Boneset – *Eupatorium perfoliatum* L.

1. Taxonomy

*Eupatorium perfoliatum* L.
Family: Asteraceae
Common names: boneset, ague-weed, crossword, feverwort, Indian sage, sweating weed, thoroughwort, wild Isaac, tea-gel, vegetable antimony.
Synonyms: There are no commonly accepted synonyms for *E. perfoliatum*.

2. Botanical description and distribution

*E. perfoliatum* is an upright perennial growing to about four feet, with a stout stem covered with long spreading hairs and branching at the summit. Leaves are opposite, sessile and lanceolate in shape with acuminate tip, the opposite leaf pairs adjoining at their bases and encircling the stem node (‘perfoliate’). Flowers are born in capitula of 9-23 white tubular florets arranged in terminal corymbbs, the florets maturing to produce dry, angular achenes (Gleason & Cronquist, 1991). *E. perfoliatum* is found in swamps and damp areas, alluvial woods and pastures throughout the Appalachian region (Krochmal, Walters & Doughty, 1969).

Figure 1. Image from *A Textbook of Botany and Pharmacognosy* by Henry Kraemer 1907. J.B. Lippencott, Philadelphia.
Part Used

Dried flowering herb harvested in summer.

3. Traditional uses

Traditional uses in Appalachia

*E. perfoliatum* was among the many indigenous plants that Appalachian settlers learned to use from the local Native Americans (Crellin & Philpott, 1989). By the 1800s, it had become a favorite household herb and was used for a variety of conditions such as fevers, colds, coughs, headaches, and rheumatism (Howell, 2006). A tea was also used for consumption and as a laxative (Krochmal, Walters and Doughty, 1969). *E. perfoliatum* remains a common remedy for promoting digestion and tonifying the gastrointestinal system. In small doses it is said to soothe the tissues while larger doses promote an emetic response useful in fevers and chronic illness. The whole plant is administered as a strengthening tonic in low grade fevers, and as a hot infusion it is known to promote diaphoresis. It has been particularly useful to the people of Southern Appalachia for “sweating a cold out of the body” (Cavender, 2003, p. 84). No other herb seemed to rival its effectiveness in dealing with fevers, with few or no ill side effects (Erichsen, 1979).

Traditional uses outside Appalachia

Native American

Most common uses of *E. perfoliatum* were for treatment of fevers and as a gastrointestinal aid for pains in the stomach. The entire plant was used, with an infusion of the leaves (and sometimes the whole plant) applied topically for headaches and fevers, and as a poultice on broken bones. An infusion of leaves and flowers was taken for a laxative effect. The smashed roots were said to cure typhoid conditions. Infusions of the leaves were also employed for early stages of colds and fevers, kidney troubles, and for “general debility” (Moerman, 1998). The Mesquakies used the root for snakebite and the aerial parts for expulsion of worms (Kindscher, 1992).

Folklore & Home

A preparation of *E. perfoliatum* in any form (tea infusion or decoction or powder) was used with “uniform success” in the treatment of intermittent fevers, in particular yellow fever. It was also a popular home remedy for dyspepsia when drunk as a cold tea throughout the day, while in the form of a warm infusion it acted as an emetic – it was dose dependent in its response (Beach, 1851). Often, it was preferred in place of chamomile as a tonic stimulant (Child, 1837). As a general tonic, it was employed with aromatics in tinctures or powders (Gardner & Aylworth, 1836). An infusion was said to be diaphoretic and was commonly drunk at the onset of fevers to promote sweating (Child, 1837).

