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POLITEHNICA BUCHAREST
Doctoral School Materials Science and Engineering

PhD Thesis Summary

RESEARCH ON THE DEVELOPMENT OF NEW DRESSINGS AND HEMOSTATIC APPLICATIONS USING ADVANCED MATERIALS AND ESSENTIAL OILS AS ANTIOXIDANT AND ANTIMICROBIAL ACTIVE SUBSTANCES

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Table of Contents

List of abbreviations

AgNPs	*Silver Nanoparticles*
ATR	*Attenuated Total Reflectance*
DD	*Degree of Deacetylation*
ECC	*Extracorporeal Circulation*
EO	*Essential Oil*
FGF-2	*Fibroblast Growth Factor 2*
FRAP	*Ferric-Reducing Antioxidant Power*
FTIR	*Fourier Transform Infrared*
GC-MS	*Gas Chromatography – Mass Spectrometry*
LEO	*Lavender Essential Oil*
MCBE	*Minimum Concentration of Biofilm Eradication*
MIC	*Minimum Inhibitory Concentration*
PAM	*Polyacrylamide*
PCL	*Polycaprolactone*
PDS	*Polydioxanone*
PEG	*Polyethylene Glycol*
PET	*Polyethylene Terephthalate*
PL	*Photoluminescence*
PLGA	*Poly (Lactic-co-Glycolic Acid)*
PU	*Polyurethane*
PVA	*Polyvinyl Alcohol*
PVP	*Polyvinyl Pyrrolidone*
RBC	*Red Blood Cells*
SEM	*Scanning Electron Microscope*
TG-DSC	*Thermal Gravimetric – Differential Scanning Calorimetry*
TGF-β	*Transforming Growth Factor-B*
UV-Vis	*Ultraviolet-Visible*

Abstract

Continued research on the development of new dressings for hemostatic and wound healing applications has resulted in obtaining high-performance biomaterials that address these issues.

Despite these important advancements, the treatment of hemostasis and wound infections which are prevalent in chronic wounds, traumatic injury or during cardiovascular surgery, remains a substantial challenge due to factors such as biofilm colonization, delayed healing, and drug resistance. To tackle these challenges, the main goal of the PhD thesis was to develop and assess the performance of a new biomaterial equipped with hemostatic, wound healing properties and an antibacterial shield against a wide range of Gram-positive and Gram-negative microorganisms. Firstly, this research aimed to pinpoint a polymer with optimal hemostatic and wound healing effects and determine the most appropriate form in which to process it. Subsequent experimental research was undertaken to choose an essential oil exhibiting optimal antimicrobial properties for incorporation into the formulation of innovative wound dressings. Therefore, through the process of freeze-drying, a chitosan-based material enhanced with antimicrobial agents such as lavender essential oil (LEO) in different concentrations and silver nanoparticles (AgNPs) was obtained. Evaluation of the properties was performed through homogeneity, absorption and degradation characterization, Ultraviolet-Visible (UV-Vis) and Photoluminescence (PL) spectroscopy, complex thermal analysis and antimicrobial assay in correlation with morphological and structural investigations. The result of these complex analyses highlights the promising potential for the utilization of wound dressings containing lavender essential oil and silver nanoparticles in clinical settings.

Key words: advanced materials; chitosan; essential oil; antibacterial activity; hemostatic agents; wound dressings; cardiovascular surgery.

Introduction

Biomaterials represent a dynamic and interdisciplinary domain within the expansive field of materials science, where the focus shifts from traditional materials to substances engineered to interact seamlessly with biological systems. In the field of biomaterials, the research and development of materials that exhibit specific biological and mechanical properties, allowing them to function harmoniously in living organisms, represents a central focus. These materials need to achieve a delicate equilibrium between biocompatibility, durability, and the ability to interact with biological structures at the molecular level [1,2].

The medical field is continually evolving, and one area that demands significant improvement is the development of medical devices for clinical surgical interventions and postsurgical patient care. This is possible by the integration of advanced materials that hold great promise in enhancing the efficiency, safety, and overall effectiveness of medical procedures [1,3]. Hemostatic and wound management products are indispensable components in various surgical specialties and clinical settings. These critical categories of medical tools play a pivotal role in controlling bleeding and facilitating effective wound healing.

Biomaterials have marked a new era in the fields of hemostatics and wound management, providing clinicians with powerful tools to optimize patient outcomes. Hemostatic biomaterials are designed to facilitate hemostasis, the physiological process that stops bleeding and marks the initial phase of wound healing. Failed or delayed hemostasis can lead to a variety of complications such as delayed wound healing and heightened susceptibility to infections [3,4]. Also, chronic wounds, including conditions like bedsores and pressure ulcers, are characterized by delayed healing that is primarily attributed to infections that are impeding the natural wound healing process [5]. In this context, the need for a biomaterial that not only accelerates the hemostasis and wound healing process but also addresses bacterial and microbial challenges, becomes imperative [6,7].

The primary objective of this PhD thesis was to conceptualize and create an optimal hemostatic and wound healing biomaterial featuring an antibacterial shield. Taking these factors into account, the experimental design was developed following the scheme presented in Figure 1. In the pursuit of creating a functionalized biomaterial, the initial phase of this research, aimed to identify a polymer exhibiting optimal hemostatic and wound healing

properties. A key focus was also placed on determining the most suitable form for processing this polymer, aiming to enhance its efficacy in addressing hemostatic and wound healing requirements.

The research developed in the **first doctoral article – "Chitosan-based Biomaterials for Hemostatic applications: A Review on Recent Advances",** revealed that despite the diverse use of materials from polymers category in related applications, synthetic polymers (polyurethane, polyvinyl alcohol, cyanoacrylates, polyethylene glycol etc.) face constraints such as limited biodegradability and potential cytotoxicity, limiting their integration into clinical practices [8]. On the other hand, natural polymers exhibit a high degree of biocompatibility, show lower immune responses, and possess antimicrobial properties, making them more favorable for such applications [9]. Among them, chitosan was found to fulfill most criteria, having absorbent attributes, high biocompatibility, antioxidant activity and the capacity to create an antibacterial layer at the wound site, providing safeguard against bacterial infection [10-12]. Moreover, chitosan exhibits cationic properties that enable interactions with negatively charged blood components, resulting in the crosslinking of chitosan with erythrocytes [13, 14]. This process leads to the formation of a "mucoadhesive barrier" at the site of the wound that effectively stops bleeding. The biomaterials in the form of chitosan sponges, produced via freeze-drying, demonstrated notable flexibility, high porosity, and absorbent capacity [15]. Additionally, the biomaterial's high permeability facilitates effective gas exchange, fostering an environment conducive to supporting wound healing.

Pursuing the improvement of the antimicrobial activity of the biomaterial, the next objective focused on evaluating the antimicrobial activity of essential oils (EO), research that was carried out in the **second doctoral article – "In Vitro Antibacterial Activity of Some Plant Essential Oils against Four Different Microbial Strains"**. Essential oils (EO) obtained from botanical sources abound in active compounds with both antioxidant and antimicrobial properties [16]. The antioxidant potential of several EOs (thyme, eucalyptus, fennel, pine, sage) was analyzed by the determination of the FRAP assay, while chemical composition was determined using gas chromatography coupled to a mass spectrometer (GC-MS). The essential oil's antimicrobial efficacy was highlighted against *Candida albicans* (yeast strain) and microbial strains – *Pseudomonas aeruginosa* and *Escherichia coli* (Gram-negative), *Staphylococcus aureus* (Gram-positive) [16]. The evaluation of antimicrobial activity involved assessing the diameter of the inhibition zone and establishing both the

minimum concentration of biofilm eradication (MCBE) and the minimum inhibitory concentration (MIC). Following qualitative tests for antimicrobial activity, it was observed that thyme EO exhibited the most significant diameters in the inhibition zones, with sage EO and fennel EO following in succession. The results from quantitative and qualitative tests indicated heightened sensitivity of the *Escherichia coli* strain to all the EO examined. Among the essential oils tested, thyme EO was the sole oil that demonstrated inhibitory effects on *Candida albicans*.

Considering the remarkable properties of EOs such as antioxidant, antimicrobial and curative, the subsequent goal was to investigate their potential as adjuvant agents in wound dressings. Hence, the research conducted in the **third doctoral article – "Essential Oils as Antimicrobial Active Substances in Wound Dressings"**, focused on examining the combining compatibility as well as the antimicrobial and cytotoxic properties of the studied biomaterials [17]. Polyvinyl alcohol/polyvinyl pyrrolidone (PVA/PVP) biomaterials incorporating EOs of peppermint, thyme, pine, and fennel were developed. One category of biomaterials was produced by directly blending essential oils into the polymeric mass, while another type involved the creation and incorporation of microcapsules loaded with EOs into the polymeric matrix. The contact angle values demonstrated a notable difference between biomaterials where EOs were directly blended into the polymer matrix and those featuring capsules loaded with EOs. Specifically, the contact angles were higher in the former scenario. This suggests that incorporating essential oils through direct mixing into the polymer matrix leads to an increased hydrophilicity, pointing towards the potential of the biomaterial to effectively absorb biological fluids from wounds. Microscopical techniques revealed consistent morphology across nearly all biomaterials developed, demonstrating suitable barrier characteristics when in contact with purulent wounds. Moreover, the biomaterials containing essential oils exhibited substantial inhibitory effects against multiple strains – *Candida albicans, Enterococcus faecalis, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli*. The MTT assay confirmed the non-toxic nature of the biomaterials, indicating no adverse impact on cell viability [17]. These findings collectively underscore the efficacy of EOs as valuable active components in wound dressings.

