

MINI REVIEW

Wound healing potential of edible plants

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Abstract: Wound healing is a natural intricate cascade process involving cellular, biochemical and molecular mechanism to restore the injured or wounded tissue. Malaysia's multi-ethnic social fabric is reflected in its different traditional folk cuisines with different nutritional important ingredients. Despite these differences, there are some commonly used pantry ingredients among Malaysians and these ingredients may possess some healing power for acute and chronic wounds. These essential nutritional ingredients are included Amla (*Ribes uva-crispa*), Cinnamon (*Cinnamomum verum*), Curry Leaves (*Murraya koenigii*), Coriander (*Coriandrum sativum*), Fenugreek (*Trigonella foenum-graecum*), Garlic (*Allium indica*), Onion (*Allium cepa*) and Tamarind (*Tamarindus indica*). This article provides a review of the remedies with confirmed wound healing activities from previous experiments conducted by various researchers. Most of the researchers have focused only on the preliminary studies through appropriate model; hence detailed investigations which including pharmacological and pre-clinical studies are needed to discover its molecular mechanisms. In this review article, we have discussed about the wound healing potential of few commonly used edible plants and their known mechanism.

Keywords: Medicinal plants, growth factors, bioactive compounds, wound healing assays.

INTRODUCTION

The wound healing process generally involves four distinct stages and they are hemostasis, inflammation, proliferation and re-modeling. Once an injury takes place, the wound healing process starts immediately with the homeostasis stage, which involves the coagulation to prevent massive blood loss by aggregating platelets. Then an inflammatory stage that requires neutrophils to fight against microbial infections and associated complications take place. Macrophages that play their role in phagocytizing debris, also stimulates the release of pro-inflammatory cytokines such as TNF- α , IL-1 β , IL- α and IL-6. These pro-inflammatory cytokines can be used to estimate the age of wound, according to the level of cytokine (Kondo and Ohshima, 1996). Then, the third stage is the proliferation stage, which takes its role in the nourishment of the wound site for the repair in the tissue. Major proteins such as Keratinocyte Growth Factor (KGF), Platelet derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), Transforming growth factor beta (TGF- β) and Granulocyte-macrophage colony-stimulating factor (GM-CSF) play vital roles in promoting

angiogenesis and vascularization for more blood supply to nourish the cells with nutrition, ultimately for a better proliferation. Keratinocytes stimulates the fibroblast to migrate to wound gap and to synthesize various growth factors, which in turn stimulate keratinocyte proliferations (Canady *et al.*, 2013). Fibroblast produces collagen, which is responsible in giving the strength and support at wound site. The collagen is composed of hydroxyproline and the measurement of the hydroxyproline could be used as an index for collagen turnover (Kliment *et al.*, 2011). Furthermore, increase in dry tissue weight also indicates the presence of higher protein content (Anitha *et al.*, 2015). Finally the re-modeling process involves further repair whereby synthesized collagens are arranged in a more organized manner. This stage determines the structure and appearance the healed skin later (Thakare *et al.*, 2011).

Currently, there are many advanced therapies in wound healing but most of them are expensive and some even possess side effects such as allergic reaction. Natural products are always preferred as they are believed to be safe and there are many nutritionally important plants proven to exhibit wound healing properties, but the lack of standardization has made it more challenging to

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determine the true efficacy of these products, thus more detailed investigations are required for standardization and commercialization the effective products (Davis and Perez, 2009).

Antioxidant is important as it is needed to decrease the oxidative stress. An oxidation process produces free radicals that are dangerous and can hinder the process of wound healing as they tend to accept electrons from the nearby healthy cells and induce the cell/tissue damage. The plant possesses its unique mechanism in combating oxidation such as Ceylon cinnamon essential oil inhibits hepatic 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase activity in rats, and suppresses lipid peroxidation via the enhancement of hepatic antioxidant enzyme activity (Lee *et al.*, 2003).

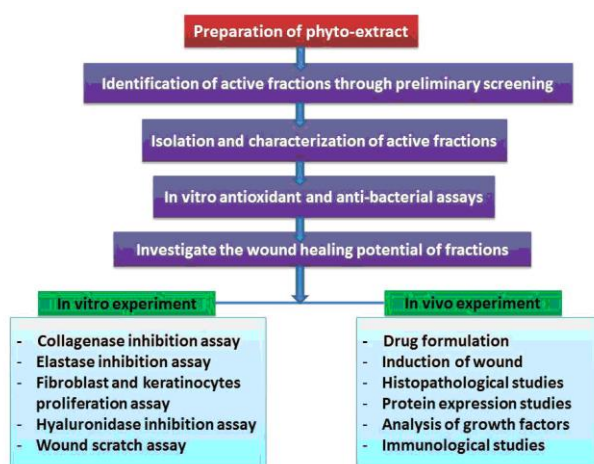


Fig. 1: Schematic sketch of the experimental plan for natural products based wound healing research.

