SAGE LEAF

Salviae officinalis folium

Synonyms: Common or Dalmatian sage leaf.

Definition
Sage Leaf consists of the dried leaves of *Salvia officinalis* L.

Monographs on (common or Dalmatian) sage leaf from *Salvia officinalis* L. and three-lobed sage leaf from *Salvia fructicosa* Mill. [*S. triloba* L. fil.] appear in the European Pharmacopoeia. Certain other well-known *Salvia* species, such as *S. lavandulaefolia* (or *lavandulifolia*) Vahl (Spanish sage) and *S. sclarea* L. (clary sage) are used primarily for their essential oils.

CONSTITUENTS

☐ ***Essential oil***, up to 3% [1] (Ph. Eur. min. 1.5% V/m for whole dried leaf, 1.0% V/m for cut dried leaf), of very variable composition depending on the source, time of harvesting and other factors. The principal components are monoterpenoids such as α-thujone (10-60%), β-thujone (4-36%), camphor (5-20%) and 1,8-cineole (2-15%), together with sesquiterpenes such as α-humulene, β-caryophyllene and viridiflorol [1-3].

☐ ***Hydroxycinnamic acid derivatives***, about 3.5%, principally the caffeic acid dimer rosmarinic acid (up to 3.3%) [4]. Caffeic acid trimers (melitric acid A, methyl melitrate A, sagecoumarin and salvianolic acid K) [5,6] and a tetramer (sagerinic acid) [6] have also been isolated.

Collectively, these and similar compounds are sometimes described as "tannins" or "Labiatae tannins" since they may be adsorbed by hide powder to some extent in methods for the determination of tannins in herbal drugs (e.g. Ph. Eur. method 2.8.14). However, they are not genuine tannins in the sense of condensed tannins (proanthocyanidins) or hydrolysable tannins (gallo- and ellagitannins).

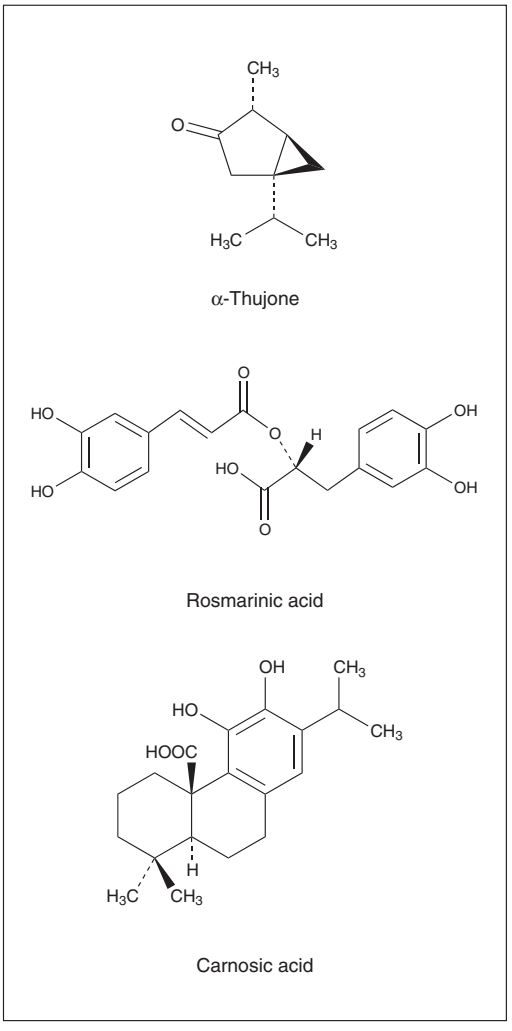
Other hydroxycinnamic compounds present include 6-feruloyl-glucose [7] and a polyalcohol derivative of it [8], three hydroxycinnamic esters of disaccharides, e.g. 1-caffeoyl-(6′-apiosyl)-glucoside [9] and free caffeic acid [8].

☐ ***Phenolic diterpenes*** Carnosic acid, a tricyclic diterpene, occurs in the fresh leaf [10] and to some extent in the dried leaf [11] and certain types of extract [12]. However, carnosic acid is fairly unstable and readily auto-oxidises to form lactones (see the diagram in the Rosemary Leaf monograph), especially the bitter-tasting lactone carnosol (0.35%) [10]. In turn, carnosol can degrade further to produce other phenolic diterpenes with lactone structures, such as rosmanol, epirosmanol, 7-methoxyrosmanol and galdosol, which have been identified in sage leaf [11,13] and/or sage oleoresin [12].

