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PLANTAGO MAJOR L A CYNOSURE OF MODERN MEDICINE: A REVIEW

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ABSTRACT

In the recent years synthetic drugs have been widely replaced with herbal medicines and plant extracts because of their little undesirable and extensive beneficial effects. Plantago major L. (also known as plantain and way bread) is a member of the Plantaginaceae family. Leaves and seeds of the plant have been widely used in folk medicine for various purposes, including treatment of an extensive range of diseases and disorders such as respiratory complications and digestive system infections. Plantago major L. leaves have been used as a wound healing remedy for centuries in almost all parts of the world and in the treatment of a number of diseases apart from wound healing. P. major contains biologically active compounds such as polysaccharides, Lipids, caffeic acid derivatives, flavonoids, iridoid glycosides and terpenoids. Alkaloids and some organic acids have also been detected. A range of biological activities has been found from plant extracts including wound healing activity, anti-inflammatory, analgesic, antioxidant, weak antibiotic, immune-modulating and antiulcerogenic activity. The medicinal benefits of Plantago major have been acknowledged around the world for hundreds of years. Correspondingly, studies have found that Plantago major is effective as a wound healer, as well as an anti-ulcerative, antidiabetic, antidiarrheal, anti-inflammatory, antinociceptive, antibacterial, and antiviral agent. It also combats fatigue and cancer, is an antioxidant and a free radical scavenger. This paper provides a review of the medicinal benefits and chemical constituents of Plantago major published in journals from year 1953 to 2021 which are available.

KEYWORDS: Plantago major L, plantain, anti-inflammatory, wound healing, caffeic acid derivatives.

INTRODUCTION

Leaves and seeds of Plantago major (normal plantain or more prominent plantain) have been utilized for quite a long time to treat infections identifying with skin, stomach related organs and blood flow like injuries, irritation and hypertension. Either entire or squashed leaves have been utilized to treat for instance consumes and a wide range of wounds to upgrade the mending system, and to quit dying. To treat shallow injuries, it is adequate to apply the juice from the leaves. The two polysaccharides and polyphenols may synergistically affect wound mending and other organic exercises. Polyphenols removed from leaves and seeds of P. major have been accounted for to have bioactive impacts particularly on injury mending, and to have antiulcerogenic, mitigating, anticarcinogenic and antiviral action. Three subspecies have been depicted of P. major, two of which have been exposed to hereditary and phytochemical investigation. Plantago major subsp. major is naturalized nearly all through the world and is for the most part found as an agronomic weed. There has been little work underlining the usage of the bioactive mixtures from P. major in current medication. The primary accentuation of the starting paper is to feature a few factors that might be significant for the use of Plantago major as a restorative spice, giving the degree to the Ph.D. study. This article surveys the customary and recently explored employments of P. significant L. alongside its pharmacological effects.[Zubair.M et al,2008]

Plantago significant L. (Plantago major ssp. Significant L.) is a lasting plant that has a place with the Plantaginaceae family. It can become around 15 cm high, however the size shifts a great deal contingent upon the development territories. The leaves fill in rosettes, and they are applaud to circular with equal venation (5–9). The leaves are glabrous and have a whole or unpredictably dentate edge. The blossoms are little, caramel green on long non-ramified spikes. P. major is pollinated by wind, and a lot of seeds are delivered, up to 20000 for every plant (Fægri, 1970; Tutin et al., 1976). The seeds are minuscule with an applaud shape (0.4–0.8× 0.8–1.5 mm) and a somewhat harsh taste. The seed endosperm has profoundly thickened cellulosic dividers with the cell lumen loaded up with oil and protein. It frames the significant piece of the seeds and encompasses the undeveloped organism totally. The seeds are situated in containers (8–16 for each case) and become tacky in moist climate because of the

enlarging of the polysaccharides present in the seed coat (Qadry, 1963). Thusly the seeds can become appended to creatures and people and accordingly be spread.[Samuelsen et al, 1999]

History

research on pollen has shown that P. major was acquainted with the Nordic nations corresponding to the prologue to the main crude developed fields in the stone age almost 4000 years prior (Jonsson, 1983). P. major was spread by man from Europe all through the world. The Indians named it 'White man's foot' since it was discovered wherever the Europeans had been. This has been adjusted into the variety name Plantago that is from Latin planta, which means underside of the foot. P. major is a plant that many individuals know just as a weed, yet P. major is likewise an old therapeutic plant that has been known for quite a long time. In Scandinavia this plant is generally known for its injury recuperating properties. The normal Norwegian and Swedish name for P. major is groblad signifying 'mending leaves. The conventional utilization of P. major in injury mending is very old. It was portrayed by the Greek doctor Dioscorides in 'De materia medica' in the principal century. The leaves were endorsed for treatment of canine nibbles (Roca-Garcia, 1972). From the 'Vølsuga adventure' it is realized that the Vikings utilized P. significant leaves for wound recuperating (Nielsen, 1969). P. major was likewise depicted in the 12–thirteenth century by the Islamic creator Ibn El Beithar having embraced the information from Greek medication (Fleurentin et al., 1983). Henrik Harpestreng from Denmark wrote in 'Liber Harbarum' that P. major could recuperate all that was destroyed. Blended in with nectar it was suggested on injuries. Overflowed with margarine and eaten, it could recuperate any organ in the human body (Nielsen, 1969).

Distribution of Plantago major

Plantago major was once discovered principally in Europe and Northern and Central Asia, and presently is broadly scattered all through the reality where it is known as normal weed. A concentrate on air dust content was directed and tracked down that this species was available in Denmark, Finland, Iceland, Norway, and Sweden just as their independent locales (the Åland Islands, the Faroe Islands, and Greenland) millennia prior. It was additionally recognized in England in 1672 and has been known in Canada since 1821. Curiously, Plantago major was nicknamed 'white man's impression' by the Indians since it was found in each spot Europeans had been . Plantago major is promptly found in regions with compacted soil like side of the road furthermore ways. In addition, it is treated by the breeze and proliferates principally by seeds, which are hung on the spikes situated over the leaves.


Ethnopharmacological Studies

Table 1.

