

# POLYMER AND BIOPOLYMER BLENDS IN WOUND HEALING AND BONE REPAIR - A REVIEW

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## Abstract

*This review paper is focused on the applications of polymeric blends in the biomedical field, with a particular emphasis on their use in wound healing and bone repair. The requirements for suitable materials in these areas arise from the complex mechanisms underlying the regeneration processes. Wound healing is characterized by four distinct phases: hemostasis, inflammation, cell proliferation, and remodeling. Similarly, bone healing also includes inflammation, cell proliferation, and remodeling stages. Natural polymers are often favored for biomaterial fabrication due to their biocompatibility, whereas synthetic polymers are selected because of their superior mechanical properties and easy fabrication of different shapes. Natural polymers play a critical role in all phases of wound healing, owing to their advantageous characteristics. Polymeric blends have the potential to integrate beneficial attributes of both natural and synthetic polymers, thereby enhancing the efficacy of wound healing and bone repair processes. The blending of polymers can lead to improved properties, particularly mechanical strength, while mitigating the limitations associated with individual polymers. A review of the scientific literature indicates a growing trend in research on polymer and biopolymer blends for potential applications across biomedical domains, specifically in areas related to wound healing, bone repair, and healthcare technology.*

**Keywords:** wound healing, polymer blends, natural polymers, synthetic polymers, bone repair, bone healing

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## Introduction

Polymers are widely used in biomedical applications, and every year, many scientific papers are published regarding polymer modifications for specific uses. Natural polymers have the advantages of biocompatibility, and synthetic polymers have excellent mechanical properties [1]. Toh et al. mentioned that individual polymers did not hold all the desired properties for biomedical applications [2]. Bao et al. reported the lack of good mechanical properties in the case of natural polymers [3]. However, several natural polymers are easy to modify [4]. Nyamweya described that polymer blending is essential to overcome the issues linked to individual polymers [5]. Kaur et al. reported that polymer blending is an economical process and may lead to interesting materials [6]. Basak et al. research mentioned the improved properties of polymer blends as compared to individual/raw polymers [7]. Polymer blending can be defined as the mixing of polymers [8]. It has been mentioned in the study conducted by Qin that the presence of at least two polymers is necessary for polymer blends fabrication [9]. Polymer blends may overcome limitations presented by single polymers [10,11]. Martinova and Lubasova mentioned polymer blending as a way of combining the characteristics of individual polymers [12]. Toh et al. highlighted that polymer blending can achieve the target of enhanced mechanical properties [2]. Afshar et al. research indicated that polymeric blending leads to improved physicochemical properties [13]. Several studies [14,15] have reported that natural polymers play a role in the mimicking of the extracellular matrix (ECM). This review paper discusses the latest achievements in the applications of polymer blends in wound healing and bone repair.

## Wound

The wound is the discontinuation of the anatomical structure of the tissue and the disruption to the epithelial integrity of the skin. The wound's creation can be unintentional or intentional, as in accidents or in surgical incisions [16,17]. Maqsood has highlighted the two main types of wounds: acute and chronic. The main reason for the acute wound has been mentioned as the environmental factors that result in the traumatic injury. In the case of chronic wounds, the main concern highlighted in the study was metabolic disorder [18]. Atiyeh et al. [19] indicated that the wound healing process in acute wounds follows an order or a time. Falanga et al. [20] wrote their concern about chronic wounds that did not heal within the expected time frame. Pađen et al. [21] also reported that chronic wounds deviate from the normal healing timeframe. Dave [22] explained the classification of chronic wounds such as vascular ulcers, diabetic ulcers, and pressure ulcers. Santo et al. [23] expressed the major vascular ulcers as either arterial or venous. Arterial ulcers usually result from the lowest supply of blood [24], and they also attack pressure points [25]. Arterial ulcers leading cause is the deficiency of blood-tissue perfusion [26]. Perfusion is the process responsible for maintaining the oxygen and nutrients supply through the blood to the tissue [27]. Venous ulcers are also called varicose or stasis ulcers [28]. Herman et al. described the four major types of wounds: class 1, class 2, class 3, and class 4 [29]. Class I wounds are expressed as the cleanest wounds by Gorvetzian et al. [30], and the absence of inflammation has been indicated in class I wounds. Class II has been highlighted as clean/contaminated wounds by Onyekwelu et al. [31]. Smilanich et al. [32] mentioned that class III wounds are contaminated wounds. Takeda et al. [33] reported that class IV wounds are dirty-infected wounds. Obviously, each class of wounds requires specific materials for wound healing.

