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Original Research

Pharmacological effects and bio-active compounds of Plantago major

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Abstract

The purpose of this review is to provide a comprehensive overview of the research conducted on the chemical constituents and biological characteristics of Plantago major, Plantaginaceae. **Methods:** A comprehensive search of scientific databases, including Google, Google Scholar, PubMed, Science Direct, Researchgate and other online collections were extensively utilized. For efficient re-trieval, specific keywords like "Plantaginaceae", "Plantago major bio-active compounds ", "Plantago major. phyto-chemicals", "Plantago major L. pharmacological activities", and "Plantago major'' traditional uses". **Results:** The medicinal benefits of herbal plants are recognized worldwide, and numerous scientific studies have been conducted to validate their effectiveness. Additionally, the emergence of drug-resistant microorganisms in recent years has prompted researchers to investigate the effects of medicinal plants on these pathogens. Plantago major one a such plant the healing properties have been acknowledged worldwide for numerous years. This particular plant contains various potent chemical compounds, including alkaloids, terpenoids, flavonoids, fatty acids, polysaccharides, vitamins, phenolic acid derivatives, and iridoid glycosides. These constituents contribute to its therapeutic effects and its wide range of medicinal qualities, such as antioxidant, antibacterial, anti-inflammatory, anti-diabetic, anti-cancer, and anti-ulcer properties. The main objective of this review is to highlight the potential use of Plantago major extracts as herbal remedies and explore their extensive therapeutic capabilities. **Conclusion:** Plantago major plays a significant role in the treatment of various diseases and specific health conditions, including diarrhoea, ulcers, bacterial infections, inflammation, and cancer. Research has demonstrated that this plant contains multiple classes of essential bioactive compounds, such as alkaloids, flavonoids, fatty acids, vitamins, iridoid glycosides, terpenoids, and phenolic compounds like caffeic acid. The therapeutic properties and biological activity of Plantago major are largely attributed to these active chemical components. However, further research is needed to fully understand the precise mechanisms and activities of the primary bioactive compounds responsible for treating specific diseases.

Keywords: Plantago major; phytoconstitution, bio-active compounds, antioxidant, antibacterial

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INTRODUCTION

Throughout the course of human history, individuals have sought out natural remedies to enhance their overall well-being and address various ailments. For thousands of years, plants have been utilized for their medicinal properties. Since ancient times, different scientists and doctors have employed various types of herbs to treat illnesses. Numerous books and treatises have been written, detailing the diverse effects of plants on different diseases[1,2]. The therapeutic advantages of medicinal plants are acknowledged globally, and numerous scientific studies have been conducted to validate their efficacy. The pursuit of commercial potential has been a driving force behind the increased research in herbal medicines[3]. In fact, it is estimated that nearly half of today's pharmaceuticals are derived from plants[4].Furthermore, the rise of drug-resistant microorganisms in recent years has stimulated researchers to assess the impact of medicinal flora on these pathogens[5]. In contrast to conventional chemicals, herbal remedies exhibit fewer adverse effects[6,7]. Given that plants are a bountiful source of bioactive secondary compounds such as phenols, flavonoids, saponins, and alkaloids, plant extracts serve as an appealing alternative. One notable example is Plantago major, a herb that has been highly regarded for centuries[8]. Plantago major (Plantago major ssp. Major L.) is a perennial plant that belongs to the Plantaginaceae family[9]. Originally prevalent in Europe, Northern and Central Asia, it has now proliferated across the globe[10-12]. Plantago major has been utilized for the treatment of different illnesses, including infectious ones[13,14]. This plant also harbours numerous bioactive substances and possesses a multitude of medicinal qualities, such as being an antioxidant, antibacterial, anti-inflammatory, anti-diabetic, anti-cancer, and anti-ulcer agent. The primary aim of this review is to showcase the viability of employing extracts from Plantago major as herbal remedies and explore their extensive therapeutic capabilities (Figure 1).

MATERIALS AND METHODS

A comprehensive search of scientific databases, including Google, Google Scholar, PubMed, Science Direct, Researchgate and other online collections were extensively utilized. For efficient re-trieval, specific keywords like "Plantaginaceae", "Plantago major bio-active compounds", "Plantago major. phyto-chemicals", "Plantago major L. pharmacological activities", and "Plantago major'' traditional uses". The manuscript comprehensively discusses the utilization of these keywords in exploring pharmacological aspects, providing a holistic overview of the gathered information

RESULTS & DISCUSSION

Chemical components

Plantago major is a valuable medicinal plant that contains a variety of biologically active substances, including phenolic compounds, flavonoids, terpenoids, iridoid glycosides, alkaloids, fatty acids, and polysaccharides. Flavonoids are widely found in Plantago major, while terpenoids can be found in the wax and leaves of the plantain. Numerous studies have demonstrated the presence of iridoid glycosides in the aerial part of Plantago major, with various parts of the plant yielding

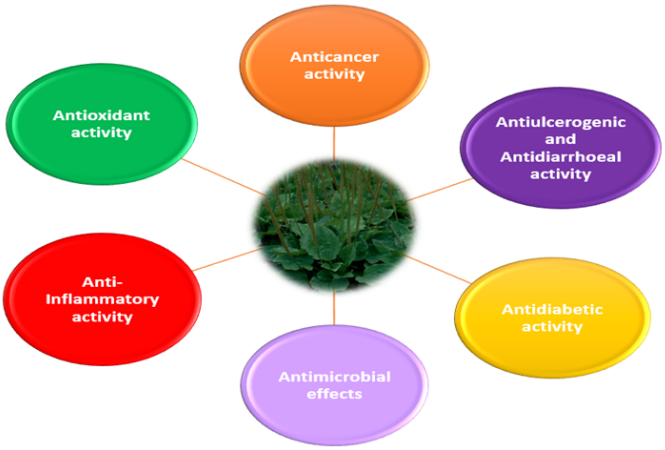

Figure 1. Pharmacological properties of *Plantago major*

different iridoid glycosides. Additionally, derivatives of caffeic acid, known as verbacosides, have been discovered in this plant. The seeds and leaves of Plantago major have also been used for the separation of fatty acids. Polysaccharides were found in the seeds of Plantago major. Numerious chemical components are present in the seeds, leaves, flowers, roots, and nearly all other parts of the plant, leading to their biological activity.