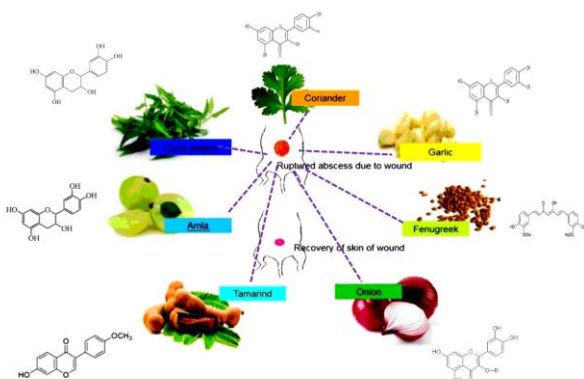


Fig. 2: Schematic diagram illustrated the wound healing potential in few commonly used edible plants.

Besides, effective management of bacterial bioburden is also an important aspect in wound healing process, as the severe microbial colonization may result in a severe chronic wound. The hydrated, warm and nutritious conditions of the wound make it a conducive environment for bacteria to multiply and become prominent (Bowler *et*

al., 2001). Infection of bacteria occurs when virulence factors are expressed for example through biofilm formation and compete (Rutherford and Bassler, 2012) with the immune system of the host that directly prolongs the inflammatory process which delays the healing process.

In studies, the effects of any drug on the rate of wound healing are assessed based on a few key parameters such as the rate of wound contraction, period of epithelialization, wet and dry weight of the granulation tissue, level of hydroxyproline and histopathological observation of granulation tissue. Histological observations are essential parameters in the wound healing investigation as it gives a microscopic anatomy view to the formation of structures. Haematoxylin and Eosin stained granulation tissues will be observed in the formation of fibroblast, inflammatory cells, macrophages as well as the blood vessels. If at all the drug that is being tested supports the wound healing process, the granulation tissue with blood vessels and fibroblast could be observed replacing hematoma that is caused by injury. Besides, we could also observe well-formed collagen supported by fibroblast proliferation and the synthesis of extracellular matrix. That would be contrary to the observation of tissue without any application of the drug, which would show clumps of degenerating neutrophils, macrophages and the persistence of inflammatory exudates in the upper dermis (Saidharan *et al.*, 2012).

Amla

(*Ribes uva-crispa*)

Amla is one of the most popular pickle and it originate from South India (Reddy and Chikkasubbanna, 2009). It has demonstrated that 50% methanolic extract of Amla, showed significant wound closure rate up to 62% compared to natural healing and it's even faster than commercial drug, Betadine (Agrawal *et al.*, 2012). Furthermore, wound healing test on dogs proved that amla extract provides lesser scar tissue compared to 1% of above mentioned commercial drug (Chansiripornchai and Nimmanit, 2008). Thus, topical application of plant extract is a potential treatment for wound healing.

Cinnamon

(*Cinnamomun verum*)

Cinnamon is often used in sweets, savoury and also one of the oldest spices (Namdar *et al.*, 2013). It is shown to exhibit the strong wound healing property in various experimental models. Studies show that ethanol extract of Ceylon cinnamon has wound healing properties and these activities probably correlate with its anti-inflammatory, antioxidant and antimicrobial characteristics, especially by their bioactive compounds, eugenol and cinnamaldehyde (Farahpour and Habibi, 2012). In addition, the ethanolic extract of cinnamon shown to inhibit the synthesis of TNF- α , a pro-inflammatory signaling protein, which in turn fastens the angiogenesis

and matrix degradation that promotes healing (Joshi *et al.*, 2010). Furthermore, cinnamon extract promotes type I collagen, a crucial component for skin regeneration, via activation of IGF-I signaling pathway in human dermal fibroblasts (Takasao *et al.*, 2012).

Curry leaves

(*Murraya koenigii*)

Curry leaves are popular and demanding for its pleasant aroma in cooking as it's commercialized in wet and dried form without losing its flavor and nutrition (Khatoon *et al.*, 2011). Polyphenol enriched curry leaf is known to promote the epithelization and the rate of wound reduction up to 50% compared to untreated animal (Kumar *et al.*, 2012). Another, *in-vivo* findings shown that wounds treated with the combination of carbazole alkaloids, mahanimbicine and extract of curry leaves essential oil showed the highest rate of collagen deposition with well-organized collagen bands, formation of fibroblasts, hair follicle buds and with less inflammatory cells compared to treatment of other alkaloids, including mahanine and mahanimbine with essential oil (Nagappan *et al.*, 2012). The alcohol: water (1:1) extracts of curry leaves showed the highest antioxidant activities (Nigappa *et al.*, 2008), and these properties involved in controlling oxidative stress to even against cadmium and lead.

