References
		Voltage (kV)	Injection velocity (ml/h)	Needle – collector distance (cm)	Other parameters	
Electrospinning by centrifugue	PCL	20	1.5	20	T_a	(42)
Vertical electrospinning by needle	PVA	20	0.3	10 cm below the needle	-	(49)
	PVA and gelatine	25	60	8.2–10.2	T_a %RH: less than 50	
Coaxial electrospinning	PVA	16	core-shell type fibers 1:3	12	-	(46) (47)

T_a. Ambient temperature; % RH. Relative percentage of humidity

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Table 8. Parameters for electrospinning by needle to obtain nanofibers with honey.

Polymers electrospun with honey		Voltage (kV)	Injection speed (ml/h)	Needle – collector distance (cm)	Other parameters	
		Electrospinning parameters				
Chitosan PVA	Fibers with Allium Sativum y Cleome droserifolia	27	0.5	13	Collection time: 4.5 h	(51)
	Fibers with extract of Cleome droserifolia	28	0.7	14	3.5 h	
PVA PET Chitosan	HPCS Fibers: miel, PVA, and Chitosan, with propolis and bee venom	27	0.5	15	-	(53)
	HPCS Fibers loaded with	27	0.5	13	-	
PVA, Chitosan		17	0.5	- Not reported	-	(35)
Cellulose acetate		15	0.7	2	25°C; %RH: 55%	
Chitosan	PET	high voltaje: data not	-	-	Collection time: 20-60 min	(57)
PUT		-PUT fibers: 16 kV	PUT Fibers: 0.70 ml/h	Biocomposite: 15 cm	-	(36)
PICT		10	-	12	-	(37)

doi: 10.25100/iyc.v26i1.12811

PVA	19	1.0	20	T_a	(41)
PVA	30	1.0	20	-	(48)
Silk fibroin (Bombyx mori)	25	4.0	18	-	(45)
PVA	16-22 kV	1 ml/ min	12	-	(50)
Any polymer selected according to patent	8 a 9 kV	2.5 y 2.8	Rotating collection Wheel at 10 cm	%RH: 60-70%	(55)
	25		20 cm	-	
Sodium alginate y PVA	15	0.4	10	-	(52)

T_a. Ambient temperature; % RH. Relative percentage of humidity

Table 9. Background on promising results for electrospun honey fibers.

Advances	Interesting results	Applications	References
Synergie between honey and natural extracts	The addition of natural extracts to honey nanofibers contributes significantly to tissue regeneration.	The addition of honey and plant extracts to the electrospinning solution improved the percentage of wound closure. Plant extracts were shown to enhance cell binding and proliferation.	(35) (51)
Biodegradable materials	Nanofibers of different polymers and honeys were obtained that were highly degradable and facilitated the controlled and continuous release of honey, as well as cell viability.	This material has potential application for biodegradable and biocompatible dressings apt for the care of the environment.	(57) (52)

doi: 10.25100/iyc.v26i1.12811

Fibers with reduced diameter	The addition of honey facilitates the electrospinning process by improving the electrical conductivity of the solution, obtaining thin fibers.	Fibers with a smaller diameter favor the mobility and development of cells such as fibroblasts and keratinocytes, with greater applicability in tissue engineering.	(36)
Hemocompatible material and with optimal porosity	The bio-nanofibrous mesh with honey allowed the development of fibroblasts, an environment permeable to oxygen and a high biocompatibility with blood cells. Delayed coagulation relative to polyurethane-only fibers.	Nanofibroses with a high percentage of porosity, an optimal pore size, and a low hemolytic index favor the conditions for sustained wound regeneration and greater compatibility with erythrocytes.	(37)
Material with good mechanical properties	The honey content contributed to good fiber elasticity and wettability.	The fibers with high elasticity allow for betterhandling handling and more adaptability of the dressing to the affected area. In addition, being easily wettable there is a more effective control of exudate.	(38)
Control of exudate	The moisture retention capacity of the fibers was increased with the addition of honey	Scaffolds composed of silk fibroin and Manuka honey modulated moisture retention. With this material you can have a better management of exudate in wounds.	(45)
Honey fibers for controlled release of drugsFibras de miel para la liberación controlada de medicamentos	The honey allowed the successful release of the anti-inflammatory and improved the antibiotic properties of the dressing without interfering with the activity of the drug.	The materials based on honey fibers and loaded with medicines are conducive to the dressing and regeneration of different types of wounds.	(41)

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Honey fibers for controlled drug release	Honey was used as an antibacterial coating on electrospun polycaprolactone fibers, demonstrating that the use of honey lends itself to other nanofabrication tools such as layer-by-layer electrostatic assembly (LbL).	The nanofunctionalization strategy allows the manufacture of biomimetic fibrous meshes that imitate the structure of the extracellular matrix, being support for cell development and allowing the design of cutting-edge medical devices.	(42)
Low concentrations of honey more effective for the microenvironment of the wound	Honey in low percentages drastically decreased inflammation in vivo, a limiting stage in the progress of healing.	The application of honey through dressings was achieved to overcome the real insufficiencies of the cellular microenvironment of the wound, as an alternative to the use of honey directly on the affected skin and at its high concentrations.	(49)
Application for the clinical diagnosis of cancer in its early stages	Nanofibers with honey were deposited on an electrode for the construction of a biosensor for clinical diagnosis of cancer in serum. The method was simple and adaptable to clinical needs.	The impedimetric immunosensor was useful for the determination of embryonic carcinoma antigen (CEA).	(47)
		The biosensor obtained allowed the monitoring of cancer therapy, through the detection of the protein breast cancer marker MUC1.	(46)
Competitiveness compared to commercial dressings	Honey dressings added with propolis and apitoxin were more effective than the commercial AquacelAg® scaffold against multi-resistant bacterial strains: - Pseudomonas aeruginosa MDR - Staphylococcus aureus (MRSA)	Dressings based on three apitherapeutics were constructed for their potential application as broad spectrum antibacterial materials.	(53)