## Wound healing

Ambekar et al. [34] reported the four significant stages/phases of wound healing: hemostasis, inflammation, cell proliferation, and remodeling. Peña et al. [35] also described the phases of wound healing. They reported the hemostasis phase as the clot formation phase and the cell proliferation phase as the new tissue formation phase. Versteeg et al. [36] mentioned that processes such as blood coagulation, activation of platelets, and vascular repair play a key role in hemostasis. Wang and Zhang [37] highlighted that in hemostasis, constriction of blood vessels encourages clot formation and discourages blood loss. The gathering of platelets supports the formation of the blood clot. Nurden et al. [38] also noted that platelets are prominent in preventing blood loss. Etulain [39] mentioned that platelets play an influential role in thrombosis. Huang et al. [40] summarized in their study that platelets promote hemostasis regulation by favoring blood coagulation. Ferrer-Raventós and Beyer [41] defined platelets as small blood cells that do not have a nucleus, so the authors termed it anucleated. Several studies [42-46] indicated the absence/lack of a nucleus in the case of platelets. Ashorobi et al. [47] defined thrombosis as the formation of a blood clot inside the blood vessel, which restricts the flow of blood. Parise [48] reported the megakaryocytes as the derivation source of platelets. Eldor et al. [49] discussed the function of megakaryocytes, and their primary function, like platelet assembly, was stressed in their study. Studies [50,51] presented megakaryocytes as precursor cells of platelets.

Holzer-Geissler et al. [52] reported the significance of the inflammatory phase of wound healing in removing debris and pathogens from the wound site. In the inflammatory phase of wound healing, the recruitment of neutrophils occurs [53]. The inherent function of neutrophils is to play a defensive role, considering the immune response [54,55]. Pang et al. [56] described the role of macrophages in the inflammatory phase of wound healing and their well-known role during the initial phase of inflammation. Macrophages also play a role in the removal of dead cells. Ellis et al. [57] also mentioned that macrophages have a key role in disposing of toxic metabolites. Zhou et al. [58] indicated that macrophages are responsible for producing cytokines, chemokines, and growth factors. Ono et al. [59] reported that chemokines activate leukocytes. Leukocyte is the widely used term for the white blood cells [60]. Ridiandries et al. [61] expressed the prime objective of chemokines to encourage and discourage angiogenesis. Cytokines are small proteins, and cytokines play a communicative role between cells [62]. Feghali et al. [63] reported the contributive role of cytokines like IL-1 in inflammation. Interleukins (ILs) have the capability to act as pro-inflammatory and anti-inflammatory [64]. Al-Qahtani et al. [65] highlighted the pro-inflammatory role of IL-1 $\beta$ , IL-6, and IL-12 in diseases such as sepsis, pneumonia, and tuberculosis, respectively. Cytokines such as IL-10, IL-1Ra, IL-4, and IL-13 show anti-inflammatory effects in diseases such as HIV infection, rheumatoid infection, allergies, and asthma, respectively. Mahmoud et al. [66] mentioned that IL-6 influenced fibrogenesis and angiogenesis during wound healing. Guth et al. [67] study indicated that the enhancement of inflammation was based on mast cells. Studies [67-70] reported mast cells as innate immune cells.

Mercandetti et al. [71] mentioned the proliferation phase of wound healing, and it has been indicated that the proliferative phase of wound healing is mainly composed of fibroplasia, matrix deposition, angiogenesis, and re-epithelialization. The fibroblast located at the edges of the wound favors collagen synthesis to promote wound healing, and this process is termed as fibroplasia.