The objective of the **fourth doctoral article – "Influence of Lavender Essential Oil on the Physical and Antibacterial Properties of Chitosan Sponge for Hemostatic Applications"** is to introduce an innovative biomaterial with hemostatic and wound healing effects, equipped with an antibacterial barrier designed to effectively combat a broad-

spectrum of microorganisms [18]. Thus, three polymeric based compositions were formulated using chitosan and lavender essential oil (LEO), alongside three additional compositions incorporating silver nanoparticles (AgNPs) and lavender essential oil into chitosan. Control samples were also prepared using only chitosan and chitosan reinforced with silver nanoparticles. Subsequently, the polymeric solutions underwent lyophilization resulting in the production of functional biomaterials [18].

Evaluation of the biofunctional properties was performed through absorption, degradation, and antimicrobial assay, in conjunction with compositional, morphological and structural investigations. Recordings of Fourier-transform infrared spectra (FTIR) were performed using a spectrometer equipped with an ATR module, while FTIR 2D maps were performed using a microscope. UV–Vis spectra was measured using a spectrophotometer, while Photoluminescence Spectrum (PL) was determined using a spectrometer. The surface morphology and microstructural characteristics of the biomaterials developed were evaluated with a Scanning Electron Microscope (SEM). Thermal behavior was assessed with ThermoGravimetry– Differential Scanning Calorimetry (TG-DSC). The generated gases were conveyed through heated transfer lines and analyzed in real-time using a FTIR analyzer equipped with an internal thermostatic gas cell.

The chitosan-based polymer with 1% LEO and AgNPs exhibited the highest absorption rate, a characteristic that correlates with its morphology that presents larger pore sizes when compared to the other samples. The inclusion of LEO in compositions had a negligible impact on the swelling degree. Instead, chitosan-based polymers with elevated levels of LEO exhibited a more degradable nature, suggesting potential applications in controlled release scenarios for active agents through degradation in damaged skin areas and the absorption of components within wounds. Regarding the quantitative assessment of antibacterial efficacy, it was observed that chitosan-based polymers containing AgNPs exhibited enhanced inhibitory effects against all tested bacterial strains.

The findings of these comprehensive studies underscore the promising potential of employing wound dressings reinforced with both lavender essential oil and silver nanoparticles within clinical settings. The combined presence of LEO and AgNPs confers a dual advantage, as it not only imparts antibacterial and antimicrobial activity but also contributes to wound healing process. This multifaceted approach suggests that such dressings could be instrumental in fostering an environment conducive to effective wound management.

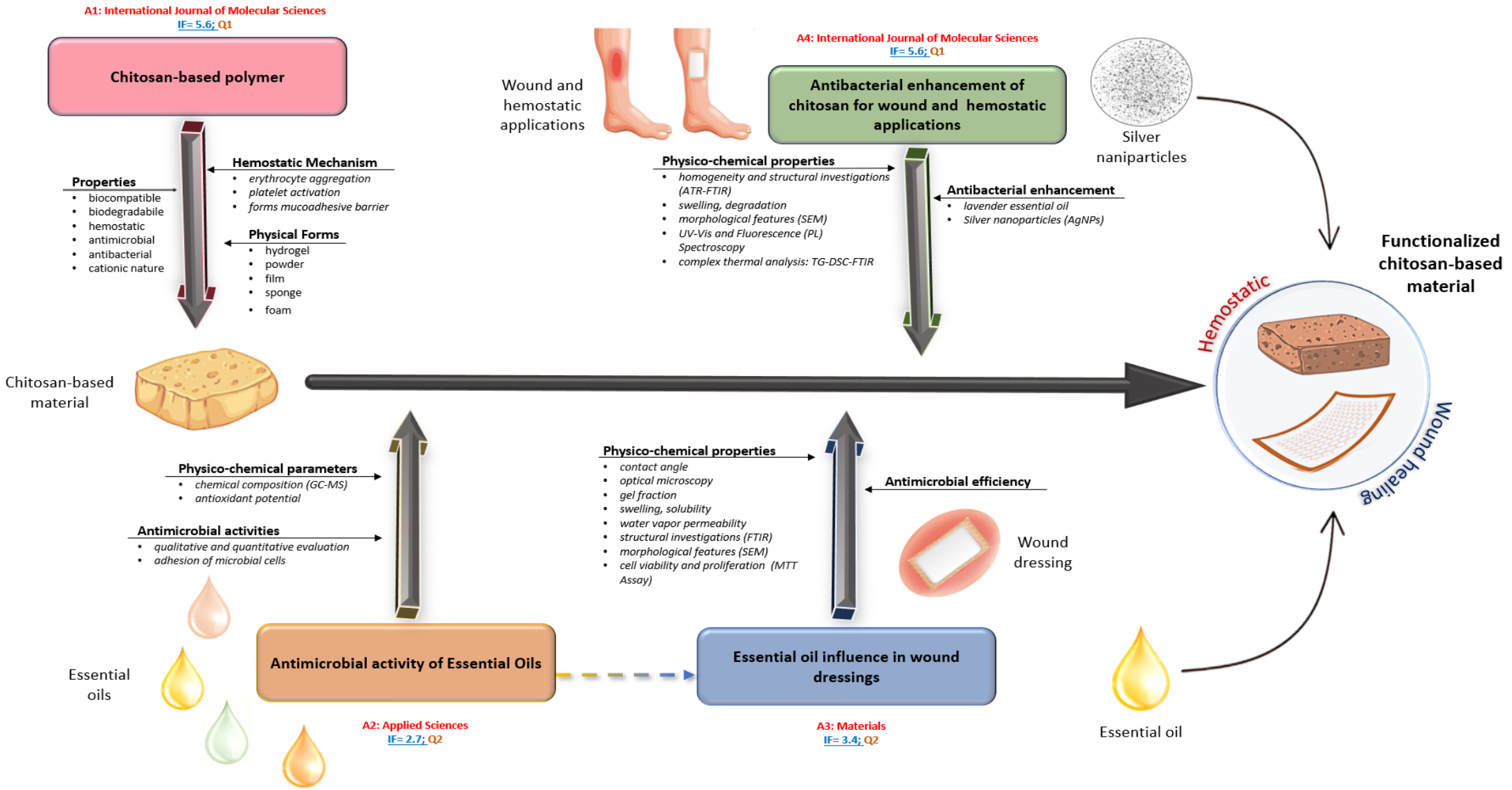

Figure 1. Graphic representation of the sequential stages undertaken in the doctoral thesis.

Chapter 1 – Literature overview relevant to the doctoral topic

1.1. Hemostatic agents and wound dressings in cardiovascular surgery

Bleeding occurring during and following open-heart procedures, which are conducted with extracorporeal circulation (ECC) and varying levels of hypothermia, is a common occurrence [19]. Bleeding represents a significant and noteworthy complication in the context of cardiac surgery.

Rapid and effective management of bleeding holds paramount importance in the surgical setting. This requirement not only provides better visualization to the surgical field, but also assumes an important role in maintaining hemodynamic stability of patients [20-22]. Furthermore, it serves to minimize both the duration of the procedure and the time under anesthesia, ultimately contributing to the reduction of complications that can arise during surgery [20,23].

Failed or delayed management of uncontrolled bleeding can lead to a variety of complications affecting both the surgical team and the patients, ultimately resulting in adverse outcomes during and after the operation. These repercussions encompass prolonged surgical durations and extended periods of postoperative hospitalization, which can disrupt the recovery process and increase the likelihood of complications such as delayed wound healing, heightened susceptibility to infections, and the onset of shock [24-27]. Moreover, the failure to address uncontrolled bleeding in a timely manner can foster the development of hematomas, causing further complications. Severe consequences may even include coagulation disorders, irreversible damage to vital organs, exemplified by conditions like renal failure, as well as multi-organ failure [28-30]. This cascade of complications augments morbidity and mortality rates.

Preventing excessive blood loss during surgery carries immense significance as it is intrinsically linked to a substantial reduction in the risk of significant perioperative complications. As a direct consequence of this, the probability of requiring surgical re-intervention diminishes significantly [31]. Notably, patients who need re-operation face a mortality risk approximately three times higher than those who do not. Furthermore, effective blood loss control leads to shorter hospitalization periods, offering the dual advantage of improving patient recovery and reducing healthcare costs [32, 33].

Hemostasis is a vital reaction of the organism towards injuries, constituting the initial phase of wound healing. It is an important process which stops bleeding through a series of interconnected steps and ends up forming a stable clot [34]. The resulting clot serves as a lid, blocking the hole that has formed in the disrupted blood vessel and thus stopping the hemorrhage. Addressing bleeding issues encompasses a range of hemostatic strategies, which include surgical measures, the administration of blood components, and the utilization of hemostatic agents, either topically or systemically [35].

Surgical measures represent one facet of hemostatic interventions, involving direct physical methods to control bleeding during a procedure. These may encompass mechanical techniques like sutures, ligatures, vascular clips, and thermal techniques like vessel cauterization [36].

Another approach involves blood component therapy, where particular blood components like plasma, platelets, or red blood cells are transfused to restore hemostatic balance in patients with underlying coagulation disorders or significant blood loss [35, 37]. This, in turn, exposes the patient to a range of potential complications including immunologic reactions, heightened susceptibility to infections, and the suppression of the immune system. These complications not only add complexity to the surgical procedure but also elevate the risks of morbidity and mortality for the patient [38-40]. Furthermore, it's crucial to recognize that bleeding-related complications play a substantial role in the consumption of blood products during cardiac surgery. This is particularly significant because the availability of blood is limited, and it serves as a finite resource in the healthcare system. Consequently, the prudent management of bleeding in surgical contexts not only optimizes patient outcomes but also conserves a precious resource that can have a far-reaching impact on the healthcare system[41].

Systemic administration of hemostatic agents became increasingly prevalent in addressing significant blood loss during major surgical procedures both in patients with normal hemostasis and in those with coagulation disorders. The reason for their widespread popularity can be attributed to the increasing demand for blood products, which has surpassed their supply, as well as concerns about the potential dangers of receiving blood transfusions. However, the use of systemic hemostatic agents like antifibrinolytics (e.g., Nafamostat, Tranexamic acid, ε-Aminocaproic Acid, Aprotinin) and procoagulants (e.g., Desmopressin, recombinant factor VIIa) can also carry significant associated risks [42-44].

