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Review

The traditional uses, chemical constituents and biological activities of *Plantago major* L. A review

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Abstract

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. These include diseases related to the skin, respiratory organs, digestive organs, reproduction, the circulation, against cancer, for pain relief and against infections. *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, immuno modulating and antiulcerogenic activity. Some of these effects may attribute to the use of this plant in folk medicine.

Keywords: Traditional uses; Chemical constituents; Biological activities; *Plantago major* L

1. Botany

Plantago major L. (*Plantago major* ssp. *major* L.) is a perennial plant that belongs to the Plantagináceae family. It can become about 15 cm high, but the size varies a lot depending on the growth habitats. The leaves grow in rosettes, and they are ovate to elliptical with parallel venation (5–9). The leaves are glabrous and have an entire or irregularly dentate margin. The flowers are small, brownish-green on long non-ramified spikes.

P. major is pollinated by wind, and large amounts of seeds are produced, up to 20 000 per plant (Fægri, 1970; Tutin et al., 1976). The seeds are quite small with an ovate shape (0.4–0.8 × 0.8–1.5 mm) and a slightly bitter taste. The seed endosperm has highly thickened cellulosic walls with the cell lumen filled with oil and protein. It forms the major part of the seeds and surrounds the embryo completely. The seeds are located in capsules (8–16 per capsule) and become sticky in

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humid weather due to the swelling of the polysaccharides present in the seed coat (Qadry, 1963). In this manner the seeds can become attached to animals and humans and thereby be spread.

2. History

Research on pollen has shown that *P. major* was introduced to the Nordic countries parallel to the introduction to the first primitive cultivated fields in the stone age nearly 4000 years ago (Jonsson, 1983). *P. major* was spread by man from Europe throughout the world. 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.

P. major is a plant that many people know only as a weed, but *P. major* is also an old medicinal plant that has been known for centuries. In Scandinavia this plant is mostly known for its wound healing properties. The common Norwegian and Swedish name for *P. major* is *groblad* meaning 'healing leaves'.

The traditional use of *P. major* in wound healing is quite old. It was described by the Greek physician Dioscorides in 'De materia medica' in the first century. The leaves were prescribed for treatment of dog bites (Roca-Garcia, 1972). From the 'Vølsuga saga' it is known that the Vikings used *P. major* leaves for wound healing (Nielsen, 1969). *P. major* was also described in the 12–13th century by the Islamic author Ibn El Beithar having adopted the knowledge from Greek medicine (Fleurentin et al., 1983). Henrik Harpestreng († 1244) from Denmark wrote in 'Liber Harbarum' that *P. major* could heal everything that was torn apart. Mixed with honey it was recommended on wounds. Boiled with butter and eaten, it could heal any organ in the human body (Nielsen, 1969).

It was also commonly used in the time of Shakespeare and is mentioned in his play 'Romeo and Juliet', Act I, Scene II from the period 1592–1609:

Romeo: Your plantain leaf is excellent for that.
Benvoleo: For what, I pray thee?
Romeo: For your broken shin.

P. major was described in 'Flora Danica' by Simon Paulli in 1648 as a very efficient wound healing remedy. At that time it was so common in use that even small children knew about it. The nerves were pulled out of the leaves, and then the leaves were applied on the wounds morning and evening. For superficial wounds to heal, it was sufficient to apply the juice from the plant (Brøndegaard, 1987). The English apothecary Nicholas Culpeper published 'The Complete Herbal' in 1649. The use of plants in the treatment of diseases was based on astrology. At that time people lacked other explanations as to why some plants had certain effects and others not. According to this theory *P. major* is under Venus: 'It cures the head by its antipathy to Mars and the privities by its sympathy to Venus. There is not a martial disease that it does not cure'. About the medicinal effects he wrote: 'It is good to stay spitting of blood and bleedings at the mouth, or the making of foul and bloody water, by reason of any ulcer in the reins or bladder' (Potterton, 1983).

3. Use in traditional medicine

More recent ethnopharmacological studies show that *P. major* is used in many parts of the world and in the treatment of a number of diseases (Table 1): skin diseases, infectious diseases, problems concerning the digestive organs, respiratory organs, reproduction, the circulation, against tumours, for pain relief and for reducing fever.

4. Chemical constituents and their biological activities

4.1. Carbohydrates

The seeds contain the monosaccharides glucose, fructose, xylose and rhamnose as well as the

Table 1
Some uses of *Plantago major* L. in traditional medicine

Traditional use	Part of plant[a]	Country	References
Skin			
Abscesses	l	Hawaii, Norway, Turkey	Nagata (1971), Høeg (1974), Yesilada et al. (1995)
	l, w	Guatemala, Turkey	Cáceres et al. (1987b), Tabata et al. (1994)
Acne	l, w	Guatemala	Cáceres et al. (1987b)
Anti-inflammatory	l, j	Madeira	Rivera and Obón (1995)
	ng	Cuba	Ruiz et al. (1996)
	l	Norway	Høeg (1974)
	p, w	Chile, Panama, Rodrigues	Rodriguez et al. (1994), Gupta et al. (1979), Gurib-Fakim et al. (1993)
	l, c+p, c	India	Jain (1991), Tiwari et al. (1979)
Bee, wasp and nettle stings	l	India, Iran	Joshi et al. (1982), Zagari (1992)
	l, j	Denmark, Norway	Brøndegaard (1987), Høeg (1974)
	p	USA	Hussey (1974)
Bruises	p	USA	Hussey (1974)
	l, c	Iran	Zagari (1992)
	l	Guatemala	Cáceres et al. (1987b)
Burns	p, c	India	Saklani and Jain (1989), Rao (1981), Jain (1991)
	l	Guatemala, Iran, Norway	Cáceres et al. (1987b), Zagari (1992), Høeg (1974)
	l, j	Cook Isl., Denmark, Rarotonga	Holdsworth (1991), Brøndegaard (1987)
Cutaneous leishmaniasis	l, w + l, c	Brazil	Franca et al. (1996)
Cuts	l	India	Saklani and Jain (1989)
	l, c	Thailand	Anderson (1986a)
	l+l, c	Denmark, Norway	Brøndegaard (1987), Høeg (1974)
Dermatitis	l, w	Guatemala	Cáceres et al. (1987b)
	l	Norway	Høeg (1974)
Desinfectant for wounds	l+l, c+l, w+l, j	Denmark, Norway	Brøndegaard (1987), Høeg (1974)
	l, c+l, w	Madeira	Rivera and Obón (1995)
	l, mix+a	Italy	Leporatti and Pavesi (1990)
	ng	Cuba	Ruiz et al. (1996)
	l, c	Thailand	Anderson (1986b)
	l, w	Chile	Houghton and Manby (1985)
Emollient	l, w+s, w	Europe	Roca-Garcia (1972)
	l, j	Madeira	Rivera and Obón (1995)
	l, w+r	Iran	Zagari (1992)
Exanthema	l	Denmark, Guatemala	Brøndegaard (1987), Cáceres et al. (1987b)
Haemostatic on wounds	l, c	India	Rao and Jamir (1982), Jain (1991)
	l, h+l, c	Denmark, Norway	Brøndegaard (1987), Høeg (1974)
On poison ivy dermatitis	l	USA	Duckett (1980)
Pruritus	l, c	Iran	Zagari (1992)
Pusformation in impetigo	l+vaseline	India	Joshi et al. (1982)
Rosen	l	Guatemala	Cáceres et al. (1987b)