doi: 10.25100/iyc.v26i1.12811

Freeze-dried honey vs liquid honey. Use of residual biomass.	With lyophilized honey, fibers with improved morphology were obtained compared to liquid honey. The use of pomegranate peels becomes an alternative for the reuse of residual biomass at a scientific and industrial level.	The fibers obtained with lyophilized honey and pomegranate peel are an economic and potential alternative for the design of dressings, meeting environmental and sustainability challenges.	(50)

Obtained for wound healing using lower concentrations of honey such as 0.1 at 40%, but fundamentally due attention must be paid to the needs of the skin at the cellular level, so as not to incur honey saturation without it being necessary(63).

Regarding the handling of solutions to be electrospun, the increase in honey content caused a complex handling of the solution due to the high viscosity and low fluidity that it produces (61), and therefore, did not allow satisfactory expulsion from the syringe. Thus, Sarhan & Azzazy (61) reported a simple experimental step to achieve electrospinning of solutions with high honey content, between 25 and 30%. The mixtures of honey, PVA and chitosan were kept at rest for a week and then their electrospinning was easier. Therefore, the balance between the concentration of honey in solution and its controlled release from the fibers must be promoted, since if excesses are present, the risk of cytotoxicity increases.

Thus, in the investigations of Sarkar, R. et al. (28) and Mancuso, E. et al.(15), concentrations of honey were moderate, which not only did not result in cytotoxicity, but also supplied better antioxidant and anti-inflammatory needs for wounds. In these studies an experimental design was done under the premise that honey in high concentrations can negatively influence the cellular environment causing toxicity to smooth muscle cells, such as myofibroblasts or mesenchymal stem cells (34).

Techniques used for the characterization of fibers with honey

For the characterization of fibers with honey, different techniques have been used that allow to understand their composition, morphology, crystalline structure, mechanical, thermal properties, wettability, degree of swelling, water absorption capacity and weight loss. The characterization techniques and the results from obtaining electrospun fibers with honey are presented below.

Analysis of composition and chemical structure of fibers with honey

Fourier Transform Infrared Spectroscopy is a characterization technique that has the ability to provide the interactions of functional groups chemical structure of functional groups of materials such as those with polymers in their composition. For fibers electrospun with honey it is important to recognize the characteristic FTIR bands of honey, since these signals will be necessary to observe the behavior of honey when it is incorporated lo cualinto fibers by electrospinning.

The bands mentioned are: 3384 cm^{-1} (-OH), 2936 cm^{-1} (CH), 1637 cm^{-1} (CO) and 1057 cm^{-1} (CO) (32). The chemical composition of the electrospun honey fibers has been confirmed

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by means of this technique and on a smaller scale by X-ray photoelectron spectroscopy or XPS. As per the study carried out by Naeimi, A. et al. (1), the FTIR spectra of chitosan and PVA fibers were analyzed in contrast to electrospun fibers with natural compounds such as honey and a phytoextract. For the fibers loaded with honey, CH bands belonging to the honey carbohydrates and polysaccharides of the Nepeta extract were observed, while in the FTIR spectrum of the polymeric fibers, only bands of functional groups of polymers were observed, such as CO and C=C of PVA, NH_2 and OH chitosan.

The intensity of the C-H bands increased when incorporating honey and Nepeta;, hence,confirming the incorporation of the natural compounds in the fibers was confirmed; there was chemical interaction between the hydroxyl (-OH) and amine groups ($-NH_2$) of chitosan and PVA with functional groups of honey and Nepeta, forming hydrogen bonds between them. Likewise, the study carried out by Khan, M. et al.(6,64) comparing the spectra of the PICT fibers Poly (1.4 cyclohexane dimethylene isosorbide terephthalate) with and without honey, confirms the incorporation of the apitherapeutic in the fibers. In the FTIR analysis, for the clean poly(1,4-cyclohexane dimethylene isosorbide trephthalate) (PICT) fibers, a characteristic band of aromatic compounds was obtained due to the presence of terephthalate and a C=C double bond stretching. In contrast, in the spectrum of the fibers with honey, these bands disappear and instead the interaction between O, C and H is evidenced, with the appearance of bands of single bonds for CO at 1270 cm^{-1} and at 1850 cm^{-1} for CH.

In turn, the PICT and honey fibers were analyzed by XPS spectroscopy. An N1s peak was observed whichthat affirms the interaction between honey and the polymer; however, this band was not visible in nanofibers without honey. (6), and the incorporation of honey and its chemical interaction with the base polymer was again evidenced. Depending on the application for which the loaded honey fibers and other natural components are to be used, it is not highly recommended that a strong bond is formed between these and the polymers, because the release of the therapeutic components into the environment is difficult, decreasing its effectiveness in the affected area. As such, the study by Sarhan & Azzazy (34)shows that when making an FTIR analysis of fibers, did not evidence the formation of bonds or chemical union between propolis and bee venom with honey fibers, PVA and chitosan. This low interaction between fiber components facilitated the constant release of the apitherapeutics, after the degradation of the polymeric fibers.

