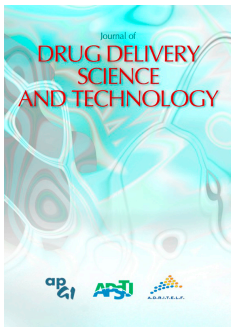

Hydrogel based scaffolding polymeric biomaterials: Approaches towards skin tissue regeneration

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AUTHORSHIP STATEMENT

Manuscript title: **HYDROGEL BASED SCAFFOLDING POLYMERIC BIOMATERIALS: APPROACHES TOWARDS SKIN TISSUE REGENERATION.**

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *Hong Kong Journal of Occupational Therapy*.

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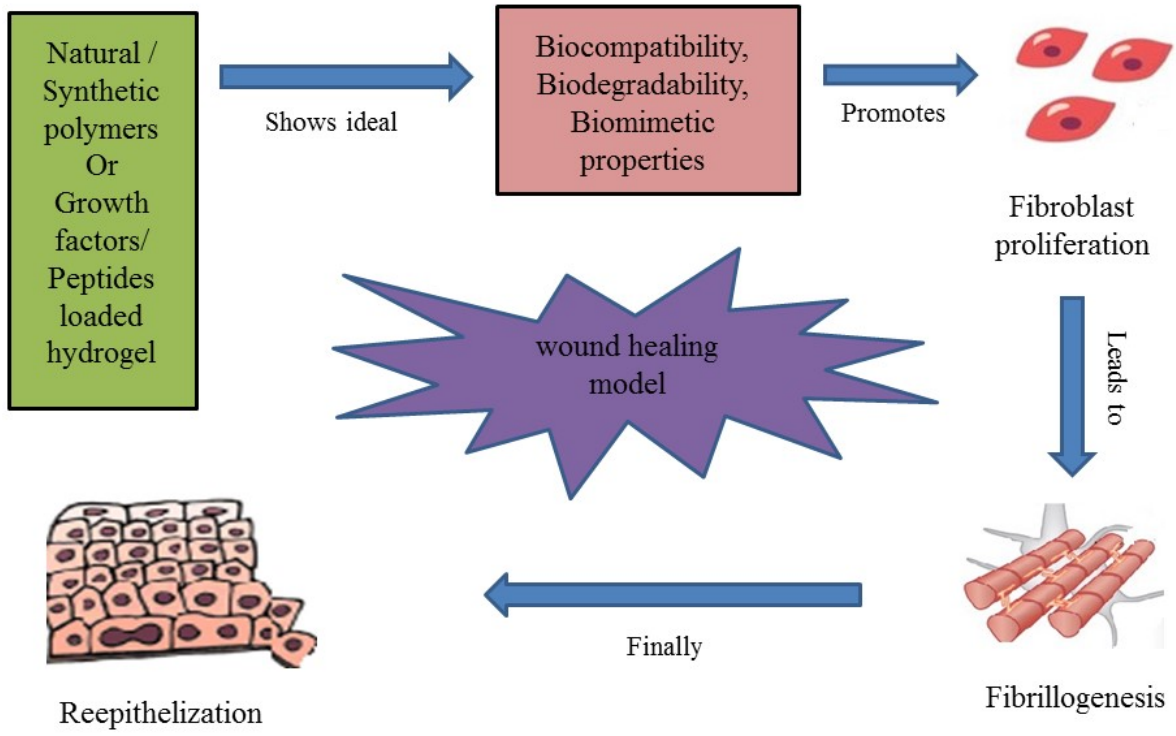
Graphical abstract



Hydrogel based scaffolding polymeric biomaterials: Approaches towards skin tissue regeneration.

Kalai Selvan N, Shanmugarajan TS*, Uppuluri Varuna Naga Venkata Arjun.

Abstract:

Skin is a complex organ with the primary function of protecting the internal tissue or cells from the external environment. In order to replicate the skin with ideal mechanical properties, special attention towards the biocompatibility and biodegradability is necessary. Whereas, in contrast to other living organisms humans has shown limited tissue regeneration owing to their variation in the genetics. Moreover, in recent years, hydrogel scaffolds are being explored for skin tissue repair and regeneration because of their ability to self-renew and proliferate the specific cell types involved in skin tissue regeneration. In this review, we outline about the natural and synthetic polymers and their potential for enhancing the applications of the polymeric hydrogel scaffolds. Further we also examined the smart healing property of the peptides and growth factors loaded hydrogel scaffolds in skin tissue regeneration.

Key words: Biocompatibility, Biodegradability, Wound healing, Tissue regeneration, Hydrogel scaffold, Swelling.

1. Introduction:

Skin damage or injury can be caused by any diversified situation like traumatic or by any natural calamities. Moreover during the traumatic conditions the healing prospective of damaged extra-cellular matrix, neovascularization and reepithelization of the damaged tissue were found to be challenging issue. In order to promote both reepithelization and revascularization signaling pathways like NF-kB, Beta-Catenin, TNF-α and TGF β1pathway and several growth factors like fibroblast growth factor, vascular endothelial growth factors plays a vital role in the wound healing. [1, 2, 3]. The most commonly used skin repair techniques like autografts and allografts were

also limited because of their lack of revascularization, innervations and complete tissue regeneration within the damaged extracellular matrix. [4, 5].

The concept of tissue regeneration was achieved by the use of hydrogel scaffolds during 1990's. In order to regenerate the damaged extracellular matrix it was important to develop the scaffolds with excellent biocompatibility and biodegradability. Moreover, the biomimetic nature of the designed scaffolds plays a vital role in complete tissue restoration within the damaged skin portion [6, 7]. Apart from above mentioned mechanical properties porosity of the scaffold had shown its significance in tissue regeneration and proliferation [8].

Hydrogels were polymeric networking structures formed by several cross linking techniques and also shows an ability to swell in aqueous medium. Moreover because of their ideal mechanical properties they achieved the attention of several researchers involved in the tissue engineering [9]. Because of their excellent biomimetic property these hydrogel plays a crucial role in the transport of several growth factors like fibroblasts, VEGF and keratinocytes more effectively and efficiently. This in turn favours the tissue regeneration and proliferation in the damaged tissue portion [10]. Biomaterials of outstanding quality and excellent fabrication play a significant role in development of novel topical hydrogel scaffolds for skin tissue engineering applications. A varied range of biomaterials of Natural, Semi-Synthetic & Synthetic origin had been exploited in order to prepare the topical hydrogels; these includes Pullulan [14], PEG (Polyethylene glycol) [13], PLGA (Poly(lactic-co-glycolic acid)) [12], PVP (Polyvinylpyrrolidone) [11], Poloxamer 407 [15], Sodium Carboxy Methyl Cellulose [16]. Topical hydrogel scaffold can be developed via physical cross linking and chemical cross linking techniques. Physically cross linking topical hydrogels were formed by weak Van der Waals forces whereas, chemical cross linked hydrogel scaffolds are mainly formed by covalent bonds [17, 18].

2. Hydrogel Scaffolds in Skin Tissue Regeneration:

In recent years, skin trauma had become one of the major cause for perishability and morbidness among all groups of population present worldwide. Therefore, the skin

tissue engineering and regeneration had pulled significant attention from the researchers as an optimistic approach for treating damaged portions on the extracellular matrix without the constraints and frailty of using either skin autografts or allografts [19, 20].

Recently, various hydrogel scaffolds with excellent moisture absorption capabilities and porosity had been extensively developed for their use in skin tissue engineering and regeneration. Among the various polymers used for development of topical hydrogels, chitosan was one of the most widely used polymer for enhancing the skin permeation in skin tissue engineering and regeneration [21]. Chen *et al* [22] had developed a novel topical hydrogel for regeneration of damaged skin portion that uses Peptide SIKVAV- modified chitosan hydrogels as scaffolds. The Peptide SIKVAV loaded chitosan hydrogels promoted angiogenesis within the damaged tissue by regulating the cytokine secretions. However, the gene expressions like TGF-β1, TNF-α, IL-1β, and IL-6 demonstrated the potentiality of the SIKVAV-modified chitosan hydrogels in skin tissue engineering and regeneration. Furthermore, in this study upon observing the results of H&E staining, Masson's trichome staining and immunohistochemistry it was clearly evidenced that peptide-modified chitosan hydrogels were proven to be promising biomaterials for skin wound healing applications.