Safficinolide and sageone [14], methyl carnosate, the lactone sagequinone methide A [11], and other related diterpenes [11] have also been isolated. Some of these compounds may be artefacts formed during extraction and isolation.

☐ ***Triterpenes*** Pentacyclic triterpene acids, mainly ursolic acid (up to 3.5%) and oleanolic acid (up to 0.4%), and the triterpene alcohols α- and β-amyrin (0.18% and 0.10% respectively) [15].

☐ ***Flavonoids***, ca. 1.1% [16], principally flavones and their glycosides including: luteolin, its 7-glucoside, 7-glucuronide, 3′-glucuronide and 7-methyl ether; 6-hydroxyluteolin, its 7-glucoside and 7-



glucuronide; 6-methoxyluteolin and its 7-methyl ether; apigenin, its 7-glucoside and 7-methyl ether (= genkwanin); 6-methoxyapigenin (= hispidulin) and its 7-methyl ether (cirsimaritin); vicenin-2 (= apigenin 6,8-di-*C*-glucoside) [13,17-19] and 5-methoxysalvigenin [20].

☐ ***Phenolic glycosides***, a diverse range including, in addition to the glycosides mentioned under Hydroxycinnamic acid derivatives and Flavonoids, picein (4-hydroxyacetophenone glucoside), 4-hydroxyacetophenone 4-(6′-apiosyl)-glucoside, *cis*- and *trans*-*p*-coumaric acid 4-(2′-apiosyl)-glucoside, isolariciresinol 3-glucoside, 1-hydroxypinoresinol 1-glucoside and others [7,8,19].

☐ ***Polysaccharides*** Crude fractions rich in water-soluble arabinogalactans and also high-MW pectin and glucuronoxylan-related polysaccharides have been isolated from aerial parts of sage [21,22].

☐ ***Other constituents*** include small amounts of benzoic acid derivatives (*p*-hydroxybenzoic, gentisic, syringic and other acids) [8,23] and phytosterols (β-sitosterol and stigmasterol, 0.001%) [15,18].

Published Assay Methods

Rosmarinic acid by HPLC [24]. Phenolic diterpenes and rosmarinic acid by HPLC [25].

PHARMACOLOGY

In vitro

Antioxidant activity

Sage leaf extracts exhibit strong antioxidant activity, largely attributable to various phenolic constituents including phenolic diterpenes such as carnosol [8] and hydroxycinnamic acid derivatives, notably rosmarinic acid [4].

In a carotene bleaching test, the antioxidative activity of a dry acetone extract (15:1) from sage leaf was found to be 101-116% of that of the synthetic antioxidant butylated hydroxytoluene (BHT) [26].

Lipid peroxidation in both enzyme-dependent and enzyme-independent test systems were inhibited more effectively by a dry 50%-methanolic extract from aerial parts of sage leaf than by α-tocopheryl acid succinate (as a positive control). The antioxidant activity was attributed mainly to phenolic compounds, rosmarinic acid being the main contributor due to its high concentration in the extract [27,28].

Affinity to human benzodiazepine receptors

A methanolic extract from sage leaf showed affinity to human brain benzodiazepine receptors (from post-mortem frontal cortex) by competitive displacement of ^{3}H-flumazenil, a specific benzodiazepine antagonist. Activity-guided analysis revealed five benzodiazepine receptor-active constituents, of which three are flavones and two diterpenes. Compared to diazepam (IC_{50}: 0.05 µM) the diterpene galdosol (IC_{50}: 0.8 µM) and the flavone hispidulin (IC_{50}: 1.3 µM) were the most active; 7-methoxyrosmanol (IC_{50}: 7.2 µM) also exhibited strong affinity, while apigenin (IC_{50}: 30 µM) and cirsimaritin (IC_{50}: 350 µM) were considerably less active [13].

Other activities

Sage oil has strong antimicrobial properties, attributed principally to the presence of thujones. Inhibitory activity of the oil against Gram-positive and Gram-negative bacteria and against a range of fungi has been demonstrated [29,30]. Antiviral activity (against vesicular stomatitis virus) was exhibited by a methanolic extract from sage aerial parts and two phenolic diterpene constituents (safficinolide and sageone) [14].

Sage oil had only a relatively weak spasmolytic effect on isolated guinea pig tracheal and ileal smooth muscle in comparison with oils from other Labiatae such as melissa leaf or thyme [31].