Granulation tissue (derivation source fibroblast) and the extracellular matrix (ECM) collective combination have been termed fibroplasia in the study [72]. Steed discussed fibroplasia as the wound healing phase [73]. It has been indicated that fibroblasts are essential in maintaining the integrity of the extracellular matrix (ECM), growth factors, and skin remodeling. The fibroblast also plays a communicative role within cells [74]. Wu et al. [75] described the multipotent nature of mesenchymal stem cells. Multipotent stem cells tended to differentiate themselves into multiple stem cells [76]. The differentiation of stem cells leads to the generation of cells such as dermal fibroblast, keratinocytes, and endothelial cells [75]. Soliman et al. [77] reported that angiogenesis is a significant step in the proliferation phase of wound healing. Song et al. [78] defined angiogenesis as the process responsible for forming new blood vessels from existing blood vessels, which aims to maintain the transportation of proteins and nutrients. Schaper and Buschmann [79] termed angiogenesis simply as capillary sprouting. Salavati and Soltani [80] indicated that the proliferation of endothelial cells was vital for the extension of the sprouts network. Several studies [81-84] mentioned the pivotal role of vascular growth factor (VEGF) in angiogenesis. VEGF regulates/promotes angiogenesis in the case of wound healing [85,86]. The VEGF family mainly comprises the VEGF-A, -B, -C, -D, and the placental growth factor (PIGF) [87]. VEGF-A is of notable importance in the initial phase of angiogenesis, as it involves the migration and proliferation of endothelial cells [88]. VEGF-B is key to heart and muscle cell survival [89]. Saaristo et al. [90] found that VEGF-C effectively healed the diabetic mice's wound, and this wound healing happened due to lymph-angiogenesis. Bouanzoul and Rosen [91] described the lymph-angiogenesis role of VEGF-D. Leitch et al. [92] mentioned that VEGF-D promoted corneal angiogenesis. It has been indicated in several studies [93-96] that VEGF-D is also called c-Fos-induced growth factor (FIGF). Odorasio et al. highlighted the well-known role of placental growth factor (PIGF) in wound healing due to angiogenesis [97]. Yoo et al. [98] presented a detailed study mentioning that PIGF-1 and PIGF-2 boosted cell proliferation. The receptor vascular endothelial growth factor (VEGF) and its members are presented in FIG. 1.

The differentiation of stem cells also leads to keratinocytes [75,99], and keratinocyte proliferation is the leading promoter of re-epithelialization [100]. Amar and Wu [101] defined the re-epithelialization process as the migration and proliferation of keratinocytes that participate in the formation of the epithelium. The remodeling phase of wound healing is connected to the progression/transformation/development of the granulation tissue into the scar [102,103]. The prime objective of remodeling wound healing is to attain the target of maximized tensile strength [104]. Lux described the last phase of wound healing as the maturation phase [105]. The remodeling phase of wound healing mainly focuses on the reorganization of collagen, and this reorganization happens from collagen III to collagen I [106].

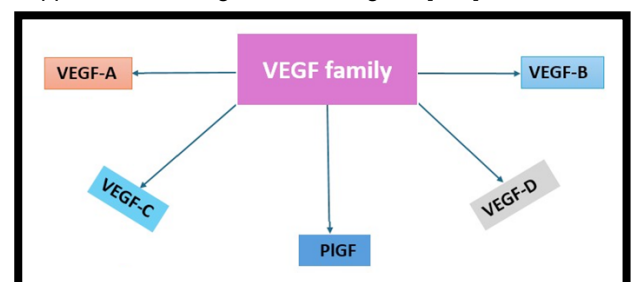


FIG. 1. VEGF family and its members.

## Bone repair/healing

Remedios discussed the composition of bone and clearly stated that the main components of bone are minerals (about 70% of the bone composition). The remaining 30% of bone composition is linked with cells and the organic matrix [107]. Steppe et al. [108] mentioned the three significant stages of bone healing: inflammation, proliferation, and remodeling. Kalfas [109] described the initiation of the inflammatory phase of bone healing, and it has been stressed that the hematoma develops in the place of the fracture. Shiu et al. [110] reported the mechanism of hematoma, which has been presented as the formation of fibrin clots. Hematoma aims to prevent excessive bleeding. Inflammatory cells involved in bone healing are mast cells, neutrophils, and macrophages [111]. Mast cells play a role in the promotion of the release of inflammatory cytokines in the case of bone healing [112,113]. Zhang et al. [114] reported tumor necrosis factor-alpha (TNF- $\alpha$ ) as an inflammatory cytokine for bone fracture healing. Torres et al. conducted a study on bone repair, and the pro-inflammatory cytokines mentioned in their research were IL-1, IL-6, and TNF- $\alpha$  [115]. IL-1 plays a regulative role in initiating the inflammation [116]. Bastian et al. [117] concluded from their study that neutrophils, in the case of bone regeneration, participated in the synthesis mechanism of the extracellular matrix (ECM).