Part of Plant & Preparation	Usage	Country	References
Whole plant decoction	Healing different kinds of wounds such as (snake bite, intestinal worms and infectious wounds), cold treating, Remedy for diabetes	Colombia, Italy	Watkins et al., 2011. Idolo et al., 2010. Jarald et al., 2008.
Fresh leaf of the plant	Internal inflammations such as cystitis, enteritis and swollen abdomen	Mexico	Watkins et al., 2011.
Internal use of leaves(oral)	Respiratory catarrh; astringent effect; bleeding, skin problems; eye inflammations; also fresh leaves applied to treat livestock hematomas and their skin problems; pruritus.	Colombia, Iran	Rahimi et al., 2010. Mir-heidari, 1994. Zagari, 1992. Neves et al., 2009.
Topical use of leaves (lotion)	Antipyretic, Antitussive, mollient. Blood, rectifier, Kidney pain	Portugal, Italia, Iran	Viegiet al., 2003. Idoloet al., 2010. Zagari, 1992.
Mix of leaf & root	Anti-infective	Iran	Mir-heidari, 1994.Zagari,1992.
Decoction and infusion of fresh leaf	Kidney pain	France	Boulogne et al., 2011.
Decoction of leaves of Plantago major	Remedy for haemorrhagic-diarrheal, Tonic, stimulant	Central America and Mexico	Vera-Kuaet al., 2010.
Seeds of plant	mouth inflammation Eye inflammation	Iran, India	Mir-heidari, 1994.
Oral use of the extract	Remedy for tuberculosis Soothing effect	Iran	Mir-heidari, 1994. Zagari, 1992

Decoction of root Decoction of P. major	Anti-haemorrhagic Remedy for pulmonary disease Antipyretic	Iran	Mir-heidari, 1994. Mir-heidari, 1994.
Decoction of leaf with vinegar	Anti-infective	Iran	Mir-heidari, 1994.
Mixture of the sap of leaves and Honey	Remedy for Ear pain and Bruises	Iran	Mir-heidari, 1994
Extract of the root	Urinary tract infection; toothache	Iran	Mir-heidari, 1994.
Decoction of P. major, Euphorbia schlechtendalii and Melochianodiflora	Stomatitis, asthma, bronchitis, ear ache, antitussive	Iran, Central America and Mexico	Vera-Kua et al., 2010
Brewed leaves and root	Remedy for Ear pain	Iran	Mir-heidari, 1994.
Whole plant Root of plant Aqueous extract	Bruises, Urinary tract, toothache Stomatitis, Asthma, bronchitis, Ear ache	Iran	Zagari, 1992. Zagari, 1992. Zagari, 1992.
Juice of the plant and honey	Anti-tussive	Iran	Zagari, 1992.
Leaves & roots	Sore throat, dry cough, stomach irritation, boils & ulcers Cancer	Balsgard India	Zubair et al (2010) Srivastava et al(2005)
Roots, leaves & seeds	blood purifier, alleviate wet asthma, diarrhoea & swelling of oral mucosa	Austin	Blumental et al (2002)
Roots & leaves	Protection against UV radiation	_____	Riault M A.et al(2006)
leaves	Bee, wasp & nettle stings	India, Iran	Joshi et al(1982), zagari et al (1992)
leaves	Skin abscesses	Hawaii, Norway, turkey	Nagata (1971), Høeg (1974), Yesilada et al. (1995)
Whole plants	Burns	India	Saklani and Jain (1989), Rao (1981), Jain (1991)
Water extract of leaf	Gum inflammation	Philippines	Lim-Sylianco and Shier (1985)
Whole plants	Stomach ache stomach cramps	Argentina, USA Guatemala	Spring (1989), Bustos et al. (1996) Logan (1973)
Juice	Menstrual disorders	USA	Eli Lilly (1898)
Leaf & whole plants	Hypnotic Nervous shock Physical weakness stimulant	Venezuela Haiti Hawaii, India	Morton (1975) Weniger et al. (1986) Nagata (1971) Joshi et al. (1982), Jain (1991)

Chemical Constituents of Plantago Major L.

Plantago major is an important therapeutic plant which contains a variety of bioactive compounds including flavonoids, alkaloids, terpenoids, phenolic compounds (caffeic acid derivatives), iridoid glycosides, fatty acids, polysaccharides and vitamins. These compounds

can be found in nearly all parts of the plant such as the seeds, leaves, flower and roots. The bioactivities of Plantago major are attributed to these chemical constituents.

Flavonoids

The presence of flavonoids (Fig. 1) in Plantago major has been widely reported. The main flavonoids present are flavones, including luteolin(1) and apigenin(2) [Kawashty, et al 1994, Nishibe, et al 1995] . A number of scholars have isolated flavonoids from this plant, including Yuting et al. who isolated baicalein(3), hispidulin(4) and plantaginin(5) [yuting et al,1990] and Sanz et al. who isolated scutallarein(6) [sanz et al,1994]. Kawashty et al. isolated a broad number of flavonoids from Plantago major in Egypt: luteolin 7-glucoside(7), hispidulin 7-glucuronide(8), luteolin 7-diglucoside(9), apigenin 7-glucoside(10), nepetin 7-glucoside and luteolin 6-hydroxy 4′-methoxy 7-galactoside [kawashty et al,1999]. Most recently, Skari et al. found homoplantaginin(11) [skari et al,1999]. The presence and content of selected flavonoids from Plantago major methanol extracts has been confirmed by using LC–MS/MS technique [beara et al,2009]. The whole plant (100 g dried plant) has been extracted in hot water (1000 ml) for one hour. The flavonoids isolated from the aqueous extract were aucubin, baicalein, leuteolin, and baicalin, the glucuronide of baicalein [chiang et al, 2002].

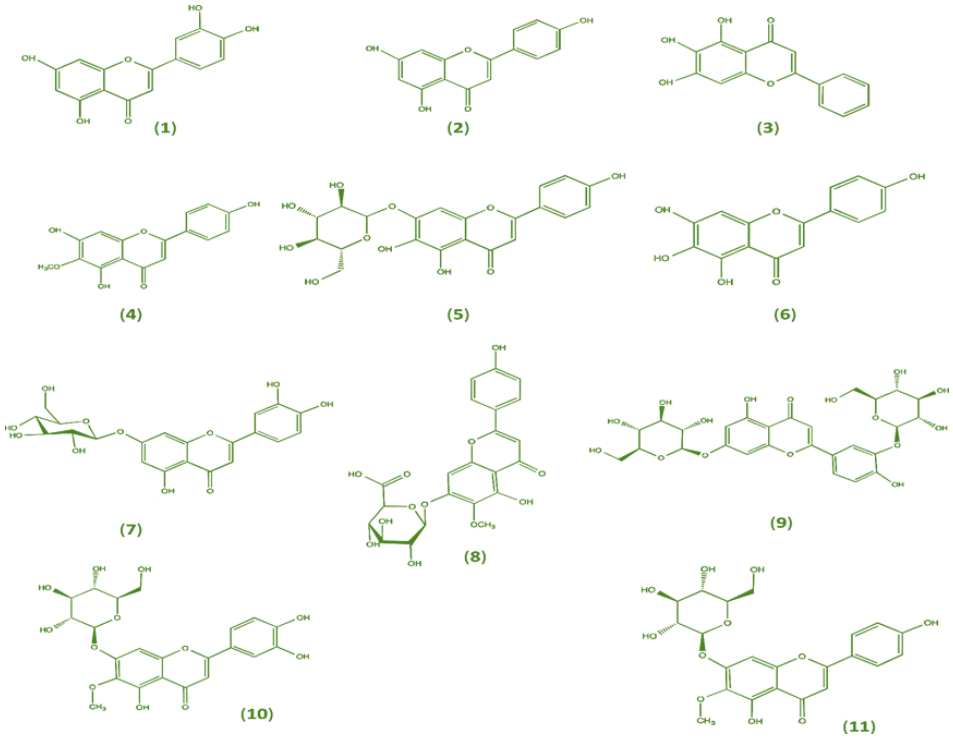

Fig. 1: Flavonoids in Plantago major.