Various traditional methods were used to extract biologically active compounds from Plantago major, such as polar and non-polar maceration (with various solvents such as methanol, ethanol, dichloromethane, ethyl acetate, 10% H_2O_2, oily and aqueous solvents). Other extraction methods, using extracts like butanol, hexane, ethyl acetate, water, and others, were also utilized to extract biologically active compounds from Plantago major (Table 1). The chemical compounds present in Plantago major undergo qualitative transformations influenced by factors like growth conditions, growth stage, climatic conditions, drying conditions, storage conditions, and soil properties (Figure 2).

Antioxidant activity

In a study conducted by Karima et al., the ethyl acetate fraction derived from the leaves of Plantago major demonstrated a potent ability to scavenge DPPH radicals. This effect increased significantly at low concentrations ranging from 0.001 to 0.063 mg/ml. Along with this, the petroleum ether fraction showed an increasing effect from 0.1 to 1 mg/ml, while the aqueous fraction exhibited moderate scavenging activity, increasing from 0.01 to 0.312 mg/ml. The ethyl acetate fraction displayed strong antioxidant activity with an IC_{50} value of 12.85 ± 0.27 g/ml. Compared than this fraction the positive controls BHA and BHT were less effective , with IC_{50} values of 13.44 ± 0.3 and 20.35 ± 0.16 g/ml, respectively. The petroleum ether fraction had a negligible IC_{50} activity of 109.67 ± 0.21 g/ml, followed by the aqueous fraction with an IC_{50} of 439.84 ± 6.51 g/ml. The ethyl acetate extract of Plantago major leaves exhibited the highest level of DPPH scavenging activity when compared to the controls (BHA and BHT). Along with this, the ethyl acetate extract, as per the β-carotene bleaching method, also demonstrated superior activity compared to other extracts. The authors suggest that the abundance of phenolic compounds and flavonoids is responsible for its high antioxidant activity[44]. Furthermore, in a similar investigation, a leaf-derived methanol extract, abundant in phenolic compounds, exhibited robust antioxidant activity by effectively scavenging DPPH free radicals. Its effects were comparable to those of butylated hydroxytoluene (BHT) at a concentration of 100 µg/mL[45]. In a other investigation, the ethanol extract exhibited promising capabilities in scavenging superoxide free radicals, demonstrating an IC_{50} value of 1.52 mM. As a positive control, rutin displayed an IC_{50} value of 0.01 mM. Furthermore, the ethanol extract effectively scavenged DPPH free radicals with an IC_{50} value of 11.27 mM, whereas the reference standard alpha-tocopherol had an I_{C50} value of 25.9 mM[46]. The presence of hydroxyl groups in the phenolic compounds of Plantago major is responsible for its antioxidant activity. These hydroxyl groups have the capability to absorb DPPH. The redox and radical scavenging properties of phenolic compounds are attributed to the hydroxyls they contain. Flavonoids function as antioxidants by scavenging reactive nitrogen species and reactive oxygen species. Additionally, in certain cases, they can chelate transition metal ions in a structure-dependent manner. The antioxidant properties of flavonoids are determined by the number and arrangement of phenolic hydroxyl groups attached to their ring structures (Table 2).

In a separate study, the ethanolic extract of Plantago major leaves was screened using two different extraction methods: classical maceration (CE) and ultrasonic (UE). The purpose

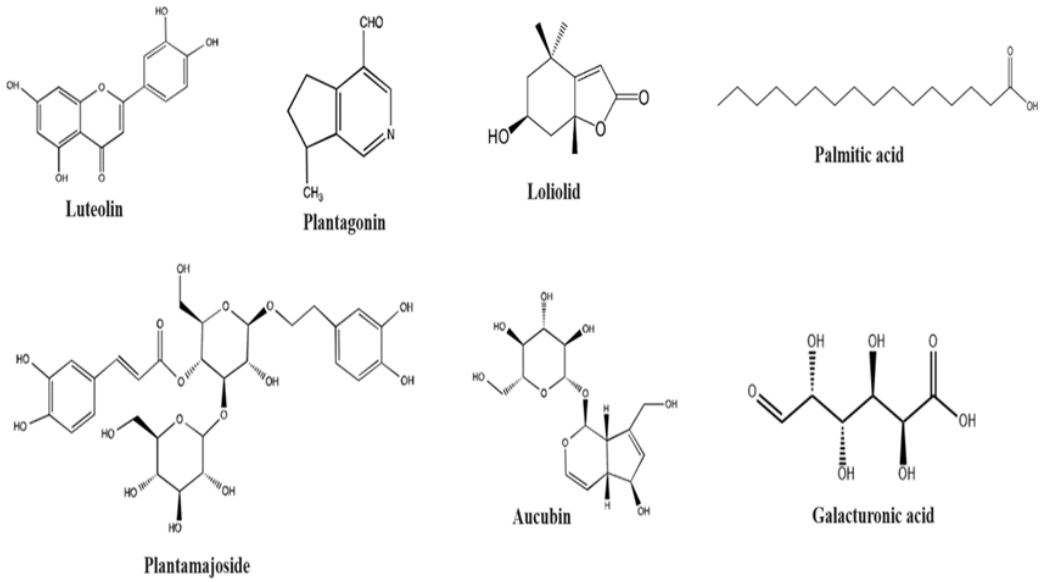

Figure 2. Chemical structures of the main biological active components of *Plantago major*

