REVIEW

PROGRESS ON CHITOSAN POTENTIAL FOR WOUND HEALING

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Abstract

Chitosan is increasingly effective in biomedical applications, especially as a wound-healing material. The above-mentioned effectiveness is due to its interesting biological properties and effect on human tissues. In wound healing, chitosan initiates recovery during the haemostasis stage, primarily through charge-mediated blood coagulation. Advancement to the next stages (such as the inflammatory, proliferative, and remodelling phases) depends solely on the successful and timely process of blood coagulation. Chitosan materials, such as films, nanofibers, and sponges, are expanding their applications in wound healing. Chitosan wound dressings were used to promote blood coagulation. They also led to support for the reduction of pro-inflammatory cytokine levels. Chitosan wound dressings were also effective in the proliferation and remodelling phase. In short, the objective of this study was to probe the potential of chitosan materials in terms of their use for wound healing over the past few years.

Keywords: *chitosan, wound healing, haemostasis, biopolymer, biomaterials, wound healing stages*

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1. Introduction

Several polymeric materials are preferred for biomedical applications owing to their biocompatibility [1]. In biomedical applications, polymeric materials are increasingly used in tissue engineering and wound healing [2], as natural polymers promote cell adhesion and mimic the extracellular matrix [3]. In natural polymers, chitosan-based materials are expanding their applications due to their ability to support wound healing at different healing phases.

Chitosan (Chit), mainly obtained by deacetylating chitin, a marine-derived polysaccharide, is cationic in nature [4, 5]. It has been reported that acetic acid and lactic acid are widely used as solvents for chitosan [6]; however, among different acids, acetic acid solutions are most often used [6–8]. The required concentration of this acid for dissolving Chit has been reported as 0.1 M [9]. In turn, Chit is insoluble in common organic solvents [10], but its solubility strongly depends on Chit's degree of deacetylation (DDA) and molecular weight (MW). In the biomedical field, the utilisation of chitosan is closely linked to its non-toxicity and biocompatibility [11–17]. Moreover, Chit possesses haemostatic properties [18] and inherent antibacterial activity [19]. Several functional groups (hydroxyl, acetamide, and amino groups) present in the Chit molecule enable its easy modification [20], and, in the case of $–NH_2$, cause the Chit polyelectrolyte nature [21]. The utilisation of chitosan in commercial applications is also linked to its degree of deacetylation (DDA), a parameter typically above 55% [22] and quantified by Nuclear Magnetic Resonance (NMR) [23]. It has been shown that Chit promotes wound healing in various forms, i.e., polymeric films, nanofibres, and hydrogels [24]. The main aim of this study was to review the literature over the past few years regarding the utilisation of chitosan for wound healing. To the best of our knowledge, although there are other review papers on chitosan applications in biomaterials, no review focuses on the role of chitosan at each stage of the wound-healing process.

2. Chitosan Applicability in the Haemostasis Stage

The first step of wound healing is haemostasis, which involves rapid vasoconstriction, platelet activation and aggregation, and the formation of a fibrin clot to limit blood loss and provide a provisional matrix for subsequent tissue repair [25, 26]. The bleeding can be categorised as either internal (occurs in the body cavity) or external (connected with traumatic wounds, which require direct treatment/engagement) [27–30]. Uncontrolled bleeding can have severe consequences and may ultimately lead to death [31]. It has been found that Chit promotes red blood cell adherence and can activate platelets [32], the latter being mediated via TLR2 [33, 34]. TLR2 is a key member of the mammalian TLR family and has potential for wound healing [35]. According to the findings of Lee *et al.* [34], platelet activation results from chitosan binding to TLR2 on the platelet surface, leading to signalling that boosts Ca^{2+} concentration. Elevation in Ca^{2+} concentration results in the expression of phosphatidylserine (PtSer) to the outer surface of platelets and activation of integrin αIIbβ3. The research also indicated that activated platelets are identified by the CD62p (P-selectin) marker.

The role of chitosan in improving cell-blood adherence results from the opposite charges of Chit (positively charged, polycationic) and red blood cells (negatively charged surface), leading to their electrostatic attraction [36–38].