Table 1 (*Continued*)

Traditional use	Part of plant[a]	Country	References
Soothing effect	l, w	Iran, Phillippines	Zagari (1992), Lim-Sylianco and Shier (1985)
	r	Iran	Zagari (1992)
	l	Europe	Roca-Garcia (1972), Høeg (1974)
Wound healing	l, w	Canary Islands, Chile, Turkey	Darias et al. (1986), Houghton and Manby (1985), Tabata et al. (1994)
		Phillippines	Lim-Sylianco and Shier (1985)
	p	USA	Hussey (1974)
	l, c	Brazil, Iran	Guillén et al. (1997), Zagari (1992)
	l	Guatemala, Russia	Cáceres et al. (1987b), Mironov et al. (1983)
	l+l, c+l, w+l, j	Denmark, Norway	Brøndegaard (1987), Høeg (1974)
	l, j	Cook Islands, Rarotonga	Holdsworth (1991)
Respiratory organs			
Anti tussive	l, w, mix	Iran	Zagari (1992)
	l, j+honey	Iran	Zagari (1992)
Asthma, bronchitis	l, r, w	Iran, Bulgaria	Zagari (1992), Markov (1992)
Colds	p, w	Panama	Gupta et al. (1979)
	l, w	Norway	Høeg (1974)
Ear ache	l, r, w	Iran	Zagari (1992)
Expectoract	l,w	Brazil	Guillén et al. (1997)
Pulmonary diseases	l	Hawaii	Nagata (1971)
	l, w	Norway, Peru	Høeg (1974), Ramirez et al. (1988)
	s, w	Europe	Roca-Garcia (1972)
Throat inflammation	l, w	Brazil, Chile	Guillén et al. (1997), Houghton and Manby (1985)
	f, mix, w	Iran	Zagari (1992)
Digestive organs			
Cholera	l, w	Haiti	Weniger et al. (1986)
Constipation	r, w	California, USA	Bocek (1984)
	s	India	Jain (1991)
Diarrhea	ng	Mexico	Ponce-Macotela et al. (1994)
	l, w	Canary Islands	Darias et al. (1986)
	j+l, w	India	Joshi et al. (1982), Jain and Puri (1984), Jain (1991)
	l, r, w	Iran	Zagari (1992)
Dysenteri	j	USA	Eli Lilly (1898)
	s, w	India	Joshi et al. (1982)
Gastritis and colitis	j, a	Russia	Mironov et al. (1983)
Gum inflammation	l, w	Phillippines	Lim-Sylianco and Shier (1985)
Oral wounds	l, w	Brazil	Guillén et al. (1997)
Stomach ache	p, w	Argentina, USA (Hmong refug.)	Spring (1989), Bustos et al. (1996)
Stomach cramps	l, w	Guatemala	Logan (1973)
Stomatitis	l, r, w	Iran	Zagari (1992)
	l	Guatemala	Cáceres et al. (1987b)
Ulcer	l, w	Brazil, Norway, Turkey	Høeg (1974), Yesilada et al. (1993), Guillén et al. (1997)
	p, w	Argentina, Panama	Gupta et al. (1979), Bustos et al. (1996)
	l, w+j	Russia	Mironov et al. (1983)
	s, w	India	Joshi et al. (1982)
Urogenital system			
Abortifacient	r	New Mexico, USA	Conway and Slocumb (1979)
	s	India	Saklani and Jain (1989)
Contraseptive	l, w	Afghanistan	Hunte et al. (1975)
	p, w	USA (Hmong refugees)	Spring (1989)

Table 1 (*Continued*)

Traditional use	Part of plant[a]	Country	References
Inhibit menstrual period	l, w	Afghanistan	Hunte et al. (1975)
Kidney stones	l, w	Greece	Lawrendiadis (1961)
	l, w, mix	Venezuela	Morton (1975)
Menstrual disorders	j	USA	Eli Lilly (1898)
	s	India	Fazal (1979)
Pregnancy and childbirth	r	South Africa	Veale et al. (1992)
Renal bladder ailments	l, j	Panama	Gupta et al. (1979)
	p, w	USA (Hmong refugees)	Spring (1989)
Urinary tract infections	l, r, w	Iran	Zagari (1992)
	l	Guatemala	Cáceres et al. (1987b)
	s, w	India	Joshi et al. (1982)
Uterine problems	p, w	Rodrigues	Gurib-Fakim et al. (1993)
Vaginitis	l	Guatemala	Cáceres et al. (1987b)
Heart and circulation			
Astringent effect	l, w+r, mix	Iran	Zagari (1992)
	l, r, w	India	Kapur (1983)
Blood rectifier	l, w+r	Iran	Zagari (1992)
Diabetes	l, w+p, w	Chile	Houghton and Manby (1985), Rodriguez et al. (1994)
Diuretic	s, w	Vietnam	Doan et al. (1992)
	ng	New Mexico, USA	Conway and Slocumb (1979)
	p, w	Chile, Rodrigues, Thailand	Rodriguez et al. (1994), Gurib-Fakim et al. (1993), Wasuwat (1967)
	l, w	Guatemala	Cáceres et al. (1987a)
	w, mix	China	Pan and Lay (1966)
	j	USA	Eli Lilly (1898)
	l, w	India	Joshi et al. (1982)
Edema	l	Turkey	Yesilada et al. (1995)
Hemorroides	l, w	Brazil, India	Guillén et al. (1997), Joshi et al. (1982)
	r,w	Denmark	Brøndegaard (1987)
Hypertention	w	Burma	Kyi et al. (1971)
	l, w	Hawaii	Nagata (1971)
Sense organs			
Eye infections	p, w	Rodrigues	Gurib-Fakim et al. (1993)
	l	Guatemala	Cáceres et al. (1987b)
	w	Panama	Gupta et al. (1979)
Eye problems	l, j	Haiti, Madeira	Weniger et al. (1986), Rivera and Obón (1995)
	l	Norway	Høeg (1974)
	l, w	Peru, Tobago	Ramirez et al. (1988), Seaforth et al. (1998)
Nerve system			
Analgesic	l, w	Brazil, Peru	Guillén et al. (1997), Ramirez et al. (1988)
	p, w	USA (Hmong refugees)	Spring (1989)
Antipyretic	r, w	California, USA	Bocek (1984)
	p, w	Brazil	Brandao et al. (1985)
	l, w	Brazil, Columbia	Guillén et al. (1997), Schultes and Raffauf (1994)
	l, r, w	India	Joshi et al. (1982), Jain (1991)