Table 1. Main biological active compounds of *Plantago major*

Extracts	Method	Plant Part	Biological active compounds	Pharmacological activity	Ref.
Flavonoids					
Methanol	HPLC, GC/MS	Aerial part	Luteolin and apigenin	Antioxidant	[16,17]
Methanol, ethanol	HPLC, GC/MS	Aerial part	Baicalein, hispidulin, plantagin	Antioxidant	[18]
Ethanol	LC–MS/MS	Whole part	Scutallarein	Antioxidant	[19]
Ethanol, ethyl acetate	HPLC,	Aerial part	Luteolin-7-glucoside, hispidulin-7-glucuronide, luteolin-7-diglucoside, apigenin-7-glucoside, nepetin-7-glucoside and luteolin-6-hydroxy-4'-methoxy-7-galactoside	Anticancer and Antioxidant	[20]
Ethanol	GC/MS	Leaf	Homoplantaginin	Antioxidant	[21]
Aqueous	HPLC, GC/MS	Whole part	Aucubin, baicalein, leuteolin, and baicalin, glucuronide of baicalein	Antibacterial, Anticancer, Antioxidant	[22]
	Alkaloids				
-	-	-	Indicain and plantagonin	-	[23]
	Terpenoids				
Hexane	HPLC	Leaf	Loliolid	Antiurolithiatic	[24]
95% ethanol	TLC, HPLC	Leaf wax	Ursolic acid, oleanolic acid, sitosterol acid and 18β-glycyrrhetinic	Anticancer, Anti-inflammatory,	[25-27]
	Caffeic acid derivatives				
Methanol, 80% ethanol	LC–MS/MS	Aerial part	Plantamajoside and acteoside	Antiviral and Antibacterial	[28]
	Iridoid glycosides				
N-hexane	LC–MS/MS	Leaf	Aucubin	Anticancer	[29]
Methanol	HPLC, GC/MS	Flower	Asperuloside	Anti-inflammatory	[30]
N-buthanol	HPLC, GC/MS	Aerial part	Majoroside	Anti-inflammatory	[31]
Hydroalcoholic	HPLC	Aerial part	10-hydroxymajoroside, 10-acetoxymajoroside	Anti-inflammatory	[32]
Methanol	TLC, LC–MS/MS	Aerial part	Catapol, gardoside, geniposidic acid and melittoside	Anti-inflammatory	[33]
	Fatty acids				
Ethanol	TLC, HPLC	Seed	Lignoceric acid	Antioxidant, Antibacterial and Anti-inflammatory	[24]
Chloroform Dichloromethane	HPLC, GC/MS	Seed	Palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid	Antioxidant, Antibacterial and Anti-inflammatory	[34]
Ethanol	LC–MS/MS	Seed	Myristic acid		[35]
Ethyl acetate	LC–MS/MS	Seed	9- hydroxy-cis-11-octadecenoic acid	Antioxidant, Antibacterial and Anti-inflammatory	[36]
Ethanol, methanol	TLC, HPLC	Leaf	Arachidic acid and behenic acid	Antioxidant, Antibacterial and Anti-inflammatory	[37]
Polysaccharides					
Aqueous	HPLC, GC/MS	Seed	Xylose, arabinose, galacturonic acid, galactose	Antibacterial	[38-40]
Aqueous	HPLC,GC/MS	Leaf, seed	Glucuronic acid, rhamnose, galactose and glucose	Antibacterial	[41-43]

Table 2. Investigation methods of extracts from *Plantago major*

Pharmacological activity	Extract	Plant part	Concentration / Used Dose	Constituent
Antioxidant	Ethanol	Leaves, Seeds	Leaves = 20 ppm	Linoleic acid, amino acids
	Crude	Leaves	Crude extract= 25, 50 mg/ml	Crude extract
	Ethanol, Ethyl acetate	Leaves, Seeds	Ethanol= 75 mg/ml	Flavonoids compound
			Ethyl acetate= 100 mg/ml	
	Methanol	Seeds	Methanol= 50 mg/ml	flavonoids compound
	Water-Methanol	WP	Water-Methanol=25 mg/ml	Crude extract
	Hydroalcoholic	Root	Hydroalcoholic=20,40,80 mg/ml	Phenolic and flavonoids compound
Antimicrobial	Ethanol	Leaves	Ethanol =100, 75, 50, 25 and 10%	Isoflavonoids compound
	Crude extract	Unknown	Crude extract=1000 mg/ml	Crude extract
	Hydroalcoholic	Leaves	Hydroalcoholic=50 mg/ml	Phenolic and flavonoids compound
	Hexane, Methanol, Ethanol and Aqueous	Leaves	Ethanol=2 mg/ml Methanol=4 mg/ml Hexane and Aqueous=8 mg/ml	Phenolic and flavonoids compound
	Ethanol	Leaves	Ethanol=250, 500, 750 and 1000 mg/ml	Unknown
Anti-Inflammatory	Methanol, Ethanol and Aqueous	Leaves	Unknown	Unknown
	Ethanol	Seeds	Ethanol =100, 300, 1000 mg/kg	Triterpenoids
	Aqueous	Seeds	Aqueous= 1 g/kg, po	Fatty acids and triterpenoids
	Soluble (SHF) and insoluble (IHF) dichloromethane extract (DCM) fractions	Unknown	SHF=560 mg/kg IHF= 280, 560 mg/kg	Oleic acid, linoleic acid, palmitic acid and oleamide
Anticancer	Methanol	Leaves	Total growth inhibition: TK–10 = none	Luteolin-7-O-β-glucoside
			MCF–7 = 97 µg/ml UACC–62 = 112 µg/ml	
	Water	Leaves	Water=25 µg/ml	Crude extract
	Methanol, water	Seeds, leaves, roots	Ethanol extract (seeds) = 153.38–247.41 µg/ml Ursolic acid = 6.27–18.33 µg/ml Oleanolic acid = 17.63–100 µg/ml	Ursolic acid, oleanolic acid, aucubin
	Aqueous and Ethanol	Leaves	Aqueous = 500 и 1000 µg/ml	
			Ethanol=50, 100, 250 µg/ml	
Antidiabetic	Methanol	Leaves	Methanol=1000 mg/kg	flavonoids, quercetin
	Methanol	Leaves	Methanol= 500 mg/kg	flavonoids, quercetin
	Ethanol	Leaves	Ethanol=400 mg/kg	7-O-метилапигенина (EPL7) и 7,4'-O-диметилапигенина
Antiulcerogenic	Aqueous and Ethanol	Leaves, Seeds	Ethanol= 500 mg/kg	Triterpenes, flavonoids, tannins and polyunsaturated fatty acids such as linoleic acid
	95% methanol solution	Leaves	200 mg/kg	Crude extract
Antidiarrhoeal	Methanol	Leaves	200 mg/kg	Crude extract