Hyaluronic acid was also referred to be one of the most commonly used biomaterial for development of self-healing hydrogels in skin tissue regeneration. Hsu *et al* [23] had developed a crosslinked Gelatin/Hyaluronic acid hydrogel for sustained release of recombinant thrombomodulin. These hydrogels exhibits ideal mechanical properties with excellent biocompatibility and bio adhesion properties. Moreover owing to the properties of the thrombomodulin, this hydrogel also enhances the reepithelization and angiogenesis within the damaged skin tissue. Further in this study, rhTM-loaded hydrogel, consisting of 4% gelatin with 0.1% HA and 0.05% EDC cross-linked, greatly improved wound healing compared to rhTM (human recombinant thrombomodulin), hydrogel alone, and rhEGF (Recombinant human epidermal

growth factor) hydrogel. For wound repair, rhTM hydrogels facilitated the development of granulation tissue, re-epithelialization, deposition of collagen, and angiogenesis.

3. Polymers used for synthesis of the topical hydrogels:

Various polymers have been utilized for the development of hydrogel scaffolds for skin tissue engineering applications, including natural, semi-synthetic & synthetic polymers. Here the Figure 1. Represents the classification of polymers, Figure 2. Describes about the significance of polymeric hydrogel scaffolds. Figure 3. Represents the role of natural/ synthetic polymers in cutaneous wound healing.

3.1 Natural polymer based hydrogel scaffolds:

Natural polymers had already demonstrated their use in development of the regenerative scaffolds for skin tissue engineering applications. However in the present review importance was given to the polymers with excellent biocompatibility and biomimetic property similar to that of skin tissue. Natural polymers recently explored for their use as hydrogel scaffold preparation include:

3.1.1. Chitosan:

Chitosan was one of the most widely used polymer for various regenerative and tissue engineering applications. Moreover, because of its excellent biocompatibility and biodegradability it has achieved profound importance in manufacturing of various hydrogel formulations. However in case of skin tissue engineering this polymer was found to be more useful because of its structural similarity to the skin tissue. Cardoso *et al* [24] fabricated a chitosan hydrogels containing Nano encapsulated Phenytoin for cutaneous wound healing. This chitosan hydrogels shows improved rate of release due to its ideal pH (4.9–5.6) non-Newtonian pseudoplastic rheological behaviour and this further enhanced the effective permeation and penetration capabilities for Nano encapsulated Phenytoin.

Huang *et al* [25] have developed a self-healing, dissolvable Cellulose nanocrystals loaded Carboxymethyl chitosan hydrogels for burn wound healing. However it was

also identified that the dialdehyde-modified cellulose nanocrystal (DACNC) was responsible for enhancing the fluid uptake capacity, integrity and high equilibrium swelling ratio (350%) within the hydrogel. Due to their excellent self-healing (~ 5 min) and dissolvable properties, these hydrogels has exhibited better wound healing by promoting painless and scarless tissue regeneration.

In recent studies, it was shown that the combination of chitosan with other chemical components resulted in development of stimuli responsive hydrogels. Rasool *et al* [26] have successfully prepared a stimuli responsive chitosan (CS) and poly (N-vinyl-2-pyrrolidone) (PVP) hydrogel with effective wound healing properties. The biocompatibility and unique behavior of these hydrogels had made them appropriate for consistent and controlled rate of drug delivery.

Moreover, the T6 pvp 0.5 demonstrated the maximum degree of swelling in distilled water (10220 per cent). The degree of swelling was dependent on the amount of pvp. However in this study degree of swelling, it was minimised with the rise in pvp quantity. Further, the Ag-sulfadiazine's loaded T6 pvp 0.5 hydrogel shown that 91.2% of the drug was released in PBS within 80 minutes in a controlled manner.

Patil *et al* [27] have reported a Fluorinated methacrylamide chitosan hydrogel dressings promotes better wound healing in acute porcine model. Further in this study the results revealed that the ideal bio adhesive property of this polymer promoted better wound healing in case of the skin defects treated with chitosan loaded with methacrylamide hydrogel dressings via an upregulated collagen synthesis pathway. Moreover, upon observing the histopathological findings it was also evidenced that in case of the damaged skin tissue portions these hydrogel dressings enhances the rate of keratinocyte maturation and neovascularization. In addition, an excessive amount of oxygen was not necessary because the results of both MACF (methacrylated fluorinated chitosan) and MACF + O_2 were identical.

Chitosan plays a vital role in enhancing the anti-microbial and mechanical properties of the hydrogel scaffolds. Xie *et al* [28] developed silver nanoparticles loaded novel

chitosan hydrogel for effective wound healing. This hydrogel because of its ultrahigh mechanical and antibacterial properties it was enhancing the wound healing by promoting the reepithelization and collagen deposition within the damaged skin tissue. Due to this reason chitosan has found its use in field of biomedicine. Further in this study it was clearly evidenced that intermolecular and intramolecular interactions resulted in the development of excellent porous three dimensional network and ultra-high mechanical properties within these novel hydrogels.

Mahmoud et al [29] developed the norfloxacin loaded scaffolds by blending the collagen with chitosan of two different molecular weights for the treatment of topical wound. Moreover in this study, the results demonstrated that high porous network further enhanced the water retention capability and biodegrability for the developed scaffolds. However when compared to the low molecular weight chitosan these high molecular weight chitosan shown the excellent bioadhesive strength and this in turn enhanced the wound healing process.

Table No. 1 represents the role of chitosan in different formulations.

3.1.2. Collagen:

Collagen was one of the molecules that was being used for various tissue regeneration process. Moreover in case of skin wound healing collagen acts as functional biomaterials because of its ability to promote controlled rate of release for several bioactive proteins. According to Thönes *et al* [30] Hyaluronan/collagen hydrogels loaded with heparin-binding EGF-like growth factor promoted controlled rate of release for over a time period of 72 hours. Moreover, sHA (sulfated hyaluronan) - containing hydrogels significantly enhanced the efficacy of HB-EGF (Heparin-binding EGF-like growth factor) in promoting the epithelial tissue growth in the porcine skin model. Finally, it was also confirmed that in this study collagen acts as an efficient and effective biomaterials for the development of vehicle based wound dressing model.

Collagen also plays a significant role in development of the novel bio hybrid dressing materials meant for wound healing and skin tissue regeneration. Marin *et al* [31] developed a Collagen- Polyvinyl alcohol bio hybrid dressings as a novel wound dressing model. This scaffold upon loading with anti-inflammatory drug (like Indomethacin) further enhanced the wound healing capabilities of these dressings. In contrast with the control group, the treatment with spongy biohybrid matrices had a beneficial effect on the healing process in the case of experimental burns to Wister rats. However the kinetic profiles of new hybrid collagen/ polyvinyl alcohol composite sponges resulted in moderate burst release of Indomethacin. Further in this study the kinetic release data proved that Indomethacin loaded collagen-PVA hydrogels promotes excellent anti-inflammatory and analgesic effect for a prolonged period of time in the burnt wound model.

Angiogenesis was one of the key steps involved in wound healing process. Moreover it was also observed that angiogenesis was sensitive to mechanical stimuli. This situation can be evaded by using collagen based hydrogel. Ruehle *et al* [32] reported that the collagen hydrogel loaded with a proteoglycan like decorin promoted excellent fibrillogenesis, vascular growth. It was also shown that the increase in the compression modulus of the decorin loaded collagen hydrogel did not show any negative effect on the microvascular growth parameters. Whereas, in case of 3% collagen hydrogels significant reduction in contraction was observed after 16 days of culture. However, in-vitro model of DCN (decorin) - supplemented collagen constructs serves as an ideal candidate for determining the effects of the mechanical loading on the 3D microvascular growth.

The ideal biocompatibility, swelling and water retention properties of the collagen based hydrogels plays a vital role in wound healing process. According to Liu *et al* [33] the composite hydrogel developed from chitosan - collagen peptide / oxidized konjac glucomannan exhibits ideal mechanical and swelling properties. Along with this it also shows good biocompatibility that plays a crucial role in significant wound healing process. However in this study, the SEM images demonstrated a three

dimensional structure within the hydrogel sample. In the meantime, hydrogels shown minimal gelation time due to the addition of OKGM (oxidized konjac glucomannan). Moreover, the absorption and retaining of moist environment made these chitosan - collagen peptide hydrogels ideal choice for wound dressing applications.Furthermore, the cytotoxicity test results revealed that the hydrogel had significant cytocompatibility and thus there by enhanced NIH-3T3 cells proliferation.

