Anti-inflammatory and antibacterial properties of almond by-products as wound healing potential agent: a review

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Abstract

Patients who have suffered significant trauma are at higher risk of developing bacterial infections which could lead to bacteremia and prolonged inflammation on wound healing process. Thus, antibacterial and anti-inflammatory agents are essential to facilitate wound healing. Since natural substances have a tendency to be less toxic, therapeutic agents like almonds are frequently used. This study is aimed to summarize the antibacterial and anti-inflammatory properties of almond by-products. According to phytochemical investigations, almond by-products phenolic compounds such as flavonoids, tannin, phenolic acids, and aldehyde. Several studies have found that almond by-products are able to inhibit the growth of some bacterial strains of gram negative and positive. In addition, it has been demonstrated that almond by-products have anti-inflammatory properties through reducing the expression of pro-inflammatory cytokines. Thus, almond by-products are potential as wound healing agents to prevent further infections through its anti-inflammatory and antibacterial activities. Therefore, additional research such as clinical trials, are recommended to investigate its effectiveness on wound healing and safety application.

Keywords: almonds, wound healing, anti-inflammatory, antibacterial

Introduction

The wound healing process occurs in order to repair damaged tissue to maintain homeostasis [1]. Patients who have suffered significant trauma are at higher risk of developing bacterial infections due to the loss of the skin barrier and the invasive procedures they have undergone. Bacteria on wound surfaces can penetrate to the bloodstream and cause infection which is called bacteremia. This condition can cause a failure of the host's innate immune system such as overproduction of proinflammatory mediators and imbalances of innate immunity regulated by the cells. A persistent imbalance of the immune system potentially causes hyperinflammation [2].

Natural compounds are now commonly used as a material of more effective medication since their contents tend to result in less toxicity. According to United States Department of Agriculture (USDA) 2020, almond global production reaches 1,696,280. During the industrial process of producing edible nuts, whole almonds can produce 70.0-85.0% residues or wastes including the skin, shell, and hull [3]. As these accumulation of wastes potentially harm the ecosystem, many researchers are interested in examining the beneficial phytochemicals compound present in almond by-products. Several studies have reported that almond by-products (kernel, skin, shell, and hull) contain phenolic compounds such as flavonoids, tannin, phenolic acids, and aldehyde [4]. These compounds are known to be a potential alternative medication to accelerate the wound healing process due to its antioxidant and antimicrobial properties. Through this article, the authors want to provide a narrative review on anti-inflammatory and antibacterial properties of almond by-products as wound healing potential agents.

Methods

Narrative review is research that critically examines knowledge, ideas, and findings in the articles. The article sources used in this narrative review were collected from online databases including PubMed, ScienceDirect, and Scopus. The search was performed based on recent searches in the last 10 years for original article, review article, and case report using keywords “Anti-inflammation activity of almond”, “Almond as anti-inflammation agent”, “Almond as antibacterial agent”, and “Antibacterial activity of almond”.

Results and discussion

Almonds (*Prunus dulcis* (Mill.) D. A. Webb, *Prunus amygdalus* Batch or *Amygdalus communis L.*) is a nut originating from Central Asia, but currently, it is widely produced around the world, particularly in the Mediterranean region with a hot-dry climate. Almonds, one of the most produced nuts in the world in 2020, were estimated to be produced in 1,684,395 tons [5]. There are two types of almonds: almonds with a sweet flavor (*Prunus dulcis*) and almonds with a bitter flavor (*Prunus amara*). The difference in hydrogen cyanide content between bitter and sweet almonds is 40 times greater in the former, which may be due to the bitter almond containing significantly greater amygdalin than the sweet one. Hence, the consumption of 50 bitter for adults and 5–10 bitter almonds is considered deadly [6]. Almonds consist of kernel, seed, or meat covered by brown skin which is edible and frequently consumed worldwide as it has high nutritional benefits. The exterior layers of almonds include a shell or a hardened endocarp, and a hull, flesh but thin mesocarp, or green shell cover [3].

