NATURAL ANTI-IRRITANT PLANTS

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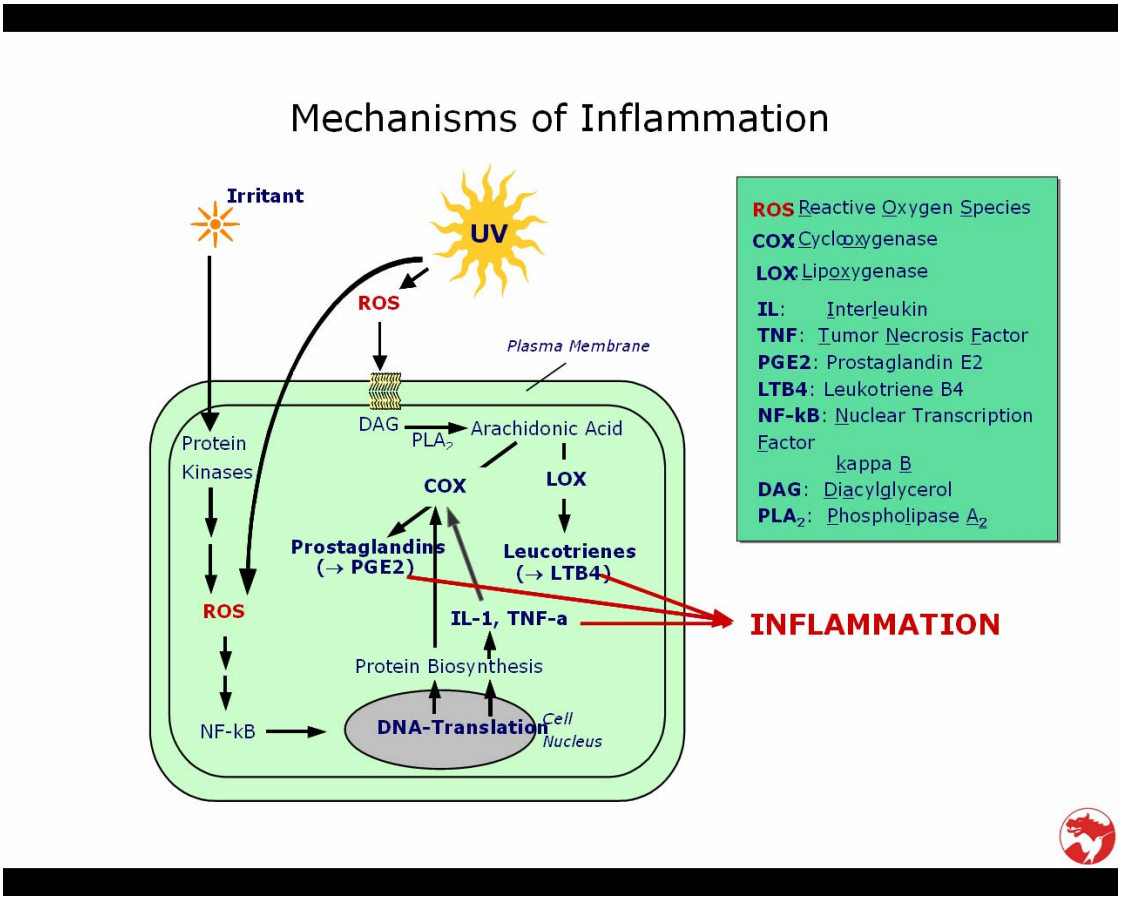
INTRODUCTION

The mechanism by which the skin becomes irritated and inflamed is both complex and dependent on numerous factors. No one pathway can be held to be entirely responsible for skin erythema or pruritic skin conditions.

Unlike modern allopathic drugs which are single active components that target one specific pathway, herbal medicines work in a way that depends on an orchestral approach. A plant contains a multitude of different molecules that act synergistically on targeted elements of the complex cellular pathway. Individually these elements may work quite effectively, however, time and again it has been proven that the overall effect is far superior when the whole plant is used.

The mechanism of inflammation shown below is one of the possible pathways.



OVERVIEW

Some of the most commonly known plants to treat inflammation and erythema are German Chamomile (*Matricaria recutita*) and Roman Camomile (*Anthemis nobilis*) which contain a wide range of actives of which bisabolol, azulene derivatives and various flavonoids (particularly apigenin) are found to be the most functional components.

Other herbal materials renowned for their anti-inflammatory activity depend on entirely different chemical moieties.

Comfrey (*Symphitum officinale*) has always been considered in herbal folklore to be an ideal solution for sore, red, inflamed and damaged skin. [The scare over comfrey was as a result of an over-zealous ingestion of the herb that caused renal failure, but this event has no relevance in topical administration for which it is still permitted]. A typical analysis of the plant illustrates the complexity of the chemical compositions and also serves to demonstrate that different parts of the plant contain different actives which can be separated out into fundamental components.

Overall composition of the plant
Ash root 140,000 ppm, Carbohydrates root 759,000 ppm, Fat root 17,000 ppm, Fiber root 72,000 ppm, Gum root 50,000 - 100,000 ppm, Protein root 94,000 ppm, Resin root, Water root 862,000 ppm,

The support ingredients
The skin is dependant on a blend of minerals, vitamins and sugars to function and metabolise normally. The presence of minerals, vitamins and sugar related molecules (much loved by the skin) are essential for normal function

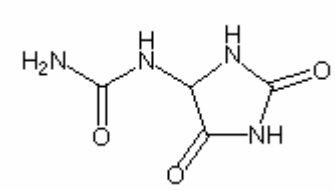
Minerals
Aluminum root 237 ppm, Calcium root 11,300 ppm, Chromium root 8 ppm, Cobalt root 129 ppm, Iron root 810 ppm, Magnesium root 1,700 ppm, Manganese root 67 ppm, Phosphorus root 2,111 ppm, Potassium root 15,900 ppm, Selenium root, Silicic-acid leaf 40,000 ppm; root, Silicon root 35 ppm, Sodium root 3,510 ppm, Tin root 6.7 ppm, Zinc root 2.8 ppm.

Vitamins
Ascorbic-acid root 132 ppm, Beta-carotene root 660 ppm, Carotenes plant 6,300 ppm, Niacin root, Riboflavin root 7.2 ppm, Thiamin root 1.2 ppm. Choline is a basic constituent of lecithin and is found in many plants e.g. hops, belladonna, strophanthus. It is almost classed as a vitamin.

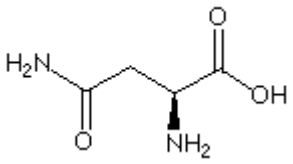
Sugars and related compounds
D-mannose root, Fructose root, Glucose root, Glucuronic-acid root, L-arabinose root, L-rhamnose root, Sucrose root, Mucilage root 290,000 ppm, Mucopolysaccharides root 250,000 - 300,000 ppm, Reducing-sugars root 51,500 ppm, Xylose root,

The phytoactives
It is the presence of these remaining constituents that give comfrey its function and we can now begin to assign specific action to each of these chemical components Allantoin leaf 13,000 ppm; root 6,000 - 8,000 ppm, Asparagine root 10,000 - 30,000 ppm, Bornesitol root, Caffeic-acid root, Chlorogenic-acid root, Consolicine root, Consolidine root 17 ppm, Echimidine root, Echinatine root, GABA root, Heliosupine-n-oxide root, Hypoxanthine root, Isobanerenol root, Lasiocarpine root, Lithospermic-acid root, Lycopsamine root, Octadecatetraenic-acid seed, Pyrocatechins root 24,000 ppm, Rosmarinic-acid leaf 5,000 ppm, Sitosterol root, Stigmasterol root, Symlandine plant, Symphytine root, Symphytocynoglossin root 21 ppm, Tannin plant 80,000 - 90,000 ppm, Viridiflorine plant.

