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A review of polysaccharide based hydrogel as cell carrier in wound healing

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Abstract--Various types of wound treatment materials have been developed that influenced by numerous wound types and wound management using hydrogel has been explored and widely used before. Among current strategies of development of hydrogel is the one that can act as a cell carrier that is applicable for wound healing. Thus, this study is conducted for reviewing the synthesis and method approaches for various polysaccharide-based hydrogel as wound healing materials. In other hand, this study is concerning on properties of hydrogel and their biological role as cell carrier that can support wound healing process by reviewing studies that related to polysaccharide-based hydrogel as cell carrier. Various types of polysaccharide-based hydrogel such as alginate, chitosan and hyaluronic acid have been developed using different type of approaches for wound healing. They can capsule various type of cells that and the formed polymers give an excellent support for the cells such as to be delivered to the host tissues as well as aiding angiogenesis to accelerate wound healing. The emerging polysaccharide-based hydrogel for wound carrier has a very promising

criterion that can be polished further due to its favorable qualities in assisting wound healing mechanisms.

Keywords---Polysaccharide-based Hydrogel; cell carrier; encapsulate cell; wound healing.

Introduction

Traditional wound dressings, such as bandages, cotton wool, and gauzes, have been found worldwide over the world and serve a significant role in wound management. Their job is to shield the wound from dangerous microorganisms and to absorb exudates released by the wound bed. Surprisingly, the advent of new dressings, such as hydrogel, has swept the nation in recent decades, resulting in better and faster wound healing. The newest types of wound treatment can create an environment that allows epithelial cells to move freely while also providing a moist environment with adequate oxygenation to aid tissue regeneration [1].

Researchers has been defining hydrogel as a water-swollen, and a network of cross-linked polymers that produced by the simple reaction of one or more monomers. It can alternatively be characterised as a polymeric material with the ability to swell and hold a huge amount of water within its structure. Another aspect of hydrogel is that it does not dissolve in water due to the crosslinking of polymer network chains inside it, making it ideal for wound treatment applications. Hydrogel can be used as a first aid treatment that function to cool down the wound and reduce the pain of the patient because it can absorbs a large amount of water due to the presence of a hydrophilic functional group, which aids in the absorption of exudate discharge from the wound bed and accelerates wound healing. As a result, hydrogel is frequently used in the industry because to its vast range of potential applications. Also, they hold a degree of flexibility quite similar to natural tissue because of their large water content [2]. 3D networks crosslinked formation can occur by physical interaction such as by hydrogen bonding, van der Waals forces and ionic interaction [3]. A study [4] has stated that among biopolymers, polysaccharide have an excellent and promising properties that make them the polymer group known to have the widest-range and longest-standing experience in medical applications. Polysaccharide also is non-toxic as it is not hazardous to health. In addition, it is water soluble and has high capacity for swelling that can be achieve by chemical modification.

Hydrogel has a smart behaviour where it can release water in reversible manner in response to the environmental stimuli such as pH, ionic strength and temperature. Thus it can change in response to the physiological variables that it faces. It also has the ability to aid in skin healing on its own. Its use has been extensively investigated by researchers, and it is currently being used in a variety of clinical settings. In addition, prevention of bacteria from entering the wound can be achieve due to its tight mesh size of hydrogel but the transport of bioactive molecules such as pharmaceutical and antimicrobial agents can still occur efficiently to the wound bed. The molecule can be easily entrapped during the gelling procedure. Because hydrogel has such a high degree of flexibility and

elasticity, it can provide the ability to adapt and alter itself to the wounds that are located in the various part of the body.

Amusingly, researchers has been synthesizing diverse dynamic hydrogel that can contain biomaterials of various cell types or active ingredients such as drugs for tissue regeneration, and it exhibits the properties needed in wound healing [5]. The review study of polysaccharide properties that give rise to acceleration and aiding wound healing has been well discussed before. However, the study of property and benefits of using polysaccharide-based hydrogel for cell encapsulation of biomaterials of cell type for wound healing has not been identified properly yet. Furthermore, this research may serve as an inspiration for future development of wound healing applications using hydrogel as a cell carrier that will be readily available. Thus, this narrative review study is conducted to review the literature on synthesis and method approaches for various polysaccharide-based hydrogel and to identify properties of hydrogel as cell carrier as well as to review the literature on biological role of polysaccharide-based hydrogel as cell carrier for wound care.

2. Materials and Methods

2.1 Research design

This narrative review study is a qualitative study where the collection of data was obtained from document search that are related to the search terms and reviewed through offline. The data collected will be categorized by thematic analysis.

2.2 Eligibility and exclusion criteria

Several eligibility criteria were determined. With regard to literature type, case study and review paper that are related to the polysaccharide-based hydrogel as cell carrier for wound care were selected while eliminating paper from synthetic-based hydrogel for wound care, book series, chapter in book, conference proceeding are all excluded. This review will be focusing on article that is published in English. With regard to the timeline, a period of 2000 to 2021 was selected. Lastly, based on the objective of the study, studies and articles have been selected from all over the world. The resources database for this study relied on two main journal which is PubMed and ScienceDirect.

