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Plantago: A plant for internists

Mahmoud Bahmani¹, Mahmoud Mirhosseini², Sheida Fasihzadeh², Paridokht Karimian³
and Mahmoud Rafieian-Kopaei^{2*}

¹Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

²Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

³Dept. of Pathology, Shahrekord University of Medical Sciences, Shahrekord, Iran

ABSTRACT

Plantago belongs to the Plantaginaceae family, with two species known as Plantago ovate Forsk and Plantago psyllium L. In herbal medicine Plantago husk powder is commonly as laxative. Application of Psyllium husk as a hydrocolloid fiber has been almost confirmed in treatment of diabetes type 2. Recent researches on Plantago indicate the effect of its fibers on reducing cholesterol, blood lipid and blood glucose of people with diabetes and reducing the risk of colon cancer. There are no side effects reported for patients under treatment with Plantago fiber. Regarding the fact that Psyllium is widely used, different aspects of it is discussed in the present study.

Keywords: *Plantago psyllium*, Mucilage, Esfarzeh, Diabetes mellitus

INTRODUCTION

Plants have been the basis for prevention and treatment of a wide variety of disorders through human history [1-4]. Hence, there are valuable sources of knowledge about these plants and their uses [5-12]. Traditional medicine is still widely practiced today and scientifically examined [12-28]. Modern medicine has recognized herbalism as a form of alternative or complementary medicine. Although herbalism is not strictly based on evidence gathered using the scientific methods, however, most of scientific experiments have confirmed the traditional knowledge [29-38]. Therefore, traditional and scientific knowledge are both important for preparation of new drugs. Modern medicine makes use of plant-derived compounds mostly based on evidence-tested knowledge [39-46].

Plantago psyllium and Plantago ovata are two of the most important of these plants with a wide variety of uses. Nowadays, Plantago has been highly and widely used in industry and medicine field in some countries around the world. Recently, Plantago psyllium plantation has been listed among the first fifteen medicinal plants which are given a high economical priority [47]. In chine, psyllium has been used for its benefits in treatment of urea, cough, diabetes, high blood pressure, hot flushes, constipation, edema and dysuria. It also has been used in treatment of eye problems and diseases such as dry eye, cataract, eye redness, inflammation, light sensitivity and lung disease (by producing mucus and sneezing). The whole herb is beneficial for heart muscle and poisoning and it is also locally useful for burnss and abscesses treatment. In the Eastern India, Psyllium seeds are used to treat dysentery, urinary problems, gonorrhoea, fever, and gastrointestinal malfunction. Additionally, it founds to be helpful in treating cold, cough and other breathing difficulties, particularly for young children. Furthermore, powdered seed is mixed with water to treat rheumatism, gout and skin irritation [48].

In Iran, psyllium seeds have been applied to treat dysentery and biliary tract disorders. A poultice of crushed psyllium seeds is very beneficial for all kinds of inflammations because mucilage produced when psyllium is soaked in water which then has softening effect. An infusion of the psyllium seeds is used for the treatment of urethritis and related disorders in affected individuals. Moreover, the seedhusks are highly prized as a herbal laxative [49].

Phytology

The genus *Plantago* belongs to the family Plantaginaceae and comprises about 250 species. *Psyllium* is cultivated primarily in India and Pakistan, but it has also been planted all around the world. Two important species are *Plantago Psyllium* L. and *Plantago ovate* Forsk called 'Esfarze' in Persian. It has been widely used in industry and medicine [51].

***Plantago ovate* Forsk.**

Plantago ovata is an annual hairy herb with short stem (5–8 cm tall), almost curved erect. The linear-lanceolate leaves grow opposite. *Psyllium* has brownish green flowers gathered in hemispherical, cylindrical oval clusters. It has ovate-spherical, glandular hairy spikes. Bracts are ovate-lanceolate to lanceolate, acute or acuminate with wide scarious margin below. Sepals are hairy and glandular, areequal, oblanceolate. Seeds are narrow-elliptic, reddish-brown. Flowering occurs between March to June. In Iran, this herb can be found in the northern (Ghazvin, Manjil, Roudbar and Firouzkooh), western (Hamedan and Mehran), southern (Bandar Abbas, Meime, between Boushehr and Shiraz, and also Kerman) and eastern (Sarchah, Khorasan) parts. This genus is commonly known as Blond *Psyllium*, Spogel, Ispaghula and Indian *Plantago* [52].