Primary fracture healing utilizes compression to reconnect fractured parts of the bone [118]. Oryan et al. [119] reported primary fracture healing as the direct fracture healing. Parker et al. [120] indicated that primary fracture healing did not involve callus formation.

Secondary fracture healing is based on callus formation, as highlighted in the study by Mori et al. [121]. Marsell and Einhorn [122] have expressed secondary fracture healing as indirect fracture healing. Studies [123,124] indicated the role of endothelial cells in the formation of the soft callus. The soft callus is referred to as a combination of fibrous and cartilaginous tissues. The main reason for the soft callus formation is reported as the differentiation of mesenchymal stem cells [125]. Kondi and Gowda emphasize that soft callus has primary responsibility in maintaining fracture stability [126]. López mentioned two processes for bone formation: direct and indirect. Direct bone formation is reported as intramembranous ossification. Indirect bone formation was termed in their study as endochondral ossification [127].

The study indicated the different mechanisms of differentiation of mesenchymal stem cells; it has been reported that if mesenchymal stem cells differentiate into osteoblasts, the mechanism of bone formation is termed intramembranous ossification. In the case of differentiation of mesenchymal stem cells to chondrocytes, then the mechanism of bone formation is termed as the endochondral ossification [123]. Intramembranous and endochondral ossification leads to the development of a hard callus [128]. Oryan et al. described that hard callus development led to the modification of the calcified cartilage into the woven bone [129]. The remodeling phase is mainly focused on the transformation of the woven bone to lamellar bone [130,131]. The significant characteristics of lamellar bone is mentioned in several studies [132-135] as the organized collagen fiber layers.

## Polymer and biopolymer blends in wound healing

Several polymers and biopolymers have so far been considered good materials for wound healing applications. One of the widely used biopolymers in biomedical fields is chitosan. Chitosan (CS) is a polysaccharide and is a polymer of natural origin [136]. The pivotal derivative source of chitosan is chitin [137]. Kulka and Sionkowska [138] in the review paper presented a detailed study of chitosan and its applications in the biomedical and cosmetic fields. Regarding chitosan biomedical applications, the highly considerable are wound-healing applications [139]. Zhang et al. [140] discussed the prominent role of chitosan for hemostasis due to its effective characteristics in preventing bleeding. Le et al. [141] mentioned in their study that chitosan is helpful in effectively removing bacteria from the wound; this is possible due to cell wall rigidity [142]. Azad et al. [143] described the chitosan role in the proliferation phase of wound healing, and it results in the form of proliferation of keratinocytes and fibroblasts [144]. Chitosan plays a well-known role in the remodeling phase of wound healing, as it leads to the enhancement of the tensile strength of the wound [145,146]. FIG. 2 represents the chitosan and its applications. Chitosan can also be used for the fabrication of polymeric blends for biomedical applications [1].