2.3 Data extraction

First, the data were extracted by reading though the abstract first and once it fulfils the criteria for this review then will move to reading of full articles to identify appropriate themes and sub-themes. Then, qualitative analysis was performed using the thematic analysis appropriate and related to the objectives of this review of polysaccharide-based hydrogel as cell carrier for wound care.

2.4 Quality assessment

For quality assessment of paper reviewed in this study, those selected paper that fit the inclusion criteria will be presented and evaluated by the expert and it will

also be reviewed by other researcher which is my research partner. Then, the data collected will be categorized by theme analysis.

3. Results and Discussion

3.1 Overall Findings

Overall a total of 120 abstract were found from two databases. (PubMed and ScienceDirect). 66 were screened and 31 papers were included that fit the inclusion criteria. Another addition of four papers were included from manual search and 35 paper were revised in full-text. 14 of them were considered for this narrative review study that focused on hydrogel as cell carrier for wound care. Figure 1 shows the trend of the paper reviewed in this study by year. It has been seen that there is an increasing number of research and peak in 2018. This is due to the challenges that become and huge burden to the healthcare system regarding to wound management that originates from the rapid growth of chronic diseases from diabetic, burn, obesity and aging population. This issue indirectly calls for modern solution for wound management of such hydrogel. That is why the development for hydrogel for wound care has been one of the main interest among the researchers [6].

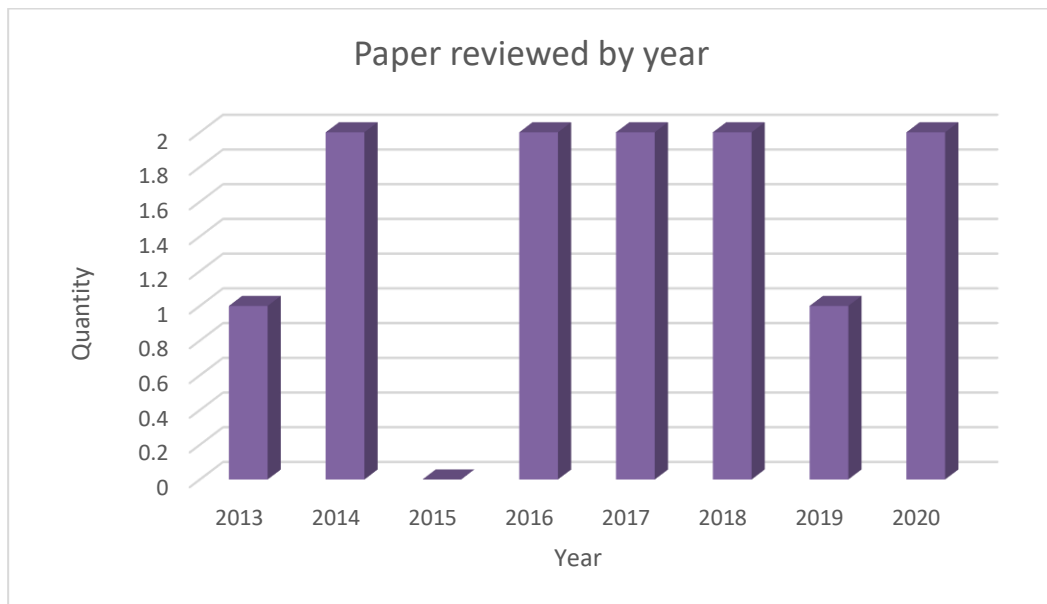


Figure 1 shows the trend of paper reviewed in this study by year.

3.2 Flow chart of paper selection

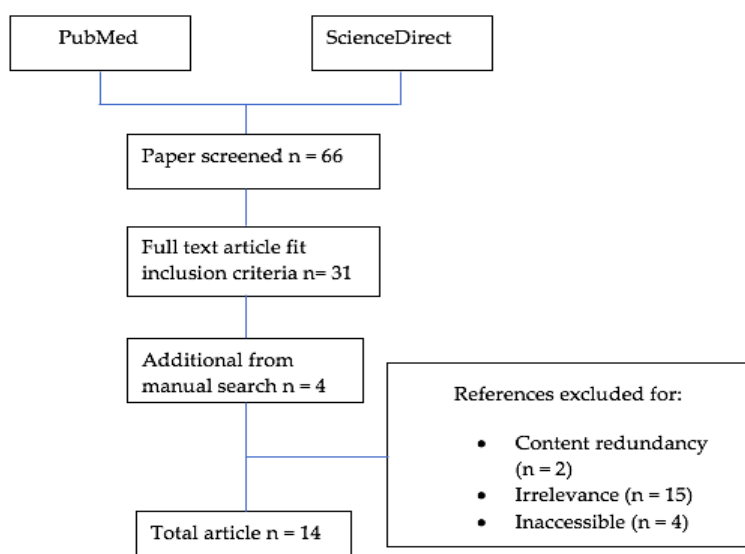


Figure 1 shows the flow of paper selection from two databases and total article collected were 14.