***Plantago Psyllium* L.**

Plantago psyllium is an annual and hairy herb grows between 15 to 40 cm. The arisen stem is erect with 1-7cm internodes by that are covered very short wooly hairs. Leaves grow opposite which occur linear-lanceolate, entire or with a few teeth, not hairy or glandular-hairy. *Psyllium* flowers are very tiny and white-greenish in color; they have 1-1.2 cm cylindrical spikes which give them a peculiar shape. Peduncle is a bit larger than leaves with 2-4 cm length. The calyx with a short narrow beak is thin has 4.5-5 mm length. Corolla has narrow ovate and acutelobes. Seeds are narrow-elliptic, reddish-brown, shining. Flowering happens between April to June. In Iran, this herb has been distributed in the northern and north-eastern (Roudbar, Manjil, Dashte Gorgan and Khorasan), western (Kordestan, Ilam and Mehran), central (Isfahan), southern (Khuzestan, Shoush, Fars, Boushehr, Bam, Bandar Abbas) parts [53].

Ecology

Species of *Plantago* known as *psyllium* are native to the Eastern Mediterranean region responding well to cool, moderate weather. So in warm climate regions like India and Australia seedling emerging is delayed until the cooler months of the year, namely October, November, March and April. It grows best on light, well drained, sandy loam soil with a pH between 7 and 8. It also demands high amounts of potassium and low levels of nitrogen. Heavy-textured soils with poor drainage and salt-affected soils are not suitable for *psyllium* cultivation [54].

The nutrient requirements of the crop are low as 25 kg/ha nitrogen and 25 kg/ha potassium can meet plant demands in the last tillage. Generally, 30 days after planting, when top dressing, 25 kg nitrogen fertilizers are applied over the soil and *Psyllium* surface. Increased amount of nitrogen fertilizer application will lead to improved inflammation factor. During almost all its life cycle, *Psyllium* needs dry and cool climate. Climate condition can even greatly affect the seed yield at the latest stage of plant growth and moderate rainfall can be harmful. During plant development stage, low night temperature can increase plant germination and also seed yield whereas high night temperature can cause to decreased plant development and the number of flowers [55].

A very important environmental requirement of this crop is clear, sunny and dry weather preceding harvest. *Plantago* which has a moderate water requirement is given 5 to 6 light irrigations. Its root system has a well-developed tap root. This herb is relatively resistant to drought and salinity [56].

Cultivation

P. psyllium and *P. ovate* are annual growing herbs that the general manner of propagation of these plants is from the seeds. However, an efficient method for in vitro micro-propagation (culture) of *P. psyllium* has been reported by some researchers. *P. psyllium* seeds lose their potency easily, so that fresh ones should be cultivated [54].

Since *Plantago* seeds are tiny and light, the seed is usually mixed with sufficient quantity of fine sand or sieved farmyard manure before sowing. Therefore, these seeds are properly broadcasted and the seed yield is likely increased. After spreading, seeds are swept softly with a broom to cover them with some soil. However, broom should be swept solely in one direction, to prevent deep burial of the seed. Maximum germination occurs at a seeding depth of 0.5 cm. Depending on the plantation (from traditional to mechanized agricultural system), seeds are broadcast at 4 to 10 kg/hectare [57].

The crop should be harvested 1 to 2 times during the plant growth. *P. ovata* has a short life span (90 to 120 days) which this period depends mainly on the climatic condition. The crop becomes ready for harvest when the spike color is

changed. For mature crop, seeds will release by your fingers easily. The average seed yield of *P. ovata* is about 1 tonne/hectare (1000 lb/acre) [57].

