Therapeutic Uses and Pharmacological Properties of *Plantago major* L. and its Active Constituents

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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 affections. It has been also used in wound healing and as an antiinflammatory, antimicrobial and antitumor agent. Moreover, plantain contains ingredients which can neutralize internal and external poisons. Recent studies have also shown its anti-fatigue properties. Phytochemical analysis of *P. major* extract has indicated that this plant contains a wide range of chemicals such as polysaccharides, lipids (saturated and non-saturated), amino acids (essential and non-essential), caffeic acid derivatives, flavonoids, iridoidal glycosides and terpenoids, which have the potential to exert different biological effects. Phenols (ferulic acid), flavonoids and tannins have the highest amount in *Plantago* leaves. The present review describes the traditional uses and recent findings (Since 2000 till date) about the pharmacological effects of *Plantago major* L.

**KEY WORDS:** *Plantago major* L.; Plantain; Ferulic acid; Plantaginaceae; Wound healing.

**INTRODUCTION**

*Plantago major* L. is a member species of the Plantaginacea family. It is an herbaceous perennial with a rosette of leaves15-30 cm in diameter. Each leaf is oval, 5-20 cm long and 4-9 cm broad, rarely up to 30 cm long and 17 cm broad, with an acute apex and a smooth margin; there are five to nine conspicuous veins. The seeds are quite small with an ovate shape (0.4–0.8, 0.8–1.5 mm) and a slightly bitter taste (Samuelsen, 2000). The flowers are small, greenish-brown with purple stamens, produced in a dense spike 5-15 cm long on top of a stem 13-15 cm tall (rarely to 70 cm tall) (Fig. 1). It grows better than the most of other plants in compacted soils, and is abundant beside paths, roadsides, and other areas with frequent soil compaction. It is also common in grasslands and as a weed in crops. It is wind-pollinated, and propagates primarily by seeds, which are held on the long, narrow spikes which rise well above the foliage (Blamey and Grey-Wilson, 1989). The plant is native to the most of Europe and Northern and Central Asia, and is widely naturalized elsewhere in the world, where it is a common weed. *P. major* was spread by man from Europe throughout the world 4000 years ago (Jonsson, 1983). The Indians named it ‘White man’s footprint’ because it was found everywhere the Europeans had been. This has been adapted into the genus name *Plantago* that is from Latin *planta*, meaning sole of the foot. Plantain was also used in the time of Shakespeare and was also named in the piece "Romeo and Juliet" Act I, Scene II of the period 1592 to 1609 (Samuelsen, 2000). The plant is well known in many countries (especially in Iran) and has been used extensively in folk medicine because of its various beneficial effects (table 1). Native Americans carried powdered roots of *P. major* as protection against snake bite or to ward off snake. As traditional Chinese medicine, *P. major* has long been used for treating viral related disease from colds and influenza to viral hepatitis (Chiang et al., 2002). Studies carried out on the chemical composition of the plant by various methods (for example: simple, rapid and accurate high-performance liquid chromatography) show extensive chemical components (tables 2). Studies conducted by Jamilah et al. (2012) on the chemical composition of various extract (petroleum ether, methanol, ethyl acetate, n-butanol and aqueous) from *P. major* leaves showed that all of them have phenol groups in their extract while having different variation of organic acid groups, flavonoids and terpenoids. *P. major* leaves contain 0.07% of oleic acid and 0.22% of ursolic acid which are two major terpenoids of the plant (Tarvainen et al., 2000; Samuelsen, 2000) (Fig. 2). These compounds exist in almost all parts of the plant. Bioactivity of *P. major* leaves and other herbal preparations which contain these secondary metabolites is attributed to these chemical constituents (Liu, 1995). It has been shown in one study that ursolic acid from *P. major* is a Selective Inhibitor of Cyclooxygenase-2 catalyzed prostaglandin biosynthesis; hence, anti-inflammatory effect of the plant is possibly via this mechanism. So many other studies are found in the literature on the pharmacological effects of these important chemicals. Leaves of the plant are rich
sources of essential fatty acids (18:2ω6 and 18:3ω3) and also of carotenes (Guil-Guerrero and Rodríguez-García, 1999). Ferulic acid which has high amounts in plantago (especially in seeds) is a hydroxyl cinnamic acid, a type of organic compound (Mohamed et al., 2011). It is an abundant phenolic phytochemical found among plant cell wall components (Fig. 2). Ferulic acid, like many natural phenols, is an antioxidant in vitro. Recently in vitro and animal model studies have suggested that ferulic acid may have direct antitumor activity against breast and liver cancer (Valentão et al., 2001; Pierre et al., 2006). Dosage range is 3-5 g of the powdered herb 1-3 times daily but the most common dose as infusion is 150 ml (one cupful) 3-4 time a day. All in all, the plant is safe and there are no limitations and drug contraindications reported so far; however, enough care should be taken regarding usage of the plant in pregnant women (Zagari, 1992).

