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Sustainable electrospun materials with enhanced blood compatibility for wound healing applications—A mini review

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Abstract

Wound healing is a complex process that requires an appropriate environment to support healing. Wound dressings play a crucial role in wound management by protecting the wound and promoting healing. Recent advancements in wound dressing technology include the development of bio-absorbable electrospun dressings incorporating essential oils, which have shown promise in enhancing wound healing potential. However, there is still a need for sustainable wound dressing technology that is effective, safe, and environmentally friendly. This review addresses this need by emphasizing the potential of bio-absorbable electrospun wound dressings incorporating essential oils and advocating for a paradigm shift toward sustainable crop-origin materials and the elimination of toxic solvents in wound dressing fabrication.

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Introduction

In clinical applications, wound dressings are used to assist the wound healing process and stop further complications. Recent research shows the efficacy of novel wound dressings by developed using sustainable origin biomaterials. Sustainable materials are typically crop origin and thus do not have a negative impact on either environment or the population. The search for effective and sustainable wound healing materials has been in progress since ancient times. The first recorded wound dressing materials were made using honey pastes, plant fibers, and animal fats [1]. Currently, a number of polymeric biomaterials have been developed as wound dressing materials and are expected to provide novel characteristics favoring the wound healing process [2]. For an effective wound dressing design, the researcher must consider the following.

1) The characteristics of the wound,
2) The wound healing time,
3) The required physical, chemical and mechanical properties of the wound dressing materials [3].

Hence, the aim of the researcher is to develop materials to aid the repair of the wound and achieve the highest rate of healing. A brief introduction to the skin and types of wounds, traditional and modern wound dressing available in the market, their drawbacks, and recent development of essential oil (EO)-incorporated electrospun materials as a sustainable source for minimizing the drawbacks of commercial wound dressings is presented in this review.

Skin and its layers

The skin is the largest organ in the human body which acts as a shield against heat, light, injury, and infection. The skin also performs other functions like regulating body temperature, storing water and fat, and acting as a sensory organ. The skin contains three layers—the epidermis, dermis, and subcutaneous fat layer (hypodermis) [4,5]. The epidermis is the thin outer layer of the skin and contains three types of cell squamous, basal, and melanocytes. The dermis forms the middle layer of the skin, and it contains the blood vessels, lymph vessels, hair follicles, sweat glands, collagen bundles, fibroblasts, nerves, and sebaceous glands. This layer provides skin flexibility and strength. The subcutaneous fat layer forms the deepest layer of skin containing a network of collagen and fat cells. This layer insulates and absorbs impact, helping to regulate body temperature heat and protect the body from injury [6].

Definition of skin wound and types of wounds

An injury or tear to the skin surface is defined as wound—formally a wound is said to be an interruption of skin structure or function. Damage to the skin may be caused by physical, chemical, mechanical, or thermal means. Generally, there are two types of wounds acute and chronic. Acute wounds are caused by trauma that may result from mechanical damage or exposure to extreme heat, radiation, or chemicals. Acute wounds may typically heal within 8–12 weeks. Treatments for these wounds depend on the severity. Chronic wounds are injuries caused by specific diseases, such as diabetes, tumors, or severe physiological contamination. These wounds might take more time to heal than 12 weeks expected for an acute wound [7].