Phytochemistry

Plantain constituents include acids (eg, benzoic, caffeic, chlorogenic, cinnamic, p-coumaric, fumaric, salicylic, ursolic, vanillic, ascorbic), alkaloids (boschniakine) and amino acids (eg, alanine, asparagine, histidine, lysine). An analysis of some *P. psyllium* seeds has identified a variety of sugar and polysaccharide components of the seed mucilage including galactose, glucose, xylose, arabinose, and rhamnose. Additionally, galacturonic acid, planteose, plant iobiose, sucrose, fructose have been found in *P. ovata* seed. The mucilage of the psyllium seed's husk constitutes 20% to 30%. Seed mucilage of *P. ovata* was identified to have better suspending and emulsifying power as compared with tragacanth and methylcellulose. Psyllium seed powder, not husk powder, contains a slight amount of the oil enriched of free fatty acids, sterols and hydrocarbons in non-edible oil seed. Oil free portion contains a high amount of protein with lots of albumin and lysine and average methionine levels. Leaf mucilage has been reported to include polysaccharides containing rhamnose, L-arabinose, mannose, galactose and dextrose [58].

Industrial application of mucilage

Mucilage has been widely used in industry and pharmacology due to its valuable characteristics such as stabilizing suspending and emulsifying power.

In pharmaceutical formulations, it has been used to make emulsions and suspensions, produce insoluble powders, oils and resins as an emulsifying agent, and constitute granules, troche and laxatives as an adhesive. However, mucilage is mainly used as a necessary component in pharmaceutical preparations for its properties. This hydrophilic polymer shows a wide range of applications such as binding, emulsifying, gelling, suspending and stabilizing agents [54].

Mucilages have been recognized as the best pharmaceutical polysaccharide hydrocolloids, since they have compatibility with other plant derived hydrocolloids as well as starch, sugar and protein. Mucilages found to be resistant to low pH as compared with most of the polysaccharide hydrocolloids, so that they are used at acidic pH. Some of the polysaccharide hydrocolloids have been used to prepare low-calorie foods. These compounds are applied for providing gels, flavors and drinks. They can delay bread deterioration when used with carrageenan and alginate. Mucilage is also used to thicken and stabilize dessert [54].

They are widely applied in cosmetics (for providing hair and skin care products), textiles, paper-making, printing inks, waxes and army industries (water proofing explosives).

Petroleum industry is one of the major consumers of mucilage. This compound is used as a lubricant added to the soil and water surrounding the digging rigs. Also some of these substances are added to the water pumped to the earth to inhibit the pressure of oil and gas and stable and slow down water movement. Pure water can quickly penetrate the rocks on the ground and prevent water flooding [55].

Pharmacology

Various therapeutic effects reported for *Plantago* are as following:

Gastrointestinal effects

Natural or synthesized dietary fibers have given lots of attentions as a supplement to avoid intestinal diseases where *P. ovata* seed and husk are widely used for this purpose. The fiber therapy with this plant fiber enhances stool transit in the intestine. It, however, does not alter colonic transit or anorectal function. Usually treatment period with *P. ovata* should be more than one week. *Plantago* seed delays time of emptying the stomach and decreases the colony transfer. *P. ovata* seeds increase weight of the feces and decrease time of intestinal transfer in the healthy individuals and also decrease content of fecal water in patients [59].

It increases the small intestine length and colon, mucous thickness of the end part of narrow intestine and height of piles, the excretion of 2, 6-aminopimelic acid, feces and its concentration that indicates bacterial mass, excreted bile acids and the capacity to maintain fecal water in seed layer diet, decreases the excreted protein concentration, the activity of mucous enzymes in duodenum. Protective activity of polyhydrozidic combinations extracted from has been also reported [57, 60].

Hypolipidemic and antidiabetic effects

Antioxidants are usually effective in reduction of lipid [61-67] and glucose [68-71]. Using diet containing high fiber, especially soluble fibers in order to control serum cholesterol in individuals having diabetes is also usual [72-75].