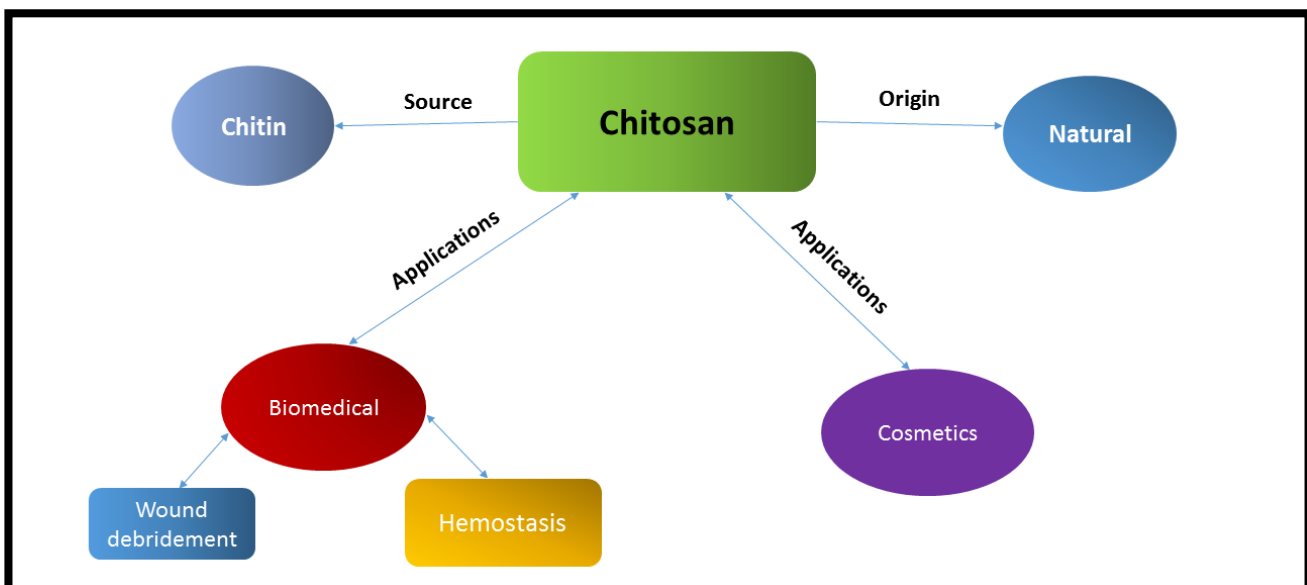


FIG. 2. Chitosan and its applications.

Liu et al. conducted electrospinning of the chitosan, polyvinyl alcohol (PVA), mupirocin (MP), and cerium oxide nanoparticles (CeNPs). The authors stressed the antibacterial nature of the electrospun membrane, which has been verified by *in vivo* and *in vitro* studies. The authors claimed that the prepared electrospun membrane was effective in the case of diabetic wounds [147]. Gobi and Babu fabricated the polymeric blend of PVA and CS with nickel oxide (NiO) using the solution casting method. It has been concluded from their research on wound healing applications that it presented better cell proliferation [148]. Abdelrazek et al. initially prepared the polymeric blend of CS and polyvinyl pyrrolidone (PVP) in the proportion of (20/80), respectively, the various weight percentages (0, 2.5, 5.0, 7.5, 10, 12.5) of copper oxide (CuO) nanoparticles have been combined to a polymeric blend of CS/PVP. The authors indicated the wound healing interest from this conducted research [149]. Fang et al. conducted a study on the polymeric blend of CS and polyethylene oxide (PEO), and the solution blow spinning technique was utilized to prepare the nanofibers. The conducted research resulted in excellent hemostatic properties [150]. Not only chitosan is considered as wound healing material, but also several other polysaccharides, such as alginate, hyaluronic acid, fucoidan, and many others.

Kruk and Winnicka reported the natural origin of alginate [151]. The extraction source of alginate is brown seaweed, as indicated in several studies [152-155]. The commercially available form of alginate is sodium alginate, and sodium alginate solubility in water is reported by Adamiak and Sionkowska [156]. Ding et al. prepared sodium alginate (SA) and PVA in the proportion of (10/90), respectively, and from this prepared solution of SA/PVA, they took 8 wt/v% to blend with 0.5 wt/v% shikonin (SK). The electrospun nanofibers have been used for *in vitro* tests, which presented effective results for diabetic wounds [157]. Ilhan et al. prepared the polymeric blend of SA and polyethylene glycol with the *Satureja cuneifolia* plant extract, and the blend was fabricated using 3D printing. The authors highlighted the antibacterial effect of the prepared wound scaffold in the case of diabetic wounds [158]. Gill et al. prepared the polymeric blend of SA and PVA mixed with the silver-ZnO nanoparticles. The prepared blend was analyzed *in vitro*, enhancing the wound healing rate. The addition of silver-ZnO nanoparticles led to the enhancement of antibacterial properties [159].