Topical hemostatic agents support hemostasis by enhancing the natural processes of blood coagulation and act as valuable adjuncts in surgical procedures when conventional methods of bleeding control, such as electrocautery, sutures or ligatures, prove ineffective [45]. Topical hemostatic agents can be divided into three main categories based on their primary components: active, nonactive, and flowable.

Active agents are substances that directly contribute to coagulation mechanisms, leading to rapid formation of fibrin clot [46]. Such agents can be used successfully in patients with impaired coagulation systems as result of mild coagulopathy, heparinization, or other conditions. Implementation of active hemostatic agents such as bovine thrombin, human pooled plasma thrombin and recombinant thrombin, in surgical practice has led to substantial improvements in clinical outcomes [47, 48]. However, their widespread use faces challenges attributed to factors such as contamination risks, potential for immunological side effects, low portability, limited shelf life, performance variability, and high cost [46, 49].

Nonactive agents lack clotting factors and include mechanical hemostatic agents like gelatins, collagens, polysaccharide spheres and cellulose. They work by activating the extrinsic coagulation process and form physical lattices as a protective barrier at the site of bleeding [50-52]. Polysaccharide spheres act by absorbing excess free water, thereby concentrating proteins and platelets in the immediate area, promoting the accelerated formation of blood clots. Since mechanical hemostatic agents lack specific coagulation factors, they are most suitable as an initial choice for minor bleeding situations, and their use is limited to patients with a well-functioning coagulation system [50, 52, 53].

Flowable agents possess characteristics of both active and nonactive agents, making them versatile options for promoting hemostasis. Flowable hemostatic agents, comprising a gelatin matrix (derived from either porcine or bovine sources) along with thrombin, offer a dual mechanism of action in a single application. This combination effectively manages bleeding by providing both mechanical and active hemostatic properties [45].

While the medical market boasts a diverse array of topical hemostatic materials, the ongoing imperative to innovate persists. The quest for new materials is fueled by the demand for heightened hemostatic efficacy, enhanced safety profiles, cost-effectiveness, streamlined preparation processes, exceptional biodegradability, and optimal biocompatibility. These criteria underscore the continuous pursuit of advancements to meet the evolving needs of medical applications.

1.2. Polymers used for hemostatic applications and wound dressings

Polymers are vital players in the world of hemostatic applications, revolutionizing the field of medical science and surgery. With their adaptable nature, these materials effectively tackle bleeding concerns by encouraging clotting and reducing blood loss in a range of procedures [54, 55]. The growth and use of polymers for hemostatic purposes have taken on immense importance, driven by the demand for efficient and biocompatible solutions [56].

Polymeric hemostatic agents are available in various forms, such as sponges, hydrogels, films, powders, particles, or foams, allowing for versatility in application across different medical scenarios [55, 57-60]. These ingeniously designed materials attach to tissues, forming a protective barrier that promotes blood clotting and stops bleeding. Polymeric materials used for hemostatic applications range from synthetic to naturally derived [61]. Compared to synthetic polymers, naturally derived polymers exhibit superior biocompatibility, biodegradability and processability, meaning they have a good integration with biological systems [62, 63].

1.2.1. Natural and synthetic hemostatic polymers

a. Natural hemostatic polymers

Hemostatic agents from natural sources comprise both biologically derived (protein-based) and naturally derived (carbohydrate-based) materials. Employing natural polymers in hemostatic applications offers a host of advantages, combining the efficacy of hemostasis with the inherent properties of these biocompatible materials [61, 64].

Employing natural polymers in hemostatic applications offers a host of advantages: high degree of biocompatibility, lower immune responses, antimicrobial properties, versatility in their applications, also representing a cost-effective alternative [65, 66].

Polymers derived from biological sources

Hemostatic agents derived from biological sources have the capacity to directly enhance coagulation factors at the site of injury, triggering blood clotting and demonstrating exceptional hemostatic effectiveness [61, 67]. Completing this process entails the enzymatic cleavage of fibrinogen, leading to the formation of fibrin facilitated by the action of thrombin. There is a multitude of topical hemostatic agents with biological activity currently accessible, exhibiting variations in composition, mode of action, and administration method. Thrombin, fibrin, fibrinogen, albumin, collagen and

gelatin are some examples of biologically derived materials, each possessing unique properties [67-69].

Thrombin is used to promote platelet aggregation by converting fibrinogen into fibrin and it can be administered in the form of powder, spray, or solution. The application of thrombin can be facilitated when combined with passive hemostatic agents, like gelatin sponges [70,71]. Fibrin serves hemostatic functions by enhancing coagulation factors, activating blood clotting, creating a sealing barrier to prevent blood loss, and acting as an adhesive to self-polymerize and bind structures together in a dry field [72]. Collagen, when exposed to blood flow, serves as a matrix structure facilitating platelet adhesion, aggregation, and activation, while simultaneously triggering the intrinsic pathway of the coagulation cascade [73, 74].

Polymers derived from natural sources

Naturally derived polymers comprise polysaccharides, which are polymeric carbohydrates characterized by either a branched or linear molecular structure, possess distinctive qualities. These include low cost, widespread availability, excellent biocompatibility, easily tunability to achieve desired mechanical properties, and a negligible risk of triggering immune responses [61,75,76]. Consequently, materials derived from polysaccharides, such as chitosan, starch, cellulose and alginate and have undergone thorough exploration as hemostatic agents [77-81]. This exploration reflects the ongoing efforts to advance the field of hemostatic agents and develop materials that can efficiently address bleeding-related challenges.

Cellulose constitutes the framework of most plant structures and plant cells. Cellulose can be chemically modified to obtain oxidized cellulose that is considered a highly promising material for hemostatic dressings [9, 82]. Its remarkable attributes including exceptional water-absorption capacity, minimal hemolysis rate and high water-absorption capacity, makes it a highly promising and effective choice for applications in the field of hemostasis [58, 83, 84].

Starch consists of glucose monomers and promotes hemostasis through the absorption of water from the blood. This action leads to the concentration of platelets and coagulation proteins at the site of application, facilitating an effective hemostatic response. It is free from allergic reactions, adverse toxic effects, or immune responses [9, 80].

Alginate, a naturally occurring anionic polysaccharide, is highly regarded as an outstanding hemostatic biomaterial. This recognition is due to its exceptional attributes, including excellent biocompatibility and biodegradability, ease of gelation, non-immunogenicity, non-toxicity and availability [12, 58, 65]. After absorption of blood or exudates, alginate-based hemostatic materials form hydrogels. They adhere to the wound surface, physically compress the bleeding wound and seal the blood vessels, achieving excellent hemostatic effects. The most used alginate hemostatic material is represented by calcium alginate.

The significance of chitosan lies in its cationic and absorbent attributes, crucial for advancing hemostasis [8, 73, 85]. The cationic nature of chitosan facilitates interaction with negatively charged blood components, while its absorbent capacity aids in promoting effective clot formation and blood coagulation [86]. Chitosan's hemostatic mechanism works autonomously, separate from the conventional coagulation cascade, setting it apart from other hemostatic agents. Furthermore, chitosan can create an antibacterial layer at the wound site, offering protection against bacterial infection and promoting the process of wound healing [87-90].

b. Synthetic hemostatic polymers

Synthetic hemostatic agents encompass a diverse array of materials, including cyanoacrylates, siloxane, polyethylene glycol (PEG), poly lactic-co-glycolic acid (PLGA), polyethylene terephthalate (PET), polyurethane (PU), polydioxanone (PDS), polycaprolactone (PCL), polyacrylamide (PAM) [91-93]. Due to their reduced immunogenic response, flexibility to be able to adapt the chemical characteristics and good stability, these agents have applications in various hemostatic procedures and display enhanced clinical performance [94, 95]. However, their limited biodegradability and potential for cytotoxicity limit their integration into clinical practices. Also, the production costs associated with synthetic polymers typically exceed those of natural polymers.

Cyanoacrylate polymer exhibits a high-bonding strength that serves as a key factor in its role as a tissue sealant. Upon interacting with different anionic substances, like water, blood, or tissue moisture, an exothermic polymerization process is initiated, resulting in the formation of a firm adhesive film that effectively adheres to the wound [96]. This mechanism provides a secure and cohesive wound closure when in contact with biological fluids. It is important to highlight that, cyanoacrylates do not technically

have an inherent "hemostatic" property. Instead, their mechanism of action involves physical sealing, creating a mechanical barrier, and facilitating wound closure. They act as a mechanical barrier by sealing or blocking holes in vessels, thereby preventing further bleeding and obtaining wound closure [97]. Cyanoacrylate adhesives are advised for closing low-tension wounds that are both clean and dry. While cyanoacrylates are biodegradable, it's important to note that they release harmful degradation products that can cause adverse effects.

Polyethylene glycol (PEG) stands out as a biocompatible and hydrophilic polymer that can efficiently initiate hemostasis by creating a mechanical seal that traps blood, leading to the formation of a solid clot [92, 98]. Due to its relevant characteristics that also include the ability of binding with biomolecules, exceptional water absorption, and the capacity to undergo multiple gelation mechanisms, PEG is extensively used in the creation of hydrogels. These properties enhance the adhesive capabilities of PEG. PEG-based tissue sealants have undergone extensive examination for their efficacy in addressing issues such as air leakage, and suture hole bleeding encountered in various surgical procedures such as coronary artery bypass, acute aortic dissection, or valve repair [99]. The research and application of PEG-based tissue sealants in these contexts reflect its potential as a valuable tool in managing specific challenges during surgery, showcasing its versatility and effectiveness in diverse medical scenarios. An important drawback associated with PEG-based adhesives is their reliance on irradiation for the polymerization of components. This method, while effective, poses practical challenges for numerous organs within the body, thereby constraining its application in emergency scenarios.