About some fibers like water aqueous fiber solution and gel fiber like Tragacanth it has been determined that as sugar solution or in combination with food stuff leads to decrease in the glucose but effects of *p. ovata* certainly have not been specified [76]. *P. psyllium* seed was able to decrease LDL and increase HDL-C. Eating plantago seed decreases concentration of total cholesterol and LDL-C. Also concentration of glucose through the day and after launch in the plantago group was reported [77]. Using plantago seed decreased absorption of glucose while no significant decrease was seen in amount of insulin. HBAIC, C-peptide, 24-hour urinary glucose and also Fructosamine decreased when using fiber diet that fructosamine decrease was just significant. Plantago causes significant decrease statistically in the total cholesterol and ureic acid. Seed layer decreases the total cholesterol, LDL-C, triglyceride and LDL-C/HDL-C and increases HDL-C [78].

Glycemic index is useful to control diabetes [79, 80]. Study of plantago effect was conducted on 18 insulin-independent diabetic patients. Plantago was eaten by patients two times a day. Glucose decreased after the breakfast and dinner 14 and 20 percent respectively. Also concentration of serum insulin after the breakfast was 12% less than control. To observe the second food effect, plantago or placebo was not eaten after the launch however glucose was decreased 31% after launch. The total cholesterol decreases after treatment with seed (81). The amount of biliary acids in feces of the healthy persons did not change while it increased about 25% after using seed but cholesterol amount did not change. This result can indicate that plantago seed may has more effect than seed layer to decrease serum cholesterol, but biliary acids in intestine has been compensated through increase in reabsorption in the colon [81].

Fibers of plantago seed leads to significant decrease in the breakfast glucose of the diabetic rats. Also increase in the insulin level in rats after eating plantago can indicate harmful effect of these fibers for diabetic people. No significant change is also seen in stomach emptying, but adding 30g of unsaturated fats and 3g of propionate sodium decreases concentrations of insulin, glucose and stomach emptying [82]. An experiment was conducted on pigs. The control group received 10g/100g cellulose and 2/5g/100g of guar gum and two experiment groups ate 10g/100g or 7/5g/100g of plantago seed layer that with cellulose the amount of the used fiber in both groups was increased to 12/5g/100g. In the study, no dosage-response relation was observed but triglyceride plasma and LDL-C in the plantago group ws respectively 34% and 23% lower than the control group. Lecithin cholesterol acetyl transferase(LCAT) and protein carrying cholesterol was affected by plantago diet. In the control group, activity of LCAT and CETP respectively was 100% and 36% higher than plantago group. The total and free cholesterol of liver was not affected by the plantago but concentration of cholstrol in the plantago group was 50% less than the control group. Activity of the HMGCoA enzyme reductase that is enzyme limiting the cholesterol synthesis speed was increased in the plantago group up to 37%. Also activity of the 7-alpha hydroxylase enzyme that regulates catabolism of the cholesterol to biliary acids was in the plantago group 32%higher than the control group. Results show that layer of the seed impose its hypolipidemic effect through affecting absorption of biliary acids and changing liver metabolism of the liver [83].

Effect on colon cancer

Study conducted on 424 persons showed that using *P. ovata* seed with aspirin and also exercising has major role in decreasing risk of developing colon cancer. It also was shown that edible using of *P. ovata* seed regulated flora of colon to increase butyrate about 40% in the patients with colon cancer. Butyrate has anticancer effects. It should be noted that continuation of effects depends to treatment following [84].

Effect on immunity responses

An experiment was conducted on rabbits in order to study effect of *p. ovata* seed on the immunity responses. Edible using of seed led to significant decrease in antibody in the primary response. Intraperitoneal injection in rat before immunization of red globules of the sheep with SRBC caused significant decrease in hemaglotinating antibodies. In both groups, significant increase was seen in WBC and leucocytes of the spleen. So seed of *P. ovata* can inhibit humoral immunity responses especially in the primary responses [85].

Other effects

There is report based on using leaves of *p. ovata* to treat toxicity. Also it is used to treat itching and skin inflammations and is used as poultice to treat ulcer, fever blister and impostum. Traditionally, it can be useful to treat bitten and gout. Also extract of leaves showed improvement in rabbits. The aqueous extract of leaves has antimicrobial activity due to having eglicon and echobizhein. Aerial parts of this plant are used as an anti-inflammation and diuretic material. Extract of plant decreases blood pressure in dogs. Also alcoholic extract of *p. ovata* seeds decreases blood pressure in dogs and cats and has cholinergic activity [57].

