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Phytochemical Properties of Plantain (Plantago SP), And Therapeutic Usage in Traditional and Modern Medicine

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Abstract:

Plantago species have traditionally been used in treatments, particularly for healing open wounds. The dried, mature seeds of Plantago sp, in particular, are widely used in Traditional Chinese Medicine (TCM). Recent research has demonstrated that extracts from this plant are rich in numerous phytoconstituents, including flavonoids, alkaloids, terpenoids, phenolic acid derivatives, iridoid glycosides, fatty acids, and polysaccharides. Studies have identified the various phytoconstituents responsible for the plant's wide range of medicinal benefits, as well as their mechanisms of action.

It has revealed the presence of approximately 60 distinct and metabolically active phytoconstituents in *Plantago* species, including, in particular, flavonoids, alkaloids, terpenoids, phenolic acid derivatives, iridoid glycosides, fatty acids, and polysaccharides. Evidences highlights the multifaceted wound-healing potential of the *Plantago* genus. Early-stage benefits—including antimicrobial, anti-inflammatory, and antioxidant activities—seamlessly transition into enhanced angiogenesis, fibroblast proliferation, and collagen deposition during the later stages of repair.

Phytoconstituents found in *Plantago* species that exhibit wound-healing activity include acteoside, astilbin/smiljitbin, caffeic acid, chlorogenic acid, ferulic acid, lupeol, luteolin, p-coumaric acid, syringic acid, ursolic acid, vanillic acid, vitexin, oleic acid, aucubin, and plantamajoside. The various pharmaceutical applications of different parts of the plantain plant (leaves, roots, flowers, and seeds) are attributed to its phytochemical constituents. Plant's bioactive constituents are known to have antioxidant, antibacterial, hepatoprotective, and immunomodulatory effects. This study summarizes the phytochemical composition, traditional medicinal applications, and biological properties of Plantain.

Keywords: Plantago, tradirional medicine, wound-healing, fitocomponents

Introduction

Plantago (plantain) is an herbaceous plant found abundantly worldwide. *Plantago* species have traditionally been used in treatments, particularly for healing open wounds. The dried, mature seeds of *Plantago sp*, in particular, are widely used in Traditional Chinese Medicine (TCM). Recent research has demonstrated that extracts from this plant are rich in numerous phytoconstituents, including flavonoids, alkaloids, terpenoids, phenolic acid derivatives, iridoid glycosides, fatty acids, and polysaccharides. Studies have identified the various phytoconstituents responsible for the plant's wide range of medicinal benefits, as well as their mechanisms of action (Adom et al., 2017).

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Furthermore, during the proliferation and remodeling phases of wound healing, plantain components stimulate blood vessel formation, exhibit antioxidant effects, and promote the formation of new tissue and collagen. It has been shown to be effective in accelerating wound healing, particularly in the case of diabetic wounds and burns. Plant extracts, traditionally used to accelerate the healing of wounds such as cuts and burns, play a significant role in enhancing the wound healing process through multifaceted mechanisms, promotion of angiogenesis, antioxidative effects, and the maintenance of a moist environment (Sharma, Khanna, Kaur, and Singh, 2021).

Use in traditional medicine

Since *Plantago major* was introduced by Europeans to newly discovered lands like the Americas, it is known among indigenous peoples as "plantain" (or "white man's footprint"). Growing naturally in various regions across the globe, this plant is particularly widespread in Central Asia, Europe, and North Asia. While people in the Americas have treated snakebites with the plant's powdered root extract, the Chinese have used it for centuries to treat viral diseases such as hepatitis and the common cold (Abbasi et al. 2022). Extracts obtained from the leaves, roots, and seeds serve as therapeutic agents for liver and spleen disorders and are recommended by many practitioners (Aboulaghras et al., 2022).

In traditional medicine, the dried leaf powder of the plant is applied directly to affected skin areas, either alone or in combination with various mineral salts. It is also used to treat lesions on the face and head (Adebayo et al., 2019). The leaves are also utilized in the treatment of gout (Adom et al., 2017). Clinical studies have demonstrated that a syrup formulation of the plant extract exerts palliative effects—defined as alleviating distressing symptoms such as pain, nausea, shortness of breath, and anxiety, and improving the patient's quality of life, rather than curing the underlying cause of a serious or progressive disease—in relieving symptoms of acute bronchitis (Al-Hussainy et al., 2022).