In case of burn wound healing collagen was essential for promoting the rapid inflammation reduction. Ghica *et al* [34] developed the Collagen- Dextran wound dressings loaded with Flufenamic acid and this acts as an ideal wound dressing for burnt wounds. Moreover it was shown that the Flufenamic acid loaded wound dressings, due to their excellent anti-inflammatory property further enhanced the reduction of the inflammation and this in turn promoted the faster rate of epithelial regeneration. Table No. 2 represents the role of collagen in different formulations.

3.1.3. Genipin:

Genipin was an aglycone obtained from geniposide existent in the Gardenia jasminoides. Due to its excellent crosslinking capabilities with several other molecules this polymer had found its importance in the development of the hydrogel scaffolds. Gao *et al* developed a Genipin crosslinked chitosan hydrogel scaffolds as a potential vehicle for silver sulfadiazine nanocrystals. According to Gao *et al* [35] this Silver Sulfadiazine nanocrystals loaded Genipin crosslinked Chitosan hydrogel acts as an ideal vehicle for local antibacterial nanomedicines. Further silver sulfadiazine nanocrystals also shows excellent uniform distribution and physical stability within the hydrogels. Moreover in case of wounds treated with the Silver Sulfadiazine nanocrystals loaded hydrogel excellent fibroblast proliferation, neo vascularization and reepithelization was observed. However in this study the swelling dependent release patterns shown by the silver sulfadiazine nanocrystals loaded hydrogels hence due to this reason peppas equation was vital for determining the release profile.

Due to its excellent swelling, biomimetic and tissue regeneration capabilities Genipin plays a crucial role in wound healing. According to Heimbuck *et al* [36] the swelling

profile of the Chitosan- Genipin hydrogel demonstrated that the lyophilized hydrogels shown five-fold increase in swelling when compared to the air dried hydrogels. Moreover it reveals about the importance of post processing techniques in determining the porosity of the developed hydrogel scaffolds. Further these findings also revealed that lyophilised hydrogel structure does not match with experimentally derived structure.

Genipin usually acts as a cross linker for several bioinspired biomaterials involved in various drug delivery and optics related applications. According to Pugliese *et al* [37] developed genipin cross linked Self assembling peptides hydrogels shows promising increase in stiffness and resilient properties of the hydrogel. Moreover these two properties were essential for promoting several tissue engineering applications.

However this genipin had acquired significant importance in tissue engineering area because of its excellent biocompatibility and bio fabrication properties. Campos *et al* [38] revealed that Genipin cross linking enhanced the tissue regeneration, biocompatibility and biomechanical and rheological properties of the Fibrin- Agarose hydrogels. In the current study, even though higher genipin concentration shows improvement inthe stiffness and elasticity of the hydrogels but sometimes it may also result in hindrance of cell function and its viability. Table No. 3 represents the role of genipin in different formulations.

3.1.4. Keratin:

Keratin was a protein moiety belongs to the family of fibrous proteins. It usually plays a crucial role in protection of epidermal cells from stress and damage. Due to its excellent rheological, and mechanical properties keratin achieved the significant importance in the wound healing applications. Zhai *et al* [39] developed n-ZnO nanocomposite loaded Keratin- Chitosan hydrogel scaffolds for the treatment of burnt wounds. However in his studies the author has developed a KCBZNs (Keratin-chitosan/n-ZnO nanocomposite) bandage with high porosity and this further enhanced the fibroblast cell proliferation. Further, it was also evidenced that keratin hydrogels

with ideal biocompatibility property was essential for promoting rapid wound healing within the damaged skin portions.

In recent studies, it was shown that Keratin exhibits excellent biodegradability and cell adhesion properties and these properties of keratin made it essential for several tissue engineering applications. Veerasubramanian *et al* [40] developed a novel Avena Sativa loaded Konjac glucomannan- Keratin hydrogels for the treatment of diabetic wounds. The study reports revealed that keratin has enhanced fibroblast proliferation and collagen levels in case of diabetic rat excision wound model treated with Avena Sativa loaded hydrogels. However, in this study it was also identified that the incorporation of Avena Sativa Konjac glucomannan- Keratin hydrogels resulted in enhancement of bioactivity of the AvenaSativa and this further minimised the wound healing duration in case of burnt wound model.

Poranki *et al* [41] demonstrated that the keratin loaded hydrogels plays a vital role in reduction of the burnt wound progression and simultaneously it was also involved in faster rate of wound healing. In case of wound defects of Yorkshire swine model the keratin loaded hydrogels promoted the efficient and effective rate of reepithelization and neovascularization within the burnt wound area.

Due to its excellent bio inherent, mechanical and biocompatibility characteristics keratin had drawn its attention towards various wound healing applications. According to Wang *et al* [42] the keratin hydrogels developed from feathers keratin was free from immunogenicity and systemic toxicity. Apart from this hydrogel also displays rapid wound healing while showing excellent biocompatibility and biodegradability properties.

In the recent studies it was also proved that keratin plays a vital role in inhibiting the infection in case of the cutaneous wound healing applications. Roy *et al* [43] developed the Ciprofloxacin loaded keratin hydrogels upon topical application this hydrogel plays a significant role in promoting the wound healing by enhancing macrophages. Further in this study author demonstrated that in case of burnt wound

model Ciprofloxacin loaded hydrogels plays a vital role in promotion of myofibroblast and collagen rich granular tissue formation within 11 days of post injury by inhibiting the P. aeruginosa growth.

Park *et al* [44] developed keratin based hydrogels showing excellent biocompatibility with the skin tissue. Moreover in this study the author clearly demonstrated that the keratin loaded hydrogel enhanced the collagen production significantly and this in turn minimised the wound healing duration in case of wound model. Further, the keratin based hydrogel also shown excellent reepithelization and connective tissue formation at the end of the study.

Keratin plays a vital role in treatment of the burnt wounds. According to Poranki *et al* [45] the developed keratin hydrogels promotes fibroblast proliferation with excellent cell viability. The study reports also revealed that when compared to α-keratin the γ-keratin promotes better wound healing in case of burnt wounds. Further in this study, it was also observed that proteomic techniques was crucial for identification of γ keratose as a smaller peptide fragments isolated from α- keratosis during the time of synthesis. Table No. 4 represents the role of keratin in different formulations.

3.1.5. Pectin:

Pectin was a natural polysaccharide obtained from the fruits of the terrestrial plants. Due to its excellent antimicrobial and biocompatibility pectin had found its use in development of novel hydrogel scaffolds. Giusto *et al* [46] developed the novel pectin hydrogels loaded with honey. The study report revealed that honey based hydrogels improved the wound healing process. Thus in turn it played a vital role in preventing further surgical complications. Huang *et al* [47] promoted the Pectin/ Polyvinyl alcohol hydrogels meant for *in vitro* cytotoxicity analysis of the NCTC L929 cells. However the study reports identified that the mild inflammation exists in case of the rats implanted with the hydrogels usually serves as an evidence for excellent biocompatibility of the developed hydrogels. Moreover in this study both PVA and CoPP (pectin/poly vinyl alcohol composite) group were used for incubating the L929 cells and this further enhanced the cell growth rate to 80% and 75% respectively. Kim

et al [48] demonstrated that the PVA/ Pectin hydrogels loaded with Hippophaerhamnoides L. extract shown effective and efficient wound reduction when compared to controlled groups and hydrogels alone. Further, the histopathological studies of the rat acute wound models revealed that there was excellent revascularization and reepithelization in case of rats treated with Hippophaerhamnoides L. extract loaded hydrogels.

Excellent cell adhesion and proliferation of these cell instructive hydrogels found their importance in several skin tissue engineering applications. Moreover in recent studies it was shown that pectin got significant role in development of these cell instructive hydrogels. Pereira *et al* [49] developed a novel cell instructive pectin hydrogels for skin tissue engineering applications by using cross linkers like thiol-norbornene. The study reports signifies about the role of these pectin hydrogels in influencing the biochemical and biophysical properties which further got its importance in modulating the cell behavior. However in case of invitro model it was clearly demonstrated that incorporation of fibroblasts and keratinocytes resulted in development of full thickness skin (invitro) with excellent morphology and architecture similar to that of natural skin.