3.3 Theme analysis

Table 1 shows the theme that have been identified to categorized the data extracted from this study.

Theme	Sub-themes
Polysaccharide-based hydrogel	Chitosan
	Cellulose
	Alginate
	Hyaluronic acid
Methods for preparation of hydrogel	Free radical polymerization
	Irradiation crosslinking
	Physical crosslinking
	Chemical crosslinking
Properties needed of hydrogel as cell carrier	Self-healing ability
	Porous structure
	Biocompatibility and biodegradability
	Ability to release cell

Biological action of hydrogel as cell carrier	General
	Wound healing
	Action of cell carrier for wound healing

3.4 Synthesis of polysaccharide-based hydrogel

3.4.1 Chitosan

Chitosan originates from shells of crabs and shrimps which is derived from deacetylated chitin that is a co-polymer of N-acetyl glucosamine and glucosamine. It has known properties such as biocompatible and this cationic polymer could dissolve in water up to pH of 6.2. Neutralization of amine group of hydrated polymers could result in gel like precipitation with increasing basicity. Thus, chitosan can produce properties of pH- responsive hydrogel [7]. Chitosan-based hydrogel also could exhibit thermo responsive characteristic when polyol salts were added like β -glycerophosphate (GP) where the formulation dissolves at normal temperature and neutral pH due to hydration of chitosan chains that is induced by β -glycerophosphate (GP). When heating at body temperature, the gelation will occur because the bounded water is relatively released thus influencing the chain reactions and influenced the gelation process.

There are various interactions that possibly occur for gelation mechanism to take place such as:

1. Interaction due to hydrogen bond between the chitosan chain molecule. This is because there is a decrease of electrostatic repulsion due to neutralization of ammonium group of chitosan by added GP.
2. The chitosan-chitosan hydrophobic interaction
3. Electrical force linking between GP phosphate group and chitosan ammonium group.

3.4.2 Cellulose

For cellulose derivatives, gelation of numerous cellulose derivatives biopolymers like methylcellulose (MC) and hydroxypropylmethylcellulose (HPMC) can be achieve upon heating. As cellulose-based hydrogel is induced by temperature, it has the ability to self-structure upon temperature variation. Both (MC) and (HPMC) gelation generated resulted from intermolecular, hydrophobic interactions of the methoxy side groups. Therefore, the macromolecules of cellulose derivatives will be entirely hydrated at a low temperature. Thus, when heating took place, the macromolecules will eventually dehydrate that gives outcome of increasing viscosity. Polymer networks of cellulose-based hydrogel is generated when polymer-polymer interaction dominating upon reaching the transition temperature. Cellulose-based hydrogel can be combined with numerous molecule such as proteins, cells and also other polysaccharides. Hemicellulose which is a simpler polysaccharide, can gives various benefits for biological activity which are

as antitumor, antioxidant and also can be used for various application such as wound treatment, drug delivery as well as tissue engineering [8].

3.4.3 Alginate

Next is alginate-based hydrogel, where it is composed of β -D-mannuronic acid and α -L-glucuronic acid that can be derive from brown algae. Alginate solution can quickly become an ionotropical gel after multivalent cation is added into the solution that is favorable in biomedical applications. To make in vivo injection of Ca^{2+} -crosslinked hydrogel available the reduction of crosslinking rate must be made. Addition of polyols inhibit instantaneous and quick complexation of Ca^{2+} by alginate and also has been known to slow down the process of hydrogel formation. Thus, alginate has been established to possess properties of biocompatible, mucoadhesive and nonimmunogenic so immune response is not provoked in human body. In addition, alginate also has been use as microcarriers that can encapsulate cells to be delivered to the body area of interest [9].

3.4.4 Hyaluronic acid

Hyaluronic acid (HA) is a major component of extracellular matrix of human skin as well as cartilage. HA also essential as it responsible for many cellular signaling and tissue functions such as wound healing and matrix organization. HA, a non-sulfated glycosaminoglycan which also known as hyaluronan, is a linear polysaccharide that has alternating units of repeating disaccharide β -1,4- D-glucuronic acid- β -1,3-*N*-acetyl- D-glucosamine exist with wide range of molecular weight of 100 000 Da in serum to 8 000 000 Da in vitreous. There are various application oh hyaluronic acid-based hydrogel that have been reported and one of it is as a molecule delivery [10].