Physiomedical

*E. perfoliatum* was a popular remedy for physiomedicalists also, and its effects were often dose and preparation dependent. Given as a cold infusion, it was a decidedly relaxing tonic acting primary on the liver and gall bladder while also acting as a mild...
laxative. It was said to target sensitive or tense tissues, providing a relaxing, calming effect on the smooth muscle. It was commonly combined with other herbs to promote a strengthening response for general debility, and also for weak tissue states. Prepared as a warm infusion, it was an excellent remedy for yellow fever as a diaphoretic. It was used to provide relief from “aching limbs” secondary to rheumatism and, in larger quantities, to promote emesis (Cook, 1869). Clymer later confirmed this approach, using the cold infusion and tincture as a tonic, warm infusion as a diaphoretic and larger doses as an emetic – however he believed it to be inferior to *Lobelia inflata* L. in that respect (Clymer, 1905).

**Eclectic**

Scudder (1898) found *E. perfoliatum* to be a useful remedy for the onset of colds and fevers, where the body becomes stiff and achy. The relaxing effect proved most useful in joint, muscle and skeletal pain, as well as promoting secretions to eliminate lingering illness. It was used by nearly every Eclectic physician in the treatment of fevers and flu and for the common cold “especially when accompanied by deep-seated, aching pain”. For respiratory conditions, Felter (1922) considered it, “efficient to relieve cough, acting best in that occurring in the aged and debilitated, where there is an abundance of secretion, but lack of power to expel it”.

The most well documented use of *E. perfoliatum* by Eclectic physicians was during the 1918-19 influenza epidemic, highlighted by two practitioner reports of over 1,000 treated cases with only five fatalities (Brinker, 2009). The two popular preparations in use at the time were the warm infusion and Lloyd’s Specific Eupatorium extract (Brinker, 2009).

**Regulars**

Following observations of Native Americans, allopathic physicians used *E. perfoliatum* for febrile conditions such as influenza, typhoid and yellow fever - especially when the pains were at their worst. In the early 1800s Dr. Brigalow of Harvard University applied it to cutaneous conditions as well as for intermittent fevers, while William Barton MD praised its use in typhus and N. Chapman MD recommended it for respiratory catarrh and as a hot infusion for the “breakbone fever” form of influenza, leading to the use of the common name - boneset (Brinker, 2009). Other physicians used it for dyspepsia and general debility (Wood & Bache, 1858). It was official in the *United States Pharmacopeia* (USP) between 1820 and 1900.

### 4. Scientific research

**Phytochemistry**

**Sesquiterpene lactones**

Sesquiterpene lactones (STLs) are signature compounds of the large *Eupatorium* genus and of the Asteraceae family in general. In *E. perfoliatum* the STLs are represented by two structural classes, the guaianolides and the germacranolides (Herz, Kalyanaraman, & Ramakrishnan, 1977). Recently Mass et al. (2011) described several new STLs using a high performance liquid chromatography (HPLC) coupled with mass spectrometry (MSMS) method. There were four new guaianolides - one dimeric guaianolide and one
germacroanolides - and all showed antiprotozoal activity against the malaria vector *Plasmodium falciparum* and other protozoa (Maas, Hensel, da Costa, Brun, Keiser & Schmidt, 2011).

**Table 1. Classification of named sesquiterpene lactones in *E. perfoliatum***

<table>
<thead>
<tr>
<th>Guaianolides</th>
<th>Germacranolides</th>
<th>Germacranolides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euperfolide</td>
<td>Euperfolitin</td>
<td>Euperfolitin</td>
</tr>
<tr>
<td>11,13 – dihydroeuperfolide</td>
<td>Euperfolin</td>
<td>Euperfolin</td>
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<tr>
<td>Eufolitin</td>
<td></td>
<td></td>
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<tr>
<td>Eufoliatorin (a dilactone)</td>
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</table>

(Herz, Kalyanaraman, & Ramakrishnan, 1977; Maas et al., 2011)

**Polysaccharides**

Two polysaccharides have been isolated from *E. perfoliatum* by HPLC coupled with nuclear magnetic resonance (\(^{13}\)C NMR) spectroscopy methods (Vollmar, Schäfer, & Wagner, 1986). The two compounds were characterized as 4-0-methylglucuronoxylans, one of high molecular weight (>500,000) and a smaller one (ca 40,000), and both showed phagocytosis-enhancing activity (Vollmar, Schäfer, & Wagner, 1986).

