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## Potential Effects of Flaxseed (*Linum usitatissimum*) in Tissue Reparative Processes: A Mini Review

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**Abstract**— Wounds are inevitable events that can occur daily due to many factors such as; physical, chemical and biological, which can cause tissue, cell and in some events bone damage. The process of wound healing is complicated as it involves many factors; therefore, an effective and safe agent is essential to ensure good healing process. Herbal medicine is considered safe and effective. Flaxseed (*Linum usitatissimum*) is an effective plant when it comes to wound healing and has been used for decades as a traditional healing agent. The bioactivities of flaxseed extract have been reported to demonstrate many beneficial effects such as antimicrobial, antioxidant and anti-inflammatory effects. It has been shown that flaxseed has positive effects on many types of wounds such as skin wound healing, burns and burn scar healing, bone healing and also has demonstrated positive results in the healing of oral ulceration besides exhibiting anti-bacterial effects in the oral cavity. This review describes the positive effects of flaxseed in multiple types of wound healing. Additionally, it is also aimed to introduce the potential applications of flaxseed in socket healing which involves series of complex changes to both soft and hard tissues in the oral cavity.

**Keywords** — *Linum usitatissimum*, extract, wound, socket healing.

### 1 INTRODUCTION

Flaxseeds (*Linum usitatissimum*) are the seeds of the herb flax. The plant is native to west Asia and the Mediterranean. The seeds are flat, oval, 4–6 mm long with a smooth, shiny surface, and brown in colour [1]. They are a member of the Linaceae family plant, which has been cultivated since 5000 BC for its richness in oil and fiber. Flaxseeds consist of fat, protein and dietary fiber; brown flaxseeds contain 41% fat, 20% protein, 28% fiber, and 7.7% moisture [2, 3]. Flaxseed is considered as an important functional food as it contains a wide range of health benefits. Additionally, it is considered safe to be consumed daily for humans [4].

Some of the most important compounds found in flaxseeds that contribute to its beneficial activity to human health include the lipids (essential omega-3 fatty acid, alpha linolenic acid), proteins, lignans and other minor compounds. Together, the components provide flaxseed with several potent health benefits. Table 1 below summarizes the major beneficial components found in flaxseeds, and their activities.

#### 1.1 Lipids (omega-3 and omega-6 fatty acid)

Lipids make up 35-45% of flaxseeds [24]. Flaxseeds contain a mixture of fatty acids, of

which include the essential omega-3 and omega-6 fatty acids, alpha- linolenic acid (ALA) and linoleic acid (LA), respectively. ALA and LA combined make up 57% of the total fatty acids in flax, which make flax the richest source of plant ALA [26]. Both fatty acids have shown cardioprotective effects by lowering the blood lipid content and plasma total cholesterol [10]. Additionally, it has shown anticarcinogenic effects in late- stage breast cancer [12].

#### 1.2 Lignans

Lignans are a complex class of polyphenolic bioactive phytochemicals. Flaxseed provides a rich source of a type of lignan called secoisolariciresinol diglycoside (SDG). SDG is a special type of plant lignan which is changed to enterodiol (ED) and enterolactone (EL); the two mammalian lignans. The process of converting plant lignan to mammalian lignan is done by the bacteria in the colon. Lignan has been proven to highly reduce the growth of many types of cancerous tumours mainly hormone-sensitive cancers like breast, endometrium, and prostate cancers. SDG also is proven to be an antioxidant agent and an immunity enhancing agent [27, 28], as well as anti-bacterial, anti-viral, and anti-fungal activities [29].

**Table 1:** Major components in flaxseeds and their functional activities

Compound	Activity	Reference
<i>Lipids:</i>	Reducing blood lipids	[5, 6]
<i>Alpha-linolenic acid (ALA)</i>	Reducing cholesterol	[5, 6]
	Cardioprotective	[7]
<i>and Linoleic acid (LA)</i>	Anticarcinogenic	[8]
<i>Lignans</i>	Phytoestrogen activity	[9]
<i>(Secoisolaricir esinol</i>	Antioxidant activity	[9]
<i>diglycoside,</i>	Reduces	[10]
<i>SDG)</i>	atherosclerosis	[10]
	Anti-cardiovascular	[11]
	Improved bone development	[12]
	Cancer protective	
<i>Proteins, peptides and amino acids</i>	Antioxidant	[13]
	Anti-inflammatory	[13, 14]
	Antifungal	[15, 16]
	Antineurodegenerative	[17]
	Antihypertensive	[18]
	Immunosuppressive	[18]
	Bone development	[19]
<i>Crude extracts</i>	Relief of gastric problems	[20, 21]
	Antimicrobial and antifungal	[22, 23, 24]
	Improvement of menopausal symptoms and osteoporosis	[29]
	Improve skin	[29]

### 1.3 Proteins, peptides and amino acids

Proteins make up around 20-30% of the flaxseed composition [25]. Flaxseed extracts are high in arginine, aspartic acid and glutamic acids [25]. Peptides in flaxseeds have been shown to have interesting antioxidant and free-radical scavenging activities [13, 17, 18]. The protein extract was also reported to contain antifungal activity [15], and inhibits bone resorption, which may be beneficial for bone development [19].