Allantoin is described in Merck as a topical vulnerary and used in skin ulcer therapy. In the veterinary field it has been used topically to stimulate the healing of suppurating wounds and resistant ulcers. In the 5th edition 1941, it reported that it was used externally to stimulate cell proliferation in 0.3-0.5% aqueous solutions. It was recommended for ulcers, non-healing wounds, fistulas etc.

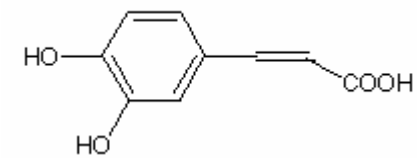


Asparagine is an amino acid that is frequently found in plant materials (e.g. mallow, chamomiles, liquorice, hops, sage and many *Pueraria* spp) most of which seem to be associated with long traditions of use for their soothing benefits.



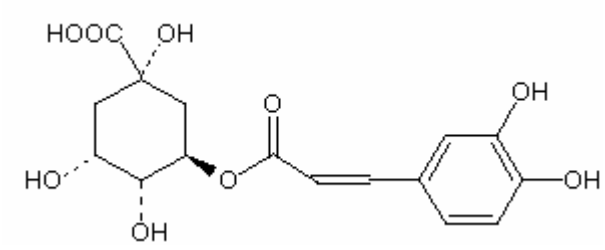
Bornesitol is very rarely found in plants, it has been found in plants like the Periwinkle or *Vinca minor* (a powerful anti-cancer drug) Borage or *Borago officinalis* and *Platycladus orientalis* none of which seem to have any relation to each other.

Caffeic acid is found in many fruits, vegetables and functional herbal materials like Horse chestnut (*Aesculus hippocastanum*), Burdock (*Arctium lappa*), Arnica (*Arnica montana*), Calendula (*Calendula officinalis*), Ivy (*Hedera helix*) and Self Heal (*Prunella vulgaris*) to name but a few. It is a selective inhibitor for leukotriene biosynthesis and can also inhibit arachidonate lipoxygenase activity. It is frequently associated with plants that are used for drainage and



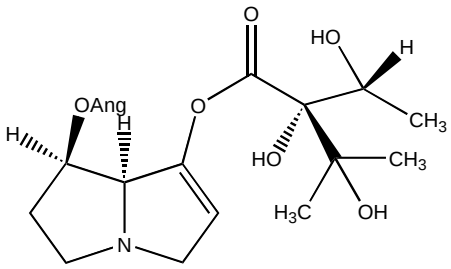
reduction of swelling and for the strengthening of cell membranes in the skin.

Chlorogenic acid – is a conjugated form of caffeic acid described above and has been cited for the stimulation of the immune system to stimulate T-lymphocytes. It often occurs in combination with caffeic acid. It is found in a multitude of plants that include Dandelion (*Taraxacum officinale*), Lime (*Tilea europaea*), St. John's Wort. (*Hypericum perforatum*), Golden Rod (*Solidago virgaurea*). Japanese Honeysuckle (*Lonicera japonica*) and Elder (*Sambucus nigra*) all respected herbal remedies for problem skin conditions.

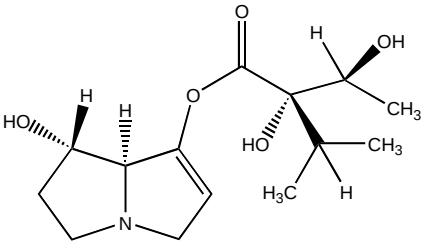


Consolicine and *Consolidine* are extremely rare and we could only find them in Alkanet (*Alkanna Tinctoria*). The effects appear to be a CNS-paralytic, curaroid and myoparalytic, but in truth little is known of the systemic or biological effects of this constituent.

Echimidine and *echinatine* are a pyrrolizidine alkaloids and though this class of chemicals have been long recognized as potential skin irritants, they are definitely skin stimulants and at low levels could trigger a cellular response that was not detrimental. As so wisely stated by Paracelsus the father of toxicology "the dose makes the poison"



Echimidine



Echinatine

GABA is a multifunctional cellular stimulant and is anti-hepatotoxic, anti-varicose and anti-oedemic leading to cellular drainage and reduction in inflammation and swelling.

Heliosupine-n-oxide is another closely related pyrrolizidine alkaloids

Hypoxanthine found in Hound's Tongue, *Cynoglossum officinale*, *C. australe*, and *C. pictum*, in Viper's Bugloss, *Echium vulgare*, and in *Heliotropium supinum*

Isobanerenol appears to be unique to comfrey and has no reported properties.

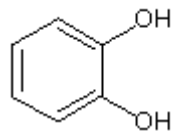
Lasiocarpine is another closely related pyrrolizidine alkaloids and again seems unique to *Symphitum* species.

Lithospermic acid is another rare molecule (an analogue of caffeic acid) that is found in Blessed Thistle (*Cnicus benedictus*), Bugleweed (*Lycopus europaeus*) and *Lithospermum ruderale*. The material seems to suppress lactate dehydrogenase leakage particularly in renal cells.

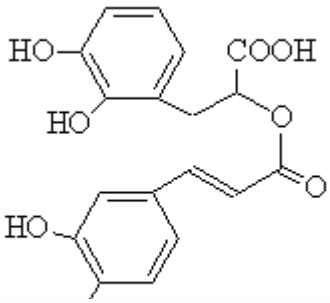
Lycopsamine is another closely related pyrrolizidine alkaloids and found in Siam Weed (*Chromolaena odorata*) and *Echium* species.

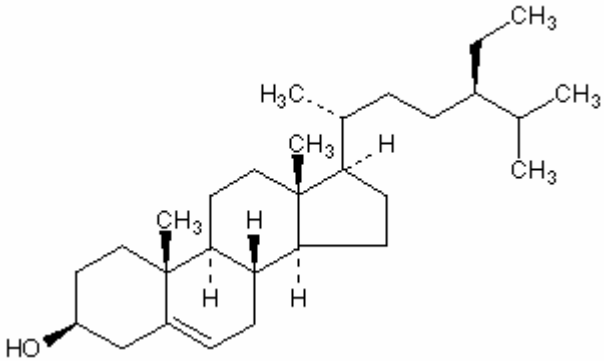
Octadecatetraenic acid is found in Stoneseed (*Lithospermum officinale*). *Lappula squarrosa* and Chickweed (*Stellaria media*). This again is extremely rare in the plant kingdom and is reported to be extremely toxic.

Pyrocatechins or *catechol* is found in numerous plants like Tea (*Camellia sinensis*), *Ginkgo biloba*, Guarana (*Paullinia cupana*), and various *Pueraria* species. Catechol is a bioflavonoid and has an antioxidant and protective effect on skin cells. It is listed in Merck as an antiseptic.



Rosmarinic acid is an anti-inflammatory, antioxidant and antimicrobial ingredient found (as you might expect) in Rosemary (*Rosmarinus officinalis*), Sage (*Salvia officinalis*), Lemon Blam (*Melissa officinalis*) and numerous other plants. It has also been attributed with antiviral, antithrombotic, antiplatelet and antihormonal activities and the suppression of cytokine-induced proliferation of murine cultured mesangial cells have also been reported for rosmarinic acid. It has been used topically in Europe as a nonsteroidal anti-inflammatory drug.