Wound healing process

Wound healing is a complex and dynamic process that involves four continuous and overlapping phases. These phases occur in a precise and regulated manner. The wound healing process can be delayed by certain interruptions and aberrancies. The four phases of wound healing [8,9] are as follows. The first phase is hemostasis which occurs immediately when blood leaks out of the body. Hemostasis is a process in which the wound is closed by vascular constriction and fibrin clot formation. The next stage is inflammatory which begins when the injured blood vessels leak an exudate resulting in localized swelling. This exudate comprises water, salt, and proteins. The role of the exudate is to remove damaged cells, pathogens, and bacteria from the wound area, and the inflammation stage is when bleeding stops and wound infection should be prevented. This phase also helps repair cells to move to the site of the wound to commence healing. The third stage is the proliferative phase in which the wound is rebuilt with the formation of the new tissue contains collagen and an extracellular matrix. In the proliferative phase, the wound begins to close as new tissues are produced. In addition, new blood vessels are constructed resulting in the generation of the healthy granulation tissue which can then receive sufficient oxygen and nutrients. Granulation tissue is composed of fibroblast cells, endothelial cells, capillaries, and keratinocytes. If the granulation tissue is pink and does not bleed easily, it is a sign of healthy wound healing. However, dark granulation tissue is a sign of infection, ischemia, or poor perfusion. In the final phase of the proliferative stage of wound healing, the wound surface will be closed by epithelial cells. Epithelialization occurs faster if the wound is kept moist and hydrated. The final stage is the maturation phase in which the remodeling of collagen from type III to type I occurs, and the wound should fully close. The cells which are no longer needed to repair the damaged tissue are removed by apoptosis. In the maturation phase, collagen tends to align in tension lines, and water is reabsorbed making the collagen fibers closer together and cross-linking occurs. Cross-linking of collagen helps in reducing the scar thickness and also makes stronger skin in the area around the wound [10]. The schematic representation of wound healing mechanism was provided in Figure 1 [11].

Wound dressings

To aid wound healing, a dressing is applied to protect the wound from complications resulting from contamination or disturbance. A variety of wound dressings are used to best suit different types of wounds. Wound dressings help to stop bleeding, activate clotting, and remove excess exudates and general wound debridement [12]. An ideal wound dressing should meet certain requirements such as:

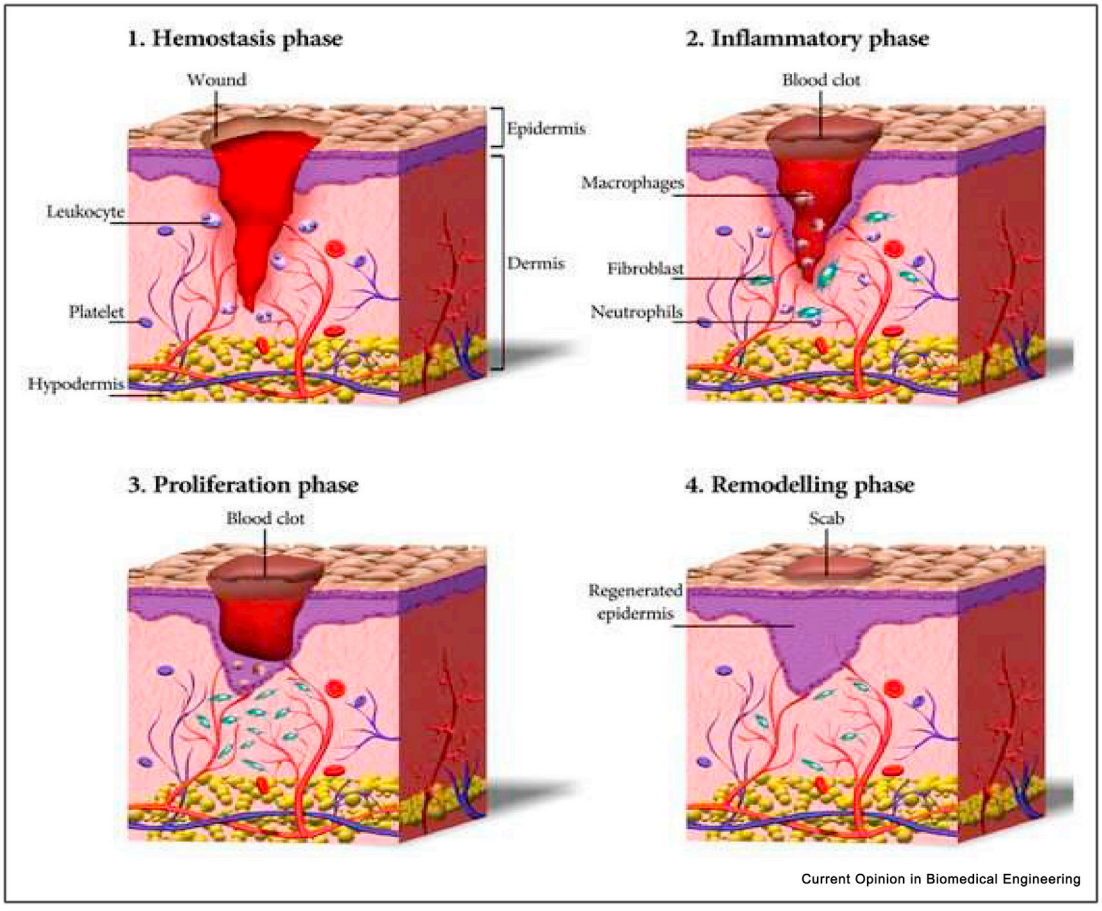
(1) maintaining moisture around the wound,
(2) gas permeability,
(3) removing excess exudates,
(4) protection against infections
(5) render mechanical protection
(6) easy to change or remove,
(7) biocompatible, biodegradable, and nontoxic,
(8) low cost [13].