Besides the therapeutic activities associated with the lipid, protein and lignan/phenolic fractions of flaxseeds, the crude extracts of flaxseeds have been reported to also have potent health benefits. These include relief of gastric, ulcer and abdominal problems [20, 21], improvement of oral health including gingival disorder via antimicrobial and antifungal action against oral pathogens [22, 23, 24], and improvement of menopausal symptoms and osteoporosis in women [29]. The extracts have also been reported to be beneficial to skin as they increase collagen production, improving elasticity,

and nourishing the hair follicles, which may also be beneficial in skin wound healing [29].

## 2 METHODS FOR FLAXSEED EXTRACTIONS

The most commercially important compound in flaxseeds is their oil which contains the omega-3 fatty acids, the lignans and phenolic acids which contain the anti-oxidative properties of the plant, and the proteins which also contribute largely to the beneficial properties of the seed. Flaxseed oil has been used in both industrial and health goods. The most important studied components in flaxseed extracts are the  $\alpha$ -linolenic acid and lignin [30]. Flaxseed oil is one of the richest plant sources of  $\alpha$ -linoleic acid, it contains 44%-57% of all fatty acids and 15%-29% linolenic acid and 13%-29% oleic acid [26, 28].

The earliest method described for extraction of flaxseed oil was solvent extraction using organic solvents [31]. The whole flaxseeds are crushed into fine powder and then extracted using Soxhlet extraction. Some of the organic solvents reported in solvent extraction of flaxseeds include hexane, methanol and ethanol which yielded proteins, intact amino acids arrangement, and removal of the anti-nutrient components in flaxseeds [22, 31, 32]. However, Soxhlet extraction using organic solvents is time-consuming, costly, and hazardous to the worker and generates environmentally harmful waste. Hence, alternative methods which are safer, more efficient and environmentally friendly are being continuously explored for extracting the beneficial compounds in flaxseeds.

Some of the methods developed for flaxseed oil extraction include supercritical CO<sub>2</sub> extraction, ultrasound assisted extraction via immobilized enzymes, supercritical fluid extraction and accelerated solvent extraction. An excellent review on the methods used in flaxseed oil extraction has been reported by Sharma *et al.* (2019), and is summarized in the table 2 below.

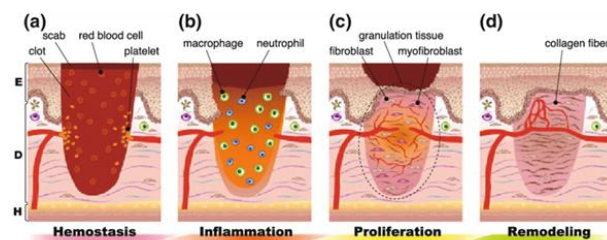
**Table 2:** Methods available for flaxseed oil extraction [33]

Techniques	Source for extraction	Strategy	Output/Yield	References
Supercritical CO <sub>2</sub> extraction	Ground flaxseed	CO <sub>2</sub> at a flow rate of 40 g/min, temp-50 °C, pressure-30 MPa, extraction time-3 hours	35.3 g	{34}
Ultrasound-assisted extraction	Flaxseed powder	The ultrasonic output power set to a desired level ranging from 0 to 100% and temperature of $\pm 1$ °C	84.9%	{1}
Ultrasound-assisted extraction by immobilized enzyme	Ground flaxseed	Incubation of flaxseed with different enzyme (cellulase, pectinase, betaglycosidase, and hemicellulase) and subsequent ultrasonic extraction (45 °C, 250 W power for 30 min)	68.1%	{35}
Super critical fluid extraction	Ground flaxseed	Extraction temperature, pressure, time and CO <sub>2</sub> flow rate were set at 50 °C, 40,000 kPa, 2 hours and 70 g/min	36.49 g/100 g	{36}
Accelerated solvent extraction	Ground flaxseed	Solvent used -hexane, temp-200 °C and pressure-10,342 kPa	41.90 g/100 g	{36}

### 3 THE EFFECTS OF FLAXSEED ON WOUND HEALING

Wounds are foreseeable incidents that can occur due to either physical / chemical trauma or microbiological infections which can cause disruption of anatomical and functional integrity of living tissue [28].