Table 1 (*Continued*)

Traditional use	Part of plant[a]	Country	References
Hypnotic	l, w, mix	Venezuela	Morton (1975)
Nervous shock	l, w	Haiti	Weniger et al. (1986)
Physical weakness	l	Hawaii	Nagata (1971)
Stimulant	s, w	India	Joshi et al. (1982), Jain (1991)
	l	Hawaii	Nagata (1971)
	p, w	Rodrigues	Gurib-Fakim et al. (1993)
Toothache	p, w	Rodrigues	Gurib-Fakim et al. (1993)
	l, r, w	Iran	Zagari (1992)
Antineoplastic			
Tumors	l, w	Canary Islands	Darias et al. (1986)
	p	Chile, Venezuela	Morton (1975), Bhakuni et al. (1976), Rodriguez et al. (1994)
	l, j	Panama	Gupta et al. (1979)
Parasitic infections			
Antihelmintic	p, w	Argentina, Rodrigues	Gurib-Fakim et al. (1993), Bustos et al. (1996)
	l, w	Guatemala	Logan (1973)
Antimalaria	p	Tanzania	Weenen et al. (1990)
Parasites	w	Mexico	Ponce-Macotela et al. (1994)
Skeleton			
For bone fractures	p	USA (Hmong refugees)	Spring (1989)
Antidote			
Snake poison	p	USA	Hussey (1974)
	l, p, c, j	India	Jain and Puri (1984), Selvanayahgam et al. (1994)

[a] f, Flowers; l, leaves; s, seeds, r, root; p, whole plant; c, crushed; j, juice; w, water extract; a, alcohol extract; mix, mixed with other plants; and ng, not given.

disaccharide sucrose and the trisaccharide planteose (*O*-α-D-Gal*p*-(1→6)-*O*-β-D-Fru*f*-(2→1)-α-D-Glc*p*) (Ahmed et al., 1965). Planteose acts as a reserve carbohydrate in the seeds (Rohrer, 1972).

The outer seed coat contains polysaccharides that swell in contact with water and form mucilage with high viscosity. Polysaccharides extracted from the seeds with cold water are composed of 61% xylose, 13.2% arabinose and 24% galacturonic acid, and the hot water extract of the residue contains 78% xylose, 13.2% arabinose, 3% galactose and 6.2% galacturonic acid (Ahmed et al., 1965). Samuelsen et al. (1999a) found that the polysaccharides in the 50°C water extract are composed of 39.7% xylose, 13.1% arabinose, 17.2% galacturonic acid, 15.5% glucuronic acid, 2.1% rhamnose, 2.5% galactose and 9.9% glucose. The acidic fractions are heteroxylans that consist of blocks of β-(1→4)-linked xylose residues and blocks of β-(1→3)-linked xylose residues in the polymer backbone. Small side chains such as single xylose and arabinose residues and the disaccharides α-L-Ara*f*-(1→3)-β-D-Xyl*p* and α-D-Glc*p*A-(1→3)-β-D-Xyl*p* are linked to position 2 or 3 of (1→4)- linked xylose residues in the backbone (Samuelsen et al., 1999a,b). The acidic fractions that had the highest Mw in size exclusion chromatography had relatively high anti-complementary activity (Samuelsen et al., 1999a).

The trisaccharide raffinose (0.3 mg/g dry weight) and the tetrasaccharide stachyose (4.5 mg/g dry weight) have been isolated from the leaves. Stachyose acts as temporary carbohydrate storage in the plant (Chatterton et al., 1990).

Gorin (Gorin, 1966a,b) isolated polysaccharides composed of galacturonic acid, galactose, arabinose and rhamnose in addition to small amounts of glucose and xylose. By separation on a DEAE-cellulose column a pectic acid polysaccharide, a galactoarabinan and a galactan were isolated. These substances are sometimes referred to as 'plantaglucid' and have been used to treat ulcers at

1.5–3 g/day (Gorin et al., 1966). Given in a dose of 1 mg/kg, plantaglucid reduced the ulceration index in rats stomachs 20 times. In dogs it intensified the secretion of gastric juice. Plantaglucid lowered the tone and reduced the range of contractions in isolated rabbit intestine and also had spasmolytic effect. It helped to reduce inflammatory oedema provoked by formalin and dextran. No toxic effects were observed after prolonged enteral administration to rats and dogs (Obolentseva and Khadzhai, 1966).

A highly esterified pectin polysaccharide with Mw 46–48 kDa, PMII was isolated from a 50°C water extract (Samuelsen et al., 1995, 1996). PMII contains both smooth polygalacturonan and two different ramified regions; one (PVa) that has relatively high amounts of (1→4)- and (1→3,6)-linked galactose residues with arabinose linked to position 6. The side chains in PVa were linked to position 4 of the rhamnose residues in the backbone. The other ramified region (PVb) contained arabinose side chains attached to position 3 of the galacturonic acid residues in the backbone. PMII had high anti-complementary activity, and PVa was the part of PMII that had the highest activity. PMII also activated human monocytes in vitro for increased production of tumour necrosis factor α (TNFα). The pectin fraction that was isolated from the 100°C water extract had very low anti-complementary activity compared to PMII, and this may be due to less of the side chains that were in PVa (Samuelsen et al., 1995, 1996). Lately it was shown that PMII activates complement mainly via the classical pathway (Michaelsen et al., 1999) and that it has prophylactic activity against *Streptococcus pneumoniae* infection in mice (Hetland et al., 1999). From the 50°C water extract an anti-complementary acidic arabinogalactan, PMIa, was isolated (Samuelsen et al., 1998). It was composed of arabinose (31%), galactose (32%), rhamnose (6%) and galacturonic acid (7%). This arabinogalactan consists of a (1→3)- linked galactan backbone with (1→6)- linked galactan side chains with arabinose residues attached to position 3 of galactose residues in the side chains. It also contains 1.5% protein with relatively high amounts of hydroxy proline (28.7%), alanine (14.9%) and serine (10.9%) indicating that this is an arabinogalactan type II due to the classification made by Aspinall (1973). The neutral fraction of the water extract had very low anti-complementary activity and consisted of high amounts of glucose and mannose (Samuelsen et al., 1995).

