American Herbal Pharmacopoeia®
and Therapeutic Compendium

Boneset Aerial Parts
Eupatorium perfoliatum L.

Standards of Analysis, Quality Control, and Therapeutics

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DEDICATION

This monograph is lovingly and respectfully dedicated to the memory of Dr. James (Jim) Duke, a pioneer in botanical medicine research who brought thoughtful reasoning to the subject and was a never-ending proponent of the need to compare the best of what botanical and conventional medicine had to offer so people could make the best health care choice possible.

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Design & Composition

Fani Nicheva, Santa Cruz, CA

Cover Photograph

Eupatorium perfoliatum in flower
Source: © 2019 Steven Foster Photography, Eureka Springs, AR

NOMENCLATURE

Botanical Nomenclature

Eupatorium perfoliatum L.

Botanical Family

Asteraceae

Pharmaceutical Nomenclature

Herba Eupatorii perfoliati

Pharmaceutical Definition

Boneset aerial parts consists of the leaves and flowering tops of *Eupatorium perfoliatum* containing not less than 1.5% chlorogenic acid calculated on a dry weight basis.

Common Names

English: Boneset, feverwort, ague weed
Dutch: Waterdost
French: Eupatoire perfoliée, herbe a fievre
German: Durchwachsenblätteriger, Wasserhanf, Durchwachsener Dost, Wasserdost
Italian: Eupatori
Spanish: Eupatorio

HISTORY

Introduction

Boneset is native to North America and has a long history of use among Native Americans and early European settlers as a cold remedy and antipyretic. Later, Eclectic physicians and traditional Physiomedicalists used boneset extensively for influenza, cough, and pain. Contemporary naturopathic doctors and modern herbalists have continued to use boneset for these indications, as well as for its laxative and diaphoretic effects. While boneset was primarily used short-term for the treatment of influenza, fever, or as an occasional emetic, laxative, or diaphoretic, it was also used as a bitter digestive. Due to recent data demonstrating the presence of potentially toxic dihydropyrrolizidine alkaloids (DHPAs), the benefit to risk has to be reconsidered and long-term use should be discouraged (see Safety).

Nomenclatural History

The genus name *Eupatorium* was so-named after Mithridates Eupator VI (123–63 BCE) (Gledhill 2008; Stearn 1996), considered the greatest ruler of Pontus, an ancient Hellenistic kingdom in Asia Minor, who himself was an herbalist. After the poisoning of his father King Mithridates V, Mithridates VI was said to have spent years in the wilderness desensitizing himself to a wide variety of botanical poisons. This resulted in the development of the legendary Antidotum Mithridaticum (McGing 1986). Mithridates was said to have used a species of *Eupatorium*, the naming of the genus reflecting the high regard attributed to the plant.

The species name *perfoliatum* is derived from the Latin *per* meaning through, and the adjectival Latin for leaf-letted *foliatus*, referring to the manner in which the stem of boneset appears to perforate through the base of the leaves (see Figures 2a & 2c). There are varying versions of the origins of the common name boneset. William PC Barton, professor of botany, University of Pennsylvania, in his *Vegetable Materia Medica of the United States* (1818) gave his opinion of the origin of the common name boneset. In his explanation William Barton refers to his uncle and mentor, professor of materia medica, University of Pennsylvania, Benjamin Smith Barton (1766–1815) stating the following:

> The origin of the common name bone-set is not easy to ascertain; though a mere suggestion of Professor Barton to have afforded a late writer on the Materia Medica a hint for a derivation, which he has not failed to avail himself of. We are told by this gentleman, upon what authority other than his own, we are left to conjecture, that the plant derived the name of bone-set from the relief it afforded in a certain 'singular catarrh or species of influenza,' which prevailed about 30 years ago, and was denominated break-bone-fever. We are satisfied the Professor will find it extremely difficult to show by any printed testimony, that the medicinal powers of *Eupatorium perfoliatum* are

Figure 1 Historical illustration of *Eupatorium perfoliatum*
Source: Barton WPC. 1818. *Vegetable Materia Medica of the United States*

> generally known even 20, much less thirty years ago, or that the vulgar name, bone-set is of earlier origin than 15 years back. …"Great indeed is the renown of the *Eupatorium perfoliatum*, as a medicine, and various as well as powerful are the virtues attributed to it. Should a wide extended experience justify, in future, only one-half the encomiums which have been lavishly bestowed upon it, it will even then be entitled to a distinguished rank in the *Materia Medica*.

Boneset was widely used historically for sicknesses that were referred to as "breakbone fever"; ague (malarial fever), dengue fever, and influenza. The term ague, which means acute from the French *aigu* (short for *fievre aigu*), has been used for several types of acute fever, including malaria and dengue fever. However, "breakbone fever" generally applies primarily to dengue, which is a virus transmitted via the mosquito bite of *Aedes aegypti*, A. *albopictus*, or A. *polynesiensis*. As dengue was sporadic, and endemic in India, Japan, the South Pacific, the Caribbean, and northern parts of South America, it is curious that a Native American herb was reported to be widely used in the early nineteenth century for a condition found in these foreign lands. Both conditions produce deep pains in the joints and bones, among other symptoms such as intermittent fever and chills, although dengue pains are primarily of the muscles and joints. Because of this, the common name of "boneset" was adopted. In the early 1800s, boneset reportedly garnered much success in the treatment of "intermittents." Since this term is typically applied to malaria, it suggests that boneset may have derived its name from its use for malaria, and according to Edwards and Vavasseur (1829), was used successfully in the New York Alms-House for "intermittents." In older usage, the word "thorough" has also been used, referring to the stem passing through the leaf, and therefore many 19th century references refer to boneset as thoroughwort (Wood 1860).

Native American Use

It is difficult to know how widespread the use of boneset was among Native Americans throughout the range of distribution of the plant. According to Moerman's *Native American Ethnobotany* database at the University of Michigan-Dearborn, the use of boneset was recorded, most specifically, among tribes of the Northeast United States and among the Cherokee and Seminole of the Southeast. There are a few other sporadic reports of Native American use in the literature. Specifically, there is documentation of the use of the herb by the Cherokee, Delaware, Menominee, Nanticoke, Seminole, and Mohegan as an antipyretic agent; by the Ojibwe, Iroquois, Shinnecock, and Mohegan as a cold remedy; and as an antirheumatic, when applied topically as a poultice, by the Ojibwe. The Abnaki of New England additionally used the plant to mend bones (Moerman 2019), while the Mesquakies used the root for snakebite and the aerial parts for expulsion of worms (Kindscher 1992).

Among the Penobscot of central Maine, boneset is known as sɑpahkʷəsihkʷipi, which literally translates as "through-stick-leaf," a clear reference to the perfoliate leaves of this species (Speck 1917). Miscellaneous other uses by individual tribes included its use for sore throat by the Cherokee; as an abortifacient, to "correct the menses," as a poultice for snake bite, and as a hunting medicine "to attract deer" among the Ojibwe; and as an analgesic, poultice for headaches, fomentation and poultice for syphilitic conditions, infusion for stomach pain and left-sided pain, and a strong decoction to reduce desire for liquor among the Iroquois.

As documented in Crellin and Philpott's (1990) *A Reference Guide to Medicinal Plants: Herbal Medicine Past and Present;*

> the Indians, when they broke a bone, they would soak the part in boneset tea. All the old-timers had it hanging around in the smokehouse and other places…They just had it hanging around for coughs and colds, chills, fever and rheumatism. If they sprained a joint, they'd soak it in boneset tea….Old-time people would put it in a tub, soak their feet in it, and steam themselves."

John R Swanton, in Creek Religion and Medicine (2000), writes of 'Sokha hiliswa' (hog medicine), "When women complained of aches and pains in the hips they were steamed in a medicine made by boiling this (boneset). The Choctaw and Chickasaw called it 'eilup tileli', which means 'something to scare away the spirits'. A decoction was made from the roots and when persons had epilepsy they were steamed in it.

In *Native Plants, Native Healing: Traditional Muskogee Way* (2001), Tis Mal Crow, a Creek herbalist, writes that boneset "is used as a treatment or preventative for osteoporosis and to speed up the healing process when recovering from broken bones."

Early Medical Use

While boneset is indigenous to North America, Europeans were familiar with another *Eupatorium* species that was used similarly, *Eupatorium cannabinum*. In Europe, *E. cannabinum* was classified similarly as boneset, being intensely bitter and aromatic. Among its common uses were jaundice, dropsy, scurvy, as a purgative and emetic; externally as a poultice and fomentation for wounds, ulcers, and sores (Green 1820); as an aperient; chronic diseases due to obstructions of the viscera; and intermittent fevers, the key indication for boneset (Lewis 1791).

The use of boneset by early European settlers was likely informed by the former European use of *E. cannabinum*, as well as the herb's use by Native Americans. By most historical accounts, the use of boneset was introduced into American allopathic, Eclectic, and Thomsonian medical practices from traditional Native American use. It was reported that the most potent boneset is found growing on or near graves. Legend has it that the plant attracts benevolent spirits and protects against "ghost sickness," which is said to afflict those who have extended contact with the dead (Henkel 1911; Hensel et al. 2011; Krochmal et al. 1969; Rogers 2014).

One of the earliest American records of the use of boneset is found in *Vegetable Productions Naturally Growing in this Part of America* of prominent American clergyman and physician Manasseh Cutler (originally published in 1784). Cutler wrote of the use of the leaf infusion as a powerful emetic (Cutler 1903). Another of the earliest records of the use of boneset occurs in the Latin writings of German Johan David Schoepf's *Materia Medica Americana* (1787). Schoepf, who travelled in America from 1783–1784 after serving as a surgeon for the Hessians fighting for England in the Revolutionary War, gives the actions of boneset as emetic, purgative, and diaphoretic, recommending its internal use for fevers, intermittents, arthritis, rheumatism, and podagra (gout), and externally for pain. This report was followed by that of Benjamin Smith Barton (1766–1815), professor of materia medica, natural history, and pharmacy (University of Pennsylvania), in his *Collections for An Essay Towards a Materia Medica of the United States* (1810). Barton was a botanist, physician, and naturalist from Philadelphia who, according to his writings, appears to have no personal experience with the botanical, beyond it being a powerful bitter with an astringent principle. Barton considered boneset to have some value based on Native American use of the plant whom he says "call it by a name, which may be translated 'Ague-weed'."

Benjamin Barton's nephew, William PC Barton (1786-1856) was quoted as saying that "few plants of our country are more deserving of the attention of physicians than this." The younger Barton was a medical botanist, physician, professor, naval surgeon, and botanical illustrator. Benjamin Barton was considered one of the foremost authorities on medicinal plants of New England. William Barton's father, interestingly, was the designer if the Great Seal of the United States.

In 1824, Dr John Sappington bought all of the quinine available in Philadelphia and brought it back to Missouri in his saddlebags. While the quinine was accepted by many, the general populace in that area was slow to abandon the use of boneset. In 1844 in his book, *Theory and Treatment of Fevers*, Sappington stated that boneset was one of the best indigenous substitutes when quinine was unavailable or in short supply in malarious districts (Hall 1974).

Professor of chemistry and materia medica (Philadelphia College of Pharmacy) George Wood (1856), considered a leading authority on materia medica among allopathic physicians, noted that boneset first passed into popular use and then professional use from Native people. Lloyd, in his *Origin and History of All the Pharmacopoeial Vegetable Drugs, Chemicals and Preparations* (1921), gives a brief history of the use of boneset in North America. "In the form of an infusion or tea, it was very popular with the settlers by whom it was employed 'in every well-regulated household'. Early members of the American medical profession were familiar with the use of boneset as a bitter tonic. In this connection, it may be stated that over one hundred years before there was in print an American materia medica (likely referring to the writings of Lewis 1791 and Stearns 1801), *Eupatorium* was a favorite remedy in the practice of American physicians." Lloyd further went on to record that medical authorities such as Thacher, Bigelow, Chapman, Rafinesque, and Zollick pronounced the highest encomiums on the value of boneset. According to Lloyd, its principal field of usefulness was in colds and influenza, with Dr Anderson of New York issuing in 1813 a special treatise on the subject of this drug and its uses, and numerous accounts reporting on its chief application as an influenza remedy. Reportedly quoting from the celebrated botanical explorer Pursh (1774–1820), concerning its early record in that direction, Lloyd recounts, "The whole plant is exceedingly bitter, and has been used for ages past by Natives and inhabitants in intermittent fevers…" This record, however, is lacking in the seminal work of Pursh, *Flora Americae Septentrionalis* (1814). Lloyd goes on to record on Pursh, "I have stated a case of its efficacy in those diseases in a letter to William Royson, Esq, who inserts it in the Medical and Physical Journal, in which I stated the benefits derived from this plant, by myself and others during my stay in the neighborhood of Lake Ontario, when both the influenza and lake fever (similar to yellow fever) were raging among the inhabitants." (Lloyd 1921).

Use of Boneset by Thomsonian and Eclectic Traditions

Samuel Thomson (1769–1843) described boneset as warming and good for coughs and other lung complaints when used as a common drink. Besides its expectorant activity, Thomson noted boneset was also a mild emetic, diaphoretic, and tonic (Thomson 1841). Depending upon the formula, boneset was used for dyspepsia, as a laxative, and for chronic coughs. Its most common use was as a warm infusion for its diaphoretic effect. Used as such to promote sweating in fevers, it retained its laxative activity and proved doubly efficacious. If taken in large quantities or in short intervals, boneset produced sudden vomiting. Giving emetic doses in "breakbone fever" appeared beneficial.

The Eclectics used boneset to treat cutaneous disease and intestinal problems; as a tonic for typhoid fever, dyspepsia, and general debility; and as a diaphoretic and emetic for fever, catarrh, and colds (Adolphus 1874; Felter and Lloyd 1898). John M Scudder noted that when given in small doses of five drops or less, boneset was an "essential tincture" for respiratory infections, to stimulate the nervous system, and to improve visceral functions (Scudder 1862a, 1862b; Scudder 1875). William Mundy reported that when given in larger doses, boneset was a diaphoretic, emetic, and cathartic, as well as an effective antimalarial (Mundy 1905). According to William Bloyer, the primary indications for the use of the Specific Medicine Eupatorium were sluggishness and general aching (Bloyer 1901).

In the early 1900s, two distinct components with differing pharmacological effects were isolated from boneset. The first, found in the dried herb, infusions, decoctions, and alcoholic extracts, possessed the diaphoretic and tonic qualities useful in influenza, coughs, and colds; the second, found in all tinctures and fluidextracts, hot decoctions, and the fresh infusion, was nauseating and cathartic. In 1918, the

Lloyd Brothers formulated a Colloidal Specific Medicine, which retained the characteristics of the first component but excluded the second. This formula was especially useful as a preventative in the influenza epidemic of 1918 (Ellingwood 1919a; Ellingwood and Lloyd 1915; Lloyd and Lloyd 1918).

There was consensus among the Eclectics that boneset was one of the safest and most effective remedies employed during flu epidemics, especially the severe influenza pandemic from 1918-19. Both the infusion and Lloyd's Specific Eupatorium were effective. With liberal use, cases were milder, severe pain was quickly relieved, cough and irritation were reduced, and recovery was hastened. For acute aching with chilliness, depression, and subnormal vitality that characterized the first stages of influenza, boneset was considered one of the top remedies. Specific Eupatorium became a routine treatment of influenza, alongside vaccines and serums (Best 1928; Felter 1924; Powers 1928). Specific Eupatorium was also effective in the relief of coughs and pleuritic pain, including in cases of the aged and debilitated, measles, and broncho-pneumonia, acting as a diaphoretic and expectorant (Best 1928; Bloyer 1901; Felter 1924).

In addition to the Eclectic use, others found boneset of great utility in flu epidemics, both for prevention and treatment. The Dominion Herbal College Post Graduate course record that a Dr Hoener claimed the successful use of boneset in combination with several other botanicals for treating influenza in more than 700 subjects during the influenza outbreak of 1891 (Nowell 1926; see Traditional Western Herbal Supplement). In a discussion of boneset for the treatment of flu, a Dr Bixel claimed that in 1918 he lost only two of 500 influenza cases he treated. A Dr Ilgenfritz stated that he treated 628 cases and lost only three using the infusion. He had his druggist make up a half-dozen one-gallon bottles of infusion daily that he carried in his car (Powers 1928).

Modern Medical Use

Towards the end of the twentieth century, boneset began to once again be recognized and used both alone and in combination with other herbs. British herbalists particularly emphasized the use of boneset for influenza epidemics, respiratory infections, and febrile conditions, and recognized its action to enhance stomach and liver secretions. By the 1980s, modern herbalists and naturopaths were using boneset for acute fevers and for flu with night sweats and aching bones (Priest and Priest 1982). Herbalist David Hoffmann reports that boneset provides quick relief from the associated aches and pains of flu, along with clearing of respiratory mucosal congestion. In addition, he notes that the cleansing laxative action and symptomatic relief of rheumatism make it a good general agent outside of acute

Table 1 Historical timeline on the medicinal use of boneset

Native American Uses	Widely used among many tribes, including the Cherokee and Seminole, for fever and as a diaphoretic, as well for other uses, such as a cold remedy by the Iroquois and an antirheumatic by the Ojibwe.
1700s	European settlers in North America use boneset to treat malaria, yellow fever, dengue fever, and influenza.
Early 1800s	American doctors and herbalists use boneset for coughs, dyspepsia, as a laxative, a mild emetic, and mainly for its diaphoretic effects.
Mid 1800s–1930s	Eclectic doctors continue to use boneset for its previous indications, as well as for general debility, pneumonia, to stimulate the nervous system, and to treat cutaneous disease and intestinal problems.
1820–1900	*E. perfoliatum* and its infusion official in the *United States Pharmacopeia* (USP).
Early 1900s	Two distinct components are isolated, one diaphoretic and with tonic qualities, and one nauseating and cathartic.
1918	Lloyd Brothers formulate a Colloidal Specific Medicine for use as a preventative in the influenza epidemic.
1820–1900	*E. perfoliatum* and its infusion official in the *United States Pharmacopeia* (USP).
1916–1946	*E. perfoliatum* and its infusion included in the *National Formulary*.
Mid-to-late 1900s	Modern herbalists utilize boneset especially for treating fever, influenza, respiratory infections, and aching bones; American naturopathic profession adopts boneset for use as a diaphoretic, mild laxative, and for aches of influenza and rheumatoid conditions.
1981	German clinical trial investigates a boneset homeopathic preparation for the common cold with positive results.
2015	Low concentrations of potentially toxic unsaturated pyrrolizidine alkaloids detected in select samples of whole plant material, calling into question the safety of the botanical.
2018-2019	AHP and researchers at USDA perform extensive analyses of numerous specimens of *E. perfoliatum* unequivocally confirming the presence of intermedine and lycopsamine and their n-oxides. Manufacturers begin removing boneset from their products and herbalists reconsider its use. The *Botanical Safety Handbook* reassesses the safety of the herb taking into consideration these new findings.
Present	Homeopathic preparations included in the *Homeopathic Pharmacopoeia of the United States* (HPUS) and *European Homeopathic Pharmacopoeia*. Regulated as a dietary supplement product in the US and as a Traditional Herbal Medicine or Anthroposophic product in Europe; listed in the *Anthroposophic Pharmaceutical Codex*. Tincture accepted as a natural health product in Canada with the following claim: Traditionally used in herbal medicine for the relief of muscle aches/pains, coughs, upper respiratory tract congestion, and catarrh associated with cold and flu. Used in Australia and New Zealand; 'Listed' medicine in the Australian Register of Therapeutic Goods.

febrile conditions (Hoffmann 1996).

The American naturopathic profession has adopted the traditional indications for boneset, using it as a diaphoretic and mild laxative during the onset of colds and employing its sedative effect for the aching tendencies of influenza and rheumatoid conditions. It is also used as an aid in bringing out the rash and controlling the cough of measles, as well as a bitter stomachic tonic to improve appetite and digestion. Since hot infusions may be nauseating and emetic if too strong, cold infusions or alcoholic extracts are considered preferable when diaphoretic effects are not desired (Kuts-Cheraux 1953; Lust 1974).

All nineteenth century *United States Pharmacopeia* (USP) included *E. perfoliatum*. Boneset infusion was official from the first edition in 1820 through the eighth revision in 1900 (Boyle 1991). Boneset was later transferred from the USP to the *National Formulary* (NF) in the fourth edition of 1916 where it was retained through the eight revision of 1946, which was published in 1947 (NF 1947).

Boneset is lacking in the current standard pharmacopoeias of the European Union (EU) and US but is included in homeopathic pharmacopoeias. Boneset tincture is accepted as a natural health product in Canada, its therapeutic indications including traditional use for the relief of muscle aches/pains, coughs, upper respiratory tract congestion, and catarrh associated with cold and flu (NNHPD 2012). Since at least the 1980s, British herbalists have been using boneset, often in combination formulas, for influenza, fever, cough, respiratory infections, febrile conditions, and for increasing stomach and liver secretions (Priest and Priest 1982). Boneset is included in the *British Herbal Pharmacopoeia* (BHP 1983) and is accepted in homeopathic and anthroposophic medicines in France and other parts of the EU. Boneset is also used in Australia, New Zealand, and the United Kingdom due to the shared Western herbal traditions with the US. However, it is reported that use in Australia has never been widespread and is diminishing. In 1981, a study employing a homeopathic preparation, *Eupatorium* D2, was shown to be equally as effective as one aspirin tablet three times daily for relieving flu symptoms (Gassinger et al. 1981), while another study in animals showed a protective effect against malaria (Lira-Salazar et al. 2006) with another homeopathic medication (boneset combined with arsenicum; *Arsenicum album*).

As a decidedly indigenous Native American plant, boneset use is not significant in the Middle or Far East, though numerous other *Eupatorium* species are used for therapeutically similar applications throughout the world (Woerdenbag et al. 1992).

IDENTIFICATION

Botanical Identification

Eupatorium perfoliatum L. Herbaceous perennial from short caudex, (30-)40-100(-150) cm tall. **Stem:** Several, angled to nearly terete in cross-section, usually unbranched below and with one or more pairs of opposite branches above, spreading-puberulent with crisp, white hairs throughout. **Leaves:** Simple, opposite (rarely whorled), sessile, usually perfoliate at the base (creating the illusion of the stem piercing through the leaf tissue), and crenate to crenate-serrate through the margins, decussate at each successive node. **Leaf blades:** 5–15(-20) × 1.2–4(-7) cm, lanceolate to oblong, truncate at the base, sometimes connate to the opposite leaf at the same node, acute to acuminate at the apex, thick, pinnately veined; abaxial surface rugose-veiny, with minute, sessile glands, pilose on the midrib and surfaces; adaxial surface impressed-veiny, lacking minute glands, typically sparsely pubescent to glabrate, though in some regions can appear densely pubescent. **Capitulescence:** Corymb-like, 5–40 cm wide, branched, the pubescent branches opposite. **Capitula:** With bisexual disk flowers only (i.e. discoid), (7-)9–23-flowered, with short peduncles, the receptacle flat or somewhat convex, lacking chaff. **Involucre:** (3.5-)4–6 mm tall, consisting of a total of 7–10 involucral bracts (i.e. phyllaries) in two or three series. **Involucral bracts:** Imbricate, 2–4.5 × 0.6–1 mm, more or less lanceolate, green with a white, scarious margin and apex, acute to acuminate at the apex, the abaxial surface villous to puberulent, and with minute, sessile glands. **Florets:** Epigynous, actinomorphic. **Corollas:** Sympetalous, can be up to 3.5 mm, white or purple-tinged (rarely), tubular, with five triangular lobes at the apex. **Stamens:** Five, connate in a ring around the style. **Style:** White when fresh, with two slender, papillate branches, minutely puberulent. (continued on page 7)

Figure 2a Botanical voucher of *Eupatorium perfoliatum*
Source: AHP Herbarium

2b.