was to determine and compare the antioxidant activity of the extracts through the DPPH free radical scavenging method. The results showed that the EC_{50} value for the extract obtained using the UE method was slightly higher compared to the CE method. However, this difference was not statistically significant at a 95% confidence interval. The extract obtained through the UE method exhibited a more effective ability to scavenge radicals, which attributed to the oxidation and decomposition of bioactive chemicals when exposed to highly reactive hydroxyl radicals generated during ultrasonic cationization of the solution[47].

Two distinct methods, FRAP and DPPH, were employed by Lukova et al. to evaluate the antioxidant efficacy of Plantago major leaf polysaccharides. The DPPH assay demonstrated that water-extractable polysaccharides (WEP) derived from Plantago major leaves exhibited higher antioxidant activity (29.39%–40.08%) compared to total acid-extractable polysaccharides(TAEP) (19.44%–24.15%). This is attributed to the abundance of galacturonic acid present in WEP. Uronic acids possess robust antioxidant properties due to the attachment of their carbonyl group to a ring molecule. The control arabinogalactan displayed a similar ability to scavenge radicals (21.19%) as TAEP (19.44%–

24.15%). The lower antioxidant capacity of TAEP attributed to its lower concentrations of galacturonic acid and higher content of galactose. The FRAP test outcomes of the examined polysaccharides exhibited a similar pattern. In contrast to TAEP (34.63–117.66 m TE/5 mg Ps), WEP demonstrated higher iron reduction (103.71–137.83 m TE/5 mg Ps). Furthermore, the antioxidant capability of Plantago major polysaccharides was compared to synthetic BHT. Comparisons revealed that the findings acquired through the DPPH and FRAP techniques were lower than those obtained with BHT[48].

Nine pure compounds extracted from Plantago major, and assessed for their efficacy in scavenging free radicals , showed good results. Among the tested compounds derived from Plantago major, ursolic acid exhibited the most powerful antioxidant effect (IC_{50} value: 5.62–22.71 g/ml), followed by baicalein (IC_{50} value: 20.25 g/ml) and oleic acid (IC_{50} value: 22.71-22.71 g/ml). Additionally, chlorogenic acid and caffeic acid demonstrated moderate DPPH scavenging activity within the concentration range of 2–300 g/ml. No other substances displayed any activity using the DPPH method. In contrast to caffeic and chlorogenic acids, which possess two hydroxyl groups, p-coumaric acid and vanillic acid, with only one hydroxyl group attached to the aromatic ring, was exhibited significantly lower activity[49].

Antimicrobial effects

A study conducted on the effectiveness of Plantago major extracts against Pseudomonas aeruginosa isolated from burn infections revealed that different concentrations of Plantago major leaf ethanol extract (100%, 75%, 50%, 25%, and 10%) resulted in varying zones of inhibition, with diameters ranging from 9.93 mm to 22.18 mm. The zone of inhibition increased as the concentration of the extract increased. The highest inhibitory effect was observed with the 100% ethanol extract, which had a zone diameter of 22.18 mm. Also during this study, a bioinformatics approach was used to investigate the antibacterial properties of Plantago major extracts against Pseudomonas aeruginosa, as well as their impact on Tox-A gene expression. The crude extracts showed significant antibacterial activity compared to other fractionated plant extracts. At a dosage of 1000 mg/ml, Plantago major extracts inhibited P. aeruginosa with an average zone of inhibition of up to 16 mm. Petroleum ether and chloroform exhibited a slight inhibitory effect when compared to the aqueous extract. The expression of the Tox-A gene was significantly reduced at most doses ($P<0.05$)[50].

Extracts obtained by two different extraction methods: ultrasonic (40 kHz) and classical (maceration) (CE) from dried Plantago major leaves at a concentration of 50 mg/ml each were tested for antimicrobial activity against gram-negative bacteria (Pseudomonas aeruginosa), two gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis), as well as one mold (Aspergillus niger) and two yeasts (Candida albicans, Saccharomyces cerevisiae). The methanol extract did not show any effect on the bacteria tested. However, the hydroalcoholic extracts obtained from Plantago major leaves showed higher antibacterial activity against yeasts compared to both gram-positive and gram-negative bacteria, regardless of the extraction method used. For Staphylococcus aureus and Pseudomonas aeruginosa, recovery approaches have been suggested. The extract prepared using CE inhibited Bacillus subtilis and both yeasts more effectively, while the extract prepared using ultrasonic extraction inhibited Escherichia coli more effectively. The most sensitive microorganism to both extraction methods was Saccharomyces cerevisiae, with diameters of 19.2 ± 0.5 mm and 23.5 ± 0.1 mm respectively[51].