Table 2
Polysaccharides in *Plantago major* L.

Polysaccharide		References
In leaves		
Plantaglucide	Pectic acid, galactoarabinan, galactan	Gorin (1966a), Gorin (1966b)
PMII	Pectin with smooth and hairy regions	Samuelsen et al. (1996)
PMIa	Arabinogalactan type II	Samuelsen et al. (1998)
Glucomannan		Samuelsen et al. (1995)
In seeds		
Starch		Samuelsen et al. (1999a)
Acidic heteroxylans		Samuelsen et al. (1999a)

According to a review article on immuno stimulants from higher plants by Wagner (1987) *P. major* was previously investigated for immunologically active polysaccharides. The isolated polysaccharides increased phagocytosis 15–50% in two in vitro phagocytosis models, and the highest rate of stimulation was achieved with a 0.1 mg/ml aqueous solution. The types of polysaccharides investigated were not stated. The polysaccharides that have been isolated from *P. major* are summarised in Table 2.

4.2. Lipids

Fatty acids, both free and after hydrolysis of triglycerides, have been isolated from the seeds and are listed in Table 3. According to Ahmed et al. (1968) 64.8% of the fatty acids are unsaturated.

Arachidic acid was isolated from *P. major* seeds only and not from any other *Plantago* species investigated. Most of the fatty acids present are generally found in plant seeds. One unusual hydroxyolefinic fatty acid, 9-hydroxy-*cis*-11-octadecenoic acid which is an isomer of ricinoleic acid was

Table 3
Fatty acids isolated from the seeds of *Plantago major* L.

Fatty acid		Percent of total fatty acids	References
Myristic acid	14:0		Swiatek et al. (1980)
Palmitic acid	16:0		Ahmed et al. (1968), Swiatek et al. (1980)
Stearic acid	18:0		Ahmed et al. (1968), Swiatek et al. (1980)
Oleic acid	18:1	37.4	Ahmed et al. (1968), Swiatek et al. (1980)
Linoleic acid	18:2	25.3	Ahmed et al. (1968), Swiatek et al. (1980)
Linolenic acid	18:3	0.9	Ahmed et al. (1968), Swiatek et al. (1980)
Arachidic acid	20:0		Ahmed et al. (1968)
Behenic acid	22:0		Ahmed et al. (1968)
Lignoceric acid	24:0		Pailer and Haschke-Hofmeister (1969)
9-Hydroxy-*cis*-11-octadecenoic acid	18:1	1.5	Ahmad et al. (1980)

isolated by Ahmad et al. (1980). It is a minor constituent (1.5%) of the seed oil.

From the fresh leaves 0.18% lipids were isolated, and the distributions of the different fatty acids are listed in Table 4. The unsaturated fatty acids, 18:3ω3 and 18:2ω6 and the saturated fatty acid palmitic acid were most abundant in the leaves.

The major components of the leaf wax are the free triterpene acids, oleanolic and ursolic acid (see Other terpenoids), and the linear alkanes $C_{27}H_{56}$-$C_{33}H_{58}$. The chloroform extract was composed of about 63% triterpenic acids, 17% linear hydrocarbons, 1% linear alcohols and 19% unidentified compounds independently of the plants age (Bakker et al., 1998).

Clinical and histological studies made by Mironov et al. (1983) showed that saturated C_{26}–C_{30} primary alcohols with even numbers of carbon atoms from the *n*-hexane extract and the non-hydrolysable fractions of the *n*-hexane extract had powerful curative effects on superficial injuries in rabbits.

4.3. Alkaloids

P. major has been tested positive for alkaloids (Rojas, 1968; Smolenski et al., 1974). Schneider (1990) identified them as indicain and plantagonin (Fig. 1).

4.4. Caffeic acid derivatives

The ethyl and methyl esters of caffeic acid were isolated from the methanolic extract (Pailer and Haschke-Hofmeister, 1969), and chlorogenic and neochlorogenic acid were isolated from the

Table 4
Fatty acids in *Plantago major* L. leaves (Guil et al., 1996)

Fatty acid		%
Myristic acid	14:0	1.8
Palmitic acid	16:0	15.9
	16:1ω7	1.5
	16:1ω9	0.1
	16:2ω6	0.4
	16:3ω3	1.0
Stearic acid	18:0	2.1
	18:1ω9	2.3
	18:2ω6	11.2
	18:3ω3	33.3
	18:4ω3	2.0
Arachidic acid	20:0	1.3
	20:4ω6	1.0
	20:5ω3	1.3
Behenic acid	22:0	1.3
	22:1ω9	3.5
	22:6ω3	1.5
	24:0	1.0

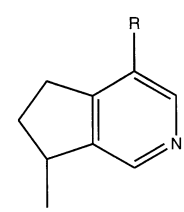


Fig. 1. Alkaloids in *P. major* L. Indicain: R = CHO; plantagonin: R = COOH.

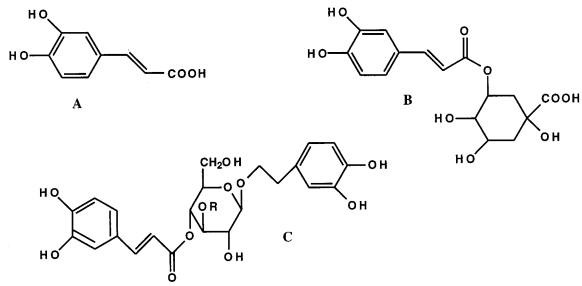


Fig. 2. Caffeic acid derivatives in *P. major* L. (A) Caffeic acid, (B) chlorogenic acid, (C) Plantamajoside R = Glc, acteoside R = Rha.

aqueous extract (Maksyutina, 1971b). According to Noro et al. (1991) plantamajoside is the main caffeic acid derivative in *P. major* L., and only small amounts of acteoside (synonym to verbascoside) are present. Skari et al. (1999a) on the other hand isolated equal amounts of each compound from the 80% ethanol extract of the plant. According to Mølgaard (1986), plantamajoside and acteoside are not found together in the same plant. In Denmark, there are two subspecies of *P. major*, *P. major* ssp. *major* and ssp. *spleiosperma*. Plantamajoside is present in both subspecies, while acteoside is found only in ssp. *spleiosperma* (Mølgaard, 1986). Plantamajoside is glycosylated with glucose to the central glucose while in acteoside it is glycosylated with rhamnose (Fig. 2).