Blood coagulation primarily occurs through three interconnected pathways: intrinsic, extrinsic, and common [39]. The intrinsic pathway is mainly involved in secondary haemostasis [40] and is initiated by the activation of four plasma proteins [41, 42],

including zymogen Factor XII (FXII), whose activation initiates this pathway [43]. In contrast, the extrinsic pathway begins with tissue factor [42]. Both pathways ultimately converge on the common coagulation pathway, in which Factor Xa plays a central role [44]. Although these pathways constitute the classical coagulation cascade, chitosan appears to exert its haemostatic effect through a different mechanism. Chen *et al.* [45] reported that chitosan does not act through the classical coagulation cascade, whereas Okamoto *et al.* [46] reported that chitosan reduced blood coagulation time. Chitosan, used as a haemostatic agent, can also prevent wound infections due to its antibacterial properties [47]. The haemostatic properties of chitosan have been utilised in the development of chitosan-based wound dressings such as HemCon. Wedmore *et al.* [48] evaluated the use of the chitosan-based HemCon wound dressing in combat casualties and reported cessation of bleeding or improvement in haemostasis in 62 of 64 cases.

Chosen Chit-based materials for blood coagulation are summarised in Table 1. Chen *et al.* [49] designed a multifunctional sponge comprising chitosan, exfoliated graphene oxide, and engineered kaolin nanotubes. The prepared sponge was tested in rat models and demonstrated haemostatic efficacy, reducing blood loss and shortening haemostasis time. Feng and Wang [50] prepared a hydrogel composed of chitosan and graphene oxide (GO) and evaluated this material in a rat liver haemorrhage model. The concentration of GO varied from 0.1, 0.2, to 0.3 wt.%. Developed hydrogels exhibited shorter haemostasis time and improved blood loss reduction in comparison to the control group (untreated liver injury). Liu *et al.* [51] prepared electrospun membranes composed of chitosan, polyethene oxide (PEO), and kaolin and analysed their haemostatic effects in a rat model of liver injury, confirming a shorter haemostasis time compared with kaolin-free chitosan/PEO nanofibers and QuikClot® Combat Gauze.

Jayabal *et al.* [52] prepared a wound patch comprising chitosan (Cs), polyvinyl alcohol (PVA), graphene oxide (GO), curcumin (Cur), and nitrogen vanadium co-doped titanium oxide TiO_2(V–N). All tested chitosan-containing patches exhibited blood clotting times ranging from 2 min 03 sec to 3 min 45 sec. Modification of the PVA/Cs matrix with GO, V–N co-doped TiO_2, and curcumin was associated with progressively improved haemostatic performance, with the PVA/Cs/GO/TiO_2(V–N)/Cur patch showing the shortest clotting time. A similar trend was observed for blood spreading, with the blood spread diameter decreasing from 5.9 cm for the PVA/Cs patch to 3.2 cm for the PVA/Cs/GO/TiO_2(V–N)/Cur. The wound-healing potential of the developed patches was further confirmed *in vivo* using male Wistar rats.

Cao *et al.* [53] fabricated a chitosan-based cryogel containing citric acid and Ag nanoparticles (Ag NPs produced by reduction of Ag^+ ions with tannic acid). The freeze-thaw method was utilised. Haemostasis was analysed on Sprague-Dawley (SD) rats with a liver injury model. The prepared cryogel showed a lower blood-clotting index (BCI) than the normal gauze. Cao *et al.* [54] designed the sponge consisting of chitosan and graphene oxide, which were initially covalently linked via 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS). Secondary crosslinking was also carried out using tannic acid (TA) as a crosslinking agent. Haemostatic ability was evaluated in a rat liver injury model. The CS/GO/TA sponges markedly shortened haemostasis time (23–27 s) compared with the gauze control (109 s). Ngo *et al.* [55] designed a sponge dressing consisting of chitosan, silk fibroin, and montmorillonite. *In vitro* analysis was conducted to evaluate the haemostatic performance of the designed sponge using human blood. Sponge dressing effectively reduced the clotting time.

Table 1. Chitosan-based materials for blood coagulation.