3.5 Methods for preparation of hydrogel

Hydrogel can be prepared using various methods [11] and has been summarized that the methods used must be depending on the design structure and the aimed application of the hydrogel. It can be divided into four types which are:

3.5.1 Free radical polymerization

Steps involved for this method are initiation, propagation, chain transfer and termination. Initiators such as thermal, ultraviolet, redox can be used for radical generation in initiation step. In the propagation step, the radicals generated will react with monomers thus converting them into active form that will further react with other monomers. At the end of the process, the long chain radical will be produced and undergo termination process by chain transfer or through radical combination resulting in formation of polymeric matrices. Preparation of hydrogel using this method can be done in bulk and also in solution form where water is normally used as solvent.

3.5.2 Irradiation crosslinking of polymeric hydrogel

Ionizing radiation is known to be a very effective tool to produce hydrogels. This method does not need any crosslinking agent or initiators that could produce unwanted side effect and is hard to remove and separated from the end product. For irradiation crosslinking of hydrogel, the ionizing radiation that has been used are electron beam and gamma-rays as they possessed a high energy that are adequate to ionize simple molecule in both air and water. What happened when ionizing radiation is exposed to the particular polymer after samples undergo sterilization, crosslinking will occur and it will change the structure and other properties of the polymer such as size, shape and solubility that result in new hydrogel formation [12].

3.5.3 Chemical crosslinking

Both synthetic and natural hydrophilic polymers can use chemical crosslinking to produce hydrogel where a bi-functional crosslinking agent is needed to combine with a dilute solution of hydrophilic polymers. To be noted that the crosslinking agent used must have a suitable functionality so that reaction between the crosslinking agent and the polymer can proceed [11].

3.5.6 Physical crosslinking

Physical crosslinking can be divided into three types which are ionic interactions or also known as polyelectrolyte complexation, hydrogen bonding and lastly is hydrophobic association. The use of physical crosslinking in formation of hydrogel is common and has been widely use in medical field all over the world. A previous study, had successfully synthesized a thermo sensitive hydrogel that made up of chitosan/glycerol phosphate sodium/cellulose nanocrystal by using physical crosslinking that enable encapsulation of Human umbilical cord-mesenchymal stem cells (hUCMSCs) for wound healing [5].

3.6 Properties needed for hydrogel as cell carrier

3.6.1 Biocompatibility and biodegradability

Since hydrogel is widely used in biomedical field on human mostly, biocompatibility is one of essential properties that must be consider properly in formation of hydrogel. It is best for a hydrogel to have a resemblance structure with the existing natural extracellular matrix. Thus, researchers now are moving toward to synthesize a hydrogel that has excellent biocompatibility by reprogram and reconstruct the chemical nature of the hydrogel so that the hydrogel formed are able to repair and reconstruct the tissues after being injected into the living things. Similarity towards the ECM could help for the attachment as well as the migration of cells delivered by hydrogel without destructing the physical, biological and also biochemical of cell tissues [13].

To explore more on the biocompatibility of the hydrogel, researcher will do in vitro biocompatibility characterization where the quantification of lactate dehydrogenase (LDH) will be observed. (LDH) is a cytosolic enzyme that will rise in

the culture medium by the membranes when there are non-biocompatible substance penetrates it. This test is done [14] on alginate-based hydrogel containing hyaluronan and the result showed that there are no remarkable differences of LDH released by the cells that is treated with alginate-based hydrogel and the one that is untreated. This finding rules out the in vitro biocompatibility features of the synthesized hydrogel. Another study reported previously, that used cellulose nanoparticle as one the polymer for synthesis of hydrogel and found that it has a good biocompatibility as well as biodegradability. [5]

3.6.2 Porous structure

Hydrogel must possess a microscopic structure because it could provide a better transport of nutrients and waste for the cell. Porous structure of the hydrogel also could affect the survival of the cell embedded inside it. The structure of hydrogel produced must be porous enough so that it could provide a suitable microenvironment that is alike to ECM so that it is beneficial for encapsulation of cell adhesion and survival [15]. Study of hydrogel with interconnected pores and appropriate surface porosity for cell culture by synthesizing RGD peptide sequence to dextran-based hydrogel has reported porous characteristic of the hydrogel by doing SEM analysis on the cross section of the hydrogel and found that there are presence of well-interconnected big pores that could provide to enhancement of cell migration and penetration inside the hydrogel [16]. The microporous structure also could give rise to absorption of liquid more effortlessly as well as could result in hydrogel that has a better swelling ratio.

3.6.3 Ability to release bioactive or cell component

Hydrogel is invented with features that able to release the bioactive component within it. An evaluation of polysaccharide release and membrane degradation of alginate based-hydrogel that is combined with hyaluronan for biomedical applications has reported that after immersion of hydrogel in the Hanks' balanced based solution (HBSS) after 3 hours, the kinetic release of both polysaccharides begin to rise. The membrane has an excellent feature as HA is being released rapidly in the first hour that parallel to the expected result by the researcher. This feature is essential because bioactive component must be delivered effectively and in timely manner locally at the wound area thus could promotes the wound healing process [14].