Plantamajoside has some known biological activities. It has an inhibitory effect on arachidonic acid-induced mouse ear oedema, i.e. anti-inflammatory activity (Murai et al., 1995), inhibitory activity on 5-lipoxygenase (Ravn et al., 1990), 15-lipoxygenase (Skari et al., 1999a) and cAMP phosphodiesterase (Ravn et al., 1990) and antioxidant activity (Miyase et al., 1991). Skari et al. (1999a) found that plantamajoside is a DPPH (diphenylpicrylhydrazyl) radical scavenger. Plantamajoside is also known to have some antibacterial activity (Ravn and Brimer, 1988).

Acteoside has superoxide anion and DPPH radical scavenging activities, has antioxidant activity and inhibits lipid peroxidation (Xiong et al., 1996; Miyase et al., 1991; Zhou and Zheng, 1991; Skari et al., 1999a,b). It inhibits 15-lipoxygenase slightly less efficient than plantamajoside (IC_{50} 117 vs. 96 μM) (Skari et al., 1999a). Acteoside inhibits protein kinase C by interacting directly with the catalytic domain of the enzyme (Herbert et al., 1991). Acteoside inhibits aldose reductase (Ravn et al., 1990) and 5-HETE formation (Kimura et al., 1987). It has antibacterial (Shoyama et al., 1987), immunesuppressant (Sasaki et al., 1989) and analgesic activity (Andary et al., 1982). Acteoside has antihypertensive effect, at a dose of 10 mg/kg on rats a significant decrease in systolic, diastolic and mean arterial blood pressure was observed (Ahmad et al., 1995). The biological activities of these and other caffeic acid derivatives are reviewed in Jiménez and Riguera (1994).

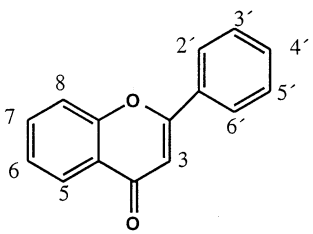
4.5. Flavonoids

Several flavonoids have been isolated from *P. major* (Table 5). According to Kawashty et al. (1994) the amount of each flavonoid isolated from Egyptian *P. major* can be ranged as follows: luteolin 7-glucoside > hispidulin 7-glucuronide > luteolin 7-diglucoside > apigenin 7-glucoside ≈ nepetin 7-glucoside > luteolin 6-hydroxy 4′-methoxy 7-galactoside. Skari et al. (1999b) isolated plantaginin and homoplantaginin in addition to several flavonoids having structures that have not been found in *P. major* earlier. Their structures remain to be published.

Many flavonoids are antioxidants (Rice-Evans et al., 1996; Bohm et al., 1998). Examples of such compounds in *P. major* are baicalein, hispidulin and plantaginin (Yuting et al., 1990; Yokozawa et al., 1997; Skari et al., 1999b). A number of flavonoids are also known to have free radical scavenging activity (Kandaswami and Middleton, 1994). Baicalein, hispidulin, scutallarein and plantaginin are free radical scavengers and inhibit lipid peroxidation (Sanz et al., 1994; Yoshino et al., 1997; Gao et al., 1999; Skari et al., 1999b). Both baicalein and hispidulin have anti-inflammatory activities. Baicalein inhibits carrageenan-induced rat paw edema (Lin and Shieh, 1996a), 12-lipoxygenase (You et al., 1999) and LPS induced production of nitric oxide in macrophages (Wakabayashi, 1999) while hispidulin has been shown to be an inhibitor of 5-lipoxygenase (Moongkarndi et al., 1991). Baicalein has hepato-

Table 5
Flavonoids in *Plantago major* L. compound

Compound



	3	5	6	7	8	2′	3′	4′	5′	6′	References[a]
Apigenin 7-glucosid	H	OH	H	OGlc	H	H	H	OH	H	H	3
Baicalein	H	OH	OH	OH	H	H	H	H	H	H	1
Hispidulin	H	OH	Ome	OH	H	H	H	OH	H	H	2
Hispidulin 7-glucuronide	H	OH	Ome	OGlcA	H	H	H	OH	H	H	3
Homoplantaginin	H	OH	Ome	OGlc	H	H	H	OH	H	H	4, 5
Luteolin 7-glucosid	H	OH	H	OGlc	H	H	OH	OH	H	H	3
Luteolin 7-diglucosid	H	OH	H	OGlc-Glc	H	H	OH	OH	H	H	3
Luteolin 6-hydroxy-4′-methoxy-7-galactoside	H	OH	OH	OGal	H	H	OH	OMe	H	H	3
Nepetin 7-glucoside	H	OH	Ome	OGlc	H	H	OH	OH	H	H	3
Plantaginin	H	OH	OH	OGlc	H	H	H	OH	H	H	4, 5
Scutellarein	H	OH	OH	OH	H	H	H	OH	H	H	1, 2

[a] References: 1, Maksyutina (1971a); 2, Harborne and Williams (1971); 3, Kawashty et al. (1994); 4, Nishibe et al. (1995); and 5, Skari et al. (1999b).

protective effect against CCl_4-induced liver injuries in rats (Lin and Shieh, 1996b). Baicalein can induce cell death of carcinoma cells (Matsuzaki et al., 1996), cause inhibition of cell growth of human hepatoma cells (Motoo and Sawabu, 1994) and has shown strong antiproliferative effect in rat hepatic stellate cells (Inoue and Jackson, 1999). Scutallarein and baicalein have antiallergic activities (Kawasaki et al., 1994; Toyoda et al., 1997). In addition, they are HIV-reverse transcriptase inhibitors in vitro; (IC_{50} 2.5 and 5.6 μM, respectively). The glucosides plantaginin, luteolin 7-glucoside and homoplantaginin are also potent inhibitors (IC_{50} 9.8, 40.2 and 43.3 μM, respectively) while apigenin 7-glucoside had no inhibitory effect on HIV-reverse transcriptase (Nishibe et al., 1997).

Table 6
Iridoidglycosides from *Plantago major* L.