1.2.2. Chitosan as hemostatic polymer

Over the past few years, a range of newly approved agents, such as those based on chitosan, has emerged. These chitosan-based agents hold considerable potential, demonstrating effectiveness in controlling significant hemorrhage not only in pre-hospital settings but also in animal models replicating major bleeding situations [8, 73, 100].

Chitosan is derived by deacetylating chitin, a very abundant biopolymer. Chitin is present in the in the outer shells of crustaceans like shrimps, crabs and insects, and it is also synthesized by fungi and bacteria. Chitosan is composed of N-Acetyl-D-Glucosamine and D-Glucosamine units, forming a linear polysaccharide. It possesses

appealing characteristics, including biocompatibility, non-toxicity, biodegradability, antibacterial properties, lack of antigenicity, antimicrobial and antifungal activity, mucoadhesive, anti-inflammatory (analgesic), antioxidant properties and the ability to stop bleeding [101-103].

How chitosan is prepared significantly influences how well it interacts with the body in a physiological environment. An important consideration in terms of biocompatibility involves taking measures to avoid allergic reactions that may result from residual proteins. The degree of deacetylation (DD) that affects the density of amino groups on the polymeric chain, appears to be a determining factor in biocompatibility, suggesting that an increase in DD is associated with enhanced biocompatibility [104]. As a naturally occurring biodegradable biopolymer, chitosan undergoes enzymatic degradation within living organisms. The resulting degradation products consist of non-toxic oligosaccharides, which can be subsequently either excreted or integrated into glycosaminoglycans and glycoproteins [105, 106].

Chitosan and its derivatives exert antimicrobial, antibacterial and antifungal activity against different microorganisms such as *S. aureus, Bacillus megaterium, Bacillus cereus, Lactobacillus brevis, E. coli, Enterobacter aerogenes, Salmonella typhimurium, Pseudomonas aeruginosa* [107, 108]. The bacteriostatic and fungistatic qualities of materials based on chitosan prove especially beneficial in wound treatment. Beyond their antimicrobial attributes, chitosan and chitosan oligosaccharides can stimulate cell proliferation. Therefore, chitosan finds its main commercial uses in the biomedical domain, particularly in the context of healing of wounds.

Chitosan demonstrates mucoadhesive properties and has found extensive application in the formulation of mucoadhesive dosage forms. Nevertheless, its usage is hindered by two significant drawbacks: restricted mucoadhesive potency and low water solubility under neutral and basic pH conditions [108, 109]. To address these challenges and enhance mucoadhesive properties, researchers have investigated several alterations to chitosan, including derivatives such as trimethyl chitosan, carboxymethyl chitosan, and thiolated chitosan [106, 110].

Chitosan has an amino group and numerous hydroxyl groups, allowing it to engage with free radicals and exhibit scavenging capabilities. The antioxidant activity is particularly noteworthy in low molecular weight chitosan compared to its high molecular weight counterpart. This heightened activity in shorter chains can be attributed to the

formation of a reduced number of intramolecular hydrogen bonds, rendering reactive groups more available and thereby enhancing the activity of radical scavenging [106]. Hence, for this study, we opted to utilize chitosan with a low molecular weight. In terms of the acetylation degree, there appears to be a correlation where antioxidant activity tends to decrease with an increase in this parameter.

In addition to its notable characteristics discussed above, chitosan possesses a remarkable ability to effectively stop bleeding, making it a valuable hemostatic agent [111]. Chitosan initiates hemostasis without engaging the intrinsic pathway of blood coagulation, indicating that the mechanism by which chitosan acts on blood clotting functions independently of the traditional coagulation cascade [112, 113]. These characteristic positions chitosan as an appealing biomaterial, especially for its ability to control bleeding in patients with coagulopathies (clotting dysfunction). Figure 2 shows the chitosan-based biomaterial hemostatic mechanism wherein erythrocytes aggregate as a result of the interplay between their negative charges and the positive charges of chitosan molecules.

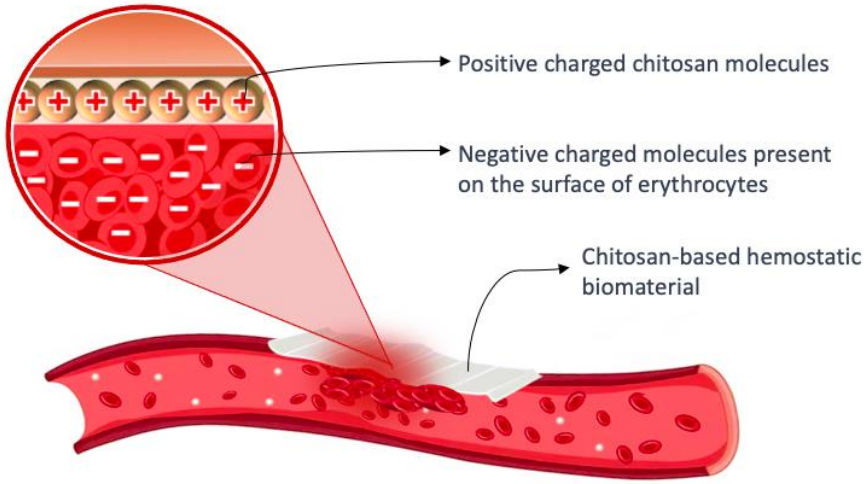

Figure 2. Schematic representation of the hemostatic mechanism of chitosan based biomaterial

The standout feature of chitosan lies in its cationic character and its exceptional behavior in solution, a trait of considerable significance in its medical uses. Chitosan stands out as the sole cationic polymer found naturally in the environment. The cationic property of chitosan significantly contributes to the promotion of hemostasis [114, 115]. The interaction between negative and positive charges between red blood cells (RBC) and chitosan suggests an attractive force, leading to the crosslinking of chitosan with

erythrocytes. This process culminates in the creation of a "mucoadhesive barrier" at the site of the wound, effectively arresting bleeding. Furthermore, the presence of positive charges allows chitosan to associate with the anions present on cell walls of bacteria, hindering their access to the cell. The antimicrobial effect exhibited by chitosan is of great importance for creating a wound healing environment [89,107].

Given the importance of the cationic properties of chitosan that play a crucial role in promoting hemostasis and antibacterial activity, studies conducted on this **PhD thesis** were directed towards the formulation and development of a hemostatic material centered around chitosan.

Chitosan's remarkable versatility opens up opportunities for its utilization in various physical forms, including dressings, films, beads, hydrogels, sponges, particles, membranes, scaffolds, fibers and nanofibers. Figure 3 shows chitin and chitosan chemical structures and the main forms in which chitosan can be processed.

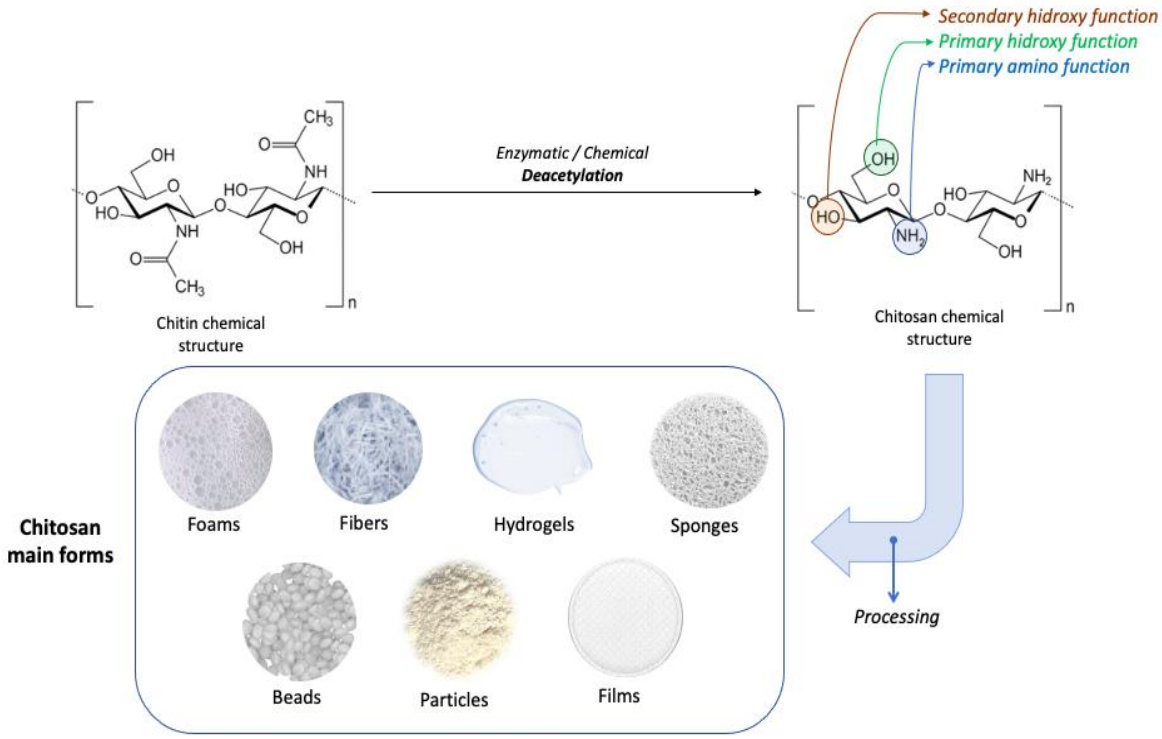

Figure 3. Chitin and chitosan chemical structures and main forms in which chitosan can be processed.