Hyaluronic acid also belongs to the natural polymer family [160]. Salih et al. presented a detailed insight into hyaluronic acid as a component of the extracellular matrix (ECM) and its vital role in skin tissue repair. Skin tissue repair effectively improves the wound healing rate [161]. Foroozandeh et al. have prepared a blend of nylon 6 (12 wt%) and hyaluronic acid (3 wt%). CS in various weight percentages: 1, 2, and 3 have been added to the blend of hyaluronic acid and nylon 6, which were electrospun to prepare the nanofibers. They concluded that nanofibers from a blend of hyaluronic acid/nylon 6/chitosan 2 wt% resulted in better mechanical properties and led to enhanced cell proliferation [162]. Hashemi et al. conducted the electrospinning of the polymeric blend of hyaluronic acid, chitosan, and polyurethane, and the prepared electrospun nanofibers presented enhanced cell proliferation of fibroblasts [163]. Increased cell proliferation enhances early wound healing [164].

Fucoidan is a sulphated polysaccharide, as reported in studies [165, 166]. Wen et al. research mentioned the role of fucoidan in angiogenesis [167]. Perumal et al. prepared the polymeric blend of collagen and fucoidan, and the prepared polymer blend presented improved cell proliferation. Their study concluded that the addition of fucoidan to a polymeric blend improved thermal properties and hydrophilicity [168].

Egle et al. prepared the polymeric blend of chitosan (2%) and fucoidan (0.25%), and this polymeric blend was fabricated by lyophilization. The fabricated polymeric blend showed enhanced cell proliferation due to the presence of fucoidan [169]. Lu et al. prepared the wound dressing by blending fucoidan and gelatin. The prepared wound dressing material showed a reduction in inflammation. The prepared polymeric blend wound dressing also fastened wound healing [170].

Gajbhiye and Wairkar reported collagen as the essential part of the extracellular matrix (ECM) [171]. Sionkowska provided detailed insights into collagen blends, mainly with natural polymers, and the study indicated collagen applications in the biomedical and cosmetic fields [172]. Huang et al. also reported collagen biomedical applications, such as wound healing and cardiovascular treatments [173]. López et al. utilized electrospinning to produce a nanofibrous membrane based on a blend of collagen, chitosan, polyvinyl alcohol, and honey. They concluded that the prepared membranes showed an antibacterial effect and recommended the prepared electrospun membranes for skin ulcers [174]. Tahir et al. indicated the valuable consideration of electrospun materials for biomedical applications such as wound healing [175].

Munarin et al. highlighted the natural route of pectin [176], and pectin owns biodegradability and biocompatibility [177]. Sultana demonstrated the applications of pectin in wound healing [178]. Pectin-based hydrogels play an essential role in fibroblast proliferation [179]. Kaliaperumal and Thulasisingh used electrospinning to prepare the electrospun nanofibers; they varied the concentrations of polycaprolactone to 15%, 17%, and 19%. It has been highlighted that variation in concentrations led to an increase in mechanical strength. Chitosan and pectin have been shown to play a role in maintaining a moist environment and enhancing fibroblast proliferation [180].

It has been stressed that cellulose-based materials reduce environmental issues [181]. Hasanin recommended cellulose in biomedical applications, such as wound dressing on a larger scale [182], and provided that cellulose is low cost [183]. Sankarganesh et al. prepared a polymeric blend of cellulose and polyvinyl alcohol, and the authors recommended a prepared blend for cancer-treated wounds [184]. Heparin is a natural polysaccharide and has been reported in Paluck's research [185]. The studies by Sardo et al. indicate the role of heparin in collagen production. Heparin has also been reported to increase cell proliferation [186]. Roberts et al. prepared the blend of polyvinyl alcohol and heparin, and it has been concluded that the prepared blend promoted endothelial cell proliferation [187].

## Polymer and biopolymer blends in bone repair

Polymer and biopolymer blends are also extensively investigated for applications in bone repair. Moghaddasi et al. developed a composite material consisting of polycaprolactone, polylactic acid and hydroxyapatite in mass ratios of 2:1:0.25, respectively. Additionally, varying concentrations of nigella oil (15%, 18%, and 20% by mass) were incorporated into the composite. Electrospinning was subsequently employed to fabricate nanofibers from the prepared blend, which demonstrated biocompatibility. The research also emphasized the antibacterial properties of the blend, and the authors proposed its application in bone healing, specifically in the context of bone tissue engineering [188].