An important piece of data is also presented in the research by Paimard, G. et al. (22,28) with evidence of the incorporation of honey as a core in PVA fibers obtained by coaxial electrospinning. In the spectrum of these core-shell fibers, only the characteristic PVA bands are present, while the honey bands are not visible. This is an interesting way of confirming the successful coating of the polymer towards the honey core and the shell-core arrangement of the fibers.

The correct incorporation of different concentrations of honey in PVA fibers was also evidenced by FTIR analysis in the work of Sarkar R. (28) The successive addition of honey to the fibers was identified as the concentration of honey was higher, by increasing successive band intensity in the spectrum. Tang, Y. et al.(32) also obtained a similar result regarding the increase in the area under the curve of the characteristic bands of honey, as its content was higher in alginate and PVA fibers; due to the increase in honey content from 5 to 20%, the intensity of the honey bands was greater. It is therefore possible to monitor the change in the concentration of honey in fibers through FTIR analysis.

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Thermogravimetric analysis (TGA) of fibers with honey

The thermal stability and strength of honey electrospun fibers were also analyzed. In the research by Arunpandian, B. et al. (10), the bio-nanofibrous membrane of polyurethane, honey and Carica papaya extract presented a greater weight loss compared to polyurethane fibers, due to a higher quantity of hydrophilic molecules, with the researchers reporting that the presence of honey and the fruit extract contribute to the thermogravimetric stabilization of the fibers.

A study conducted by Fatma Nur, P. et al. (19) indicates that the thermal stability profiles of polyamide 6/honey and composite fibers containing boric acid at different concentrations were observed. three stages of Weight Loss for polyamide 6 fibers. A small and a larger mass loss will be observed in the temperature range of 57 to 250 °C and 343 to 518 °C, respectively. The initial stage represents the evaporation of water with a weight loss of 2.9% in the temperature range of 57 to 250 °C. The second stage, with a significant weight loss of almost 94% at 343-518 °C, was caused by the degradation of the polyamide backbone macromolecule. The third step is formed after the change of atmosphere from N2 to O2 at 600 °C. It also indicates that the addition of honey changed the decomposition behavior of pure polyamide 6 fibers. PA6-HB0 fibers showed four decomposition steps related to the presence of more hydrophilic groups [58]. The first and second degradation stages were formed together between 103 and 216 °C and 216-286 °C with a weight loss of 8.7% corresponding to the loss of water molecules from PA6 and the volatile content of honey. . . It is clear that the PA6 sample exhibited higher thermal stability compared to PA6H-B0 fibers. This determining the lower thermal stability of electrospun polyurethane fibers loaded with honey and Carica papaya fruit extract compared to pure polymeric fibers. The TGA clearly shows that nanofibers made from honey exhibit good thermal stability below 195 °C, which is higher than polyvinyl alcohol/chitosan fibers incorporated into honey (120 °C). (65)

The study of Naeimi, A. et al. (1) determines the thermal characteristics of the PVA/Chit nanocomposite and the PVA/Chit@Nep/honey nanofibers were obtained using TGA. In TGA curing of PVA/Chit nanocomposite, there are two degradation stages. The first weight loss began at 250 °C starting temperature in relation to the melting point of PVA. The second degradation occurs at 350 °C, which corresponds to chitosan. On the other hand, these two steps exist and in TGA of PVA/Chit@Nep/Honey and considering the carbon residue it is shown that the honey component acted as a good carbon insulator in the polymer matrix. In TGA of PVA/Chit@Nep/Honey nanofibers, it appears that the formation of carbon particles of honey layered structure in the network of PVA and chitosan that resembles carbon. In fact, this carbonization-like layer acted as an effective barrier for oxygen permeation improving the carbon residue. The presence of crystalline structure and the great compactness between honey and the Nepeta dschuparensis plant and the PVA/Chit matrix lead to high thermal stability of this bio nanocomposite (66).

Morphological analysis of electrospun fibers with honey

Honey Fiber size

Different results have been reported regarding the size of fibers electrospun with honey, as they are analyzed mostly by Scanning Electron Microscopy (SEM) and to a lesser extent by Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) (1,10). In some studies, the inclusion of honey has caused the fiber diameter to increase, but elsewhere honey has influenced the fiber size to decrease. In the work by Arunpandian, B.

doi: 10.25100/iyc.v26i1.12811

et al.(10) the diameter of the polyurethane nanofibers was distributed between 200–650 nm, but with the addition of honey and Carica papaya extract it decreased between 60–260 nm. The addition of honey and natural extract changed the viscosity and conductivity of the solution due to the addition of hydrophilic species that contribute to an improvement in the electrical condition of the solution. Thus, the electric charge density in the electrospinning system was increased, which allowed some instability and a wide stretching of the precursor jet to the formation of fibers. The study by Maleki, H., et al.(14) manifests the same trend, with a decrease in fiber diameter from 446 to 220 nm when adding honey to PVA solutions, which is highlighted by the increase in conductivity. Furthermore, in the research by Kadakia, P. et al. (20) the silk fibroin meshes with honey presented diameters that varied from 2.4 to 5.9 µm and the pore areas between 68.4 to 365.4 µm2. However, at a higher concentration of honey, the effect of viscosity in reducing the fiber size began to be verified, because the diameters and pore area actually decreased. Similarly, in the manufacture of fibers based on PET, chitosan and honey, the fiber size was slightly decreased from 780 nm to 668 nm, by increasing the honey content from 10 to 40%.[6] Sarkar, R. et al. (28) found the same tendency when electrospinning PVA and honey fibers, where the diameter of the fibers with 0.5% honey was 280 nm, even thinner than PVA-only fibers with an average size of 300 nm.