Alkaloids

Furthermore, Schneider isolated the alkaloids indicain(12) and plantagonin(13)from Plantago major, however the process used to extract the chemical constituents from the plant was not stated [scheneider et al,2009] (Fig. 2).

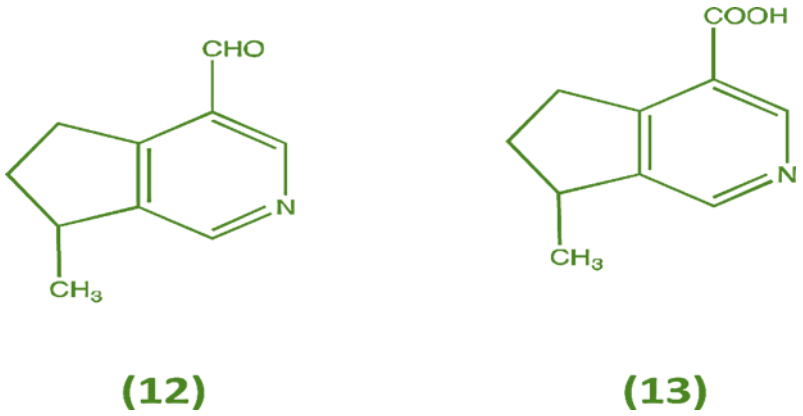

Fig 2: Alkaloids in Plantago major.

Terpenoids

Terpenoids (Fig. 3) have been isolated from the leaves and leaf wax of Plantago major; Pailer and Haschke-Hofmeister isolated loliolid(17) from the leaves [pailer et al, 1969] and Hiltibran et al., 1953 found ursolic acid(14), oleanolic acid(15), sitosterol acid(16) and 18β-glycyrrhetinic from the leaf wax extract in 95% ethanol [hiltibran et al, 1953]. The findings of the latter were supported by Ringbom et al. which also found the same terpenoids from hexane extract [ringbom et al, 1998]. The leaf wax of Plantago major is readily extractable with chloroform, toluene and dichloromethane [bakker et al, 1998].

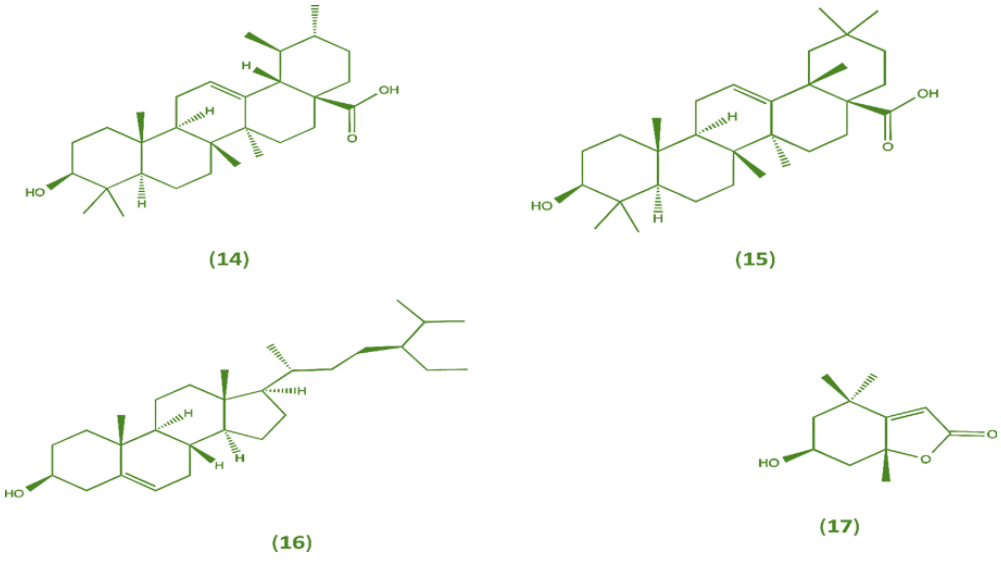

Fig. 3: Terpenoids in Plantago major.

Caffeic acid derivatives

Noro et al. found caffeic acid derivatives (Fig. 4), namely plantamajoside(18) and acteoside(19), also known as verbacoside [noro et al, 1991]. They found that the amount of plantamajoside is higher than acteoside in methanol extract. However, from 80% ethanol extract, the amount of plantamajoside is similar to the amount of acteoside. These findings were also proven by Skari et al. [skari et al, 1999].

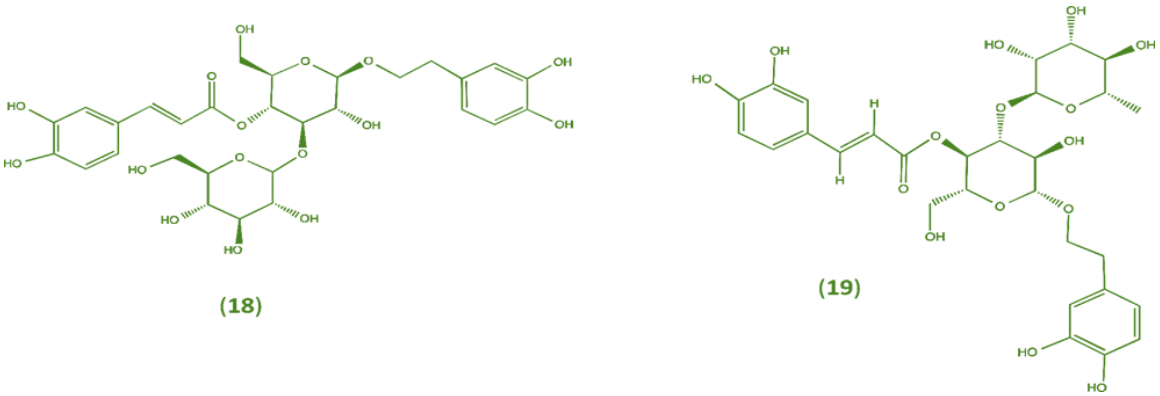

Fig. 4: Caffeic acid derivatives in Plantago major

Iridoid glycosides

The main iridoid glycosides present in Plantago major are aucubin (20), which Long et al. isolated from the leaves [long et al, 1995]. A number of other iridoid glycosides (Fig. 5) have been isolated from other parts of the plant. While Bianco et al. isolated asperuloside (21) from the flowers [bianco et al, 1984], a number of studies have shown the presence of iridoid glycosides in the aerial parts of Plantago major. These include the study by Handjieva et al. which found majoroside(22) in the aerial part of Plantago major when extracted in n-buthanol [handjieva et al, 1991], the study by Taskova et al. which isolated both 10-hydroxymajoroside(23) and 10-acetoxymajoroside(24) [taskova et al, 1999], and the study by Murai et al. that added catapol(25), gardoside(26), geniposidic acid(27) and melittoside (28) to the substances extracted from the aerial part [murai et al, 1995].