2c.

2d.

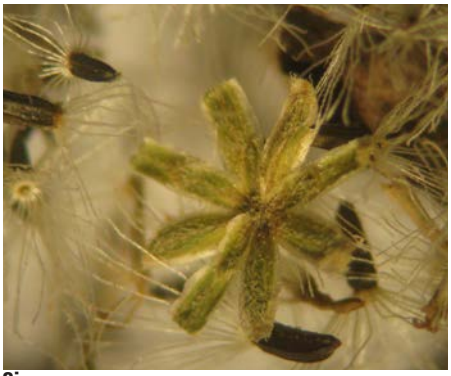
2e.

2f.

2g.

2h.

2i.



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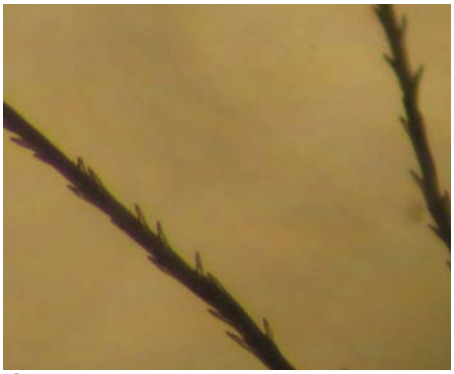


2l.

Figure 2a–l Botanical characteristics of *Eupatorium perfoliatum*

2a. Botanical voucher
2b. Flowering aerial parts showing habitat
2c. Close-up of perfoliate leaves
2d. Flowering top
2e. Closeup of flowers (capitulae)
2f. Hirsute stem
2g. Flowering top
2h. Close-up of flowers (side view)
2i. Close-up of flowers (top view)
2j. Achene with pappus attached
2k. Achene-pappus
2l. Barbed pappus magnified

Source: 2a. AHP Herbarium. 2b, 2c, 2g, 2h. Courtesy of Arthur Haines, Delta Institute of Natural History, Canton, ME. 2d-f ©2019 Courtesy of Steven Foster photography, Eureka Springs, AR; 2j-l Lynette Casper, Planetary Herbals, Scotts Valley, CA

Table 2 Botanical differentiation of *Eupatorium perfoliatum* and potential adulterating species

	Eupatorium perfoliatum	***Eupatorium cannabinum***	***Eutrochium purpureum**** (formerly *Eupatorium purpureum*)	***Ageratina altissima*** (formerly *Eupatorium rugosum*)
Common name	Boneset	Hemp agrimony	(purple) Joe Pye weed (purple) gravel root	White snakeroot
Part used	Aerial parts	Aerial parts	Root	Root
Floret count per head	(7-)10-15(-20)	(4-)5-6	(4)5-7(-8)	10-30
Corolla color	White	Pinkish-purple (lilac to mauve)	Pinkish-purple to purple or bluish-purple, sometimes whitish	Bright white
Leaf blade	Simple, unlobed	3(-5)-lobed or -divided	Simple, unlobed	Simple, unlobed
Leaf pubescence	Upper surface pubescent, lower surface densely pubescent	Both surfaces puberulent	Upper surface very sparsely pubescent , lower surface slightly tomentose	Both surfaces sparsely pubescent (mostly on veins)
Leaf base/ petiole	Connate-perfoliate (opposite leaf bases are united around the stem)	Subsessile or short petiolate	Petiolate [5–15(–20) mm]	Long petiolate [(5–)10–30(–50) mm]
Leaf Images	 **a.**	 **b.**	 **c.**	 **d.**
Flower Images	 **e.**	 **f.**	 **g.**	 **h.**

* *Eutrochium purpureum* is morphologically variable, and known to hybridize with all other species in the genus (Lamont 1995 as cited in FNA Vol. 21).
Photographs courtesy of: a., d., e. © Arthur Haines, the Delta Institute of Natural History, Canton, ME; b., c. 7Song, Northeast School of Botanical Medicine, Ithaca, NY; f., g., h. © 2019 Steven Foster Photography, Eureka Springs, AR

Fruit: Cypsela, 1.5–2(-2.5) mm long, five–ribbed, dark brown to black, glabrous, with minute, sessile glands, topped by a pappus of 20–30 white, minutely barbellate bristles 3–3.5 mm long. **Chromosome number:** 2n = 20. **Flowering:** August through October (Fernald 1950; Haines 2011; Radford et al. 1964; Siripun and Schilling 2006).

Habitat: Eastern North America: Quebec to Manitoba, south to Florida and Texas. The various habitats include fairly dry to very wet locations, such as swamps, marshes, wet fields, shores, thickets, low clearings, alluvial woods, and on river and stream banks. (Belt 2009; Landis et al. 2014; Plants for a Future 2014).

Distribution: Canada: Manitoba, New Brunswick, Nova Scotia, Ontario, Prince Edward Island, Quebec. United States: AL, AR, CT, DE, FL, GA, IA, IL, IN, KS, KY, LA, MA, MD, ME, MI, MN, MO, MS, NC, ND, NE, NH, NJ, NY, OH, PA, RI, SC, SD, TN, TX, VA, VT, WV, WI. United States Department of Agriculture (USDA) cold hardiness zones 2–10 (Belt 2009).

Macroscopic Identification

Boneset consists of the dried aerial parts (leaves and flowering tops) of *E. perfoliatum* collected during the flowering period before the flower buds open. As traded, it typically includes pieces of cut leaf and involucres from the inflores-

cences, usually matted together with florets and occasional fruits with pappus hairs. Numerous individual pappus hairs occur in the cut herb. The plant bolts into seeding immediately upon harvesting of flowering tops. As such, a considerable amount of seed may be present in commercial material. Yellow-green to dark red ribbed stem pieces may split to show white pith (BHP 1983).

Stems: Simple or branched; cylindrical, 3–6 mm in diameter, yellowish green, tomentose (hairy), longitudinally striated; nodes distinct, internodes 5–8 cm in length (Felter and Lloyd 1898; Kraemer 1920; Mansfield 1937). In transverse section, outline is wavy and cylindrical; cortex and wood thin, pith large, white; fracture fibrous (Mansfield 1937).

Leaves: Blade lanceolate, 10–20 cm long, 1.5–5 cm wide; base broad; apex acuminate; margin crenate-serrate; primary venation pinnate, secondary venation reticulate, midrib prominent on lower surface; upper surface dark green, rough, wrinkled, sparsely pubescent to glabrous; lower surface lighter green, dotted with yellow resin masses, tomentose, showing numerous, minute, shiny, glandular hairs (Felter and Lloyd 1898; Kraemer 1920; Mansfield 1937; Remington and Wood 1918).

Flowers: Corymbs dense, with numerous white to white-yellow flower heads, each head composed of 10–15 florets (2–4 mm in length); involucre oblong, composed of imbricated, light green, linear-lanceolate, hairy scales; corolla whitish, five-toothed (star-shaped), with bristly pappus; anthers five, purplish or black, included; style filiform, deeply cleft into two filiform, exserted branches (Felter and Lloyd 1898; Kraemer 1920; Maisch 1892; Remington and Wood 1918).

Fruit: Achene; oblong, black, five-angled with persistent pappus composed of single row of bristles (Felter and Lloyd 1898; Kraemer 1920; Mansfield 1937).

Differentiation can be made between *E. perfoliatum* and *E. cannabinum*. *E. cannabinum* is lacking or has fewer and shorter trichomes compared to *E. perfoliatum*, dark brown stem bark parts, and florets larger (5–8 mm in length) than *E. perfoliatum* (Hensel et al. 2011).

Sensory Characteristics (organoleptics)

Aroma: Slightly aromatic.

Taste: Strongly bitter, slightly astringent.

Texture: When dry, leaf surface rough and scratchy.

Fracture: Stem fracture fibrous.

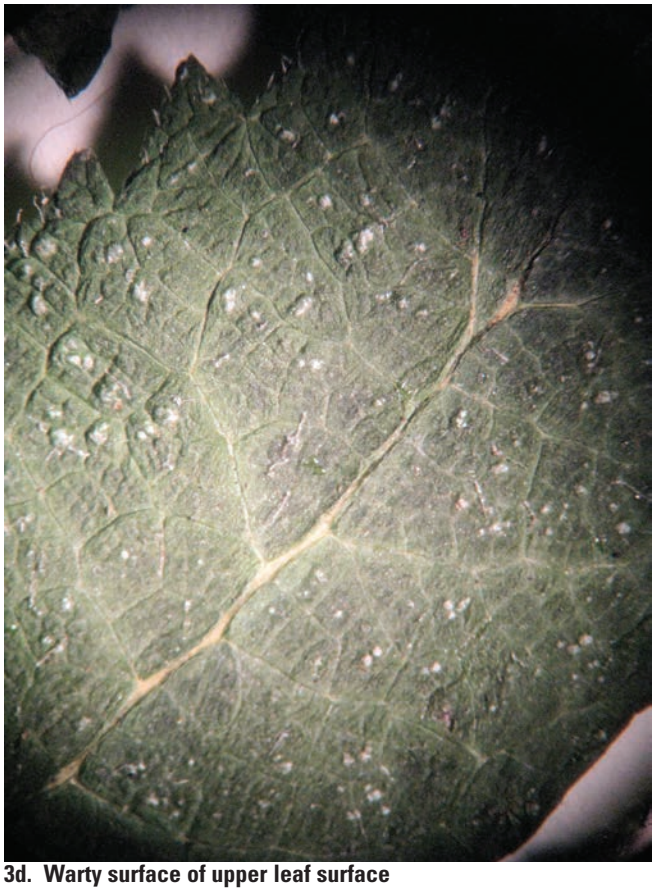
Powder: Yellowish-green; aroma fragrant, hay like; taste bitter, slightly astringent.

Figure 3a–i Macroscopic characteristics of *Eupatorium perfoliatum*

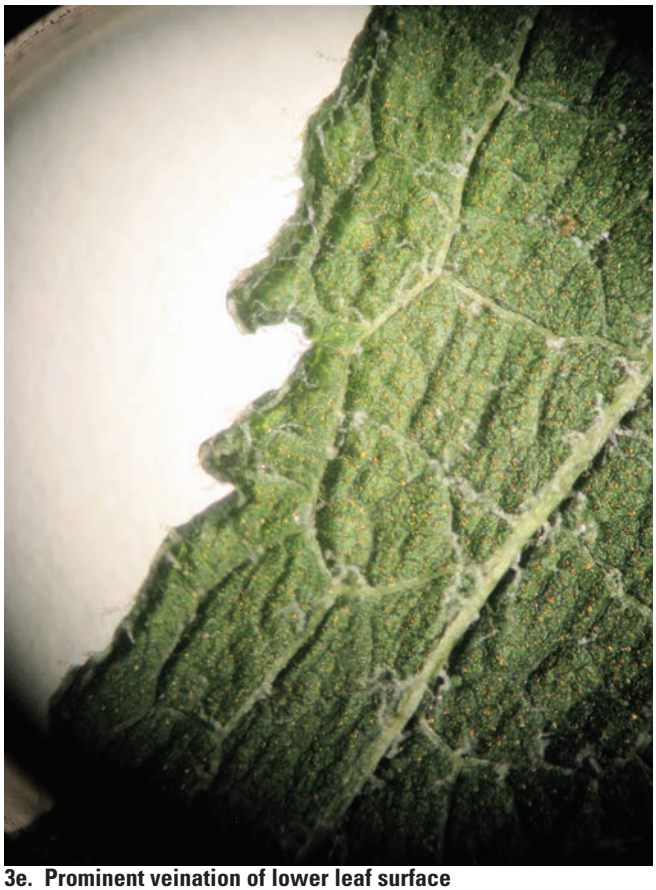
3a. Cut and sifted of aerial parts

3b. Commercial sample of mostly stem and bolted flower head

3c. Bolted flower head



3d. Warty surface of upper leaf surface

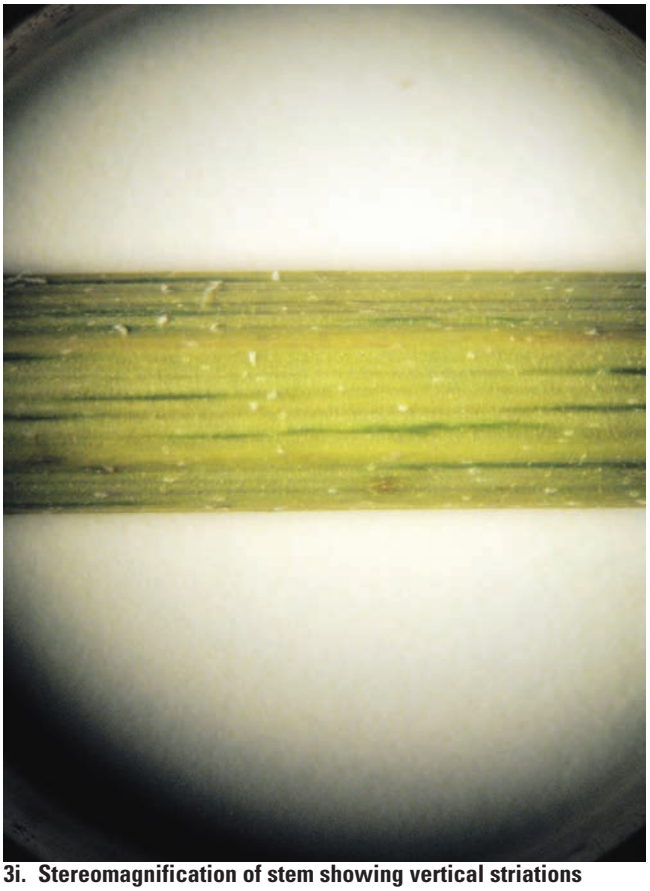


3e. Prominent veination of lower leaf surface

3f. Serrated margin leaf

3g. Stereo magnification of stems of flowering head

3h. Stereo magnification of flowering head and indifividual inflorescences



3i. Stereomagnification of stem showing vertical striations

Microscopic Identification

A. Leaf

Surface view: Epidermal cells isodiametric, with wavy anticlinal walls more pronounced on the lower surface; anomocytic stomata ~25 µm long on lower surface; infrequent schizogenous resin ducts containing green secretions occur in the mesophyll and are visible through the surface adjacent to veins; multicellular covering trichomes of two types occur on the upper surface: (a) 50–350 µm long, often slightly bowed, consisting of two to seven thick-walled cells, terminal cell tapered, basal cell up to 70 µm wide, often heavily thickened; (b) up to 200 µm long, straight or appressed, consisting of a short uniseriate stalk and a transparent terminal region; epidermal cells arranged in a rosette-like pattern around basal cell of trichomes; covering trichomes on lower epidermis dense, of same type as occur on upper epidermis, except often up to 1,200 µm long; biseriate glandular trichomes frequent on lower surface, the cuticle of the terminal two cells is detached, with fluid build-up between the cell wall and cuticle, causing the head to form a large sphere up to 80 µm diameter.

Transverse section: Bifacial; palisade cells in one row; spongy mesophyll dense, with schizogenous resin ducts ~30–50 µm diameter adjacent to vascular bundles.

B. Stem

Surface view: Covering trichomes up to 2,000 µm long and glandular trichomes resemble those found on the leaf lower surface; cuticle often striated.

Transverse section: Collenchyma occurs in a layer beneath the epidermis; stele with numerous vascular bundles arranged circumferentially; phloem capped by fibers; schizogenous resin ducts ~40 µm diameter occur between adjacent groups of fibers.

C. Inflorescence and Flower

Phyllary: Epidermal cells elongated with wavy anticlinal walls, a striated cuticle, and anomocytic stomata ~25 µm long; uniseriate covering trichomes consisting of three to seven cells are frequent on both surfaces, 50–300 µm long, with a rounded terminal cell and striated cuticle; glandular trichomes frequent, of the same type found on the leaf lower surface; uniseriate trichomes occurring on the bract margins are composed of numerous very short cells and a rounded terminal cell.

Disk floret: Hermaphroditic; pappus of bristles, approximately equal in length to the floral tube; corolla five-lobed, covered by glandular trichomes similar to those found on the leaves; anthers five, connivent, dark brown; pollen tricolpo-

(continued on pg.13)

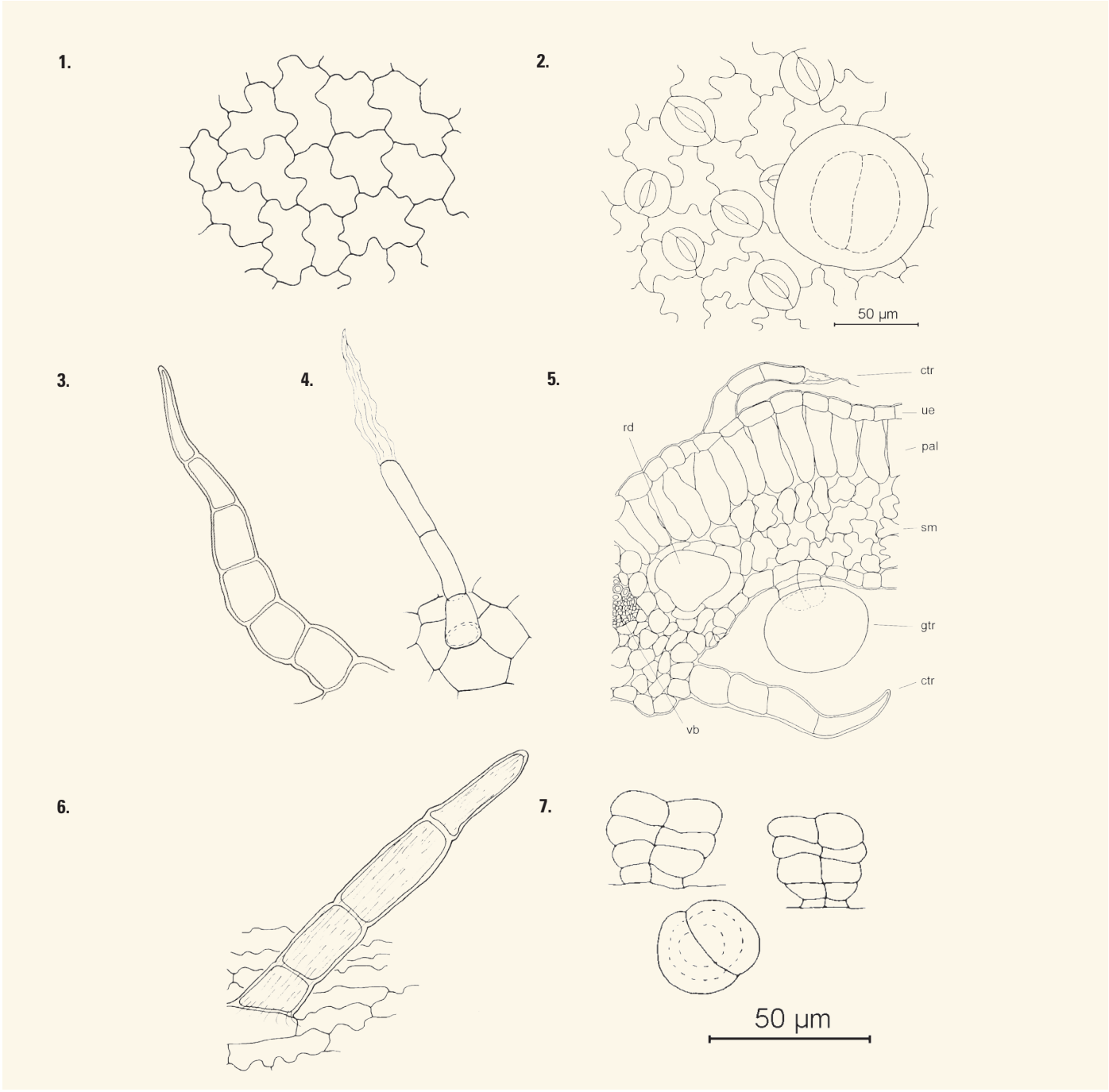
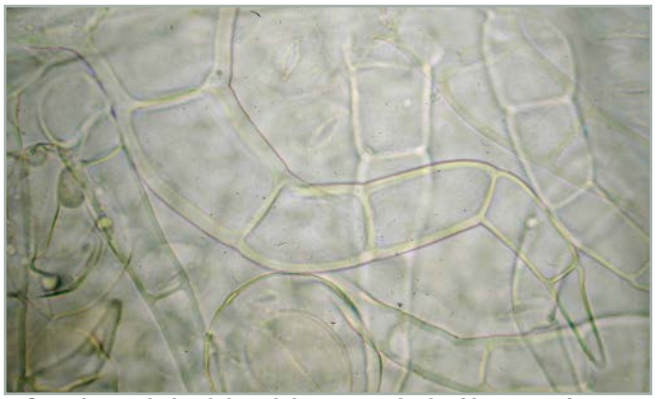


Figure 4a **Microscopic characteristics of boneset aerial parts**

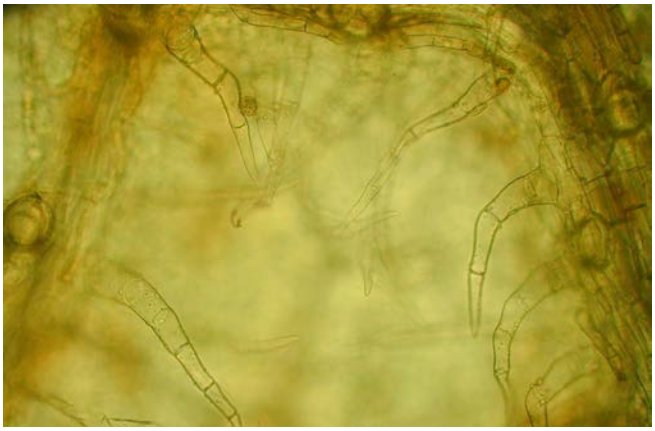
1. Leaf upper epidermis surface view (sv) showing wavy anticlinal walls
2. Leaf lower epidermis showing wavy anticlinal walls, anomocytic stomata, and a glandular trichome showing the enlarged head (sv)
3. Uniseriate covering trichome from a leaf
4. Uniseriate covering trichome from a leaf, showing the transparent terminal region
5. Leaf transverse section: upper epidermis (ue); covering (ctr) and glandular (gtr) trichomes; a single row of palisade cells (pal); spongy mesophyll (sm) with a schizogenous resin duct (rd); a portion of a vascular bundle (vb); and the lower epidermis (le)
6. Uniseriate covering trichome from a phyllary, showing a striated cuticle
7. Biseriate glandular trichomes from a cypsela