However, Akkuş and Hiziçekliyurt found that antimicrobial activity in vivo and the minimum effective dose of hexane, methanol, ethanol, and aqueous extract of Plantago major leaves were active against Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Candida albicans, and Candida tropicalis at a dose of 4 mg/ml. Plantago major extracts in water and hexane were less effective than those in ethanol and methanol. At a dosage of 8 mg/ml, hexane and aqueous extracts of Plantago major had the least efficacy against the microorganisms Escherichia coli and Pseudomonas vulgaris.Plantago major ethanol and methanol extracts were efficient against Staphylococcus aureus, Enterococcus faecalis, and Pseudomonas aerouginosa at dosages of 2 mg/ml and 4 mg/ml[52]. In addition, Soliman et al. (2022) made a discovery that the antibacterial activity of aqueous and ethanol extracts from Plantago major leaves was lower compared to methanol extracts. The most effective agent against P. aeruginosa was found to be a methanolic extract from Plantago major leaves sourced from canal banks, followed by an extract from orchards against S. aureus[53]. The extracts of Plantago major leaves possess the ability to inhibit bacteria due to the synergistic action of phenols, flavonoid components, terpenoids, and tannins. These chemicals can penetrate the bacterial peptidoglycan and alter the cytoplasmic membrane, leading to changes in fluidity and the outer layer of the cell wall. As a result, leakage of cytosolic fluid occurs, causing structural modifications in the membrane and ultimately leading to bacterial cell death[54].

Anti-Inflammatory activity

The development of mice's ear dermatitis caused by croton oil was hindered by the utilization of Plantago major leaves extracted using chloroform, n-hexane, methanol, and their corresponding extracts. Each extract (300 μg/cm^2) significantly decreased the extent of edema, with the chloroform extract proving to be the most efficient. Its effectiveness was only two times lower than that of the reference drug indomethacin: their ID_{50} values (the dosage required to achieve 50% suppression of swelling) were 177 and 93 μg/cm^2, respectively[55]. Additionally, both aqueous and ethanol extracts of Plantago major leaves exhibit anti-inflammatory properties on oral epithelial cells in laboratory testing. The concentration of 0.1 mg/ml demonstrated the highest anti-inflammatory activity (with a total phenol content of 1.67, 0.22, and 0.94 mg and a plantamaoside GAE content of 1.24, 0.19, and 0.71 mg/ml for ethanol, aqueous extract, and a combination of both extracts). However, at lower and higher concentrations, the anti-inflammatory response was weakened or absent. Nonetheless, ethanol-based extracts and a combination of

water and ethanol-based extracts displayed anti-inflammatory effectiveness at a dosage of 1.0 mg/ml[56].

The anti-inflammatory properties of Plantago major seed extract were assessed at varying doses (100, 300, and 1000 mg/kg) in comparison to sodium salicylate (300 mg/kg) and distilled water. Male rats were injected with 2.5% formaldehyde subcutaneously in their paws to evaluate the impact on paw inflammation. Plethysmometry was used to measure inflammation on the first day (acute inflammation) and seven days later (chronic inflammation). Plantago major extract at 1000 mg/kg ($p<0.003$) and sodium salicylate at 300 mg/kg ($p<0.003$) both exhibited a significant acute anti-inflammatory effect with no significant difference. At a dosage of 1000 mg/kg, Plantago major extract had a notable chronic anti-inflammatory effect ($p < 0.05$) on days 4, 7, and 8. However, for sodium salicylate and other extracts, this effect was only significantly evident on day 4[57].

Plantago major microemulsified ethanolic extract exhibited anti-inflammatory properties on croton oil-induced ear swelling in mice. The application of microemulsions locally reduced both ear swelling and the presence of proinflammatory cells in the tissues. The effectiveness of the microemulsion was comparable to that of 1% hydrocortisone ($p>0.05$) [58]. Plantago major aqueous and alcoholic extracts have shown anti-inflammatory effects at dosages of 20 and 25 mg/kg, respectively. When compared to indomethacin, the control marker, the reduction in inflammation was 90.01% for Plantago major at 3.10% when 5 mg/kg was used, 41.56% when 10 mg/kg was used, 45.87% when 20 mg/kg was used, and 49.76% when 25 mg/kg was used. The average effective dose (ED50) of Plantago major was determined to be 7.507 mg/kg[59]. Furthermore, prior treatment with a water-based solution (1 g/kg orally) derived from Plantago major demonstrated a decrease in acetic acid-induced writhing in mice, without any effect on the response to thermal nociceptive stimuli. In rats, the oral administration of a water-based solution (1 g/kg) reduced paw edema and pleuritis induced by carrageenan, but had no impact on dextran-induced paw edema. The anti-inflammatory effect of the water-based solution on carrageenan-induced responses was more pronounced compared to ear swelling caused by croton oil in mice. Additionally, daily oral administration of the water-based solution (1 g/kg/day for 8 days) suppressed the exudative process triggered by the application of croton oil to the rat's ear. Plantago major extracts, both aqueous and ethanolic, contain numerous biologically active compounds such as terpenoids, fatty acids, and their derivatives. Several naturally occurring fatty acids and triterpenoids, along with all semisynthetic thioester fatty acids, exhibit inhibition of COX-2-catalyzed prostaglandin biosynthesis, with alpha-MNCs showing sensitivity to COX-2 inhibition.It is common knowledge that COX-2 serves as a producer of prostanoids in instances of inflammation. The primary reason behind the anti-inflammatory properties of Plantago major lies in its ability to inhibit COX-2[60].