Iridoidglycoside	Part of plant	%	References
Asperuloside	Flowers	0.023	Bianco et al. (1984)
Aucubin	Leaves	0–1.3	Long et al. (1995)
Catapol	Aerial parts	0.003	Murai et al. (1996)
Gardoside	Aerial parts	0.001	Murai et al. (1996)
Geniposidic acid	Aerial parts	0.005	Murai et al. (1996)
Majoroside	Aerial parts	0.004	Handjieva et al. (1991)
10-Actoxymajoroside	Aerial parts	0.03	Taskova et al. (1999)
10-Hydroxymajoroside	Aerial parts	0.02	Taskova et al. (1999)
Melittoside	Aerial parts	0.004	Murai et al. (1996)

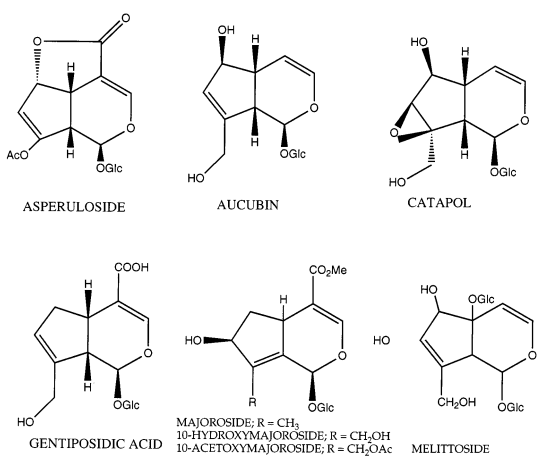


Fig. 3. Iridoid glycosides from *P. major* L.

4.6. Iridoid glycosides

The iridoid glycosides isolated from *P. major* are listed in Table 6, and the structure formulas are given in Fig. 3. The major iridoid glycoside found is aucubin, but its content varies over the seasons. The highest aucubin level registered (1.3% in dried leaves) was in June. *P. major* contains less aucubin than *P. lanceloata* (Long et al., 1995). Three unusual iridoid glycosides with 8,9 double bonds, majoroside (Handjieva et al., 1991), 10-hydroxymajoroside and 10-acetoxymajoroside have been isolated from the aerial parts of the plant (Taskova et al., 1999).

Aucubin has anti-inflammatory properties: when applied topically aucubin has an inhibitory effect on TPA (12-*O*-tetradecanoylphorbol acetate) induced mouse ear oedema with a maximum effect at a dose of 1 mg/ear. This effect is close to that of indomethacin at 0.5 mg/ear (Recio et al., 1994).

Aucubin has also spasmolytic properties on acetylcholine induced contraction on rat uterus and rat vas deferens (Oritz de Urbina et al., 1994). Aucubin has antidote activity for poisonous amanita mushrooms in mice by protection against liver damage induced by α-amanitin. The mechanism is thought to be due to a competitive effect of aucubin on α-amanitin inhibition of liver RNA synthesis (Chang et al., 1984). It also has liver protective activity against CCl_4-induced hepatic damage in mice (Chang, 1998) in addition to antiviral activity against hepatitis B virus (Chang, 1997).

The aglycon of aucubin, aucubigenin, has antimicrobial activity against bacteria and moulds (Davini et al., 1986).

4.7. Other terpenoids

The terpenoid loliolid has been isolated from the leaves (Pailer and Haschke-Hofmeister, 1969).

The triterpenoids oleanolic acid, ursolic acid, 18β-glycyrrhetinic acid and sitosterol were isolated from the leaf wax (Hiltibran et al., 1953; Ringbom et al., 1998). Ursolic acid inhibits cyclooxygenase-2 (IC_{50} 130 μM) and cyclooxygenase-1 (IC_{50} 295 μM) catalysed prostaglandin biosynthesis in vitro while the structural isomer oleanolic acid is less active. 18β-Glycyrrhetinic acid had no significant inhibitory effect (Ringbom et al., 1998). The mechanisms of the anti-inflammatory effects also include inhibition of histamin release from mast cells, inhibition of elastase and inhibition of complement activity. Ursolic acid and oleanolic acid also have hepatoprotective, tumor promotion inhibiting activity and an anti-hyperlipidemic effect (Liu, 1995).

4.8. Glucosinolates

Intact glucosinolates have not been isolated from *P. major* seeds or leaves (Larsen et al., 1983).

4.9. Vitamins

P. major has been used as a food supply, especially during spring before the harvest of the common vegetables. The vitamin contents have, therefore, been examined. The fresh leaves of old plants that had gone to seed, collected in early spring, were reported to contain 6 mg β-carotene (provitamin A)/100 g and 19 mg ascorbic acid/100 g (Zennie and Ogzewalla, 1977). According to a study of young plants *P. major* contains 25 mg ascorbic acid, 31 mg dehydroascorbic acid and 8.5 mg carotenoids/100 g young leaves. Thus, *P. major* can be considered as a good source of vitamin C and carotenoids. In addition, the oxalic acid, nitrate and erucic acid were present in low amounts (67 ± 36 mg/100 g, 101 ± 18 mg/100 g and 3.45%, respectively) indicating a low toxicity of the plant (Guil et al., 1997).

Shoots of *P. major* collected in June contained 37 mg/g dried leaf material of phylloquinone (vitamin K_1). A high vitamin K level might be of importance in the resistance of weeds to the herbicide 2,4 dichlorophenoxyacetic acid. The vitamin K level in *P. major* was intermediate compared to other plant species, and it was also moderately resistant towards the herbicide (Jansson, 1974).

4.10. Other organic acids

From the methanol extract the following organic acids were isolated: fumaric acid, syringic acid, vanillic acid, *p*-hydroxy benzoic acid, ferulic acid, *p*-coumaric acid, gentisic acid, traces of salicylic acid, benzoic acid and cinnamic acid (Pailer and Haschke-Hofmeister, 1969).

5. Biological activity of extracts

P. major is used for different purposes in traditional medicine around the world, therefore, researchers have tested it for different types of biological activities. Most tests have been performed on crude extracts without examining the nature of the active compounds. The results of these studies are listed below and include both positive and negative results.

5.1. Antiulcerogenic activity

P. major has been used in Turkey in the treatment of ulcers. The powdered dried leaves were taken together with honey daily before breakfast. A water immersion-stress ulcer model was used on rats to test the plant extract's ability to inhibit ulcers. A test sample was given just before immobilisation in a stress cage. After 7 h immersed in a water-bath the rats were killed and the stomachs were taken out for examination. The combined methanol- and water extract (1.2 g/kg) inhibited ulcer formation by 40% relative to the control group which received only the vehicle. The water extract (1 g/kg) inhibited ulcer formation by 37% and the methanol extract inhibited it by 29%. *P. major* was not among the most active plants tested (Yesilada et al., 1993).