Material / composition	Chit and material characteristics	Blood coagulation effect	Testing method	[Ref]
chitosan - exfoliated graphene oxide - engineered kaolin nanotubes	MW: 50,000 material form: porous, 3D matrix sponge	relative to control: blood loss decreases to 0.1 g; relative to control: haemostasis time shortens to 60 s after tail amputation	rat model (liver incision, tail amputation, femoral artery puncture, and liver incision)	[49]
chitosan - graphene oxide	MW: 30,000 DDA: > 85% material form: hydrogel, 3D porous structure	control: blood loss 1100 mg, haemostasis time 215 s; chit-based materials of varied GO content: 0.1 wt.%: 833.3 mg, 103 s; 0.2 wt.%: 300 mg, 80 s; 0.3 wt.%: 233.3 mg, 90 s	rat liver haemorrhage model	[50]
chitosan - polyethylene oxide - kaolin	DDA: > 95% 100–200 mPa·s material form: nanofibers, porous	after the addition of 10 wt.% of kaolin: haemostasis time 57.3 ± 4.1 s (control 111 ± 7.1 s); blood loss 0.131 ± 0.026 g (control 0.678 ± 0.088 g)	rat liver injury	[51]
chitosan - polyvinyl alcohol - graphene oxide – curcumin - titanium dioxide(V-N)	MW: high DDA: 85% material form: polymeric film, porous	blood clotting time: 2 min 03 s (control 3.75 min); blood spread diameter 3.2 cm (control 5.9 cm)	Wistar male rats	[52]

Table 1. (continued) Chitosan-based materials for blood coagulation.

Material / composition	Chit and material characteristics	Blood coagulation effect	Testing method	[Ref]
chitosan - citric acid - Ag	MW: 50–100 kDa DDA: ≥ 95% 100–200 mPa·s Material form: shape memory cryogel, porous	BCI of normal gauze (control): 92.13 ± 9.03% BCI of reported cryogel: 18.61 ± 5.30%	Sprague-Dawley rats liver injury model	[53]
chitosan - graphene oxide (crosslinked with EDC/NHS) - tannic acid of increasing TA (CS/GO/TA1, CS/GO/TA2, CS/GO/TA3)	material form: sponge, 3D structure, porous	haemostasis time: 109 s (gauze), 31 s (CS/GO), 26 s (CS/GO/TA1), 27 s (CS/GO/TA2), 27 s (CS/GO/TA3); blood loss: 1.45 g (gauze), 0.65 g (CS/GO), 0.51 g (CS/GO/TA1), 0.42 g (CS/GO/TA2), 0.37 g (CS/GO/TA3)	rats rat liver	[54]
chitosan - silk fibroin - montmorillonite	MW: 575 kDa DDA: 90% material form: composite sponge, porous	coagulation time: medical dressings (197.3 ± 14.4 s) chitosan (188.7 ± 4.6 s) chitosan - silk fibroin (159.7 ± 4.5 s) chitosan - silk fibroin - montmorillonite (127.7 ± 4.0 s)	*in vitro* using human blood	[55]

Table 1. (continued) Chitosan-based materials for blood coagulation.

Material / composition	Chit and material characteristics	Blood coagulation effect	Testing method	[Ref]
chitosan (30%) - polyvinyl alcohol	MW: 100–150 kDa DDA: 85, 90, 95% material form: sponge, porous	PVA achieved complete bleeding control in 6 min; chitosan(30%)-PVA achieved complete bleeding control in 2–3 min	Sprague-Dawley rats Bama miniature pigs (femoral artery puncture, gunshot wound)	[56]
chitosan - polyvinyl alcohol - neem seed oil	MW: low DDA: 90% material form: polymer film, porous due to neem oil	blood clotting index: gauze 96.63 ± 2.45 (5 min), 88.36 ± 2.02 (10 min) chitosan-PVA 76.34 ± 2.22 (5 min), 67.36 ± 2.61 (10 min) the addition of neem oil caused a slight change	female mice blood sample collection	[57]
chitosan - polyvinyl alcohol - carbon dot	MW: ~193.4 kDa DDA: 75–85% 200 – 800 mPa·s material form: nanocomposite sponge, porous	blood loss gauze ~3.8 g (tail amputation), ~8.3 g (liver injury), ~11.2 g (leg artery injury); chitosan - polyvinyl alcohol - carbon dot sponge ~1.3 g (tail amputation), ~3.8 g (liver injury), ~4.6 g (leg artery injury)	male rats tail amputation liver trauma model leg artery injury	[58]

Zhao *et al.* [56] designed a chitosan-polyvinyl alcohol sponge and analysed its haemostatic effect in SD rats and Bama miniature pigs. Its haemostatic performance was evaluated using femoral artery injury and gunshot wound models. In SD rats, the poly(vinyl alcohol)/chitosan (30%) sponge reduced both haemostasis time and blood loss compared with pure poly(vinyl alcohol) and gauze. Similarly, in pigs, the poly(vinyl alcohol)/chitosan (30%) sponge reduced blood loss compared with both control materials.