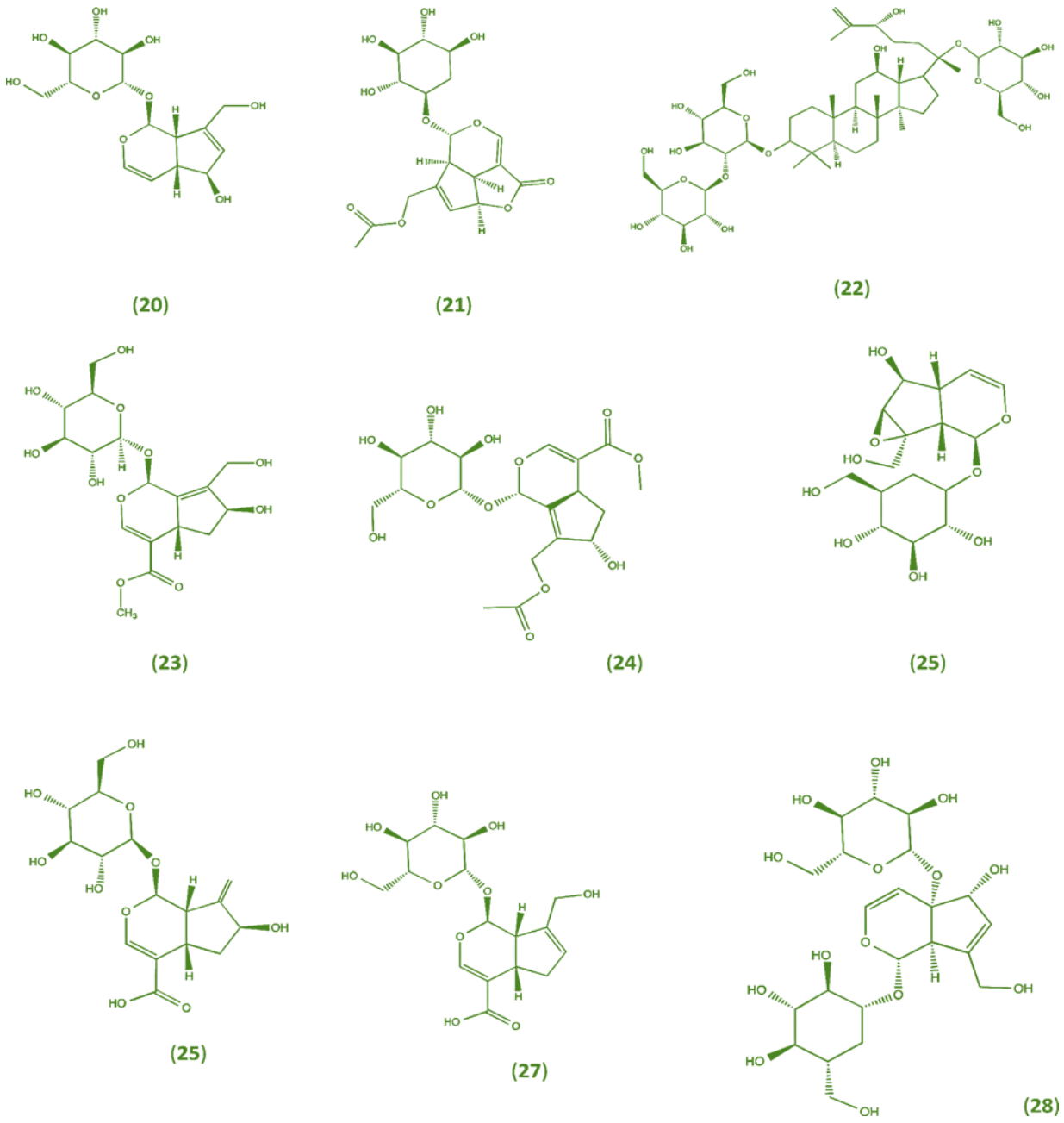

Fig. 5: Iridoid glycosides in Plantago major.

Fatty acids

Fatty acids (Fig. 6) have also been isolated from the seeds and leaves of Plantago major. Pailer and Haschke-Hofmeister isolated lignoceric acid (29) from the seeds [pailer et al, 1969]. Besides, the presence of palmitic acid(30), stearic acid(31), oleic acid(32), linoleic acid(33) and linolenic acid(34) was confirmed in Plantago major by using gas-liquid chromatography as well as permanganate oxidation and spectrophotometric techniques [Ahmed et al, 1968]. Likewise, myristic acid(35) was isolated from the seeds by Swiatek et al. [swiatek et al, 1980]. Ahmad et al. found a minor occurring component of fatty acids in

Plantago major seed oil extracted in petrol which is 9- hydroxy-cis-11-octadecenoic acid [Ahmad et al,1980]. In addition, Guil et al. isolated arachidic acid(36) and behenic acid(37) from the leaves [guil et al,1997].