Traditionally, it is administered 3–4 times daily in the form of either powder (3–5 g per dose) or a liquid preparation (up to 150 mL per dose) (Bai et al., 2021). Various clinical studies have supported its beneficial effects in the management of diabetic neuropathy and cancer [Bairagi et al., 2018], while preclinical and clinical findings have confirmed that plantain extract exhibits dose-dependent anxiolytic activity and could serve as a natural intervention for anxiety disorders (Bakrim et al., 2022).

The effect of plantain on target proteins involved in chronic wound healing has been demonstrated—particularly through studies on various medicinal plants used in traditional Chinese medicine—which provide clear insights into their biologically active mechanisms (Li et al., 2023; Noor et al., 2022; Zhao et al., 2023).

Clinical studies on second-degree burns have yielded remarkable results, comparing a 10% plantain ointment with the standard treatment of 1% silver sulfadiazine ointment. It was observed that, by the 10th day, the plantain ointment was capable of combating infection at a level equivalent to the standard treatment. In particular, plantain offers advantages over the standard treatment due to its analgesic effects and ability to promote faster wound healing (Keshavarzi, Khosravi, and Foolad, 2022).

Phytoconstituents of Plantain

The various pharmaceutical applications of different parts of the plantain plant (leaves, roots, flowers, and seeds) are attributed to its phytochemical constituents. The seeds contain various carbohydrates, including monosaccharides (glucose and fructose), disaccharides (sucrose and planteose), and trisaccharides [planteose (O-α-D-Galp-(1→6)-O-β-D-Fruf-(2→1)-α-D-Glcp)] (Baltzis et al., 2014). Upon contact with aqueous solutions (both hot and cold), the seed coat releases some mucilage rich in xylose, arabinose, galacturonic acid, and galactose (Baltzis et al., 2014).

The leaves and seeds of the plantain plant are rich in phenolic and flavonoid compounds (Amaro-Luis et al., 1997), and the plant contains two key phytochemicals: ursolic acid and oleanolic acid (Antoniadi et al., 2023). Ursolic acid, a significant bioactive plant constituent, exhibits notable anti-inflammatory properties by suppressing prostaglandin biosynthesis. Fatty acids are present in both the leaves and the seeds, and approximately 65% of these fatty acids are in the unsaturated form (Bektas et al., 2020).

The leaves and seeds are rich in fatty acids, carotenes, and various other phenolic compounds, such as ferulic acid (Bhattamisra et al., 2020). Acidic extraction of plantain yields various fractions composed of high-molecular-weight carbohydrates; these include heteroxylans characterized by xylose blocks linked via β-(1→3) and β-(1→4) bonds, along with side chains consisting of xylose and arabinose residues (Beara et al., 2012).

Plantain contains high concentrations of flavones, particularly luteolin and apigenin. A wide variety of flavonoids—such as baicalein, hispidulin, plantaginin (Chahardoli et al., 2023), scutellarein (Chen et al., 2021), luteolin 7-glucoside, hispidulin 7-glucuronide, luteolin 7-diglucoside, apigenin 7-glucoside, nepetin-7-glucoside, luteolin 6-hydroxy-4'-methoxy-7-galactoside (Cho et al., 1998), and homoplantaginin (Comalada et al., 2005) have been isolated from the plant using various extraction protocols.

The wound-healing effect of the plant is attributed to various phytoconstituents, including aesculetin, amentoflavone, apigenin, astilbin, acteoside, aucubin, caffeic acid, chlorogenic acid,

chrysoeriol, cis-7-hexadecenoic acid, erucamide, ferulic acid, geniposidic acid, gentiopicroside, gentisic acid, L-phenylalanine, lupeol, lupeol acetate, luteolin, N-hexadecanoic acid, oleamide, oleic acid, p-coumaric acid, p-hydroxybenzoic acid, palmitoleate, phytol, plantamajoside, quercetin, quercetin 3-O-glucoside, rutin, stigmasterol, syringic acid, umbelliferone, ursolic acid, vanillic acid, vitexin, 9,12-octadecadienoic acid, and quinic acid.

In addition to flavonoids such as plantaginin, baicalein, and hispidulin, other phytoconstituents like homoplantaginin also exhibit significant antioxidant activity by mitigating lipid peroxidation (Daraban et al., 2013). Phytochemical analyses further reveal that the leaves contain higher levels of phenolics and flavonoids compared to the seeds (Das et al., 2022).

The aqueous extract of the plant contains an alkyl ester of caffeic acid, as well as the components plantamajoside and acteoside (Daraban et al., 2013). Among the caffeic acid derivatives, plantamajoside (glycosylated with glucose) and acteoside (glycosylated with rhamnose) are significant constituents (Altintas & Celik, 2024). It contains moderate levels of vitamin K (Fakhrudin et al., 2017) and also comprises iridoid glycosides and aucubin (Fakhrudin et al., 2019).