Figure 4b Microscopic characteristics of boneset aerial parts

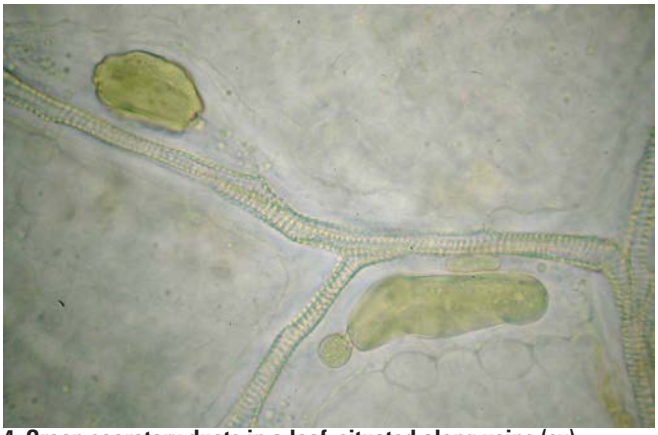
1. Uniseriate covering trichome on the leaf upper surface



2. Covering and glandular trichomes on the leaf lower surface

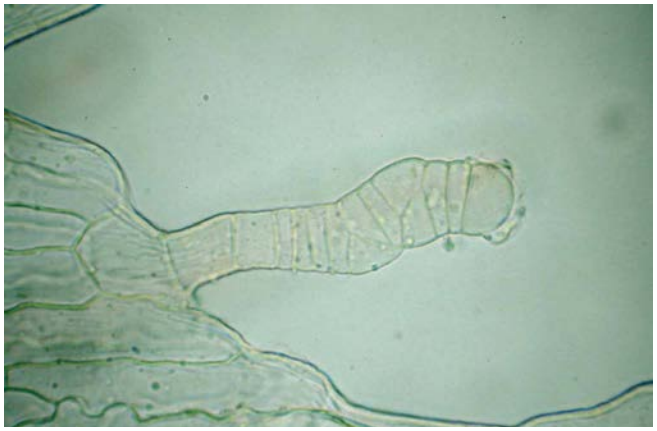


3. Covering trichomes along a vein on the leaf lower surface

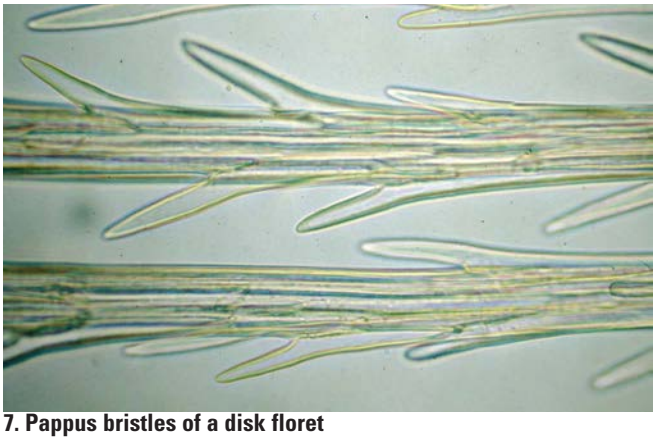


4. Green secretory ducts in a leaf, situated along veins (sv)

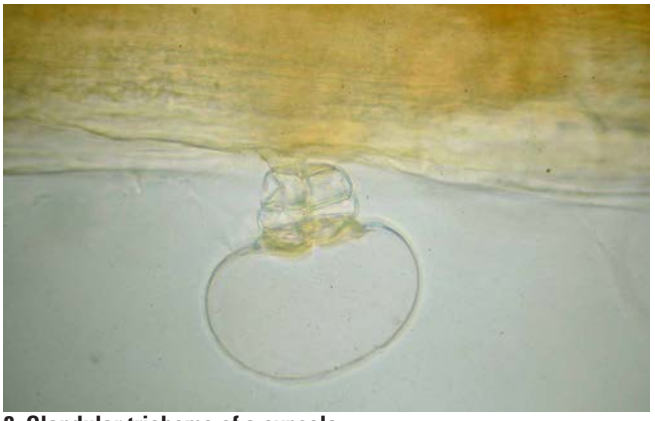
5. Covering trichomes from a phyllary



6. Trichome composed of numerous short cells on the margin of a phyllary



7. Pappus bristles of a disk floret



8. Glandular trichome of a cypsela

5a.

5b.

5c.

Figure 5a-c

5a. Wild stand of boneset
5b. Flowering tops and leaf
5c. Dried flowering tops and leaf (l-r: perfoliate leaf, floweing top, upper leaf surface, lower leaf surface)

rate with a spiny exine ~15 µm diameter; stigma of two long slender lobes exserted from the corolla by ~2 mm; the lobes have papillae ~30 µm long which become smaller towards the lobe apex.

Cypsela: Biseriate glandular trichomes numerous, up to 30 µm long, enlarged heads absent; glandular trichomes similar to those found on the leaves occur infrequently.

Powder: Yellowish-green. Sclerenchyma with bast fibers; annular ducts with bordered pits; glandular and non-glandular trichomes; stomata; pollen ellipsoidal.

COMMERCIAL SOURCES AND HANDLING

There are approximately 38 species of *Eupatorium*, mostly found in East Asia and North America. *Eupatorium perfoliatum* herbal material is most prevalent in North America, though European cultivation of this species is increasing as market demand rises (Hensel et al. 2011).

Cultivation

A native perennial wildflower, boneset can be grown from seed or plug material. Boneset is suitable for light (sandy), medium (loamy), or heavy (clay) well-drained soil. It grows in full sun to partial shade, depending upon moisture. However, it is reported to grow best in shady, moisture-laden areas, reaching four to six feet tall. Boneset is commonly seen along streams and swamps, spreading into surrounding fields, which are rough native growing areas without maintenance. It is reported to not tolerate much competition from other plants that tend to grow much taller and choke it out. Heavy field mowing by farmers adversely affect its stand and spreading. Cattle pressure is not a problem as they graze around the plant (Vickers 2015, personal communication to AHP, unreferenced).

A cold-hardy plant, boneset can tolerate temperatures down to -4 °C. Boneset can grow in any pH soil; the soil should contain considerable organic material for moisture retention. It is not drought tolerant; regular water is important with deep irrigation needed at least once weekly. While boneset can withstand flooded conditions for short periods, it is not aquatic. Due to its size, early cultivation is necessary. Plants bloom from July to September, with some reports of blooming into October, and peak at the end of August. Prolific white, flat flower clusters grow on plants three to five feet tall, which fill in well. The flowers are hermaphrodites and pollinated by insects. They provide a solid carpet of white at plant tops when fully bloomed. Seeds are carried by the wind to the surface of ponds during high water season. They then float to the shore where they are protected by flotsam, a favorable medium for germination the next season (Belt 2009; Choukas-Bradley and Brown 2008; Evans 1915; Hilty 2012; Landis et al. 2014; Plants for a Future 2014; Rogers 2014).

Propagation

Boneset is easily propagated from seeds or cuttings. Seeds, which ripen approximately one month after flowering, should be collected when heads are dry, split, and seeds begin to disperse. If sown directly, seeds should be sown in fall. Seeds germinate best with stratification, typically taking two to three weeks with 80–90% germination. For container propagation, moist pretreatment at 4 °C for three weeks to three months increases germination rate. After pretreatment, seeds should be sown in a mix containing milled sphagnum moss. Seeds need light and germinate at 20–30 °C. Cuttings, which root easily, are best taken when not in flower, in late spring or early summer. Older plants can be easily divided in early spring and should be replanted in late spring on 18–24 inches centers and rows spaced 24–30 inches. Plants should be divided in fall as they go dormant, or in spring as shoots appear (Belt 2009; Janke and DeArmond 2004; Pengally et al. 2011; Rogers 2014).

Collection

Historically, all aerial parts of the plant (leaf, flower, stem) have been used and considered by authorities (e.g. Barton 1818) to be equal in efficacy. Harvest should take place when in the flowering stage but before the buds open (Hensel et al. 2011), as fruit and pappi should not be present (Hensel et al. 2011). This is typically starting in mid-summer. A second fall harvest may be possible. The leaves and flowering tops are collected by hand when in flower, stripped from the stalk, and dried. Coarse stems should be avoided. Plants can be harvested in the same location in successive years. It must be fertilized if left in the ground for many years.

Janke and DeArmond (2004) provide field trial data for three years of harvest (Table 3). They note that the yield in year three was very low as the plant was harvested slightly earlier than in year two, after having peaked. The plants had flowered and/or declined faster in year three than year two, possibly due to plant maturity or an exceptionally hot, dry summer.

In one study, distribution of the major constituents between flowers, leaves, stems, and total herb was investigated during various times of spring, summer, and fall over the course of three years. Results were determined using a validated high performance liquid chromatography

Table 3 Kansas State University boneset field trial data (2000–2002)

				Average	Comments
Age of plants in years	1	2	3		
Number of test sites	3	2	2		Grown in Wichita and Olathe for three years; Colby for one year
Survival rate (%)	88.7	77.5	69.5	78.6	
Vigor rating[1]	3.1	4.8	3.3	3.7	
Height (cm)	37.3	95.5	94.0	75.6	
Dry weight herb (g/plant)	21.0	310.7	30.8	-	The low third-year yield as compared to the second year is because the plants had begun to senesce before harvest (see maturity index of 5.9 vs 4.9), even though fall harvest was at about the same time, in early to mid-September.
Dry weight root (g/plant)	12.0	230.9	62.5	-	
Maturity rating[2]	2.3	4.9	5.9	4.4	
Insect damage rating[3]	1.1	1.2	4.5	2.3	The high insect rating in year three was due to late stage of growth and feeding by opportunistic insects.
Disease rating[4]	0.4	2.2		1.3	
Estimated planting density (number of plant/A)	10,890	10,890	10,890	-	Assume two-by two-ft. spacing.
Plant density[5]	9,659	8,440	7,569	-	
Kg/A dry weight (g/plant x plant number) – tops	203	2,622	233	-	
Estimated marketable yield (dry weight lbs/A) – tops	447	5,776	513		

[1] Vigor rating (1 = very poor, 3 = slightly above average. 5 = very good, well adapted).
[2] Maturity rating (1 = vegetative, 2 = early bud, 3 = early flower, 4 = full flower, 5 = seed production, 6 = senescence).
[3] Insect damage rating (scale of 0 to 5; 0 = no damage, 5 = severe damage).
[4] Disease rating (scale of 0 to 5; 0 = no damage, 5 = severe damage).
[5] Calculated as starting plant density x survival rate.
Adapted from Janke and DeArmand (2004).

(HPLC) method (Maas 2011). Chlorogenic acid, which is found mainly in leaves, with traces in stems, was shown to be the most prominent constituent of total material (~2.5%). Amounts were more or less constant from May to September. The caffeic acid 3,5-dicaffeoylquinic acid, which is found mainly in flowers (up to 3.5%) with small amounts in leaves and none in stems, accounted for approximately 1.5% of total herb, decreasing from late summer to fall. Dicaffeoylglucaric derivatives, which accumulate almost exclusively in flowers, reached peak levels during flowering in late June to July and accounted for at most 0.1% of total material. The flavonoid quercetin 3-glucoside (often reported as isoquercitrin), which is found mainly in leaves, accounted for approximately 2% during early vegetation, steadily decreasing to about 0.6% in fall. Amounts of hyperoside, trifolin, and astragalin (~0.2%, 0.1%, and 0.15% total herb, respectively) remained constant throughout the year. As well, the flavonoid aglycone eupafolin, which accumulates in leaves (~0.1% to 0.2%), remained relatively constant (see Table 4) (Hensel et al. 2011).

Handling and Processing

Harvested material should be immediately put in the shade, as it begins to decompose rapidly. Boneset is easily bruised so care must be taken in handling. Drying should take four to six days (Rogers 2014). There is considerable loss of leaf material (up to approximately 8%) during post-harvesting processing due to fragility and brittleness. Sometimes following the harvesting of the flowering tops, the proper time to harvest, the plant bolts into seeding, suggesting it was harvested after the opening of the flower buds.

Contact irritation due to harvesting, which resolves quickly, has been reported by some collectors (Fletcher 2015, personal communication to AHP, unreferenced).

Storage

There is no specific data regarding optimum storage conditions of boneset aerial parts. Follow general principles for storage. Protect from moisture, air, light, high temperatures, and insect infestation. Seeds last up to three years when stored in a cold (4 °C) and dry (30% relative humidity) environment (Belt 2009).

Sustainability

The most attracted natural enemies include the insects *Orius insidiosus*, *Plagiognathus politus*, *Chalcidoidea*, *Cantharidae*, *Thomisidae*, and *Cynipoidea*. Boneset also attracts grasshoppers, lygus bugs, leaf beetles, and weevils (Landis et al. 2014). Wildcrafting, while widespread and common, appears to not significantly affect native populations, due to insufficient market demand (Yarnell 2007) and presumably the renewability of crops if allowed to seed. 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. Some sources report a *E. perfoliatum* var. *colpophilum*, also called common boneset or estuary boneset, as endangered. Its habitat is reported throughout New England and Eastern Canada (Quebec) and occurs along shorelines and in marshes, swamps, wetland margins, and ditches (USDA 2015). However, this "variety" is not accepted as a distinct taxon (ITIS 2015). Rather, when *E. perfoliatum* is exposed to tidal water on the coast, its leaves become narrower, the pubescence of the stem decreases relative to non-tidal populations, and, in its extreme Northeastern range, the leaves become more leathery (Haines 2011). The greater the tidal pressure, the more extreme the morphological changes (Haines 2015, personal communication to AHP, unreferenced). Currently, the Maine Natural Areas Program (2008) does not list *E. perfoliatum* on its endangered, threatened, and rare list (Pengally et al. 2011).

Potential Substitutions and Adulterants

Some regional herbalists utilize the aerial parts of other *Eupatorium* species as "boneset" (Upton 2015; personal communication to AHP, unreferenced). The most common other species of *Eupatorium* in commercial trade is *E. purpureum* (now *Eutrochium purpureum*), the root of which is traded as gravel root.

Ageratina altissima (previously called *Eupatorium rugosum*), known as white snakeroot or richweed and designated a poisonous plant by the FDA, has historically been confused with *E. perfoliatum* due to similarity in appearance as well as the same geographical growing areas, despite obvious macroscopic and phytochemical differences. Furthering the confusion, both species have been identified as boneset in certain herbal texts (e.g. in Spoerke 1980). Most notably, while the stem of *E. perfoliatum* appears to puncture the middle of the pairs of opposite leaves, the stem of A. *altissima* does not appear to puncture the leaves. Furthermore, fresh undried A. *altissima* contains tremetol, a toxic chemical that causes nausea, vomiting, anorexia, tremors, severe constipation, blood sugar changes, and severe ketosis. At high doses the compound has been reported to result in coma and death in animals (Beier et al. 1993; Nicholson 1989; Olson et al.1984). This species has not been reported in the modern trade of boneset. Regionally, some herbalists substitute the aerial parts of gravel root for boneset. The high performance thin layer chromatography (HPTLC) fingerprints of these species are almost identical. The European *E. cannabinum* is another species reported in commercial trade, though it is easily distinguished from *E. perfoliatum* via botanical assessment (see Table 2).

Quality Assessment

According to historical literature, all aerial parts of boneset are equally efficacious, though some authors report a preference for the leaf. Caffeic acid derivatives have been proposed as quality control markers. This compound primarily occurs in the leaves, and only in traces in the stems. Thus, it is recommended that stem material, especially larger stems, be discarded. Other compounds of specific interest similarly predominate in the leaves (e.g. quercetin 3-glucoside) while others (e.g. dicaffeoylquinic acids) accumulate in flowers

(3.5% vs 1% to 1.5% in leaves), supporting the historical recommendation of harvesting material in its flowering stage. Commercial materials consisting mostly of flowers that have bolted to seed are sometimes traded and have not been fully analyzed.

Hensel et al. (2011) reported on the lack of quality in commercial material, likely due to prolonged storage, and proposed the following values as reflecting acceptable quality: chlorogenic acid > 1.5%, 3,5-dicaffeoyl quinic acid > 1.0%, quercetin 3-glucoside > 0.4%, hyperoside > 0.2%, eupafolin > 0.2%. These compounds do not necessarily reflect pharmacological activity.

Preparations

Infusion:	1–2 tsp dried leaves per cup of boiling water; steep for 10–20 minutes (Rogers 2014)
Decoction:	35 g/250 mL water; boil for 15 minutes covered (Yarnell 2007)
Tincture (1:2–1:3*):	40% to 60% ethanol (Yarnell 2007)
Fluidextract (1:1):	25% alcohol (Haughton 2014)
Salve:	Mix equal parts ground herb with Vaseline (Rogers 2014)

* 1:5 is also a typical herb to extract ratio used in tinctures.

CONSTITUENTS

The scientific study of boneset constituents began in the late 1800s with the isolation of a compound then known as euparin. Since then, a number of classes of components have been isolated and identified, including flavonoids, sesquiterpene lactones, triterpenes and sterols, caffeic acid derivatives, fatty acids and fatty alcohols, and polysaccharides. The existence of volatile oils has been established, although reported composition is not consistent. Recently, two potentially hepatotoxic, unsaturated pyrrolizidine alkaloids (PAs), commonly found in the genus *Eupatorium* though not previously detected in *E. perfoliatum*, were found and confirmed (Avula et al. 2015; Colegate et al. 2018). Uncharacterized alkaloids have also been reported (Hensel et al. 2011; Woerdenbag et al. 1992, 1993). Caffeic acid derivatives have been proposed as identity quality control markers (Hensel et al. 2011), though these are not necessarily associated with the pharmacological activity attributed to boneset. Chlorogenic acid occurs predominantly in the leaves and is relatively consistent in its concentration (~2.5%) throughout the growing season. Only traces of chlorogenic acid occur in the stems. Restrictions on internal consumption of PA-containing plants have been instigated in the European Union and are now relevant to boneset (see Safety: Pro-toxic pyrrolizidine alkaloids—Brief Review).

Volatile Oil

Early reports excluded volatile oils. Later literature included 0.05% volatile oils, namely β-gurjunene, β-caryophyllene oxide, limonene, linalool, borneol, bornyl acetate, (iso)-eugenol, α-copaene, β-elemene, ar-curcumene, β-caryophyllene, humulene, and δ-cadinene (Woerdenbag et al. 1992). More recent studies, based upon gas chromatography-mass spectrometry (GC-MS) analysis of dried herbal material, report 1.8 mL/kg volatile oil, consisting mainly of *E*-anethole (16.5%), carvone (7.6%), linalool (4.0%), camphor (2.5%), selin-11-en-4-α-ol (5.5%) and caryophyllene oxide (3.8%), β-selinene (2.8%), 1,2-humulene-epoxide (3.1%), *E*-nerolidol (2.6%) (Maas 2011). Further investigation is needed to address the inconsistency and to determine the effects of seed material, growing conditions, harvest time, etc. on the composition of volatile oils (Hensel et al. 2011).

Flavonoids

The primary flavonoids reported to be present in crude methanol/water (70/30 v/v) extract are the flavonols kaempferol, astragalin (kaempferol-3-O-β-D-glucoside), nicotiflorin (kaempferol-3-O-β-D-rutinoside), quercetin, hyperoside (quercetin-3-O-β-D-galactoside), and rutin (quercetin-3-O-β-rutinoside) (Habtemariam 2008; Wagner et al. 1972). Maas et al. (2009) additionally identified quercetin-3-O-β-glucoside and trifolin (kaempferol-3-O-β-D-galactoside). Later nuclear magnetic resonance (NMR) and mass spectrometry (MS) analysis of a CH_2C_{l2} extract from the methanol-soluble part of *E. perfoliatum* also revealed the methoxylated flavonoid aglycones hispidulin, eupafolin, and patuletin (Maas et al. 2011a). Thin layer chromatography (TLC) and MS investigation of fresh leaves washed with CHCl3 identified eupafolin as the predominant flavonoid of the epicuticular fraction, with lesser amounts of hispidulin also present (Maas et al. 2011a).

The methoxylated flavone eupatorin had been considered in early literature, but it was not detected in later investigations (Hensel et al. 2011; Herz et al. 1972).

Since isolated eupafolin (nepetin) has been shown to exhibit anti-inflammatory activity in in vivo studies (Clavin et al. 2007; Pelzer et al. 1998; Williams et al. 1999), it is assumed that *E. perfoliatum* plant material containing eupafolin will also result in anti-inflammatory effects (Hensel et al. 2011).

Sesquiterpene Lactones

A number of sesquiterpene lactones have been isolated from *E. perfoliatum*. Among these are guaianolides, including euperfolide, eufoliatin, and dihydroeuperfolide (roots), and eufoliatorin; and germacranolides, such as euperfolitin, euperfolin, and the novel heliangolid (3α,14-dihydroxy-8β-tigloyloxy-6βH,7αH,11αH-germacra-1(10)Z,4Z-dien-6,12-olide) (Bohlmann et al. 1977; Bohlmann and Grenz 1977; Herz et al. 1977; Maas 2011; Maas et al. 2011a). Also, 5S,6R,7R,8R,11R-2-oxo-8-tigloyloxyguaia-1(10),3-diene-6,12-olide-14-carboxylic acid has been identified, a constituent described only in *E. perfoliatum* (Maas

Table 4 Batch analysis (HPLC) of five representative batches of herbal material of *Eupatorium perfoliatum* for development of analytical specifications

	Content [g/100 g dry wt]				
Peak designation	**Batch 1a**	**Batch 2b**	**Batch 3c**	**Batch 4d**	**Batch 5e**
3-Caffeoylquinic acid	0.24 ± 0.04%	0.43%	0.04%	0.06%	0.02%
5-Caffoylquinic acid	1.53 ± 0.10%	1.90%	1.67%	1.61%	0.12%
2,4/3,5-Dicaffeoylglucaric acid	0.09 ± 0.01%	0.03%	0.07%	0.08%	0.02%
3,4-Dicaffeoylglucaric acid	0.06 ± 0.07%	0.04%	0.07%	0.07%	0.02%
2,5-Dicaffeoylglucaric acid	0.04 ± 0.04%	0.01%	0.03%	0.04%	0.01%
3,5-Dicaffeoylquinic acid	1.18 ± 0.18%	2.15%	1.56%	1.42%	0.25%
4,5-Dicaffeoylquinic acid	0.21 ± 0.01%	0.12%	0.11%	0.13%	0.04%
Hyperoside	0.19 ± 0.02%	0.38%	0.53%	0.29%	0.06%
Quercetin 3-glucoside	1.16 ± 0.15%	0.82%	0.83%	0.43%	0.07%
Trifolin	0.10 ± 0.02%	0.14%	0.23%	0.11%	0.05%
Astragalin	0.19 ± 0.04%	0.17%	0.23%	0.09%	0.04%
Eupafolin	0.19 ± 0.04%	0.52%	0.34%	0.59%	0.13%

[a] Herbal material from agricultural farming at author's laboratories botanical garden, mean values from determinations from July 2008–2010.
[b] Botanical Garden Institute of Pharmaceutical Biology, Muenster, July 2008.
[c] Botanical Garden Institute of Pharmaceutical Biology, Muenster, July 2009.
[d] Commercial sample (Germany).
[e] Commercial sample (Germany).
Source: Modified from Hensel et al. 2011

et al. 2011a).