Usually the amorphous nature of the pectin makes it an ideal polymer for skin tissue applications. Mishra *et al* [50] developed the novel glutaraldehyde cross linked pectin hydrogels loaded with ethanolamine. Moreover the characterization study signifies the excellent swelling nature, porosity of these developed hydrogel**s**. Further in this study it was also reported that amidation was responsible for making the proteins, peptides, enzymes or drugs immobilize on the pectin's surface. Table No. 5 represents the role of pectin in different formulations.

3.2.Synthetic polymer based hydrogel scaffolds:

Due to their excellent tractable and proliferation characteristics some of the synthetic polymers had achieved the profound importance in the skin tissue engineering applications. These were the few polymers that played a vital role in development of hydrogels for wound healing applications they include PEG [51, 52, 53, 54, 55, 56,

57.], Carbopol [58, 59, 60.], Polyacrylamide (PAM) [61, 62, 63.], Carboxymethyl cellulose [64, 65, 66.].

3.2.1. PEG (Poly Ethylene Glycol):

The blending property of PEG with different polymers made it useful for several tissue engineering applications. Masood *et al* [51] have reported a novel Chitosan-PEG hydrogels impregnated with silver nanoparticles. These Chitosan-PEG hydrogels exhibited ideal swelling and biodegradability. In turn this hydrogel also promoted sustained release of silver nanoparticles, this property of hydrogels was essential for various tissue engineering applications. Moreover the hydrogels loaded with silver Nano particles had shown efficient wound healing with significant anti-microbial and antioxidant activity.

Stone *et al* [52] developed the PEG-Plasma hydrogels with excellent reepithelization by using the *Ex vivo* human skin models. However, upon observing the histopathological findings and immunohistochemical staining's (WG and α-SMA) it was proved that the *in vitro* models treated with this hydrogel system had shown significant improvement in the wound healing process. Moreover, in this study it was also evidenced that this *ex vivo* model can be used for screening the different therapies meant for wound healing.

In case of impaired wound healing the microbial threat had been increased to an alarmed level in case of worldwide population. Hence the polymers which are showing both antimicrobial and antioxidant properties were preferred for wound healing. According to Wang *et al* [53] this dual functional Dextran-PEG hydrogel loaded with Polymyxin B and Vancomycin (Vanco) played a crucial role in promoting the antimicrobial activity by controlling the gram negative bacteria (*Escherichia coli (E. coli)*) with minimal toxicity in case of fibroblast cell line NIH 3T3. Moreover it was also found that this hydrogel was used as an ideal dressing in case of complex biological systems.

The sustained release drug delivery plays a role in preventing the unpredictable and premature drug delivery. Basically PEG was used as a polymer in several formulations in order to promote the sustained release and hence, due to this reason the polymer was preferred for designing the hydrogel scaffolds [54]. According to Jain *et al* [55] the developed PEG hydrogels loaded with platelet rich plasma protein had shown the sustained release until there was degradation within the PEG hydrogel. Moreover this PEG hydrogel loaded with platelet rich plasma protein had promoted excellent proliferation in case of human dermal fibroblast and this indicates that the entire activity in case of hydrogels depends upon extent of encapsulation and release profiles only. Thus, it demonstrated that the hydrogel scaffolds can be used as an effective vehicle for the delivery of several multicomponent mixtures.

Due to its ideal swelling, biodegradability PEG had acquired an attention in field of skin tissue engineering. Salvekar *et al* [56] developed the biodegradable photo cross-linked hydrogel in which water responsive shape recovery induced buckling was seen. This study was mainly performed in order to understand the role of the original diameter and prestretching time in minimizing the buckling time that involved in the development of the biodegradable photo crosslinked PEG hydrogel. Moreover, the study reports also revealed that the dry hydrogel had shown high swelling when compared to the wet hydrogels. Further in this study it was also reported that buckling induced shape memory effect was responsible for promoting the time controlled activation.

Because of its sustained release and thermosensitive characteristics, PEG had found its importance in designing the intracameral injection. Han *et al* [57] developed the PEG-PCL-PEG hydrogel loaded with Bevacizumab meant for regulating the intraocular pressure in case of trabeculectomy. It was also demonstrated that this hydrogel system plays a crucial role in post-operative scarring. Moreover, the histopathological and Massons trichome studies revealed that there was excellent bleb survival in case of the rabbits treated with Bevacizumab loaded hydrogel. Table No. 6 represents the role of polyethylene glycol in different formulations.

3.2.2. Carbopol:

Because of its excellent gelling characteristics this polymer had found its use in several pharmaceutical applications. Moreover, the positive effects on the zone of the stasis made this Carbopol an ideal polymer for the development of hydrogel for tissue engineering applications. Hayati *et al* [58] developed the Carbomer 940 hydrogels meant for burnt wound healing. In his studies, histopathological analysis revealed that the Carbomer 940 hydrogels enhanced the collagen deposition and reepithelization within the damaged portions when compared to controlled group. Further, the cell viability results also revealed that hydrogels were nontoxic to the fibroblast cells.

The treatment of the chronic wounds had become one of the major health care issue world-wide. Due to its excellent biocompatibility and soothing effect this polymer was used for decreasing the healing time. According to Grip *et al* [59] the sprayable Carbopol hydrogel loaded with beta- 1, 3/ 1, 6- glucan promotes excellent revascularization and reepithelization in case of the damaged tissues. Moreover, in this study even though carbopol 971P was preferred due to its excellent gelling and high transparency characteristics, but this alone cannot minimise the wound healing duration.

Zinov'ev *et al* [60] developed carbopol hydrogels meant for wound healing in case of alloxan induced diabetes rat model. In this study the Carbopol hydrogels were modified by using the electrical signals with the antibiotics like Poviagrol and it resulted in enhancing the reepithelization and also minimized rate of suppuration. Moreover in this study, it was also proved that this modified Carbopol hydrogel shows the bactericidal property and this property makes Carbopol useful in treatment of the necrotic lesions. Table No. 7 represents the role of Carbopol in different formulations.

3.2.3. Polyacrylamide (PAM):

The ideal mechanical, biological properties and aggregate behaviours of this polymer made it useful in designing the hydrogel scaffolds for tissue engineering applications. Wei *et al* [61] developed the polyvinyl alcohol (PVA)/ polyacrylamide (PAM)

composite hydrogels and it demonstrated about the aggregate behavior of nano-silica on loading into the composite hydrogels. However, on observing the study reports, it was identified that upon increasing the concentration of the nano-silica the aggregation behavior will also increase. Moreover, upon increasing the concentration of polyacrylamide the uniformity within the nano-silica loaded hydrogel scaffolds will also be enhanced simultaneously.

Pafiti *et al* [62] developed a polyacrylamide based composite hydrogels into which the hallow particles were entrapped. In this study, it was observed that this polymer was useful in making the hydrogels with ideal tunable mechanical properties. However in this study, in case of all dispersions percolated hallow particle network enhanced the modulus and ductility in the expected manner. Further, the pH responsive nature of the polyacrylamide based hydrogel scaffolds makes it useful in wound healing applications.

It was reported that burst release of antibiotics was possible by entrapping the antibiotics within the polyacrylamide hydrogel scaffolds. In this study, Pulat *et al* [63] developed the novel Piperacillin-Tazobactam and epidermal growth factor were loaded into polyacrylamide based hydrogels that acts as an effective system for wound healing. Moreover, in this study it was also reported that burst release of Piperacillin-Tazobactam hydrogels happens with in 1hour. Whereas, the epidermal factor loaded into these hydrogels plays a significant role in enhancing the mitogenic activity within the wound healing process. Further in this study, it was reported that when compared to the free epidermal growth factor in culture medium the incorporated epidermal growth factor had shown efficient rate of L929 mouse fibroblast cells proliferation for the longer duration of time.