Another parameter that influences the fiber size is the polymer concentration, whereby decreasing the fibroin concentration means thinner fibers were obtained with a smaller pore area (20). In addition to the fluctuations in the conductivity of the solution, there are other parameters that can make it possible to obtain smaller fibers. Sarhan & Azzazy (61) report that an increase in the applied voltage, changing the distance between the tip and the collector, increasing the solution temperature or lowering the injection speed directly decrease the diameter of the fibers. On the other hand, the fiber diameter of PICT increased with the addition of honey at increasing concentrations from 10 to 20%. The fiber size increased from 328 nm to 482 nm on average, compared to PICT fibers without honey, which resulted in an average diameter of 190 nm.

The difference in diameter between the fibers with honey and the polymeric fibers without honey can be used as an indicator to verify the successful incorporation of honey into the fibers (6,9). By means of coaxial electrospinning, it was possible to obtain PVA and honey fibers with diameters less than 100 nm, that is, nanofibers of honey (20,34). For this reason, using this method of electrospinning significantly decreased the size of the core-shell fiber with honey as a core. In the design of fibers for scaffolds, the scale of natural collagen fibers in the range of 50 to 500 nm must be taken into account.

The fiber sizes obtained in the aforementioned investigations mostly adjust to the optimal diameter range to imitate collagen dregs and allow skin regeneration very similar to the original (20). According to this, it is also reported (1) that fibers with a diameter between 250 and 300 nm, based on PVA, chitosan and three apitherapeutics, favored cell proliferation in a more efficient way, in contrast to fibers with 1 µm in diameter. Therefore, the importance of achieving a nanoscale fiber size is notable, with the incorporation of conductive solvents or salts[13] for a greater affinity with cell dimensions in vivo.

Another interesting fact is that obtained by Abou, S. et al.[11] who obtained fibers with powdered or lyophilized honey, with a finer and more uniform diameter, compared with fibers from liquid Manuka honey. Freeze-dried honey has its components in a higher concentration since it has 20% less moisture content, which makes it a good alternative to increase the therapeutic potential of polymeric fibers (19).

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On the other hand, the incorporation and concentration of biologically active molecules in the solution to be electrospun has also influenced the size of the fibers from honey, as presented below.

Fiber morphology with honey

In this space, real results were captured about the effects that the addition of honey had on the morphology of polymeric fibers and that the researchers analysed by SEM, TEM and AFM microscopies. The researchers obtained smooth fibers from the PICT polymer only, but by incorporating honey, the fibrous surface was more rough. On the other hand, in the same study, the researchers reported that up to a maximum of 20% honey, fibers were formed without beads, with the fiber beads increasing at higher concentrations. It was found that PVA nanofibers without honey presented a homogeneous morphology, but when adding honey at 20% (v/v) the morphology was less uniform, with a wide distribution of diameters (32). Similar results were presented[4] with a honey concentration of 40%, when beading and spindles formed in the fibers. These fibers were also observed with an AFM microscope presenting smooth and uniform surfaces with a cylindrical structure in all weight ratios (10). However, when the honey content was at 40%, beads or spindles began to form. In the study by Naeimi, A. et al. (1), fiber magnifications were obtained by TEM and confirmed the presence of spherical honey particles and Nepeta extract in the fibrous PVA and chitosan meshes. The distribution of the honey particles was random and contributed to a higher roughness in the fibers.

The concentration of honey is an important factor that affects fiber morphology. Sarkar R. et al (28) used in their research minimum honey concentrations such as 0.2 and 0.5%, obtaining PVA and honey fibers with a dense, smooth and homogeneous arrangement and without defects such as beading. When increasing the content of honey there were no significant differences, therefore estimating that the minimum changes in the concentration of honey do not alter the morphology; however, at very high concentrations such as 40%, the effect of the concentration of honey is important. The study by Abou, S. et al.(33) also reported obtaining fibers with a totally cylindrical structure, a smooth surface and no beads. In this work, the increase in the concentration of honey with values of 10, 20 and 25% did not affect the shape of the fibers. It should be noted that these fibers were also electrospun with pomegranate juice, bee venom and lyophilized honey, components that could influence the homogeneity of the fibers.

On the other hand, the study carried out by Sarkar, R. et al (28) indicates an unusual result when it comes to fibers with honey. Flattened fibers were obtained with a concentration of 1% honey. It is reported that this morphological change is due to the high viscosity of the precursor solution, where the rapid evaporation of the solvent is prevented and consequently the fibers reach the collector wet and flatten on impact.

Porosity of fibers electrospun with honey

The measurement of fiber porosity is very important in wound healing dressings because high porosity allows perspiration, gas exchange between the external environment and that of the wound, and maintains oxygenation and humidity while allowing the diffusion of exudate, and so aids the necessary conditions for correct healing (9). The abundance of pores in the fibrous mats promotes the aseptic state of the wound, as it prevents the emergence of infections and attack by bacteria (10). The dressing must be designed to a specific porosity since the pore size will allow the accommodation and proliferation of cells of a certain size.