The sesquiterpene lactones present in boneset, particularly euperfolid, are considered to contribute to the plants anti-inflammatory effects (Hensel et al. 2011).

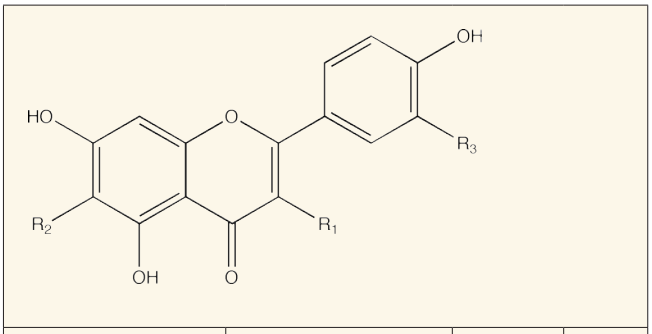
Triterpenes and Sterols

Early investigation with a petroleum benzene extract of *E. perfoliatum* leaves displayed α-amyrin, β-sitosterol, stigmasterol, 3β-hydroxy-ursa-20-ene, 3β-acetoxy-ursa-20-ene, ursa-20-en-3-one and 3β-hydroxy-ursane (Dominguez et al. 1974). Later, campesterol, β-sitosterol, α-amyrin, β-amyrin, lupeol, taraxasterol, and pseudotaraxasterol were described in both the leaves and the blossoms (Hooper and Chandler 1984). More recent GC-MS analysis identified and/or confirmed β-amyrin acetate, α-amyrin acetate, β-amyrenone, and lupenone; β-amyrin, lupeol, taraxasterol, stigmasterol, campesterol, and β-sitosterol (Maas 2011).

Caffeic Acid Derivatives

Six caffeic acid derivatives, including chlorogenic acid, neochlorogenic acid, 3,5-dicaffeoylquinic acid, and three depsides of caffeic acid with glucaric acids novel to *E. perfoliatum* (2,5-dicaffeoylglucaric acid, 3,4-dicaffeoylglucaric acid, and 2,4- or 3,5-dicaffeoylglucaric acid) have been identified from an ethyl acetate fraction of a methanol/water extract via 1D- and 2D-NMR spectroscopy (Maas et al. 2009).

Recent investigations have confirmed the presence of caffeoyl quinic acids and N-(E)-cinnamoyl-L-aspartic acid (Hensel et al. 2011; Maas 2011).



	R_1	R_2	R_3
Kaempferol	OH	H	H
Astragalin	O–β-D-glucose	H	H
Trifolin	O–β-D-galactose	H	H
Nicotiflorin	O–β-D-rutinose	H	H
Quercetin	OH	H	OH
Isoquercetin	O–β-D-glucose	H	OH
Hyperoside	O–β-D-galactose	H	OH
Rutin	O–β-D-rutinose	H	OH
Hispidulin	H	OCH_3	H
Eupafolin	H	OCH_3	OH
Patuletin	OH	OCH_3	OH

Figure 6a Structural features of boneset flavonoids
Source: Modified from Hensel et al. 2011

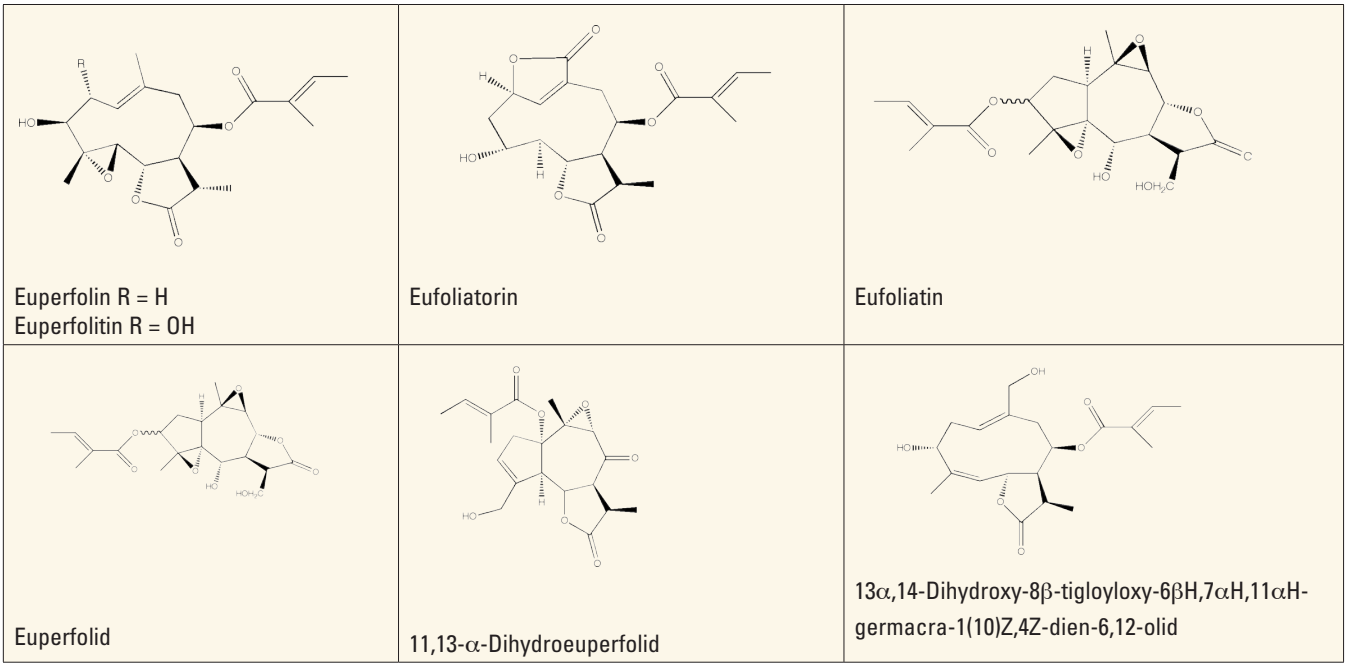


Figure 6b **Sesquiterpene lactones of boneset**
Source: Modified from Hensel et al. 2011

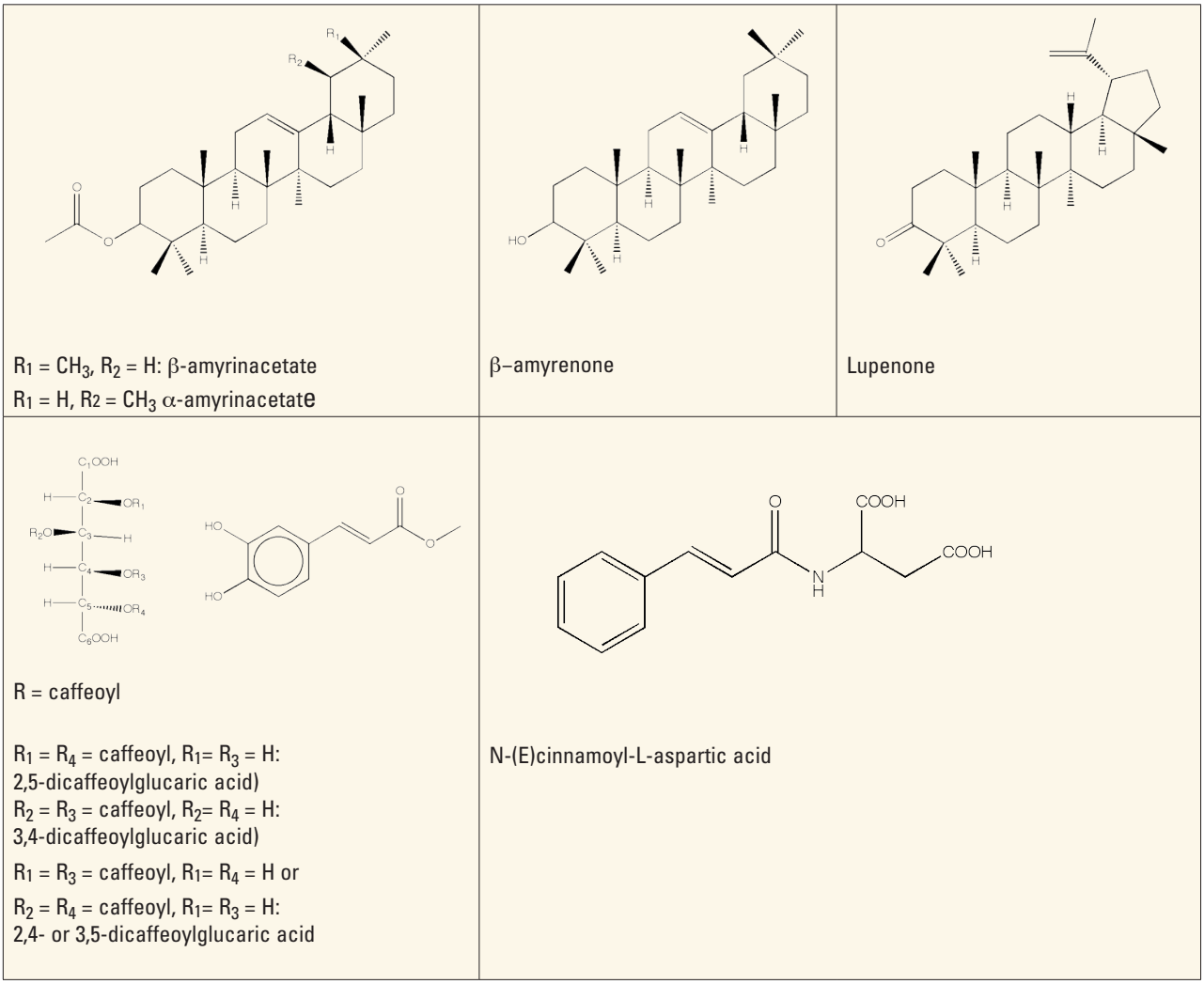


Figure 6c **Structural features of triterpenes, phytosterols, dicaffeoylglucaric acid esters and N-phenyl-propenoyl amino amide of boneset**
Source: Modified from Hensel et al. 2011

Fatty Acids and Fatty Alcohols

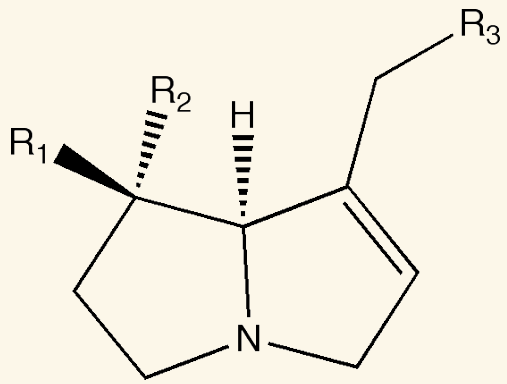
Free saturated fatty acids, namely C_{16} (palmitic), C_{17} (margaric), C_{18} (stearic), C_{19} (nonadecylic), C_{20} (arachidic), C_{21} (heneicosylic), C_{22} (behenic), C_{23} (tricosylic), and C_{24} (lignoceric), were identified through GC-MS analysis of fractions obtained from a CH_2C_{l2} extract. The unsaturated fatty acids oleic acid, linoleic acid, and α-linolenic acid have also been identified, along with the free fatty alcohols n-octadecanol, n-eicosanol, n-docosanol, and n-tetracosanol (Maas 2011).

Polysaccharides

Cold-water soluble polysaccharides (1.1%) have been obtained from water extracted herbal material, fructans (1.3%) from a hot water extract, and xylans from an alkaline extract (Maas 2011; Vollmar et al. 1986).

Pyrrolizidine Alkaloids (PAs)

A number of species of *Eupatorium* contain potentially toxic pyrrolizidine alkaloids (PAs), specifically those that occur with an unsaturated necine ring. Analyses of boneset over a period of more than 20 years did not detect unsaturated PAs (Hensel 2011; Locock 1990; Woerdenbag et al. 1992), presumably due to the lack of sensitivity of the methods used. However, after an analysis revealed the presence of intermedine and lycopsamine in a single sample (Avula et al. 2015), analyses of more than 40 samples revealed that 50% contained 0.0002% to 0.02% (w/w) total dihydropyrrolizidine alkaloids (DHPAs) while the other 50% contained between 0.02% to 0.07% (w/w) total DHPAs consisting predominantly of intermedine and lycopsamine and their N-oxides (Colegate et al. 2018). Both compounds possess the structural characteristics (unsaturated PAs) considered a prerequisite for toxicity (See Safety). Analysis of a broad sampling of boneset populations was conducted with virtually all confirmed *E. perfoliatum* samples containing these potentially toxic compounds. Two different infusions prepared from 3.3 g of boneset contained 0.859 and 0.931 mg of DHPAs; two decoctions yielded 1.065 mg and 1.145 mg DHPAs (Colegate et al. 2018). These preparations would yield approximately 1 mg DHPAs per cup of tea, or yield a daily dose of several mgs daily. One tincture yielded approximately 0.3 mg/mL of DHPAs. At a low dose of 3 mLs daily the expected DHPA exposure would be approximately 0.9 mg, whereas acute doses of up to 20 mL daily could yield 6 mg daily. The toxicological risk of internal use of this herb must be carefully considered based on dose, duration of use, and pre-existing conditions that may make consumers more susceptible to PA toxicity (pregnancy, neonates, those with liver disease), and considered against the perceived benefit.



R_1 = OH; R_2 = H; R_3 = OH: =	retronecine
R_1 = H; R_2 = H; R_2 = OH: =	heliotridine
R_1 = OH; R_2 = H; R_3 = I: =	**lycopsamine***
R_1 = H; R_2 = H; R_3 = II: =	supinine
R_1 = H; R_2 = OH; R_3 = II: =	rinderine
R_1 = OH; R_2 = OH; R_3 = II: =	**intermedine***
R_1 = H; R_2 = OH; R_3 = I: =	echinatine
R_1 = H; R_2 = VII; R_3 = III: =	lasiocarpine
R_1 = VII; R_2 = H; R_3 = I: =	symplandine
R_1 = OH; R_2 = H; R_3 = V: =	leptandine
R_1 = VII; R_2 = H; R_3 = IV: =	echimidine
R_1 = OH; R_2 = H; R_3 = VI: =	indicine

Figure 6d Dihydropyrrolizidine alkaloids (DHPAs)
*** Lycopsamine and intermedine occur in boneset.**
Source: Colegate et al. (2018)

ANALYTICAL

High Performance Thin Layer Chromatography (HPTLC) Characterization of *Eupatorium perfoliatum* and Closely Related Species

The following HPTLC method was adapted by CAMAG (Muttenz, Switzerland) for the identification of *Eupatorium perfoliatum* and its differentiation from closely related species.

Sample Preparation

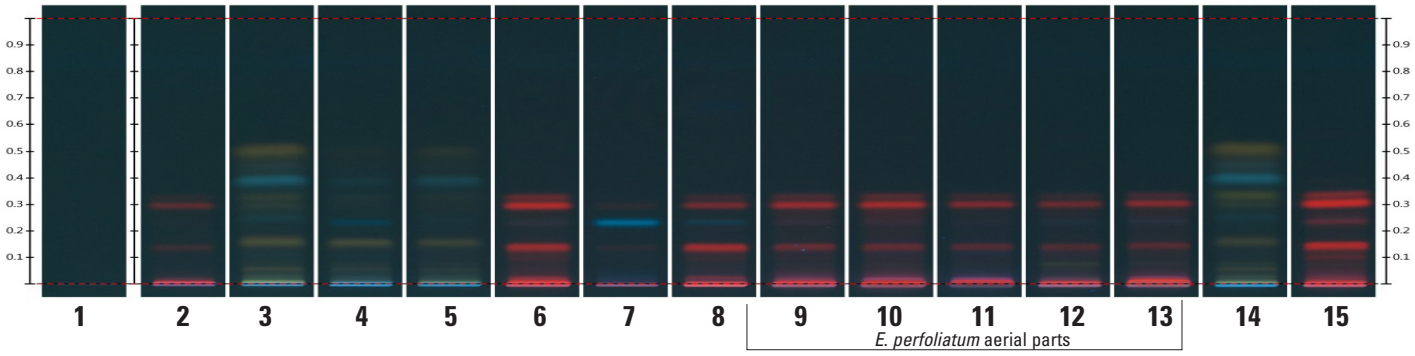
Mix 0.5 g of powdered sample with 5 mL of methanol and sonicate for 10 min, then centrifuge or filter the solutions and use the supernatants/filtrates as test solutions.

Standards Preparation

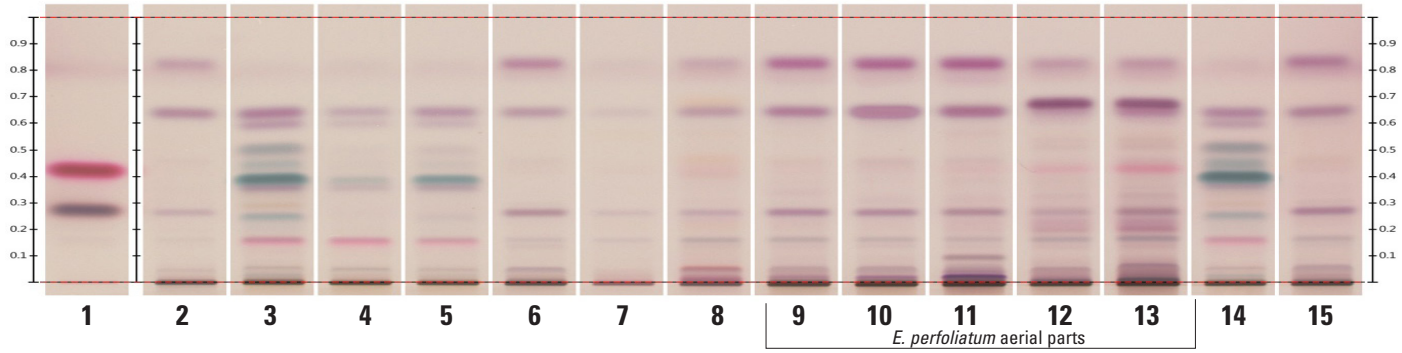
Dissolve 25 mg of bornyl acetate and borneol in 1 mL of methanol. Dissolve 4 µL of linalool and 1 mg of caryophyllene oxide in 1 mL of toluene.

Application

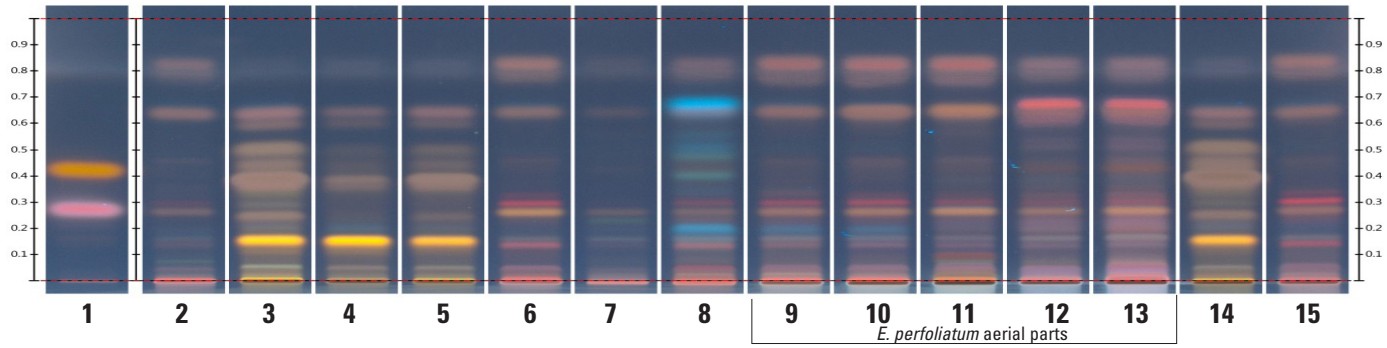
5 µL of references, 5 µL of test solution.



7a. Image of plate prior to derivatization under UV 366 nm



7b. Image of derivatized plate WRT



7c. Image of derivatized plate under UV 366 nm

Figure 7a-c HPTLC profile of *E. perfoliatum* and related species

1. Linalool, caryophyllene oxide with increasing Rf.
2. *Eutrochium purpureum* aerial parts
3. *Eutrochium purpureum* root
4. *Eutrochium purpureum* root
5. *Eutrochium purpureum* root
6. *Eupatorium purpureum* aerial parts
7. *Eupatorium fortunei* (Shanghai) aerial parts
8. *Eupatorium fortunei* (Anhui) aerial parts
9. *Eupatorium perfoliatum* aerial parts
10. *Eupatorium perfoliatum* aerial parts
11. *Eupatorium perfoliatum* aerial
12. *Eupatorium perfoliatum* aerial
13. *Eupatorium perfoliatum* aerial
14. *Eupatorium maculatum* aerial root
15. *Eupatorium cannabinum* aerial parts

Reagent Preparation

Anisaldehyde reagent: Carefully add 20 mL of acetic acid, 10 mL of sulfuric acid, and 1 mL of anisaldehyde to 170 mL of ice-cooled methanol. Mix well.

Use: Dip (time 0, speed 5), heat at 100 °C for three minutes.

Chromatographic Conditions

Stationary Phase:

HPTLC plates 20 x 10 cm or silica gel 60 F_{254} (Merck or equivalent).

Sample Application:

Apply 5 µL of test solution(s) and 5 µL of each reference standard as an 8 mm band with minimum of 11.44 mm distance between bands. Application position should be 8 mm from lower edge of plate.

Mobile Phase:

Toluene:ethyl acetate 93:7 (v/v).

Development:

10 x 10 cm or 20 x 10 cm Twin Trough Chamber (CAMAG or equivalent), lined with filter paper, saturated for 20 min with 5 or 10 mL, respectively, or developing solvent in each trough. Developing distance is 70 mm from lower edge of the plate. Dry the plate in a stream of cold air for five min.

Detection:

Examine the plate under UV 366 nm (no diagnostic information is evident at UV 254).

Dip the plate in anisaldehyde reagent and then heat at 100 °C for three min.

Examine under white light. No additional diagnostic data is provided when viewing the derivatized plate under UV 366 nm.

Results:

Compare to the chromatograms provided.