This article reviews the traditional and newly investigated uses of _P. major_ L. along with its pharmacological effects.

**Figure 1.** _P. major_ L. (leaves and seeds).

**Figure 2.** Chemical structures of UA, OA, and FA.

<table>
<thead>
<tr>
<th>Name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ursolic acid</td>
<td><img src="image" alt="Ursolic acid" /></td>
</tr>
<tr>
<td>Oleanolic acid</td>
<td><img src="image" alt="Oleanolic acid" /></td>
</tr>
<tr>
<td>Ferulic acid</td>
<td><img src="image" alt="Ferulic acid" /></td>
</tr>
</tbody>
</table>
Table 1. Traditional uses of Plantago major L. in different countries especially Iran.

<table>
<thead>
<tr>
<th>Part of plant and preparation</th>
<th>Usage</th>
<th>Country</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole plant decoction</td>
<td>Healing different kinds of wounds such as (snake bite, intestinal worms and infectious wounds), cold treating, Remedy for diabetes</td>
<td>Colombia, Italia</td>
<td>Watkins et al., 2011.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Idolo et al., 2010.</td>
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<td></td>
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<td>Jarald et al., 2008.</td>
</tr>
<tr>
<td>Fresh leaf of the plant</td>
<td>Internal inflammations such as cystitis, enteritis and swollen abdomen</td>
<td>Mexico</td>
<td>Watkins et al., 2011.</td>
</tr>
<tr>
<td>Internal use of leaves(oral)</td>
<td>Respiratory catarrh; astringent effect; bleeding, skin problems; eye inflammations; also fresh leaves applied to treat livestock hematomas and their skin problems; purritus.</td>
<td>Colombia, Iran,</td>
<td>Rahimi et al., 2010.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neves et al., 2009.</td>
</tr>
<tr>
<td>Mix of Leaf and Root</td>
<td>Anti-infective</td>
<td>Iran</td>
<td>Mir-heidari, 1994.</td>
</tr>
<tr>
<td>Decoction and infusion of fresh leaf</td>
<td>Kidney pain</td>
<td>France</td>
<td>Boulponge et al., 2011.</td>
</tr>
<tr>
<td>Decoction of leaves of Plantago major</td>
<td>Remedy for hemorrhagic-diarrheal, Tonic, stimulant</td>
<td>Central America and Mexico</td>
<td>Vera-Kua et al., 2010.</td>
</tr>
<tr>
<td>Seeds of plant</td>
<td>mouth inflammation</td>
<td>Iran, India</td>
<td>Mir-heidari, 1994.</td>
</tr>
<tr>
<td>Mixture of the sap of leaves and honey</td>
<td>Remedy for Ear pain and Bruises</td>
<td>Iran</td>
<td>Mir-heidari, 1994.</td>
</tr>
<tr>
<td>Extract of the root</td>
<td>Urinary tract infection; toothache</td>
<td>Iran</td>
<td>Mir-heidari, 1994.</td>
</tr>
<tr>
<td>Decoction of P. major</td>
<td>Stomatitis, asthma, bronchitis, ear ache, anti-tussive</td>
<td>Iran, Central America and Mexico</td>
<td>Vera-Kua et al., 2010.</td>
</tr>
<tr>
<td>Euphorbia schlechtendalii</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melochianodiflora</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqueous extract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juice of the plant and honey</td>
<td>Anti-tussive</td>
<td>Iran</td>
<td>Zagari, 1992.</td>
</tr>
</tbody>
</table>

Table 2. Biological active compounds of P. major L. leaves and seeds (mg/g on dry weight basis) (Mohamed et al., 2011)