Rahman and Mondal [57] developed a polymeric film comprising chitosan, polyvinyl alcohol, and neem seed oil. In their designed study, the casting method was used to prepare a polymeric film. The haemostatic effect was analysed in female mice, and blood samples were collected to determine the blood clotting index. The results showed that the blood-clotting index reported for the chitosan and polyvinyl alcohol polymeric films, and for chitosan, polyvinyl alcohol, and neem seed oil, was lower than that of gauze, which showed excellent blood clotting. Shakiba-Marani and Ehtesabi [58] created a chitosan-polyvinyl alcohol-carbon dot-based material. The freezing-thawing method has been selected for the formation of the nanocomposite sponge. Haemostatic effect was analysed in the tail, liver trauma, and leg artery injury models in male rats. It demonstrated the improved haemostatic effect of the prepared sponge.

3. Chitosan Applicability in the Inflammatory Stage

At the second wound healing stage – inflammatory phase - chitosan acts by effectively removing bacteria and necrotic tissue [59]. The former results from chitosan's cationic functional groups [60]. The primary mode of antibacterial action of Chit is due to direct electrostatic interactions between these functional groups and the negatively charged bacterial cell wall [61–63].

The anti-inflammatory properties of chitosan have been reported in several studies [26, 64–67], also in chronic wound healing [68]. The primary driver of chronic inflammation is oxidative stress, caused mainly by free radicals [69, 70]. Delayed inflammation, as in diabetic wounds, prolongs the wound-healing [71]. As reported by Xu *et al.* [68], Chit's anti-inflammatory activity results from scavenging free radicals, upregulating cytokine levels, and modulating the immune response [72]. Chitosan also acts as an immunomodulator, effectively modulating T cells, which in turn modulate cytokine levels [73–75]. This immunomodulatory effect is also reflected in the regulation of key pro- and anti-inflammatory cytokines involved in wound healing. Nabil *et al.* [76] reported that chitosan increased IL-10 (Interleukin 10) levels, which were mediated by PI3K (Phosphoinositide 3-kinase) signalling. Huang *et al.* [77] utilised a chitosan coating on CeO_2 nanocubes and reported reduced TNF-α (Tumour Necrosis Factor alpha) levels and boosted IL-10 levels, which were analysed by RT-PCR (Reverse Transcription Polymerase Chain Reaction) in wound tissues. Amin *et al.* [78] designed a chitosan-based material containing bee venom (Table 2). The material was formed into a polymeric film by solvent casting. The anti-inflammatory effect was observed using a rat paw oedema thickness technique following carrageenan injection. It was demonstrated that a chitosan film containing 6% bee venom reduced carrageenan-induced paw oedema by approximately 50%, showing an anti-inflammatory effect comparable to that of indomethacin (53% reduction) [78].

Table 2. Impact of chitosan-based materials on the inflammation phase.

Material / composition	Chit and material characteristics	Impact on inflammation	Reference Sample	[Ref]
chitosan - bee venom	MW: 0.8–1 MDa DDA: 75% highly viscous material form: polymer film	50% reduction of carrageenan-induced inflammation	1% indomethacin reduced inflammation by 53%.	[78]
chitosan - polyethylene oxide nonfibrous membrane	30–70 mPa·s viscosity material form: nanfibrous and porous	lowering TNF-α to a concentration 983.2 ± 62.4 pg/mL	TNF-α concentration for transparent Tegaderm™ wound dressing 677.7 ± 59.4 pg/mL	[79]
chitosan - *Aniba rosaeodora* essential oil (of 0.5, 2.5, and 5.0% oil concentration)	DDA: 77.28% material form: membrane	34.7, 44.4, and 33% TNF-α reduction membranes of 0.5, 2.5, and 5.0% concentrations	lipopolysaccharide	[80]
chitosan hydrocolloid	MW: low material form: hydrocolloid dressing	For the ELISA assay, a reduction in: TNF-α (24.0±6.7 pg/mL) For immunofluorescence staining, a reduction in: TNF-α (19.9±0.8 pg/mL) IL-6 (13.7±1.1 pg/mL) MCP-1 (16.5±0.9 pg/mL) IL-1β (13.9±0.6 pg/mL)	Control (without treatment) TNF-α (75.0±12.6 pg/mL) TNF-α (28.7±1.7 pg/mL) IL-6 (27.7±1.8 pg/mL) MCP-1 (27.7±1.3 pg/mL) IL- 1β (18.9±0.9 pg/mL)	[81]