Discussion of Chromatograms

UV 366 nm: Neither linalool nor caryophyllene oxide are visualized in this chromatogram. *Eupatorium perfoliatum* (Lanes 9–13) is characterized by three red bands; one at the application zone and at ~Rf 0.15 and 0.3. The aerial parts of both *Eutrochium purpureum* (Lanes 2 & 6) (formerly *Eupatorium purpureum*), one of the Asian *Eupatorium fortunei* (Lane 8) samples, and the European *Eupatorium cannabinum* (Lane 15) have almost identical chromatographic fingerprints as shown by the three prominent red bands in these samples. The fingerprint of *Eutrochium purpureum* root (Lanes 3–5) differs and is characterized by a blue band

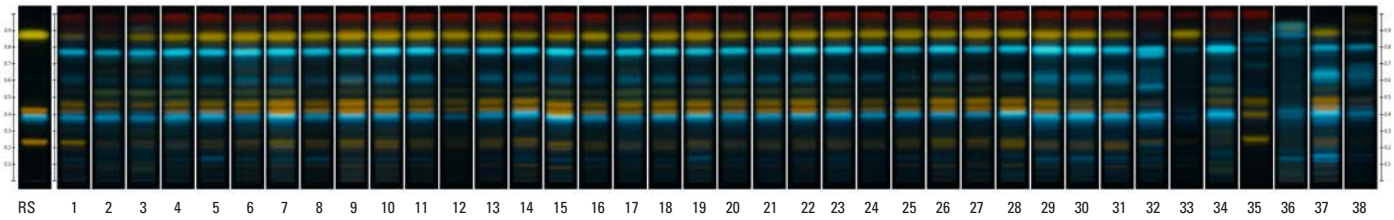


Figure 7d. HPTLC characterization of flavonoids of boneset and related species (UV 366 nm)

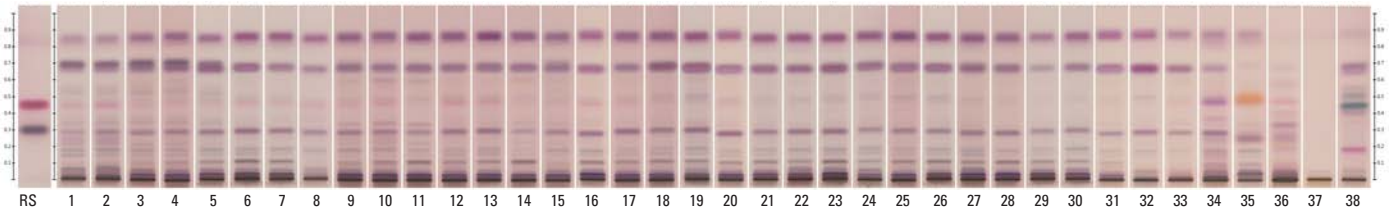


Figure 7e. HPTLC characterization of apolar compounds of boneset and related species (UV white light)

RS.	Reference standards linalool and caryophyllene oxide (with increasing Rf)
Lanes 2-31	*Eupatorium perfoliatum*
Lane 31	*E. fistulosum*
Lane 33	*E. pilosum*
Lane 34	*E. serotinum*
Lane 35	*E. leucolepsis*
Lane 36 & 37	*E. perfoliatum* tincture
Lane 38	*Eutrochium purpureum* root

at the application zone, a brown band at ~Rf 0.14, a blue band at ~Rf 0.4, and another brown band at ~Rf 0.5. The fingerprint of *Eupatorium maculatum* root (Lane 14) has an almost identical profile as those of *Eutrochium purpureum* root (Lanes 3–5). The fingerprint of the sample of Asian *Eupatorium fortunei* (Lane 7) is anomalous and does not match any other sample, including the other sample of *Eupatorium fortunei* (Lane 8).

Image of derivatized plate WRT: Linalool (Lane 1) is visualized as a brown band at ~Rf 0.29 and caryophyllene oxide (Lane 1) is visualized as a red band at ~Rf 0.43. As described above with UV 366 nm, *Eupatorium perfoliatum* (Lanes 9–13) displays a relatively consistent fingerprint across the samples, and similarly are consistent with the aerial parts of *Eutrochium purpureum* (Lanes 2 & 6), *Eupatorium fortunei* (Lanes 7 & 8) and *Eupatorium cannabinum* (Lane 15), with slight variations. These are primarily characterized by a pink band at ~Rf 0.16, a light blue band at ~Rf 0.26, a light brown band at ~Rf 0.37, a prominent blue band immediately above this at ~Rf 0.04, two blue bands at ~Rf 0.43 and Rf 0.5, and two reddish brown bands at Rf 0.6 and 0.63. The aerial parts of both *Eutrochium purpureum* (Lanes 2 & 6) (formerly *Eupatorium purpureum*) and the European *Eupatorium cannabinum* (Lane 15) have banding patterns that are more similar to those of *Eupatorium perfoliatum* than when visualized under the previous conditions. These display a light brownish band reflecting the color and positioning of linalool (Rf 0.29) and two purplish bands in the upper Rf region at ~Rf 0.65 and 0.82. The fingerprint of *Eutrochium purpureum* root (Lanes 3–5) is characterized by a light bluish band just above the application position, a pink band at ~Rf 0.16, a light blue band at ~Rf 0.26, a light brown band at ~Rf 0.37, a prominent blue band immediately above at ~Rf 0.4, two bluish bands at ~Rf 0.42 and 0.52, and two reddish bands at ~Rf 0.6 and 0.62, with varying intensity of some bands between these samples. The fingerprint of *Eupatorium maculatum* root (Lane 14) has an identical fingerprint as those of *Eutrochium purpureum* root. As seen in Figure 7d, boneset has a very consistent fingerprint with minor natural variations between samples.

Image of derivatized plate under UV 366 nm

Linalool (Lane 1) is visualized as a pink band at ~Rf 0.29 and caryophyllene oxide (Lane 1) as an orange band at ~Rf 0.43. As above, *Eupatorium perfoliatum* (Lanes 9–13) displays a relatively consistent fingerprint across the samples, and similarly are consistent with the aerial parts of *Eutrochium purpureum* (Lane 2 & 6), *Eupatorium fortunei* (Lane 7), and *Eupatorium cannabinum* (Lane 15), with slight variations. The aerial parts of both *Eutrochium purpureum* (Lanes 2 & 6) (formerly *Eupatorium purpureum*), one Asian *Eupatorium fortunei* sample (Lane 7), and the European *Eupatorium cannabinum* (Lane 15) have similar chromatographic fingerprints in terms of primary banding patterns with some variation in banding intensity. The fingerprints of *Eutrochium purpureum* root (Lanes 3–5) and *Eupatorium maculatum* root (Lane 14) have similar banding patterns. The *Eupatorium fortunei* sample (Lane 8) similarly presents an anomalous fingerprint that differs from all other *Eupatorium* samples, including the other *Eupatorium fortunei* sample (Lane 7).

High Performance Liquid Chromatography (HPLC) Analysis of *Eupatorium perfoliatum*

The following HPLC method can be used as a fingerprint method for identification of *Eupatorium perfoliatum* and quantitation of caffeic acid derivatives, most notably chlorogenic acid and quercetin 3-glucoside. The method was developed by Maas (2011) and was validated according to ICH-Guidelines (ICH, 1995, 1997) for specificity, linearity, accuracy, and precision for purposes of establishing specifications in the European Union (Hensel et al. 2011).

For analysis of PAs, there are numerous qualitative and quantitative methods for the lycopsamine-like dehydropyrrolizidine alkaloids in plants and food products. A high pressure reversed phase liquid chromatography-positive electrospray ionization (RP-HPLC-esi(+)) mass spectrometry (MS) and tandem MS/MS method of analysis was specifically used to quantitatively study the dehydropyrrolizidine alkaloids in *Eupatorium perfoliatum* (boneset) and related species (Colegate et al. 2018).

Equipment

HPLC

Alliance 2690 Separations Module

Column

Luna 5 µm C18(2) 100A, 5 µm, 250 x 3.00 mm with pre-column Security Guard 4 mm x 2 mm i.d. (Phenomenex, Torrance, USA)

Detector

996 Photodiode Array Detector (Waters, Milford, MA USA), or equivalent (e.g. 2998 photodiode array detector)

Sample Preparation

Extract 2 g of plant material three times with 30 mL of methanol-water (70:30) for three min via Ultra-Turrax (T25 IKA, Staufen).

Internal Standards (available from PhytoLab, Germany)

Chlorogenic acid

Quercetin 3-glucoside

Preparation of Internal Standards

2 mL of each internal standard was added before extraction via Ultra-Turrax (ferulic acid, 1 mg/mL in methanol).

Calibration Line

3 x 10 mg weighted sample respectively, dissolved in 10 mL methanol to receive the stock solutions. Create serial dilutions containing 1, 10, 20, 50, 100, and 200 µg/mL.

Chlorogenic acid: Linearity: y = 121130x – 30540 (range: r^2= 0.9989)

Quercetin 3-glucoside: Linearity: y = 57357x + 3641 (range: r^2 = 1.0000)

Storage of Reference Compounds

Store in dessicator protected from light.

Chromatographic Conditions

Column Temperature

40 °C

Injection Volume

20 µL

Mobile Phase

Time (min)	Methanol (%)	0.1% TFA in Aqua millipore (%)	Flow (mL/min)
0	10	90	0.5
5	20	80	0.5
30	45	55	0.5
37	60	40	0.5
40	100	0	0.5
45	100	0	0.5
50	10	90	0.5
60	10	90	0.5

Flow Rate

0.5 mL/min

Detection

325 nm

Run Time

60 min

Chromatography Data System

Empower Pro, Empower (Waters, Milford, MA USA), or equivalent.

Quantification Parameters and Calculations

Caffeic acid-derivatives and flavonoid-glycosides were evaluated. Caffeic acid-derivatives were evaluated via chlorogenic acid-calibration line as chlorogenic acid, and flavonoids as quercetin 3-glucoside via quercetin 3-glucoside-calibration line.

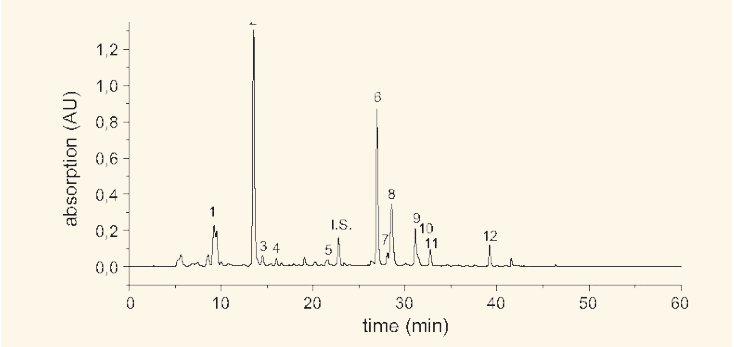


Figure 8 Typical HPLC fingerprint of *Eupatorium perfoliatum*

1. 3-Caffeoyl quinic acid (neochlorogenic acid)
2. 5-Caffeoyl quinic acid (chlorogenic acid)
3. 2,4/3,5-Dicaffeoyl glucaric acid
4. 3,4-Dicaffeoyl glucaric acid
5. 2,5-Dicaffeoylglucaric acid
6. 3,5-Dicaffeoyl quinic acid
7. Hyperoside
8. Quercetin 3-glucoside
9. 4,5-Dicaffeoyl quinic acid
10. Trifolin
11. Astragalin
12. Eupafolin

I.S. Ferulic acid (internal standard)

Limit Tests

Foreign Matter:	Not more than 2% with the exception of stem (NF 1947)
Stems:	Not more than 10% (NF 1947)
Total Ash:	Not more than 10% (NF 1916)
Acid-insoluble Ash:	Not more than 2% (NF 1947)
Loss on Drying:	Not more than 65% (Phf 2005 for homeopathic preparations)

THERAPEUTICS

Pharmacokinetics

There is no data available on the pharmacokinetics of boneset. Pharmacokinetic information does exist on classes of components found in boneset which are considered to contribute to its therapeutic effects based upon preclinical studies. These include flavonoids and sesquiterpene lactones. While it may be possible to extrapolate information from the classes themselves, further investigation is needed to determine the pharmacokinetics of boneset and its plant-specific compounds.

Clinical Efficacy and Pharmacodynamics

Although boneset has an extensive history of traditional use, preclinical and clinical studies on its pharmacological and therapeutic activities are minimal. Furthermore, much of the preclinical data is based on isolated constituents rather than the whole plant or combination formulas. The few human clinical trials have been limited to homeopathic preparations that are outside the scope of whole plant material monographs.

Immunological Activity

Animal Studies

An in vivo investigation with mice of boneset heteroglycan polysaccharides (10 mg/kg intraperitoneal [ip]) resulted in significantly increased macrophage phagocytosis activity as demonstrated in a carbon clearance test (Wagner et al. 1985).

In Vitro Studies

In vitro studies with boneset polysaccharides have resulted in conflicting conclusions, regarding the effects on macrophage phagocytosis activity. Older studies (Vollmar et al. 1986; Wagner et al. 1985) showed increased phagocytosis while more recent studies did not show macrophage stimulation (Maas et al. 2011b). In addition, down-regulation of macrophage-produced cytokines and chemokines has been observed (see Anti-inflammatory Effects below).

Cytotoxic and Antibacterial Effects

In Vitro Studies

While weak antibacterial effects have been shown in one study (Habtemariam and Macpherson 2000) with an unfractionated ethanolic extract of boneset against gram-positive bacteria (*Staphylococcus aureus*, *Bacillus megaterium*), other investigations did not result in significant cytotoxic or antibacterial activity.

Anti-inflammatory Effects

Animal Studies

An ethanol extract of boneset (100 mg/kg; two administrations) reduced rat paw edema by 12% when administered subcutaneously (Benoit et al. 1976).

In Vitro Studies

Boneset extracts have exhibited anti-inflammatory effects in one in vitro investigation. Mechanisms of action include inhibition of macrophage nitric oxide (NO) release, as well as the down-regulation of cytokines (including tumor necrosis factor [TNF]), chemokines, and surface receptors associated with anti-inflammatory activity. In this study, methanol, ethanol, and dichloromethane extracts expressed anti-inflammatory activity against lipopolysaccharide (LPS)-stimulated macrophages via inhibited NO release (IC_{50} >100, 89, 19 µg/mL, respectively). The flavonoid eupafolin and a sesquiterpene lactone guaianolide are the constituents shown to prominently inhibit NO by reducing NO synthase (Maas et al. 2011b).

Antioxidant Effects

In Vitro Studies

In antioxidant studies, fractionation of a fresh leaf ethanol extract produced significant antioxidant properties in a DPPH test. Ethyl acetate and n-butanol fractions displayed the most potent activity, respectively. In the ethyl acetate fraction, protocatechuic acid was the most potent of the compounds followed by hyperoside, quercetin, and rutin. In the n-butanol fraction, rutin and trace amounts of hyperoside were identified (Habtemariam 2008).

Antiplasmodial Effects

In Vitro Studies

A sesquiterpene lactone-enriched extract of the aerial parts of boneset has shown significant antiprotozoal activity in vitro. Effects were observed for *Plasmodium falciparum* (IC_{50} 2.7 µg/mL) but not for *Leishmania donovani*, *Trypanosoma brucei rhodesiense*, or *Trypanosoma cruzi*. The dimeric guaianolide expressed the most activity, while eupafolin activity was low and selective (Maas et al. 2011a).

Antiviral Effects

In Vitro Studies

Two hydroalcoholic extracts from the aerial parts of *E. perfoliatum* strongly inhibited growth of a clinical isolate of IAV(H1N1)pdm09 and the IAV strain PR8 (H1N1). A homeopathic mother tincture (1:10) exhibited a half-maximal inhibitory concentration (IC_{50}) of 7 µg/mL and a selectivity index (SI) (half-maximal cytotoxic concentration (CC_{50})/IC_{50})) of 52. The second extract was prepared by ultrasound treatment (30 min) of a suspension and exhibited an IC50 of 14 µg/mL, and a SI of 26. Interestingly, a standard macerated (21 days) tincture (herb to extract ration not reported) did not exhibit significant antiviral activity. Activity was correlated with a fraction that contained polyphenols, though the exact compound(s) responsible for the antiviral activity is not known (Derksen et al. 2016).

At extract concentrations >1 to 10 µg/mL plaque formation of IAV(H1N1)pdm09 was abrogated. The extract was also active against an oseltamivir-resistant isolate of IAV(H1N1)pdm09. This is significant considering that oseltamivir-resistance is on the rise and there are few approved antivirals for use against it. TNF-α induced signal transduction in A549 cells was not affected, while the EGF-induced signaling to phosphorylated ERK was slightly upregulated by the extract. The extract blocked attachment of IAV and interfered with virus-induced hemagglutination. Bioassay-guided fractionation and subsequent LC-MS analysis indicated that the antiviral activity might be due to polyphenolic compounds with higher molecular weights, which strongly interact with stationary phases of different chromatographic systems. A variety of different flavonoid glycosides and

caffeoyl quinic acids obtained from *E. perfoliatum* did not contribute to the antiviral effect of the extract and its respective fractions. These still unknown active compounds likely are of high molecular weight and could not be isolated using standard analytical techniques.

Considering worldwide concern regarding treatment-resistant strains of influenza, identification of antiviral compounds is significant and may partially explain the traditional use of boneset for flu, which is worthy of further research.

Summary

Despite extensive use as an herbal medicine, preclinical and clinical research on boneset is lacking. Its extensive and apparent efficacious use for influenza supports further investigation, though, due to the presence of potentially toxic PAs, an appropriate benefit-risk assessment is required or PA-free preparations must be developed.

Animal-studies and in vitro experiments with plant preparations strongly indicate both an antiplasmodial effect against *Plasmodium falciparum* and an anti-inflammatory effect. In particular, its effects on the immune system, inflammation, and *Plasmodium* warrant additional research. While the preclinical anti-inflammatory and antiplasmodial effects of boneset have been predominantly attributed to an isolated flavonoid and/or sesquiterpenes, more studies with the whole herb are needed. Anti-inflammatory actions associated with the tincture correlate well with clinical symptoms related to diseases for which the herb has traditionally been used (e.g. colds, fever, and arthritis), as well as for athralgias and myalgias associated with other infections such as Lyme disease. However, without an appropriate benefit-risk assessment, long-term use should be avoided and short-term use must be questioned.

Medical Indications Supported by Clinical Trials

There are no clinical trials to date on non-homeopathic single preparations or formulas of boneset.

Actions

Antibacterial, antipyretic, anti-inflammatory, antioxidant, antispasmodic, aperient, astringent, bitter tonic, carminative, diaphoretic, emetic, laxative, immunostimulant (enhanced macrophage activity).

Indications

Boneset has historically been used for fever, common cold, aches and pains due to influenza and rheumatoid conditions, cough and acute bronchitis, dyspepsia, inflammation, and constipation.

Substantiated Structure and Function Statement

Due to the recent identification of potentially toxic PAs, unsupervised and long-term use of boneset must be discouraged until formal safety studies to the contrary or PA-free boneset preparations are available.

Dosages

Powder:	2 g (NF 1947)
Infusion:	3–5 g of cut and sifted herb per 250 mL water, steeped 15 min; drink one cup every two to three hours (acute); 3–5 mL three times daily (chronic). Hotter tea is diaphoretic and emetic; cold tea is more of a bitter tonic (Yarnell 2007)
Tincture (1:2–1:3*):	3–5 mL every two to three hours (acute); 3–5 mL three times daily (chronic) (Yarnell 2007)
Fluidextract (1:1):	1–2 mL three times daily (BHP 1983)

* 1:5 tinctures are also commonly available. Adjust dose accordingly.

SAFETY PROFILE

Based on its traditional use, boneset has historically been considered to be a very safe herb when used within its typical daily dosage range (2–3 g), and typically no observable adverse events are experienced at these levels. However, this must be reconsidered in light of the recent detection of potentially toxic pyrrolizidine alkaloids (PAs) that can result in adverse effects with long-term exposure (see Pro-toxic Pyrrolizidine Alkaloids—Brief Review below and Tables 5–7).

Most regulatory agencies strive to minimize exposure to PAs to the greatest extent possible to avoid any risk. This has led some to impose restrictions based on the available data, but not based on individualized dose-response of individual PAs, some of which are highly toxic and others of which are of low to moderate toxicity. Some researchers believe that because PAs are cleared through glutathione detoxification pathways that small amounts of PAs will generally not result in a toxic event in otherwise healthy people (Habs et al. 2017). There is considerable evidence of individualized sensitivity to the toxic effects of PAs, such as in the inability to clear through glutathione conjugation, or susceptibility to liver damage in developing fetuses and neonates. While the acute symptoms of PA toxicity are clear, oftentimes validated methods for distinguishing between PA toxicity and other potential causes of acute hepatotoxicity are not employed, resulting either conjugation an under- or over-reporting of acute hepatic toxicities. Validated liver-specific toxicity tests (e.g. Council for International Organization of Medical Sciences [CIOMS] are available and recommended to be used when acute herb-induced liver injury (HILI) is suspected (Teschke et al. 2013). Conversely, many of the concerns regarding PAs arise due to chronic use in which the toxic effects may be initiated with early exposure to PAs but may not manifest for years, which makes drawing conclusions

about causality difficult. Lastly, the benefits of either food or herbal product consumption that may contain PAs (honey and herbal teas) must be weighed against the potential for risk and the ability to reduce exposure through adherence to Good Agriculture and Collection Practices (GACP), Good Manufacturing Practices (GMPs), selection of low- or no-PA containing clones, and extraction techniques that may preserve beneficial compounds and eliminate or minimize the presence of potentially toxic PAs in finished products.

Regarding boneset, no formal safety evaluation has been conducted. While the PAs contained in boneset are among the least toxic of this class of compounds, their presence in other botanicals has been implicated in acute toxicity of a developing fetus (Rasenack et al. 2003).

Adverse Effects

Large dosages, defined as a decoction made of 5.5–7 g, may be emetic or cathartic (Felter and Lloyd 1898; Woerdenbag et al. 1992; Wood and LaWall 1926). Vomiting is more likely to occur with consumption of hot tea. Diarrhea, accompanied by profuse sweating, can occur six to seven hours after administration of large doses. However, since emetic and cathartic effects are desired therapeutic actions in some acute conditions, these are not considered adverse effects when appropriately applied (Brinker 2010).

Interactions

There are no known interactions for boneset. Findings of one animal study revealed that vitamin E (tocopherol; 6 mL/kg ip) completely prevented the lethality of the PA heliotrine (300 mg/kg sc) (a compound not contained in boneset) (Savin 1983). Whether this has any clinical relevance to PAs in general is not known. Along similar lines, glutathione conjugation is one of the primary pathways of detoxification of toxic pyrrolic esters (CFS 2017; Fu et al. 2004), raising the possibility that supplementation with N-acetyl cysteine may help to prevent PA-induced toxicity in individuals choosing to use boneset. Again, the clinical efficacy of this has not been investigated.

Reproductive and Developmental Effects

While no studies on reproductive or developmental effects of boneset have been identified boneset should not be used in pregnancy, lactation, or in children. Considering the recent detection of potentially toxic PAs, there is potential for negative reproductive and developmental effects as the developing fetus is particularly susceptible to PA toxicity and human fatalities due to exposure of other PA-containing plants have been reported (Rasenack et al. 2003). Boneset also contains high levels of nitrate, which have been correlated with spontaneous abortions in cattle grazing on the herb. In addition, free nitrate ingestion creates methemoglobin formation and tissue anoxia that has the potential to precipitate miscarriage.

Carcinogenicity and Genotoxicity

No direct studies on carcinogenicity of boneset have been identified. Most PAs are confirmed as animal carcinogens and, based on the mechanisms of carcinogenesis, are suspected though not verified as carcinogens in humans. Investigations of lycopsamine and intermedine specifically suggest a low genotoxic (Chen et al. 2010; Chen and Mei 2014), cytotoxic (Field et al. 2015), and tumorigenic risk (Xia et al. 2013).