Wound dressings may be broadly classified into traditional and modern wound dressings.

Traditional wound dressing

Traditional wound dressings were made from gauze, lint, plasters, bandages (natural or synthetic), or cotton wool. Gauze dressings were produced from woven and nonwoven cotton, rayon, and polyester fibers. Bandages were made from cotton wool, cellulose, or polyamide materials. Some commercial wound dressings of this type are Xeroform™, Bactigras, Jelonet, and Paratulle. Traditional dressings are typically used for treating clean and dry wounds, and one of the major disadvantages of

Figure 1



A schematic illustration depicting the four stages of wound healing: hemostasis, inflammatory phase, proliferative phase, and remodeling phase, highlighting the key cellular and molecular events involved in each stage (Reproduced for Shima Tavakoli and Agnes S. Klar 2020).

these traditional dressings is failure to maintain the moist environment required for wound healing [14].

Modern wound dressings

Over recent years, modern wound dressings have undergone significant advancements and now come in various types, each specifically designed to address particular wound types and healing requirements. Hydrocolloid dressings are ideal for wounds with moderate to heavy exudate due to their high absorbency. Foam dressings, on the other hand, are absorbent and created for wounds with heavy exudate. Alginate dressings, made from seaweed, are highly absorbent and primarily used for wounds with heavy exudate. Hydrogel dressings promote a moist wound environment and are recommended for wounds with minimal to moderate exudate. Transparent film dressings act as a barrier against moisture and bacteria and are frequently utilized for superficial wounds or as a secondary dressing to secure other dressing types in place. Antimicrobial dressings contain agents that can prevent wound infections, whereas collagen dressings encourage new tissue growth and facilitate the healing of chronic wounds [15–17].

Advancement of electrospun bioactive dressings for wound

Modern wound dressing has the ability to maintain the wound in a suitably moist environment but can fail to meet certain requirements of the ideal wound dressing such as cell adhesion, accelerating wound healing, and eradicating infections [18]. Synthetic polymers are reported to possess low cell attachment behavior and antibacterial effects which may slow the wound healing process [19,20]. Hence, there is a need for advanced bioactive polymeric dressings with better blood/biocompatibility and excellent antimicrobial activity.

Blood compatibility is an important criterion, the lack of which limits the clinical applicability of wound healing dressings. Advanced wound dressing materials are designed to interact with the wound environment which is predominantly comprised of blood components [21].