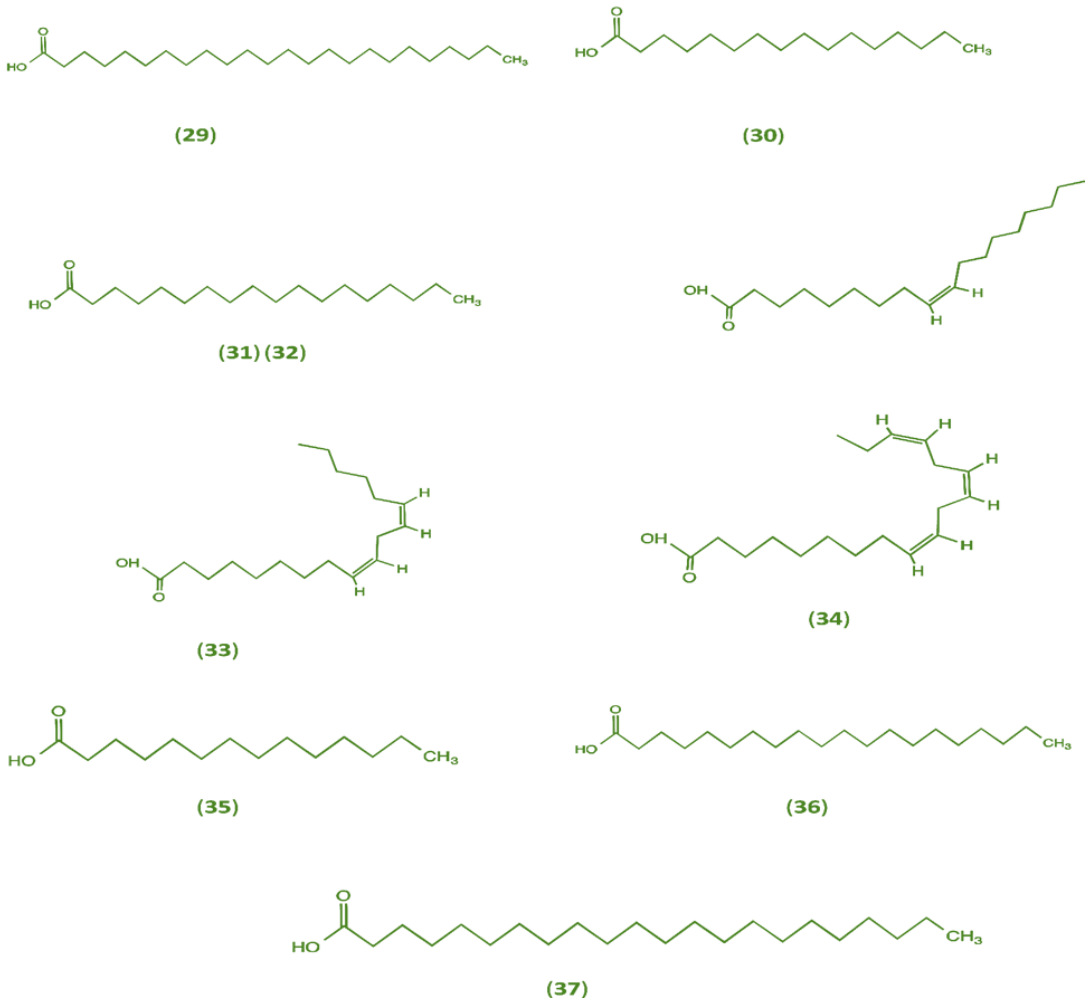

Fig. 6: Fatty acids in Plantago major.

Polysaccharides

Ahmed et al. extracted polysaccharides from the seeds of Plantago major. They also isolated xylose(38), arabinose(39), galacturonic acid (40) in cold water extract and found galactose(41) from hot water extract . This is supported by Gorin and Samuelsen et al. [gorin et al, 1966; samuelsen et al,1999]. Additionally, Samuelsen et al. isolated glucuronic acid(42), rhamnose (43), galactose and glucose(44) from 50 °C water extract (Fig. 7). Earlier studies by Samuelsen et al. isolated a highly esterified pectin polysaccharide, PMII. These findings were followed by continued examination leading to Samuelsen et al. wherein an anti-complementary acidic arabinogalactan, PMIa composed of arabinose, galactose, rhamnose, and galacturonic acid was isolated from 50 °C water extract.

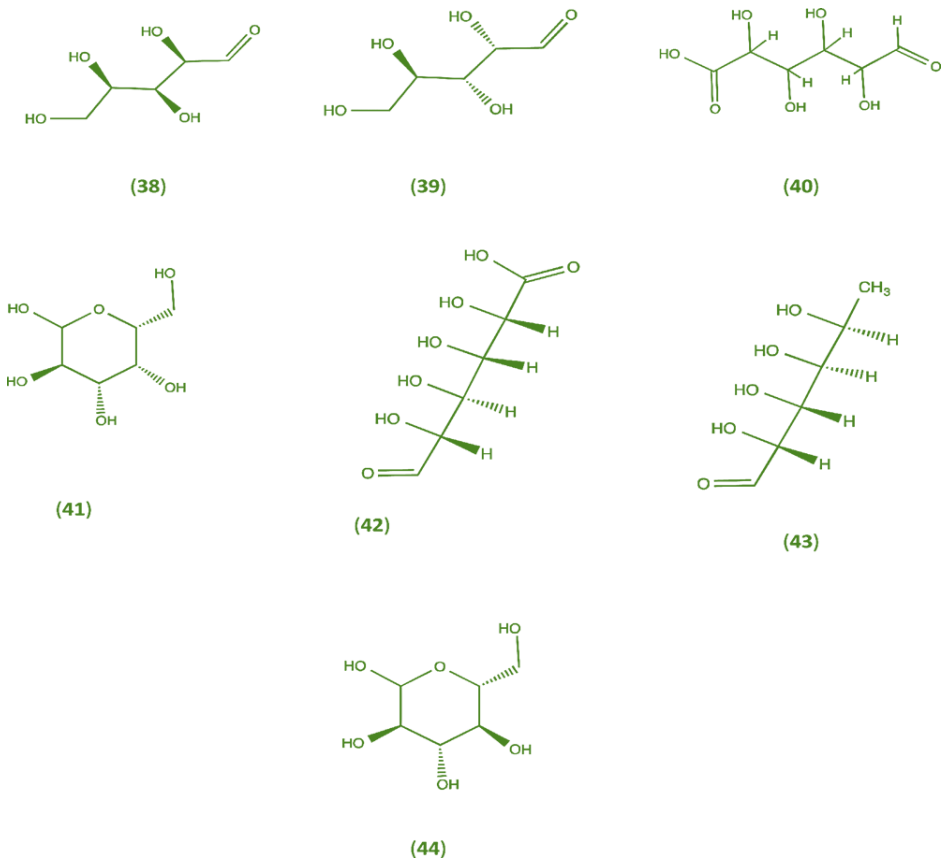

Fig. 7: Polysaccharides in Plantago major.

Vitamins

Additionally, Plantago major is a good source of vitamin C and carotenoids. This is confirmed in the study by Zenni and Ogzwewalla where ascorbic acid(45) and β-carotene (provitamin A) were isolated (46). (Fig. 8).

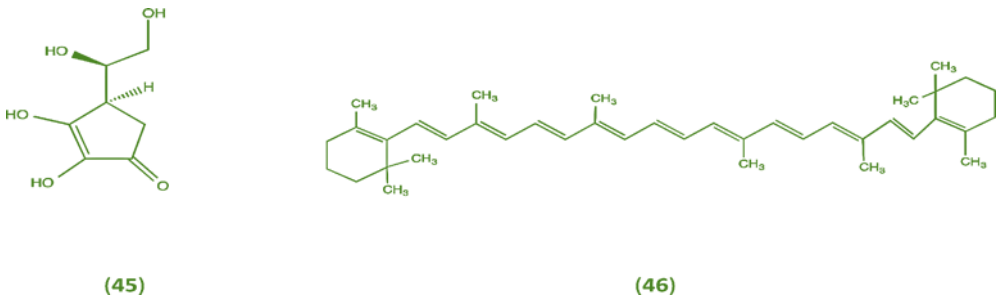

Fig. 8: Vitamins in Plantago major.

Pharmacological Uses of Plantago major L.