<table>
<thead>
<tr>
<th>Constituent</th>
<th>P. major L. leaves</th>
<th>P. major L. seeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total phenol (mg gallic/g)</td>
<td>13.05±0.10</td>
<td>7.43±0.07</td>
</tr>
<tr>
<td>Total flavonoid (mg Quercetin/g)</td>
<td>6.41±0.04</td>
<td>3.0±0.03</td>
</tr>
<tr>
<td>Tannins (mg Catechine /g)</td>
<td>5.63±0.06</td>
<td>2.43±0.03</td>
</tr>
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</table>

PHARMACOLOGICAL EFFECTS

Immune Enhancing Effects
Endotoxin-free methanol extracts of P.major leaves, in the absence of IFN-γ or LPS, increased production of nitric oxide (NO) and TNF-α by rat peritoneal macrophages and stimulated lymphocyte proliferation in a dose-dependent fashion. NO and TNF-α 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, Flores et al., 2000). For instance, activated macrophages produce mediators of cytotoxicity such as nitric oxide and tumour 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; Hibbs et al., 1988.)

Hepatoprotective Effects
Hepatic disorders have grown in recent years and are the cause of billions of deaths all over the world (Williams, 2006). In one study the hepatoprotective activity of P. major seed extract in an experimental rat model of carbon tetrachloride (CCl4) induced hepatotoxicity was evaluated. Control, CCl4 and reference groups received isotonic saline solution, CCl4 and silybinin, respectively. P. major groups were injected CCl4 (0.8 ml/kg) and the extract at doses of 10, 20 and 25 mg/kg, respectively for seven days. After sacrificing animals on
operations were recorded. 

*et al.*

... of 

... doses (200 and 400 mg/kg).

... total acidity. It was also observed that

*et al.*

on. The leaf extract at the 

... (2010)

... assay for determination of free radical 

(Kumpulainen and Salonen, 1999; Cook and Samman, 1996). Free radical scavengers are any compounds that 

induce such analgesic effect (Atta *et al.*, 2005). Further research is, however, needed to determine what compounds are responsible for the Antidiarrheal effect.

**Antinociceptive Effects**

Methanolic extracts of leaves and seeds separately were studied on acetic acid-induced writhing and tail-flick test in mice, to investigate their anti-nociceptive effects. Oral administration of 400 mg/kg of the seed extract showed significant nociceptive activity against acetic acid-induced writhes with a protection of <82.3%. However, at same doses the protection rate of the leaf extract was only 48.8%. These values were compared to 80.5% for the standard dipyrone (50 mg/kg) which is the synthetic drug. The smaller dose (200 mg/kg) of the plant extract did not protect animals from painful acetic acid stimulation. The leaf extract at the dose of 400 mg/kg produced significant increase in the latency to the tail response to thermal stimulation. Mild or no effect was observed at the small dose. No detail study has been carried out so far, about the ingredients that can induce such analgesic effect (Atta and Abo EL-Sooud, 2004).

**Antioxidant and Free Radical Scavenging Effects**

Free radicals contribute to more than one hundred disorders in humans including atherosclerosis, arthritis, and ischemia and reperfusion injury of many tissues, central nervous system injury, gastritis, cancer and AIDS (Kumpulainen and Salonen, 1999; Cook and Samman, 1996). Free radical scavengers are any compounds that react with free radicals in a biological system, thus reducing free radical-induced damage and protecting against the indirect effects of free radicals. Ethanolic, hot and cold water extracts of *P. major* leaves and seeds were assayed for determination of free radical-scavenging activity using stable 1, 1-diphenyl-2-picryl hydrazyl radical (DPPH)*in vitro*. Highest antioxidant activity was observed with the ethanolic leaf extract even at a low concentration of 20 ppm (78% activity). In the same concentration the ethanolic seed extract had really low activity (25%). The antioxidant activity of both mentioned extracts increased in a concentration-dependent fashion, up to 60 ppm. The rate of antioxidant activity for both extracts was so close in a concentration of 100 ppm. Hot and cold water extracts of *Plantago* leaves were more effective than the seed extract. It was also observed that, the ethanolic extracts were more active than the hot and cold water extracts of the samples under

