Retrospective Analysis of the Safety of Bitter Herbs With an Emphasis on *Artemisia absinthium* L (Wormwood)

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Abstract

Bitter herbs such as *Artemisia absinthium* L (wormwood) remain important gastrointestinal tract therapy among botanical prescribers. All patients prescribed a bitters formula including wormwood were retrospectively identified over a nine month period from a naturopathic practice. Nine patients who took over 32 ounces of this formula developed no signs of toxicity. Several other patients who took smaller quantities showed no signs of toxicity. This provides preliminary evidence that a bitters formula containing 11% wormwood tincture may be safely employed as a digestive bitter for at least nine months at a dose of 5 ml three times daily. (J Naturopathic Med 2000; 9:32-39)

ORIGINAL RESEARCH

Introduction

Medicinal plants with a bitter taste often stimulate digestive function (1). They also have a reputation for safety (2). The important bitter of European origin, *Gentiana lutea* L (yellow gentian), is regarded by clinicians as a potent gastrointestinal stimulant that may irritate persons with sensitive stomachs (3). It is in the Gentianaceae family. Like all bitters, it increases stomach acid production and thus may theoretically worsen hyperchlorhydric conditions (3). However, many people with hyperchlorhydria may have only episodic problems related to transient lower esophageal sphincter relaxation (4), and dosing bitter herbs such as gentian at the appropriate time might avoid aggravating the condition. Bitters may also aggravate persons with colitis, diarrhea or significant intestinal hypermotility by stimulating further gut activity. It should not be used when there is bile duct obstruction (2). Other than this, gentian is essentially without adverse effect or contraindication.

Gentian is approved for use in patients with loss of appetite, dyspepsia and flatulence in the Commission E monograph of the German government (2). A double-blind study has been reported on an encapsulated product containing gentian, *Foeniculum vulgare* Mill (fennel), *Carum carvi* L (caraway), and *Mentha* x *piperita* L (peppermint) (5). Although the bitter flavor of gentian was not a factor in this encapsulated product, a significant improvement in digestive symptoms and ultrasonographic evidence of decreases in intestinal gas compared to placebo were noted. Various contradictory studies have been published regarding the effect of bitters on the appetites of generally healthy people (6).

Amarogentin, gentiamarin and gentiopicrin are three major, iridoid, bitter compounds in yellow gentian roots. Amarogentin is one of the most bitter substances ever identified, able to be tasted even at a 1:50,000 dilution (3). Only quassias (*Picrasma excelsa* (SW) Planch and *Quassia amara* L) are regarded as more potent bitters in the German Pharmacopoeia (6).

There is significant variation in the level of bitter compounds depending on when the plant is harvested; levels seem to be highest just before flowering (7). Traditionally gentian has also been prepared by mild fermentation before drying, a process requiring extensive

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experience in order to prepare the most potent product (8).

Two other digestive bitters with minimal toxicity are *Taraxacum officinale* GH Weber ex Wiggers (dandelion) and *Achillea millefolium* L (yarrow) (3). Similar to gentian, both are approved by the German Commission E for treatment of dyspepsia and loss of appetite, among other things (2). Both are members of the Asteraceae family. Other than allergy to yarrow, there are no listed adverse effects or contraindications to its use. Dandelion leaf and root are said to be contraindicated in patients with obstructed bile ducts. R. F. Weiss, MD, a well-respected German physician who used herbs clinically for several decades, regarded dandelion as "entirely harmless even if taken for extended periods" (3). The bitter compound in dandelion is known as taraxacin and is poorly characterized. The bitter compounds in yarrow have not been extensively studied or characterized.

The influence of bitter herbs on the digestive tract is profound and widespread. In particular, it has been documented that bitters stimulate production of gastrin even as soon as they are tasted, possibly via the glossopharyngeal and vagus nerves (9). Via stimulation of this hormone and other effects of autonomic activation, bitters increase gastric secretion, promote intrinsic factor secretion, stimulate pancreatic enzyme and bicarbonate secretion, improve appetite, increase bile flow, enhance absorption of nutrients, dilute and improve the quality of bile (thereby reducing its lithogenicity), promote cell division and growth of gastric and intestinal mucosa, improve the tone of the lower esophageal sphincter, and enhance peristalsis (9). It has been documented that bitters can increase appetite even in patients in whom gastric secretions cannot be stimulated (6), suggesting a direct effect of bitters on the appetite centers in the brain. Because bitters have a regenerative effect on the epithelium of the digestive tract, they may actually help to heal the damage of esophagitis or peptic ulcer (9). Nevertheless it is important to use caution when administering bitters to patients with these conditions as the stimulation of stomach acid can occasionally cause worsening of symptoms.

