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MINI REVIEW

Polysaccharides as wound healing agent: a mini review

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Abstract

Medicinal eukaryotes, such as plants and fungi, have prompted researchers to conduct extensive studies on their medicinal values for drug discovery. Current trends focus on bioactive compounds of medicinal plants to produce inventions in the medical and health fields. Among many bioactive compounds, polysaccharides attract attention because they are non-toxic and have no side effects. Polysaccharides have been widely used in food and pharmaceutical industries as a secondary ingredient for several decades. This paper reviewed the applications of polysaccharides as wound healing agents. Wounds can affect the patient's well-being, self-image, working capacity and independence. Research studies on different sources of polysaccharides by *in vitro* and *in vivo* model have been investigated. Based on the scientific evidence related to polysaccharides, this work will be a baseline study for future investigations in different fields. All literature was accessed through available electronic databases.

1. Introduction

Carbohydrate polymers which consist of many units of monosaccharides are known as polysaccharides (Lin *et al.*, 2009). Those long chains of monosaccharide units are connected by glycosidic linkages (Xie, Jin, Morris *et al.*, 2016). Polysaccharides can be extracted from numerous sources, such as animals, plants, microorganisms, and seaweeds (Gomez-Zavaglia *et al.*, 2019).

Among many sources, organic products capture more attention because they are innately less toxic and have fewer side effects than synthetic products (Xu *et al.*, 2008). Nowadays, many researchers have changed the focus of medicinal plant studies to further explore bioactive compounds of the plants (Xie, Tang, Jin *et al.*, 2016). Among numerous bioactive compounds, the polysaccharide has been the most studied. This polymer is non-cytotoxic and has beneficial pharmacological properties. The changes on trend focus and interest gain on polysaccharide research can be proven with the number of articles published (Xie, Tang, Jin *et al.,* 2016).

Studies on polysaccharides and its antioxidant (Jeddou *et al*., 2016), hypoglycemic (Li *et al*., 2006), anticancer (Huang, 2013), wound healing (Khamlue *et al*., 2012), and antihypertensive (Kolsi *et al*., 2016) properties were conducted. Moreover, journals on the polysaccharides' characteristics, such as lipid profile (Chen *et al*. 2010) and radio-protective effects (Li and Zhou, 2007), were published.

Every 30-second leg is lost due to diabetes in some part of the world (International Diabetes Federation, 2017). It shows the failure of current treatment methods of wound healing. Religious and vegetarian lifestyle choices may prohibit certain consumer groups from taking animal-based wound healing products (Boyer, 2013). Effective wound care from plant-based is needed because some people do not like the peculiar taste of snakehead fish and sea cucumber when taken orally, which are the popular animal-based products with wound healing properties. Hence, this review aims at providing some updated information on polysaccharides as wound healing agent for supporting the data on the effectiveness of wound care from plant-based. All literatures were accessed through available electronic databases.

2. Polysaccharides in wound healing

Plant polysaccharides are made up of long carbohydrate chains with either linear or branched structures. These polysaccharides build up 80% of the

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compounds and each compound has a specific function in the cell, which mostly contribute to biological functions. Polysaccharides, which appear to have biological functions, have glycuronic acids, primarily D-galacturonic and D-glucuronic acids, in their structure (Ovodov, 2010).

In recent times, a number of research on the correlation of polysaccharides with wound healing activity have been published. Valizadeh *et al*. (2015) stated that some monosaccharide units, arabinose and tannin compounds, shorten wound healing duration by coagulating surface proteins. Besides, pectin was found to ease the wound healing process by providing a favourable environment for angiogenesis and epithelialization. On the other hand, Carvalho *et al*. (2014) suggested that mucilage could be a growth factor that increases collagen production to promote wound healing in a dose-dependent manner. Thus, this mini review will tackle the role of polysaccharide in the wound healing process.

3. Overview of wound healing process

Repair of the skin or other soft tissues, which happens after different injuries, is known as wound healing (Nayak and Pereira, 2006). This process entails hemostasis, inflammation, reepithelization, and remodelling phases, which are interconnected and overlapping with one another (Demirci *et al*., 2014).

The phase which occurs right after injury is known as hemostasis. During this phase, platelets rush to the site of injury, and a clot begins to form. This event subsequently triggers the release of growth factors and cytokines, which act as promoters of the inflammatory phase. Entries of inflammatory cells, such as neutrophils, monocytes, and macrophages, increase tissue debridement and influx of growth factors, which are needed for wound healing (Lakshmi *et al.,* 2011). Although the presence of neutrophils at the site of wound area benefits the process by clearing the microbial contamination and cellular debris, neutrophils also leave a negative effect by releasing protease and reactive oxygen species (ROS). Monocytes in blood, which identify macrophages when they enter the wound site, are responsible for cleaning mechanism and pave a way to end the inflammation state. During this period, macrophage undergoes differentiation while in the repairing state by inducing the needed cells, such as keratinocytes and fibroblasts, as well as angiogenesis.