3.6.4 Self-healing ability

For injectable type of hydrogel, it is essential for the hydrogel to be able maintaining their stability by expressing rapid self-recovery when is subjected to damage caused by external forces. Their properties could decline or worse when they experiencing damage cause by cracks at micro or macroscale might be due to the forces exerted on them. This could affect the mechanical properties and network structure of the hydrogel thus shortening their lifetime to carry out their action. Thus, researchers developed novel smart gels that has self-healing ability that can repair themselves so that objectives of the hydrogel can be restored after being exposed to damages. A review study that has been conducted of self-healing

gels and reported that there are two features that is possessed by self-healing gel systems which is first, it can create a mobile phase at the damage area that can fill and bridge the cracked area of the hydrogel. In order for hydrogel to create this feature, they must have a superb flowability. The second one is the self-healing gels can be automatically and non-automatically heal themselves with the help of external energy such as light, certain pH, temperature, and catalyst. With the assistance of these energy, they could recuperate to their initial structure and features. This study also summarized that the mechanism of self-healing of hydrogel can be obtain chemically and physically [17].

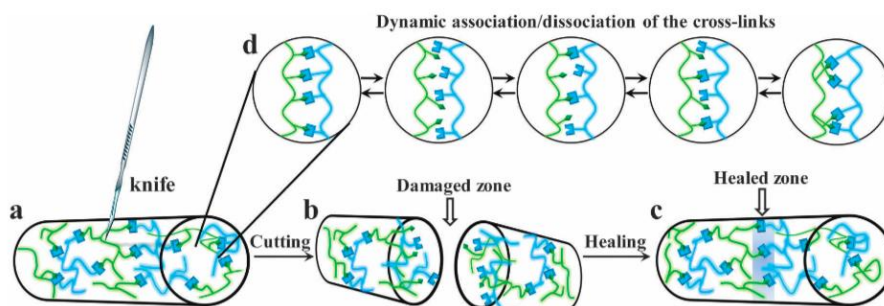


Figure 3 shows a concept of self-healing gels [17]

Figure 3.6 above is the mechanism concept of self-healing gels where when a gel is cut into half, that will cause presence of damage zone to it. The healing process occur by reformation of dynamic bonds within the gels. This concept is referred as concept of constitutional dynamic chemistry (CDC) that can undergo dynamic and reversible bond breaking and bond reformation.

3.6.5 Swelling ability

One of the most essential aspects in the biomedical use of hydrogel scaffolds is their swelling degree, also known as water uptake, which directly represents hydration ability and indirectly relates to mechanical stiffness and structural properties. The scaffolds' swelling creates a moist environment, which is essential for wound healing. A study of cellulose-based hydrogel that is developed for wound healing application has resulted in high swelling property which give them the ability to incorporate various types of biomolecules such as nucleic acids, enzymes, antibodies as well as a whole cell due to the porous structures together with water when it swells. The swelling ability property of hydrogel aids in release and cellular process support in biomedical applications [8].

3.7 Biological function of hydrogel as cell carrier

3.7.1 General

3D scaffold hydrogels are known to be able to carry cells for *in vivo* and *in vitro* studies. Therefore, many researches have been conducted to produce hydrogel that have excellent properties as a carrier for cell or tissue. Tissues, biomaterials, cell as well as bioactive factors are normally used for incorporation in formation of 3D gels for tissue generation. The response of damage tissues due to injury is

influenced by their cellular and matrix compositions. Thus, the crosstalk between the hydrogel synthesized and matrix compositions of the host tissue will determine the action of cell behavior therefore will affect the tissue fate whether it will promote cell healing or regeneration. It also can result to failure when the crosstalk is unsuccessful [18].

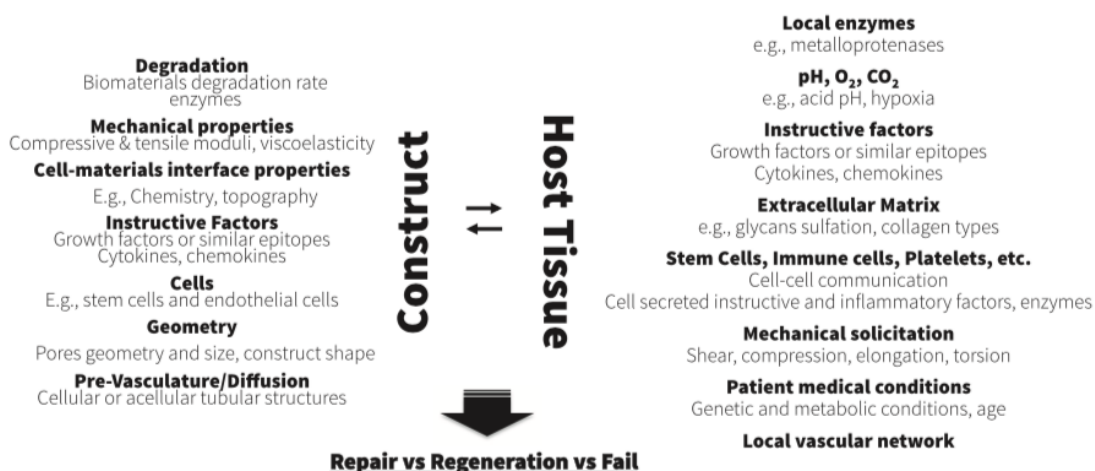


Figure 4: showed [18] where multidirectional instruction between the construct and host tissue occur where favorable crosstalk will lead to successful tissue generation