3.2.4. Carboxy methyl cellulose (CMC):

Cutaneous wound healing had become a challenging aspect among the population across world-wide. Bilayered hydrogels usually plays a significant role in designing cutaneous wound healing process. The ideal swelling and mechanical properties made this Carboxy methyl cellulose useful in development of the bilayered hydrogel

scaffolds meant for skin tissue engineering applications. As in case of Li *et al* [64] developed the PVA/ CMC/ PEG hydrogels while gradually altering the pore sizes for these cutaneous wound dressings. Moreover, the study reports also revealed that the developed bilayered hydrogel scaffolds while showing ideal mechanical properties it also prevents the bacterial penetration into these hydrogel scaffolds. Due to this reason the wound closure time for the animals treated with these scaffolds were minimized. Further the MTT assay also revealed about the excellent biocompatibility shown by the single layer hydrogels

Due to its excellent biocompatibility, biodegradability and drug entrapment capabilities these cellulose derivatives were found to be useful for designing the hydrogels meant for promoting the local effect in case of damaged skin portions. Ali *et al* [65] developed the biofilm type of wound dressing by loading the graphene oxide into the sodium Carboxymethyl cellulose hydrogels. These developed hydrogels promoted the wound healing with excellent antibacterial activity via regulation of the epidermal and fibroblast growth factors. However in the study reports it was clearly shown that reduced graphene oxide hydrogel plays a significant role in preventing the intrinsic virulent factor developed by bacteria.

Carboxymethyl cellulose exhibits excellent environmental friendly characteristics hence, due to this reason this polymer was extensively used for the development of the skin repair substitutes. Capanema *et al* [66] developed the potential wound healing hydrogels with excellent super absorbent characteristics by using the Carboxymethyl cellulose and PEG polymers. Moreover, in this study it was also demonstrated that Carboxymethyl cellulose was essential in promoting superabsorbent characteristics in case of these hydrogel dressings.

4. Growth factors in skin tissue regeneration:

In case of damaged skin portions growth factors were essential for promoting the rapid skin tissue regeneration. Moreover, upon loading these growth factors into the hydrogels further enhanced the angiogenesis, reepithelization, and neovascularization within the damaged portions. Xu *et al* [67] developed the granule-lyophilised platelet

rich fibrin loaded hydrogel dressing for the treatment of skin wounds. Upon using the PVA (Polyvinyl Alcohol) as a polymer further enhanced the biodegradability and mechanical properties of these hydrogel dressings. Finally, the results of this study demonstrated that the granule- lyophilised platelet rich fibrin loaded hydrogel promoted the faster rate of wound healing with excellent neovascularization and reepithelization.

Hsieh *et al* [68] developed the novel vascular endothelial growth factors loaded chitosan/ fibrin hydrogel involved in the vascular repair within the damaged portions. Usually the combination of the fibrin and chitosan resulted in improvising the environmental stimuli responsiveness within these developed hydrogel scaffolds. Further, the report of this study also suggests that this VEGF loaded hydrogels promotes excellent angiogenesis and capillary formation within the damaged portions of the skin. Moreover in this study, it was clearly shown that capillary inducing and self-healing properties were the results of interpenetrating networks present in hydrogel.

Collagen was a natural substance that was mainly present within the skin structure. Moreover, this collagen had got a significant role in promoting the smooth muscle formation and reepithelization within the damged skin portions. Latifi *et al* [69] have fabricated a tissue mimetic collagen III loaded nano-fibrillar hybrid hydrogel scaffolds and this has achieved the significant importance in case of soft tissue engineering applications. Moreover, these developed hydrogels shows excellent porosity along with ideal mechanical and biodegradability characteristics. Hence, due to this reason these developed hydrogels also plays a promising role in the vocal cord and heart valve regeneration. Further in this study it was clearly demonstrated that matrix integrity was completely dependent on glycol- chitosan solution concentration.

In case of the skin wound healing platelet had got significant role in minimizing the skin scarring by enhancing the rate of neovascularization within the damaged portions. Samberg *et al* [70] developed the adipose derived stem cells loaded with platelet rich plasma hydrogel in order to enhance the angiogenic potential of these

developed hydrogel scaffolds. Moreover, in this study it was also clearly evidenced that upon usage of more than one growth factors along with adipose derived stem cells further enhanced the revascularization and reepithelization within the damaged extra cellular matrix.

Zhang *et al* [71] developed the basic fibroblast growth factors loaded hydrogels and this bioinspired hydrogel in turn stimulated wound healing process in case of balb mice. The study reports of this work demonstrated that this basic fibroblast growth factors loaded hydrogels has shown effective cellular migration and this further enhanced the reepithelization and neovascularization in case of the skin defects treated with the bFGF (basic fibroblast growth factor) loaded hydrogels. Figure 4. Describes about the role of growth factors loaded hydrogels in cutaneous wound healing. Table No. 8 represents the role of growth factors in different formulations.

5. Peptides in skin tissue regeneration:

Due to the excellent proliferation and regenerative characteristics these peptide have found their use in several tissue engineering applications. However, upon loading this peptides into hydrogels further enhanced the regenerative potential of these hydrogel scaffolds. Carrejo *et al* [72] fabricated the multi domain hydrogels in turn these hydrogels accelerated the wound healing in the diabetic mice. Moreover in this study it was also shown that excellent biocompatibility, angiogenesis and neurogenesis properties of the multi domain hydrogels resulted in the rapid tissue regeneration. Further, the study reports of this article also demonstrated that at the end of the 14^{th} day the peptide hydrogels promotes the wound closure with excellent neovascularization and reepithelization.

When compared to their counterparts (like synthetic polymers) peptides show ideal viscoelastic property and this property of peptides plays an important role in enhancing the stimuli response in case of the several skin tissue engineering applications. According to Dimaio *et al* [73] developed peptide hydrogels modifies the rigidity according to the requirements of the microenvironments of the biological tissue. Further, the study reports also revealed that self-assembling property of this

peptide loaded hydrogels made it useful in promoting the efficient drug delivery and wound healing. Moreover in the current study, specific and selective non covalent cross linking plays a vital role in altering the viscoelastic property of the peptide hydrogel and this further in turn resulting in modification of in situ hydrogel with response to the biological microenvironment.

The biomimetic and biodegradability characteristics of these peptide loaded hydrogels created a new series of platforms in regenerative medicine. As reported by Liu *et al* [74] the ideal biodegradability, biocompatibility and biomimetic properties of these peptide loaded PEG hydrogels made these hydrogels promote the significant rate of cellular attachment and proliferation and this was proved in this study upon performing the *in vitro* studies for these peptide hydrogels. Further in this study it was also revealed that fabricating temperature peptide structure and concentrations plays a significant role in enhancing the physicochemical and biological performance of the developed hydrogels.

In the past few years the concept of cellular migration had achieved significant importance in the therapeutic strategies meant for regenerative medicine. Wang *et al* [75] developed the REG peptide loaded hyaluronic acid hydrogel involved in wound healing activity. In this study REG peptide played a significant role in promoting the cellular migration by activating the Rac1 and pERK1/2 (Immuno modulatory signals). Further, these signals enhanced the MMP (Matrix metallo peptidase) expressions involved in the skin tissue regeneration. Finally the study reports also demonstrated that in case of the damaged skin tissue REG peptide loaded hydrogels promotes the significant rate of angiogenesis and cellular migration. Hence, due to this reason REG peptide was found to be useful in advanced wound care management.

Crosslinking nature of the peptides plays a significant role in modification of the rheological properties of the developed hydrogel scaffold. Seow *et al* [76] developed the ultrashort peptide cross linked hydrogel scaffolds meant for accelerating the wound healing process in case of full thick wounds. Moreover, in this study it was clearly stated that disulfide bond formation within peptide hydrogels was responsible

for enhancing the stiffness and crosslinking capabilities of these hydrogel scaffolds. Further, the study reports of this article also demonstrated that in case of female SCID mice with full thick excision wound model LK6C (Peptide Sequence) loaded hydrogels has shown excellent reepithelization and neovascularization when compared to control.Figure 5. Depicts about the Role of Peptides Loaded Hydrogels in Cutaneous Wound Healing. Table No. 9 represents the role of peptides in different formulations.

6. Conclusion:

Over the past few decades researchers were focusing on the development of the novel topical hydrogel scaffolds for skin tissue repair. Owing to their excellent swelling and biocompatibility and biomimetic properties these topical hydrogel scaffolds were found to be promising for several skin tissue engineering applications. In this review, we highlighted mainly the variety of the polymers, growth factors and peptides involved in the development of the hydrogels meant for skin tissue regeneration.