When combined with various organic acids, chitosan produces viscous solutions. Functional films are created by using these solutions, followed by drying through either oven drying or infrared drying processes. Chitosan films are characterized as resilient, durable, and flexible. These qualities make them suitable for wound dressings where a

combination of strength and flexibility is essential. The strength ensures that the film remains intact and securely covers the wound, preventing the entry of external contaminants, while the flexibility allows conforming to the contours of the wound. Physical and mechanical properties of chitosan films are influenced by its morphology, a factor determined by molecular weight, solvent evaporation, degree of N-acetylation and the mechanism of free amine regeneration. This offers the potential to create a diverse range of films by utilizing various chitosan sources and organic acid solvents [116, 117].

Hydrogels are biphasic materials that have attracted interest for use in clinical applications, primarily for their capacity to create and sustain a moist wound environment, thereby effectively sealing tissues during hemostasis. They exhibit a moist, flexible, and soft nature, due to their significant water content. The swelling capacity of hydrogels is a result of the hydrophilic groups found within the polymeric constituents of the gels, providing an advantage in absorbing blood and wound exudate. Another benefit of hydrogels lies in its ability to conform to the shape of the wound, ensuring optimal superficial contact [103, 118].

Chitosan sponges are solid structures characterized by high porosity, demonstrating exceptional characteristics that make them beneficial for diverse applications. Their high permeability facilitates efficient gas exchange, contributing to an environment that sustains wound healing [119]. Chitosan sponges, developed through the freeze-drying process, exhibit remarkable flexibility, and possess the capability to absorb substantial amounts of liquid. Moreover, these sponges play a dual role by simultaneously promoting tissue regeneration. The ability to support moisture balance while facilitating tissue repair makes them particularly well-suited for applications in wound dressings and regenerative medicine [120, 121].

Fibers can be manufactured through both dry and wet spinning methods employing various solvents, as well as through electrospinning. This innovative technique offers a notable advantage, enabling the production of polymer fibers at the nano- and micro-scale, depending on the specific processing conditions [10, 109].

1.3. Essential oils as antibacterial active substances in polymer based medical applications

Bacterial and microbial infections represent a significant contributor to mortality rates in hospitals globally. Bacteria have the tendency to proliferate on various surfaces, giving rise to the formation of biofilms when they colonize a surface. In this context, a significant concern arises from the formation of biofilms on medical devices such as urinary or venous catheters, pacemakers, and different prosthetics [122, 123].

Moreover, a significant number of people experience severe impacts from diabetes and cardiovascular diseases, which, at advanced stages, can result in challenging complications such as bedsores and pressure ulcers [124]. These wounds, often referred to as chronic wounds, exhibit a prolonged healing process extending beyond the typical timeframe of four weeks to three months. Characterized by a displaying a slow recovery pace, they also have a tendency to reoccur persistently [11]. A common cause that contributes to this phenomenon is the presence of bacterial, viral, or fungal infections, which impede the natural healing process of wounds. Annually, there has been a notable increase, estimated at 2-6 times higher, in the mortality rates caused by complications associated with these diseases compared to those resulting from other medical conditions. This underscores the urgency of effectively addressing and managing the complexities associated with these specific health problems.

Additionally, the challenge of surgical site infections is a critical concern in diverse medical domains such as cardiovascular surgery, orthopedics, neurosurgery, general surgery, and dentistry. These infections, if not effectively managed, hold the potential to give rise to complications in the postoperative phase [125, 126]. In worst case scenarios, complications arising from postoperative infections have the potential to escalate to life-threatening conditions. Addressing this concern across all medical disciplines becomes imperative to enhance overall surgical success and minimize the risk of complications associated with postoperative infections.

Given the prevalent use of polymeric materials in all these applications and the vulnerability of polymeric surfaces to bacterial colonization, the imperative for intensive research and development of polymer-based antibacterial and antimicrobial biomaterials becomes evident. Therefore, research into advanced polymeric biomaterials incorporating antibacterial properties is essential to proactively mitigate the risk of infections associated with these medical applications.

1.3.1. Antibacterial agents employed in wound healing strategies

The skin serves as a formidable barrier, and its ability to repair and regenerate is essential for the body's resilience and continued vitality. Being the body's largest organ, the skin plays a crucial role in safeguarding internal organs from the external environment. Any compromise to the integrity of this living tissue can be classified as a wound [127]. Ensuring the integrity of the skin and stimulating the ability to heal wounds are indispensable prerequisites for promoting and sustaining general health and well-being. Challenging complications that arise from diabetes and cardiovascular diseases include diabetic foot ulcers, pressure ulcers, venous leg ulcers, and ischemic wounds [128]. These wounds are characterized by a slow rate of healing and a tendency to persistently reappear and are called chronic wounds or non-healing wounds. The wound healing process represents a substantial challenge and financial burden for healthcare systems. Surgical wounds represent the largest expense in wound care, followed closely by diabetic foot ulcers.

The market for medical products used to treat chronic wounds is predominantly led by dressings, which must fulfill a spectrum of requirements. These include the capacity to absorb wound exudate, ensuring the maintenance of a moist but not macerated wound environment. Additionally, dressings need to exhibit characteristics such as optimization of wound pH, pain relief and water permeability [38,129,130]. A critical attribute that dressings must have, is their antibacterial and antimicrobial characteristics. This crucial feature ensures that the dressing not only provides a protective barrier for the wound, but also actively combats bacterial and microbial threats, creating an environment conducive to effective healing. Antimicrobial agents stand out as the predominant compounds when it comes to functionalization of wound dressings. These agents encompass antibiotics (e.g., tetracycline, gentamicin), antiseptics (e.g., chlorhexidine hydrogen peroxide), nanoparticles (e.g., silver, copper) and natural biomaterials (e.g., honey, essential oils) [131, 132].

In the field of wound care, a diverse array of strategies exists for addressing wound infections. Conventional antimicrobial approaches, such as antibiotics and antiseptics, operate by directly diminishing the number of bacteria. This is achieved through the inhibition of microbial growth and bacterial cell division, or by extermination of the microorganisms [133].

The standard approach to fighting bacterial infections involves the use of antibiotics. However, the widespread application of antibiotics has led to the emergence of multidrug-resistant bacteria. Consequently, the demand for stronger and complex antibiotic formulations has increased to effectively combat these resistant strains.

Non-antibiotic antimicrobials find extensive application in wound care. These encompass antiseptics, such as chlorhexidine, cadexomer iodine, hydrogen peroxide or povidone. These non-antibiotic alternatives contribute to the diverse arsenal of wound care solutions, each offering unique mechanisms of action and therapeutic benefits. In topical application, antimicrobials can prove beneficial in addressing localized infections on the surface of chronic wounds [134]. However, it is crucial to acknowledge that certain topical antiseptics may pose drawbacks particularly with prolonged use. They are manifested by inducing irritation in the surrounding area of the wound and potentially exerting cytotoxic effects in the wound bed, delaying the healing process. Similar to the concerns associated with antibiotic use, the extensive application of antiseptics has raised concerns regarding the potential development of antiseptic resistance. Also, the unfavorable aspects of antiseptic treatment have raised questions about the suitability of employing topical antimicrobials in wound treatment.

This Phd study comes as a paramount necessity to address these challenges, expedite the wound healing process and to improve hemostasis but also to eliminate the risk of infections by incorporating antimicrobial agents.

Currently, there is an increasing therapeutic importance in exploring the potential use of phytochemicals, particularly in the form of extracts from plants, for healing open skin wounds [135-137]. This trend underscores a shift toward more natural approaches to wound care, reflecting a broader awareness of the therapeutic benefits that plant-derived compounds can provide in the field of medical product development.

Specifically, essential oils (EO) derived from various plant components are rich in active compounds possessing antioxidant and antimicrobial properties [138, 139]. Numerous studies have been undertaken with the objective of substituting antibiotics and other synthetic compounds in the therapeutic approach to microbial infections. Simultaneously, considerable emphasis is placed on the meticulous selection of materials for formulating the polymer matrix. These materials play an essential role not only in the treatment of skin lesions but also serve as an ideal medium for the targeted delivery of essential oils directly to the wound site [140-143]. This dual consideration highlights the

importance of both the therapeutic agents (essential oils) and the carrier matrix (polymers) in developing effective strategies for the treatment of skin-related ailments, encouraging a synergistic approach to enhance therapeutic outcomes.

The use of these agents underscores the multifaceted nature of wound management, where a combination of approaches is often used to address the complexities associated with microbial control and facilitate optimal wound healing. The effectiveness of these dressings significantly depends on the selection of key materials and the incorporation of additives in their composition.

1.3.2. Effects of essential oils in medical applications

Derived from plant sources, essential oils (EO) typically comprise 20 to 60 constituents, with the majority falling within the terpene family, including esters, phenols, hydrocarbons and oxygenated derivatives. Scientific studies indicate that EOs have antioxidant and antimicrobial properties, making them commonly utilized in alternative medicine [145-148].

The modernization of harvesting and processing methods for medicinal plants has resulted in maintaining their nutritional and antioxidant attributes. Consequently, there has been an expansion in the potential applications of these substances across various pharmaceutical and cosmetic sectors. Simultaneously, as there is a heightened focus on enhancing the conditions of the environment, we are witnessing the emergence of green pharmacy. In this paradigm, chemical components are substituted with phytopharmaceuticals, reflecting a commitment to sustainable and environmentally friendly practices.

The manufacturing of phytopharmaceutical and nutraceutical formulations has resulted in a yearly surge in revenue. This trend is driven by the people preference for natural origin products, owing to several benefits such as widespread accessibility, minimal side effects, potential for combined use with other therapies, non-addictive properties and cost-effectivenes [149, 150]. Globally, the market for herbal product consumption is continually expanding.

The applications of extracts derived from medicinal and aromatic plants are diverse and depend on the type and concentration of active constituents (phytochemicals) present [151-153]. These chemical compounds present variability based on the cultivation area which are influenced by factors such as soil characteristics and weather conditions, and on the biological conditions of the plant species. For instance, the

concentration of linalool, usually the dominant chemical element in the lavender essential oil, has been discovered to undergo significant variations in response to changes in these environmental factors [154]. Consequently, optimizing the technological processes involved in the harvesting, processing and storage of these products represents a very important aspect.