The n-hexane fractionated extracts of Plantago major, specifically the soluble (SHF) and insoluble (IHF) dichloromethane (DCM) fractions, exhibited anti-inflammatory properties in three animal models with paw edema. In rats, as well as in mice, DCM, SHF, and IHF were able to inhibit paw edema and reduce leukocyte migration. At a dosage of 560 mg/kg, the inhibitory effect of DCM, IHF, and SHF was 47.33%, 55.51%, and 46.61% respectively. In comparison to diclofenac, IHF at doses of 280 and 560 mg/kg decreased the formation of osteoclasts and the expression of COX-2 in an animal model of rheumatoid arthritis (RA). This particular activity has been attributed to various molecules found in DCM, IHF, and SHF, including oleic acid, linoleic acid, palmitic acid, and oleamide. Additionally, studies have demonstrated that oleic and linoleic acids can reduce inflammation in rat macrophages by regulating the synthesis of inflammatory mediators such as IL-1, IL-6, and cytokine-induced neutrophil chemoattractant-2αβ. The DCM, IHF, and SHF extracts were also found to decrease leukocyte migration in a thioglycolate-induced peritonitis model. Oleic acid has been demonstrated to raise the levels of the anti-inflammatory cytokine IL-10, while decreasing the levels of the pro-inflammatory cytokines TNF-α and IL-1β. In human neutrophils that were isolated, oleic acid had a similar effect in preventing lipopolysaccharide-induced cell migration. In an animal model of CFA-induced rheumatoid arthritis, IHF reduced COX-2 expression and the occurrence of rheumatoid arthritis. This beneficial outcome is attributed to the ability of oleic acid and linoleic acid to inhibit COX-2[61].

Anticancer activity

Cytotoxic investigations on the alcoholic, hot, and cold aqueous extracts of Plantago major leaves and seeds have revealed varying degrees of anticancer activity in all extracts. The majority of the extracts exhibited a dose-dependent inhibition of cell growth. The most substantial impact on tumor cell proliferation was observed with a hot water extract of Plantago major leaves (dead 54.6% 1.21) and an alcoholic extract of Plantago major leaves (dead 74% 0.35)[62].

According to Piyaviriyakul et al., comprehensive studies have demonstrated the cytotoxicity of all parts of Plantago major, including the seeds, against five cancer cell lines in terms of antiproliferative activity. Among these, the seed extract exhibited the highest activity, with IC_{50} values ranging from 153.38 to 247.41 g/ml. While the aqueous extracts of leaves, petioles, and roots of Plantago major specifically targeted MCF-7, the aqueous extracts of seeds were effective against the cell lines KB, MCF-7, MDA-MB-231, and A549. Furthermore, it has been established that the roots of Plantago major possess cytotoxic properties comparable to its leaves and petioles[63].

An ethanolic extract of Plantago major's aerial parts was found to have more potent antiproliferative effects in the HCT-116 cell line than the SW-480 cell line in a different investigation. Additionally, at the maximum concentration (400 g/ml) over 24, 48, and 72 hours, the acetone extract of the aerial part had the largest inhibitory effect (59%, 43%, and 27% and 37%, 29%, and 23%, respectively) on the viability of HCT-116 cells and normal cell lines. Even while alcohol and acetone extracts had less cytotoxicity on SW-480 cells than they did on HCT-116 cells, after 24 hours, alcohol extracts showed a viability of 92–94%

at a concentration of 400 g/ml, while the acetone extract had no effect on SW-480 cells as compared to HCT-116 cells at the similar time. Additionally, on SW-480 cells, the acetone extract had the same action as the alcohol extracts. The ethanolic extract was more cytotoxic than the methanol extract in both cell types. Following a 72-hour experiment, the cytotoxic effects of alcoholic extracts were compared to those of acetone extract on normal HEK-293 cells. The findings indicated that ethanolic extracts exhibited a minor inhibitory impact (ranging from 2% to 13%) only at concentrations of 200 and 400 g/ml, while the acetone extract displayed a significant cytotoxic effect on HEK-293 cells across all tested concentrations (25-400 g/ml). Conversely, ethanol extracts derived from the aerial parts of Plantago major demonstrated considerable cytotoxicity against cancer cell lines, despite their modest reduction in cell growth for normal cells at high concentrations. The use of acetone extract is not recommended for colorectal cancer treatment due to its high cytotoxic activity against both cancerous and normal cell lines. Similar to the extracts from the aerial parts, ethanol, methanol, and acetone extracts obtained from the root of Plantago major showed stronger cytotoxic properties against HCT-116 cells compared to SW-480 cells. However, the root extracts of Plantago major exhibited greater antiproliferative activity on SW-480 cells than the aerial parts extract. Although the root's methanol extract had less antiproliferative effects than the ethanolic extract of Plantago major's root, it displayed higher cytotoxic effects on HCT-116 cells than the extracts from the aerial portions. The 100 g/ml acetone extracts of Plantago major roots displayed a significant (65%) negative impact on the viability of healthy HEK-293 cells. Although the cytotoxic effects on cancer cell lines were more pronounced, the impact of root extracts was comparatively smaller (76%) than extracts obtained from the aerial parts after 72 hours. The IC_{50} values for ethanolic, methanol, and acetone extracts on HCT-116, SW-480, and HEK-293 cells, respectively, after 72 hours were 405, 470, and 82 g/ml; 513, 687, and 698 g/ml; and 948, 1563, and 125 g/ml. Among these, acetone extract demonstrated the lowest IC_{50} in its interaction with HCT-116 and HEK-293 cells. The ethanolic extract exhibited favourable properties as its IC_{50} values on HCT-116 and SW-480 cell lines (405 and 513 g/ml) were lower compared to normal cells (948 g/ml). Furthermore, the IC_{50} values of ethanolic and acetone extracts of Plantago major roots on cancer cell lines were lower compared to extracts obtained from the aerial parts[64].