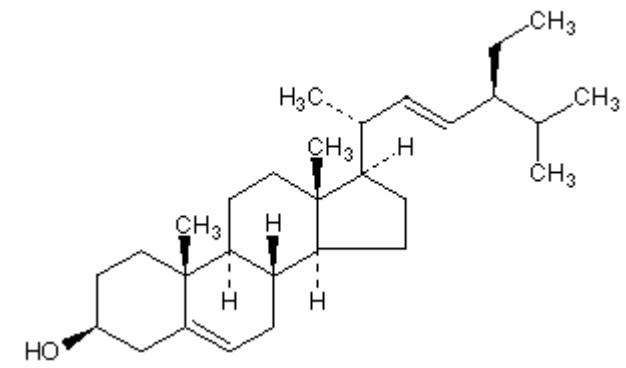




Sitosterol is a plant sterol and like its synthetic analogues hydrocortisone and corticosterone it has powerful skin properties including the reduction in skin erythema (skin redness), the reduction of pruritis (skin itching)

and the reduction in inflammation. Major plants that contain β-sitosterol : *Annona cherimola* MILL. [Annonaceae] Seed 10000-14000ppm, *Crataegus laevigata* (POIR.) DC [Rosaceae] Flower 6500-7800ppm, *Crataegus laevigata* (POIR.) DC [Rosaceae] Leaf 5100-6200ppm, *Nigella sativa* L. [Ranunculaceae] Seed 3218-3218ppm, *Oenothera biennis* L. [Onagraceae] Seed 1186-2528ppm, *Salvia officinalis* L. [Lamiaceae] Leaf 5-2450ppm, *Morus alba* L. [Moraceae] Leaf 2000ppm, *Senna obtusifolia* (L.) H.IRWIN & BARNEBY [Fabaceae] Seed 1000-2000ppm, *Fagopyrum esculentum* MOENCH. [Polygonaceae] Seed 1880ppm, *Ocimum basilicum* L. [Lamiaceae] Leaf 896-1705ppm, *Zea mays* L. [Poaceae] Silk Stigma Style 1300ppm, *Salvia officinalis* L. [Lamiaceae] Stem 1214ppm, *Ocimum basilicum* L. [Lamiaceae] Flower 1051ppm, *Syzygium aromaticum* (L.) MERR. & L. M. PERRY [Myrtaceae] Essential Oil 1000ppm, *Hippophae rhamnoides* L. [Elaeagnaceae] Seed 550-970ppm, *Glycine max* (L.) MERR. [Fabaceae] Seed 900ppm, *Nepeta cataria* L. [Lamiaceae] Shoot 900ppm, *Glycyrrhiza glabra* L. [Fabaceae] Root 500ppm, *Ocimum basilicum* L. [Lamiaceae] Root 408ppm, *Viola odorata* L. [Violaceae] Plant 330ppm, *Cnicus benedictus* L. [Asteraceae] Seed 243ppm, *Ocimum basilicum* L. [Lamiaceae] Sprout Seedling 230ppm, *Withania somnifera* (L.) DUNAL [Solanaceae] Root 200ppm, *Serenoa repens* (W. BARTRAM) SMALL [Arecaceae] Fruit 189ppm, *Turnera diffusa* WILLD. EX SCHULT. [Turneraceae] Shoot 33ppm, *Agrimonia eupatoria* L. [Rosaceae] Shoot 25ppm, *Medicago sativa* subsp. *sativa* [Fabaceae] Fruit 5ppm. [Phytochemical and Ethnobotanical Databases]

Stigmasterol is a closely related phytosterol and has similar properties to the sitosterol described above.



Other plants that contains stigmasterol (the main contenders): *Annona cherimola* MILL. [Annonaceae] Seed 3080-4000ppm, *Panax quinquefolius* L. [Araliaceae] Plant 500ppm, *Vigna radiata* (L.) WILCZEK [Fabaceae] Seed 230-230ppm, *Limonia acidissima* L. [Rutaceae] Fruit 150-150ppm, *Limonia acidissima* L. [Rutaceae] Leaf 120-120ppm, *Fagopyrum esculentum* MOENCH. [Polygonaceae] Seed 92ppm, *Centella asiatica* (L.) URBAN [Apiaceae] Plant 40ppm, *Medicago sativa* subsp. *sativa* [Fabaceae] Fruit 40ppm, *Salvia officinalis* L. [Lamiaceae] Leaf 5ppm.

Symlandine appears to be unique to comfrey and has no reported properties. It is another pyrrolizidine alkaloid.

Symphytine is another pyrrolizidine alkaloid.

Symphytocynoglossin is unique to comfrey and the properties are not known

Tannin is an astringent that firms microcapillary vessels

Viridiflorine is rarely found in the plant kingdom but is present in Hound's Tongue or *Cynoglossum officinale*. The function is unclear.

Conclusion

We have demonstrated that the choice of a plant for its anti-inflammatory properties is rarely dependant on one chemical entity present in the plant, but a symphony of individual components that work synergistically in order to bring benefit to the skin by acting as potentiators of a complex cellular metabolic pathway. In some cases the plant contains seemingly potent and toxic components, however, these are at such trace levels that they are more likely to act as triggers and initiators rather than toxins. A small spark that on its own would not be enough to cause a fire, but which in combination with other accelerants would cause a conflagration.

It has also been shown that specific chemical components occur in other plant genera and species. Comparison of the properties of one plant to another where similar components are present shows that these plants often exhibit similar properties and that specific functional benefits are down to components that are unique to that plant. Examples are the bisabolol in chamomile, glycyrrhetenic acid in liquorice, allantoin in comfrey and asiaticoside in gotu kola.

SPECIFIC ANTI-INFLAMMATORY PLANTS

There are many plant extracts that have been traditionally used for their anti-inflammatory activity. The evidence for the anti-inflammatory activity mostly derives from animal experiments or investigations with immune competent cells. Data from human skin or skin cells are often not available even for very well known plant extracts. In addition, the knowledge on the type of inflammatory enzymes and mediators, respectively, which are blocked by the extracts, is limited.

Honeysuckle Flower (JinYin Hua)

Lonicera japonica is Japanese Honeysuckle, which has fragrant flowers, white tinged with purple, fading to yellow. The fruit is a black fleshy berry. China, Japan, Korea, Taiwan (syn. *Lonicera chinensis* Wats., *Lonicera flexuosa* Thunb., *Lonicera confusa* Miq., *Lonicera brachypoda* DC., *Lonicera japonica* var. *chinensis* Bak.). It is a member of the Caprifoliaceae family, and found in China, Japan and Korea.

Folklore and traditional use

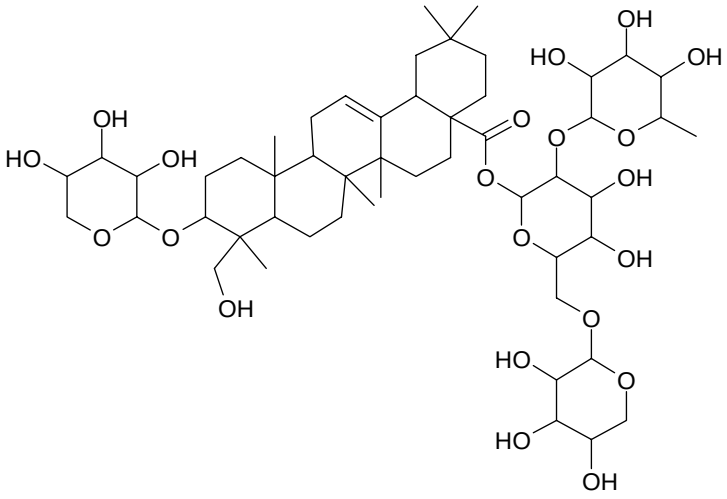
The flowers are used, usually dried.

Prescribed as a diuretic, refrigerant, antiphlogistic in acute infectious diseases; as antidiarrheic in dysentery and enteritis. Dose 10-17g. An infusion of the floral buds is used topically for cutaneous infections [Keys]. The entire plant is used in medicine; and infusion of the fresh flowers is applied externally to skin sores and infections [Reid]. The use of drug was first recorded in *Pen Tsao Kang Mu* (A.D. 1593), because of its antipyretic, anti-toxic, and refrigerant effects, Chinese medicine uses it for fever of the warm diseases, and for swelling carbuncles and scabies [Hsu].

Symptoms: inflamed and swollen throat. Treatments: blood in stools or sputum, ulcers, skin sores and infections, eczema, heat injuries, external heat becoming inner heat. Dosage: 10-15g. There is a European species of honeysuckle, *Lonicera periclymenum*, also called woodbine, which has similar properties but is less potent. In the West, honeysuckle is used for catarrh [Windridge].