There is a necessity to avoid harmful interactions between the blood and the developed material, which could be investigated by examining the activation and destruction of blood components. The purpose of the blood compatibility assessment is to evaluate any adverse effects of blood-contacting materials on hemolysis, thrombosis, coagulation, and platelets. Different tests such as activated partial thromboplastin time (APTT), prothrombin time (PT), and hemolysis are performed to evaluate the blood compatibility of the developed materials [22]. Biocompatibility is defined as the degree of interaction between developed materials and the host tissues and cells. Biocompatibility determines the cell response to newly developed dressings behavior in terms of adhesion, spreading, proliferation, and differentiation [23]. Biocompatibility of the new wound dressing could be improved by mimicking the structure of extracellular matrix (ECM) of human tissues. It has been reported that the dressings based on electrospinning have the ability to mimic the ECM of the human tissue.

Electrospinning is a simple and versatile method that produces ultrathin fibers with diameters ranging from micro- to nano-meters [24,25]. Typical electrospinning apparatus comprises a high voltage power supply, a syringe pump, and a collector drum. The spinnable solution is placed in the syringe pump and subjected to a high voltage electric field. A fiber strand is drawn from the syringe tip by electrostatic attraction and dries to fibers while in flight to the collector drum. The fibrous product possesses a high surface area-to-volume ratio and a porous structure [26]. The porous structure of electrospun membranes contains tiny pores that can help in reducing bacterial infections [27]. Moreover, the high surface-to-volume ratio of nanofibers facilitates wound closure through cell adhesion, proliferation, and differentiation [28].

Antimicrobial activity in a wound dressing is essential as it inhibits the growth of microbes in the wound and thus promotes effective wound healing by reducing the risk of infection. The most common bacterial strains that cause wound infections are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Acinetobacter baumannii*. Among these, Gram-positive bacteria, particularly *S. aureus*, tend to colonize the wound site in the initial phase of the infection. Later in the infection, Gram-negative bacteria, such as *P. aeruginosa* and *A. baumannii*, start to colonize the wound, which can delay the healing process [29]. Suitable antimicrobial effects are widely displayed by sustainable natural materials, such as EOs. EOs are natural materials derived from plants. They are organic and volatile compounds present in complex mixtures as secondary metabolites. Plants typically contain 20–60 components at varying concentrations. Plants EOs are characterized by two or three main components present in high (20–70%) concentrations. Some important compounds of EO are mono and sesquiterpenes, carbohydrates, phenols, alcohols, ethers, aldehydes, and ketones. These components of EOs are reported to have various activities such as antibacterial, antiviral, antifungal, antimycotic, and insecticidal properties. EOs are reported to hold commercial importance in a number of applications such as cosmetics, food and pharmaceutical industries, and agriculture [30]. In wound healing applications, certain EOs play an important role in accelerating the wound healing process. Some studies report the use of EOs for wound healing applications demonstrating a positive effect on wound healing [31,32]. The next section will focus on recent developments of electrospun wound dressings decorated with EOs.

Essential oil-incorporated electrospun polymeric materials for wound healing

Several studies have demonstrated that electrospun polymers incorporating natural materials have proven to be bioactive in wound healing applications [33–38]. Few studies also reported the polymers containing nanoparticles in making wound dressings [39–45]. More recently, there has been significant interest in essential oilEO-loaded electrospun dressings for use in wound healing applications. These dressings have been shown to offer improved wettability, biocompatibility, accelerated wound healing, and enhanced antimicrobial activity. The putative mechanism of action of EOs in the wound healing process is thought to involve the stimulation of fibroblast migration to the wound site, as well as potential antimicrobial activity. This stimulation results in heightened collagen production and remodeling at the wound site, while the antimicrobial properties of certain EOs may help prevent or reduce infection [46]. Studies have reported the direct loading of diluted EO into a homogenous polymer solution, followed by stirring for several hours to ensure even dispersion. Finally, the solution is converted into fibers using the electrospinning technique [47,48]. Pakolpakçıl et al. developed a novel material by using polylactic acid loaded with herbal-infused *Hypericum perforatum* (HP) oil for wound dressings. An HP oil-loaded polylactic acid displayed high antibacterial properties for wound dressing applications [49]. Unnithan et al. developed a scaffold based on polyurethane containing emu oil (derived from emu (*Dromaius novaehollandiae*) body fat) for wound healing applications. Their PU/emu oil scaffold showed long-term cell growth and provided good antibacterial activity compared to the pure polyurethane [50]. In another study, Manikandan et al. developed a polyurethane scaffold loaded with murivennai oil (a coconut oil-based medicated ayurvedic oil formulation). The murivennai-polyurethane scaffold displayed hydrophilic behavior and improved blood compatibility compared to pure polyurethane fibers. The APTT and PT values of pure PU were 157 $\pm$ 5.55 s and 38.33 $\pm$ 1.15 s and while PU/