In recent years, there has been extensive research on the antimicrobial properties of essential oils. Studies have demonstrated that certain essential oils have the capability to impede the growth and proliferation of microorganisms resistant to antibiotics. Given their antimicrobial properties, EO could be regarded as a potential alternative to antibiotic treatments. For instance, cinnamon, sage, and clove essential oils exhibit antimicrobial effects on various strains within the species *Salmonella typhi, Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli* [155-157]. Additionally, tea tree oil has demonstrated bactericidal effects against the *Staphylococcus aureus* microbial strain.

The effectiveness of essential oils as antioxidants is widely recognized and hinges on their chemical composition, specifically the existence of phenolic structures, along with alcohols, ethers, monoterpenes, and ketones. These components play an essential role in preventing certain diseases by counteracting free radicals and facilitating peroxide decomposition. Therefore, essential oils derived from *Citrus aurantium, Anthemis nobilis, Abies koreana, Anthemis aciphylla, Foeniculum vulgare, Eucalyptus globules, Salvia sp*. and *Mentha sp.* are employed for treating dermatological fungal infections [158-160]. Additionally, essential oils extracted from *Citrus aurantifolia*, *Salvia officinalis L.,* and *Curcuma longa L.* have the potential to enhance conditions associated with hyperlipidemia [161,162]. EO from *Citrus aurantium* and *Lavandula angustifolia* demonstrate the ability to alleviate both blood pressure and anxiety in individuals experiencing acute coronary syndrome [160, 163]. Peppermint EO was incorporated into the acrylic-based bone cement formulation, showcasing its antimicrobial effects against *Pseudomonas aeruginosa* and *Staphylococcus aureus* strains [164].

Inspired by the historically proven healing attributes of lavender, scientists are currently researching the expansion of its applications, particularly in domains like surgery and dentistry. The essential oils of lavender, rich in compounds such as linalool, camphor, linalyl acetate, terpinene, cineole, camphene, and others, exhibit noteworthy antimicrobial properties [165, 166]. These properties, particularly effective against both Gram-positive and Gram-negative microorganisms, as well as against fungi, open new

ways for the exploitation of lavender in various medical contexts. Noteworthy examples of microorganisms targeted by these properties include *Escherichia coli, Aspergillus nidulans, Candida albicans, Trichophyton mentagrophytes and Staphylococcus aureus.*

Numerous studies have brought to light the increased antimicrobial efficacy achieved through the incorporation of lavender essential oils into certain antibiotic drugs. Beyond their traditional uses, the essential oils of lavender have been subject to detailed investigations, unveiling distinctive properties [167-170]. This ongoing research not only deepens our understanding of lavender's therapeutic potential but also paves the way for expanding its practical applications in the ever-evolving landscape of healthcare.

Also, many studies endorse the utilization of lavender essential oil for healing of wounds and propose various distinctive mechanisms by which the oil might influence the process of wound recovery.

Lavender essential oil application was observed to elevate the levels of fibroblast growth factor 2 (FGF-2), Transforming Growth Factor-β (TGF-β) and type I collagen. This is particularly noteworthy because TGF-β and FGF-2 are known to stimulate the proliferation of fibroblasts, crucial in the wound contraction process by facilitating tissue shrinkage. Consequently, this leads to an enhanced and accelerated wound contraction, thereby promoting a more rapid and efficient healing response. Linalool and linalyl acetate, the main constituents of lavender EO, are believed to be the primary contributors to the influence on these proteins associated with tissue remodeling [171].

It is thus demonstrated that applying lavender essential oil topically for wound healing exhibits potential therapeutic benefits, manifested through various mechanisms: accelerated wound contraction, heightened activity of proteins participating in tissue restructuring, and heightened collagen expression. Notably, these EOs have also demonstrated anti-inflammatory and anxiolytic effects.

Considering these desired properties for wound healing process, in this PhD study, lavender essential oil was integrated as an adjunctive agent in the formulation of hemostatic and wound healing biomaterials.

1.4. Novel chitosan sponges loaded with lavender essential oil for hemostatic applications

A novel biomaterial based on chitosan with hemostatic application and wound healing properties equipped with an antibacterial shield to reduce the likelihood of infection, was developed in this study. To achieve a synergy of hemostatic and wound-healing properties determined the integration of functional elements within the chitosan-based biomaterial. Lavender essential oil has garnered attention for its remarkable properties that promote wound-healing and combat inflammation. Its efficacy in promoting wound healing has been proven through both in vitro and in vivo studies, showcasing its regenerative potential and significant benefits in the treatment of bacterial infections within wounds. With exceptional antimicrobial properties, silver nanoparticles effectively combat various microorganisms, finding application in wound healing materials to reduce the risk of infections. Therefore, composite materials based on chitosan were developed: three biomaterials based on chitosan in which lavender essential oil (LEO) was introduced and other three biomaterials based on chitosan in which lavender essential oil and silver nanoparticles (AgNPs) were integrated, as well as control samples of chitosan and chitosan with silver nanoparticles [18]. The polymeric solutions formed were lyophilized in a freeze dryer in order to obtain the functional biomaterials in the form of sponges.

Morphology and microstructure of the experimental chitosan-based polymers, show that the biomaterial exhibits homogeneity, without of agglomerations or inclusions. Additionally, biomaterials present a network characterized by a significant density of interconnected open pores, with varying diameters. All biomaterials show a pronounced absorption of fluids. The chitosan-based polymers containing lavender essential oil demonstrate an elevated absorption rate and exhibit enhanced swelling characteristics. However, the biomaterial exhibiting the most notable increase in absorption is the one characterized by the largest dimensions of pore channels within the mass of the biomaterial.

For chitosan-based polymers containing the highest concentration of lavender essential oil a more pronounced mass loss is observed. This creates a clear association between the elevated presence of LEO and the degradation of biomaterials. The phenomenon can be attributed to a process that involves disintegration, fragmentation, and the diffusion of a greater volume of components in the chitosan-based compositions explored in this study. The complex interaction of these factors underlines the influence of LEO on the dynamic degradation processes in the studied biomaterials [18].

In order to perform a complete investigation, the antimicrobial assay was performed using standard strains: Chitosan-based polymers containing only lavender essential oil display a notable inhibitory effect, particularly observed in the context of Gram-positive microbial strains. Consequently, there was a significant inhibition observed in both the proliferation of planktonic cells and their attachment to the biomaterial, in comparison to the growth control and chitosan-based polymer sample control. The inhibitory effect against Gram-negative strains was particularly pronounced in terms of cells adhering to the biomaterial. Also, the presence of AgNPs substantially enhances the inhibitory effect against all bacterial strains tested.

Chapter 2 – Published scientific articles *in extenso* as scientific results of the doctoral thesis

Within this chapter, the experimental results of the doctoral thesis are showcased through comprehensive scientific articles presented *in extenso*, published in journals indexed ISI Web of Science (WOS). These articles provide an in-depth exploration of the research findings, offering a detailed and thorough image of the contributions made within the science and engineering of materials field. The publication of research findings in the form of scientific articles in ISI WOS indexed journals (**Q1, Q2**) underscores the quality and impact of the disseminated research.

Research results were published in **4 scientific articles,** with a cumulative **Impact Factor of 17.3**, as follows:

1. **Gheorghiță, D.**; Moldovan, H.; Robu, A.; Bița, A.I.; Grosu, E.; Antoniac, A.; Corneschi, I.; Antoniac, I. Bodog, A.D.; Băcilă, C.I. Chitosan-based Biomaterials for Hemostatic applications: A Review on Recent Advances. *INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES*, 2023, 24(13), Article number 10540. eISSN: 1422-0067, DOI: 10.3390/ijms241310540, WOS:001037279600001. **IF = 5.6, Q1.**
2. **Gheorghiță, D.**; Robu, A.; Antoniac, A.; Antoniac, I.; Ditu, L.M.; Raiciu, A.-D.; Tomescu, J.; Grosu, E.; Saceleanu, A. In Vitro Antibacterial Activity of Some Plant Essential Oils against Four Different Microbial Strains. *APPLIED SCIENCES-BASEL*, 12(19), 2022, Article Number 9482. eISSN: 2076-3417, DOI: 10.3390/app12199482, WOS:000866648700001. **IF = 2.7, Q2**.
3. **Gheorghiță, D.**; Grosu, E.; Robu, A.; Ditu, L.M.; Deleanu, I.M.; Pircalabioru, G.G.; Raiciu, A.-D.; Bita, A.-I.; Antoniac, A.; Antoniac, V.I. Essential Oils as Antimicrobial Active Substances in Wound Dressings. *MATERIALS*, 15(19), 2022, Article Number: 6923. eISSN: 1996-1944, DOI: 10.3390/ma15196923, WOS:000866914900001. **IF = 3.4, Q2.**
4. **Gheorghiță, D.**; Antoniac, I.; Moldovan, H.; Antoniac, A.; Grosu, E.; Motelica, L.; Ficai, A.; Oprea, O.; Vasile, E.; Ditu, L.M.; Raiciu, A.D. Influence of Lavender Essential Oil on the Physical and Antibacterial Properties of Chitosan Sponge for Hemostatic Applications. *INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES*, 2023, 24, Article number 16312. DOI: 10.3390/ijms242216312. **IF = 5.6, Q1.**

Chapter 3 – General conclusions

Biomaterials represent an interdisciplinary field that serves as the cornerstone for innovations at the intersection of materials science and medicine. An essential area that needs substantial improvement in the medical field is the development of biomaterials specifically designed for hemostatic and wound management. These biomaterials stand as indispensable components in most clinical settings and in all surgical specialties, playing a crucial role in ensuring effective patient care and optimal outcomes.