<table>
<thead>
<tr>
<th>Extract Type</th>
<th>Ethanolic</th>
<th>Hot Water</th>
<th>Cold Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf Extract</td>
<td>25%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Seed Extract</td>
<td>0%</td>
<td>10%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Anticancer Effect
In one study, methanolic extracts from seven Plantago species used in traditional medicine among them P. major, were evaluated for cytotoxic activity against three human cancer cell lines: the human renal adenocarcinoma (TK-10), the human breast adenocarcinoma (MCF-7) and the human melanoma (UACC-62) cell lines using the sulforhodamine B (SRB) assay in vitro. P. major and the other six Plantago species showed cytotoxic activity on the breast adenocarcinoma (MCF-7) and melanoma (UACC-62) tumoral cell lines in a concentration-dependent manner at the recommended NCI (USA) doses. None of the extracts, with the exception of Plantagobellardii (GI50 = 86µg/ml), showed cytotoxic activity against renal adenocarcinoma (TK-10) cells. It is thought that the cytotoxic activity depends basically on flavonoids, flavone and luteolin present in the extract (Gálvez et al., 2003).

Another in vitro study was carried out on Plantagoethanolic, hot and cold water extracts of leaves and seeds separately. A dose dependent inhibition was observed for all tested extracts. The ethanolic extract of P. major leaves had the greatest effect on tumor cell growth (Dead 74% ± 0.35) follow by its hot water extract of the leaves (Dead 54.6% ± 1.21) (Mohamed et al., 2011). Luteolin-7-O-β-glucoside, the major flavonoid found in all species of Plantago, is known to be the responsible agent for the anti-cancer activity of the plant. The precise mechanism responsible for the cytotoxic activity of luteolin-7-O-β-glucoside is not thoroughly understood, however it is thought that topoisomerase-mediated DNA damage is the involved mechanism. Luteolin-7-O-β-glucoside acts as a potent DNA topoisomerase I poison as well as its aglyconluteolin. (Gálvez et al., 2003)

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-Lezama et 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 (Gounet 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-Lezama et 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.

Wound Healing Effects
Use of P. major in wound healing has a very long history. Greek physicians described its wound healing activity in the first century and the leaves were used as a remedy for dog bites (Samuelsen, 2000; Roca-Garcia, 1972). It is also well known for its wound healing property in Scandinavia. The common
Norwegian and Swedish name for *P. major* is *groblad* meaning "healing leaves" (Samuelsen, 2000). Hence, the plant’s Water (fresh and dried leaves) and ethanol-based leaves extracts were studied using scratch assay with the oral epithelial cells *in vitro* to validate it’s ancient traditional use. Concentrations of 0.1, 1 and 10mg/ml of the plant extracts added to cell culture media to observe cell proliferation/migration. Apart from the highest concentration of 10mg/mL, ethanol-based extracts had the most beneficial effect, followed by water extracts of fresh leaves, ethanol plus water extracts of dried leaves and, finally, water extracts of dried leaves. Maybe polyphenols are the responsible compounds for wound healing. Phytochemical analysis showed that high levels of plantamajoside and other polyphenols exist in ethanol-based extract compare with other tested extracts. Other involved substances are polysaccharides (Zubaitet al., 2012). In a whole, a mixture of antioxidants are said to be effective the wound healing process of the plant (Yokozaaet al., 1997).

**Anti-inflammatory Effects**

Inflammation is a complex event linked to tissue damage whether by bacteria, physical trauma, chemical, heat or any other phenomenon and inflammatory response is the critical protective reaction to these kinds of injuries remarked by redness, fever, oedema (swelling) and pain of involved tissue (Morais Lima et al., 2011; Levine and Reichling, 1999). Methanol extract of *P. major* L. seeds was assayed on carrageenan-induced rat paw oedema to evaluate the anti-inflammatory activity. *P. major* showed anti-inflammatory effect in a dose dependent fashion, but it was not more effective than indomethacin (reference drug). Median effective dose (ED$_{50}$)was determined to be 7.507 mg/kg (Türel et al., 2009). It could be thought that inhibition of COX-2-catalyzed prostaglandin biosynthesis may be the involved mechanism for the anti-inflammatory action (Ringbom et al., 1998). Furthermore, flavonoid derivatives which are high in *P. major* are other responsible constituents present in the plant (Middleton et al., 2000; Havsteen, 2002).