Table 1

Electrospun combination of essential oils and polymeric materials for wound healing.

Name of the researcher's	Polymer	Additives	Findings	Reference
Pakolpakçõl et al.	Polylactic acid	Herbal-infused oil (*Hypericum perforatum*, HP)	High antibacterial properties	[25]
Unnithan et al.	Polyurethane	Emu oil	Long-term cell growth and provided good antibacterial activity	[26]
Manikandan et al.	Polyurethane	Murivennai oil	Hydrophilic behavior and improved blood compatibility	[27]
Jaganathan et al.	Polyurethane	Turmeric oil	Improved wettability and enhanced proliferation of fibroblast cells	[28]
Nordin et al.	Polyurethane	Fish oil	Hydrophilic nature and improved hemocompatibility behavior	[29]
Fawal et al.	Polycaprolactone/ gelatin	Oregano oil	Biocompatibility and significant antimicrobial results	[30]
Zargham et al.	Polyethylene oxide/ chitosan/PCL	Olive oil	Higher antibacterial activity and cell proliferation of HDF fibroblast cells	[31]
Jaganathan et al.	Polyurethane	Peppermint oil/copper sulfate	Hydrophilic behavior, improved blood clotting time, less toxic behavior, and higher cell viability	[32]
Mani et al.	Polyurethane	Neem oil/magnesium oxide	Improved physicochemical properties	[33]