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In some investigations of electrospinning with honey, the researchers have managed to obtain fibers with adequate porosity to aid in wound healing. For example, the fibrous polyurethane mesh, extract of Carica papaya and honey (10), presented an average pore size of 12.54 μm and a distribution between 4 and 50 μm. This porosity is optimal for the deposition of fibroblasts because the cells themselves need a range of 5 to 15 μm to proliferate (10). For their part, the work by Maleki, H. et al.(14) referes to the manufacture of a dressing of PVA with honey with a porosity value of 81.43%, an optimal percentage to facilitate constant wound healing.

Mechanical properties of fibers with honey

Tensile strength of honey fibers

Fibers electrospun with honey have also been susceptible to mechanical characterization. Properties such as tensile strength, contact angle, wettability and hydrophilicity have been evaluated. The tensile test is carried out by subjecting an elastic material to a longitudinal tensioning force, until breakage or irreparable deformation occurs. From this test, Young's Modulus is obtained, which refers to the maximum force that the material can withstand until it breaks.

It has been found that the addition of honey in polymeric fibers contributes to the decrease in the tensile resistance of the material. Thus, in the study by Ullah, A. et al. (6), it was reported that the resistance to breakage of cellulose acetate nanofibers loaded with honey was lower than their resistance without honey. X-ray diffraction analysis showed that the inclusion of honey in the fibers changes the crystalline structure of the polymer. The backbone of the polymer deteriorates, the molecules lose their linearity, the polymer chains become disfigured and therefore the tensile force that the material can withstand decreases. In this case it was shown that the honey and the cellulose acetate did not form chemical bonds, but rather that the honey was mechanically trapped in the polymer; this behavior made the fibers susceptible to breakage. In the investigation of Khan, M. et al.(64) there are results that agree with those of Ullah, A. et al.(6) The polymeric fibers of PICT presented a Young's Modulus of 6 MPa and this decreased to a value of 0.7 MPa when the honey content increased from 10, 15 to 20% by weight. Therefore, the tensile force decreases as the concentration of honey increases.

Effect of honey content on the elasticity of electrospun fibers

In the study carried out by Khan, M. et al. (64) the percentage of deformation in the fibers was greater with increase in honey content. This percentage ranged from 9 to 45%. The fibers with 15% honey presented satisfactory mechanical properties with 45% elasticity and a Young's Modulus of 2.7 MPa. This indicates that the highest percentage of honey is not always the most suitable for the design of a dressing with good mechanical properties; the balance between tensile strength and elongation capacity making the handling of the wound dressing more comfortable. In agreement with the mechanical tests results from PICT fibers and honey obtained by Khan, M. et al. (64), where the fibers with a 15% concentration of honey presented the most adequate mechanical properties, the study carried out by Ping & He (25) states that a high concentration of honey in PVA fibers is needed to achieve satisfactory mechanical properties, that is, greater than 7.5% by weight.

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Contact angle and wettability of fibers with honey

The water contact angle measurement is used to evaluate the hydrophilicity of materials, while the water absorption capacity is a fundamental property of the wound dressing, useful in improving the wound recovery process (10,32). It is possible to verify that the material actually retains moisture and therefore has good wettability, causing a better exudate management and reduction of the time for dermal fibroblasts to adhere, migrate (6) and spread through the affected area (20).

Ullah A. et al. (6), observed that when electrospinning cellulose acetate with honey, the contact angle decreased and so the fibers were more hydrophilic. Arunpandian, B. et al. (10) confirmed something similar in their research by adding honey and Carica papaya extract to the polyurethane nanofibers, a decreased contact angle indicating that the fibers are wettable. This behavior is justified by the presence in the solution of a greater number of hydroxyl groups (OH-) and hydrophilic biomolecules in general.[15] Therefore, when adding honey, the hydrophobicity decreased as confirmed by Khan, M. et al.(2)

In contrast, Kadakia, P. et al. (20), confirmed an increase in the contact angle when adding Manuka honey to silk fibroin fibers. This generally unexpected effect manifests when the glucose and fructose of the honey, partly responsible for the hydrophilic character of the fibers, are wrapped between the polymer chains without exposure to the fibrous surface. As a consequence, the hydrophobic behavior typical of silk fibroin was maintained, without being significantly affected by the presence of honey. Nevertheless, the honey scaffolds had contact angles of less than 90 °, which indicates that the fibers did have the ability to absorb and retain water.

Degree of swelling of the honey fibers

By means of the swelling capacity of the nanofibers, the scaffold's ability to absorb moisture, that is, exudates from the wound, is evaluated. The swelling behavior also controls the release of active principles or drugs towards the affected area,[2] it is an indicator of the material's breathability or its ability to allow the flow of water vapor (4). This measure is obtained by immersing electrospun fibers in phosphate buffered saline (PBS) at different time periods. Thus, when the fibers come into contact with the saline solution, they absorb moisture and their weight can be measured at the end of the process. This test has been applied in different investigations of fibers from honey and the researchers have obtained the following results: Sarhan, W. et al.(34) designed a fibers based on PVA, chitosan, honey and natural extracts, which presented a good capacity to swell, and so easily adhering to the affected area without the need for biological adherents. Also Sarkar, R. et al.[7] obtained similar results for PVA fibers and honey at different concentrations. The fibers with 0.5 and 1% honey showed swelling degrees of 5.7 and 6.0 respectively, higher than the fibers with 0.2 and 0% honey, with values of 4.9 and 3.7, meaning that the fibers with a higher percentage of honey had a greater capacity to absorb moisture. Taking into account that PVA is a polymer with good swelling capacity, the polymeric fibers incorporated with honey notably improved this property, due to the high osmolarity of honey due to its high concentration of sugars; therefore, the higher the osmolarity, the greater the capacity to absorb water.