A study of host tissue response in tissue engineering that focused on crosstalk between immune cells and hydrogel that entraps cells within their crosslinked polymer which is called cell-laden scaffolds [19], has reported that there are interaction that can occur through juxtacrine or paracrine signaling between macrophages and the cells that are entrapped in the cell-laden scaffolds. Juxtacrine signaling happens when there are cell-cell contact while paracrine signaling is a type of cellular communication where a signal is induced by certain cell that will affecting the surrounding cells. The macrophages can signal the cells embedded in the gels and same goes to the other way around thus making this two-way signaling capable of producing positive results in tissue regeneration.

The application of hydrogel that functions as cell carrier has been widely use in tissue engineering to promotes tissue regeneration. Some of them has been use to promotes cardiac tissue repair [20], for cartilage and bone tissue engineering [21], [22] and many more.

Table 2: List of paper reviewed in this narrative review study

By:	Polysaccharide-based hydrogel	Carrier used
[15]	Chitosan-based hydrogel	human umbilical cord-mesenchymal stem cells
[23]	Hyaluronic Acid/Alginate Hydrogel	Adipose-derived stem cell

[24]	Dextran-based hydrogel containing chitosan microparticles	Growth factors of EGF and VEGF
[16]	Dextran-based hydrogels	RGD and Human umbilical vein endothelial cells (HUVEC)
[14]	Alginate-based hydrogel	Hyaluronan
[25]	Dextran-based hydrogel	adhesion molecule-1 (ICAM-1)
[13]	A review on biocompatibility nature of hydrogels with 3D printing techniques, tissue engineering application and its future prospective	-
[26]	Dextran-based hydrogel	Polydopamine
[17]	Self-healing gels based on constitutional dynamic chemistry and their potential applications	-
[8]	Hemicellulose-reinforced nanocellulose hydrogels	NIH 3T3 fibroblast cell
[27]	Hyaluronic acid-based hydrogel	Solubilized amnion membrane (SAM)
[28]	Hyaluronic acid-based hydrogel	Adipose-derived mesenchymal stem cell exosomes (AMSCs-exo)
[29]	Cellulose-based hydrogel	Fibroblast and keratinocytes
[30]	Chitosan-based hydrogel	LL-37 peptide

As this review will be focusing on the application of cell carrier hydrogel for wound healing, several papers have been observed that has been summarized in table 2 and many polysaccharide-based hydrogels combined with various cells have a positive impact in accelerating wound repair. A study of human umbilical cord mesenchymal stem cell (hUCMSCs) [15] that has been incorporated in the injectable thermo-sensitive chitosan-based hydrogel resulting in acceleration of wound closure and promoting tissue remodeling. The chitosan-based hydrogel formed has an excellent structural support for survival of hUCMSCs together with adhesion at wounded area. These superb features help in promoting growth factors secretion together with inhibition of inflammatory mediators thus resulting in faster cell proliferation and migration.

Another study where adipose-derived mesenchymal stem cell (hAdMSCs) is embedded inside the polymeric crosslink of hyaluronic acid/alginate hydrogel that is used for healing of vocal fold wound injury. This study is conducted [23] by synthesizing hydrogel that gives benefit in improving the process injured vocal cord wound healing where the matrices of hydrogel give a helpful microenvironment for placement of stem cell that can be released at site of injury. In addition, the alginate hydrogel, gives stability for incorporation of cells.

Next is a study regarding fabrication of a dextran-based hydrogel with functionalized RGD (Arginyl-glycyl-aspartic acid) peptide that homing human umbilical vein endothelial cell (HUVEC) [16] that has reported that the scaffold provides structural support that can hold (HUVEC) for more than 7 days which allowing optimum cell proliferation and local cell delivery. Dextran based hydrogel is greatly available as it is known to be non-toxic, biocompatible, biodegradable as they can be cleared by dextranases in the gastrointestinal group and has a low cost for production. Also, dextran-based hydrogel provides natural base that can support the addition of various biomolecules. The purpose of incorporation of RGD peptide together with the dextran-based hydrogel is to provide cell attachment site as it can be found as integrin binding sequence in the ECM of host tissue. Thus, by incorporating RGD together with the hydrogel it can maximized the cell delivery towards the host tissue.