Salkovskiy *et al.* [79] designed a nanofibrous membrane based on chitosan and polyethene oxide, which was analysed in SD rats (Table 2). The investigation showed that it reduced TNF-α, a pro-inflammatory cytokine. The value reported in their study for TNF-α in a nanofibrous membrane was 983.2 ± 62.4 pg/mL, while the TNF-α of 1677.7 ± 59.4 pg/mL was noted for transparent Tegaderm™ wound dressing. Buriti *et al.* [80] prepared a polymeric film composed of chitosan and *Aniba rosaeodora* essential oil at varying concentrations (0.5, 2.5, and 5.0%). The effect of TNF-α has been examined *in vitro* using the ELISA assay. The study revealed the effectiveness of the materials in lowering TNF-α levels. The noted TNF-α percentages were lower than those for lipopolysaccharide by 34.7%, 44.4%, and 33%, respectively, for oil contents of 0.5, 2.5, and 5.0% [80].

Le *et al.* [81] developed a novel chitosan hydrocolloid and evaluated its wound healing ability in SD rats. The ELISA assay and immunofluorescence staining were utilised to investigate the pro-inflammatory response. Based on the ELISA assay, a chitosan-based patch reduced TNF-α levels to 24.0 ± 6.7 pg/mL, whereas the control sample had 75.0 ± 12.6 pg/mL. No treatment was applied to the control group samples. For immunofluorescence staining, TNF-α was found 19.9 ± 0.8 pg/mL in the chitosan-based patch, while 28.7 ± 1.7 pg/mL in the control. In the case of the chitosan-based patch, IL-6 reported was 13.7 ± 1.1 pg/mL, whereas 27.7 ± 1.8 pg/mL was reported for the control. MCP-1 levels in the control group were 27.7 ± 1.3 pg/mL and decreased to 16.5 ± 0.9 pg/mL with a chitosan-based patch. The IL-1β level, expressed relative to the control sample, was 18.9 ± 0.9 pg/mL and decreased to 13.9 ± 0.6 pg/mL with the chitosan-based patch [81].

4. Chitosan Applicability in the Proliferative Stage

Several studies have demonstrated the action of chitosan-based materials during the proliferative stage (Table 3). Mawazi *et al.* [82] reported that chitosan boosted cell proliferation during the wound healing mechanism [82]. Cai *et al.* [83] investigated chitosan's impact on cell proliferation and reported that L929 cell proliferation was boosted. Ribeiro *et al.* [84] investigated chitosan hydrogels for use as wound dressings and showed that they promoted fibroblast proliferation. Şalva *et al.* [85] utilised a complex consisting of chitosan and granulocyte-macrophage colony-stimulating factor. The prepared complex was examined for keratinocyte and fibroblast proliferation using the MTT assay. They found that the complex enhanced cell proliferation in both cell types [85]. Sangeetha *et al.* [86] developed a scaffold composed of chitosan, polyvinyl alcohol, and montmorillonite clay, fabricated by electrospinning. The MTT assay was utilised to investigate L929 cell proliferation. The study indicated that the chitosan-based scaffold supported cell proliferation and was biocompatible with the tested cell line [86]. Tezcan *et al.* [87] developed electrospun nanofibers from chitosan and poly(ethylene oxide), with glutaraldehyde serving as the cross-linker. Cell proliferation was evaluated using a scratch assay in the HEK293 cell line. It was found that the electrospun material favours cell proliferation [87]. Also, other crosslinkers were utilised to fabricate chitosan-based materials for tissue engineering and biomedical applications, including genipin and tripolyphosphate polyanion (TPP) [88]. Sonowal *et al.* [89] formulated electrospun nanofibers comprising chitosan, polyvinyl alcohol, and ulvan and used the EZBlue cell assay to test them. The cell line adopted for the cell proliferation analysis was HaCaT. The presented results suggested that the prepared material can promote cell proliferation.

Table 3. Impact of chitosan-based materials on cell proliferation.