Antibacterial and Antifungal Effects

Microbiological studies have shown that the acetone extract of plantain leaves significantly inhibits the growth of *Bacillus cereus*, *Salmonella enteritidis*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

Alcoholic extracts have been shown to exhibit inhibitory effects against *Bacillus cereus* and *E. coli*. Additionally, the methanolic extract of plantain has been found to inhibit the growth of *S. aureus*, *Lactobacillus* spp., *Enterococcus* spp., *P. aeruginosa*, *E. coli*, and *Proteus* spp. (Fierascu et al., 2021).

De Sousa et al. evaluated the antimicrobial efficacy of plantain leaves and found that the plant extract exhibited synergistic activity against resistant *Klebsiella pneumoniae* and bacteriostatic effects against methicillin-resistant *S. aureus* when used in combination with imipenem, cephalothin, and oxacillin, respectively. Furthermore, in combination with amphotericin B, it demonstrated synergistic and fungistatic activity against *Candida auris*.

It has been found that the dichloromethane extract of plantain roots possesses strong antibacterial activity against *Salmonella paratyphi* and exhibits notable anticancer properties. Gas chromatography-mass spectrometry analysis revealed that the biological activities of the extracts are attributable to *n*-hexadecanoic acid, linolenic acid, and stearic acid (Gendrisch et al., 2021).

Antioxidant Effects

Plantain species possess strong antioxidant properties due to their content of secondary metabolites such as flavonoids, phenolic acids, and iridoid glycosides. These compounds exhibit significant free radical scavenging activity, thereby protecting cells against oxidative damage. Various solvent fractions of plantain leave (petroleum ether, ethanol, ethyl acetate, and aqueous fractions) contain flavonoids (1.24 to 5.48 µg QAE/mg) and phenolics (5.79 to 114.45 mg GAE/g) and demonstrate notable antioxidant potential in iron ion chelating activity, DPPH free radical scavenging, and β-carotene bleaching assays [Hrichi et al., 2022].

The antioxidant potential of the plant extracts showed a concentration-dependent increase at a concentration of 100 ppm, and both leaf and seed extracts exhibited equivalent levels of free radical scavenging activity. The aqueous leaf extract possesses a higher antioxidant potential compared to the plant's seed extract (Hwang et al., 2017). The free radical scavenging effect of plantain may be attributed to its total phenolic content (Imran et al., 2015).

Antitumor Effects

The cytotoxic activity of seven *Plantago* species was evaluated against three human cancer cell lines: melanoma (UACC62), breast adenocarcinoma (MCF-7), and renal adenocarcinoma (TK-10). All plants exhibited dose-dependent cytotoxicity against breast and melanoma cells.

Flavonoids, particularly luteolin-7-O-β-glucosides, may be responsible for the cytotoxic and antitumor activity of the extracts (Joseph et al., 2018). In a study evaluating anticancer properties, intracellular fluid derived from plantain was injected into female mice. The incidence of tumors was significantly reduced in the treatment group. Tumors developed in approximately 18% of the mice, representing a 93% reduction compared to the control group (Karakaş et al., 2012).

Anticancer activity varied significantly among plant organs and extract types. Notably, leaf extracts yielded promising results in in vitro studies conducted on mice. Furthermore, silver nanoparticles (Ag NPs) synthesized using leaf extracts exhibited remarkable anticancer activity, further highlighting the plant's therapeutic value.

Molecular docking analyses have revealed that compounds such as apigenin, aucubin, baicalein, caffeic acid, and luteolin possess high binding affinity for EpCAM. Therefore, plantain extracts show promise as potential therapeutic agents in the treatment of gastrointestinal cancers (Karima et al., 2015). Wu et al. synthesized carbon dots using plantain as a precursor via a single-step hydrothermal process and demonstrated that they exhibited anticancer activity against MCF-7 cells (Kartini et al., 2018).

Anti-ulcer and wound-healing activities

Gastrointestinal ulcers are erosions occurring in the gastric or intestinal mucosa as a result of exposure to hydrochloric acid, the use of non-steroidal anti-inflammatory drugs, or *Helicobacter pylori* infection (Kumar et al., 2007). Medicinal plants with anti-ulcer properties are gaining increasing importance in various traditional folk medicine practices.