Constituents

Caffeoylquinic acids: Chlorogenic acid, neo-, crypto- and isochlorogenic acids
Flavonoids: Luteolin-7-O-neohesperidoside, Ochnaflavone L
Iridoid glucosides: Loniceracetalide A & B
Triterpene glycosides (hederagenin type): Loniceroside A-C, Macranthoidin B

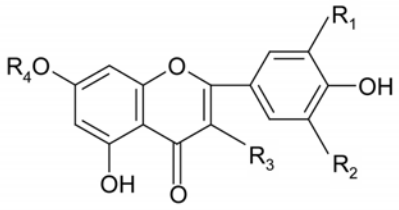


Loniceroside A

Flavonoids are an important bioactive group in the commonly used herbal medicine *Flos Lonicerae*. It is well-known that flavonoids are potent anti-inflammatory mediators and occur widely in the botanical world of herbal medicines. [Chen *et al*]

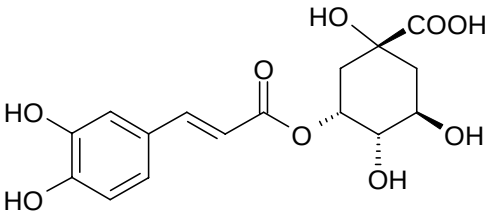
The *n*-butanol (BuOH) fraction of *Lonicera japonica* was prepared and its anti-inflammatory activity was evaluated using several experimental animal models of

inflammation. At oral doses of 100-400 mg/kg, the BuOH fraction showed anti-inflammatory activity against acute, granulomatic and chronic inflammation models in mice and rats. Although the activity was not potent compared with prednisolone, the results supported the traditional use and suggest that this fraction of *L. japonica* would yield a safe and mild anti-inflammatory agent for treating various inflammatory disorders [Lee *et al*].

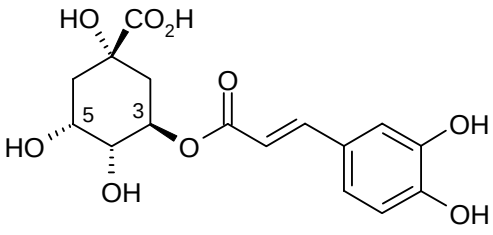


1:	R_1 = OCH_3;	R_2 = OCH_3;	R_3 = H;	R_4 = -Glc-Rha
2:	R_1 = OCH_3;	R_2 = H:	R_3 = H;	R_4 = -Glc-Rha
3:	R_1 = OH;	R_2 = H;	R_3 = OH;	R_4 = -Rha-Glc
4:	R_1 = OH;	R_2 = H;	R_3 = H;	R_4 = -Gal
5:	R_1 = OH;	R_2 = H:	R_3 = -O-Glc-Rha;	R_4 = H
6:	R_1 = OH;	R_2 = H;	R_3 = -O-Gal;	R_4 = H
7:	R_1 = OH;	R_2 = H;	R_3 = OH;	R_4 = H
8:	R_1 = OH;	R_2 = H;	R_3 = H;	R_4 = H
9:	R_1 = OH;	R_2 = H;	R_3 = -O-Ara;	R_4 = H

Chemical structures of eight flavonoids (1–8) in *Flos Lonicerae* and the internal standard (9). **1**, chrysoeirol-7-O-neohesperidoside; **2**, tricin-7-O-neohesperidoside; **3**, lonicerin; **4**, luteolin-7-O-galactoside; **5**, rutin; **6**, hyperoside; **7**, quercetin; **8**, luteolin; **9**, avicularin.



The plant contains chlorogenic acid, and although there are no reports on anti-inflammatory activity of honeysuckle extract or chlorogenic acid on human skin cells, we know from other studies that this is the case [Huang 1988; 1991].

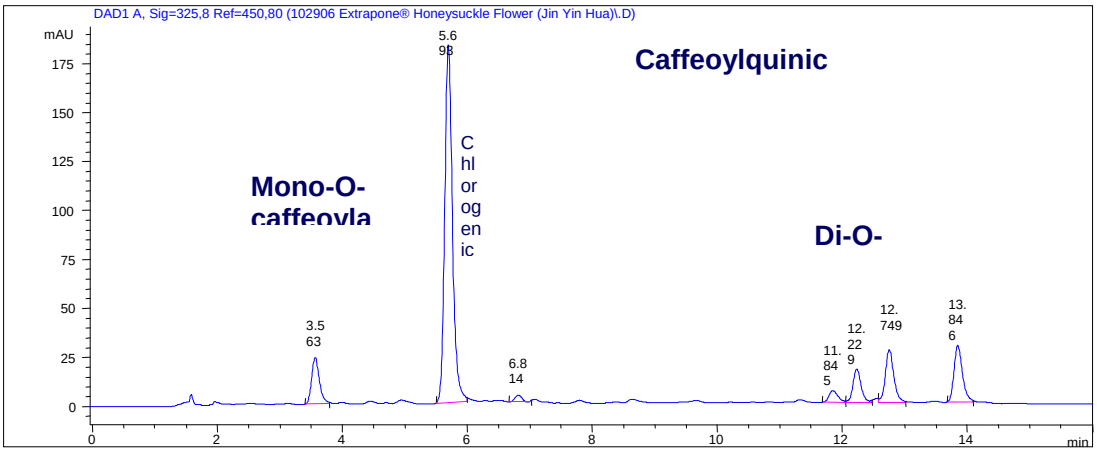


Caffeoylquinic acids:

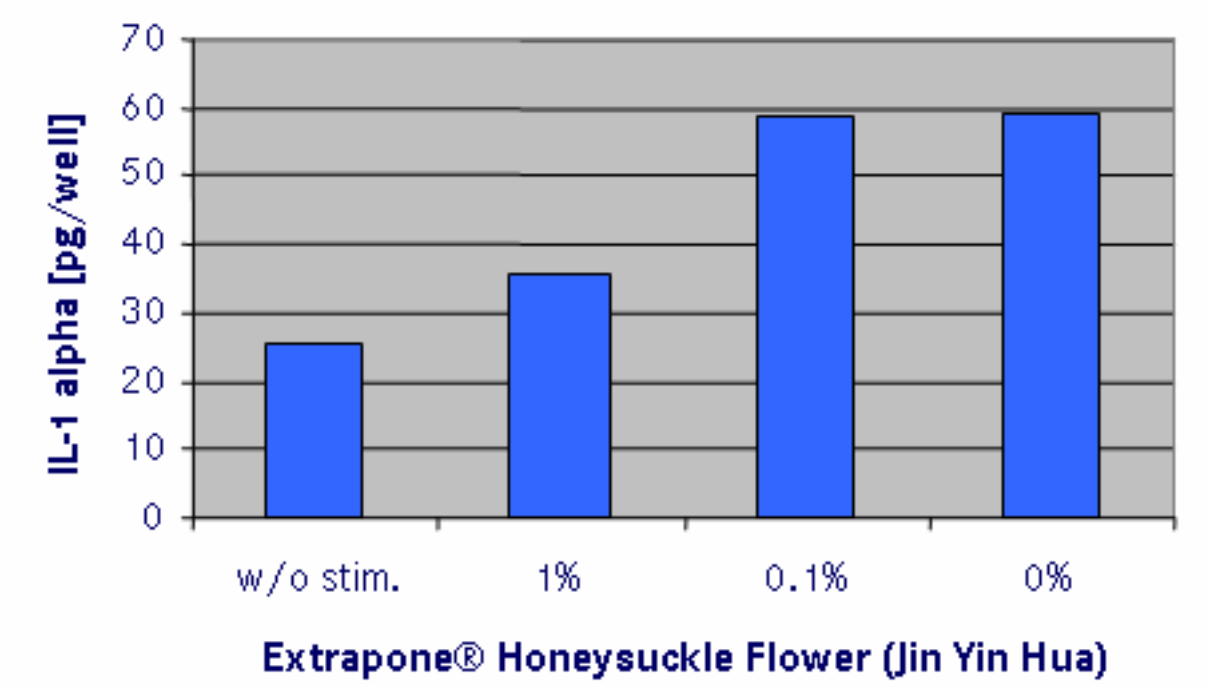
5-O-Ccs = Neochlorogenic acid
3-O-Ccs = Chlorogenic acid
4-O-Ccs = Cryptochlorogenic acid

3,4-, 3,5- and 4,5-Di-O-caffeoylated = Isochlorogenic acids a, b and c

Detection wave length: 325



Extrapone® Honeysuckle Flower exhibits significant anti-inflammatory activity in keratinocytes. At 1 % dosage it inhibits IL-1α release by 40 % relative to the stimulated control.