An 80%-ethanolic extract from sage leaf exhibited dose-dependent cholinesterase-inhibiting activity. It was a more selective inhibitor of butyrylcholinesterase (IC_{50}: 0.054 mg/ml) than of acetylcholinesterase (IC_{50}: 0.365 mg/ml) [32].

It has recently been shown that water-soluble polysaccharides isolated from aerial parts of sage possess immunomodulatory activity [21,22].

In vivo

Topically applied chloroform extracts from sage leaf (obtained from four different plant populations) dose-dependently inhibited croton oil-induced ear oedema in mice with an ID_{50} corresponding to dried leaf at 2-4 mg/cm^2. Almost 50% of the extract proved to be ursolic acid which, as an isolated compound, exhibited strong anti-inflammatory activity in the same test with an ID_{50} of 0.14 µMoles/cm^2, almost twice as potent as indometacin with an ID_{50} of 0.26 µMoles/cm^2 [33].

Pharmacological studies in humans

In a double-blind, placebo-controlled, crossover study, 30 healthy young volunteers (17 males, 13 females; mean age 24 years) were given, on three separate days at 7-day intervals in accordance with a randomized scheme, different single-dose treatments in identical opaque capsules: 300 mg or 600 mg of dried sage leaf, or placebo. On each test day, pre-dose and at 1 hour and 4 hours post-dose, each participant underwent mood assessment, requiring completion of Bond-Lader mood scales and the State Trait Anxiety Inventory (STAI) before

and after a 20-minute performance on the Defined Intensity Stress Simulator (DISS) computerized multitasking battery. The last comprised a set of four cognitive and psychomotor tasks presented concurrently on a split (quartered) screen layout, to which responses had to be made with an external mouse, giving attention simultaneously to all four tasks while monitoring the cumulative score (reflecting accuracy and speed of response) in the centre of the screen. The DISS engenders increases in self-ratings of negative mood, arousal and stress-related physiological responses.

Both doses of sage leaf led to post-dose improved ratings of mood before performing on the DISS, with the lower dose reducing anxiety and the higher dose increasing 'alertness', 'calmness' and 'contentedness' on the Bond-Lader scales. However, the lower dose reduced alertness on the DISS and, as a result of performing on the DISS, the previously reduced anxiety effect of this dose was abolished. After the higher dose, task performance on the DISS battery improved at both post-dose sessions, but after the lower dose task performance decreased. The results indicated that single doses of sage leaf can improve cognitive performance and mood in healthy young participants, although the lower dose (300 mg) appeared to fall somewhat below the level required for beneficial effects. It is possible that inhibition of cholinesterases by sage leaf (demonstrated only *in vitro*) could be involved in the mechanism causing these effects [32].

CLINICAL STUDIES

In a randomized, double-blind, placebo-controlled study, patients aged 65-80 years of age with a diagnosis of mild to moderate dementia and probable Alzheimer's disease were treated for 16 weeks with 60 drops/day of either a sage leaf liquid extract (1:1, 45% ethanol; n = 15) or a placebo liquid (n = 15). Compared with the placebo group, patients in the sage leaf group experienced significant benefits in cognitive function by the end of treatment, as indicated by improved scores in the Clinical Dementia Rating (CDR; $p<0.003$) and the Alzheimer's Disease Assessment Scale (ADAS-Cog; $p = 0.03$). Within the limitations of a fairly small number of patients and short period of follow-up, the results suggested efficacy of the sage leaf extract in the management of mild to moderate Alzheimer's disease [34].

Several open studies, carried out mainly in the 1930s on patients or healthy volunteers but including a larger 1989 study (unpublished) on 80 patients with idiopathic hyperhidrosis (the secretion of an abnormally large amount of sweat), supported the longstanding belief that sage leaf aqueous extracts have anti-hyperhidrotic activity [35].

THERAPEUTICS

Actions
Antioxidant [4,26-28], anti-inflammatory [33], antimicrobial [29,30], carminative [36,37], weakly spasmolytic [31,37], astringent [36-39], antihidrotic (inhibits perspiration) [37-40]. Considered to be a stimulant and tonic to the digestion and nervous system [36,39].

Recent human studies have demonstrated beneficial effects of sage leaf on cognitive performance and mood in healthy young volunteers [32] and cognitive function in elderly patients with mild to moderate Alzheimer's disease [34].

Indications
None adequately substantiated by pharmacological or clinical studies.