**Anti-fatigue Effects**

Fatigue is a condition which is marked by the feeling of exhaustion due to heavy physical activity and generally can cause muscular pain. Ethanol extract of *P. major* seeds were studied on forty eight male mice to determine its effect on physical strength. Forced swimming test and biochemical assays of blood were carried out and marker factors were registered. According to the results, the extract increased swimming time by increasing tissue glycogen (as energy source) and decreasing serum urea nitrogen and blood lactate (as fatigue agents). Therefore, it is suggested that the extract possesses anti-fatigue effects and can improve endurance exercise capacity (Mao-yeand Li-guo, 2011). There is little evidence about this effect of *P. major* and the precise mechanisms responsible, therefore more studies are required to be conducted in this regard.

**Pest Organism Managing Properties**

An ethno medicinal survey was applied in the city of Pelotas, Brazil, with professionals and patients in the Unified Health System (SUS), showed that the most frequent symptom reported for herbal drug usage was infection (55.3%), and tanc$_c$, agem (*P. major*) was the plant mentioned to be the most often used to treat this problem (37.3%) (Dias Oliveira et al., 2012).

In order to evaluate efficacy of mayan (a large family of American Indian) traditional potions in treating of infectious bowel disease *P. major* L. and thirty-eight other plants were studied *in vitro* using bacteria including Escherichia coli, Klebsiella pneumonia, Shigella flexneri, Salmonella typhi and protozoa such as Entamoeba histolytica and Giardia lamblia. Mixture of Melochia nodiflora, Euphorbia schlechtendali and *P. major* was active against Giardia lamblia (IC$_{50}$ = 21.78 µg/ml). The efficacy of this formulation for both protozoa was comparable with positive control (metronidazole). Moreover, another formula composed of four herbs, Trema micrantha, Euphorbia schlechtendali, Diphyysa carthagenensis and *P. major* showed good activity against Giardia lamblia with an of IC$_{50}$ = 12.71 µg/ml. Both formulae of *P. major* were so close to the efficacy index of metronidazole against Giardia lamblia and Entamoeba histolytica. These two formulae showed no considerable effect against bacteria (Vera-Ku et al., 2010). In another study, extracts of 13 Brazilian medicinal plants were screened for their antimicrobial activity against bacteria and yeasts. Leaves extract of *P. major* presented some degrees of antibacterial activity and was not among the most active plants (Holetz et al., 2002).

Similar works were carried out by Saltn Çiçoğlu and Alanlar (2003), but the results were adverse. According to this study, when compared with the standard antibiotics, *P. major* extract was found to have good activities against *E. coli* and *S. aureus*. However, *P. major* did not show any activity against *B. subtilis*. Further details are available in table 3.
Antibacterial effects of acetone and ethyl alcohol extracts of *P. major* L. leaves were studied, using macro dilution liquid (tube) method. Both extracts were tested for nine bacteria species (*Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Salmonella enteritidis*). The ethyl alcohol extract was only effective against *E. coli* and *B. cereus*, but acetone extract was effective on all selected bacteria species at different concentrations (Metiner et al., 2012).

Previously, parallel studies were carried out by Sharifa et al. (2009). The whole plant methanolic, ethanolic and aqueous extracts of *P. major* were tested on *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans* and *Candida tropicalis*. The methanolic and ethanolic extracts at concentrations of 100-200 mg/ml showed bactericidal activity against both Gram positive and Gram negative bacteria tested. Electron microscopic observation demonstrated collapse in Gram positive bacteria cell wall and blebs formations on Gram negative bacteria. No activity was observed against yeast by any of the extracts.

In one study, the aqueous, methanol, chloroform and hexane extracts of the aerial parts (leaves and seeds) of *P. major* were added to *Escherichia coli*, *Bacillus subtilis* and *Candida albicans* cultures and antibacterial activities were observed in different ranges (Velasco-Lezama et al., 2005).

The antibacterial effect of a soluble pectin polysaccharide (PMII), isolated from the leaves of *P. major* was examined against systemic *Streptococcus pneumoniae* serotype 6B using animal model of mice. It was observed that PMII can have prophylactically protective effects (Hetland et al., 2000).