5.2. Anticancer activity

In a screening of anticancer activity of Chilean plants a 50% ethanol extract of leaves, stems and seeds of *P. major* had no activity in vivo against

lymphocytic leukaemia in mice (Bhakuni et al., 1976).

A *P. major* preparation was reported to be effective in a screening system for prophylactic oncology. The effect included antimetastatic activity in models of tumour metastasis in mice. The details in this study were not described (Yaremenko, 1990). In another study, an aqueous extract was shown to have a prophylactic effect on mammary cancer in mice (Lithander, 1992). The leaves were extracted with phosphate buffer pH 7 containing 0.9% NaCl and injected subcutaneously in mice of the C3H Strong strain. Among mice of this strain more than 90% develop cancer induced by a virus infection. After 60 weeks, 93.3% of the untreated and 18.2% of the treated mice had tumours. The observed effect is thought to be due to stimulation of the immune system rather than a direct effect on the virus. No experimental results support this idea, only some observations made without experimental verification. The *P. major* extract had good effect on human herpes infections but had no effect on the herpes virus in in vitro tests. The same observations have been made for bacteria; only weak antibacterial activity of *P. major* extracts in vitro, but they had an effect on infected wounds in vivo. While antibiotics on infected wounds had no effect, topical treatment with *P. major* extract eradicated the infections and healed the wounds.

5.3. Immunomodulatory activity

The leaves extracted in saline for 2 h at 50°C had chemotactic activity on neutrophils using the Boyden migration chamber method, but it did not enhance neutrophil intracellular killing activity by the nitrozoblue tetrazolium reduction test (Basaran et al., 1997).

5.4. Antiinfective testing in vitro

5.4.1. Antibiotic and antifungal activity

P. major has been included in screening studies of plants used in folk medicine in fighting bacterial and fungal infections in the skin or in the treatment of gastrointestinal disorders.

Discs containing plant extracts were applied to bacteria cultured on agar plates, and the inhibition zones measured after some time. Water extracts, methanol extracts, 50% and 70% ethanol extracts were tested.

The methanol extracts were most active against *Salmonella typhimurium* (Table 7) and had weaker activity against methicillin resistant *S. aureus* and *M. phlei*. The methanol extracts were active (8–10 mm inhibition zone) against the fungi *F. tricuictum* and *M. gypseum*, and an incomplete inhibition of *C. albicans* and *S. cerevisiae* was observed (Table 8). The antifungal activity was weaker than the antimycoticum nystatin (15–20 mm inhibition zone).

The 50% ethanol extracts were active against *S. aureus*, *B. subtilis*, *S. dysenteriae* and *E. coli* . These include both gram negative and gram positive bacteria. The 70% ethanol extracts were most effective against *S. flexneri* and had weaker activity against *S. aureus*, *S. sonnei*, *E. coli*, *Esherichia 'crim'* and *M. smegmatis*.

The antibiotic activities registered were weaker than the positive controls used. Incubation of gentimicin and a *P. major* methanol extract gave inhibition zones of >25 mm and 10–15 mm, respectively on *S. typhimurium*.

In conclusion there seems to be some intermediately polar or nonpolar substances of relatively low molecular weight in *P. major* that have antibiotic activity against some gram negative and gram positive bacteria in addition to a weak antimycotic activity.

5.4.2. Antigiardiasic activity

P. major is used in Mexico against diarrhoea and/or parasites. A decoction in a saline solution was made of the plant, and this was incubated with trophozoides of *Giardia duedenalis*. The mortality was 76 ± 1.2 which was at the level of the positive control tinidazol (79 ± 1.9) (Ponce-Macotela et al., 1994).

5.4.3. Antimalarial activity

P. major has been used in the treatment of malaria in Tanzania. In vitro activity against *Plasmodium falciparum* strain K_1 which is multidrug resistant was performed by measurement of

Table 7
Antibiotic activity of *Plantago major* L. water extract, methanol extract (MeOH), 50% and 70% ethanol extract (EtOH) determined by measurement of inhibition zones of discs containing extracts on bacteria cultures on agar plates[a]

Bacteria	H_2O	MeOH	50% EtOH	70% EtOH	References[b]
Staphylococcus aureus	−		++	+	1, 2, 3
S. aureus, methicillin resistant		+			5
S. aureus, methicillin sensitive		−			5
Streptococcus pyogenes			−		3
Bacillus subtilis		−	++	−	2, 3, 5
Shigella sonnei				+	2
S. flexneri			−/+	++	2, 3, 4
S. dysenteriae			++		4
Salmonella typhi			−/+		3, 4
S. enteritidis			−		4
S. typhimurium		++			5
Serratia marcescens		−			5
Enterobacter aerogenes		−			5
Esherichia coli	−	−	++	+	1, 2, 3, 4, 5
Escherichia "crim"				+	2
Klebsiella pneumonia		−			5
Pseudomonas aeruginosa		−	−		3, 5
Proteus vulgaris			−		3
Mycobacterium phlei		+			5
M. smegmatis				+	2

[a] Effects as defined by the authors: −, inhibition zone <6–8 mm; +, inhibition zone 6–10 mm; ++, inhibition zone 10–15 mm.
[b] References: 1, Gaw and Wang (1949); 2, Moskalenko (1986); 3, Cáceres et al. (1987b); 4, Cáceres et al. (1990); and 5, McCutcheon et al. (1992).

the ability of the extracts to inhibit the incorporation of [^{3}H]-hypoxantine into the malaria parasites. The dichloromethane extract of the whole plant had some effect (IC_{50} 10–49 mg/ml), the petroleum ether extract and the methanol extract had little activity (IC_{50} 100–499 mg/ml and >499 mg/ml, respectively). For comparison, the methanol extract of a *Cinchona* species had an IC_{50} of 0.5 mg/ml (Weenen et al., 1990).

5.4.4. Antiviral activity

No antiviral activity against herpes and polio virus of ethanol extracts of the entire plant was registered in the in vitro study of Suganda et al. (1983). Neither was the methanol extract of the plant active in vitro against bovine coronavirus, bovine herpesvirus type 1, bovine parainfluenza virus type 3, bovine rotavirus, bovine respiratory syncytial virus, vaccinia virus or vesicular stomatitis virus (McCutcheon et al., 1995).