Toxicology

From a traditional use perspective, boneset was historically considered a very safe herb when used according to its therapeutic dosing patterns. Recent detection of potentially toxic PAs in boneset requires a reevaluation of the overall safety and potential for toxicity even when used within normal dosing and despite the lack of adverse events associated with its use.

In one study, an ethanol extract of dried boneset leaves resulted in cytotoxicity in three mammalian cell lines with EC_{50} values of 12–14 µg/mL, comparable to the cytotoxic agent chlorambucil (Habtemariam and Macpherson 2000). Neither lycopsamine nor intermedine, the two primary PAs in boneset, elicited acute hepatotoxicity in rats injected at doses of 60 and 120 mg/kg (Culvenor et al. 1976).

Pro-toxic Pyrrolizidine Alkaloids—Brief Review

PAs and their N-oxides are a sub-class of pyrrolizidine alkaloids that have specific structural characteristics (El-Shazly and Wink 2014) that, when ingested and absorbed into the body, form toxic metabolites. As a result of the consequent damage that can occur to the liver (hepatotoxicity) and lungs (pneumotoxicity) in livestock and humans (Molyneux et al. 2011), the occurrence, chemistry, toxicology, and precautions associated with PAs have been extensively studied from about the middle of the 20th century and continues to the present day. For a detailed review of the chemistry, toxicology, case studies, and regulations of PAs, see the United Kingdom Committee on Toxicity report (COT 2008).

Approximately 650 PAs have been identified and estimated to occur in about 6,000 species of plants with an extensive distribution worldwide. The main genera represented are in the *Boraginaceae*, *Asteraceae*, and *Fabaceae* plant families. Many plants within these families are used for medicinal purposes and produce PAs (Roeder 1995; Roeder and Wiedenfeld 2009, 2011; Roeder et al. 2015) and now need to be assessed for safety with the increasing knowledge of the acute to chronic potential for PA toxicity

In addition to their ability to cause acute hepato- and pneumotoxicity, the PAs have been shown to cause damage to DNA (genotoxicity), cause various cancers (carcinogenicity), and potentially cause or contribute to the development of other chronically-developing disease in humans (Edgar et al. 2015). While the National Toxicology Program in their review of the carcinogenicity of PAs classified only riddelliine as a potential human carcinogen, potential disease outcomes of oral (dietary and medicinal) exposure to the PAs include:

1. Toxic destruction of hepatic sinusoidal endothelial cells with further blockage of blood vessels

in the liver (hepatic veno-occlusive disease also referred to as hepatic sinusoidal obstruction syndrome) that leads to a massive distension of the abdomen due to fluid build-up (ascites) and pro gresses to cirrhosis of the liver
2. Pulmonary arterial hypertension due to the toxic effects of PAs on the lungs
3. Various cancers (proven in animal studies but not yet unequivocally proven to occur in humans)
4. Congenital abnormalities due to PAs ingested by the mother being transferred across the placenta to the developing fetus

Therefore, health-related concerns about PAs range from the more acute cases of poisoning that can be clearly associated with the ingestion of the PAs, through to chronic development of diseases that can be very difficult to associate with exposure to PAs due to the time lag involved. While the metabolic fate of all PAs are the same toxic entities within the body (in vivo), not all PAs are equally pro-toxic nor are all humans equally susceptible. PAs themselves differ in their toxicity according to their structural makeup with retrorsine from *Senecio* spp. representing the more toxic form and lycopsamine and intermedine in boneset representing PAs with low to intermediate toxicity. Though of lesser toxicity than other PAs, concern still remains, especially if used long-term. Physiologically, toxicity is also influenced by the efficiency of absorption and distribution within the body following ingestion of the PAs and how efficiently the absorbed PAs can be metabolized to the toxic entities. Other, idiosyncratic factors may also exacerbate the effects of ingested PAs, such as elevated blood and tissue copper levels and prior or concurrent adverse effects on the liver due to viral infection, bacterial endotoxins, or mycotoxins such as aflatoxins. However, despite this intrinsic variability, fetuses, neonates, and older infants are particularly susceptible. There are some claims that males may be more susceptible than females but, like other generalizations that attempt to predict PA intoxication, it does not universally apply. For example, while a woman developed a severe case of liver disease attributed to her exposure to echimidine (a PA found in many plants including comfrey) in a homemade pollen preparation, her husband, who also used the pollen supplement, was not overtly affected (Rollason et al. 2016).

Humans can be exposed to PAs through the diet, dietary supplements, and herbal medicinal products, both for topical use and for ingestion, though concerns regarding exposure from topical preparations may be overly conservative (Jedlinszki et al. 2017). The most extensive poisonings of humans have been related to products derived from grains contaminated with seeds or parts of PA-producing plants. In these circumstances the main effects are related to the liver and the formation of veno-occlusive disease and cirrhosis with its often fatal outcomes. Some other dietary and diet supplementary exposures include foods such as milk, eggs, and meat derived from animals exposed to the PAs; salads, either comprised of leaves from PA-producing plants (e.g. comfrey), or contaminated with leaves of similar-looking PA-producing plants, honey, pollen, and teas (Edgar et al. 2011; Wiedenfeld 2011).

PA-producing herbs can be used individually or in mixtures as cooking spices or medicines. Reports of poisoning of humans due to consumption of herbal products (teas and medicines) have been well-documented (Huxtable 1989; Neuman and Steenkamp 2009; Ridker et al. 1985; Wiedenfeld 2011). In particular, Wiedenfeld (2011) compiled a table showing all unequivocal cases of human poisonings due to PAs, most from contaminated foods, some from herbal teas, and a single report of a comfrey product.

Highlighting the low confidence in predicting the potential toxicity of individual PAs, studies of the effects of lycopsamine and intermedine, the major PAs detected in boneset, have indicated a relatively low toxic potential. For example, neither lycopsamine or intermedine elicited acute hepatic toxicity when each given as a single injection to two-week-old rats at an upper dose of 0.7 micrograms/kg bodyweight (Culvenor et al. 1976) and both showed relatively low toxicities in chicks and in cultivated CRL-2118 chicken hepatocytes (liver cells) (Stegelmeier et al. 2016). Conversely, lycopsamine (6 microgram/g), intermedine (3.5 microgram/g), their C7 acetylated derivatives (3 microgram/g), and senkirine have been reported in an herbal cooking mixture associated with the fatal veno-occlusive disease of a pre-term neonate, though only metabolites of lycopsamine and intermedine were found in the liver of the deceased neonate. The mother consumed 2 g of the mixture as part of her daily diet (Rasenack et al. 2003). This case also highlighted the increased susceptibility of the fetus considering the mother was unaffected.

Given the variation in response to PAs both between and within species, affected by age and biochemical status of an individual, including the ability to metabolize the PAs, a toxic dose is difficult, if not impossible, to predict with confidence. Nonetheless confirmed intoxications can be used to approximate ranges of doses that cause clearly defined adverse effects. For example, Ridker et al. (1985) estimated that a 49-year-old woman developed hepatic veno-occlusive disease following prolonged (less than six months) exposure to 15 micrograms PA/kg bodyweight/day in the form of a comfrey (*Symphytum* spp.) tea (echimidine, lycopsamine, and symphitine occurring as dominant PAs). Using observations like this, in 2001 the Food Standards Australia New Zealand (FSANZ) authority proposed a recommended exposure limit of 1 microgram PA/kg bodyweight/day to avoid hepatic damage and concluded there is no evidence that PAs cause liver cancer in humans (ANZFA 2001). However, in a 2018 Public Health and Safety report FSANZ states that they have "identified some critical gaps in the data that would be needed for us to set a new and more appropriate health standard for Australia and New Zealand" (FSANZ 2018). Meanwhile other developed countries have developed regulations or recommendations to limit human exposure to PAs that vary from a total exposure of 0.1 microgram PA/day (regardless of bodyweight) and 0.007 microgram/kg bodyweight/day (to avoid cancer development) to 0.1 microgram/kg bodyweight/day (to avoid non-cancer effects) (COT 2008; Edgar et al. 2011).

The current and proposed regulations or recommendations governing human exposure to PAs refer to the total PA exposure from all sources. Therefore, it would not necessarily be adequate simply to ensure that use of a single herbal preparation would conform to the exposure limitations. Allowances would be needed to account for possible exposure to PAs from other sources.

After a consideration of PAs either as contaminants or natural components of herbal preparations the European Herbal & Traditional Medicines Practitioners Association (EHTPA), with the support of the British Herbal Medicine Association (BHMA) issued cautionary advice: "With the new research published on PA toxicity over the last couple of years and with the recommendations from the FSA for herbal teas, the EHTPA with the support of the BHMA, issued advice to its member practitioner associations in February 2016, advising that all use of PA-containing herbs for internal use should be suspended until more research could be undertaken to assess their safety" (EFSA 2017)

Table 5 Pathogenic classification of herbal hepatotoxicity

Definition	Required Criteria
Idiosyncratic type	Lack of predictability and dose dependency, variable latency period, low incidence in humans, lack of experimental reproducibility
Metabolic type	Duration of exposure: One week to 12 months; possible weak dose dependency; lack of hypersensitivity features; delayed response to re-exposure (weeks)
Immunologic type	Duration of exposure: One to five weeks; hypersensitivity features; prompt response to re-exposure; occurs with one to two doses
Intrinsic type	Predictable: Dose dependent, short and consistent latency period, high incidence in humans, experimental reproducibility

Table 6 Primary clinical features of hepatic obstructive sinusoidal syndrome (HSOS) and herb-induced liver injury (HILI)

HSOS related to PAs	HILI unrelated to PAs
Ascites	Fatigue
Hepatomegaly	Appetite loss
Jaundice	Jaundice
Elevated ALT/AST levels	Nausea
	Fever
	Dark urine
	Pruritus
	Vomiting
	Dyspepsia
	Bloating
	Abdominal discomfort/pain
	Pale stools

Contraindications

Not for use in pregnancy, lactation, or children.

Not for use in those with impaired liver function.

Precautions

Due to the potential for PA toxicity to be accumulative, boneset should only be used if a careful assessment determines there is no alternative treatment, and if used, should only be used acutely for short periods of time to reduce PA exposure.

Hypersensitivity due to sesquiterpene lactones (Herz et al. 1977; Warshaw and Zug 1996; Woerdenbag et al. 1992) or sensitivity to *Asteraceae* may occur with handling of the material but is considered an uncommon occurrence (Fletcher 2015, personal communication to AHP, unreferenced).

Caution dictates that non-PA-containing plants with actions similar to boneset be used instead of boneset until appropriate dose-response or benefit-risk assessments have been made, or until PA-free boneset is available.

Lactation

Due to the presence of potentially toxic PAs, boneset should not be used during lactation.

Influence on Driving

Specific data are lacking. Based on a review of the available literature and the experience of modern herbal practitioners, no negative effects are to be expected.

Overdose

No reports of overdose associated with boneset have been identified. High doses (decoction of 5.5–7 g) can elicit emetic and cathartic effects (Felter and Lloyd 1898; Wood and LaWall 1926), uses that, based on the detection of potentially toxic PAs should be strictly avoided.

Treatment of Overdose

Specific data are lacking. Detoxification of PAs occurs via glutathione conjugation. Because of this, the amino acid N-acetyl cysteine may be a potential adjunct to boneset therapy to prevent PA accumulation and toxicity. This has not been investigated.

Classification of the American Herbal Products Association (AHPA)

The third electronic edition of the *Botanical Safety Handbook* proposes boneset as safety class 2b, 2c, 2d "Not to be used during pregnancy, "Not to be used while nursing", "Other restrictions as noted", regarding the content of potentially toxic PAs; interaction class A, "No clinically relevant interactions are expected." Currently AHPA maintains a policy that member companies should not trade in products designed for internal use that contain potentially toxic PAs. This policy is under consideration for revision to make it

consistent with international recommendations regarding acceptable limits of PA exposure.

Conclusion

When used within the recommended dosage range, boneset was historically considered to be a very safe botanical widely used in the clinical practice of Native Americans, early European settlers, American herbalists, and physicians. The recent discovery of the presence of potentially toxic PAs requires for the overall safety of boneset to be reassessed and certain uses, such as high doses as a cathartic and emetic, or long-term use as a bitter, be completely avoided. There may be opportunity where boneset is uniquely effective such as for influenza, but only if an adequate benefit-risk assessment has been made regarding alternative therapies.

INTERNATIONAL STATUS

United States

Dietary Supplement: Up until recently, it had been assumed that boneset-containing preparations could be labeled and marketed as dietary supplement products (USC 1994), requiring FDA notification and substantiation to support permissible structure/function claim statements (FDA 2000). Although there are boneset-containing dietary supplement products listed in the National Institutes of Health (NIH) Dietary Supplement Label Database (DSLD) [NIH, Version 7.0.6 - February 2019 (bac7065)] at the time of this writing (April 2019), the recent publication by Colegate et al. (2018) regarding the detection of potentially toxic pyrrolizidine alkaloids (PAs) in *Eupatorium perfoliatum* and related species calls into question the use of boneset in dietary supplement products. While the US Food and Drug Administration (FDA) has not established general restrictions on the use of PA-containing botanicals (Roeder et al. 2015), the agency did publish a notice in 2001 concerning *Symphytum* spp., advising all dietary supplement manufacturers to remove from the market products that contained comfrey and were intended for internal use (FDA 2001). In the 2014 second edition of its '*Bad Bug Book*', the agency discussed sources of PAs, but without establishing tolerances, in a context of product adulteration and poisoning cases linked to dietary supplements such as, in particular, PA-containing herbal remedies and herbal teas (FDA 2014). From advisories and statements made by the agency, and in the absence of rulemaking, it may be ascertained that dietary supplement products containing boneset may be viewed similarly by the agency as other PA-containing herbs such as comfrey.

Drug: Boneset herb is not classified as a generally recognized as safe and effective (GRASE) active ingredient for use in over-the-counter (OTC) botanical drug products. It is however monographed in the *Homœopathic Pharmacopœia of the United States (HPUS)* and therefore present in OTC homoeopathic drug products at retail. In 2016, based on recommendations of the HPUS Toxicology and Safety Committee, the medication level was revised in monographs of several PA-containing drugs, including *Borago officinalis*, *Eupatorium perfoliatum*, *Heliotropium peruvianum*, *Senecio jacobaea*, *Symphytum officinale*, and *Tussilago farfara*, among others (HPCUS 2017).

Food: Boneset herb is not classified as generally recognized as safe (GRAS) for use in food products.

Australia

Complementary Medicine: *Eupatorium perfoliatum* is scheduled as a 'specified permissible ingredient' that may be used as an 'active ingredient' of complementary medicine products or as an 'ingredient' of homoeopathic preparations (TGA 2018a).

Quality: As the basis of active ingredient quality specifications, the Therapeutic Goods Act recognizes acceptable pharmacopoeias as *British Pharmacopoeia (BP)*, *European Pharmacopoeia (PhEur)*, and *United States Pharmacopeia-National Formulary (USP-NF)*, including general monographs 'Herbal Drugs', 'Herbal Drug Preparations', and 'Extracts'. In the absence of an official monograph, specifications to ensure consistent quality must be developed by the applicant (TGA 2018b). Due to the absence of a boneset monograph in the *BP*, *PhEur* and/or *USP-NF*, this AHP monograph could form the basis of an acceptable specification.

Indications: There are no listed mono-preparations of boneset herb. At the time of this writing (April 2019), there were 10 boneset-containing poly-preparations listed in the Australian Register of Therapeutic Goods (ARTG), some traditional Western herbal medicinal products but most either homoeopathic or anthroposophic medicines (TGA 2019).

Canada

Natural Health Product: *Eupatorium perfoliatum* plant material (fresh or dried) is classified as a medicinal Natural Health Product (NHP) under Schedule 1 of the NHP regulations, requiring pre-marketing authorization and issuance of product license for OTC human use, with the additional requirement that testing must be performed to ensure the absence of PAs (NNHPD 2019).

Quality: If a monograph is published in one of the NNHPD accepted pharmacopoeias (*BP*, *Food Chemicals Codex [FCC]*, *Japanese Pharmacopoeia [JP]*, *PhEur*, *Pharmacopée Française [PhFr]*, *Pharmacopoeia Internationalis [PhI]*, and *USP*), the pharmacopoeial monograph specifications should be considered as minimum specifications used for testing of the medicinal ingredient and finished product (NNHPD 2015). Due to the absence of a boneset monograph in any of the aforementioned NNHPD acceptable pharmacopoeias, the applicant could propose the use of this AHP monograph as the basis for the establishment of an appropriate specification.

Indications: At the time of this writing (April 2019) there were over 90 licensed NHPs containing boneset, almost entirely homoeopathic preparations. Approved indications for a licensed boneset tincture used in traditional Western herbal medicine are for the relief of muscle aches/pains, coughs, upper respiratory tract congestion and catarrh associated with cold and flu (NNHPD 2012).

European Community

Herbal Medicinal Product: Boneset may be regulated as an active ingredient of Traditional Herbal Medicinal Products (THMPs) requiring pre-marketing authorization and product registration (EPCEU 2004).

Quality: For boneset herb to be used as an active ingredient of a registered THMP, conformance with pharmacopoeial quality standards would be required, including control of PA levels in finished products, as well as production according to European Medicines Agency (EMA) good agricultural and collection practice (GACP), and product manufacture under European pharmaceutical good manufacturing practice (GMP). In the absence of an official monograph, appropriate specifications (based on *PhEur* standards) must be proposed by the applicant and approved by the regulatory authority. In January 2019, the Committee on Herbal Medicinal Products (HMPC) of the EMA agreed by consensus to extend the transitional period for THMPs with levels up to 1.0 µg PAs per day for two years (through 2021). Furthermore, in 2017, the European Directorate for Quality of Medicines (EDQM) established a Working Party to develop a general *PhEur* method for testing PAs in herbal drugs. A revision of EMA's 2016 public statement on contamination of herbal medicinal products with PAs was also planned (HMPC 2019).

Indications: Product-specific, depending on the evidence submitted by the applicant for THMP registration. As of 2019, the EMA had not yet prioritized the development of a Community Herbal Monograph for boneset. EMA monographs provide labeling standards for herbal medicinal product labels and patient information leaflets. There are no known boneset mono-preparation THMPs with marketing authorization for sale in the European Union. There is at least one registered THMP poly-preparation containing aqueous liquid extract (1:1) of boneset herb as one of the active ingredients (MHRA 2018).

Note: In Europe, boneset is far more frequently used as an ingredient of licensed 'anthroposophic medicines' and of 'homoeopathic medicines,' especially in France, Germany, the Netherlands and Switzerland, countries where a special regulatory framework exists for anthroposophic medicine. For use in these classes of products, there are European quality standards monographs for boneset (fresh, flowering aerial parts of *Eupatorium perfoliatum* L., harvested at the beginning of the blooming season) available from France (*PhFr*) and Germany [*Homöopathisches Arzneibuch (HAB)*]. In Switzerland, boneset (fresh aerial parts of *Eupatorium perfoliatum* L., collected at start of flowering) is listed in the fourth edition of the *Anthroposophic Pharmaceutical Codex* with quality specified as per *HAB* or *PhFr* monographs (IAAP 2017).

The empirical applications of boneset in Western herbal medicine supports its use as a diaphoretic, emetic, and mild laxative; to relieve the aches and pains of influenza and rheumatoid conditions; and for general debility. Historically, it was considered invaluable in treating influenza even in flu epidemics. The detection of potentially toxic pyrrolizidine alkaloids (PAs) suggests that the historical uses ascribed to boneset against a backdrop of perceived safety requires that these uses be reconsidered. Conversely, attestations of its efficacy in flu epidemics, suggests that boneset cannot be summarily discarded. In the future, appropriate risk-benefits assessments perhaps can determine if it continues to have utility should alternative therapies for influenza fail.

European Use of *Eupatorium* Species

Boneset is native to North America. Because of this, there is no historical use of this specific species in other traditions. European herbals do record the use of other *Eupatorium* species, most notably *Eupatorium cannabinum*, whose medicinal effects are similar to those recorded for North America's boneset and are worthy of consideration.

Chemical investigation of *Eupatorium* species reveal that both *E. cannabinum* and *E. perfoliatum* contain the same sesquiterpene, eupatorin. The overall sesquiterpene and flavonoid profile of the two botanicals is similar. Additionally, Woerdenbag et al. (1992) report that many other species of *Eupatorium*, including those in China, India, Japan, Nepal, Nigeria, Puerto Rico, and Vietnam, have the same or similar medicinal uses as *E. perfoliatum*, suggesting consistency of effects across the species.

Early American Medical Botany

Manasseh Cutler wrote in 1784 of the leaf infusion being used as a powerful emetic (Cutler 1784). According to William Barton, an early authority on medical botany of the United States, recounts the herb's use as a decoction and spirituous infusion in influenza and "lake fever," which was also epidemic. According to other medical records of New York's Alm's-House by a Dr Andrew Anderson, boneset was used extensively in the treatment of intermittent fevers, seemingly more so than cinchona bark (the source of quinine and a primary treatment for malarial fever). Given in either decoction or powder at doses of 1.3–1.9 g every three or four hours, the physicians reported considerable success with boneset (Edwards and Vavasseur 1829).

Physician James Thatcher in 1810 declared boneset a sudorific and emetic and extolled its purgative powers for fevers, taken as a decoction or as powdered leaves, though he believed the flowers were the most active. By 1814, botanist Frederick Pursh described the whole plant as exceedingly bitter but effective in treating influenza and other fevers (Anonymous 1918).

Virtually all early writers of materia medica, including allopathic, homeopathic, Eclectic, Physiomedicalist, and Thomsonian, are consistent in their reporting of the nature and uses of boneset, with little variation. The primary actions attributed to boneset are as a tonic, stimulant, diaphoretic, emetic, cathartic, astringent, and deobstruent. The primary medical uses for boneset are for intermittent fevers such as occur in dengue, malaria, yellow fever, and typhus. Among 19th century physicians, there was almost universal consensus regarding its efficacy for these indications. Other primary indications of boneset historically include dyspepsia, gastrointestinal complaints, and as a tonic, the latter according to specific principles of therapeutics as articulated in the Eclectic literature (see discussion below). Topically, mild astringent and vulnerary properties are attributed to boneset.

According to his own writings and experience, William Barton (1818) considered the tonic and diaphoretic properties of boneset to be unequivocal, powerful, and most worthy of attention. Barton also regarded boneset as somewhat of a stimulant, an action he deemed transient and consistent with the effects of all bitters when used in debility due to disease, or in a state of excitement from fever. Barton also reported boneset as efficacious in remitting biliousness, yellow fever, and especially typhus fever, which at the time was common in the US. Conversely, Barton also felt that practitioners might rely on it too much for affections for which it is not efficacious, admonishing that it be applied according to principles of differential diagnosis. Commenting on the efficacy of the various plant parts, Barton reported there to be no difference in activity between the stems, flowers, and leaves and so used the entire plant, similarly finding infusions and decoctions to be equally efficacious.