**Flavonoids**

Methoxyflavonoids are another characteristic compound group among the *Eupatorium* genus. Herz et al. (1972) isolated three dihydroxyflavonols from *E. perfoliatum* in the early 1970s, while Wagner et al. identified astragalin, hyperoside, quercetin and kaempferol (Maas, Petereit, & Hensel, 2009). More recently four methoxylated flavonoid aglycones - eupafolin, hispidulin, patuletin and kaempferol - were identified using HPLC coupled with \(^1\)H and \(^{13}\)C NMR and mass spectroscopy (MS) (Maas et al. 2011) as well as glycosides of quercetin and kaempferol (Maas et al. 2009).

**Phenolics**

Using reverse phase HPLC coupled with diode array (DAD-UV), six caffeic acid derivatives were isolated and identified by NMR spectroscopy. They were quinic acid, chlorogenic acid, neochlorogenic acid and three depsides of caffeic acid (Maas et al. 2009). A chromatogram showing eight caffeic acid derivatives and four flavonoids is presented in appendix 1.
Other constituents

Other less well characterized constituents of *E. perfoliatum* are chromenes and the triterpene alpha-amyrin, sterols, diterpenes dendroindinic acid and hebenolide, dotriacontane – a hydrocarbon, and volatile oils (Skenderi, 2003; Brinker 2009; Natural Standard, 2011).

Pharmacology

General

Sesquiterpene lactones from *E. perfoliatum* have been shown to have cytotoxic and immune-stimulating actions *in vitro* (Herz, Kalyanaraman, & Ramakrishnan, 1977; Wagner, Proksch, Vollmar, Kreutzkamp, & Bauer, 1985) while an ethanolic extract of the dried leaves showed strong cytotoxic effects against three mammalian cell lines and weak antibacterial effects against two gram-positive species (Habtemariam & Macpherson, 2000). Aqueous extracts and isolated polysaccharides have also shown immune modulating effects – by significant enhancement of phagocytosis *in vitro* and *in vivo* (Wagner et al., 1985; Vollmar, Schäfer, & Wagner, 1986). Studies conducted in the early 1900s demonstrated antibacterial activity against *Staphylococcus aureus* *in vitro* (Brinker, 2009).

Antimalarial effects

*E. perfoliatum* has long had a reputation for treating febrile disorders, and was widely used by Indians for this purpose (Hall, 1974; Brinker, 2009). Studies with STLs indicate many of these compounds have potent effects against protozoans, though the effects may be linked to their inherent cytotoxicity (Schmidt, Nour, Khalid, Kaiser, & Brun, 2009). Chloroform extract of *E. perfoliatum* aerial parts actively inhibited the malarial vector *Plasmodium falciparum in vitro*, and a dimeric guaianolide STL was shown to be the most active constituent (Maas et al., 2011). The cytotoxicity of this compound was relatively weak. Using a rodent malaria, Lira-Salazar and co-workers found that homeopathic potencies of *E. perfoliatum* tincture demonstrated significant – though not completely inhibitory – effects against *Plasmodium berghei*, which were stable over several days (Lira-Salazar, Marines-Montiel, Torres-Monzón, Hernández-Hernández, & Salas-Benito, 2006).
Clinical trials
No published clinical trials were found in the literature review.

5. Modern Phytotherapy

Modern therapeutic use of *E. perfoliatum* reflects traditional indications. The German herbal physician Rudolf Weiss (1988) lists boneset alongside other tonics such as *Echinacea* spp. for treating acute viral infections and enhancing overall immunological resistance. Modern herbal practitioners continue to value the therapeutic benefits of fever, and boneset’s diaphoretic effect is seen as playing a key role in the treatment of the common cold and influenza (Mills & Bone, 2000). Kuts-Cheraux (1953) suggests that boneset’s positive influence on body aches associated with infections can be extended more broadly to treatment of rheumatic pains in general. A classic indication is fevers with “dry skin, not followed by perspiration, with deep seated aching pain and great thirst” (Harper-Shove, 1952).