Pueraria Root (Ge Gen)

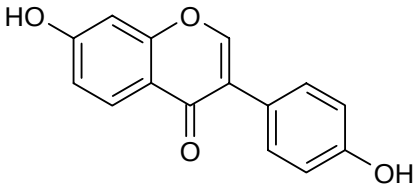
A species that is native to east and southeast Asia with considerable folklore in China and Japan. The roots yield a starch that is used in speciality foods [Burkill]. Known as *Ge Gen* in Chinese the dried roots are used and sometimes *Pueraria thomsonii*.

P. lobata is an important oriental crude drug used as a perspiration, antipyretic and antispasmodic agent as well as treatment for the common cold [Arao].

Based on investigations of 9 species and 1 variety of Pueraria, P. lobata and P. thomsonii are regarded as the main botanical source of the traditional Chinese drug Kudzu. P. lobata, found in most provinces in China, has abundant resources. P. thomsonii has been cultivated in Guangxi for a long time. The other species are mainly distributed in southwestern China; a few of these are also used as Kudzu in some areas. Based on the results of quantitative analysis of active constituents, other Pueraria species besides P. lobata and P. thomsonii cannot be used as Kudzu. Further studies of P. omeiensis are needed; its quantitative composition is similar to that of P. thomsonii, but differs from that of P. lobata var. Montana [Gu].

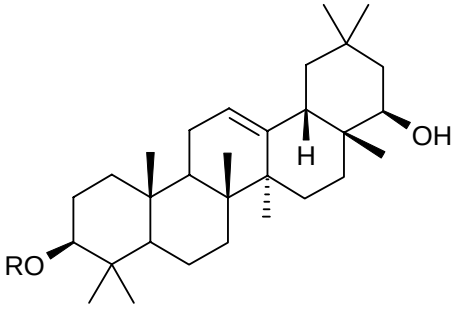
Constituents
The bottom line

Isoflavonoids:
Isoflavones and isoflavone-C- and -O-glycosides
Main component: Puerarin (= daidzein-8-C-glucoside) with minor constituents being daidzein, daidzin and others



Daidzein

Triterpene saponins (oleanene-type):
Kudzusaponin A1- A5, C1, SA1-SA4, SB1, SB3
Kaikasaponin I and III



Kaikasaponin I
R = 3-O-galactosyl(1->2)glucuronid

In greater detail
As with most species of this material the roots contain isoflavonoids daidzin, daidzein, puerarin and a number of related glucosides and derivatives. The roots also contain a number of sapogenins and complex sterols (including β-sitosterol) and their glucosides

[Zhu]. The corresponding genistein derivative (genistein-8-C-glucoside) occurs in *P. lobata* (Kinjo, 1987). Mirificin has been identified as puerarin-*O*-apiofuranoside, with the apiose residue being linked 1 —>6 to the glucose unit, the first time that such an arrangement has been recognized in a natural product. Kinjo et al. (1987) have also obtained mirificin (which they refer to as daidzein-8-C-apiosyl(1—>6)glucoside) and the corresponding genistein derivative from *P. lobata*.

The aerial parts (leaves and stems) and roots of tropical kudzu (*P. phaseoloides*), and the leaves, stems and roots of kudzu (*P. lobata*), also have very low oestrogenic activity, comparable with that found in the leaves and stems of *P. mirifica* (Jones and Pope, 1961).

Isoflavonoids (formononetin, genistein, daidzein, daidzin and puerarin) were detected in both crude root and leaf extracts of kudzu using TLC and HPLC. The other flavonoid glycones and glycosides detected were apigenin, luteolin, quercetin, rutin, hyperoside and quercitrin. Phenolic acids such as caffeic, chlorogenic, p-coumaric and ferulic acids were detected [Matkowski**]**.

2-hydroxyisoflavanone dehydratase has also been isolated I cell culture [Hatsamasuka]. 4’,5,7-trihydroxy-6-methoxyisoflavone (tectorigenin) and 4’,7-dihydroxy-6-methoxyisoflavone (glycitein) [Cho].

Radix of Pueraria spp. is a popular traditional Chinese medicine. There are two major species of Pueraria in Taiwan, i.e., P. montana and P. lobata [P. montana var. lobata]. The major constituents of Puerariae radix were isoflavonoids, which include puerarin, daidzin, genistin, genistein, daidzein and daidzein-4',7-diglucoside. Results showed that the highest level of isoflavonoids was observed in the root and vine of P. lobata, and the daidzein-4',7-diglucoside was only found in root and vine of P. lobata. Levels of isoflavones existed among species, as well as organs, were significantly different [Yang].

Puerariae radix, a commonly used Chinese herb drug derived from the dried roots of Pueraria lobata and P. thomsonii, contains a series of isoflavones as its chief pharmacologically active constituents. Twelve Pueraria components (i.e. 3'-hydroxypuerarin, puerarin, 3'-methoxypuerarin, 6"-O-D-xylosylpuerarin, daidzin, genistin, 6,7-dimethoxycoumarin, daidzein, genistein, formononetin, isoliquiritigenin and biochanin A) as markers. Most of the markers used in this study could be classified, respectively, into three major categories, namely isoflavones, O-glycosidic isoflavones and C-glycosidic isoflavones [Lin], soyasaponin I, kaikasaponin III and kakkasaponin I [Kinjo]. The three major isoflavonoids in the roots of P. lobata, puerarin, 3’-methoxypuerarin and daidzin were isolated in one step, using an n-butanol-t-butylmethylether-acetonitrile-water solvent system [Pei].

The root of Pueraria lobata, is an important oriental crude drug used as an antipyretic and antispasmodic agent. Four new oleanene-type triterpene glycosides, named kudzusaponins SA1, SA2, SA3 and C1, were isolated from the fresh roots of P. lobata

plants, collected from Kumamoto Prefecture, Japan. Their structures were identified as 3-O-beta-D-galactopyranosyl-(1->2)-beta-D-glucuronopyranosyl soyasapogenol A; 3-O-beta-D-galactopyranosyl-(1->2)-beta-D-glucuronopyranosyl soyasapogenol A 22-O-alpha-L-arabinopyranoside; 3-O-alpha-L-rhamnopyranosyl-(1->2)-beta-D-galactopyranosyl-(1->2)-beta -D-glucuronopyranosyl soyasapogenol A 22-O-alpha-L-arabinopyranoside; and 3-O-alpha-L-rhamnopyranosyl-(1->2)-beta-D-galactopyranosyl-(1->2)-beta -D-glucuronopyranosyl kudzusapogenol C 21-O-beta-D-glucopyranoside, respectively [Arao].

The major glycosides were derived from daidzein and most were 8-C-glycosides. 3'-hydroxypuerarin-4'-O-deoxyhexoside and 3'-methoxy-6''-O-D-xylosylpuerarin were identified as new constituents. MS data were obtained for puerarin-4'-O-D-glucoside, 3'-hydroxypuerarin, puerarin, 3'-methoxypuerarin, 6''-O-D-xylosylpuerarin, daidzin and 3'-methoxydaidzin, which were previously characterized by NMR analysis. Isoflavones identified comprised 3'-methoxydaidzein, genistein, daidzein-7-O-methyl ether, 3'-methoxydaidzein-7-O-methyl ether or 3'-methoxyformononetin and biochanin A, while previous characterization of daidzein and formononetin was substantiated by MS data [Rong].