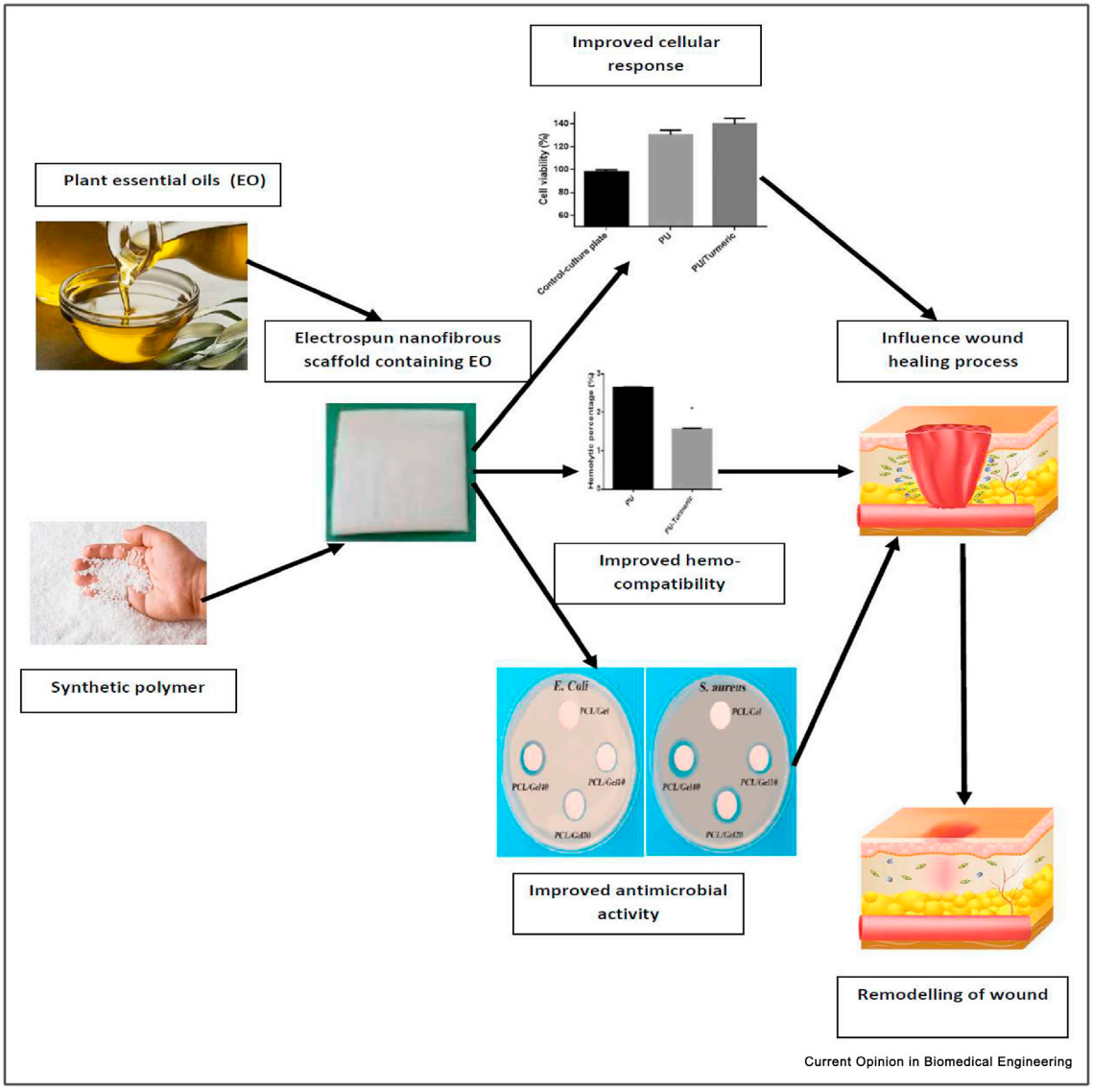
murivennai showed APTT and PT values of 211 ± 2.45 s and 51 ± 1.54 s, respectively. Further, the hemolytic value of pure PU was 2.73% compared to 0.86% for PU/murivennai leading to the conclusion that it is potential material for wound healing applications [51]. Jaganathan et al. fabricated a polyurethane scaffold with turmeric *(Curcuma longa)* oil for wound healing applications. The fabricated polyurethane/turmeric oil showed improved wettability and enhanced proliferation of fibroblast cells compared to the pure polyurethane suggesting suitability for wound healing applications [52]. Nordin et al. also developed a wound dressing scaffold based on polyurethane added with *Channa striatus* (CS) oil. The polyurethane containing CS showed hydrophilic nature and improved hemocompatibility behavior suitable for wound dressing applications [53]. Fawal et al. developed a hybrid film based on PCL/gelatin containing oregano (*Origanum vulgare*) oil for wound healing applications. The developed PCL/gelatin/oregano oil demonstrated biocompatibility and significant antimicrobial results compared to the PCL/gelatin for wound dressing applications [54]. In another study, Zargham et al. developed a wound dressing hybrid scaffold based on polyethylene oxide (PEO)/chitosan/polycaprolactam (PCL)/olive (*Olea europaea*) oil. The developed PEO/CS/PCL/olive oil nanofibrous dressing displayed higher antibacterial activity and cell proliferation of Human Dermal Fibroblasts (HDF) cells facilitating wound healing applications [55]. An electrospun combination of EOs with metallic salts combining peppermint (*Mentha* × *piperita*) oil mixed with copper sulfate displayed hydrophilic nature and enhancement of blood clotting time and cell viability compared to the pure polyurethane [56]. In a recent study, Mani et al. developed an electrospun polyurethane scaffold with the combination of neem oil and magnesium oxide. The developed composite showed improved physicochemical properties suggesting it as a suitable candidate for wound healing applications [57]. A summary of these studies is listed in Table 1. The EOs used in this study were obtained from medicinal plants that are easily accessible, and thus offer a cost-effective and natural source of bioactive compounds for incorporation into electrospun dressings [58]. However, one of the major limitations of EOs is their potential to induce allergic reactions, which emphasizes the need for careful consideration of the optimal concentration of these compounds in wound healing applications [59].