Natural polymers such as Chitosan, Collagen, Genipin, Keratin, and Collagen were among the optimised polymers meant for preparation of the topical hydrogels, owing to their ideal biodegradability, minimal cytotoxicity and similarity to the extracellular matrix of the skin. However, synthetic polymers such as PEG, Carbopol, Polyacrylamide (PAM), Carboxymethyl cellulose exhibits excellent stability and mechanical properties when compared to the natural polymers.

Various study reports of both peptide loaded hydrogels and growth factor loaded hydrogels revealed that these hydrogels plays a crucial role in enhancing the cellular migration towards the damaged portions. This key property of these hydrogels further enhanced the angiogenesis, moisture retaining capability and reepithelization process in the skin defects model. An important future work is to accelerate the regenerative potential of hydrogel by fabricating both the synthetic and natural polymers, whereas the incorporation of growth factors, peptide sequences, signaling molecules formed an ideal microenvironment to support cell growth and tissue regeneration. Further there

was a need to explore the novel strategies in the multifunctional hydrogel-based scaffold for cell-based therapies and tissue engineering.

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Conflict of interest:

The authors declare no conflict of interest

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Figure Legends:

Figure 1. Represents the Classification of Polymers.

Figure 2. Describes About the Significance of Polymeric Hydrogel Scaffolds.

Figure 3. Represents the Role of Natural/ Synthetic Polymers in Cutaneous Wound Healing.

Figure 4. Describes About the Role of Growth Factors Loaded Hydrogels in Cutaneous Wound Healing.

Figure 5. Depicts About the Role of Peptides Loaded Hydrogels in Cutaneous Wound Healing.

Table Legends:

Table. 1 represents the role of chitosan in different formulations.

Table. 2 represents the role of collagen in different formulations.

Table. 3 represents the role of genipin in different formulations.

Table. 4 represents the role of keratin in different formulations.

Table. 5 represents the role of pectin in different formulations.

Table. 6 represents the role of polyethylene glycol in different formulations.

Table. 7 represents the role of carbopol in different formulations.

Table. 8 represents the role of growth factors in different formulations.

Table. 9 represents the role of peptides in different formulations.

Table. 1 represents the role of chitosan in different formulations

Sl.no	Polymer combination	Formulation	Role	References
1.	Chitosan + Phenytoin.	Chitosan hydrogels containing nanoencapsulated phenytoin for cutaneous use: Skin permeation/penetration and efficacy in wound healing.	Enhanced the rate of permeation and penetration.	24
2.	Carboxy Methyl Chitosan + cellulose nanocrystals	On-Demand Dissolvable Self-Healing Hydrogel Based on Carboxymethyl Chitosan and Cellulose Nanocrystal for Deep Partial Thickness Burn Wound Healing.	Self-healing & Scar less skin tissue regeneration.	25
3.	Chitosan + poly (N-vinyl-2-pyrrolidone) (PVP)	Stimuli responsive biopolymer (chitosan) based blend hydrogels for wound healing application.	Biocompatibility, controlled rate of release.	26
4.	Chitosan + methacrylamide	Fluorinated methacrylamide chitosan hydrogel dressings enhance healing in an acute porcine wound model.	Bio adhesive property.	27
5.	Chitosan + Silver Nanoparticles	Novel chitosan hydrogels reinforced by silver nanoparticles with ultrahigh mechanical and high antibacterial properties for accelerating wound healing.	Anti-microbial & ideal mechanical property.	28
6.	Chitosan+ Collagen	Norfloxacin-loaded collagen/chitosan scaffolds for skin reconstruction: Preparation, evaluation and in-vivo wound healing assessment.	High Porosity and Water Retention capability	29

Table. 2 represents the role of collagen in different formulations

Sl.no	Polymer combination	Formulation	Role	References
1.	Collagen + Hyaluronan.	Hyaluronan/collagen hydrogels containing sulfatedhyaluronan improve wound healing by sustained release of heparin-binding EGF-like growth factor.	Controlled rate of release.	30
2.	Collagen + Polyvinyl Alcohol.	Collagen-Polyvinyl Alcohol-Indomethacin Biohybrid Matrices as Wound Dressings.	Novel Bio hybrid dressing.	31
3.	Collagen + Decorin	Decorin-containing collagen hydrogels as dimensionally stable scaffolds to study the effects of compressive mechanical loading on angiogenesis.	Angiogenesis, evades mechanical stimuli, promotes excellent fibrillogenesis and vascular growth.	32
4.	Collagen + Chitosan	Preparation and characterization of chitosan - collagen peptide / oxidized konjac glucomannan hydrogel.	Ideal biocompatibility, swelling and retention properties.	33
5.	Collagen + Dextran	Development, Optimization and In Vitro/In Vivo Characterization of Collagen-Dextran Spongious Wound Dressings Loaded with Flufenamic Acid.	Anti-inflammatory property.	34

Table. 3 represents the role of genipin in different formulations

Sl.no	Polymer combination	Formulation	Role	References
1.	Genipin + Chitosan	Evaluation of genipin-crosslinked chitosan hydrogels as a potential carrier for silver sulfadiazine nanocrystals.	Local antibacterial vehicle	35
2.	Genipin + Chitosan	Effects of post-processing methods on chitosan-genipin hydrogel properties.	Ideal Porosity, Swelling and Biomimetic property	36
3.	Genipin + Peptides	Self-assembling peptides cross-linked with genipin: resilient hydrogels and self-standing electrospun scaffolds for tissue engineering applications.	Acts as a cross linker for bio inspired biomaterials	37
4.	Genipin + Fibrin + Agarose	Generation of genipin cross-linked fibrin-agarose hydrogel tissue-like models for tissue engineering applications.	Biocompatibility and bio fabrication property.	38

Table. 4 represents the role of keratin in different formulations

Sl.no	Polymer combination	Formulation	Role	References
1.	Keratin + Chitosan	Keratin-chitosan/n-ZnO nanocomposite hydrogel for antimicrobial treatment of burn wound healing: Characterization and biomedical application.	Ideal biocompatibility	39
2.	Keratin + Avena Sativa	An investigation of konjac glucomannan-keratin hydrogel scaffold loaded with Avena sativa extracts for diabetic wound healing.	Enhanced fibroblast proliferation and collagen levels	40
3.	Keratin	Assessment of Deep Partial Thickness Burn Treatment with Keratin Biomaterial Hydr ogels in a Swine Model.	Reepithelization and neovascularization	41
4.	Keratin	Feather keratin hydrogel for wound repair: Preparation, healing effect and biocompatibility evaluation.	Biocompatibility and biodegradability properties.	42
5.	Keratin + Ciprofloxacin	Ciprofloxacin-Loaded Keratin Hydrogels Prevent Pseudomonas aeruginosa Infection and Support Healing in a Porcine Full-Thickness Excisional Wound.	Enhances macrophages	43
6.	Keratin	Effect of discarded keratin-based biocomposite hydrogels on the wound healing process in vivo.	Ideal Biocompatibility, reepithelization and connective tissue formation.	44
7.	Keratin	Evaluation of skin regeneration after burns in vivo and rescue of cells after thermal stress in vitro following treatment with a keratin biomaterial.	Excellent fibroblast proliferation and cell viability.	45

Table. 5 represents the role of pectin in different formulations.

Sl.no	Polymer combination	Formulation	Role	References
1.	Pectin + Honey.	Pectin-honey hydrogel: Characterization, antimicrobial activity and biocompatibility.	Excellent antimicrobial activity.	46
2.	Pectin + Polyvinyl alcohol.	Evaluation of the biocompatibility of pectin/poly vinyl alcohol composite hydrogel as a prosthetic nucleus pulposus material.	. Ideal biocompatibility	47
3.	Pectin + Polyvinyl alcohol.	Wound healing potential of a polyvinyl alcohol-blended pectin hydrogel containing Hippophaerahmnoides L. extract in a rat model.	Revascularization and reepithelization	48
4.	Pectin + Thiolnorbornene.	Cell-instructive pectin hydrogels crosslinked via thiol-norbornene photo-click chemistry for skin tissue engineering.	Modulating cell behavior.	49
5.	Glutaraldehyde + Pectin	Preparation and characterization of amidated pectin based hydrogels for drug delivery system.	Ideal swelling and porosity.	50

Table. 6 represents the role of polyethylene glycol in different formulations.