The process is then transited to the next phase (Guo and DiPietro, 2010). Proliferative phase takes over; this phase is characterized by epithelization, the formation of blood vessels, formation of granulation tissue, and deposition of collagen. Continuing the sequence of previous phases, cell detachment, cell migration, and cell differentiation occurs, which are all initiated by transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), and multiple cytokines (Gothai *et al.,* 2016). Formation of new blood vessels, known as angiogenesis, also provides nourishment for newly formed cells and tissues. As a final phase of wound healing, fibroblasts replication and collagen production are accelerated to gain 80% of the tensile strength of the uninjured tissue, which is called as remodelling phase (Velnar *et al*., 2009).

4. Wound healing polysaccharides sources

4.1 *Aloe barbadensis (*Aloe vera)

This plant, which belongs to family Liliaceae, originated from South Africa and is very popular at subtropical and tropical climate areas, including the South USA (Radha and Laxmipriya, 2015). Traditionally, Aloe vera was the preferred medication for wounds, burns, or infections. These medicinal purposes have attracted researchers to study more about Aloe vera properties (Sandhya and Gowri, 2015). Shi *et al*. (2017) have conducted the extraction and fractionation of Aloe vera leaf skin polysaccharides. The plant contained a huge amount of monosaccharide molecules, particularly acetylated glucomannan. Several studies were done on the wound healing activity of Aloe vera and proved that the possible effect was due to the presence of glucomannan polysaccharides (Hashemi *et al*., 2015).

Although studies on Aloe vera alone proved to have effective wound healing properties, the latest attempt on combining Aloe vera with other plants was done to further examine its wound healing activity. The main aim of the study was not to isolate any particular compound but rather to study the effect of the formulations on fibroblast cell and main cell at all phases of the wound healing process (Negahdari *et al*., 2017).

4.2 *Phellinus gilvus* (Mustard-yellow polypore)

Mushrooms have become a well-used natural source in the pharmaceutical industry and have been recognized as a functional food (Chang *et al*., 2008). Among various genera of *Phellinus*, *P. gilvus* is in demand because it only requires a short duration for growth, which makes it more affordable and easier to produce than others (Park *et al*., 2009). Bae *et al*. (2005) conducted a pharmacological study to determine the wound healing effect of *P. gilvus* polysaccharide in streptozocin-induced diabetic rat. The findings showed that the polysaccharides extract of the plant has a positive effect in wound healing at different doses, which might be due to the antioxidant activity. Moreover, free radical damages the cells and prolongs the wound healing process. Chang *et al*. (2008) stated that *P. gilvus* increased scavenging activities more as compared with the standard compound, ascorbic acid. The wound-healing effect might be due to the anti-inflammatory properties of mushrooms. Inflammation is one of the stages in the wound healing process; thus, inhibiting the phase would fasten the healing activity (Kim *et al*., 2011).

4.3 Tremella fuciformis (White jelly mushrooms)

Tremella fuciformis, commonly known as white jelly mushrooms, "snow fungus", or "silver ear", is a member of *Tremellaceae* family and is widely found in subtropical areas, especially in China (Wen *et al*., 2016). This mushroom has unique physical characteristics: gelatinous, smooth, and elastic when wet but rigid and curved when dry. Since this species is edible, this mushroom has been traditionally used as a basic ingredient in food formulation, such as ice cream, porridge, soup, and drinks (Permana and Purnawan, 2015). Aside from the traditional uses, polysaccharide of this mushroom possesses many biological activities because the chemical structure of the polysaccharides comprises (1→3)-β-d-glucans and (1→3)-α-mannan backbone with small xylose- and glucuronic acid-containing side chains (Bin, 2010). Furthermore, Khamlue *et al.* (2012) have conducted wound healing study using porcine skin wound model ex-vivo. Two different types of mushrooms were used in the study, and both purified polysaccharide extracts had significantly promoted wound healing activities at different doses. The inconsistent results between different plants may be due to the different monosaccharide compositions in the plant polysaccharides. Collagen formation is an important factor in the remodeling phase.

According to Wen *et al*. (2016), *T. fuciformis* polysaccharide treated group enhanced collagen production up to 26%. Increased production of collagen will help the wound to heal. Moreover, the wound healing potentials may also due to the antioxidant activity of the mushroom polysaccharides. As mention earlier, free radicals damage cell epithelization, thereby prolonging the wound healing process. Bin (2010) studied the antioxidant properties of *T. fuciformis* polysaccharides and revealed that it can scavenge those free radicals at 78% in a 0.2 mg/mL solution.

4.4 Opuntia ficus-indica (Barbary fig)

Another widely used medicinal plant is *Opuntia ficus -indica* from the family of Cactaceae; it is a native plant of South America and also available in tropical and subtropical regions (Zhong *et al*., 2010). A number of researchers have compared the composition of the plants, and the compositions were different even though the species are the same. The results varied possibly because of the different methods of cultivation (Matsuhiro *et al*., 2006). Therefore, the main component of the plant is similar to pectins, which are available from other species (Majdoub *et al*., 2001). Moreover, a study on wound healing activities of two types of lyophilized polysaccharides extract was evaluated by Trombetta *et al.* (2006) using an animal model. The results obtained suggested that plant polysaccharides with a molecular weight greater than 10^4 Da had effective wound healing properties in rat model wounds by hastening the reepithelization and remodelling phases. Similarly, a wound healing study done by Galati *et al*. (2003) confirmed that the polysaccharide fractions from the plant significantly speeded up the healing process by reducing the inflamed cell and stimulating fibroblast, angiogenesis, and collagen production. Both findings complement each other. The isolated polysaccharides acted on the proliferation and remodelling phases.