From the above studies, EO-incorporated electrospun polymeric materials improve the quality wound treatments (Figure 2). Coagulation and hemolysis assessments signify superior blood compatibility of the EO-incorporated electrospun wound dressings. Cell adhesion and proliferation studies revealed the improved biocompatibility, and antimicrobial tests demonstrated the desirable inhibitory effect of the electrospun EO wound dressings. These dressings are not yet available for clinical applications, and this is mainly due to the lack of validating clinical studies. However, before initiating these clinical studies, it is essential to conduct more research on using biodegradable polymers and process optimization to make this a sustainable option.

Overcoming electrospinning drawbacks

In the electrospinning technique, a wide range of synthetic polymers have been successfully as spun. The

Figure 2



Electrospun combination of polymer and essential oils for wound healing dressings.

polymers commonly used in wound dressings are petroleum-derived products. Some petroleum-derived polymers are not readily biodegradable owing to their resistance to microbial degradation resulting in excessive environmental persistence [60]. The toxic solvents used in the process of fabrication like dimethylformamide (DMF) and trichloromethane (AKA chloroform) release toxic vapors which may harm the environment and human health. If scale-up is required, especially at a large scale, the usage and storing of organic solvents pose severe risks like explosion and flammability [61]. Toxic vapors of the organic solvents have been linked to carcinogenicity, and it further restricts the use of these advanced electrospun biomaterials.

The prospective solution requires future sustainability which will be the development of "green" wound dressings using non-toxic aqueous solvents instead of the organic ones. Researchers are investigating the use of aqueous and some food grade solvents (Q3C) and are able to show characteristic fiber properties conducive for medical devices [62]. Another route to achieve sustainability of EO dressings is to explore modified electrospinning process like emulsion electrospinning where

the creation of an emulsion within an aqueous solution using EOs, thereby minimizing the need for organic solvents. Further, instead of using polymeric solution, direct polymer melts technologies like melt electrospinning, and electro-writing could be explored for EO dressings.

Conclusions and future prospects

In conclusion, this review highlights the potential benefits of electrospun wound dressings incorporating EOs for wound healing. EOs have demonstrated antimicrobial properties that make them desirable candidates for wound care products. Electrospun dressings offer several advantages, including high porosity, good mechanical properties, and the ability to incorporate various bioactive agents. The use of natural bio-derived polymers and non-toxic solvents in the electrospinning process can lead to the development of environmentally sustainable wound dressings. However, further research is needed to optimize the effectiveness of electrospun dressings incorporating EOs. Testing for antimicrobial activity and other properties simultaneously for all oils can provide a better understanding of which oils are most effective for wound healing. New studies should explore different oil types, concentrations, and the use of different polymer matrices. In addition, the development of sustainable wound dressing materials remains a challenge. Future research should focus on developing biodegradable materials synthesized from natural bio-derived polymers and avoiding the use of toxic solvents to meet the demand for environmentally friendly and high-performance wound dressings. Overall, the findings of this review provide valuable insights for researchers, clinicians, and stakeholders in the wound healing field to facilitate the development of effective and sustainable wound dressings. The potential benefits of electrospun wound dressings incorporating EOs are promising, and further research in this area could lead to the development of innovative and effective wound care products.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

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* of special interest
** of outstanding interest

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