On the other hand, silk fibroin scaffolds incorporated with Manuka honey demonstrated greater water absorption at 28 days, confirming the moisture retention effect that honey attributes to nanofibrous meshes (20); however, not in all cases did honey allow maximum water absorption. In the work of Sarhan, W. et al.(34), nanofibers of sodium alginate, PVA and variable concentrations of honey were obtained. By increasing the amount of honey,

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the fibers reduced their ability to absorb moisture. This effect is justified because honey is highly soluble in water and therefore the dressing was completely dissolved in an aqueous medium, losing the mesh structure and thus all its ability to retain water (34). Similarly, when manufacturing nanofibers based on PVA, pomegranate juice and honey at different percentages, Abou, S. et al.(33) found that scaffolds containing honey showed moderate water absorption compared to scaffolds without honey, which presented greater swelling capacity, probably because honey is very soluble in water and caused the degradation of the fibers. To solve this tendency, it might be necessary to subject the fibers to the crosslinking process for a longer time, to make the fibrous structure more resistant, compact and durable within an aqueous environment; however, it can be verified that the result of the swelling capacity of the fibers depends on the interaction of each polymer with the honey in the middle of an aqueous environment.

Fiber weight loss with honey

The weight loss test has also been implemented to characterize nanofibers with honey, since this is an indicator of the release of therapeutic components towards the wound and of the biodegradation of the material, due to the breaking of the polymer chains (13). Honey fibers have been susceptible to weight loss due to increased honey content, which more easily allows water to penetrate the fibers, followed by leaching, hydrolysis and dissolution of the polymer.

In three investigations the same results were obtained with honey and PVA fibers (13,58). These meshes generally exhibited good degradation properties, compared to PVA-only fibrous meshes. As such, the potential of honey-based fibrous materials for their application in dressings that fulfill their therapeutic function is confirmed, and in a moderate time they degrade and do not add to the polluting agents of the environment.

Effect of the solution parameters in obtaining fibers with honey

The effect of the physical characteristics of the electrospinning solution, such as polymer concentration, viscosity and conductivity, has also been studied to analyze its impact on the process of obtaining the fibers with honey. The influence of these solution variables on the ease and success of fiber formation with honey was analyzed.

Polymer concentration in solution with honey

The researchers demonstrated the effect of the polymeric concentration of PET and chitosan in fibers with honey (5). They supplied total concentrations of 17 and 19% w/v for either one of the polymers or both. At polymer concentrations below a weight of 19%, discontinuous, rolled and beaded fibers were obtained. By contrast, at a concentration above 19%, the electrospinning process was not carried out because as the viscosity of the solution increased, it was difficult for the solution to be expelled from the syringe (5). In the study by Paimard, G. et al.(21) also analyzed the effect of polymer concentration on the morphological quality of the fibers. These authors manufactured fibers based on honey and PVA by coaxial electrospinning **(**Table 7**)**. The polymer solution was used as the covering and the honey as the center or core of the fiber, and at a concentration of 10% PVA w/v, they obtained smooth and uniform nanofibers; by increasing the concentration to 20%, the fiber diameter was greater and the uniformity of the fibers decreased. Even with this result, more experiments were carried out with PVA concentrations greater than 20% w/v. The morphology obtained was of low quality and not very promising (21).

As a result, it is evident that the concentration of the polymer directly affects the morphology of the fibers. For this reason, the polymer concentration must be well balanced:

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not so low in order not to interrupt the formation of the Taylor cone that precedes the formation of the fibers and not so high to allow normal flow of the solution. Therefore, caution and knowledge of the effect of polymer concentration vs. morphology, must be exercised for the design of fibers with honey from polymers such as PET, Chitosan and PVA reported so far in the referenced articles.

Viscosity of the polymer solution with honey

In general, the viscosity of the polymer solution decreased as the honey content increased. In the work by Tang, Y. et al.(32) a solution to be electrospun of sodium alginate and PVA with 20% v/v of honey, presented a very low viscosity of 419 mPa·S, with respect to solutions with a lower honey content. This value led to the formation of bulbs in the fibers, so we can conclude it is necessary to control the viscosity values to have a better follow-up to the fiber morphology.

Maleki, H. and their work group (10,19) reported that the appearance of fiber defects is due to the fact that there was an increasing percentage of honey, which caused the polymer chains not to resist the stretching force from high voltage, and caused the fibers to take on a varied morphology throughout, i.e. accumulated polymer and very thin fiber parts.