Sl.no	Polymer combination	Formulation	Role	References
1.	Polyethylene glycol + Chitosan	Silver nanoparticle impregnated chitosan-PEG hydrogel enhances wound healing in diabetes induced rabbits.	Ideal swelling and biodegradability	51
2.	Polyethylene glycol + Plasma	PEG-Plasma Hydrogels Increase Epithelialization Using a Human Ex Vivo Skin Model.	Reepithelization	52
3.	Polyethylene glycol + Dextran	Dual-Functional Dextran-PEG Hydrogel as an Antimicrobial Biomedical Material.	Anti-microbial & Antioxidant property	53
4.	Polyethylene glycol + Platelet rich Plasma Protein	Sustained release of multicomponent platelet-rich plasma proteins from hydrolytically degradable PEG hydrogels.	Promotes sustained release.	55
5.	Polyethylene glycol	Water-Responsive Shape Recovery Induced Buckling in Biodegradable Photo-Cross-Linked Poly (ethylene glycol) (PEG) Hydrogel.	Ideal swelling and biodegradability	56
6.	PEG + PCL	Effects of bevacizumab loaded PEG-PCL-PEG hydrogel intracameral application on intraocular pressure after glaucoma filtration surgery.	Sustained release and thermosensitive characteristics	57

Table. 7 represents the role of carbopol in different formulations

Sl.no	Polymer combination	Formulation	Role	References
1.	Carbomer 940	Effects of carbomer 940 hydrogel on burn wounds: an in vitro and in vivo study.	Positive effects on the zone of stasis, collagen deposition, reepithelization.	58
2.	Carbopol 971P + beta-1, 3/ 1, 6-glucan	Sprayable Carbopol hydrogel with soluble beta-1,3/1,6-glucan as an active ingredient for wound healing - Development and in-vivo evaluation.	Excellent gelling and high transparency characteristics.	59
3.	Carbopol	Wound-healing effect of carbopol hydrogels in rats with alloxan diabetes model.	Bactericidal property, necrotic lesion treatment.	60
4.	Polyacrylamide + Polyvinyl alcohol	Aggregation Behavior of Nano-Silica in Polyvinyl Alcohol/Polyacrylamide Hydro gels Based on Dissipative Particle Dynamics.	Promotes the uniformity with in the developed hydrogel scaffolds.	61
5.	Polyacrylamide	Composite hydrogels of polyac rylamide and crosslinked pH-responsive micrometer-sized hollow particles.	Promotes ideal tunable mechanical properties into the hydrogel scaffolds.	62
6.	Polyacrylamide + Piperacillin-tazobactam + epidermal growth factor	Sequential antibiotic and growth factor releasing chitosan-PAAm semi-IPN hydrogel as a novel wound dressing.	Promotes burst release of formulation.	63
7.	Carboxymethyl cellulose + Polyvinyl Alcohol + Polyethylene glycol.	A Bi-Layer PVA/CMC/PEG Hydrogel with Gradually Changing Pore Sizes for Wound Dressing.	Ideal mechanical properties, Prevents the bacterial penetration.	64
8.	Sodium Carboxymethyl cellulose + Graphene oxide.	Sodium carboxymethyl cellulose hydrogels containing reduced graphene oxide (rGO) as a functional antibiofilm wound dressing.	Excellent Antibacterial activity	65
9.	Carboxymethyl cellulose + Polyethylene glycol.	Superabsorbent crosslinked carboxymethyl cellulose-PEG hydrogels for potential wound dressing applications.	Promotes super absorbent characteristics.	66

Table. 8 represents the role of growth factors in different formulations

Sl.no	Growth factor combination	Formulation	Role	References
1.	Granule-lyophilised platelet rich fibrin + PVA	Effects of incorporation of granule-lyophilised platelet rich fibrin into poly vinyl alcohol hydrogel on wound healing.	Neovascularization, Reepithelization	67
2.	Vascular endothelial growth factors + Chitosan + Fibrin	A novel biodegradable self-healing hydrogel to induce blood capillary formation.	Angiogenesis, Capillary formation.	68
3.	Collagen III	A tissue-mimetic nano-fibrillar hybrid injectable hydrogel for potential soft tissue engineering applications.	Smooth muscle formation,	69
4.	Adipose derived stem cells + Platelet rich plasma	Platelet rich plasma hydrogels promote in vitro and in vivo angiogenic potential of adipose-derived stem cells.	Enhances the angiogenic potential, minimizing the skin scarring.	70
5.	Basic fibroblast growth factor	Stimulation of wound healing using bioinspired hydrogels with basic fibroblast growth factor(bFGF).	Promotes effective cellular migration, Reepithelization, Neovascularization.	71

Table. 9 represents the role of peptides in different formulations

Sl.no	Peptides combination	Formulation	Role	References
1.	Peptides	Multidomain Peptide Hydrogel Accelerates Healing of Full-Thickness Wounds in Diabetic Mice.	Neovascularization and Reepithelization	72
2.	Peptides	Modulating Supramolecular Peptide Hydro gel Viscoelasticity Using Biomolecular Recognition.	Enhances the stimuli response, ideal viscoelastic property	73
3.	Peptide + PEG	Biodegradable poly(ethylene glycol)-peptide hydrogels with well-defined structure and properties for cell delivery.	Cellular attachment and proliferation.	74
4.	REG peptide + Hyaluronic acid	Development of Biocompatible HA Hydrogels Embedded with a New Synthetic Peptide Promoting Cellular Migration for Advanced Wound Care Management.	Promotes cellular migration, enhances the MMP expression	75
5.	Ultrashort peptides	Transparent crosslinked ultrashort peptide hydrogel dre ssing with high shape-fidelity accelerateshealing of full-thickness excision wounds.	Enhances the stiffness and crosslinking capabilities of the hydrogel scaffolds, shows excellent reepithelization and neovascularization.	76

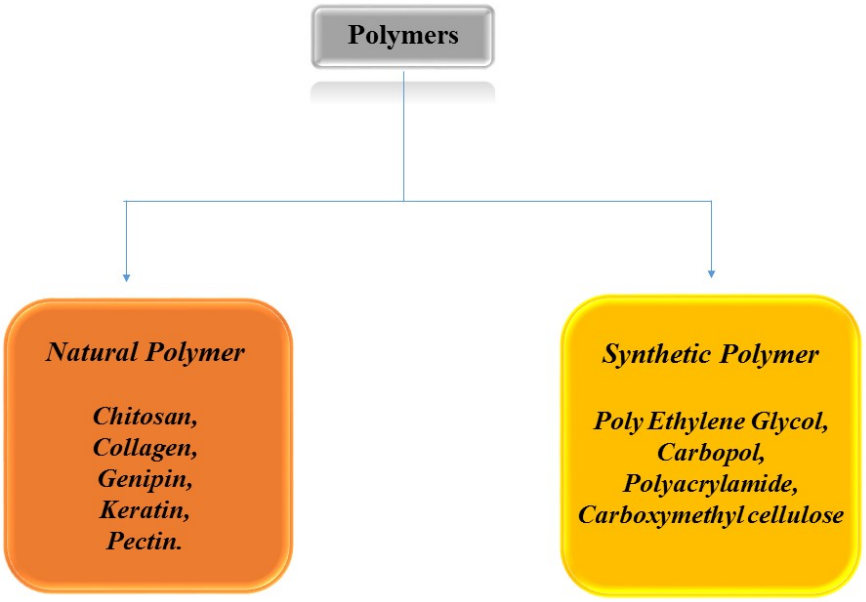

Figure 1. Represents the Classification of Polymers

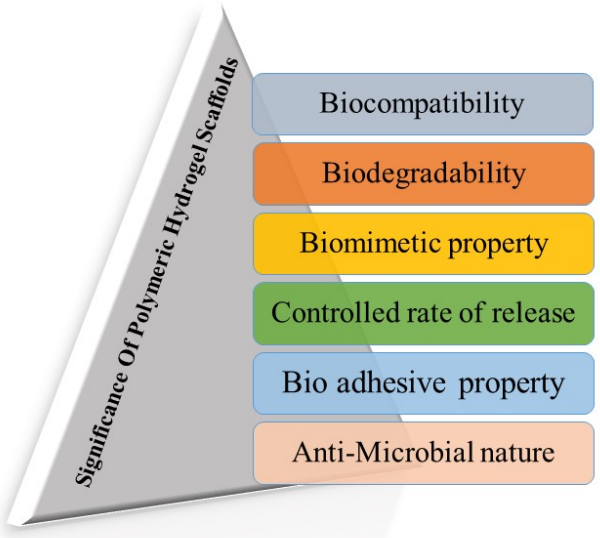

Figure 2. Describes About the Significance of Polymeric Hydrogel Scaffolds.