For the past few decades, a growing number of people have been turning to alternative forms of medicine in response to disillusionment with the modern medical system. Many botanicals, especially herbal, products have gained popularity for the treatment of ailments and diseases

such as the common cold, wounds, hypertension, inflammation, viral infections, depression, insomnia, and even cancer (Blumenthal et al., 2006).

Plantago major has been used for different purposes in folk medicine all over the world. The biological activities of P. major leaves and seeds are wound healing, anti- inflammatory, analgesic, antioxidant, weakly antibiotic, immuno-modulating, antiulcerogenic, antihypertensive (Samuelsen, 2000; Nyunt et al., 2007), antileukemia, anticarcinogenic, antiviral, cell-mediated immunity modulating (Chiang et al., 2003), anticandidal (Holetz et al., 2002), antitumor (Yaremenko, 1990), antinociceptive (reducing sensitivity to painful stimuli) (Atta & El-Sooud, 2004) and reduction of immune-depressive effects of anticancer drugs (Shepeleva & Nezhinskaya, 2008). This plant has traditionally been used in e.g., China for numerous diseases varying from cold to hepatitis (Chiang et al., 2002). Plantago major has also been used to neutralize poisons internally and externally (Lithander, 1992).

Antiulcerogenic activities

Plantago major leaves produce an antiulcerogenic effect against alcohol- and aspirin-induced gastric ulcer (Atta et al., 2005; Than et al., 1996). The leaves have been used as an antiulcerogenic in Turkey (Yesilada et al., 1993). A combined methanol and water extract inhibited ulcer formation by 40% relative to the control group, while a water extract inhibited ulcer formation by 37% and a methanol extract by 29%. However, when compared to other Turkish plants with antiulcerogenic properties, P. major leaves did not constitute one of the most active remedies against ulcer (Yesilada et al., 1993).

Anti-inflammatory and immuno-modulating activities

Extracts of P. major enhance the production of nitric oxide and tumor necrosis factor-alpha (TNF-∝), which protect the host against the development of infection and tumors (Nathan & Hibbs, 1991). The main effect of nitric oxide is to inhibit the synthesis of DNA and ATP. Tumor necrosis factor-alpha (TNF-∝) is one of the essential mediators of host inflammatory responses in natural immunity. The regulation of immunity parameters induced by P. major may be clinically relevant in numerous disease processes including tuberculosis, AIDS and cancer (Flores et al., 2000).

Antiviral activities

Certain pure compounds of P. major possess antiviral activity. Chemical compounds found in extracts of P. major (mainly phenolic compounds) exhibit potent anti-herpes virus and anti-

adeno virus activities (Chiang et al., 2002). Extracts of P. major also showed antimicrobial activity against yeasts (Stanisavljevic et al., 2008). Plantago major leaves extract exhibited weak antibacterial activity in vitro, but the extract has an effect on infected wounds in vivo. While the application of antibiotics on infected wounds had no effect, treatment with a P. major extract removed the infections and healed the wounds (Samuelsen, 2000). Leaves have also traditionally been used for the treatment of skin infections and for bacterial infections (Holetz et al., 2002).

Wound healing

Plantago major and wound healing Leaves of the common weed P. major have been used, and are still being used as a wound healing remedy in almost all parts of the world in folk medicine. Greek physicians described the traditional use of P. major in wound healing already in the first century A.D. (Samuelsen et al., 1999). Either whole or crushed leaves are used to treat for example burns and other kinds of wounds to enhance the healing process, and to stop bleeding. The leaves of P. major have thus been prescribed for the treatment of wounds caused by for example dog bites (Roca-Garcia, 1972). Normally, it is sufficient to apply only the juice from leaves to heal superficial wounds (Brondegaard, 1987). In Scandinavian countries, P. major is well-known for its wound healing properties. The Norwegian and Swedish people call this plant ‘groblad’ which can be translated as ‘healing leaves’ (Samuelsen, 2000). The extract of P. major contains a mixture of antioxidants; those antioxidants may constitute one of the mechanisms that contribute to its wound healing properties (Yokozawa et al., 1997).

Antidiabetic

The most recent study conducted by Abdulghani et al. found that Plantago major has a potent antidiabetic activity in streptozocin-induced diabetic rats. Plantago major methanol extract also has a hypoglycemic activity in oral glucose tolerance test (OGTT). OGTT of Plantago major extracted in methanol was studied on overnight fasted normal rats. The concentration for the extract was 500 and 1000 mg/kg per oral dose. The results showed that maximum glucose tolerance in Plantago major extracts after 30 min glucose administration was observed in the higher dose (1000 mg/kg) and minimum glucose tolerance was observed in the lower dose (500 mg/kg). For the effect of Plantago major on blood glucose level of STZ-induced diabetic rats, continuous post-treatment for 14 days with the 1000 mg/kg of Plantago major showed potential hypoglycemic activity. The mechanism of reducing blood glucose

levels in diabetic rats may be caused by enhancing the control of glycemic mechanisms from remnant pancreatic-cells in diabetic rats. However, the exact chemical constituents responsible for the antidiabetic effect have not been stated. Only some studies claimed that the hypoglycemic effect of Plantago major is due to the presence of flavonoids, sterols and sugars in the dichloromethane extract and tannins in the hexane extract.(Samuelsen et al, 2000)

Antidiarrheal

Plantago major is one of the traditional medicinal plants used in management of diarrhea . However, there have been very few of scientific studies to confirm the efficacy and activity of Plantago major as treatment of diarrhea. A study conducted by Atta & Mouneir studied the effect of Plantago major leaves methanol extracts on diarrhea induced by castor oil, as well as the gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits. A significant antidiarrheal effect of Plantago major methanol extracts against castor oil-induced diarrhea in rats was achieved by 200 mg/kg orally for at least 4 h. The Plantago major methanol extracts given at a dose 400 mg/ kg administered orally showed greater potency than the 200 mg/kg oral dosage. Besides, at doses of 200 and 400 mg/kg, Plantago major methanol extracts also significantly decreased the gastrointestinal motility by significantly decreasing the distance travelled by the charcoal meal in the gastrointestinal tracts. The higher dose was slightly more effective than the lower one. Plantago major ethanol extracts in a concentration of 1.6 mg/mL and produced a transient stimulation followed by an inhibition of the duodenal motility. A higher dose produced rapid relaxation. The initial stimulant effect may be attributed to the presence of irritant substances and may explain the contradiction in the folkloric use of this plant. The antidiarrheal effect of Plantago major could be attributed to their content of tannins, flavonoids and alkaloids. Tripathi and Mukherjee et al. suggested that tannins showed antidiarrheal action by forming protein tannate which reduces intestinal secretion. (Shoba et al, 2001)