4.5 Althaea officinalis

Marshmallow, scientifically known as *Althaea officinalis,* is a member of family Malvaceae and is commonly found in Europe (Deters *et al*., 2010). Traditionally, this plant is used in treatments for respiratory disorders, such as asthma, bronchitis, and sore throat (Ghavi, 2015). Benbassat *et al*. (2013) stated that the roots of the plant contain 5% to 10% of water-soluble polysaccharides and other phenolic compounds. Additionally, Valizadeh *et al*. (2015) have taken the initiative to study the wound healing effects in rabbits. The outcome showed that the wounds which were treated with the different concentration of flower extract healed within 14 days. However, the control group took 21 days to heal completely. The flower polysaccharides positively influenced the wound healing activities on the rabbit model. This possible mechanism is due to the enhancement of epithelization process by the polysaccharides.

Furthermore, Kardošová and Machová (2006) found that *A. officinalis* possesses higher antioxidant activity (30%) than the standard compound, α-tocopherol. Inhibition of microbial growth shortens the inflammatory stage and fastens the healing process (Valiei *et al*., 2011); hence, the antimicrobial activity of the flower extract plays a role in this positive mechanism.

4.6 Ganoderma lucidum

Ganoderma lucidum is a well-known medicinal mushroom from the family Polyporaceae. The fruiting bodies of this species are known in different names in different countries. In China, this plant is called "Lingzhi", whereas, in Japan, it is known as "Reishi" (Zhonghui *et al*., 2014). This mushroom is rich in bioactive secondary metabolites with a vast range of chemical structures (Veljović *et al.,* 2017). Although it contains many bioactive compounds, polysaccharides of this fungi are available in high amount (Zhang and Lin, 2004). Additionally, Cheng *et al.* (2013) have studied the wound healing properties of the *G. lucidum* polysaccharides on diabetic rats.

Polysaccharides application in aqueous cream significantly shortened the wound healing process in streptozocin-induced rats, possibly due to the increased antioxidant effect of the extract, which inhibited the cell damages. Similarly, Jia *et al.* (2009) reported that polysaccharides from *G. lucidum* naturally had an antioxidant activity that inhibited the oxidative stress occurring on plasma and liver of streptozocin-induced diabetic rats. In addition, Barbieri *et al*. (2017) stated that the polysaccharides of this plant exhibited anti-inflammatory properties by activating the cytokines associated with an inflammation response. This characteristic is essential in the wound healing process; delayed inflammatory phase will result in the delay of the whole process of healing.

5. Proposed mechanism of polysaccharide in wound healing process

ROS were formed as a consequences of neutrophil release to the site of injury (Guo and DiPietro, 2010). An unstable atomic or molecular structure with imbalance electron arrangements is known as free radical; this molecule plays a negative role in various fields, such as food science, pharmacology, and physiology (Köksal *et al*., 2017). During tissue metabolism, ROS are formed and maintained in low levels by the redox reaction. However, imbalance in redox reactions leads to oxidative stress that interrupts the physiology of cells and tissues (Cao *et al.,* 2017).

Generally, antioxidants from herbal compounds work as scavengers of free radicals. Through scavenging activity, antioxidant indirectly promotes faster healing mechanism by reducing inflammation, the formation of tissue, reepithelization, and differentiation of skin layers (Ktari *et al.* 2017). Song *et al*. (2017) also stated that the phenolic compounds, such as caffeic acid, which possesses antioxidant activity, regulate TGF-β. TGF-β with VEGF accelerates wound healing process by inducing angiogenesis, the formation of granulation tissue, and synthesis of collagen.

Apart from antioxidant activity, anti-inflammatory properties also help in the wound healing process. A defensive approach by an organism or tissue to clear the site of injury is known as inflammation. Many inflammatory promoters were released during this condition. The main targets of this stage are to prevent microbial infestation and to remove cellular debris through phagocytosis mechanism (Hadagali and Chua, 2014). During the inflammatory phase, macrophages released to the wound are supposed to clear the neutrophils and other foreign matter. Afterwards, macrophages undergo apoptosis and stimulate the needed functions for the next proliferative phase.

6. Conclusion

Plant based-polysaccharides have attracted researchers to study their therapeutic value because of the nature of the polysaccharides. Plant polysaccharides are less toxic, biodegradable and biocompatible. Plant-based wound healing may cause minimal adverse effects. Although previously plant polysaccharides have been widely used in pharmaceutical and food industry as a stabilizer, thickener and dissolving agent, it will be an added advantage if polysaccharides from plants have been identified for its biological activity so that they can act as a functional food in both industries.

Conflict of interest

The authors declare no conflict of interest

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