The profound global impact of wound infections reverberates across individuals and healthcare systems alike. Arising from the infiltration of bacteria, microbes, or other pathogens into wound site, these infections trigger a domino effect of complications that extend beyond the immediate context. When hemostasis is delayed, wounds remain open for a more extended period, providing an opportunity for infections to take hold. This heightened susceptibility to infections poses a serious threat to individuals undergoing surgery, trauma victims, or those with certain medical conditions. Moreover, in chronic wounds, the presence of persistent infections presents an important challenge. Pathogens not only exacerbate tissue damage but also create a hostile environment that hinders the intricate cellular and molecular processes essential for healing.

Increased infection rates contribute to higher healthcare costs, with implications for both individuals and healthcare systems. Furthermore, the global impact is not limited to immediate healthcare concerns. Delayed wound healing and the subsequent risk of infections can lead to long-term health issues, diminished quality of life, and potential socioeconomic challenges. Considering the impact of wound infections, the need for an effective biomaterial capable of counteracting these complications becomes imperative. The ideal biomaterial should not only expedite hemostasis and enhance the wound healing process but also effectively confront the challenges posed by bacterial and microbial infections. This experimental research aimed to develop an innovative biomaterial with optimal hemostatic and wound healing functionalities, featuring a built-in antibacterial shield to effectively address challenges posed by bacterial and microbial infections.

Several polymers are employed as biomaterials in the hemostatic and wound healing field, each possessing different characteristics. Natural polymers are preferred for these applications due to their high biocompatibility and versatility. Beyond its impressive

advantages such as high biocompatibility, absorbent attributes and antioxidant activity, chitosan has an important distinctive property among these natural polymers – it is the only cationic polymer in nature. This property facilitates interactions with negatively charged blood components, leading to the crosslinking of chitosan with erythrocytes, a process that results in the creation of a "mucoadhesive barrier" at the wound site, effectively stopping bleeding. Chitosan functions independent of the coagulation system, demonstrating hemostatic impact even in individuals with coagulopathy. Considering the noteworthy attributes emphasized earlier, this Ph.D. study was based on the development of an innovative biomaterial based on chitosan.

By integrating additional functional elements such as wound-healing, anti-inflammatory, pain relievers and antimicrobial agents, chitosan-based biomaterials can be optimized to create a multifunctional biomaterial with synergistic effects capable of achieving hemostasis, contributing to the enhancement of the wound healing process. Derived from various plant components, EOs are packed with a diverse range of active compounds, each contributing to their notable antioxidant and antimicrobial properties. These natural extracts offer a rich array of bioactive elements that make them valuable in medical applications offering benefits that extend across psychological, pharmacological, and physiological dimensions.

In this PhD study, fennel, peppermint, pine, thyme, sage, eucalyptus, and lavender essential oils underwent complex characterization. The essential oils were subjected to detailed antimicrobial analysis, revealing substantial antimicrobial activity against a diverse range of microorganisms that included: *Candida albicans, Staphylococcus epidermidis, Escherichia coli, Enterococcus faecalis, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Staphylococcus aureus*. MTT assay results showed that biomaterials containing essential oils exhibited non-toxicity, did not induce cellular death, and also did not cause substantial changes in the morphology of fibroblast cells. Contact angle determination and barrier properties of the biomaterials showed their hydrophilic nature indicating their suitability for application in skin lesions.

This comprehensive analysis highlights the potential broad-spectrum antimicrobial efficacy of the essential oils, indicating their possible utility in applications related to wound healing. Lavender essential oil exhibits antimicrobial, anti-inflammatory, and antioxidant characteristics, which collectively contribute to its efficacy in supporting the healing process of wounds. Linalyl acetate and linalool, typically the primary chemical

constituents in lavender essential oil, sustain the proliferation of fibroblasts, leading to improved wound healing effect. Given these valuable properties, lavender essential oil was incorporated as an additional component in the formulation of biomaterials developed in this PhD study.

Considering the important advantages of chitosan polymer and the valuable properties of lavender essential oil, as well as the well-known antimicrobial effects of silver nanoparticles, an innovative biomaterial with hemostatic, wound healing, antimicrobial and antibacterial properties was developed in this study. Therefore, three chitosan-based materials were developed by incorporating lavender essential oil (LEO) and silver nanoparticles (AgNPs). Control samples of chitosan and chitosan with AgNPs were also developed. The compositions were lyophilized in order to obtain functional biomaterials in the form of sponges. Morphology and microstructure of the chitosan-based materials were homogenous, without agglomerations or inclusions. They also presented a network of dense, interconnected pores, with varying diameters that enabled significant fluid absorption. The biomaterials containing lavender essential oil demonstrated a higher absorption rate, the most remarkable absorption rate being shown in the case of the biomaterial with largest dimensions of pores. The biomaterial with the highest lavender essential oil concentration exhibited a more noticeable mass loss, establishing a distinct correlation between the increased presence of LEO and the degradation of the biomaterials. This phenomenon can be attributed to a process encompassing dissolution, fragmentation, and the increased diffusion of components from the chitosan-based materials investigated in this study.

In conclusion, the investigation on biomaterials enhanced with (i) essential oils renowned for their diverse array of active compounds with significant antimicrobial and antioxidant features, and (ii) silver nanoparticles known for their antimicrobial effects, carries substantial promise in the field of hemostasis and wound care management with important implications in surgery, trauma, and different clinical settings. To develop an optimal biomaterial, interdisciplinary research is essential. This approach involves integrating insights and methodologies from both engineering and medical fields to address the complexity of designing a biomaterial that meets the highest standards in terms of functionality, biocompatibility, and applicability.

Chapter 4 – Original scientific contributions to the field

The experimental research presented in this PhD thesis involved a series of original contributions that aimed to create an innovative biomaterial that combines superior hemostatic and wound healing capabilities while incorporating an antibacterial defense mechanism. These contributions can be outlined as follows:

- Development of novel biocompatible materials by incorporating essential oils, silver nanoparticles, and other different additives (stabilizers – Zn stearate, plasticizers - glycerol and PEG, antioxidants - vitamin E and A). Through this integration, synergistic effects were achieved in the developed biomaterials, aiming to not only facilitate hemostasis but also contribute to the overall improvement of the wound healing process.
- Two approaches were used to introduce essential oils into the biomaterial: (i) encapsulation of the essential oils in sodium alginate and (ii) direct mixing of the essential oils into the composition of the material.
- A complex analysis of scientific literature was conducted, which led to obtaining new results and interpretations, many being innovative and original. These findings have the potential to shape and advance the current understanding of the interaction of biomaterials in the complex environment of wound healing.
- The results obtained from the experimental research corroborated with the studies in the literature contributed to a comprehensive understanding of the multifaceted requirements of biomaterials intended for use in hemostasis.
- The physico-chemical analysis of different essential oils, along with an assessment of their antimicrobial impact, was undertaken with the explicit aim of showcasing their antimicrobial properties against a broad spectrum of microorganisms: *Klebsiella pneumonia, Staphylococcus epidermidis*, *Escherichia coli, Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Candida albicans*. These findings show that essential oils prove to be usable in the development of new biomaterials with hemostatic and wound healing applications.
- Original compositions were created in which different types of essential oils (pine, fennel, sage, thyme, eucalyptus, peppermint, and lavender) were incorporated directly or in the form of microcapsules in polymers such as PVA/PVP and chitosan.

- The incorporation of lavender essential oil into chitosan-based materials for hemostatic and wound healing applications, as explored in this research study, represents a novel concept that has not been published before. The concept of introducing lavender essential oil into chitosan-based material, is driven by the goal of creating an innovative biomaterial that harmoniously integrates advanced capabilities in hemostasis, wound healing, and antimicrobial properties.
- A distinct correlation was established between the heightened concentration of lavender essential oil within the polymer matrix and the subsequent degradation of the material, indicating possible uses in controlled release scenarios for active agents, involving degradation in damaged skin areas and the absorption of components within wounds.
- The modern characterization techniques employed in this study facilitated a complex analysis of the developed biomaterials, enabling a comprehensive and comparative assessment of their properties. The application of ATR-FTIR analysis proved essential in obtaining results that demonstrate the good interaction between components of the essential oil and polymers. This interaction is significant as it enables these biomaterials to retain essential oil components over an extended duration, subsequently facilitating a prolonged release of active components into the wound. This sustained release mechanism holds promise for enhancing the therapeutic efficacy of the biomaterial, contributing to an effective impact on wound healing processes. For example, the results obtained from this analysis in the case of chitosan-based materials demonstrated that even at the highest concentrations of lavender essential oil, the biomaterial shows good homogeneity, indicating an effective absorption of the essential oil components in the chitosan matrix.
- Incorporating lavender essential oil and silver nanoparticles into the composition of the chitosan-based material resulted in an enhancement of its antimicrobial properties. The concomitant presence of these elements in the biomaterial demonstrates a strategic approach to fortifying its antimicrobial attributes, presenting potential applications in areas where antimicrobial characteristics are paramount. This multifaceted approach implies that these biomaterials could play a pivotal role in creating an environment conducive to efficient wound management. Thus, it can be stated that nanoparticles linked with natural products and phytochemicals emerge as highly promising platforms in the field of antibiofilm technologies.

The original contributions of this doctoral thesis, emphasized in the field of materials science and engineering, were validated and acknowledged by the publication in ISI WOS indexed journals (**Q1, Q2**) of **4 scientific articles** with a cumulative **Impact Factor of 17.3**.