An in vitro investigation to assess the potential cytotoxicity of ethanolic extracts derived from Plantago major on human breast cancer cell lines (MCF-7) demonstrated good results. The study revealed that the leaf extracts of Plantago major had a suppressive effect on the growth of MCF-7 cells and also exhibited some impact on healthy HUVECs. The sensitivity of MCF-7 and HUVEC cells to the plant extract, at various concentrations (50, 100, 250, 500, and 1000 g/ml), was evaluated after 24 and 48 hours. The results indicated that the ethanolic extract significantly inhibited the growth of MCF-7 cells and, to some extent, HUVEC cells in a dose-dependent and time-dependent manner. Notably, MCF-7 cells displayed higher sensitivity to the inhibitory effects of Plantago major extracts compared to HUVEC cells[65]. Another similar study examined the cytotoxic effects of the methanol extract on breast adenocarcinoma (MCF-7) and melanoma (UACC-62) tumor cell lines using concentrations recommended by the NCI (USA). Etoposide, an anticancer drug, was used as a positive control. The methanolic extract of Plantago major completely suppressed the growth of MCF-7 cells (TGI = 97 g/ml) and completely inhibited the growth of the UACC-62 cell line (TGI = 244 g/ml). However, the methanol extract test did not fully halt the development of the TK-10 cell line. Luteolin-7-O-glucoside and its aglycone luteolin, derived from the plant Plantago major, also have been discovered to possess cytotoxic effects against three different cell lines when tested at specific concentrations. Luteolin showed the highest activity against a melanoma cell line (UACC-62), with a GI50 value of 10 g/ml. On the other hand, luteolin-7-O-glucoside demonstrated the greatest effectiveness in a breast cancer cell line (MCF-7), with a GI50 value of 40 g/ml. Moreover, both flavones were observed to induce OC production similar to camptothecin, which was used as a positive control in the topo I assay at a concentration of 100 M. At a lower measured dose of 50 M, luteolin-7-O-glucoside generated 8.56% OC, while its aglycone produced 8.58% at the same concentration. At the highest dose of 100 M, luteolin-7-O-glucoside resulted in 9.02% OC production, whereas its aglycone generated 8.65%. In comparison, camptothecin produced 14.54% OC at a concentration of 100 M. Both luteolin-7-O-glucoside and its aglycone luteolin act as potent DNA topoisomerase I poisons, highlighting their ability to cause topoisomerase-mediated DNA damage and exert cytotoxic effects[66].

Antidiabetic activity

The antidiabetic activity of Plantago major was investigated in streptozotocin-induced rat models. The rats were treated continuously with a methanolic extract of Plantago major for a period of 14 days. To evaluate the antidiabetic activity, both a glucose tolerance test and the STZ-induced model were utilized. During the glucose tolerance test, it was observed that a dose of 0.25 mg/kg body weight of the standard drug glibenclamide (GCL) and a dose of 1000 mg/kg body weight of the Plantago major extract significantly ($p<0.05$) lowered blood glucose levels after one hour. However, a dose of 500 mg/kg body weight did not produce the same effect. After 5, 10, and 14 days of treatment, the methanolic extract of Plantago major at a dose of 1000 mg/kg significantly reduced blood sugar levels by 8.48 ± 3.59 ($p<0.05$), 9.17 ± 3.36 ($p<0.05$), and 8.12 ± 2.22 ($p<0.05$), respectively. At same time, glibenclamide, used as a control, reduced blood sugar levels by 20.02 ± 3.95, 19.87 ± 3.84, 17.82 ± 4.71, and 11.93 ± 0.55. As stated by the authors, the hypoglycemic influence of Plantago major is attributed to the existence of sterols, flavonoids, and tannins in the methanol extract[67]. In a similar examination carried out by Abud et al., the methanol extract of Plantago major leaves was evaluated in the OGTT (oral glucose tolerance test) in rats with normal, moderate, or severe alloxan-induced diabetes (100 mg/kg - intraperitoneal administration). The oral administration of methanolic extracts at doses of 500 mg/kg body weight demonstrated that the extract enhanced glucose absorption

in rats with efficient insulin-secreting pancreas (which have pancreatic cells capable of secreting insulin)[68].

Positive outcomes were achieved when addressing blood sugar levels in obese mice with type 2 diabetes using specific fractions and raw extract of Plantago major. The ethanol fraction demonstrated the ability to decrease blood glucose levels in mice with obesity and type 2 diabetes by 67.73%. Following a 15-day period, the effectiveness of the ethanol fraction in the control group was comparable to the outcome of treating patients with type 2 diabetes using Glucophage, the current standard medication. Fasted mice were given a dosage of 500 mg/kg Plantago major extract before receiving an oral glucose tolerance test with 1.25 g/kg glucose to assess its efficacy in eliminating excess glucose from the body after an oral glycemic test. After 120 minutes of treatment with the extract, the diabetic mice exhibited blood glucose levels that were 27% lower than those in the control group.Even within a collective of individuals who are in good health and do not have diabetes, those who were administered Plantago major extract observed a decrease in their blood glucose levels to a normal range without any treatment (23%). This reduction was comparable to the normal blood glucose levels seen in individuals who were taking the medication glibenclamide, which is commonly prescribed for type 2 diabetes (26% decrease from the initial level without treatment). The antiglycemic effects of Plantago major extracts, conducted on mice, were rigorously evaluated over a 14-day period, a dose of 1000 mg/kg resulted in a 47% reduction in blood glucose levels compared to the untreated group. By the 14th day, there was a remarkable 54% decrease in glucose levels. Notably, in diabetic mice that were given 400 mg/kg of Plantago major extract, blood glucose levels dropped by 65% compared to the untreated group after just 3 days, and further decreased by over 70% within 15 days of treatment. Research has indicated that when Plantago major extracts are administered orally, they can enhance the beta cells' ability to stimulate insulin synthesis, promote beta cell renewal, and maintain beta cell mass in the pancreas. Consequently, this leads to improved glycemic regulation and enhanced glucose uptake by cells[69].