Anticancer

A study conducted by Ozaslan et al. tested the anticancer activity of Plantago major against Ehrlich ascites carcinoma in mice. Plantago major leaves were extracted with hot water. Then, the extract was administered orally for ten days in three different concentrations (25 µg/mL, 50 µg/mL and 75 µg/mL). The effect of the extract as an anticancer agent was

determined by using pathological investigations. The intestines and the colons of the animals were stained with haematoxileneosin for histological examination. The results from pathological findings found that Plantago major leaves aqueous showed inhibitory effect against Ehrlich ascites carcinoma. The inhibition decreased due to increasing the extract concentration. The most effective concentration was found to be 25 µg/mL dose when compared to the other experimental doses. However, some ingredients of Plantago major have shown toxicity or adverse side effects on lower gastrointestinal tissues, so that the acceptable concentration is from 25 to 50 µg/mL. These promising results propose that Plantago major could be an effective agent for cancer prevention. Another study conducted by Gálvez et al. studied Plantago major extract with methanol to evaluate the cytotoxic activity against three human cancer cell lines, human melanoma (UACC-62), human breast adenocarcinoma (MCF-7) and human renal adenocarcinoma (TK-10) cell lines, using the sulphorhodamine B (SRB) assay in vitro. The results found that Plantago major methanol extract showed a cytotoxic effect on the melanoma (UACC-62) and breast adenocarcinoma (MCF-7) tumor cell lines. The cytotoxic activity of the extract is dependent on the concentration administered. Nevertheless, the extract showed no cytotoxic activity against renal adenocarcinoma (TK-10) cells. Flavonoids, flavone and luteolin in Plantago major are thought to be the bioactive compounds responsible for the cytotoxic activity present in the extract. Although, the exact mechanism responsible for the cytotoxic activity of luteolin-7-O-β-glucoside is not thoroughly understood, it is suggested that topoisomerase-mediated DNA damage is the involved mechanism. Meanwhile, Luteolin-7-O-β-glucoside acts as a potent DNA topoisomerase I poison. (Anne et al, 2000)

Antinociceptive

A study was conducted by Atta & Abo El-Sooud to examine the activity of Plantago major as antinociceptive. Herein, Plantago major leaves and seeds were extracted separately in methanol. Then, the extracts were studied on mice in an acetic acid-induced writhing and tail flick test. The results found that the seed extract with the oral dose of 400 mg/kg showed significant antinociceptive activity against acetic acid-induced writhes with a protection of 62.3%. The protection rate of the leaf extract at the same doses was decreased by only 48.8%. The plant extract of 200 mg/kg (smaller dose) showed no antinociceptive activity on the pain stimulated by acetic acid. The leaf extract of 400 mg/kg showed significant prolonged effect in the latency to the response of the tail towards heat stimulation, while the smaller dose showed no effect. More needs to be known about the chemical constituents responsible for

activity of Plantago major as antinociceptive and the exact mechanism involved in this activity.(Stanisvejelic et al, 2008)

Anti-fatigue

Fatigue is a symptom that is marked by the feeling of tiredness due to vigorous physical activity and usually can lead to muscular pain. A study was conducted by Mao-ye & Li-guo that examined the anti-fatigue activity of Plantago major. Herein, the seeds were extracted in ethanol, and the effect of the extract was studied on forty-eight male mice. The anti-fatigue activity of Plantago major seed ethanol extract was determined by using forced swimming test and biochemical assays of blood of the mice. The results showed that the extract prolonged swimming time by increasing glycogen in the tissue (as an energy source) and reducing lactic acid in the blood as well as serum urea nitrogen. (Glycogen acts as source of energy while lactic acid is one of the causes of fatigue.) Therefore, it is proposed that Plantago major seed ethanol extract possesses anti-fatigue activity so that it can be used to enhance endurance exercise capacity. However, more evidence is required to determine the exact mechanisms involved in Plantago major as anti-fatigue agent and the bioactive compounds which are responsible for the effect [Mao et al, 2011].

Antibacterial

A study was conducted by Hetland et al. on mice to test the anti-bacterial activity of Plantago major. They found that the soluble pectin polysaccharide (PMII) isolated from Plantago major leaves had defensive effects against systemic Streptococcus pneumoniae serotype 6B. In another study, Velasco et al. found that antibacterial activities of Plantago major leaves and seeds in aqueous, methanol, chloroform and hexane extracts were positive on Escherichia coli, Bacillus subtilis and Candida albicans cultures in different ranges. Besides, a study conducted by Sharifa et al. tested the whole plant aqueous, methanol and ethanol extracts of Plantago major on Bacillus subtilis, Staphylococcus aureus, Candida albicans, Candida tropicalis and Escherichia coli. The results showed that the methanol and ethanol extracts posed bactericidal activity against both Gram positive and Gram-negative bacteria at concentrations of 100–200 mg/mL, but there was no activity on yeast. This was proved by using microscopy observation. Under electron microscope, it showed the rupture of Gram-positive bacteria cell walls and the formation of blebs on Gram negative bacteria. (Stanisvejelic et al, 2008)

Hypotensive effect

In Burma, the infusion of P. major is taken orally to produce a fall in blood pressure. Lipophilic compounds were removed from a P.major water extract containing high molecular weight compounds and injected at doses of 15, 20 and 25 mg/kg into anaesthetized dogs. The dose response effect was not very consistent, and there were large individual variations in the response. The study was of a preliminary nature and without any statistics (Kyi et al., 1971). In another study normotensive rats were given a P. major extract intravenously. The extract was lyophilized 70% ethanol extracts dissolved in a physiological solution. Maximum effect was obtained 0.2 min after injection and lasted for 0.5 min. The reduction in arterial blood pressure was not significant (Schmeda-Hirschmann et al., 1992).

Diuretic effect

In Guatemala the leaves are used as a diuretic agent. In a screening study of 67 plants a 10% decoction of the dried leaves of P. major was tested on rats. The decoction was administered by a nasogastric catheter at a dose of 1 g/kg. It had an intermediate diuretic activity; urinary output increased by 108944% after 6 h. Hydrochlorothiazide increased urinary output by 286938 % (Ca´ceres et al., 1987a). In Vietnam, the extracts of the seeds of P. major taken orally are said to have a diuretic effect. A possible diuretic activity was tested on healthy human volunteers in a placebo controlled double-blind crossover model. No significant diuretic effect through increased urinary output or sodium excretion was registered in this study (Doan et al., 1992).

Immune Enhancing Effects

Endotoxin-free methanol extracts of P.major leaves, in the absence of IFN-gamma or LPS, increased production of nitric oxide (NO) and TNF-alpha by rat peritoneal macrophages and stimulated lymphocyte proliferation in a dose-dependent fashion.NO and TNF-alpha production by untreated macrophages was negligible. The regulation of immune parameters by the extract of P. major may be helpful in treatment of numerous diseases (Gomez- Floreset al., 2000).For instance, activated macrophages produce mediators of cytotoxicity such as nitric oxide and tumor necrosis factor-alpha (TNF-α), kinds of lymphokines which protect the host against the development of tumors and infections by organisms such as Cryptococcus, Schistosoma, Leishmania, Francisella, Listeria and Mycobacteria (Nathan and Hibbs, 1991;Hibbset al., 1988.)