On the other hand, it was shown that the addition of natural extracts to polymeric solutions with honey is useful to balance the viscosity of the solution and therefore facilitates the electrospinning process (19). However, if a solution with too low a viscosity is supplied, an unwanted dripping occurs at the tip of the needle, which does not allow the stretching of the jet or the subsequent formation of fibers. In contrast, Sarkar, R. et al.(28) achieved the opposite effect, with the viscosity increasing the higher the concentration of honey added. This little-known effect perhaps depends on the variety of honey, solvent or mixture of solvents as well as the nature and concentration of the polymer used in the research and its specific composition: The addition of honey to the polymer solution can provide different viscosity values and influence the morphology of electrospun fibers in a certain way.

Biological methods applied to evaluate the functionality of electrospun fibers with honey

Different biological methods in vitro and in vivo have been used to evaluate the potential of fibers with honey, in order to:

combat pathogenic microorganisms present in skin wounds, evaluate the ability to contribute to cell regeneration, and determine the antioxidant or anti-inflammatory potential, which all together promote wound healing.

Antibacterial activity of fibers with honey

The antibacterial activity of fibers with honey has been measured using the agar diffusion method, the dynamic contact method and the viable cell count technique.

It is necessary to evaluate the antibacterial and antibiofilm capacity of the materials that have the potential to be applied as dressings, since these must have the ability to combat the proliferation of bacteria in their early stage and prevent the formation of colonies that are precursors of infection, because these factors are also responsible for the chronicity of wounds in soft tissues (16). In the study carried out by Sarkar R. et al. (28), honey nanofibers with improved antibacterial activity against E. coli were obtained. The antibiofilm test also indicated that the nanofibers were able to reduce E. coli colonization by E. coli by 300%, by increasing the content of honey in the fibers.

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In another study it was found by means of the dynamic contact test, that PVA / sodium alginate and honey matrices significantly decreased bacterial growth depending on the dose of the apitherapeutic. In addition, the honey fibers that were incubated for 24 h, showed prominent antibacterial activity, compared with those incubated for 12 h only. This is an indication that the honey had enough time to continuously release and gave good antibacterial properties to the medium. In contrast, the fibers without honey content allowed the rapid development of S. aureus and E. coli after 24 h (32).

Although honey is an efficient antibacterial agent, its properties can be enhanced by enriching the fibers with natural extracts. This is how Abou, S. et al.(33) achieved a strong antibacterial effect against gram-negative (E. coli), thanks to the incorporation of pomegranate juice in honey fibers and PVA. For their part, in the research by Sarhan, W. et al.(61), electrospun scaffolds with honey and Allium sativum and Cleome droserifolia extracts provided complete protection against S. aureus and the resistant strain, compared to the commercial scaffold AquacelAg®.

The antibacterial activity of these extracts is due to the presence of thiosulfinates in Allium sativum and sesquiterpenes in Cleome. These components alter the cellular activity of bacteria, blocking their normal functioning.

Tang, Y. et al. (32), when evaluating the antibacterial activity of sodium alginate, PVA and honey fibers through the disk diffusion method, found that they were more active against S. aureus strains than against E. coli. Similarly, Sarhan & Azzazy (33) found that adding an apitherapeutic propolis agent to honey fibers provided greater activity against S. aureus when compared to the commercial AquacelAg® dressing. These results are consistent as it has been reported that honey has a better antibacterial effect against gram-positive than gram-negative bacteria(32).

Sarhan & Azzazy (33) found a way to broaden the spectrum of antibacterial effectiveness of fibers with honey by incorporating bee venom. By counting viable cells, they observed that these fibers allowed complete inhibition against E. coli, the honey matrices being effective against gram-negative as well as gram-positive strains. Furthermore, the antibacterial potential of these fibers was similar to that of the commercial AquacelAg® dressing for E. coli, but it showed improved activity against gram-positive strains: S. aureus and MRSA.

Contribution of electrospun fibers with honey in cell viability and tissue regeneration

Cytocompatibility studies have revealed that the addition of honey to polymeric fibers promotes the development of cells on scaffolds. Honey improved the biocompatibility of cellulose acetate nanofibers, by contributing to the mat's affinity with stem cells for their proliferation and propagation. Likewise, PCL fibers loaded with layers of honey were cytocompatible with different cell lines, such as skin fibroblasts and endothelial cells (16). In the work group of Kadakia, P.(20), honey caused the release of growth factors from human dermal fibroblasts, which totally infiltrated the electrospun silk fibroin meshes. The mats with honey showed a higher cell density after 28 days compared to the controls, and when compared to the commercial scaffold AquacelAg®, (19) high levels of viability and cell proliferation caused by the polymeric fibers loaded with honey and natural extracts.

Similarly, alginate, PVA and honey fibers showed a value higher than 93% of cell viability, while the fibers without honey showed values below 93%. In the same research, they related the concentration of honey with cell viability. It was found that 10% honey led to a 102%

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viability; however, by increasing the honey content to 20% the viability percentage dropped to 96%. This result indicates that increasing the concentration of honey is not always favorable for cell development. The study carried out by Abou, S. et al.(33) also verified the cytocompatibility of PVA nanofibers, pomegranate juice and honey: the scaffolds had a 100% cell viability, verifying that the fiber components did not show cytotoxicity. Therefore, the ability of honey to contribute to cell viability in artificial media that helps to heal affected skin in vivo continues to be confirmed (32). Sarkar R. et al (28) measured the effect of low concentrations of honey in the development of cells, with fibrous PVA meshes without honey showing reduced cellular activity when compared to fibers loaded with 0.5 and 1% honey. These concentrations effectively improved cell behavior. The formation of parts of the cytoskeleton and dispersed morphologies was observed with the fibers at 0.5% honey, confirming the normal growth of the cells. However, it is found that a concentration of honey in average values is the one that optimally contributes to the adhesion of epithelial cells and the subsequent re-epithelialization (28).