Wu et al. designed the research on blending collagen, hydroxyapatite, propranolol, and PVA. The authors selected 3D printing as the fabrication technique for the prepared blend, and the 3D printed scaffold presented bone regeneration properties in the case of *in vitro* research [189].

Akerlund et al. prepared a polymeric blend of hyaluronic acid, polylactic acid, and polycaprolactone. The authors added 15 wt% of hydroxyapatite to the blend of polylactic acid and polycaprolactone. The weight percentage of hydroxyapatite was fixed, but the ratios of polylactic acid and polycaprolactone were 90:10, 80:20, and 70:30, respectively. The fabrication of the blend was achieved using 3D printing, and the authors claimed that the blend had better mechanical and chemical properties. Due to the better mechanical properties, the authors claimed bone regeneration from this blend [190]. Shankar et al. conducted the lyophilized method for collagen and gelatin with the addition of hydroxyapatite. Their research used collagen (10%), gelatin (10%), and hydroxyapatite (1%). The authors mentioned the blend for guided bone regeneration, and it was concluded in their research to analyze *in vivo* results [191].

## Bibliometric analysis

To sum up our review, we have performed a bibliometric analysis. The data was analyzed using Scopus data from 2000 to 2024; the terms “polymer” and “wound healing” were searched within the “Article title, Abstract, Keywords”.

The obtained results were compared to the terms “polymer blend” and “wound healing” search. The results show that terms “polymer blend” and “wound healing” results are limited in comparison to “polymer” and “wound healing”. Research in this field is increasing annually, which shows the importance of the study in this field. The compared results are presented in the form of a graph in FIG. 3.

The terms “polymer” and “bone repair” were searched within “Article title, Abstract, Keywords.” The obtained results were compared to the terms “polymer blend” and “bone repair” search. The results show that the results for “polymer blend” and “wound healing” are limited in comparison to “polymer” and “bone repair” terms. The compared results are presented in the form of a graph in FIG. 4.

The Scopus data files for the searched terms have been imported to the VOSviewer software. FIG. 5 analyzes the co-occurrence of all keywords in the data file of Scopus searched for the terms “polymer blend” and “wound healing”. FIG. 6 analyzes the co-occurrence of all keywords in the data file of Scopus searched for terms “polymer blend” and “bone repair”.