Uses based on experience or tradition
Internal: Digestive disorders such as dyspepsia, flatulence, poor digestion and bloating [37-40]; to reduce excessive perspiration [37-40,42], e.g. in the menopause [39,42]. Also taken as a gentle, stimulating tonic [39].
Topical (as a gargle or mouthwash): Inflammations of the mouth or throat mucosa, such as pharyngitis, tonsillitis, stomatitis, gingivitis and glossitis [36-40].

Contraindications
Sage leaf should not be taken during pregnancy or lactation (except in amounts present as a flavouring in foods) [35,42]. Epileptics are also advised to avoid it due to the convulsant potential of thujones [40].

Side effects
None reported.

Interactions with other drugs
None known.

Dosage
Internal daily dose: 3-6 of dried leaf, usually as an infusion [37,38]; liquid extract 1:1 in 45% ethanol, 2-6 ml [34,37].
For topical use in mouthwashes and gargles: 2.5 g of dried leaf to 100 ml of water as an infusion [38].

SAFETY

The amount of sage leaf consumed as a culinary herb in food presents no hazard, but a degree of caution is necessary with larger amounts due to the presence of thujones and camphor in the essential oil. Recommended dosages should not be exceeded or taken over prolonged periods, and sage leaf preparations should be avoided during

pregnancy and lactation [43]. The pure essential oil should never be used [44].

In a randomized clinical study, 15 elderly patients treated with 60 drops/day of a sage leaf liquid extract (1:1, 45% ethanol) for 16 weeks experienced slightly more mild gastrointestinal complaints than those receiving placebo, but the differences were not statistically significant [34].

The oral LD_{50} of the essential oil in rats was found to be 2.6 g/kg [45]. α-Thujone, which is more toxic than β-thujone [46] and is present as a higher proportion of the essential oil [2], is a convulsant. Its intraperitoneal LD_{50} in mice is about 45 mg/kg, while 60 mg/kg causes a tonic convulsion leading to death within 1 minute. The mechanism of α-thujone neurotoxicity has been shown to be modulation of the γ-aminobutyric acid (GABA) type A receptor. However, α-thujone is rapidly detoxified in mice by conversion to less toxic metabolites [46].

In tests for mutagenicity neither ethanolic extracts [47,48] nor the essential oil [49] from sage leaf showed any mutagenic potential.

REGULATORY STATUS

Medicines

UK	Accepted for general sale, internal or external use [50].
France	Accepted for specified indications [41].
Germany	Commission E monograph published, with approved uses [38].

Food

USA	Generally recognized as safe (21 CFR 182.10 and 182.20) [51].
Council of Europe	Permitted as flavouring, category N2 with provisional limits on the content of thujones (α and β) in the finished product (0.5 mg/kg, with some exceptions) [52].

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Ph. Eur. Sage Leaf (Salvia officinalis)

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REGULATORY GUIDELINES FROM OTHER EU COUNTRIES

FRANCE

Médicaments à base de plantes [41]: Sauge officinale, feuille.

Therapeutic indications accepted

Oral use
Traditionally used in the symptomatic treatment of digestive disorders such as epigastric distension, sluggish digestion, eructation and flatulence.

Topical use
Traditionally used locally in mouthwashes, for buccal hygiene.

GERMANY

Commission E monograph [38]: Salviae folium (Salbeiblätter).

Uses
Internal Dyspeptic complaints; excessive perspiration.
External Inflammation of the mouth and throat mucosa.

Contraindications
The pure essential oil and alcoholic extracts should not be taken during pregnancy.

Side effects
Prolonged ingestion of alcoholic extracts or pure essential oil can cause epileptiform convulsions.

Interactions with other drugs
None known.

Sage Leaf

Dosage
Unless otherwise prescribed:
Internal Daily dose: 4-6 g of the drug; 0.1-0.3 g of essential oil; 2.5-7.5 g of tincture (in accordance with Erg. DAB 6); 1.5-3 g of fluid extract (in accordance with Erg. DAB 6).
Gargles and rinses 2.5 g of the drug or 2-3 drops of essential oil to 100 ml of water as an infusion, or 5 g of alcoholic extract to a glass of water.

Mode of administration
Cut drug for infusions; alcoholic extracts and distillates for gargles, rinses and other topical applications, as well as for internal use; also as pressed juice from the fresh plant.

Actions
Antibacterial, fungistatic, virustatic, astringent, promotes secretion and inhibits perspiration.