Figure 9 Historical illustration of boneset
Source: Beach W. *British and American Reformed Practice of Medicine* (1859)

William Barton relates that a Dr Samuel Hopkins was particularly partial to sweating therapy for typhus, having used it as a successful strategy for several years. Boneset was the primary diaphoretic used for this purpose, prescribing it freely in warm and cold decoction, but preferring it warm. Hopkins did report that boneset often caused emesis and that sometimes he would intentionally induce emesis "to excite free purging," a strategy related by others. Hopkins also reported on the self-use of boneset by farmers for typhus, taking it as a strong decoction for several days and nights consecutively, while wearing warm bed clothing to facilitate sweating, according to Hopkins, "uniformly with benefit." Ironically, Hopkins died of typhus.

The experiences of Hopkins and others led Barton to use boneset himself, after which he considered it an inestimable medicine, preferring the hot infusion of the dry leaves and flowers over cold infusions and also recommending consumption of the plant itself in material form. Barton employed boneset in what he deemed "repeated small purgings," using smaller amounts more frequently than other physicians. This way, he reportedly avoided inducing vomiting. As a diaphoretic and to avoid emesis, Barton administered one to two tablespoons (hot) every half hour, though noted that nausea could ensue. As a tonic, Barton preferred to give the plant in material form at doses of approximately 1.3 g of powdered leaves and flowers three to six times in the course of 24 hours.

Other physicians reportedly depended on the diaphoretic effects of boneset, almost exclusively, for yellow fever, but as an adjunct with sudorifics and laxatives. Despite the glowing reports on the efficacy of boneset for serious fevers, Barton cautions against using it solely, except in mild cases, but rather as an adjunct with other appropriate therapies.

In the treatment of cutaneous conditions, Barton's own experience led him to believe the herb completely ineffective, though other authorities considered it efficacious. For dropsy, a therapeutic claim made by others, Barton equally found boneset to be ineffective, referring to the herb as possessing "inconsiderable diuretic consequences." Others equally shared this opinion, with few authors providing confidence in the herb's claimed diuretic properties. Grieve in her A *Modern Herbal* (1931) suggests any reference of diuretic activity attributed to boneset is a mistaken attribute rightly applied to gravel root (*E. purpureum*), and additionally suggests the use of boneset for tapeworm. William Barton did believe that boneset had benefit in general debility. Based on his own experience and the evidence provided by others, Barton considered boneset to be a valuable tonic bitter "at least equal to the chamomile." His uncle Benjamin Smith Barton had stated in 1804 that it was superior to chamomile flowers (*Matricaria chamomilla*) as a tonic bitter.

William Barton considered it of additional value due to its abundance and easy access by country physicians and by those residing in cities or towns. Barton explains that he feels much of the benefit ascribed to boneset is based on exaggerations, but goes on to report that he uses the herb "frequently and extensively" and considers it a "highly important article" when appropriately applied for the indications for which it is peculiarly suited.

Jacob Bigelow (1787–1879), professor of materia medica and botany (Harvard University), another early authority on American medical botany, repeats all the same indications as those previously given. Bigelow reports on his own use of boneset for alleviating mild fevers through diaphoresis "without materially increasing the heat of the body," and found the cold infusion or decoction to be a tonic for loss of appetite, dyspepsia, and general debility. He similarly reported on its use as a tonic and emetic. Bigelow compares the effects of boneset to those of cinchona, chamomile, and gentian (Bigelow 1817). A Dr John Sappington, himself a purveyor of "anti-fever pills" made of quinine, licorice, myrrh (*Commiphora* spp.), and oil of sassafras (*Sassafras albidum*), in his *The Theory and Treatment of Fevers* (1844), described boneset and culver's root (*Veronicastrum virginicum*) as the best indigenous substitutes for quinine. Sappington was also noted for his opposition to the standard practices of blood-letting and calomel (mercury chloride) emetics prevalent among "regular" (allopathic) physicians of the time.

Dr Frances Porcher in *Resources of the Southern Fields and Forests* (1863), documents the primary use of boneset by Southern troops during the Civil War:

> Thoroughwort or boneset tea used hot, in the cold stages of malarial fever, and cold in the hot stages, is believed by many physicians in South Carolina, who have used it since the beginning of the war, to be the very best of our indigenous antiperiodics as a substitute for quinine… The hot decoction may be given in the hot stages of fevers without exciting the system. Small quantities of the cold infusion, repeatedly given will, it is said, purge, and are prescribed in constipation… From its actions on the capillaries, it has been recommended in chronic cutaneous diseases." It is also written, "The 'Indian doctors' make a pill to act upon the liver, which they call the 'hepatic pill', by boiling thoroughwort leaves until their strength is extracted, then strain the decoction and continue boiling till it becomes thick – an extract in other words. It is made up with starch into pills, and three are given at a dose.

Gunn in his *Gunn's New Family* Physician (1868) recommended a saturated tincture made by bruising the fresh plant and covering with alcohol or whisky, letting it stand a few days, evaporating with low heat, straining, and evaporating again to an extract consistency. Gunn made ague pills using this boneset extract as the base and adding 12 grains (~777 mg) quinine, 6 grains (~388 mg), cayenne, 6 grains ipecac, and 3 grains (~195 mg) pulverized opium to make 18–20 pills giving two to three pills every two hours until all were taken.

Eclectic, Thomsonian, and Allopathic Medical Use of Boneset

Numerous authors reported on the specificity of boneset for intermittent fever in which there was little or no perspira-

tion and severe aching of the bones (e.g. Ellingwood and Lloyd 1903). One of the earlier of the materia medicas of unknown authorship, *The Eclectic and General Dispensatory* (American Physician 1827), though not a formal work of the Eclectics, supports the aforementioned uses of boneset and adds that it is used in all cases where Peruvian bark *(Cinchona)* is proper. The powder in the dose of ~1 g operates as a gentle purgative and diaphoretic and "in convalescence from inflammatory diseases it has been used with great effect."

In the early 1800s, Samuel Thomson (1769–1843) declared this herb to be warming and good for coughs and other lung complaints when used as a common drink. Besides its expectorant activity, he noted it was also a mild emetic, diaphoretic, and tonic (Anonymous 1918). Thomson used boneset for the same indications as other writers and additionally noted that "in order to induce vomiting it must be given in copious draughts. It is good in complaints of the lungs, to be used as a common drink. A decoction of boneset, taken cold in repeated small doses, will operate as a cathartic" (Thomson 1841). In a further articulation of the use of boneset by Thomsonian practitioners, JW Comfort (Comfort 1845) agrees with Bigelow (1817) on the use of a cold infusion as a tonic, useful in dyspepsia and fevers.

The uses of boneset in early American medicine were formally codified in Dr AT Thomson's A *Conspectus of the Pharmacopoeias of the London, Edinburgh and Dublin Colleges of Physicians and of the United States Pharmacopoeia* (Thomson 1849) which cited the following, "Tonic, diaphoretic, emetic, aperient, according to dose. Use. As a diaphoretic in catarrh and rheumatism; in intermittents and remittents, and inflammatory diseases; as a tonic in dyspepsia and general debility; given cold." For inducing diaphoresis, the warm infusion was given every two hours while the patient was covered in bed; as emetic and cathartic, a strong decoction, in doses of 0.5 pint or more was administered.

Another mid-nineteenth century authority on materia medica, representing the "allopathic" (versus botanic) physicians, was George B Wood, a professor of materia medica and chemistry (Philadelphia College of Pharmacy) from 1822–1835. Wood in his *A Treatise on Therapeutics and Pharmacology or Materia Medica* (Wood 1856) recorded that the components responsible for the properties of boneset were soluble in both alcohol and water. At moderate doses, Wood noted that boneset produced an effect like that of simple bitters, but better, especially when taken as a hot infusion, and had a decided diaphoretic action. In large doses, he considered it emetic and laxative.

Later Eclectic writers provide a solid record of the "botanico-medical" use of boneset. Wooster Beach, considered one of the primary founders of the reformed practice of medicine (Eclectics), in his various writings, gives an interesting history of boneset and sets the stage for its appropriate use. In his *The American Practice* (Beach 1851), he specifies the application of boneset in intermittent fever, first recommending *common emetic* (composition unknown) along with capsicum to produce vomiting, giving a little boneset, pennyroyal (*Mentha pulegium*), or chamomile (*Matricaria chamomilla*) to assist evacuation. Thereafter for "stimulating," Beach recommends boneset be given during the cold stage of the fever, then used as a tonic after a cure has been affected to assist in the convalescence period (Beach 1851).

In his *The British and American Reformed Practice of Medicine* (Beach 1859), Beach reports that boneset was "a valuable agent in domestic practice" (folkloric use). Long valued by African Americans in the southern US as a tonic and febrifuge and for treating rheumatism and dropsy, it was "long despised" by physicians. Despite this, Beach reports that Dr Benjamin Rush, the most prestigious representative of allopathic medicine at the time, used boneset for influenza that was prevalent in the northern states (Beach 1859). As described above, boneset seems to have been well represented in the medical literature of allopathic physicians. Beach further describes the use of boneset, "In those anomalous cases of fever attended with dry, purplish, crisped tongue, and poising as it were between active inflammation and congestion, where it is frequently hazardous to give stimulating or drastic evacuants of any kind, this article seems truly invaluable."

Lorenzo Jones and John M Scudder in their seminal Eclectic medical text *The American Eclectic Materia Medica and Therapeutics* (1859) considered boneset a valuable diaphoretic, recommending that the infusion be taken freely while warm for promoting perspiration in colds, coughs, pneumonia, inflammation, and the various forms of fevers, especially in the early stages. These authors recommended pushing the dosage to a degree as to produce nausea and vomiting, though they also considered it useful in smaller doses in the advanced stages of the same diseases, when a sustaining diaphoretic action was desired. Jones and Scudder (1859) are among the first to specify that boneset could be used singularly or in combination with other botanicals, most notably with chamomile (*Matricaria chamomilla*), blood root (*Sanguinaria canadensis*), pleurisy root (*Asclepias tuberosa*), and Virginia snakeroot (*Aristolochia serpentaria*). Boneset was also macerated in brandy when a powerful stimulant, combined with a sudorific, is desired, which these authors considered often to be the case in chronic febrile diseases.

Kost (1858) in his *The Elements of Materia Medica and Therapeutics Adapted to the American Reformed and Eclectic Practice*, classifies boneset as an emetic and diaphoretic, previously classifying it as a "topical emetic." As explained by Beach in 1852, a "topical emetic" is an agent that induces vomiting via ingestion, while a "specific emetic" produces its effects via injection. Kost further describes the physiological effects of boneset as at first exciting the pulse followed by a softening and slowing of the pulse within 15–30 minutes after administration of ~1–2 g. If the dose is repeated, it causes nausea and diaphoresis; if continued further it can produce emesis. Kost further states, "no permanently unpleasant effects have yet been observed from its administration." As an emetic, Kost considered it to be persistent and certain in its effects, giving the extract or decoction for autumnal fevers and bilious diseases at doses of ~320–640

mg for the solid extract, given in emulsion, or two to three fluid ounces of the decoction, combining the decoction with ~320 mg of powdered lobelia (*Lobelia inflata*) for greater effect. As a tonic, Kost described boneset as a "very certain and permanent diaphoretic," as well as an aperient. As a diaphoretic, Kost contends that its effects can last for several days. Like other writers, Kost states that clearing of the stomach and bowels followed by freely drinking the infusion will increase the efficacy of the herb in autumnal fevers and "generally complete the cure." Kost goes on to record his own success in treating yellow and typhus fever with boneset. As an infusion, Kost recommends that one ounce of herb be macerated in one pint of boiled water for one hour, taking a wineglassful every half hour, or as needed.

One formula used in the purported successful treatment of the flu epidemic of 1891 by a Dr Hoener, contained 1.5 ounces each of elixirs of boneset and *E. alternifolium* (false boneset), along with 1.0 ounce each of *Verbena hastata*, *Leptandra virginica*, and *Agrimonia eupatoria*. Used alternatively as a decoction, these quantities of dried herbs were extracted with six pints of boiling water and given as two to four tablespoon doses every two to three hours (Nowell 1926).

The eclectic preparation Specific *Eupatorium*, became a routine treatment of influenza, taking its place alongside vaccines and serums (Powers 1928). In the aged and debilitated Specific *Eupatorium* helped bring relief to coughs with abundant secretions that could not be expelled. It was also used for the cough of measles (Bloyer 1901; Felter 1924). Specific *Eupatorium* was considered admirable in breaking up the common cold, but in children needed to be administered in an aromatic syrup. It relieved pleuritic pains and pains associated with the cough of broncho-pneumonia (Felter 1924). In these types of cases it acts both as a diaphoretic and expectorant (Best 1928).

Felter and Lloyd provide an extensive review of boneset in *King's American Dispensatory* (1898):

> Action, Medical Uses, and Dosage - This is a very valuable medicinal agent. The cold infusion, or extract is tonic and aperient; the warm infusion diaphoretic and emetic. As a tonic, it is useful in remittent, intermittent, and typhoid fevers, dyspepsia, and general debility, and combined with bitartrate of potassium and camphor, the powdered leaves have been serviceable in some forms of cutaneous disease. In intermittent fever, a strong infusion, as hot as can be comfortably swallowed, is administered for the purpose of vomiting freely. This is also attended with profuse diaphoresis, and sooner or later by an evacuation of the bowels. During the intermission, the cold infusion or extract is given every hour as a tonic and antiperiodic. It is not well adapted to ordinary cases of ague that may be cured with quinine, but is more particularly useful in the irregular cases which that drug does not seem to reach. The chill and succeeding fever is slight, the skin dry, and not, as a rule, followed by perspiration; there are 'pains in the bones, praecordial oppression, and great thirst. If, however, the case is one in which the fever lasts all day, a slight sweating may follow at night. Another indication in ague is vomiting, especially of much bile'. *Eupatorium* given as above, or sometimes in small doses, may relieve headache of intermittent character when the intermissions are irregular. In epidemic influenza the warm infusion is valuable as an emetic and diaphoretic, likewise in febrile diseases, catarrh, colds, with hoarseness and pleuritic pains, and wherever such effects are indicated. In influenza it relieves the pain in the limbs and back. Its popular name, 'boneset,' is derived from its well-known property of relieving the deep-seated pains in the limbs which accompany this disorder, and colds and rheumatism. Often this pain is periosteal, and if neuralgic in character, or due to a febrile condition, *Eupatorium* will relieve it. But it is not a remedy for periosteal pain due to inflammation or to organic changes in the periosteum. On the other hand, when given until the patient sweats, and then continued in 5-drop doses of specific *Eupatorium*, it has relieved the severe nocturnal muscular and 'bone pains' of syphilis. In pneumonia, if an emetic is indicated in the early stage, this agent is as efficient as any that may be used; but it is of greater value in the latter stage when given as syrup. This is kindly received by the stomach, improves digestion, and allays the irritable cough. It is a remedy for the cough of the aged, that cough in which there is an abundance of secretion, but lack of power to expectorate. The cough of measles, common colds, of asthma, and hoarseness are also relieved by it. Unless given in excess it acts as a good tonic to the gastric functions, increasing the appetite and power of digestion. The stomach disorders of the inebriate are, in a measure corrected by the use of small, tonic doses of *Eupatorium*. Although slightly stimulant, it is of service in most inflammatory states, administered according to the indications given below. The warm infusion may be administered to promote the operation of other emetics. Externally, used alone or in combination with hops or tansy, etc., a fomentation of the leaves applied to the bowels has, been useful in inflammation, spasms, and painful affections. Dose of the powder, from 10–20 grains [~648 mg to 1.3 g]; of the extract, from 2–4 grains [130–260 mg]; of the infusion, from 2–4 fluid ounces; of the syrup (1 pint of the decoction of 1 ounce of the herb sweetened with 2 pounds of white sugar), 1–4 drachms [~3.5–14.5 mL]; specific *Eupatorium*, 1–60 drops. As an emetic administer the warm infusion freely.
>
> Specific Indications and Uses - Pulse full and large, the current exhibiting little waves; skin full and hot with a tendency to become moist, even during the progress of fever, cough, embarrassed breathing, and pain in the chest; urine turbid and urination frequent; deep-seated aching pains in muscles and periosteum. For acute aching with chilliness, depression and sub-

normal vitality that characterized the first stages of influenza, boneset was considered one of the most effective remedies (Best 1928).

As noted previously, Eclectic physicians were largely unanimous in their opinion that boneset was one of the safest and most successful remedies employed during flu epidemics. Both the infusion and Lloyd's Specific *Eupatorium* were effective. Eventually, boneset began to be used as a prophylactic. Cases were reported as milder, the severe pain in the back and limbs was quickly relieved, cough and irritation were reduced, and recovery was hastened with its liberal use (Best 1928; Felter 1924; Powers 1928). The simple infusion of the leaves and flowers was found to be safer and of greater advantage than the bacterins, coal-tar compounds, quinine sulphate, and opiates that were typically prescribed (Best 1928; Powers 1928).

Specific *Eupatorium* became a routine treatment of influenza, taking its place alongside vaccines and serums (Powers 1928). In the aged and debilitated Specific *Eupatorium* helped bring relief to coughs with abundant secretions that could not be expelled. It was also used for the cough of measles (Bloyer 1901; Felter 1924). It was considered admirable in breaking up the common cold, but in children needed to be administered in an aromatic syrup. It relieved the pleuritic pains and those associated with the cough of broncho-pneumonia (Felter 1924). In these types of cases it acts both as a diaphoretic and expectorant (Best 1928).

Eclectic physicians considered boneset among the most important medicines for influenza, with bone ache being the seminal differentiating symptom. The original collection of data from the 237 physicians who answered the survey sent to doctors by the Lloyd Brothers reflects that many of the physicians treated hundreds of cases of influenza; many considered boneset to be their most important influenza remedy. A later tally of 1000 physician responses showed boneset was one of the favorite overall remedies in America for the ongoing influenza pandemic. Most physicians reported their application of it based on principles of specific diagnosis and specific medications (Ellingwood 1919b), many of which have been described above.

In this regard, Harvey Wickes Felter (Felter and Lloyd 1922) further reported specific indications of boneset as, "Large full pulse, the current showing little waves; skin hot and full, with a tendency to become moist, even during the progress of fever; deep seated aching pain (so-called 'bone pains') in muscles and periosteum; cough, embarrassed breathing, and pain in the chest; urine turbid and urination frequent; influenzal cough and aching pain." Felter (Felter and Lloyd 1922) further noted that during the flu epidemic of 1918–1919, "it was one of the safest and most successful remedies employed and contributed much to the successful management of the disease under Eclectic treatment." He also reported its prophylactic use by those wishing to prevent the disease, though he stated its prophylactic power "should not be seriously relied upon." He notes boneset relieves hoarseness and can benefit "humid asthma," an indication reported by Cook (1869). For children, Felter (Felter and Lloyd 1922) recommended boneset to be given in an "aromatized syrup" and in the elderly, considered boneset as 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."

A Dr Peebles (1844) reported on his own successful use of boneset in influenza stating:

> The herb, it is known, derived its domestic name of Boneset from its prompt manner of relieving pains in the limbs and general muscular system which attended a peculiar form of febrile disease which prevailed many years ago in the northern parts of this country. It was this fact, together with the knowledge of the remarkable combination of properties possessed by it, which led to the suggestion of its employment in epidemic influenza; and nothing could be more marked and satisfactory than the prompt manner in which it answered the expectations which had been formed in this respect. The pain in the back and limbs, and the lassitude of the general muscular system, subsided so soon as the system was placed under its influence; its immediate and salutary operation in this way, at once prominently exhibiting its great value in the treatment of the disease. But its curative agency was not confined to this effect alone, for blended with this prompt action on the nervous system—we can in no other way account for its speedy removal of the pains and the general muscular prostration except by referring its operation to the nervous system—the *Eupatorium perfoliatum* united in its operation, other qualities, each one eminently adapted to fulfill some important indication in the treatment of the disease in question. Among the first of these, we shall name its diaphoretic powers. The sudorific influence of this herb is of that peculiar character which eminently fitted it for employment under the circumstances. For, in this disease, the skin was not unfrequently imbued with perspiration. But, probably, from a peculiar condition of the cutaneous surface, the sweating was of a morbid character—a sort of passive excretion, resulting apparently from a lax condition of the skin, which was always under such circumstances pale, and morbidly sensitive. *Eupatorium perfoliatum* not only induced a healthy and free perspiratory discharge, but promptly altered the condition of the skin, restoring its natural of chilliness with flushes of heat were replaced by an agreeable glow of the general surface. So soon as this healthy diaphoresis was induced, together with the relief already mentioned as occurring, the disposition to cough subsided, and there was an immediate amelioration of all the pulmonary symptoms. The subsidence of the cough, the removal of the dypsnoea, and that painful irritation of the pulmonary organs, which in many cases scented to have extended to the remotest air vesicles of the lungs, were more directly due to the medicine, administered after the method adopted by us, becoming a prompt and efficacious expectorant.

> Indeed, we know of no article or combination to be preferred to it, as an expectorant in the disease under consideration. Together with the properties already mentioned, this medicine has further proved itself sufficiently aperient for the treatment of most cases of epidemic influenza. After the commencement of the treatment, it was rarely found necessary to use any other cathartic, and not then, except in those cases in which the constipation of the bowels had been persistent, or where the head was unusually affected.

Eclectic Use of Boneset as a Tonic

Jones and Scudder (1859), under their heading of tonics, gives an extensive accounting of the use of boneset that is perhaps more complete than all other records. Therein, boneset is described as tonic, diaphoretic, emetic, aperient, and expectorant and noted that it is difficult to classify boneset due to its possessing numerous indications depending on mode of administration and dose. However, they appear to most highly regard boneset for its tonic properties, considering it as a mild, simple, valuable bitter employed in all cases where the simple tonics are indicated. Jones and Scudder (1859) go on to give a full account of their understanding of tonics as follows:

> Medicines that produce a permanent exaltation of the energies of the general system, without materially increasing the vital manifestations in any particular organ. They tone the muscular system without increasing the temperature of the body or rapidity of circulation, producing no marked stimulant effect; their action is slow and permanent exaltation of organic action, evinced by an increased force of the circulation, and increased muscular power; the heart contracts with more force but does not increase in frequency; the pulse acquires fullness and firmness, and loses the soft, flaccid, and atonic character which is a manifestation of debility. Protracted use of tonics may produce an increased temperature of the body and acceleration of the pulse that are secondary effects arising from increased nutrition and are particularly adapted to atonic states of the system. The primary actions of boneset these writers consider to be on the nervous system, muscular system, and in improving the state of secretions, augmenting the force and fullness of the pulse, and in the increased rapidity and perfection of digestion. The increased energy which they impart to the nervous system, the impetus which they give to the circulation, and the improvement in the digestive functions, together with the increased secretion and absorption which they effect, are among the many evidences of their sanative powers" [conducive to health or healing].