Toxicity

Medicinal plants may have dual actions. While they might be toxic they also might be antioxidant due to having flavonoids and antioxidants [86-95] P. ovata seed contains about 16 antigens that 6 of them are allergen that react with concanavalin A, well combined with IgE. All three parts of layer, endosperm and embryo contain similar antigens. There are many reports that show different degrees of P. ovata anti-allergy effects. Anaphylaxis reactions like congestion, sneeze and tear. Powder of P. ovata seed on the skin may lead to feeling specially IgE antibodies which is positive response to P. ovata seed . Seeds have pigment that can be harmful for kidneys but this combination is removed in the stages of preparing seeds to be used. In several experiments by layer and seed of p.ovata no important side effect like change in the weight, effect on concentration of vitamins A,E and plasma salts or decrease in the food was seen. Since simultaneous using of drugs and seed of P. ovata can creates problem in absorbing drug, it is recommended to eat seed of this plant 30 minutes or one hour after using the drug. P.ovata seeds that are used mainly as laxative can cause the flatulence. Large amount of water should be used with P. ovata to maintain water of faeces . In order to decrease sensitivities resulted from powder of p.ovata seed, its aspiration should be avoided. To decrease production of dust in the air, powder of p.ovata is transferred to a glass directly in each consumption time and immediately water should b added. It has been emphasized that if consumption of p.ovata products lead to diarrhea more than 3 or 4 days, physician should be consulted [48].

Medicinal interactions

Insulin-dependent diabetic patients should decrease insulin dosage when using P. ovata seed. Medicinal interaction has been reported between P. ovata seed with lithium and carbamazepine .So seed inhibits lithium absorption in the GI tract and decreases level of blood lithium that this was seen in a 47 years old woman. Also effect of P. ovata seed in decreasing carbamazpin bioavailability was seen in 40 men [48].

Use in Breastfeeding, pregnancy and Children

No side effect resulting from using p.ovata seed or layer of its seed was seen- if it's used normally- in the breastfeeding and pregnancy periods . A research in china inhibits using seed in the pregnancy due to replacement in the embryo position. Proposed dosage for children 6-12 years old is half dosage than dosage used by adult. For children younger than 6 years old, physician should be consulted [48].

CONCLUSION

With regard to P. ovata plant consumption history by human, it has been determined that it is safe and its side effects are recognized. Now, new industrial and pharmaceutical consumptions are found for plant. Layer of seed has unique effect due to mucilage that is fiber hydrocolloid and solvable has unique effects that are different from other insolvable fibers. Results indicate cholesterol lowering effects and glucose by this plant in patients with cholesterol and diabetes and is effective in treatment of ulcerative colitis same as Mesalamine. Also complementary research in the future will find new consumptions for P. ovata including its consumption to avoid colon cancer that is of most prevalent cancers in the country. This plant is cheap and available and so can be a good alternative in treatment of chronic and expensive diseases like diabetes and cholesterol.

The mechanism actions of Plantago are not clear. It contains flavonoid components and antioxidant activities. Oxidative stress is involved in various diseases [95-103]. Hence, antioxidant properties are very important in various diseases [104-120]. Other than antioxidant activity, the other important factor in the physiology performance of plantago order to regulate intestinal actions is its jelly-like property due to polysaccharides with high molecular weight. When seed is entered to GI tract due to presence of liquid inside the intestine or since the liquid is inflated. This inflation leads to occurrence of feeling of fully stomach that finally increases volume of stomach and its water is maintained and leads to intestine emptying [48]. Ability of plantago to decrease stomach emptying is resulted from its ability to increase viscosity of food. Materials with high viscosity lead to surface contractions of the stomach. Also seed my cause change in pharmaceutical effect of carbohydrates like lactose, fructose, and sorbitol consumed to treat IBS [48].

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