Ethnobotanical uses

The properties of the plant are cited for mainly for internal conditions such as coronary and cerebral vasodilation, hypotensive effects, platelet aggregation inhibition, β-adreneigic blocking effect, antiarrhythmic effect, immunostimulant effect, and antipyretic effects [Zhu]. Although the reported effects are mainly internal, the phytochemistry of this plant would suggest great promise in topical preparations.

Alcohol abuse treatment

The plant seems to have enjoyed some success as an alcohol abuse treatment, helping suppress the desire for alcohol. The ground roots (no doubt because of the reported starch they contain) are used in macrobiotic cooking to thicken sauces [Bown; Shin; Keung].

Kakkalide, one of the major isoflavonoid components of Puerariae flos [Pueraria flowers]. These results suggested that kakkalide might be useful for counteracting the effects of alcohol and might be effective for treating hepatic injury [Yamazaki]. Opinions might differ as two isoflavone constituents, daidzin and daidzein have been said to account for this effect [Keung].

Modern studies

The effect of puerarin (the main isoflavone glycoside in Pueraria lobata) on hydrogen peroxide-induced apoptosis in PC12 cells was studied. The results suggest that puerarin could protect neurons against oxidative stress. It could block apoptosis in its early stages via the regulation of anti- and pro-apoptotic proteins, as well as by the attenuation of caspase-3 activation in H_2O_2-induced PC12 cells [Jiang; see also Ji].

The mechanism(s) of the plasma-glucose-lowering action of puerarin (a constituent of Pueraria lobata, a herbal drug) in streptozotocin-induced diabetic rats (STZ-diabetic rats) was studied. Puerarin may activate alpha^{1}-adrenoceptors on the adrenal gland to enhance the secretion of beta-endorphin to result in a decrease of plasma glucose in STZ-diabetic rats [Chen].

A study was conducted to investigate the effect of puerarin (a constituent of Pueraria spp.) on expressions of MMP-2 and TIMP-2 in the kidney of diabetic rats. Puerarin showed some renal protective effect on diabetic nephropathy, partly through inhibition of excessive deposition of glomeruli extracellular matrix by up-regulating MMP-2 and down-regulating TIMP-2 expressions besides reducing the blood glucose [Duan].

The differential anti-proliferation effect of white (Pueraria mirifica), red (Butea superba) and black (Mucuna collettii) Kwao Krua plant extracts on the growth of MCF-7 cells was evaluated after 4 days of incubation. The percent cell growth comparison was based on protein determination of the harvested cells in parallel with the control group and Pueraria lobata treatment group. Pueraria lobata led to no proliferation and a mild anti-proliferation effect on the growth of MCF-7 cells. Pueraria mirifica caused proliferation at 1 microg/mL and an anti-proliferative effect on the growth of MCF-7 cells at 100 and 1000 microg/mL with an ED50 value of 642.83 microg/mL. Butea superba led to no proliferation and an anti-proliferation effect on the growth of MCF-7 cells at 10, 100 and 1000 microg/mL with an ED50 value of 370.91 microg/mL. Mucuna collettii led to no proliferation and an anti-proliferation effect on the growth of MCF-7 cells at 100 and 1000 microg/mL with an ED50 value of 85.36 microg/mL. The results demonstrated that only Pueraria mirifica showed an estrogenic effect on MCF-7 cell growth and a clear antagonistic effect with E2 at high concentration. Butea superba and Mucuna collettii exhibited only anti-proliferation effects on the growth of MCF-7 cells in relation with a possible anti-estrogen mechanism or a potent cytotoxic effect [Cherdshewasart].

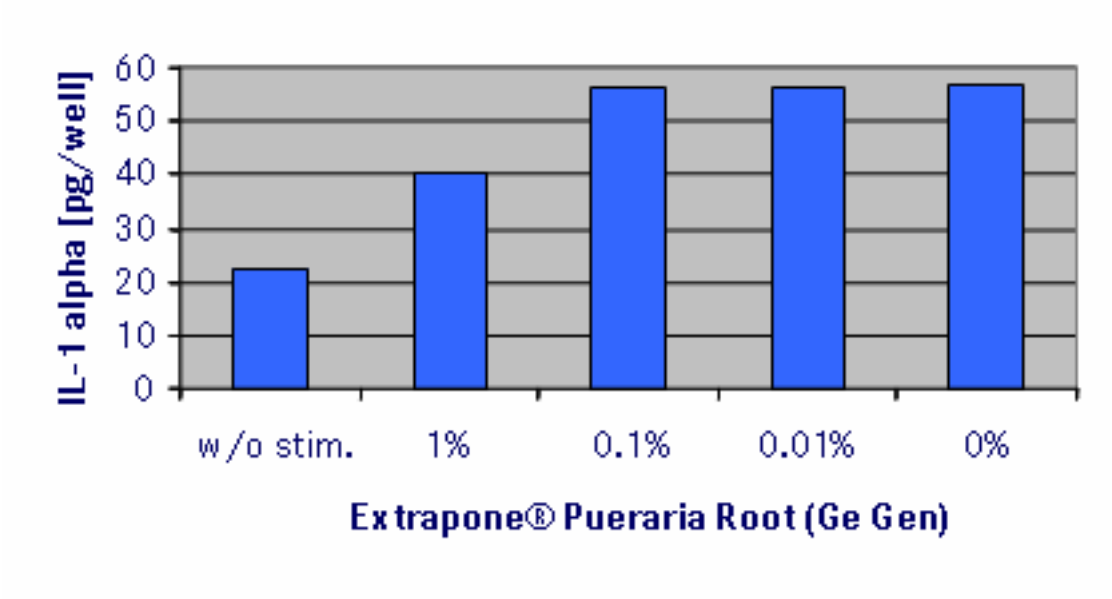
The roots of Pueraria thomsonii and Pueraria lobata are officially recorded in Chinese Pharmacopoeia under the same name Radix puerariae. However, the aqueous root extract of Pueraria lobata showed more potent antioxidant activity than that of Pueraria thomsonii. A qualitative HPLC method was developed to compare the chemical profiles of Pueraria thomsonii and Pueraria lobata, which revealed four major common peaks (daidzein 1, daidzin 2, puerarin 3 and 5-hydroxypuerarin 4) and two major different peaks (3-hydroxypuerarin 5 and 3'-methoxypuerarin 6) in their chromatograms. Semi-quantitative analysis showed that the contents of 1-3 in Pueraria lobata are about three, three, and five times higher than those of Pueraria thomsonii, respectively. The higher contents of isoflavonoids in Pueraria lobata were inferred to be responsible for its more potent antioxidant activity as compared with that of Pueraria thomsonii [Jiang].

It has also been demonstrated that Pueraria might prevent bone loss [Wang], could be useful in the treatment of diabetes [Yasuda], and used to increase ocular blood flow in

the case of eye disease [Xuan]. It has also been examined for its antithrombotic and antiallergic activities which are as a result of daidzein [Choo].

It is a potent antioxidant [Speroni]

Extrapone® Pueraria Root (Ge Gen) exhibits significant anti-inflammatory activity in keratinocytes. At 1 % dosage it inhibits IL-1α release by 30 % relative to the stimulated control.



Toxicology

P. tuberosa is used in traditional medicine as a fertility control agent, and as an aphrodisiac, cardiotonic, diuretic and galactogogue. A butanol extract (150 mg/kg, p.o.) of P. tuberosa (collected from India), a prospective postcoital contraceptive agent, was administered to rats for 6, 12, 18 or 24 days. The concentrations of blood sugar and serum proteins showed variations within the normal range. The concentrations of serum GPT [alanine aminotransferase] and GOT [aspartate aminotransferase] were significantly higher following treatment at the highest regimens. Leucocyte counts and haemoglobin values were within normal limits. Generally, the concentrations of proteins, glycogen and total and esterified cholesterol, and the activities of acid and alkaline phosphatase, adenosine triphosphatase and glucose 6-phosphatase showed no significant changes in the kidney, liver and spleen of treated animals; significant changes were observed in the adrenal glands, particularly with the 24-day regimen. No significant histopathological lesions were observed following treatment [Sangeeta].