Table 2: Modern phytotherapeutic uses of *E. perfoliatum*

<table>
<thead>
<tr>
<th>ACTIONS</th>
<th>THERAPEUTIC INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphoretic</td>
<td>Early stages of colds and influenza</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngeal catarrh</td>
</tr>
<tr>
<td>Expectorant</td>
<td>Acute bronchitis</td>
</tr>
<tr>
<td>Aperient</td>
<td>Fever accompanied by aching bones and muscles</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid and gouty arthritis</td>
</tr>
<tr>
<td></td>
<td>(Priest &amp; Priest, 1982; British Herbal Medicine Association, 1983; Mills &amp; Bone, 2000)</td>
</tr>
</tbody>
</table>

Specific indication

Influenza with deep aching, and congestion of the respiratory mucosa (British Herbal Medicine Association, 1983)

Combinations

With *Sambucus nigra* L. and *Salix* spp. for prostrating fevers with aching in the bones. With *Scutellaria lateriflora* L. and *Asclepias tuberosa* L. for influenza (Clymer, 1905).

Preparations and dosage

Dried herb 1-2g three times daily or by infusion. FE 1:1, 1-2 mL, 3 times daily (British Herbal Medicine Association, 1983).
Toxicity and contraindications

The *Botanical Safety Handbook* classifies *E. perfoliatum* as Class 4 – “Herbs for which insufficient data is available for classification,” because of the possibility of other potentially toxic *Eupatorium* species being substituted (McGuffin, Hobbs, Upton, & Goldberg, 1997). While toxic pyrrolizidine alkaloids have been identified in some *Eupatorium* species (Smith & Culvenor, 1981), none have ever been identified in *E. perfoliatum* (Skenderi, 2003; Maas & Hensel, 2008). This herb has a long history of documented usage and few side effects have been reported, although large doses are emetic and purgative. *E. perfoliatum* may cause contact allergic dermatitis in persons hypersensitive to Asteraceae plants containing sesquiterpene lactones (Skenderi, 2003). It should be avoided during pregnancy and lactation.

*E. perfoliatum* does not contain the toxic alcohol tremetol, found in the related species *E. rugosum*, (now reclassified as *Ageratina altissima*), which is responsible for trembles in livestock and milk sickness in humans (Lee et al., 2010; Brinker, 2009).

*E. perforatum* is regulated in the USA as a dietary supplement.

6. Sustainability

Ecological status-RTE status

While *E. perfoliatum* is not considered an endangered or threatened species, it is native to US wetlands and as wetlands continue to disappear, the status may change.

A variety, *E. perfoliatum* var. *colpophilum* also called common boneset or estuary boneset is only found in Connecticut, Massachusetts, Maine, New Hampshire, Vermont and Ontario. Estuary boneset is listed by the USDA as endangered and possibly extirpated in Maine. Currently however, the Maine Natural Areas Program (2008) does not list *E. perfoliatum* on its endangered, threatened and rare list.

Harvesting & Collection regulations

Maine does not have any laws protecting rare plant species (MNAP, 2008), but people gathering plants in the wild should be able to identify related species and varieties that may be endangered. (Robinson, Agurkis, & Scerbo, 2007).

Market data - harvesting impact, tonnage surveys

According to Jancke (2004) market potential was low to medium as most is gathered in the wild, but buyers may prefer to purchase from a known organic source. Jancke also notes that studies mentioning the possibility of liver toxicity have limited its popularity. In 2004, retail prices ranged from $10.36 to $23.15/lb dry weight.