Tonics are described as acting in two ways to produce their restorative effects. They not only produce specific impressions when taken internally but also when applied to the surface of the body, from which they may be absorbed. First, their topical influence gives increased nervous and muscular energy to the stomach and bowels, and stimulates the mucous membrane to normal action, thus improving digestion, increasing the appetite, and improving the quantity and quality of chyle. Secondly, this class of agents is readily soluble in the fluids of the body; hence, they are absorbed into the circulation and act from it upon every part of the system. Jones and Scudder (1859) reason that if tonics exert a toning and strengthening effect when applied topically, then they likely will have a similar action internally after absorption. Specifically regarding boneset, a strong decoction is recommended to be used as a wash frequently for indolent ulcers and gangrenous tissues and also applied as a poultice mixed with slippery elm. Of boneset, Jones and Scudder (1859) write:

> Administered alone, or associated with other tonics, aromatics, or stimulants, it answers a valuable purpose in the convalescent forms of acute diseases. The same may be said of it in dyspepsia, and almost all chronic diseases, as a general tonic, exhibited in the form of powder or small doses of a cold infusion, it answers an admirable purpose.

Jones and Scudder (1859) further articulate the energetic nature of boneset and its actions, stating that the warm infusion is diaphoretic but devoid or nearly devoid of stimulant activity, thus considering it well adapted to treating a multitude of acute diseases. They considered few other herbs to be superior to boneset in the treatment of early stage febrile and inflammatory attacks, again recommending the frequent administration of a warm infusion to the point of producing diaphoresis, nausea, and vomiting, and in advanced stages of febrile diseases, "even after the vital energies have become very much impaired—to the extent of maintaining gentle diaphoresis… In advanced and sinking stages of all fevers, it is peculiarly valuable due to its combined tonic and diaphoretic properties; during convalescence, few tonics will answer a better purpose. In intermittents, remittents, continued fevers, typhus fever, yellow fever, and in the synochal grades of fever, if used as suggested, boneset will not fail. If a strong decoction be taken warm in doses of half-pint or more, every 10 or 15 minutes, it will promote emesis, cleanse the stomach, excite all secretions, and remove congestions. It is frequently prescribed with great advantage in the early stages of intermittents and remittents as an emetic. It acts mildly and yet efficiently. Arrests paroxysms of intermittents, breaks up remittents in their incipient stages, if properly exhibited. For this purpose, the patient should commence the use of the warm infusion or decoction 1 or 2 hours before the expected paroxysm, and continue it so as to excite frequent vomiting and excite perspiration,—the patient being closely confined in bed until after the hour for the paroxysm shall have passed. He may follow up with the extract or a cold decoction, at remote intervals, so as to induce purging; subsequently the powder or cold infusion may be taken in small doses as a tonic. No

article with which we are acquainted is capable of fulfilling so many important indications as boneset. Its importance in the early stages of intermittents and remittents is attributable to its emetic and diaphoretic action in the first instance, and to the simple tonic and aperient effects in the second, and not to any antiperiodic or febrifuge powers. As a general rule it is employed in those diseases as an auxiliary to more efficient means, and not as a primary agent. In colds, catarrhal fevers, in acute rheumatism, scarlatina, measles, variola, etc. it is highly useful…"

The various stages of intermittent fevers and how each stage was managed, including using adjunctive therapies such as emetics, the importance of appropriate treatment in the early stage, and botanicals, are fully articulated in Hollister Potter's *Notes of Lectures on the American Practice of Medicine* (Potter 1855).

In Jones and Scudder's text (1859), we learn that some considered no other tonic was possessed of "equal activity," noting that boneset can be used freely in fever "with less danger of increasing or producing congestion." In pneumonia, in all its forms, it was considered a valuable auxiliary, and even curative agent. In those cases, it was used as an expectorant as well as diaphoretic, and was considered especially beneficial in typhoid fever, often being combined with the more energetic expectorants such as racemed milkwort (*Polygala polygama*), Seneca snakeroot (*Polygala senega*), squill (*Urginea scilla*), or bloodroot (*Sanguinaria canadensis*), when indicated, or with more mild expectorants when demulcents and tonics are required, such as with licorice root (*Glycyrrhiza glabra*), pleurisy root, bethroot (*Trillium erectum*), or Iceland moss (*Lichen islandicus*), sometimes employing these as syrups for pulmonary infections.

Jones and Scudder (1859) additionally classify boneset as an expectorant, recommending its use in coughs, colds, and pectoral affections, especially valuable in chronic pulmonary conditions accompanied with debility. For use as an expectorant in acute pneumonia, Jones and Scudder (1859) recommend a combination of boneset, pleurisy root, and bloodroot.

In later writings of George B Wood (1860), moderate doses of boneset were reported to produce an effect similar to those of simple bitters and to act as a diaphoretic when taken as a warm infusion, "Used in 'pure dyspepsia' or general debility but liable to irritate the stomach." A Dr Burgon (Pennsylvania) is reputed to have preferred boneset to all other tonics for loss of appetite due to excessive alcohol intake. Wood reports on a Dr Eberle's use in indigestion in the elderly, "in whom it restored tone in the stomach." Acknowledging the previous reported success of boneset in New York hospitals, Wood reported that continued experimentation proved to be less favorable. He considered boneset unreliable in its effects, seemingly relative to the use of sulphate of quinine in efficacy, but more agreeable than quinine in terms of adverse effects and as an alternative to quinine. In the time Wood was practicing, he reports that boneset was seldom used for intermittent fevers, having been overtaken by quinine compounds.

Wood (1860) considered boneset's primary indication to be for influenza. For this purpose, he recommended the rapid use of the hot infusion as soon after the attack as possible, giving it freely before bed, the patient well covered to provoke perspiration; if emesis was to occur, the benefits would be more certain. Wood often observed that the condition would be completely abated or "very much moderated" the morning after. Thereafter, small repeated doses "so as not to nauseate" were to be given. Like Barton, Wood (possibly deferring to Barton) considered boneset to be ineffective in cutaneous conditions and dropsy, acknowledging its use in rheumatic pain and as a tonic but offering no personal experience to these uses. The infusion was considered a formal drug and was prepared one ounce of herb to one pint of water. Dose one to two fluid ounces repeated more or less frequently depending on need; three to four times daily as a tonic for chronic debility; and repeating the advice of Lewis (1791), every one, two, or three hours as an antiperiodic or "joint tonic" and diaphoretic in more acute cases. As an emetic, six to eight ounces of the hot infusion was given.

A detailed accounting of the effects and actions of boneset in treating gastrointestinal disease is given in an 1874 article by Joseph Adolphus published in the *Eclectic Medical Journal* (Adolphus 1874), including a case history of a physician colleague and the herb's use topically and as a glycerin macerate. In describing the treatment, Adolphus wrote that boneset is a prime remedy for gastrointestinal diseases, noting that when the cold infusion is given in small doses, it gives tone to the gastric glands, modifies their secretion by controlling the capillary circulation in and around them. He reports that *Eupatorium* is indicated in gastro-intestinal diseases attended by excessive action of the gastrointestinal glands, which the following case illustrates:

> A medical friend who had been a dyspeptic for many years had become broken down, as he called it, from excessive study and professional labor. His food would very rapidly after being swallowed, become acid, intensely so, and accompanying this would be foul eructations of gas, intense nervous suffering, his heart would beat as rapidly as 160 per minute, and a horridly harassing sense of constriction would be felt across the precordia, as a sense of approaching dissolution. This would pass off in an hour or two and would be followed by vomiting of an offensive mess-food and mucus in a state of partial decomposition. He was reduced to a skeleton, as a matter of course, and his nervous system so shattered that he was fast becoming an imbecile I put him on a cold infusion of the green leaves of *Eupatorium perfoliatum*, one ounce to a quart of water at eighty degrees, and two ounces of glycerine added. As nourishment he had Graham mush and milk, and a bolus of raw minced meat, the size of a hickory nut in the shuck, twice a day. The curative effect of the medicine, of which he took four ounces every four hours, was marvelous from the very onset; and after one week his physical and mental condition had remarkably improved, and after six weeks the unfavorable symptoms had disappeared. The difficulty

in this case was due to an engorgement of the capillary system that supplied the gastric glands, whose function had thereby become absolutely perverted, and *Eupatorium* removed it. In like manner it is curative of constipation, diarrhea of children, mucous diseases of the alimentary canal. In the mucous diarrhea of children and in the early stages of cholera infantum it is as reliable a remedy as we have. As an external application it is equally valuable, and here, too, it seems to act on the capillary circulation and cutaneous tissues in the same way it does on the mucous ones. A strong, watery infusion of the leaves applied to angry looking sores and inflamed parts affords relief. The green leaves applied to forming boils, swellings and other local painful parts will give rapid relief. It is also valuable in dropsy, scrofula, and disordered states of the liver and other glands, by controlling and modifying the circulation in the stroma of tissues and secreting glands. A permanent preparation may be made by covering the bruised green leaves, in the proportion of eight ounces to the pint, in one part of glycerine and three parts of soft water; digest for two weeks, strain and press. This may be employed both for internal and external use."

John M Scudder, in his *Specific Medication and Specific Medicines* (1884), advises to prepare a tincture from the recently dried herb in the proportion of eight ounces to one pint of proof spirit given at a dose of a fraction of a drop to 10 drops. Scudder (1870) notes that boneset increases the functional activity of the skin and to a lesser extent, secretion from the kidneys. It also influences the circulation, to a slight extent, and does well combined with the sedatives.

In quite small doses, it stimulates the sympathetic nervous system and improves all the vegetative functions. It is not an active remedy, and too much must not be expected of it; yet in many cases, it may well supplant costly foreign drugs. According to Scudder (1884), the best indication for boneset is a frequent, full pulse, and flushed skin inclined to be moist. Throbbing pain is the local indication.

Culbreth in his *A Manual of Materia Medica and Pharmacology* (1927) gives clear dosing guidelines, recommending two to four grams dry powdered leaves and flowering tops; fluidextract one to four mL; or infusion 30–60 mL. When used cold it is tonic, when taken warm it is emetic and diaphoretic. Classified as stimulant, tonic and diaphoretic, and diuretic (as previously noted, putative diuretic effects may have been associated with the use of gravel root). Large doses are emetic, aperient, antiperiodic; it is similar to chamomile as a bitter tonic. Boneset is also used for intermittent fever, rheumatism, influenza, and bronchitis.

Ellingwood (1919a) provides a few brief case histories that illustrate the broader use of boneset by Eclectics of the time:

> It is valuable in catarrhal disorders of whatever nature, whether gastric, intestinal, post-nasal, bronchial or vesical. It has an undoubted soothing influence on the nervous system, and is of much value in stomach disorders of nervous origin. In a case of neurasthenia of long standing, complicated with emphysema, the patient, an extremely nervous woman, persistently regurgitated all the food she took. There was no nausea, no vomiting; the food simply came back after it was swallowed. Fifteen drops of the fluidextract of boneset every two hours was given. The second day the patient was relieved, and there was no return of the disorder after the fifth day, for several months, when it recurred for a short time, but was promptly relieved by the same medicine. In a case of intractable hiccough in an old man, when every possible remedy had failed and death seemed inevitable, boneset, fifteen drops in an infusion of capsicum, every hour, produced a permanent cure.

Regarding its tonic activity, the aforementioned Dr Peebles (1844) stated:

> Its tonic property is the remaining one which we shall point out, as particularly adapting this medicine to the treatment of certain cases of epidemic influenza. It certainly is a great desideratum in the management of this disease in aged subjects, where there is such a tendency to prostration long before any impression is made on the violence of the attack, to have a remedy which, with due evacuant powers adequate to the removal of all the symptoms, unites a tonic influence sufficient to support the general strength, and to maintain at the same time the integrity of the circulatory functions. The admirable association of its tonic with its other properties, creates in the *Eupatorium perfoliatum* such an agent, and endows it with an advantage over all articles or combinations, in the management of the disease under these circumstances. Indeed, where the disease was treated from the first with this medicine,—the cold infusion alternated with the warm according to the circumstances of the case, and the amount of prostration present,-—no case occurred where more decided stimulants or tonics were required, and we are convinced that the former preparation of this herb is the very best article of this class not only to prevent, but to overcome when existing, the prostration so frequently supervening upon this disease in old persons. Nor were its salutary powers in this way confined alone to the aged. There is yet another class of cases, which this property of the herb, from its peculiar association, renders it particularly applicable. The disease occurring in the habitually inebriate, induces a train of morbid effects in the highest degree embarrassing, and for the treatment of which we found nothing so salutary as its cold infusion, combined with the tincture or infusion of hops, according as the nature of the case required sedation.
>
> Manner of administration.—In the severest cases, where it was determined to treat the disease with the

herb alone, the patient after being covered in bed, was induced to swallow a wine-glass full of the infusion, prepared by infusing an ounce of the dried leaves in a pint of boiling water, warm every half hour. After the fourth or fifth dose, considerable nausea, sometimes vomiting, with free diaphoresis ensued, and there was an immediate amelioration of all the symptoms. Along with the nausea, free expectoration commenced, and after the former symptom had subsided, the patient was freed from every annoyance, and remained in every respect comfortable. Sufficient to keep up the impression on the system, the infusion was now given only every third or fourth hour in the same dose. The bowels were generally opened in about six hours after the commencement of the treatment, and afterwards continued in a lax condition. Towards the evening of the second day, and particularly if the patient had been guilty of imprudent exposure, the symptoms frequently returned, and it was necessary to repeat the course adopted at first. But generally, the medicine, continued as directed, kept the symptoms completely in check, and the patient was out on the fourth day. In cases where the treatment was commenced with calomel, etc. the infusion, to secure its diaphoretic and expectorant effects, was introduced on the second day in wine-glassful doses every second hour. To correct the debilitating effects of the disease, frequently remaining after all its acute and more violent symptoms had subsided, a wine-glass full of the cold infusion was directed three times a day. The treatment of the disease in old persons, or in other cases where there was a marked tendency to prostration, was commenced in the same manner. As soon as the effects already mentioned as occurring were induced, the cold substituted for the warm infusion was directed in the same dose every second hour, to be continued, gradually lessening the period throughout the disease, unless the violent symptoms returned, when it was to be discontinued until the same course was repeated with the warm infusion, and then resumed. From the foregoing exposition of the properties and mode of action of the *Eupatorium perfoliatum*, we feel convinced that it will be awarded, that its introduction is an acquisition of some value to the therapeutics means of managing the curious disease under consideration. Not the least of our reasons for believing so, is, that whilst it allows the patient treated by it, to pass out of the disease as speedily and as perfectly as any other remedy or course of treatment, it leaves him with less impairment of his general health, and causes fewer interruptions to the natural healthy functions of the body. In short, the universality of the disease when it prevails, finds an exact counterpart in the cheapness, as well as the simplicity of the remedy.

Physiomedical Use

The Physiomedicalist William Cook (1869) considered boneset to be underutilized by the profession and an invaluable home remedy, reporting that the herb's intense bitterness was the reason for it falling out of use. In describing boneset's function in Physiomedical terms, Cook considered it as purely relaxant, acting slowly and persistently, an action contrary to the "scarcely noticeable stimulant" effects reported by earlier authors. He believed boneset primarily affected the stomach, gall-ducts, bowels, and uterus, referring to actions not recorded by others. He further described its exerting effects on the nervous peripheries and a decided action on the skin. As a cold infusion, Cook considered boneset to be a soothing and relaxing tonic suitable to irritable forms of dyspepsia. He deemed it "gently relaxant to the hepatic apparatus, promoting both the secretion of bile and its injection from the gall-ducts; and finally securing a mild laxative action on the bowels." Indications for the use of this preparation included: biliousness difficulties due to tension of the tissues, chronic constipation with thirst and dry feces, skin conditions of hepatic origin, and for recovery from febrile conditions such as intermittent fevers and biliousness. In contrast, Cook notes that it is not to be used for "cold and sluggish states of the stomach, to torpor of the liver and bowels when accompanied by flaccidity of the tissues, to low intermittents, nor as a tonic when the bowels are inclined to free action." As a tonic, Cook recommended boneset to be combined with more stimulant tonics such as gentian (*Gentiana* spp.), American century (*Sabatia* spp.), goldenseal (*Hydrastis canadensis*), wormwood (*Artemisia* spp.), and a small portion of cayenne (*Capsicum* spp.), writing that it proves useful to help maintain a steady laxative effect for the treatment of biliousness. In addition to its digestive tonic effects, Cook recommended boneset for "weakness of the chest, dull aching through the lungs, and chronic coughs, especially in slightly irritable conditions." He considered this soothing and tonic effect on the respiration system to be too often overlooked, recommending its combination with coltsfoot (*Tussilago farfara*).

As a diaphoretic, Cook recommended the warm infusion, repeating the same recommendations as earlier writers and practitioners, though casting doubt on the herb's effects for treating ague. Combined with prickly ash bark (*Zanthoxylum americanum*) Cook considered boneset to be an effective antispasmodic. As a rectal injection to relax the bowels and bring blood to the surface, it was combined with ginger and demulcents. In making a strong infusion, Cook recommends one ounce of herb to one quart of water, in contrast to the one ounce to one pint recommended by others, giving one to three ounces per dose as needed.

Prepared as a base for pills when other tonics or relaxants are to be used, evidently the diffusive properties of boneset help to distribute the effects of the other botanicals. For a variety of uses, Cook combined the boneset pill base with Lady's slipper (*Cypripedium* spp.), quinine, cayenne, lobelia, skullcap (*Scutellaria lateriflora*), etc. For preparing a fluidextract, one pound of herb was macerated in one quart of 50% alcohol then percolated until a half pint passed this was set aside and warm water added to the percolator until the herb was fully extracted. This water portion was evaporated to eight ounces and then combined with the

eight ounces of alcoholic extract and filtered, dissolving any residue with added alcohol. This was used as an ingredient in other preparations, such as in syrups as a tonic for chronic coughs and sluggish liver, and in alterative preparations for skin diseases. Syrups were given at doses of 20 drops to half a fluid drachm (2 mL) three or more times daily as indicated. The Physiomedicalist and Rosicrucian grandmaster Reuben Swinburne Clymer (1878–1966) recommended for boneset to be combined with elder and willow (Salix spp.) for protracted fevers and aching bones and combined with skullcap and butterfly weed (likely *Asclepias tuberosa*) for influenza (Clymer 1905).

Modern Use of Boneset

Throughout the twentieth century amongst herbalists, boneset was recognized and used both alone and in combination with other herbs. German naturopathic physician Otto Mausert in his *Herbs for Health* (1932) classified boneset as a diaphoretic, febrifuge, and tonic, providing the following:

Formula #58: Diaphoretic or *Sweat Producing Tea*—Mild

Thoroughwort herb (*Eupatorium perfoliatum*)	3.4 g
Elder [sam] flowers (*Sambucus nigra*)	6.8 g
Black birch leaves (*Betula lenta*)	3.4 g
Watermint leaf (*Mentha aquatica*)	3.4 g

The description of the formula is given as follows: Boneset is a reliable diaphoretic, elder flowers promotes perspiration, black birch works on the kidneys and opens the pores, watermint is an aromatic stimulant. Mix well and divide into 10 equal doses. Add a single dose to two cups boiling water, let stand for three to five minutes, strain, drink hot before going to bed. For children, decrease the amount of water and sweeten if needed. Dose 30–60 grains.

The Master Herbology Course of Dominion Herbal College included boneset in its materia medica, citing the primary actions and indications given in earlier materia medicas (diaphoretic, laxative, febrifuge, and expectorant used in fevers and catarrhal deafness) (Dominion 1926). In another herbal medicine course by Deschauer (1940), the following formula is given for the treatment of fever: boneset two ounces, blue vervain two ounces, skullcap one ounce, Virginia snakeroot one ounce; drunk as a tea, warm and freely, but not to produce vomiting. The German physician Rudolf Fritz Weiss (1961) reported on the use of the European *E. cannabinum* in combination or instead of echinacea for enhancing non-specific immune resistance. Weiss' *Herbal Medicine* does not reflect any personal experience with boneset but reflects his feeling that evidence for immune resistance, while at the time lacking, was supported by practical experience. Interestingly, Maas et al. (2011b) and Wagner et al. (1985) provide some evidence for an immunomodulating and anti-inflammatory effect (see Therapeutics). British herbalists particularly emphasized the use of boneset for influenza epidemics, respiratory infections, and febrile conditions, and recognized its action to enhance stomach and liver secretions. In the 1980s, modern herbalists and naturopaths were still using boneset for acute fevers and for flu with night sweats and aching bones (Priest and Priest 1982). Herbalist David Hoffmann confirms that boneset provides quick relief from the associated aches and pains of flu, along with clearing of respiratory mucosal congestion. In addition, he notes that the cleansing laxative action and symptomatic relief of rheumatism make it a good general agent outside of acute febrile conditions (Hoffmann 1996). In addition to actions previously attributed to boneset by others, Hoffmann in his *Medical Herbalism* (2003) includes carminative and antispasmodic actions for boneset. Mills and Bone (2000), reemphasize the importance of boneset in managing fevers due to diaphoresis.

The American naturopathic profession adopted the traditional indications for boneset, using it as a diaphoretic and mild laxative during the onset of colds and employing its sedative effect for the aching tendencies of influenza and rheumatoid conditions. It is also used as an aid in bringing out the rash and controlling the cough of measles, as well as a bitter stomachic tonic to improve appetite and digestion. Since hot infusions may be nauseating and emetic if too strong, cold infusions or alcoholic extracts are preferable when diaphoretic effects are not desired (Kuts-Cheraux 1953; Lust 1974). Naturopathic physician Bill Mitchell (2003) noted that modern naturopath John Bastyr used a boneset tea in those with food regurgitation and otherwise cited Eclectic uses, valuing it as an "excellent diaphoretic" when one-quarter cup is drunk every 30 minutes, or sipped until the fever reduces. Boneset was one of Bastyr's favorite flu remedies. Mitchell similarly records his own use of the herb for flu, using "30 drops" (preparation not disclosed but likely a tincture) four times daily in hot water, often combining it with the flowers and fruits of elder for flu with muscular aches. As an emetic, Mitchell states that at least 150 drops (approximately 4.2 mL) are needed to induce emesis. As a stomachic, Mitchell recommends 5–60 drops of the tincture.

Conclusion

It is clear from the experience of all sects of medical practitioners of the middle to late nineteenth century that boneset was regarded as highly effective against influenza. Its reported high level of efficacy is relatively unique in the level of confidence physicians of the era had in its power to both prevent and treat influenza. Modern medical herbalists similarly support its use for flu suggesting that this is not a remedy that should be immediately discarded due to the more recent findings of DHPAs. Rather, risks versus benefits regarding its own use and use relative to the risk and benefit of other medications, botanical or conventional, must be weighed regarding its future use.

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Ode to boneset

Eupator is its Latin from Mithridates fame, and for break bone fever we derive its vulgar name.
Regulars and eclectics considered it best, for chills and fevers to diphoress.
In such cases, physicians proclaimed, hundreds were saved in epidemics when others were slain;
slain down from dengue, malaria, and flu the bitter infusion or decoction was freely imbuded.
While other uses were known, diaphoresis reigned supreme, but as an emetic and purgative, boneset was keen.
As a bitter tonic for weakness and dyspeptic complains boneset found employ, but modern findings suggest that maybe
these uses are no longer enjoyed. For compounds contained may the liver they injure, though infrequently used,
due to nature's pathways, we can endure.

Roy Upton (2019)

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