Cytotoxic Activity

The cytotoxic activity of P. major methanol extract on human transformed cells: HCT-15 (colon carcinoma), SQC-UISO (cervical carcinoma), OVCAR (ovary carcinoma) and KB (nasopharynx carcinoma) cultured in RPMI-1640 medium has been also evaluated, in vitro. The extract (1µg/mL) was cytotoxic against the UISO and OVCAR cell lines but stimulated the proliferation of KB cells. (Velasco- Lezamaet al., 2006). Ina screening of anticancer effect of forty- five Russian plants, used in folk medicine, a parallel in vitro study was carried out using Mouse leukemia cells (L1210).Methanolic extract of P.major had 80-100% cytotoxic effect (Goun et al. , 2002). Similar work was done in Vietnamese and seventy-seven medicinal plants tested for their antiproliferative activities against human HT-1080 fibro sarcoma cells. P. major was not among the most active plants (Ueda, 2002). Studies on the efficacy of hot water extract of P. major leaves on Ehrlich ascites tumors in male mice were also undertaken. The extract was most effective at a dose of 25µg/ml against the tumor cells. The results show that P. major could be proposed as an effective agent in cancer prevention (Ozaslan et al., 2009).

Hematopoietic Effects

Aqueous and methanolic extracts of the aerial parts of P. major were added to bone marrow and spleen cell medium to investigate their hematopoietic potential. The results were as following: Bone marrow cultures: The aqueous and methanolic extracts stimulated cell proliferation in similar manner using a dose of 0.4and 0.2 gr/mL. Maximum hematopoietic activity was observed at0.1 and 0.05 g/mL doses of the methanolic extract(Velasco-Lezama et al., 2005). Spleen Cultures: Doses of 0.4 and 0.2 g/mL of the aqueous extract increased the cell population by 3.30- and 4.40-fold, respectively. The same concentrations of the methanolic extract increased the population by 6.25- and 4.28-fold, respectively. The increase was significantly higher in spleen cultures than in bone marrow cultures(Velasco-Lezamaet al., 2005).This effect of P. major on spleen as a hematopoietic organ is thought to be the second mechanism through which the plant exerts hematopoietic effects. (Samuelsen, 2000)

Antipyretic Activity

Indonesian people use plantain (Plantago major L.) leaves as antipyretics empirically. The purpose of this study was to determine the antipyretic activity of the plantain leaf extract. Antipyretic activity test was conducted to Swiss Webster mice, which induced by yeast with paracetamol as a positive control. The mice were fasted overnight but provided with water ad

libitum before the experiments. The mice were divided into five groups of five animals each. Basal rectal temperatures were measured with a 3 cm digital thermometer. The mice were administered 20% yeast suspension per subcutaneous, after 4 h, rectal temperatures of the hyperpyrexic mice were measured. Antipyretic dose was referring to anti-inflammatory dose of plantain leaf extract, i.e., 25 mg/kg BW. The plantain leaves extracts (0.35, 0.70, and 1.40 mg/20 g BW), saline, and paracetamol (1.30 mg/20 g BW) were administered to the mice orally. The rectal temperatures were measured every 1 h up to 4 h. The last temperature was compared with pre-treatment temperature, i.e., 4 h after yeast suspension injection. Phytochemical screening was shown that plantain leaves contain flavonoids, phenols, tannins, steroids, and triterpenoids. Plantain leaf extract (0.35, 0.70, and 1.40 mg/20 BW) had antipyretic activity. The antipyretic activity of the plantain leaf extract was dose-dependent.(nyi mekar et al,2019)

Anthelmintic Effect

The aim of the present study was to investigate the anthelmintic activity of Plantago major L. (plantain) in Swiss albino mice naturally infected with Aspiculuris tetraptera. Methanolic and aqueous extracts of P. major leaves were evaluated for their in vivo anthelmintic activity. The mice were housed in the standard cages with pellet food (Van Animal Feed Factory, Van-Turkey) and water libitum, in the regulated light and temperature conditioned room (22±2 □C, 12 h of dark/light cycle. The stool samples of 100 mice were examined for detecting naturally infected animals using centrifugal flotation technique in saturated zinc sulphate solution. Thirty-nine infected mice (both sexes) were randomly divided into four groups. Th animals were fasted for 4 h before treatment. The mice received 250 µl of 2% Tween 80 orally every day during 7 days in Group I (control). Ivermectin as reference drug was administered by intramuscular injection at a dose 0.2 mg/kg in Group II. Mice were orally received 250 µl of aqueous extract (100 µl /10g mouse) in Group III and 250µl of methanol extract (5 mg/10 g mouse) in Group IV daily for 7 days. The mice fecal samples from the mice were examined on day 1 (pre-treatment), day of the treatment and for 7 days post-treatment on a daily basis using centrifugal flotation technique in saturated zinc sulphate. The mice were euthanized on the 8th day pos-treatment. Gastrointestinal tract was removed and washed with sterile saline solution. The contents were examined under a stereomicroscope to count and identify A. tetraptera. The results showed that methanolic tract of P. major possessed only a slight anthelmintic activity. The results showed that methanolic extract of

P.major possessed only a slight anthelmintic activity (27.62%). In contrast, aqueous extract exhibited more potent anthelmintic effect (39.25%)[Ali Nazarizadeh et al,2012]

External Poison Detoxification

Heavy metals such as lead are toxic for humans and animals and can cause various diseases. P. major L. was grown hydroponically in a water medium supplemented with concentrations of lead ion under different duration times and temperature regimes to evaluate the efficacy of lead detoxification by different parts of the plant (roots, stems, leaves and whole plant). Roots of the plant showed the highest removal rate of lead than other parts (Akram et al., 2007). As a concern in public health, the use of agents which can purify water and environment from heavy metals is necessary. Therefore, P. major can act as a bio filter for the removal of Pb cations from water.

CONCLUSION

Plantago major plays an important role in the management of certain ailments and diseases such as ulcers, bacterial and viral infections, diarrhea, pain, inflammation and cancer. This plant has been shown to contain several classes of essential biologically active compounds; flavonoids, alkaloids, iridoid glycoside, fatty acids, vitamins, phenolic compounds (caffeic acid) and terpenoids. The biological activities and medicinal properties of Plantago major mainly depend on the activities of the responsible active chemical constituents. However, this field still needs more study to determine the exact mechanisms and the main bioactive compound activity responsible for treating certain diseases. This review presents up to date findings about P. major, based on the most recent pharmacological studies that support its traditional uses. The leaf extract is reliably nontoxic with strong hepato-protective and wound healing activities, however data about the responsible constituents is little and further research is required. Anti-fatigue effect of the plant is also one of the newly investigated effects of P. major that needs to be further investigated.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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