Another study of dextran-based hydrogel that contain chitosan microparticle is done [24] where oxidize dextran (DeOX) that has been loaded with particle of growth factors, EGF+VEGF and the action of the hydrogel on wound healing is observed. The DeOX-based hydrogel has a porous structure that assist in drainage of the wound and avoiding presence of exudates build-up. Also, it can enlarge the surface area-to-volume ratio of cell carrier hydrogel that result in improvement of cell growth and cell influx, and also aid in transportation of nutrient to the wound bed. Incorporation of growth factors in this study is helpful in wound healing as EGF and VEGF can be found abundant in ECM and they are known to aid in natural skin regeneration. Since the study combine two systems which are hydrogel (Dextran) and microparticles (chitosan), it gives advantageous of protection of wounded area from unwanted toxins and harmful microorganisms as well as provide extra hydration to the wound area. Hydrogel formed also could prolong release of growth factor thus giving a longer time for wound healing process to complete.

Lastly, the study of nanocellulose hydrogel that is combined with hemicellulose where it can carry NIH 3T3 fibroblast cell is done [8] where the polymers can affect the microscopic and mechanical properties of composite hydrogels, allowing for control of features vital for medical applications such as wound healing and tissue engineering. The cellulose-based hydrogel formed has a tunable porous structure which meet the pore size that is suitable for optimum cell adhesion, cell growth and proliferation as well as transportation of nutrients and metabolites. The all-polysaccharide composite hydrogels created are intended to serve as support networks as well as boost cell survival and proliferation.

With supportive evidences by various studies the action of hydrogel as cell carrier can be summarize as follows:

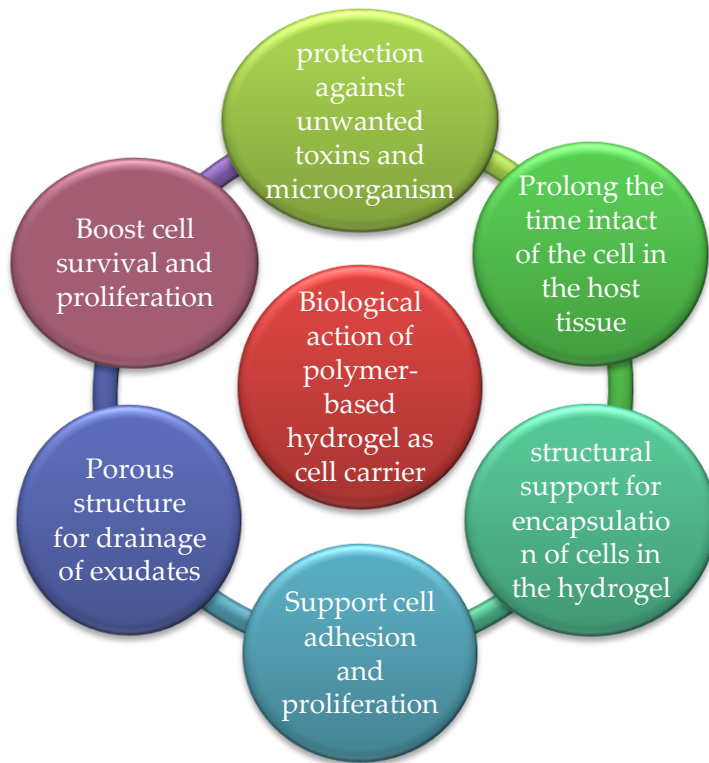


Figure 5: Summarized actions of hydrogel as cell carrier that promotes wound healing.

These excellent features provided by hydrogel could give rise in many possibilities to enhance faster and better process of wound healing that is safe to be use in many medical applications.

3.8 Action of cells encapsulate that support wound healing

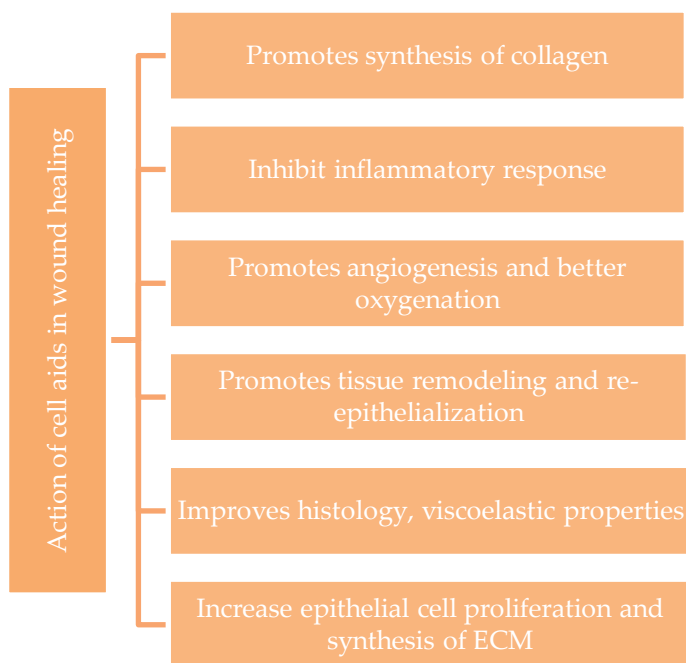


Figure 6: Shows various benefits and actions from cells incorporated in the hydrogel for aiding wound healing process.