Sophora Flower (Huai Hua)

Sophora japonica [Syn. *Styphnolobium japonicum* Scott.) is also known as the Japanese Pagoda Tree. It is a tall deciduous tree, which has creamy white flowers from June-July.

It is found in China, Korea, northern Vietnam. The fruit is a pod, constricted between the three or four black, bean-shaped seeds. *The seeds are poisonous.*

The Japanese Pagoda tree is native to eastern Asia but it is widely grown elsewhere as an ornamental tree in parks and gardens. There are pendant forms and ones with violet flowers. The tree flowers profusely in late summer but does not bear fruits in Europe. The generic name comes from the Arabic name *sufayra* for a tree of the bean or pea family.

The flower buds, the leaves and the bark are used medicinally. When dry they have a bitter taste. Most important of the active constituents is the glycoside rutin (up to 20%), which decreases the permeability of the capillaries. It is extracted by the pharmaceutical industry and included in medicines prescribed for circulatory and neurological disorders [Bunney].

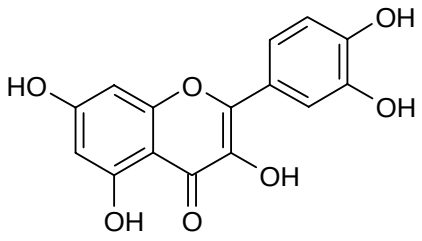
The flowers, under the name *Wai-fa* or *Wai-hwa*, are used in those countries for dyeing silk a yellow color, and to produce a beautiful green, when mixed with a proper proportion of blue.

Constituents

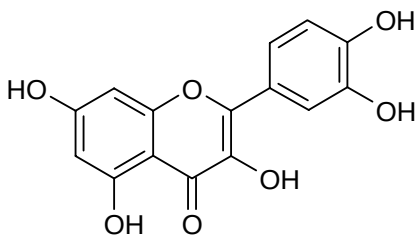
Flavonoids:
main component: Rutin (= quercetin-3-O-rutinoside)
minor constituents: kaempferol-3-O-glycosides

Isoflavonoids:
Sophorocoside and other genistein-glycosides

Triterpene saponins (oleanen-type):
Kaikasaponin I, II and III and others



Quercetin



Quercetin

The seeds and flowers are used medicinally. The fruits contain rutin, sophoretin (quercetin), rhamnose, sophoricoside, sophorabioside. The floral buds contain rutin.

Injection of the extract of the fruit induces hyperglycaemia from diminuition of red corpuscles and impaired haematosis; this hyperglycaemia is of short duration; the total extract of the fruit is very toxic [Keys].

Foerster (1882) obtained from it the yellow glucosid, *sophorine*, which splits into *sophoretin* and *isodulcite* when treated with diluted sulphuric acid (also see R. Wachs, *Amer. Jour. Pharm.*, 1894, p. 35).

Rutin

Rutin, synonyms quercetin-3-rutinoside, rutoside, eldrin, and sophorin.

Rutin is a glycoside containing quercetin as its aglycone and rutinose (rhamnose and glucose) as its sugar portion. It is widely distributed in the plant kingdom, being found in many families of higher plants and also in ferns.

It is present in high concentrations in the leaves of *Eucalyptus macrorhyncha* F.vM. (10 to 24%), flowers of *Viola tricolor* L. var. *maxima* (18 to 21%), flower buds of *Sophora japonica* L. (13 to 30%), and in buckwheat, *Fagopyrum esculentum* Moench (0.1 to 6.4%).

S. japonica is one of major sources of rutin.

Rutin has been reported to have many pharmacological properties. One of its ascribed attributes is its ability to decrease capillary permeability and fragility. It is considered a "vitamin P" or "permeability" vitamin. Other pharmacological activities include anti-inflammatory, antispasmodic, hypotensive and protective against X-ray irradiation in mice, among others. Rutin was formerly an official drug in the United States and has been used in treating capillary haemorrhage due to increased capillary fragility in degenerative vascular diseases (e.g. arteriosclerosis and hypertension), diabetes, and allergic manifestations. It is no longer official in N.F. (National Formulary), but rutin still is quite widely used, both as a prescription drug and as a vitamin supplement. Flower buds of *Sophora japonica* containing high concentrations of rutin (usually about 20%) and the plant has been used for centuries in Chinese medicine for the treatment of internal bleeding (e.g. bloody urine, spitting blood and intestinal bleeding) and bleeding haemorrhoids. It is also used in the prevention of strokes [Leung].

Sophoricoside

The anti-inflammatory action of sophoricoside, an isoflavone glycoside isolated from immature fruits of Sophora japonica [Styphnolobium japonicum] was studied. When administered orally at > 100 mg/kg or injected intravenously at > 10 mg/kg, sophoricoside showed significant reduction of carrageenin-induced paw oedema in mice. Sophoricoside was identified as a selective inhibitor of cyclooxygenase (COX)-2 activity, with an IC50 value of 3.3 microM [Kim].

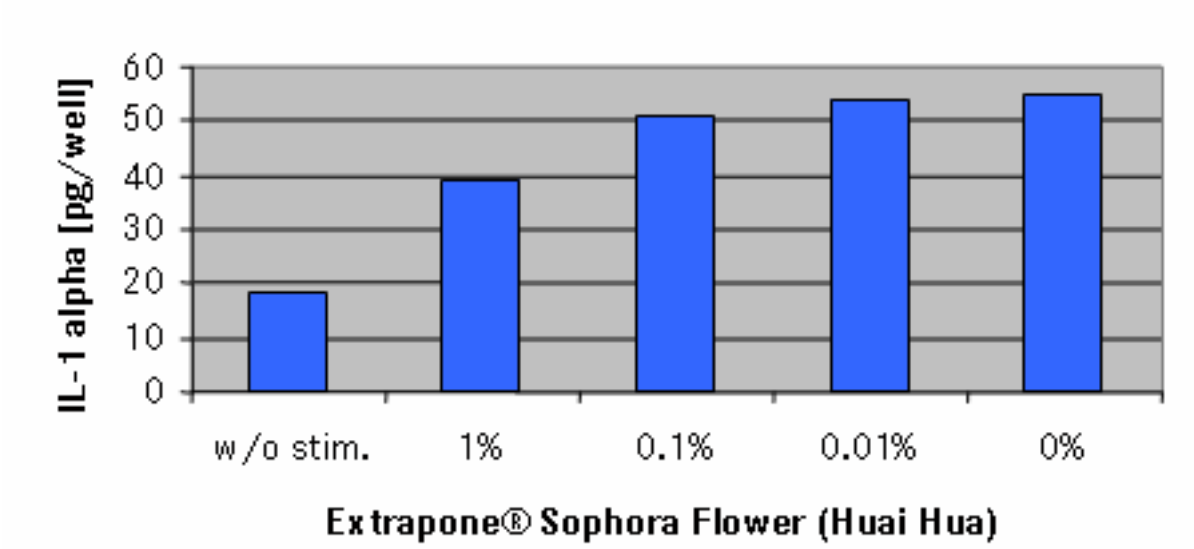
Fruits of S. japonica [Styphnolobium japonicum] exhibited an inhibitory effect in the interleukin (IL)-5 bioassay of mIL-5-dependent Y16 (murine cell line) proliferation. The isoflavonoids of sophoricoside, genistein, orobol and genistin were isolated as the IL-5 inhibitors from the fresh fruits by activity-guided fractionation. Among the IL-5 inhibitors, sophoricoside exhibited the highest inhibitory effect with 89% inhibition at 12.5 μM, 82% at 6.3 μM , 72% at 3.1 μM , 59% at 1.6 μM , and 24% at 0.8 μM ; 50% inhibition (IC_{50}) was shown at the concentration of 1.5 μM. Oxyphenylbutazone as the positive control exhibited an IC_{50} value at a concentration of 31.7 μM . In the order of IC_{50} values, the inhibitory potency in the IL-5 bioassay was sophoricoside > orobol (9.8 μM) approx = genistin (10.6 μM) > genistein (51.9 μM). The position of O-glycosylation and number of hydroxy groups in the isoflavonoids seem to play an important role in the inhibitory effect in the IL-5 bioassay [Min].