Coriander

(*Coriandrum sativum*)

Coriander is commonly used for seasoning purposes in food preparation all over the world, particularly Asia (Bhat *et al.*, 2014). Methanolic extract of coriander leaves is said to be a better antibacterial formulation with broad spectrum activities when compared to aqueous and acetone extracts since its known that colonization of bacteria is one of the major problems in wound healing (Bhat *et al.*, 2014; Dash *et al.*, 2011). Another studies showed that the active compounds such as terpenoid and phenol from coriander possess antioxidant property and wound healing capability (Labiri *et al.*, 2015).

Fenugreek

(*Trigonella foenum-graecum*)

Fenugreek, which originates from India and Northern Africa said to be a panacea as it has the capability to aid in many ailments (Basch *et al.*, 2003). As such, previous reports mentioned that aqueous extract of fenugreek seed when combined with honey gives a better healing activity compared to ethanol extract, towards gastric ulcer in rats and this activity is believed due to the presence of flavonoids (Mahmood *et al.*, 2005). In addition, hydroalcoholic extract of fenugreek seed reduces liver cirrhosis in rats by inhibition of xanthine oxidase, scavenging free radicals and these reductions contributes to the normal wound healing activity (Zargar, 2014; Madigan *et al.*, 2015).

Garlic

(*Allium sativum*)

Benefits of garlic were proven since 3200 BC ago as the illustration of garlic was found in an Egyptian crypts and it is believed that Egyptians fed their workers with garlic to boost their immune system to work harder (Petrovska and Cekovska, 2010). Notably, the ethanolic extracts of bulbs of garlic have significant wound healing properties in rats and the rate of healing was faster when compared to animal treated with Framycetin, a commonly used antibiotic (Zuber *et al.*, 2013). In addition, *in vivo* studies were conducted on dogs using allicin, an active compound in garlic that produces strong smell. This active compound has very strong antimicrobial, vasodilating and anti-inflammatory potential. Topical application of garlic formula increases the amount of fibrocytes and fibroblast and it is assumed that allicin possess inhibitory action towards collagen synthesis thus, this specific active compound does not solely support the wound contraction and epithelialization (Sardari *et al.*, 2006a; Sardari *et al.*, 2006b). Fermented black garlic contains more antioxidant properties than non-fermented one; therefore this could be taken into consideration while preparing topical formula for wound healing therapy (Sato *et al.*, 2006).

Onion

(*Allium cepa*)

The depth flavor of onion is so popular in the food industry that onion powder was commercialized for a more efficient work (Gouda *et al.*, 2014). It also has significant therapeutic values in wound healing. The ethanolic extract of onion bulb showed a promising result in wound healing and they could be possibly supported by its antibacterial and antioxidant activities present in the extract (Shenoy *et al.*, 2009). A study showed that onions are rich in flavonoids content, and 25 of its important flavonoids have been characterized and among them one the most important one is quercetin and its derivatives (Slimestad *et al.*, 2007). Quercetin, a flavonoid of onion extract was studied and they seem to induce matrix metalloproteinase-1 (MMP-1), a prototype of collagen, which is an agent of anti-scar by playing its role as anti-fibrotic (Cho *et al.*, 2009).

Tamarind

(*Tamarindus indica*)

Tamarind is a multipurpose tree as its root to fruit are useful for human, especially in food preparation such as curries, chutneys, sauces, beverages, sweets, desserts, and sherbet (Khanzada *et al.*, 2008). Based on the study, different types of tamarind seed extract on induced wound model, PBS, water, methanol and ethanol extracts increases the wound healing rate, but ethanolic extract was faster during the early phase of healing, while PBS extract was the fastest at a later phase of wound healing. Alkaloid, flavonoid, saponin and tannin are the major

phytochemicals present and responsible in wound healing activity. PBS extract showed the best activity and at the same time it showed highest protein yield and it believed to play a very important role in the activity (Muhammad *et al.*, 2012). Xyloglucan polysaccharide of the tamarind was known to reduce the effect of damage to skin caused by UV by reducing the loss of dendritic cells (Kuchel *et al.*, 2005). Another study regarding two types of xyloglucan with different molecular weight was studied and they both seem to support skin regeneration, but differ in molecular signal response (Nie and Deters, 2012).

CONCLUSION

The search for an effective, safe with lower cost therapeutic approaches for wound healing remains a challenge and it is a continuous process in the drug development industries. Edible plants derived products are believed to be safe without producing any adverse effects to normal tissue. However, further studies are required to understand the further cellular and molecular mechanisms of specific bioactive compounds present in the edible plants. Previous findings on edible plants have suggested that most of the extracts and its identified/isolated active compounds are useful to prepare the topical formulation to enhance the wound healing rate in various experimental models.

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