Histological evaluation of in vivo wound healing induced by honey fibers

The functionality of electrospun fibers with honey to contribute to wound healing has been evaluated in vivo. Researchers have caused artificial wounds in mice, by means of excision and the fibrous scaffold has been delivered to the affected area. Overall, promising results have been obtained in tissue regeneration, by inhibiting tissue inflammation and promoting skin development.

Ability to induce wound closure was evaluated for the scaffolds (19) obtained with honey and pomegranate extract. Honey scaffolds potentially increased the percentage of wound closure when compared to PVA-only scaffolds. The healing progress was evaluated for time periods of 3, 5 and 10 days: at day 10 the honey scaffolds obtained an almost complete wound closure percentage, while with the commercial Medihoney® scaffold (composed of calcium alginate and honey) it took 13 days to heal. This is a successful result because the electrospun fibers with honey and extract allowed the total closure of the wound in a shorter time, compared to the commercial scaffold; that is to say, the electrospun fibers with honey and vegetable extracts are highly effective, which could displace commercial scaffolds. In addition to wound sealing, the scaffold obtained produced a good histological result, since it mainly induced collagen deposition, epidermis re-epithelialization and healing, in contrast to the Medihoney® scaffold. However, an even more satisfactory result was obtained when other apitherapeutic agents such as propolis and bee venom were added to the fibers. The apitherapeutic fibers allowed the development of skin very similar to the original. These fibers have a promising potential for the regeneration of the affected tissue, without visual scars.

In turn, in another study (19) polymeric meshes were manufactured with honey and added with extracts of Allium Sativum or Cleome droserifolia, which allowed a good percentage of wound closure similar to that produced by the commercial silver-based AquacelAg® scaffold. The fibers they obtained are a good alternative as dressings, based on natural compounds compared to commercial scaffolds made from synthetic compounds.

Antioxidant and / or anti-inflammatory activity of electrospun fibers with honey

Phenolic compounds in honey, such as flavonoids, give electrospun fibers witha high antioxidant potential (32); the deficiency in antioxidant enzymes provides the conditions for an oxidizing environment in the wound, affecting skin regeneration. It is important to know how scaffolds act against oxidative stress, due to the excessive exposure of reactive oxygen species and nitrogen, which leads to inflammation, poor healing and chronicity in the wounds (13).

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It is reported that dressings should be designed to meet the needs of both the wound (13) internal and external microenvironment, because most studies have focused on factors related to the external well-being of the wound, such as the correct management of exudates, debridement, permeability and antimicrobial activity; however, the internal need of the wound, such as the control of oxidative stress, is essential for total healing. A piece of research was therefore found that evaluated the antioxidant potential and, consequentially, the anti-inflammatory capacity of honey scaffolds, since the presence of antioxidant molecules is a direct indicator of the anti-inflammatory potential. that fibers may have. Sarkar, R. et al. (28) presented results related to the measurement of the expression level of inflammatory markers Interleukin (IL-6) and Cyclooxygenase-2 (COX-2) against PVA and honey scaffolds. The matrices with 0.5% honey showed the lowest expression of markers, with respect to the fibers loaded at 1%, despite the fact that the latter fibers fought microorganisms more effectively. Controls and PVA fibers without honey demonstrated the highest expression of inflammatory markers. Thus, honey clearly contributes to the elimination of pro-inflammatory markers. Therefore, it is clear that a significant antioxidant activity can be obtained with small concentrations of honey that will be better accepted at the cellular level in the microenvironment.

Conclusions

The electrospinning of fibers with honey has been strongly studied worldwide. According to the application given to the fibers, the researchers have established the most suitable experimental parameters for obtaining fibers with anti-inflammatory, antioxidant and antibacterial activity.biological functionality, which define the existence or not of chronicity. The fibers obtained have been competent against commercial scaffolds due to their antimicrobial property and their potential to allow tissue regeneration until its final stage. Researchers have shown that the addition of fruit or plant extracts and apitherapeutics such as propolis and bee venom, improve the functionality of the fibers as advanced materials for the restoration of damaged skin. For their part, researchers have extended the field of application of electrospun fibers coated with honey, by constructing biosensors for the detection of biological markers, useful for the clinical diagnosis of cancer.

Through this review, the effects of that the electrospun solution parameters may have on the morphology and applicability of the fibers with honey were known. In this way, a deep compilation of very specific and adequate information was made for the design and electrospinning of new dressings with regional honeys that have not yet been used for biomedical applications.

This research suggests the incorporation of regional, natural plant-based extracts, whether little explored or well recognized by the community due to their medicinal properties, in order to achieve a synergistic therapeutic effect between honey and the therapeutic components of the plants. In the future, with the development of electrospun fibers with apitherapeutics and other plants, a better use of bee products could be obtained, through innovation with technologies that do not yet exist in the region, for the large-scale production of different lines of dressings, strengthening the competitiveness in this economic sector.

Obtaining fibers with honey is an avant-garde topic, which sees new applications being discovered, as the scope with which it is studied widens. It is necessary to continue with this type of applied research, using regional honey as an initial prototype and extending it in the solution of emerging social problems, such as effective wound healing, through the administration of biologically safe and sustainable scaffolds.

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