Antiviral activity of aqueous extract and pure compounds of *P. major* was assayed using herpes viruses (HSV-1, HSV-2) and adeno virus species (ADV-3, ADV-8, ADV-11) The aqueous extract possessed only a slight anti-herpes activity. In contrast, the pure compounds were active against selected viruses. Among them caffeic acid exhibited the strongest activity against HSV-1 (EC$_{50}$=15.3 g/ml, SI=671), HSV-2 (EC$_{50}$=87.3 g/ml, SI=118) and ADV-3 (EC$_{50}$=14.2 g/ml, SI=727), whereas chlorogenic acid possessed the strongest anti-ADV-11 (EC$_{50}$=13.3 g/ml, SI=301) activity. The potency relates to the presence of hydroxyl group in the chemical structure. Compounds that contained hydroxyl groups at the R$_1$ and R$_2$positions (caffeic acid, chlorogenic acid) were more potent than the compounds containing one hydroxyl group at the R$_1$ position (ferulicacid, p-coumaric acid). Results suggest the use of these compounds as a remedy for infections caused by these two viruses (Chiang et al., 2002). Results are in contrast with those reported by McCutcheon et al. (1995).

According to a pilot study by Ali et al. (2004), interview with 492 informants from 13 villages indicated that macerated, dried leaves of *P. major* can be used as a remedy for malaria. Screening study must be carried out to determine antimalarial activity of *P. major* and also to isolate and identify the active compounds, which may be regarded as future promising phytotherapeutics in the treatment of malaria.

### Table 3

<table>
<thead>
<tr>
<th>plantago major</th>
<th>E.coli</th>
<th>P.aeruginosa</th>
<th>B. subtilis</th>
<th>S. aureus</th>
<th>C.albicans</th>
<th>C.galabrata</th>
<th>C. krusei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (25 fig)</td>
<td>11</td>
<td>10</td>
<td>-</td>
<td>13</td>
<td>7</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Fluconazole (25 mg)</td>
<td>N.T.</td>
<td>N.T.</td>
<td>13</td>
<td>15</td>
<td>N.T.</td>
<td>N.T.</td>
<td>N.T.</td>
</tr>
</tbody>
</table>

N.T.: not tested. (-): no inhibition zone; Ampicillin and Fluconazole are positive control.

Antigenotoxic Effects

Anti genotoxic property of the sap from greater plantain (*P. major* L.) was investigated using two bacterial test systems (SOS chromo test and Rec assay). *P. major* showed sizable anti genotoxic effect in none of the test systems. This means that *P. major* extract cannot be used as a dis mutagen (prevent DNA damage) or bio anti mutagen (repair of damaged DNA) agent (Karamova et al., 2010).

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.
Toxicity Evaluation

In recent years synthetic drugs have been widely replaced with herbal medicines in both developed and non-developed countries (Verma and Singh, 2010). Some possible reasons are: the development of new diseases with severe complications for which there is still no appropriate treatment and the belief that herbal medicine have less or no side effects. In addition to the belief that herbal medicine is naturally superior to synthetic drugs, economically plants are cheaper sources of remedies (Capasso et al., 2000). Apart from advantages of herbal drugs, their safety has not been confirmed scientifically and there are still some risks in their usage. Presence of toxic constituents (pyrrolizidine alkaloids, saponins, cyanogenetic glycosides, etc.) is the main risk in this regard. Evaluation of toxicity of chemical and natural products isolated from 20 plants was carried out using *Artemia salina* L. (Artemiidae) as *in vitro* test and Swiss albino mice as *in vivo* test. LC50 and LD50 for *P. major* were determined as 4.74 (µg/mL) and 182.54 (mg/kg), respectively. *P. major* was not among the most toxic plants (Parra et al., 2001). Analysis of the anti-nutritional and toxic components showed low content of oxalic acid (6736 mg) and erucic (3.45%) in *P. major* extract (Guil et al., 1997). Laboratory studies have reported uterine stimulatory activity of *P. major*; therefore it should be only used under medical supervision during pregnancy (Shipochliev, 1981). In conclusion, *P. major* is a safe plant, with low content of toxic factors, however some adverse reactions such as: nausea, vomiting, diarrhea, anorexia, bloating, hyper-sensitivity and dermatitis may arise after treatment with the plant. Life threatening anaphylaxis may occur in more serious cases, which is observed in high dose usage.

Conclusion and Further Scope

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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