The anti-gastrointestinal ulcer activity of plantain seeds and leaves was evaluated using an alcohol-induced model. Compared to the seed extract, the leaf extract resulted in a significantly greater reduction in inflammatory bowel disease symptoms and the ulcer index. When administered alongside alcohol, the leaf extract reduced the ulcer index by 87.50%, a result superior to the reduction achieved with aspirin (38.90%). In contrast, the seed extract did not demonstrate a significant reduction in ulcer severity under similar conditions.

Furthermore, plantain has demonstrated strong potential in suppressing *Helicobacter pylori*, a key pathogen in the development of gastrointestinal ulcers (Kuranel et al., 2016; Kurt et al., 2018). The anti-ulcerogenic activity of plantain was

evaluated in rats subjected to stress-induced ulcers via the water-immersion method. The rats were administered leaf powder mixed with honey.

While the methanol extract achieved a 29% reduction in ulceration, the aqueous extract (1.0 g/kg) showed a 37% reduction. Notably, the combined extracts (1.2 g/kg) exhibited the strongest inhibitory effect, reducing ulcer formation by 40%. These findings highlight the synergistic potential of combining plantain extracts with honey in alleviating stress-induced ulcers (Lan et al., 2024).

Marzuki et al. determined that plantain leaf extract at a concentration of 500 µg/mL did not have any adverse effects on the viability of RAW264.7 cells. The leaf extract (31–500 µg/mL) significantly promoted wound closure and healing in NIH/3T3 and RAW264.7 cells by increasing nitric oxide production during inflammation, activating fibroblast migration, and accelerating fibroblast proliferation (Li et al., 2020).

Cardoso et al. investigated the effect of a cream containing plantain extract on wound healing in hyperglycemic rats. The experimental group exhibited a higher number of inflammatory cells, blood vessels, and fibroblasts compared to the control group. Plantain extract increased the number of inflammatory cells without increasing cytokine protein expression (Lin et al., 2023).

Hepatoprotective Activites

The liver is the primary organ responsible for the detoxification of harmful substances. However, prolonged exposure to toxins, certain medications, or viral infections can lead to oxidative stress and inflammation in hepatocytes, ultimately causing hepatocellular damage. Due to the limitations and side effects of conventional pharmacological agents, there is growing interest in identifying effective, low-toxicity hepatoprotective agents of natural origin.

In a study conducted by Türel et al., carbon tetrachloride (0.8 mL/kg), liquid paraffin, and normal saline were administered to albino mice to induce hepatotoxicity. Subsequently, the mice were treated with plantain extract (5, 10, 20, and 25 mg/kg) for 7 days. The results demonstrated a significant reduction in serum aspartate aminotransferase and alanine aminotransferase levels in the groups treated with the extract. Similar hepatoprotective effects were also observed with plantain seed extract (Moon et al., 2018).

Therapeutic Activities

Various *Plantago* species contain a rich diversity of bioactive metabolites including phenolic acids, flavonoids, iridoid glycosides, terpenoids, and fatty acid-derived compounds that contribute to the plants' broad therapeutic potential. These phytoconstituents in *Plantago* species have been shown to exhibit activities that promote wound healing, regulate inflammatory responses, and suppress microbial growth.

In the clinical management of chronic wounds such as diabetic foot ulcers and burns, current treatments typically address different aspects of the healing process—such as antimicrobial agents, debridement, offloading, moisture-retentive dressings, and, more recently, growth factors or cell-based therapies individually, requiring multiple interventions to achieve wound closure (Patel et al., 2019; Spampinato et al., 2020). In contrast, *Plantago* species have demonstrated a broad and holistic spectrum of efficacy in clinical settings, effectively mirroring a "comprehensive care" package. Constituents of *Plantago* trigger metabolic processes such as antioxidant and antidiabetic effects, anti-inflammatory activity, and the stimulation of new tissue formation.

It has been found that plantain (Sinirotu) phytoconstituents exert positive effects on markers of wound healing—specifically TGF-β1, TGF-β2, and α-SMA (which support tissue repair and regeneration); Coll-I and Coll-III (which stimulate collagen synthesis and deposition); CD-31 (which promotes angiogenesis); and iNOS, IL-1β, IL-6, IL-12, IL-17, IL-22, IFN-γ, p65, and NO (which reduce pro-inflammatory responses).

Similarly, it has been suggested that IL-10 (which enhances the anti-inflammatory response); CAT and SOD (which increase antioxidant enzyme activity); MMP-1, MMP-2, MMP-3, MMP-6, and MMP-13 (which reduce MMP activity); TIMP-1 and TIMP-2 (which raise TIMP levels); and NF-κB, JAK-STAT, TLR, and PG (which suppress inflammation-related signaling pathways) may also be effective in disrupting bacterial cell membranes and cell cycle progression.