Various types of biomolecules have been incorporated in the hydrogel for aiding wound healing process. In this review study the action of the cells homed within the hydrogel has been identified where they give rise to various benefits in wound healing. Based on figure 6, where study has been done that [15], [28] the hydrogel developed can successfully carry human umbilical cord-mesenchymal stem cells and adipose-derived mesenchymal stem cell exosomes (AMSCs-exo). They claim that by introducing these cells, they can increase the creation of collagen, mainly type I and III collagens, which are commonly found in the dermal ECM and play an essential role in wound healing. The study of collagen deposition analysis in vivo which used (AMSCs-exo) has showed that collagen fibers were plentiful and relatively well-organized on day 7, and the number of collagen fibers increased as healing progressed compared to the use of hydrogel only and on day 21, the wounds are totally healed, and the skin appendages are visible.

On the other hand, similarly, Hydrogel-hUCMSCs also reported to increase collagen deposition by intensify fibroblast expansion thus will promotes secretion of ECM which is collagen. Collagen deposition is essential in generating of suitable microenvironment for better aid in cell proliferation, migration and speedy skin regeneration. These investigations also found that the hydrogel created could speed wound closure by enhancing re-epithelialization, which involves the production of new epithelial cells. Plus, it is suggested that hUCMSCs incorporated could promotes tissue remodeling where there was formation of keratinocyte at the early stage of wound healing process. In addition, incorporation of growth factors such as EGF and VEGF within the hydrogel also help to increase the cell proliferation and ECM synthesis. Where with the

formation of new epithelial layer, it will increase the thickness of the skin and can lead to formation of new hair follicle around the wound area that is needed for wound healing [24].

Next, with the presence of cells such as VEGF, HUVEC, and AMSCs-exo, the blood flow of the wounded area has increase better than the use of hydrogel alone. This is because the incorporation of those cells has been proven to promotes angiogenesis. VEGF can give a potent effect towards the vascular system where it can enhance new vessel formation and thus will increase vascular permeability. This will lead for a better oxygenation and to aid exchanges and transportation nutrient to the wound area. To assess the formation of new blood vessel, a study has been conducted ²⁸ where the level of alpha-smooth muscle actin (α -SMA) was observed and it has shown that the α -SMA level of hydrogel combined with AMSCs-exo is the highest compared to the use of hydrogel alone. The number of vessels formed that connect to the smooth muscle also can be determined by using α -SMA and similarly to the previous result, the hydrogel that encapsulate AMSCs-exo has the highest number observed. These results can support the action of these cells that give benefits of enhancing angiogenesis in wound healing application.

Another study [23] where hydrogel has been developed that are able to carry adipose-derived stem cell and has found that the incorporation of the cell result in improvement of tissue histology. The viscoelastic properties of the hydrogel also is better with the presence of the cell and the hydrogel produced are able to strengthen the hydrocellular foam activity where hydrogel formed can provide a moist environment suitable for wound healing activity to take place and it can absorbs huge amount of exudate discharged from the wound bed. The cell incorporated within the hydrogel can successfully be delivered to the wounded area and remain visible for more than one month. This will result in prolonging the action of the hydrogel for wound healing process. Lastly, development of hydrogel that incorporate hUCMSCs [15] has reported that the hydrogel can inhibit the inflammatory response where it can inhibit the mediators of TNF- α which then can prevent induce of fever and inflammation of host tissue.

Overall, the combination of various polysacchatide-based hydrogel with numerous biomaterial give rise to many advantages that aids and accelerate wound healing process. The hydrogels synthesised are non-toxic, has a good swelling properties and can result in faster wound closure.

5. Conclusions

The review study of polysaccharide-based hydrogel as cell carrier for wound healing has successfully conducted where their properties and benefits can be identified. The hydrogels can be developed using various methods are able to carry diverse type of cells such as stem cells, growth factors and also other types of polymers such as hyaluronan within the polymer matrix that will be release once the hydrogel is introduced to the wound area. This finding fits numerous studies of polysaccharide-based hydrogel where they can provide suitable environment for entrapment of cells and give the structural support needed for a cell to be release gradually once entering the host system. They also have

promising properties for wound healing as they are non-toxic, has a good biocompatibility, biodegradable, superb swelling ability that has a high-water absorption capacity that could absorb the exudates as well as providing hydration to the wounded area. Numerous wound healing materials have been developed and used for wound healing applications to date, but there is still a need for an absolute and adaptable choice. Thus, these findings could give an insight for further development of various polysaccharide-based hydrogel that able to store various type of cell so that they are available to be use in clinical practice as they provide a promising role in management of wound healing especially as they aid in accelerating tissue regeneration, providing better oxygenation by angiogenesis.

Conflict of interest: The authors declare no conflict of interest.

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