Almond by-products are a source of bioactive compounds such as polyphenols. Bolling (2017) analyzed several studies on the polyphenols in almonds, and the data indicates flavonoids and tannins are the major polyphenolic compounds present in almonds, while other compounds found at lower levels include phenolic acids, aldehydes, lignans, and stilbenes [4]. These compounds are known to have antioxidant, anti-inflammatory, and antibacterial activity that are important to accelerate the wound healing process. Flavonoids and other phenolic compounds have been shown in prior research to exhibit antibacterial activity against some pathogenic bacteria, including *Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia, Bacillus cereus, Bacillus subtilis, Salmonella typhi, and Escherichia coli* [7]. Although the antibacterial mechanisms of phenolic compounds have not yet been fully discovered, it is known that these compounds have involved cellular sites of action. Several studies explain that polyphenols can affect cell membrane permeability by disrupting the phospholipid or lipid bilayers, those affecting fluidity, rigidity, and integrity of the cell wall and membranes. Increased permeability of membranes alters ion transport pathways and enhances intracellular components leakage [8, 9]. Polyphenols can also penetrate the cytoplasmic membranes and bind to some cellular protein components such as enzymes, adhesin, and cell envelope transport proteins, all of which play critical roles in bacterial growth [10]. Thus, polyphenols can inhibit the protein's activities, resulting in decreased DNA synthesis, biofilm formation, and bacterial virulence factor [3, 11].

The damaged tissue is more at risk of bacterial invasion and infection. The continued presence of bacteria within the wound increases the release of pro-inflammatory cytokines that leads to prolonged inflammation [2]. Therefore, preventing bacterial invasion on wound surfaces is crucial for effective wound healing. Several studies reported that almond by-products have antibacterial activity against some bacterial strains due to its bioactive compounds as provided in a summary on Tables 1.

Tables 1: Antibacterial Activity of Almond

Almond fruit parts	Bioactive compounds	Results	Experimental model	Reference
Almond kernel (seed)	Gallic acid, pyrogallol, ethyl gallate, p-hydroxybenzoic acid, vanillic acid and protocatechuic acid	Inhibit bacterial growth of *S. aureus, B. subtilis, P. aeruginosa, S. typhi, P. vulgaris, and E. coli*	In vitro	Dhingra, Kar, Sharma, & Bhasin, 2017
Almond skin	hydroxybenzoic acids, hydroxycinnamic acids, flavanones, flavonols, and flavanols	Inhibit bacterial growth of gram positive (*S. aureus, S. epidermidis, S. mutans L. monocitogenes*) and gram negative (*E. coli, P. aeruginosa, S. marcescens*)	In vitro	Smeriglio *et al*., 2016
Almond skin	Polyphenols	Inhibit bacterial growth of *H. pylori*	In vitro and in vivo	Bisignano *et al*., 2013
Almond skin	Polyphenols	Inhibit bacterial growth of *S. Aureus*	In vitro	Musarra-Pizzo *et al*., 2019
Almond shell	Phenolic acids, aldehyde, flavonoids	*E. coli, P. aeruginosa, L. monocytogenes, S. aureus and Salmonella spp*	In vitro	Moreira *et al*., 2016
Almond shell	-	*E. coli*	In vitro	Pettinari *et al*., 2018
Almond hull	Triterpenoids and hydroxycinnamic acids	Inhibit bacterial growth of *P. aeuroginos, S. aureus, E. coli*	In vitro	Fibroni *et al*., 2022
Almond leaf	Alkaloids, terpenoids, glycosides, resins, saponins, tannins, flavonoids, phenols, and amino acid	Inhibit bacterial growth of *S. aureus, E. coli, P. aeruginosa*, and *Klebsiella sp.*	In vitro	Al-Deen *et al*., 2019

According to the findings of an in vitro study, almond kernel showed an ability to inhibit the growth of some bacterial strains such as *S. aureus, B. subtilis, P. aeruginosa, S. typhi, P. vulgaris,* and *E. coli* [12]. Several studies on the bioactive compounds of almond showed that almond skin has antibacterial activity against gram positive bacteria strains as *S. aureus, S. epidermidis, S. mutans* and *L. monocytogenes* as well as gram negative strains *E. coli, P. aeruginosa, S. marcescens, H. pylori* [13, 14, 15]. Almond shells are also shown an inhibition to the growth of *E. coli, P. aeruginosa, L. monocytogenes, S. aureus and Salmonella spp.* [16, 17]. Some bioactive compounds isolated from almond hulls such as triterpenoids and hydroxycinnamic acids are also showed an inhibition to the growth of *P. aeuroginos, S. aureus, E. coli* [18].