Material / composition	Chit and material characteristics	Impact on cell proliferation	Cells	Assay	[Ref]
chitosan - granulocyte - macrophage colony stimulating factor	MW: low, 150 kDa DDA: 75–85%	boosted cell proliferation	keratinocyte fibroblast	MTT assay	[85]
chitosan - polyvinyl alcohol - montmorillonite clay	MW: 190–310 kDa DDA: 92%	supported cell proliferation	L929 cell line	MTT assay	[86]
chitosan – poly(ethylene oxide) (glutaraldehyde as a crosslinker)	MW: medium, < 190,000 Da DDA: ~80%	favours cell proliferation	HEK293 cell line	Scratch assay	[87]
chitosan - polyvinyl alcohol - ulvan	MW: ~ 20 kDa	favours cell proliferation	HaCaT cell line	EZBlue cell assay	[89]
chitosan - glycerol - turmeric	MW: medium, 274,000 g/mol	boosted the cell proliferation	L929 cell line	PicoGreen assay	[90]

Table 3. (continued) Impact of chitosan-based materials on cell proliferation.

Material / composition	Chit and material characteristics	Impact on cell proliferation	Cells	Assay	[Ref]
chitosan - pectin - zinc oxide	MW: 193.4 kDa DDA: 75%	enhanced cell proliferation	HFCs cell line	wound scratch assay	[91]
chitosan - polyvinyl alcohol - collagen (oxidised pullulan as a crosslinking agent)	medium viscosity DDA: 83%	alignment with cell proliferation	HSFs cell line	AlamarBlue assay	[92]
chitosan - arginine - gold nanoparticles	DDA: ≥ 95%	improved cell proliferation	Balb/c3T3 cells	CCK-8 assay	[93]
chitosan - keratin	DDA: low	increased cell proliferation	HaCat cells	CCK-8 assay	[94]
chitosan - polyvinyl alcohol - nickel oxide	MW: high DDA: ≥ 75%	improved cell proliferation	NIH3t3 fibroblast	MTT assay Scratch assay	[95]

Macedo *et al.* [90] designed chitosan-based wound dressings incorporating glycerol and turmeric and described the preparation as a casting method. Cell proliferation was evaluated using the PicoGreen assay. The cell line used in their *in vitro* studies was L929. Their wound dressings significantly enhanced cell proliferation in the cell lines used [90]. Soubhagya *et al.* [91] prepared porous films composed of chitosan, pectin, and zinc oxide. Cell proliferation of the prepared material was analysed using the wound scratch assay. The cell line used for cell proliferation was a human fibroblast cell line (HFCs). The research confirmed enhanced cell proliferation. Kang *et al.* [92] designed the polymeric films consisting of chitosan, polyvinyl alcohol, and collagen. In the study, oxidised pullulan was considered as a cross-linking agent. The authors analysed human skin fibroblasts (HSFs) cell proliferation using the AlamarBlue assay and confirmed the material's effectiveness at that stage of wound healing. Wang *et al.* [93] designed a polymeric film comprising chitosan, gold nanoparticles and arginine. Cell proliferation of the dressing material was analysed with the CCK-8 assay. Balb/c3T3 cells have been utilised for the proliferative test. The designed chitosan film, incorporating arginine and gold nanoparticles, improved cell proliferation in the cells used in the experiment. Wang et al. [94] fabricated films comprised of chitosan and keratin. Cell proliferation analysis in their study was conducted utilising the CCK-8 assay. HaCat cells were indicated in the referenced study, so it's possible that HaCat cells were used in the proliferative analysis. The analysis indicated that the prepared chitosan-based film improved cell proliferation. Gobi and Babu [95] developed a chitosan-polyvinyl alcohol-nickel oxide polymeric film and analysed its proliferation-promoting properties using the MTT assay. To analyse cell migration, a scratch assay was also utilised. NIH3t3 fibroblasts were chosen as a cell line. Improved cell proliferation of the polymeric material was confirmed.

5. Chitosan Applicability in the Remodelling Stage

The last stage of wound healing, the remodelling stage, comprises tissue organisation. In this phase, the prime objective of the healing process is the replacement of collagen 3 with collagen 1 [25, 96, 97]. This collagen remodelling aimed to enhance tensile strength [98].