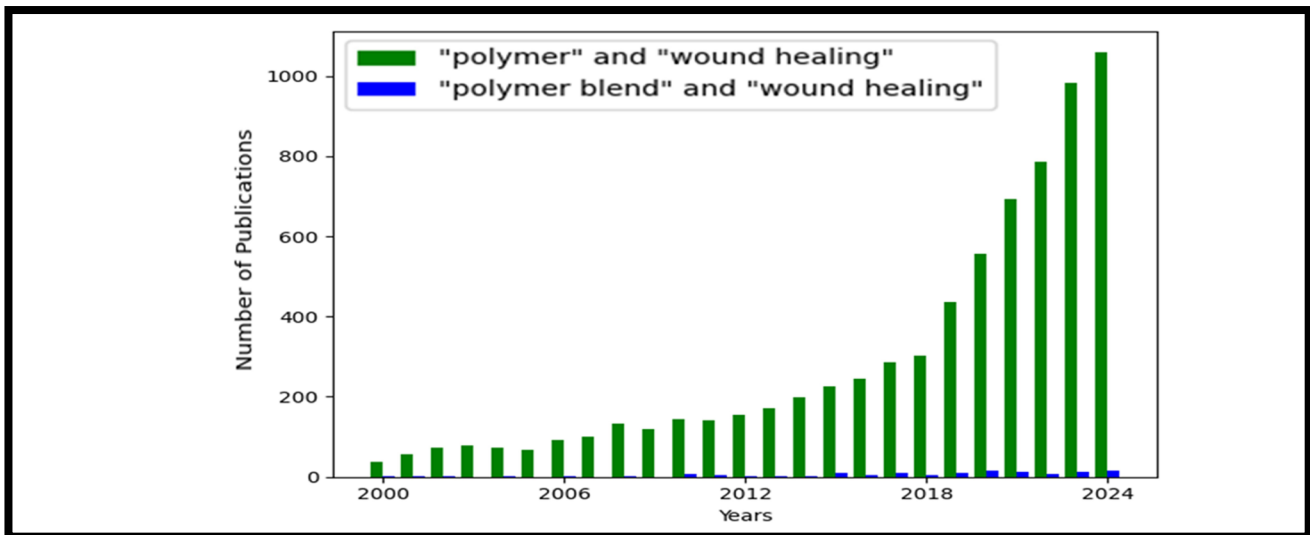


FIG. 3. Scopus (accessed on 9 December 2024) data of the number of publications over the years searched with the terms “polymer” and “wound healing” and compared to the results of terms “polymer blend” and “wound healing”.

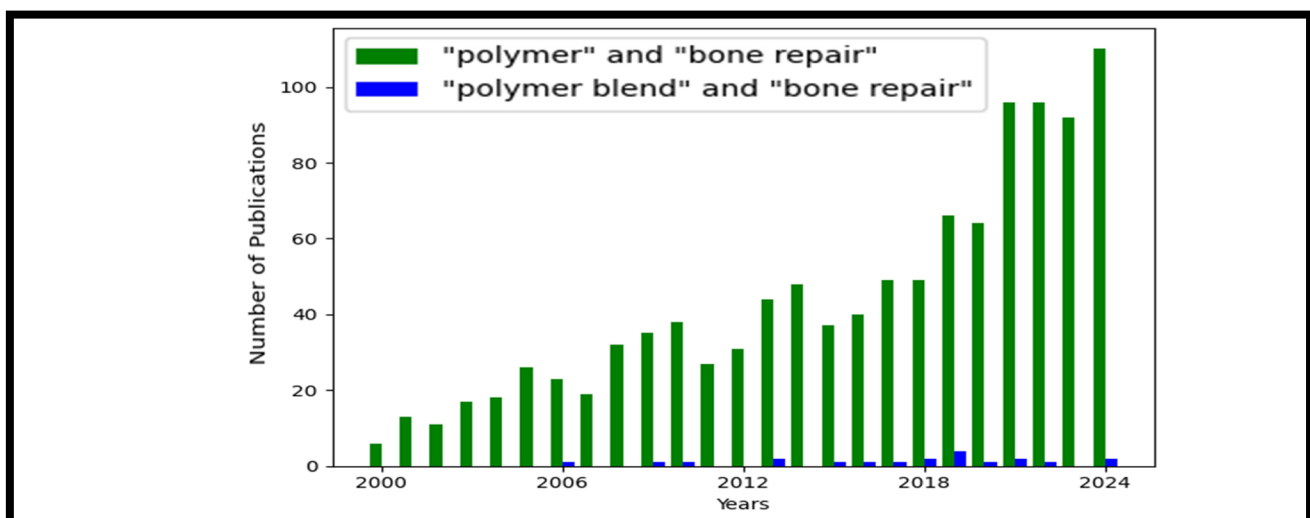


FIG. 4. Scopus (accessed on 09 December 2024) data of the number of publications over the years searched with the terms “polymer” and “bone repair” and compared to the results of terms “polymer blend” and “bone repair”.



## Conclusions

Based on the literature review, we can conclude that the number of papers regarding the applications of polymer and biopolymer blends in biomedical applications has been increasing recently. Nevertheless, after checking the literature report regarding polymeric blends for bone healing/repair, it has been observed that research is limited in this topic in comparison to applications of polymers in bone tissue engineering. Polymeric blends of natural and synthetic polymers are important in wound healing to preserve the biological and mechanical strength of wound dressings. However, again after checking the literature report regarding polymeric blends for wound healing, it has been observed that there are much fewer reports on this topic in comparison to applications of polymers in wound healing.

In biomedical fields, there is an increasing need for the fabrication of new materials for both wound and bone healing, so new polymer and biopolymer blends are likely to be studied and proposed for further applications.

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