Bacterial toxins such as LPS and cytokines induce iNos and catalyze the formation of nitric oxide from L-arginine in macrophages and microglial cells. Therefore, iNos play an important role in the inflammatory response. The pathogenesis of inflammation begins with tissue damage leading to infiltration and activation of macrophages and antigen-presenting cells (APCs), tumor necrosis factor-α (TNF-α), and interleukins (ILs) [19]. Almonds have an anti-inflammatory function that can be seen on Tables 2.

Tables 2: Anti-inflammatory Activity of Almond

Almond fruit parts	Bioactive compounds	Results	Experimental model	Reference
Almond skin	Polyphenols	Inhibits the tumor necrosis factor-α (TNF-α)-induced cell inflammatory response	In vitro	Huang, Chen, & Wu, 2017
Almond kernel (seed)	phenolics, carotenoids, tocopherols and phytosterols	Downregulates TNFR, decreasing IL-1 and TNF-α, IkappaB kinase-beta and transforming growth factor beta receptor 1	In vivo	Torres *et al*., 2016
Almond kernel (seed)	Polyphenols	Reduced the LPS-induced expression of iNos, COX-2, TNF-α, IL-1β, and IL-6 mRNAs in macrophages	In vitro	Müller *et al*., 2019

The anti-inflammatory activity of Almond works through down-regulating TNFR, which reduces the expression of IL-1, TNF-α, IkappaB kinase beta, and transforming growth factor beta receptor 1, components involved in the inflammatory process [20]. TNF-α is a key mediator of immune and inflammatory responses that regulates the expression of inflammatory gene networks. In an in vitro study by Huang, Chen & Wu (2017), showed that almond can inhibit tumor necrosis factor-α (TNF-α) expression, which can lead to suppression of cellular inflammatory responses [21]. In 2019, Muller conducted an in vitro study to investigate the effects of digested and saponified nut oil extracts macrophage inflammatory processes. Nut samples obtained after digestion contained substances available to the body after absorption. Research results show that almond oil extract is known to have anti-inflammatory properties and can inhibit the expression and formation of inflammatory mediators in macrophages [22]. Almonds are known to contain flavonoid compounds such as quercetin that have antioxidant and anti-inflammatory properties. A study on the ability of quercetin to promote skin wound healing in rats was conducted by Gopalakrishnan *et al*. (2016). In this study, the samples were divided into two groups, control group and treatment group. The treatment group was then divided into several groups and sacrificed according to the day of observation for histopathological examination. The tissue samples from the Quercetin treatment group on day 3 which had been stained with HE showed less inflammatory cell infiltration and more fibroblast infiltration compared with the control group [23]. Neutrophils are the earliest inflammatory cells to migrate to the wound area and can be found 24-48 hours after injury. Then on the 3rd day the neutrophil cells are replaced by macrophage cells. T lymphocytes experienced an increase in migration to the wound area on day 5 and reached its peak on day 7. Quercetin is known to be able to inhibit IL-8 secretion which functions as a chemotactic agent and induces migration of neutrophil cells to the wound area. When IL-8 production is inhibited, the migration of inflammatory cells is also limited [24]. Persistent neutrophils will interfere with the wound healing process and result in acute wounds developing into chronic wounds [25]. The addition of quercetin accelerates the inflammatory phase of wound healing and initiates the proliferative phase earlier to regain fibroblast cell infiltration by day 3. An in vitro study led by Wheater and Byars in 2017 showed that kaempferol at a dose of 5 μM was able to effectively stimulate the migration of fibroblast cells isolated from gingival tissue. The migration of fibroblast cells from the edge to the center of the wound is an important part of the healing process, as it will help accelerate wound closure [26].

Conclusions

Thus, almond by-products are suggested to be a potential alternative medication material for wounds due to its phytochemical contents that accelerate the wound healing process through various pathways and prevent further infections through its anti-inflammatory and antibacterial activities. However, the evidence is limited to in vivo and in vitro studies about antibacterial and anti-inflammatory activity of almond by-products. Therefore, further research such as clinical trials are recommended to investigate its effectiveness on wound healing and safety of ingestion of almond by-products.

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Conflict of Interests

The authors declare no conflict of interest. This paper was written independently and is not associated with another party.

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