Elmi *et al.* [99] designed chitosan-based polymeric films consisting of chitosan, acid-soluble collagen, and glycolipoprotein. The new material was found to enhance collagen remodelling. The low-molecular-weight chitosan was used. Ahunon *et al.* [100] designed a biomaterial composed of chitosan and platelet-rich plasma and demonstrated enhanced collagen deposition upon application. Linju and Rekha [101] designed a conjugate consisting of chitosan and proline. Their study confirmed enhancements in collagen deposition, resulting from fibroblast cells. The chitosan-based conjugate was also effective in remodelling the wound microenvironment. Tchemtchoua *et al.* [102] reported that chitosan effectively promoted granulation tissue remodelling.

6. Chitosan Commercial Wound Dressings

The laboratory research was transferred to the commercialisation stage. As a result, several commercial chitosan haemostatic wound dressings have been reported.

6.1. ChitoFlex

ChitoFlex is a wound dressing that is wrapped around the device using polymer layers, after which the device is placed at the wound site. ChitoFlex was manufactured by HemCon Medical Technologies in Portland, OR [103] mainly as gauze rolls [104].

Chitoflex has been reported as the lyophilised form of chitosan material [105]. Shah *et al.* [106] reported that Chitoflex pro contains 95% of chitosan (70–95% DDA and 100–500 kDa molecular weight).

Its haemostatic effect results from interactions between chitosan and red blood cells. In this process, red blood cells contribute to the formation of a mucoadhesive barrier [106]. ChitoFlex performs efficiently at low pressure; however, at high pressure, it may break, leading to further bleeding [107–109]. In addition to its haemostatic properties, ChitoFlex exhibits antibacterial activity and biocompatibility [110–112] and offers ease of detachment, achieved by utilising saline or water [110].

ChitoFlex has been approved by the FDA [113, 114]. However, Sanyal *et al.* [114] highlighted that ChitoFlex is not recommended for complex injuries.

6.2. TraumaStat

Next would-healing material based on chitosan is Trauma Stat, that consists of chitosan, polyethylene, and silicon dioxide [107, 115]. TraumaStat involves the chitosan in its freeze-dried form [107]. The clotting time of the TraumaStat wound dressing measured *in vitro* was reported as 190 ± 16 s [115]. The FDA recognises haemostatic agents as Class II medical devices, which are considered under the 510(k) [103]. Under these regulations, TraumaStat has been approved by the FDA [116–118]. The literature research confirmed biodegradability and biocompatibility of this material [119].

6.3. Celox

Other material involving chitosan is Celox, reported as containing a haemostatic agent [120]. Cassano *et al.* [107] reported that Celox primarily controls bleeding (e.g., in the case of liver injury). Kadyseva *et al.* [121] confirmed a 76% chitosan degree of deacetylation in Celox and reported a Celox coagulation time of 20.9 ± 0.7 s. Celox^{TM} bacteriostatic and antibacterial activities against *S. aureus* were reported as 3.80 and 1.50, respectively, while 6.70 and 3.60 against *E. coli* [122].

7. Conclusions and Future Outlook

The biocompatibility of polymeric materials plays a pivotal role in biomedical applications, particularly in wound healing. Chitosan is inherently biocompatible, and its biocompatibility can be further supported by combining it with natural polymers. Chitosan-based materials are applicable at each stage of wound healing. During the haemostasis phase, chitosan-based materials have been shown to reduce haemostasis time, the blood clotting index, and blood loss volume. During the inflammatory phase, chitosan materials exhibit anti-inflammatory effects, as evidenced by reduced levels of pro-inflammatory cytokines, particularly TNF-α. During the proliferative phase, chitosan materials have been found to be beneficial due to a significant increase in cell proliferation. In the remodelling phase, chitosan materials support tissue remodelling, particularly collagen.

Several studies have shown increasing interest in the use of chitosan materials for wound healing. In the future, chitosan materials are expected to play a leading role in wound dressings for diabetic wounds, which are characterised by a prolonged inflammatory phase. Significant anti-inflammatory and inherent antibacterial properties of chitosan make it particularly relevant for their treatment.

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9. Author Contributions

Conceptualisation, M.T., S.V., and A.S.; methodology, M.T., S.V., and A.S.; resources, M.T., S.V., and A.S.; data curation, M.T., S.V., and A.S.; writing—original draft preparation, M.T.; writing—review and editing, M.T., S.V., and A.S.; visualisation, M.T., S.V., and A.S.; supervision, S.V. and A.S.; project administration, S.V., A.S.; funding acquisition, M.T., S.V., and A.S. All authors have read and agreed to the published version of the manuscript.

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