Antiulcerogenic and Antidiarrhoeal activity

A research conducted by Rahimi et al. showed the efficacy of Plantago major as a treatment for ulcers. The plant's leaves and seeds were extracted using methanol, and the impact of the extract was examined in rat models by inducing gastric ulcers with ethanol. The findings indicated that the leaf extract of Plantago major effectively reduced the ulcer index in rat models, resulting in an 87.50% cure rate for ethanol-induced gastric ulcers. However, the seed extract did not show any significant effect on the same model. Administering an oral dose of 400 mg/kg of Plantago major leaf extract significantly decreased the incidence of gastric ulcers. Moreover, both leaf and seed extracts of Plantago major demonstrated a general reduction in total acidity[70]. Another similar study demonstrated that high doses of ethanolic extract from Plantago major leaves significantly lowered the levels of IL-6, TNF-α, PGE2, IL-1, MPO, and MDA compared to the control group, as well as reducing ulcer index and histological lesions. Low doses of leaf extract also led to a notable decrease in certain indicators. The use of two doses of seed extract resulted in a moderate reduction in ulcer index and histological damage[71].Alternatively, Kogo et al. argue that Plantago major possesses the capability to inhibit H. pylori in laboratory conditions, which is the predominant factor behind digestive system ulcers[72]. It is assumed that phytoconstituents found in Plantago major, such as triterpenoids, phenolic acids, and alkaloids, possess antioxidant properties and safeguard the gastric mucosa against damage.

Ragheb et al. conducted a study on the prevention of gastric ulcers caused by indomethacin (IND) in rats . They used aqueous and ethanol extracts from Plantago major seeds. The researchers induced gastric lesions leading to ulcers by administering a single oral dose of IND (30 mg/kg). To compare the effectiveness, they also administered Pantozol, a reference drug, as well as the aqueous and ethanol extracts (500 mg/kg each), orally 14 days prior to the IND induction. The results of the analysis showed that pretreatment with the aqueous-alcoholic extract reduced gastric lesions, minimized ulceration of the surface epithelium, and maintained the normal histological structure of the gastric mucosa induced by IND. Additionally, both the aqueous and ethanol extracts, along with Pantozol, increased the levels of nitric oxide (NO) and prostaglandin E2 (PGE2) in the gastric tissue. The presence of various compounds in Plantago major, such as tannins, triterpenes, polyunsaturated fatty acids like linoleic acid, and flavonoids, explains the gastroprotective effect of this plant according to the researchers.Due to their ability to safeguard the mucous membrane against acid attack, triterpenes are considered to be the active components responsible for their antiulcer properties. Furthermore, tannins, which are astringent compounds, form a protective film on the ulcer site of the mucous membrane, preventing the absorption of harmful substances[73]. In a separate investigation, the efficacy of an ethanol extract of Plantago major in preventing ulcers was examined using a rat model induced by water stress. The rats were given the Plantago major extract just before being immobilized in the stress cage. After spending 7 hours in the water bath, the rats were sacrificed and their stomachs were collected for analysis. The results showed that both the methanol and aqueous extracts significantly reduced the likelihood of ulceration compared to the control group receiving only the vehicle. The aqueous extract (1 g/kg) and the methanol extract reduced the likelihood of ulceration by 29% and 37%, respectively[74].

The oral administration of methanolic extracts from the leaves of Plantago major at a dosage of 200 mg/kg showed a significant antidiarrheal effect against castor oil-induced diarrhea in rats for a minimum of 4 hours. A higher dosage of 400 mg/kg of methanol extracts from Plantago major leaves taken orally was found to be more effective compared to the 200 mg/kg dosage. Moreover, both the 200 mg/kg and 400 mg/kg doses of methanolic extracts from Plantago major significantly reduced gastrointestinal motility, leading to a decrease in the distance traveled by charcoal meal within the gastrointestinal tract. The higher dosage exhibited slightly greater effectiveness than the

lower dosage. The antidiarrheal properties of Plantago major are attributed to the presence of tannins, flavonoids, and alkaloids. Tannins, in particular, have an antidiarrheal effect by forming protein tannat, which reduce intestinal output[75].

CONCLUSIONS

Plantago major plays an important role in the treatment of various diseases and certain health conditions including diarrhea, ulcers, bacterial infections, inflammation and cancer. Studies have shown that this plant contains several classes of major bioactive compounds such as alkaloids, flavonoids, fatty acids, vitamins, iridoid glycosides, terpenoids and phenolic compounds such as caffeic acid. The therapeutic properties and biological activities of Plantago major are largely attributed to these active chemical constituents. However, further research is required to fully understand the exact mechanisms and actions of the major bioactive compounds responsible for the treatment of certain diseases. Therefore, further research is required using clinical disease models in randomized controlled double-blind studies to evaluate and demonstrate the efficacy of these herbs in the treatment of various health conditions. Furthermore, it is imperative to elucidate the underlying mechanisms of action of this renowned medicinal plant based on the isolated major bioactive compounds through explanatory mechanistic studies using direct biomechanical methods. This will serve to confirm the authenticity of the traditional knowledge associated with this revered herbal remedy.

AUTHOR CONTRIBUTIONS

Conceptualization, Baiken Baimakhanova, Amankeldi Sadanov, Saltanat Orasymbet, Alma Amangeldi, Irina Smirnova, Gul Baimakhanova, Lyudmila Trenozhnikova, Irina Ratnikova; formal analysis and visualization, Zhanat Toxanbayeva, Klara Zhumalina, Aigul Ibragimova, Rabiga Anarbayeva, Zhanar Nurgaliyeva; writing—original draft preparation, Aknur Turgumbayeva and Jamilya Assilbayeva; writing—review and editing, Nesipkul Asylova.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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