Effects of sophoricoside and its analogues on pro-inflammatory cytokines have been investigated. Sophoricoside, genistein and orobol exhibited inhibitory effects against IL-5, IL-3, GM-CSF and IL-6 bioactivities. Genistein showed inhibitory effects on IL-5 and IL-3 bioactivities, but did not inhibit GM-CSF and IL-6 bioactivities. None of the sophoricoside analogues showed inhibitory effects against IL-1beta and TNF-alpha bioactivities. Among the compounds, sophoricoside exhibited the highest inhibitory effects on IL-5, IL-3 and IL-6 bioactivities with IC50 values of 1.9, 6.9 and 6.0 microM, respectively. Orobol inhibited GM-CSF bioactivity with an IC50 value of 18.0 microM. The result would provide an additional mechanism by which the compounds exert immunosuppressive and anti-inflammatory effects [Yun].

The effects of genistein analogues isolated from Sophora japonica [Styphnolobium japonicum] on oxygen radical production have been analysed in human neutrophils, human monocytes or murine macrophages Genistin and sophoricoside are genistein glycosides with a glucose moiety at 7 or 4' position, respectively. The genistein glycosides exhibited 23-37% inhibitory effects at 100 microM on the oxygen radical production [Yun].

The seeds and flowers are used as haemostatic. Dose 5-10g.

Extrapone® Sophora Flower (Huai Hua) exhibits significantly anti-inflammatory activity in keratinocytes. At 1 % dosage it inhibits IL-1α release by 30 % relative to the stimulated control.



Toxicology
All parts of the tree are purgative, and persons who prune it, as well as workmen who are engaged in turning the dry wood, are affected by it.

Nutgrass (Motha) Root

Not completed

Witch Hazel
Hamamelis virginiana

This shrub, long known in cultivation, consists of several crooked branching trunks from one root, 4 to 6 inches in diameter, 10 to 12 feet in height, with a smooth grey bark, leaves 3 to 5 inches long and about 3 inches wide, on short petioles, alternate, oval or obovate, acuminate, obliquely subcordate at the base, the margin crenate, dentate, scabrous, with raised spots underneath, pinnately veined and having stellate hairs. The leaves drop off in autumn, after which the yellow flowers appear, late in September and in October, in clusters from the joints, followed by black nuts, containing white seeds which are oily and edible. In Britain, the nut does not bear seeds, but in America, they are produced abundantly, but often do not ripen till the following summer. The seeds are ejected violently when ripe, hence the name Snapping Hazelnut. The leaves are inodorous, with an astringent and bitterish aromatic taste. The twigs are flexible and rough, colour externally, yellowish-brown to purple, wood greeny white, pith small. The bark as found in commerce is usually in quilled pieces 1/16 inch thick, 2 to 8 inches long, with silvery grey, scaly cork; longitudinally striated; fracture fibrous and laminated; taste and odour slight [Grieve].

Common names

It is also called Hazel Nut, Pistachio, Snapping Hazel, Spotted Hazel, Striped Alder, Tobacco Wood, Winterbloom, Hamamelis, Long Boughs, White Hazel, Spotted Alder, Tobacco Wood.

Constituents

Witch Hazel contains an astringent compound hamamelitannin, which is found in the leaves and the bark; also traces of a saponin and flavonoid pigments [Schauenberg]. Witch hazel leaf contains about 7 to 10% tannins.There is some dispute as to the actual composition of the tannin with hamamelitannin, digallylhamamelose and various gallotannins having been identified. Recent sources list from 8% to no hamamelitannin in leaves. The bark contains from 1% to 7% hamamelitannin and smaller amounts of condensed tannins. Other components include flavonoids (e.g. kaempferol, quercetin), gallic acid, saponins, a fixed oil and a volatile oil. The volatile oil contains small amounts of safrole and eugenol and numerous other minor components, such as resin, wax and choline. Witch hazel water is a steam distillate of the extract and does not contain any tannins [Lawrence]. It also contains methyl heptenone, linalool, terpineol, carvacrol, eugenol, ß-ionone.

Flavonoids (leaf) Flavonols (e.g, kaempferol, quercetin) and their glycosides including astragalin, quercitrin, afzelin, and myricitrin.
Tannins (about 8%) Hamamelitannin (hydrolysable), less amounts of condensed tannins (bark) including *d*-gallocatechin, *l*-epicatechin, gallate, *l*-epigallocatechin
Volatile oils (about 0.5%). Hexen-2-ol, hexenol, α- and β-ionones, eugenol, safrole, sesquiterpenes
Other constituents Fixed oil (about 0.6%), resin (hamamelin, hamamamelitannin), wax, saponins, choline, free gallic acid, free hamamelose [Newall].

Ethnobotanical uses

The fluid extract is haemostyptic and is recommended for menopause problems, haemorrhoids and varicose veins (because it is a venous vasoconstrictor). It is also used to treat bruises because it has decongestive properties. Witch hazel, either as a fluid extract or as a tincture stimulates the circulation of the blood without causing irritation and is widely used in cosmetics as a skin tonic [Schauenberg].

The medicinal qualities were understood by the American Indians. The leaves and bark are both astringent, tonic and sedative. The astringent action is because of its relatively high tannin content, and is used in the treatment of varicose veins. Preparations can be used for minor burns. It is used as a poultice for inflammation, a wash for bed sores, and a lotion for stings. As a snuff in dried form it stops nose bleeds when sniffed [Gordon].

The bark of this plant was used as a mouthwash to remedy gum soreness and inflamed throat areas. The aqueous extract of witch hazel was used in shaving products. A boiled solution of the plant is used as a massage to keep athletic legs toned and active.

The distilled extract of the leaves and twigs is soothing when applied to a chapped or sunburnt skin. It can be used to eliminate pimples and blackheads [Genders].

Preparations have been used topically for symptomatic treatment of itching and other skin inflammations and in ophthalmic preparations for ocular irritations [Lawrence].

Hamamelis has astringent properties and is used in ointment and suppositories in the treatment of haemorrhoids. Hamamelis water is used as a cooling application and has been applied as a haemostatic [Martindale].

It has been used in the treatment of atopic dermatitis. The treatment produced a reduction in the intensity of the symptoms, affecting desquamation most. [Swoboda]

Mode of action

Depending on how the preparation is made witch hazel products contain varying amounts of active compounds such as flavonoids, tannins (hamamelitannin and proanthocyanidins), small amounts of volatile oil, and other components, which may be responsible for its astringent action and to act as a haemostat bleeding. The tannins have been characterized as hamamelitannin and there are a number of proanthocyanidins as well.

A specially filtered fraction of the extract that contained mostly proanthocyandins, was found to have significant anti-viral activity against *Herpes simplex* virus type 1. The same fraction was also found to have a strong antiphlogistic (inflammation-reducing) effect. The fractions high in hamamelitannin were found to have weaker antiviral or antiphlogistic activity. Compounds other than tannins may play a role in witch hazel's recognized antiphlogistic effects, as well as in topical antiviral activity.

Antioxidant, radiation-protective, and anti-inflammatory activity have been confirmed. Recently hamamelitannin and proanthocyanidins isolated from witch hazel were evaluated for their mechanisms of action in reported anti-inflammatory activity. It was found that some proanthocyanidin fractions inhibit inflammatory mediators derived from arachidonic acid and inhibited the formation of platelet-activation factor, a chemical mediator of inflammatory processes.

Strong antioxidant activity against superoxide (a highly reactive form of oxygen), released by several enzymes during the inflammatory process may also play a role in witch hazel's anti-inflammatory effects. In a recent study, Japanese researchers sought plant compounds that protect cells in skin tissue from damage against harmful forms of oxygen. Witch hazel was found to have strong activity against reactive oxygen in skin tissue [Foster].

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