Plantain Metabolites and Promote Wound Healing

Phytoconstituents found in *Plantago* species that exhibit wound-healing activity include acteoside, astilbin/smiljitbin, caffeic acid, chlorogenic acid, ferulic acid, lupeol, luteolin, p-coumaric acid, syringic acid, ursolic acid, vanillic acid, vitexin, oleic acid, aucubin, and plantamajoside.

Chlorogenic acid has been shown in *in vivo* studies to enhance epithelialization and collagen production. Furthermore, a hydrogel containing this compound at a concentration of 2.5 µg/mL significantly accelerated wound healing by day 14 (Chahardoli, Pourmoslemi, Soleimani Asl, Tamri, and Haddadi, 2023). Ferulic acid was encapsulated into nanoparticles and administered both orally at a dose of 6.5 mg/kg (representing a 35% reduction in dosage) and topically via a hydrogel loaded with FA-NPs (ferulic acid nanoparticles) at a concentration of 1.136%.

Both modes of administration resulted in a significant reduction in the wound area in diabetic rats by day 8. This effect can be attributed to increased collagen deposition, elevated Zn and Cu levels, and the rapid maturation of granulation tissue, as observed in wound healing studies conducted on diabetic rats (Bairagi, Mittal, Singh, and Mishra, 2018).

Interestingly, in the same study, oral administration at doses of 10 mg/kg and 20 mg/kg (body weight)—without a nanoparticle formulation—and topical application at a 10% concentration accelerated wound closure. This effect was observed on days 5, 8, 11, and 14; however, the 10 mg/kg oral dose did not show a significant effect on day 5. The most pronounced wound-healing effect was observed with the 20 mg/kg oral dose. Furthermore, all three dosage regimens effectively suppressed lipid peroxidation, increased catalase and superoxide dismutase activities, and elevated serum levels of glutathione, nitric oxide, Zn^{2+}, and Cu^{2+}, likely contributing to the healing process (Ghaisas, Kshirsagar, & Sahane, 2014).

Similarly, in diabetic wounds, the p-coumaric acid scaffold increased Col-1 and TGF-β3 levels by 41.9-fold and 30.0-fold, respectively; these increases compare to 8.3- and 10.8-fold increases achieved with Col scaffolds, and 13.9- and 14.6-fold increases achieved with Col-OxP3 alone. In parallel, MMP-9 expression in diabetic wounds was most effectively suppressed (0.31-fold) by the Col-OxP3-Ca group, compared to the diabetic control group (1.0-fold) and the Col (0.85-fold) and Col-OxP3

(0.79-fold) groups (Selvakumar & Lonchin, 2023).

Topical creams containing syringic acid (at both 2.5% and 5% concentrations) have demonstrated significant therapeutic effects in *in vivo* models of diabetic wound healing. These creams exhibited effects such as the suppression of pro-inflammatory responses (NF-κB, p65, TNF-α, IL-1β, IL-8, and IL-2) and the enhancement of anti-inflammatory responses (IL-10); the inhibition of high oxidative stress; the reduction of MMP-2, -8, and -9 levels; the increase of TIMP-1 and TIMP-2 concentrations; the upregulation of CD31 and CD68 expression; and the significant promotion of collagen deposition and re-epithelialization mediated by growth factors (TGF-β1, collagen-I, α-SMA, and VEGF) (Ren, Yang, Xu, Chen, and Ma, 2019).

A topical cream containing vitexin at a concentration of 10 mg/mL significantly accelerated wound closure in a full-thickness excisional wound model in rodents; it promoted healing by days 7 and 14 and resulted in complete wound closure by day 21. Histological examinations reveal that this compound accelerates skin regeneration (Bektas, Şenel, Yenilmez, Özatik, and Arslan, 2020).

As a result, it has revealed the presence of approximately 60 distinct and metabolically active phytoconstituents in *Plantago* species, including, in particular, flavonoids, alkaloids, terpenoids, phenolic acid derivatives, iridoid glycosides, fatty acids, and polysaccharides.

Evidences highlights the multifaceted wound-healing potential of the *Plantago* genus. Early-stage benefits, including antimicrobial, anti-inflammatory, and antioxidant activities seamlessly transition into enhanced angiogenesis, fibroblast proliferation, and collagen deposition during the later stages of repair.

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