The findings derived from this doctoral thesis will be augmented in the future through additional experimental perspectives:

→ *in vitro* assays that focus on: (i) biomaterial compatibility with blood components, and essential hemostatic parameters including clotting time, platelet aggregation, fibrin formation and (ii) biomaterial interaction with a diverse array of cell types relevant to wound healing, such as fibroblasts, endothelial cells, and immune cells;

→ *in vivo* assessments using animal models to evaluate the efficacy and safety of the biomaterials in a living organism and investigate the biomaterial's performance in promoting hemostasis and wound healing under physiological conditions;

→ investigations on the impact of different chitosan derivatives and variations in the formulation (cross-linking agents, essential oils, additives) to optimize the biomaterial's physical and chemical properties for enhanced hemostatic and wound healing capabilities.

Chapter 5 – Dissemination of research results

5.1. Publications based on the PhD topic (5)

5.1.1. Publications in internationally recognized journals – part of the PhD thesis – principal (first) author (4)

1. **Gheorghiță, D.**; Moldovan, H.; Robu, A.; Bița, A.I.; Grosu, E.; Antoniac, A.; Corneschi, I.; Antoniac, I. Bodog, A.D.; Băcilă, C.I. Chitosan-based Biomaterials for Hemostatic applications: A Review on Recent Advances. *International Journal of Molecular Sciences*, 2023, 24(13), Article number 10540. eISSN: 1422-0067, DOI: 10.3390/ijms241310540, WOS:001037279600001. **IF = 5.6, Q1.**
2. **Gheorghiță, D.**; Robu, A.; Antoniac, A.; Antoniac, I.; Ditu, L.M.; Raiciu, A.-D.; Tomescu, J.; Grosu, E.; Saceleanu, A. In Vitro Antibacterial Activity of Some Plant Essential Oils against Four Different Microbial Strains. *Applied Sciences-Basel*, 12(19), 2022, Article Number 9482. eISSN: 2076-3417, DOI: 10.3390/app12199482, WOS:000866648700001. **IF = 2.7, Q2**.
3. **Gheorghiță, D.**; Grosu, E.; Robu, A.; Ditu, L.M.; Deleanu, I.M.; Pircalabioru, G.G.; Raiciu, A.-D.; Bita, A.-I.; Antoniac, A.; Antoniac, V.I. Essential Oils as Antimicrobial Active Substances in Wound Dressings. *Materials*, 15(19), 2022, Article Number: 6923. eISSN: 1996-1944, DOI: 10.3390/ma15196923, WOS:000866914900001. **IF = 3.4, Q2.**
4. **Gheorghiță, D.**; Antoniac, I.; Moldovan, H.; Antoniac, A.; Grosu, E.; Motelica, L.; Ficai, A.; Oprea, O.; Vasile, E.; Ditu, L.M.; Raiciu, A.D. Influence of Lavender Essential Oil on the Physical and Antibacterial Properties of Chitosan Sponge for Hemostatic Applications. *International Journal of Molecular Sciences* 2023, 24, Article number 16312. DOI: 10.3390/ijms242216312. **IF = 5.6, Q1.**

5.1.2. Publications in internationally recognized journals – part of the PhD thesis – principal (corresponding) author (1)

1. Moldovan, H.; Antoniac, I.; **Gheorghiță, D.**; Safta, M.S.; Preda, S.; Broasca, M.; Badila, E.; Fronea, O.; Scafa-Udriste, A.; Cacoveanu, M.; Molnar, A.; Costache, V.S.; Zaharia, O. Biomaterials as Haemostatic Agents in Cardiovascular Surgery: Review of Current Situation and Future Trends. *Polymers* 2022, 14 (6), Article number 1189. eISSN: 2073-4360, DOI: 10.3390/polym14061189, WOS:000776311300001. **IF = 5, Q1**.

5.1.3. Selective presentations at international conferences (2)

1. **Gheorghiță, D.**; Grosu, E.; Robu, A.; Ditu, L.M.; Deleanu, I.M.; Gradisteanu Pircalabioru, G.; Antoniac, A.; Antoniac, I.; Antimicrobial effects generated by essential oils in wound dressings, *RoMat - The 9th International Conference on Materials Science and Technologies, November* 24-25, 2022, Bucharest, Romania. Oral presentation.
2. **Gheorghiță, D.**; Antoniac, I.; Moldovan, H.; Antoniac, A.; Robu, A.; Bița, A.I.; Ficai, A.; Motelica, L. Influence of lavender essential oil on antioxidant, physical and biological properties of chitosan sponge for hemostatic applications, *BioReMed - The International Conference on Biomaterials and Regenerative Medicine*, July 19-21, 2023, Sibiu, Romania. Poster presentation.

5.2. Complete list of publications (25)

1. Moldovan, H.; Tiganasu, R.; Calmac, L.; Voica, C; Broasca, M.; Diaconu, C.; Ichim, V.; Cacoveanu, M.; Mirea, L.; Nica, C.; Minoiu, C.; Dobra, I.; **Gheorghiță, D.**; Dorobantu, L.; Molnar, A.; Iliuta, L.; Same Clinical Reality of Spontaneous Rupture of the Common Iliac Artery with Pseudoaneurysm Formation-Comparison of Two Therapeutical Solutions, Endovascular Stent-Graft and Open Surgical Correction, for Two Cases and Review of the Literature. *Journal of Clinical Medicine*, 2023, 12(2), Article number 713. eISSN: 2077-0383, DOI: 10.3390/jcm12020713, WOS: 000915500700001. IF = 3.9, **Q2**.
2. Petreanu, C.A.; Vlasceanu, S.; Zaharia, D.; Jipa, D.; Moldovan, H.; **Gheorghiță, D.;** Iliuta, L.; Radulescu, B.; Badarau, I.A.; Savu, C.F. Spontaneous Pulmonary Hematoma: Case Report of a Giant Post-COVID-19 Hematoma and Literature Review. *Healthcare*, 2023, 11(4), Article number 527. eISSN: 2227-9032, DOI: 10.3390/healthcare11040527, WOS: 000938622900001. IF = 2.8; **Q2**.
3. Buhas, C.L.; Pascalau, A.; Judea-Pusta, C.T.; Pop, O.L.; Judea, A.S.; Negrutiu, B.M.; Marcut, L.; Buhas, B.A.; **Gheorghiță, D.**; Bodog, A.D. Epidermoid Cyst of the Uterine Cervix, an Unusual Location: Literature Review and Case Report. *Healthcare*, 2023, 11(2), Article number 257. eISSN: 2227-9032, DOI: 10.3390/healthcare11020257, WOS:000915192700001, IF = 2.8; **Q2**.
4. Vlasceanu, S.; Bobocea, A.; Petreanu, C.A.; Badarau, I.A.; Moldovan, H.; **Gheorghiță, D.;** Antoniac, I.V.; Mirea, L.; Diaconu, C.C.; Savu, C.; Pulmonary Crohn's Disease or Crohn's Disease with Lung Sarcoidosis? A Case Report and Literature Review. *Healthcare*, 2022, 10(11), Article number 2267. eISSN: 2227-9032, DOI: 10.3390/healthcare10112267, WOS: 000910785500001. IF = 2.8; **Q2**.
5. Moldovan, H.; Bulescu, C.; Cacoveanu, M.; Voica, C.; Safta, S.; Goicea, M.; Dobra, I.; Antoniac, I.; **Gheorghiță, D.;** Zaharia, O. Minimally Invasive Surgical Repair of a Partial Atrioventricular Canal Defect in a 20-Year-Old Patient—A Case Report and Review of Literature. *Journal of Cardiovascular Development and Disease*, 2022, 9(10),

Article number 352. eISSN: 2308-3425, DOI: 10.3390/jcdd9100352, WOS:000873168200001. IF = 2.4, **Q3**.

6. Moldovan, H.; Ciomaga, I.; Nechifor, E.; Tiganasu, R.; Badea, A.; Dobra, I.; Nica, C.; Scarlat, C.; **Gheorghiță, D.**; Antoniac, I.; Ondin, Z. A Rare Case of Left Ventricular Malignant Peripheral Nerve Sheath Tumour—Case Report and Review of the Literature. *Medicina-Lithuania*, 2022, 58(10), Article number 1404. eISSN: 1648-9144, DOI: 10.3390/medicina58101404, WOS: 000873278000001. IF = 2.6, **Q3**.

7. Robu, M.; Marian, D.R.; Vasile, R.; Radulescu, B.; Stegaru, A.; Voica, C.; Nica, C.; **Gheorghiță, D.**; Zaharia, O.; Iulian, A.; Moldovan, A.; Pavel, V.; Moldovan, H.; Iliescu, V.A. Delayed Surgical Management of Acute Type A Aortic Dissection in a Patient with Recent COVID-19 Infection and Post-COVID-19 Bronchopneumonia—Case Report and Review of Literature. *Medicina-Lithuania*, 2022, 58(10), Article number 1357. eISSN: 1648-9144, DOI: 10.3390/medicina58101357, WOS:000873242900001. IF = 2.6, **Q3**.

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11. Moldovan, H.; Bulescu, C.; Sibisan, A.M.; Tiganasu, R.; Cacoveanu, C.; Nica, C.; Rachieru, A.; **Gheorghiță, D.**; Zaharia, O.; Balanescu, S.; Scafa-Udriste, A. A Large Ascending Aorta Thrombus in a Patient with Acute Myocardial Infarction—Case Report. *Medicina-Lithuania*, 2021, 57(11), Article number 1176. eISSN: 1648-9144, DOI:10.3390/medicina57111176, WOS:000728222200001. IF = 2.6, **Q3**.

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13. Moldovan, H.; Sibisan, A.M.; Tiganasu, R.; Nechifor, E.; **Gheorghiță, D.**; Zaharia, O.; Albu, M.; Popescu, D.; Molnar, A.; Craciun, M.; Scafa, A. Surgical Treatment in a High-Risk Pulmonary Embolism: Case Report, *Medicina-Lithuania*, 2021, 57(7), Article number 725. eISSN: 1648-9144, DOI: 10.3390/medicina57070725, WOS:000678190700001. IF = 2.6, **Q3**.

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