The natural wound healing reaction initiates instantly after the tissue injury, after which the inflammatory response begins and the cells below the dermis starts to produce higher number of collagens, subsequently the epithelial tissue starts to restore [28]. Wound healing involves various physiological steps involving cellular and biochemical procedures which finally results in the restoration and regeneration of wounded tissue [37,38]. Wound healing process (Figure 1) contains a series of events that can be divided into three stages that begins with inflammation, then granulation tissue formation and lastly remodeling of the extra-cellular matrix [43]. The inflammation process which occurs after the initiation of the skin injury is caused by the release of leukotrienes, prostaglandins, and free radicals. The next step of wound healing is cellular proliferation which includes collagen deposition, epithelization, and angiogenesis which is regulated by growth factors. The final stage of wound healing is the remodeling of tissue with the fibroblast proliferation and collagen fiber synthesis [40, 41, 43].



**Figure 1:** Wound healing process [40]

Antioxidants and antimicrobial agents have a very important part in facilitating wound healing. Anti-inflammatory agents are given to control the intensity of the wounds; they are also useful in managing microbial infections that can arise in severe wounds [42]. Healing of wound is a procedure that involves special factors and conditions. Many drugs are being developed nowadays to speed up the wound healing process with big concern to the safety of those agents for human beings. Herbal drugs are being

studied and produced due to their effectiveness and safety.

Flaxseed oil extract has diverse biologically active components which work on the different stages of wound repair. Flaxseed oil used on wounded skin demonstrated three interesting outcomes when compared to other skin healing products; firstly, high wound contraction; secondly, elevated collagen and thirdly stronger skin [45]. Additionally, the components in flaxseed extract work together to stimulate wound healing by lowering inflammation and stimulating the extracellular matrix remodeling and skin proliferation. This happens due to the synergic action between all the components on flaxseed extract such as  $\beta$ -sitosterol, phytosterol, polyunsaturated fatty acids and other components [46].

High wound contraction may be related to the action of flaxseed which stimulates the proliferation of fibroblast cells and their differentiation into myofibroblasts in the granulated tissue which contributes to wound closure [28; 45]. Meanwhile, elevated collagen levels can be attributed to the flavonoids content of flaxseed works in stimulating the collagen fibrils which results in the strengthening of collagen fibers and lowering of the cell damage by improving the synthesis of DNA [46, 48]. The antioxidant activity of flavonoids also stimulates collagen production via the reduction of oxidative stress [46]. Finally, flaxseed may contribute to stronger skin by lowering lipid peroxidation levels. This inhibits cell necrosis and elevates angiogenesis. The increased blood flow allows more efficient transport of the key nutrients essential to tissue regeneration and wound healing [45]. Furthermore, recent study has shown that at low concentrations, flaxseed extract mildly influences the growth of stem cells, suggesting the potential effect of flaxseed in promoting cell growth [28, 32, 47].

A study on wounded Wistar rats showed the significant effect of flaxseed oil extract in accelerating the wound healing process thus suggesting that flaxseed is a safe herbal wound healing agent for skin wounds [14]. Recently, flaxseed extract also has been demonstrated to affect the skin elasticity during the process of wound healing in rabbit model [49]. Therefore, it possesses positive effects when applied topically in the healing of wounds, as demonstrated in adult male New Zealand rabbits [4].

The safety assessment of flaxseed oil has been tested on white New Zealand rabbits where the rabbits were given flaxseed for the period of three months and the result showed decrease in glycaemia and cholesterolemia, normal serum hepatic and renal marker enzymes, and normal histology of the liver and kidneys without any anatomically detectable anomalies, these findings confirms the safety of prolong usage of flaxseed in rabbits [4].

A study reported that the high antioxidant level in flaxseed extract would make it the best material for linen wound dressing which is due to the presence of antioxidants in flaxseed such as phenolic acids which has the ability to stimulate the macrophages to restore the natural process of wound healing. A bandage made from flaxseed extract can inhibit fibroma formation and keep an ideal humidity which can help epithelial cells migration [50].

### 3.1 The effect of flaxseed in skin burns healing

Burns are wounds that are caused by exposure to heat, electricity, lightning, caustic chemical compounds, radiation, friction or excessive cold; they are one of the most predominant wounds in humans. Burns result in great amount of health care and sustained or long-lasting physical, social and psychological consequences. Deep burn wounds cause high physical dysfunctions, high psychological and psychosocial problems [51, 52]. Burns usually occur in the skin and the degree of the burn is classified according to the size and depth of tissue injury [53]. Burn wound healing is very complicated to be treated as many treatment protocols including burn wound healing creams showed unsuccessful healing results especially in deep burn wound [54]. Furthermore, the available burn wound healing creams are expensive with many negative side effects, including significant cytotoxic activity on the host cell and a slowing down of the wound healing process [55], hence the need to substitute burn wound healing agents with better healing efficacies, less expensive and less negative side effects leading to formulation of burn wound healing agents from plant extracts [56]. Flaxseed could be one of the potential wound healing agents as the flaxseed extract has been proven to heals scars, protects inflamed skin, improves its elasticity [4] and when applied topically flaxseed heals the burn wounds in adult male New Zealand rabbits [4].