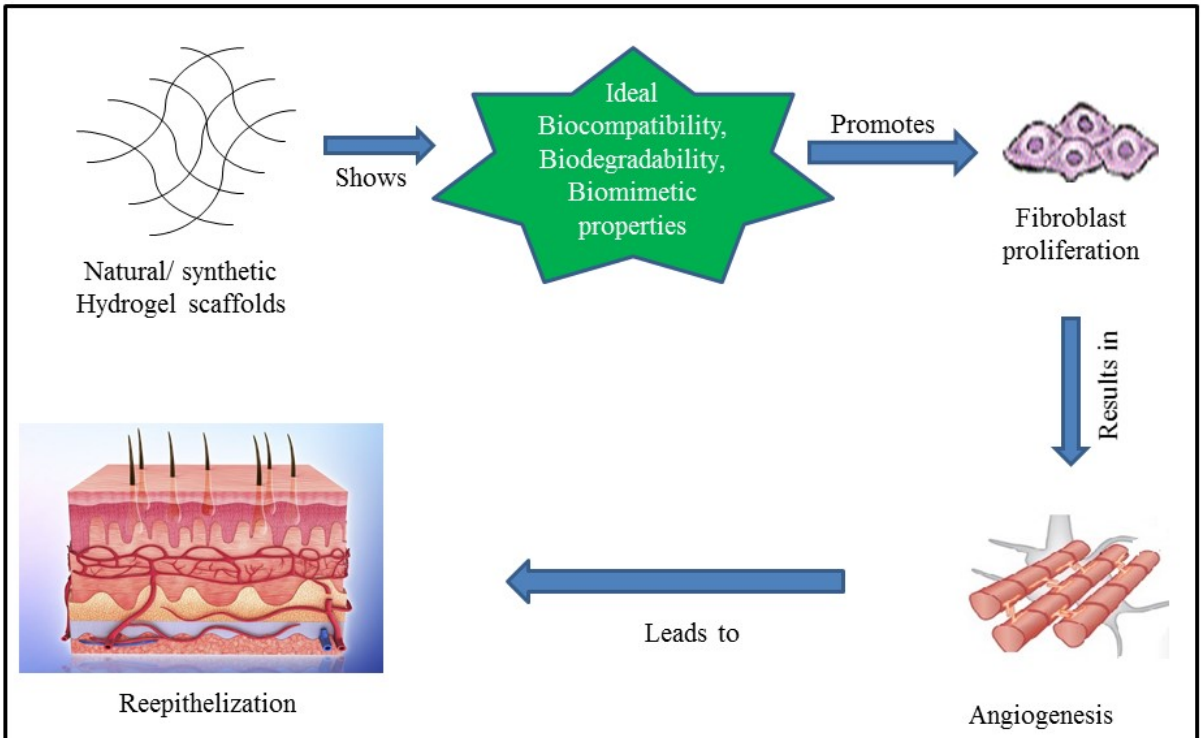

Figure 3. Represents the Role of Natural/ Synthetic Polymers in Cutaneous Wound Healing

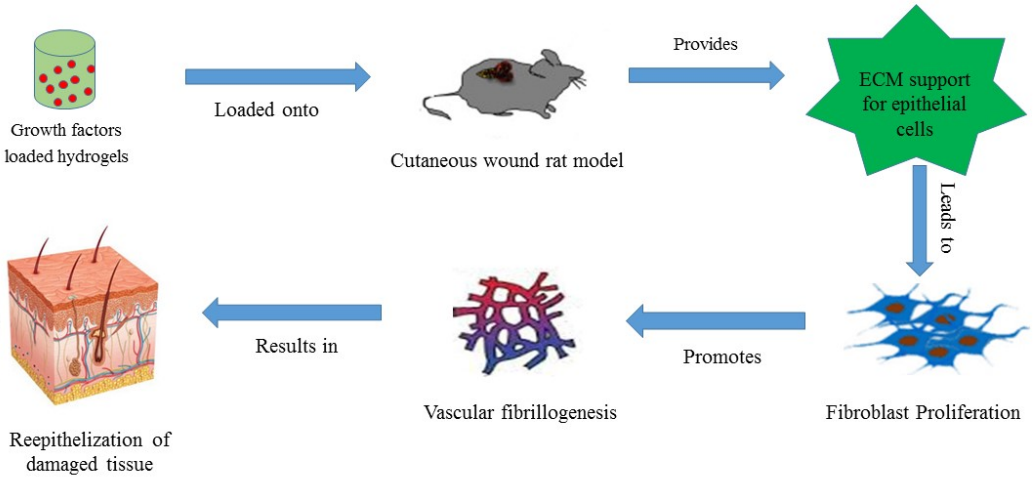

Figure 4. Describes About the Role of Growth Factors Loaded Hydrogels in Cutaneous Wound Healing

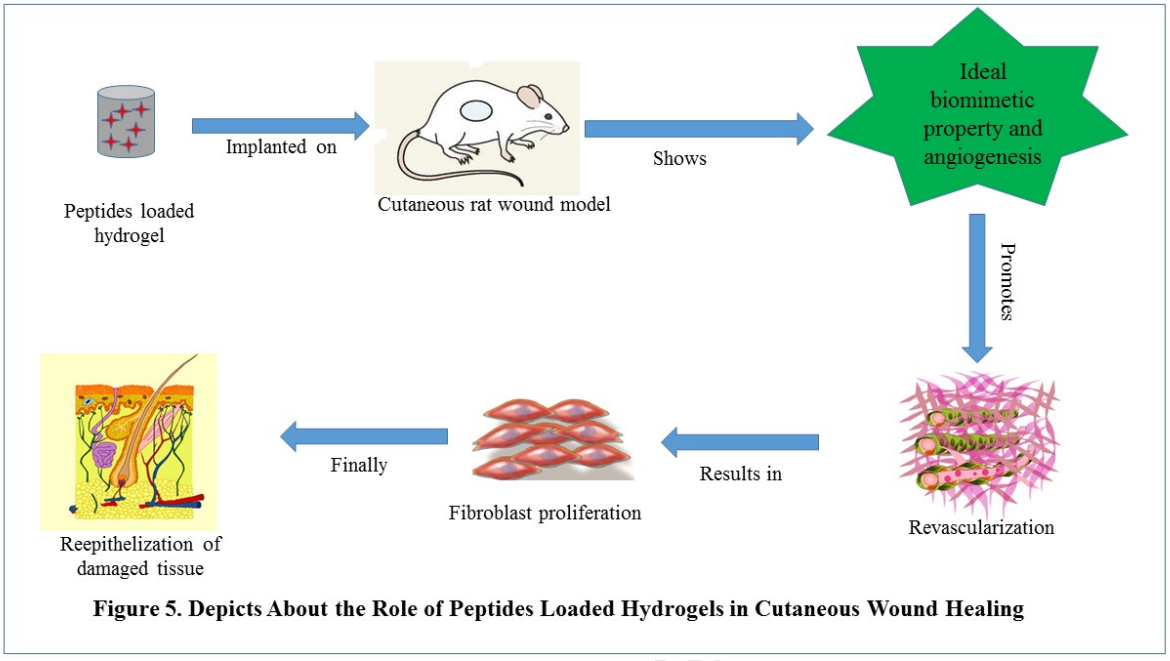

Figure 5. Depicts About the Role of Peptides Loaded Hydrogels in Cutaneous Wound Healing

Conflicts of Interest Statement

Manuscript title: Hydrogel based scaffolding polymeric biomaterials: Approaches towards skin tissue regeneration

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