Table 8
Antifungal activity of *Plantago major* L. methanol extract (MeOH), 50% ethanol extract (EtOH) determined by measurement of inhibition zones of discs containing extracts on bacteria cultures on agar plates (Cáceres et al., 1987b; McCutcheon et al., 1994)[a]

Fungi	MeOH	50% EtOH
Aspergillus flavus	−	
A. fumigatus	−	
Fusarium tricuictum	+	
Sacchariomyces cerevisiae	+i	
Trichoderma viridae	−	
Microsporum cookerii	−	
M. gypseum	+	
Trichophyton mentagrophytes	−	
Candida albicans	+i	−

[a] Effects as defined by the authors: −, inhibition zone <6–8 mm; +, inhibition zone 6–10 mm; I, incomplete inhibition.

5.5. Anti-inflammatory and analgesic activity

The aqueous extract (72°C, 30 min) of dried *P. major* leaves given orally has shown anti-inflammatory and analgesic activities related to inhibition of prostaglandin synthesis in mice and rats. Anti-inflammatory activity in rats was demonstrated by the inhibition of paw oedema induced by carrageenan. The extract did not affect oedema produced by dextran, indicating that the mechanism involved inhibition of cyclooxygenase synthesis rather than an antihistamine activity. The extract also inhibited the formation of exudate and leucocyte mobilisation induced by intrapleural injection of carrageenan, the latter being a known activity of non-steroidal anti-inflammatory compounds. Activity against chronic inflammation was measured as the inhibition of exudate in the air pouch after oral treatment with extract.

Peroral treatment of mice with extract inhibited acetic acid induced writhing (i.e. non-steroid anti-inflammatory activity) but had no effect on the tail flick test (i.e. no opioid-like analgesic activity) (Guillén et al., 1997).

5.6. Antioxidant and free radical scavenger activity

Antioxidant capacity by bleaching of the absorbance of pre-formed 2,2′-azinobis (3-ethylbenzthiazolinesulfonic acid) radical cation in the presence of infusions made from *P. major* herbal tea bags and *P. major* leaves were determined. The infusion of *P. major* tea contained small amounts of free radical scavengers compared to black tea. The antioxidants had low reactivity, measured as a relatively high $t_{1/2}$. The antioxidant capacity of the green leaves was higher than that of the *P. major* tea indicating that processing can lead to significant loss of activity (Campos and Lissi, 1995).

5.7. 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 $108 \pm 44\%$ after 6 h. Hydrochlorothiazide increased urinary output by 286 ± 38 % (Cáceres 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).

5.8. 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 anaesthetised 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 lyophilised 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).

5.9. Hypoglycaemic activity

Rodriguez et al. (1994) have tested a 70% ethanol extract for its hypoglycaemic activity in normoglycaemic rats without finding any significant effect. The extract was given orally at a dose of 500 mg/kg. The background for the testing was that the Mapuche Indians in Chile have used the infusion of *P. major* in the treatment of diabetes (Houghton and Manby, 1985).

Table 9
The toxicity of *Plantago major* L. leaf extracts

Extract	Test	Toxic	Comments	Ref.[a]
Decoction	Ames test, strains TA 1537 and TA 98	+	Direct frameshift mutagens	1
Saline extract	Ames test strains TA 100 and TA 98	–		2
Alcohol extract	Plate incorporation assay with *Aspergillus nidulans* D-30	–	Stimulation of colony growth	3
Alcohol extract	*Aspergillus nidulans* somatic segregation assay	–		3
70% Ethanol extract	Brine shrimp (*Artemia salina*)	+	$LC_{50} = 7$ μg/ml	4
Not stated	i.p. and oral administration in rats	–	$LD_{50} = 1000$ mg/kg i.p., $LD_{50} > 4000$ mg/kg oral	5
Saline extract	COMET assay in human lymphocytes	+	DNA strand brakeage	2

[a] References: 1, Lim-Sylianco and Shier (1985); 2, Basaran et al. (1996); 3, Ruiz et al. (1996); 4, Schmeda-Hirschmann et al. (1992); and 5, Angelov et al. (1980).

6. Toxicity

As shown in Table 9 the genotoxicity of *P. major* extracts on prokaryotes are somewhat contradictory. In the Ames test (*S. typhimurium* microsomal activation assay), water extracts caused reversions of tester strains TA1537 and TA98. This indicates the presence of direct frameshift mutagens (Lim-Sylianco and Shier, 1985). The *P. major* saline extract had, however, no response in the Ames test with strains TA98 and TA100 (Basaran et al., 1996).

An alcohol extract showed no toxicity on the diploid strain *Aspergillus nidulans* D-30, on the contrary, a stimulation of colony growth was observed. The *A. nidulans* strain used in the somatic segregation assay carry four recessive mutations for conodial colour, and coloured sectors are used as an indicator of genotoxic events leading to somatic segregation. No significant differences in frequency of coloured sectors per colony compared to the negative control were observed. Thus, no genotoxic effect was found of the plant extract (Ruiz et al., 1996).

The 70% ethanol extract was found to be toxic to shrimps (Schmeda-Hirschmann et al., 1992) but *P. major* possesses a low toxicity in rats at oral and i.p. administration (Angelov et al., 1980).

DNA damage by strand breakage was suggested after examination of human lymphocytes treated with the saline extract. It had an increased activity in the alkaline COMET assay compared to the negative control (Basaran et al., 1996).

7. Concluding remarks

Taking the claimed wound healing activity of *P. major* into consideration, it is not necessarily only one single compound that is responsible for this effect, the effect may as well be due to several compounds that act in a synergistic manner or to compounds which regulate one another.

There are several of the isolated compounds that may aid the healing of wounds. Plantamajoside and acteoside have antibacterial activities. Some flavonoids and the caffeic acid derivatives plantamajoside and acteoside have antioxidative and free radical scavenging activities. Pectic polysaccharides have been reported to be effective against ulcers in rats and for having immunostimulatory activities. Finally, the long chained saturated primary alcohols that are present in the leaf wax aid the healing of superficial wounds. However, the leaves also contain compounds with anti-inflammatory activity, namely plantamajoside, baicalein, hispidulin, aucubin, ursolic acid and oleanolic acid. Since the inflammatory phase in general is necessary in the wound healing process, anti-inflammatory activity may be undesirable. On the other hand, these substances' activities when acting together with other compounds present in the leaves are not known at present. Thus, the full picture of *P. major* as a wound healing remedy may be rather intricate.

Due to the very long tradition in using *P. major* for wound healing and also because of what is known today about its chemical constituents and biological activities, it seems to be worth the effort of exploring this plant further.

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