Cultivation

The preference is full or partial sun, and wet to moist conditions. The soil should contain considerable organic material so that it can retain moisture. This plant can withstand flooded conditions for short periods of time, but it is not really aquatic. The foliage
appears to be little bothered by pests and disease (Hilty, 2002-2011). Jancke (2004) notes that boneset can also be field grown in Kansas under fairly dry conditions.

**Height:** 2 to 5 feet

**Sun:** Full sun to partial shade

**Soil:** Prefers a rich, moist soil

**Water:** Natural habitat is on wet sites, and plant prefers regular, deep watering. However, boneset also appears to withstand Kansas heat and drought fairly well.

**Propagation:** Easily propagated from seeds or cuttings. Take cuttings before the plant has flowered. Seeds will germinate without stratification, but will germinate better with stratification. Seeds need light to germinate. Do not cover. Germination is typically two to three weeks, with 80 to 90 percent germination. Older plants can be divided and replanted in the spring. Plant on 18 to 24 inch centers, with row spacing of 24 to 30 inches, because each plant will form a clump.

**Pests:** No major pests

**Harvesting:** Harvest aboveground portion when flowers are starting in early or midsummer.

Dry quickly, or it will decompose. A second, fall harvest may be possible (Jancke, 2004).

*E. perfoliatum* is being grown for seed by inmates at Michigan's Saginaw Correctional Facility as part of a program to restore the prairie at the Shiawassee refuge (Conat2010).

7. **Summary – some possibilities moving forward**

According to Millspaugh (1892) “There is probably no plant in domestic practice that has more extensive or frequent use” (in reference to *E. perfoliatum*) and it is mentioned in virtually all of the historic books on American plant medicine (Kindsher, 1992). With the advent of antibiotics and so called “magic bullets” in the 20th century, traditional use of *E. perfoliatum* for respiratory infections and fevers has declined, and demand is confined largely to herbalists and phytotherapists in the USA and abroad. The decline in popularity has not been helped by unfounded reports that the species contains hepatotoxic pyrrolizide alkaloids (PAs), at a time when there is a great need for alternatives to antibiotics and to the influenza drugs now in use.

Further analytical studies are needed to determine decisively whether PAs are present and if so, at what concentrations, as well as toxicological investigations to assess potential for acute or chronic adverse effects. Provided safety can be demonstrated by such studies, *E. perfoliatum* would be an excellent candidate for clinical research.
8. References


Appendix-1
Summary of Endangered, threatened or rare Eupatorium species

<table>
<thead>
<tr>
<th>Area</th>
<th>Status</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>global</td>
<td>secure</td>
<td>Natural Heritage Endangered Species Program (2010)</td>
</tr>
<tr>
<td>federal</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Ma</td>
<td>Endangered E. novae-angliae</td>
<td>Natural Heritage Endangered Species Program (2010) - threatened by any activity that affects the water quality or soil integrity: shore development, eutrophication, horse &amp; foot traffic, camping, boat launches and digging.</td>
</tr>
<tr>
<td>ME</td>
<td>E. perfoliatum var. colpophilum possibly extirpated</td>
<td>Range: New England and Ontario (estuary boneset)</td>
</tr>
<tr>
<td>MD</td>
<td>E. leucolepsis G5 S2-S3 Threatened</td>
<td>white bracted boneset - MD RTE 2010 - <a href="http://www.dnr.state.md.us/wildlife/Plants_Wildlife/rte/pdfs/rte_Plant_List.pdf">http://www.dnr.state.md.us/wildlife/Plants_Wildlife/rte/pdfs/rte_Plant_List.pdf</a> basionym: E. novae-angliae (IPNI, 2005)</td>
</tr>
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</table>
Appendix II.

Voucher specimen lodged at the Claude E. Phillips Herbarium, Delaware State University. Specimen collected from Tai Sophia Institute garden, 8/1/11.