### 3.2 The effect of flaxseed in bone healing

Bone healing is a complicated process that involves many mediators like growth factors and cytokines [57]. Three types of cells are involved in the bone formation process; osteoblasts, osteocytes, and osteoclasts [58]. Osteoblasts are the cells found at the surface of the bone and in the synthesis of the osteoid. At later stages of bone mineralization, osteoblasts lose their bone forming ability and they become osteocytes. Osteoclasts, the third type of cells are in charge of bone resorption [58]. Bone remodelling is a process that is based on the tight connection that happens between osteoblasts, osteoclasts and osteocytes. The cellular communication that occurs between the three types of cells is crucial for bone remodelling which can sustain bone integrity [59, 60].

Few studies have been undertaken to see the effects of flaxseed in bone health. A study was done on ovariectomized female rats by Sacco et al., who concluded that a diet of flaxseed combined with a low dose estrogen therapy can prevent bone loss caused by ovariectomy [61]. The flaxseed also showed an alteration in the fatty acid composition in the ovariectomized rat skeleton. The composition of fatty acids is associated with bone mass density and plays a role in maintaining skeletal density, as several studies reports [62, 63, 64]. Additionally, incorporating lignans from flaxseed, in the daily diet of women has been proven to decrease the risk and the severity of osteoporosis in post-menopausal women and in promoting an overall healthier bone growth [645].

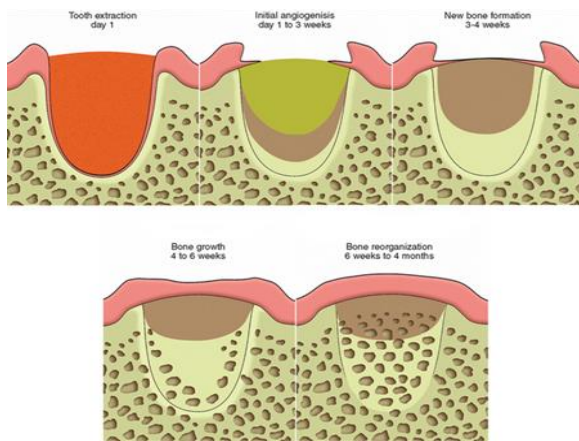
In a pilot study on the effect of flaxseed oil on bone in twelve white New Zealand male rabbits, an implant containing flaxseed oil was administered in the bone wound site. After three days, the authors reported improved healing in the injured bone [65]. The flaxseed oil- coated implant decreased inflammation and increased active bone growth via bone apposition. Hence, flaxseed oil can potentially be used as an implant coating material to improve and accelerate the healing process [65, 66].

### 3.3 Potential used of flaxseed in socket healing

One of the common procedures in the field of dentistry is tooth extraction. This commonly practiced procedure results in a major bone loss and breakdown of the surrounding gingiva. On the other hand, a large percentage of extraction sites results in abnormal healing or referred to as post-operative complications [67].



Socket healing (Figure 2) is the process that takes place after the extraction of the tooth which causes many complicated local changes to the existing soft and hard tissues. These changes occur for the purpose of closing the wound and restoring tissue homeostasis [68]. Socket healing is a complicated process; involving both soft and hard tissues, which can take few weeks for the soft tissue to heal and up to six months for the bone to completely heal; hence it would be highly beneficial for patients if the healing process of the socket can be accelerated. Due to its wound-healing and bone-healing properties, flaxseed extract offers potential natural agent for the acceleration of the socket healing process which requires healing of both soft and hard tissues.



**Figure 2:** Socket healing process [68]

#### 4 CONCLUSION

Flaxseed is a therapeutically important plant that contains compounds with activities that are beneficial to human health. The lipid/oil, protein, lignan/phenolic and flavonoid profile of flaxseeds contribute to its wound healing properties. Flaxseeds have been proven to show positive results in soft tissue healing such as in the skin and in burn wounds and in bone healing. Thus, this plant has a high potential to be used for wound healing as it is both safe and effective. Flaxseed also has a great potential to become a good healing agent for the socket after tooth extraction as it has the ability to heal soft and hard tissues. This shows the necessity to exploit the flaxseed as a natural agent for wound healing.

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