The major European bitter with a reputation for causing harm is *Artemisia absinthium* L (wormwood). It is a member of the Asteraceae family and the Anthemidae or mayweed tribe. It has grey-green, downy, divided leaves with inconspicuous, green-yellow flowers. Wormwood, like the other components of bitters formula, is an approved digestive stimulant in the German Commission E monographs (2). Its bitter compounds are thought to be sesquiterpene lactones such as absinthin and anabsinthin. A fixed combination of wormwood, gentian and Zingiber officinale Roscoe (ginger) rhizome is also approved by Commission E for dyspepsia and loss of appetite.

Wormwood is regarded as a useful choleretic, carminative, and even an invigorating central nervous system stimulant by Weiss (3). It is used to treat patients with chronic biliary dyskinesia (not for acute biliary spasm), gastric atony leading to ptosis, and dyspepsia (10, 11). Frequently patients who do well with wormwood have low blood pressure, aversion to food and lack of appetite, chronic low energy, low body weight, and are often elderly (3). It also has a restorative function and is recommended for influenza and recovery from surgery or severe illnesses such as pneumonia (3). Weiss recommends long courses of small doses of tincture or tea, taken after meals if there is gallbladder dysfunction (3). The efficacy of *Artemisia absinthium* in stimulating bile secretion by the liver and gastric secretion has been radiographically documented in humans (1). Additional studies suggest wormwood may have significant anti-inflammatory properties (12).

Artemisia absinthium is only one of many species of *Artemisia* used medicinally. In traditional European herbalism, it is considered the most effective for serious pathology, with the most potential for adverse effects. The authors believe the closest native American analog is perhaps *Artemisia tridentata* Nutt (big sagebush); this hypothesis is also supported by reports that it is the strongest of native *Artemisia* species (13). Thujone levels vary among species of *Artemisia*. Levels are relatively high in wormwood, and minimally present or absent in species such as the now famous antimalarial herb *Artemisia annua* L (sweet Annie) (14).

Other species in this genus include *Artemisia vulgaris* L (mugwort), *Artemisia dracunculus* (tarragon), and *Artemisia abrotanum* L (southernwood). Tarragon is a common cooking spice because of its pleasant flavor. Its use as a food indicates it is of minimal toxicity, though also with gentler medicinal activity than that of wormwood, based on empirical use. Mugwort also contains minimal thujone, has little if any other toxicity (though it is reportedly an emmenagogue and thus should be avoided in pregnancy), and is regarded as milder than wormwood as a medicine (2). Intravenous infusion of a water extract of an unspecified Chinese *Artemisia* was shown to regulate gall bladder motility and to induce choleresis in one uncontrolled study (15). Southernwood is perhaps of middle strength in the *Artemisia* genus, based on reports of having actions similar to but milder than wormwood with no particular reference to toxic effects (16). Clearly, not all members of the *Artemisia* genus are the same.

In the nineteenth century, a beverage known as absinthe prepared in part from wormwood became popular among the intelligentsia in Europe (17). Originally absinthe was prepared by distilling ethanol that had been soaked in wormwood leaves (18). *Cinnamomum spp.* (cinnamon bark), *Angelica archangelica* L (angelica) root, *Acorus calamus* L (sweet flag) rhizome, *Foeniculum vulgare* Mill (fennel) seeds and *Illicium verum* (star anise) seeds were also added. It should also be emphasized that absinthe in any form is not the same as tincture of wormwood. Wormwood tincture is not distilled (a complex evaporation and concentration process) like true absinthe was. Tincture can be produced by maceration of the herb in ethanol for approximately two weeks followed by straining, or by percolation if dried herb is used as the raw material. Wormwood oil is an entirely different product altogether. It is generally prepared by distillation and all but the essential oil is removed. The oil contains high levels of thujone and is dramatically more toxic than absinthe or tincture (17).

The French factory where the original, distilled absinthe was prepared, owned by the company Pernod Fils, was destroyed by fire in 1901. The growing demand for absinthe among the lower classes

combined with the lack of availability of the expensive liqueur led to the rise of numerous other manufacturers preparing absinthe-like beverages. However, these were made by adding essential oils to ethanol, along with numerous coloring agents (such as copper sulfate) to approximate the deep green hue of real absinthe and additives (such as antimony trichloride) to mimic the white sediment seen in true absinthe. These resultant beverages were far more widely imbibed and this was when absinthism first began to show up. Absinthism consisted of episodes of aggressive inebriation followed by prolonged depression after inebriation subsided, anxiety, hallucinations, loss of appetite, and aberrant behavior (19). Chronic use of even moderate amounts of the new absinthe-like formulations was said to cause absinthism.

Homeopathic indications for wormwood are seizures, severe giddiness, nervous excitement with sleeplessness, spasms and cerebral irritation (19). Such indications are taken partly from the literature on poisonings by wormwood.

The essential oil of wormwood contains thujone (20). This compound has been widely blamed for causing the neurological effects of absinthe (20). However, one author pointed out that true absinthe likely contained only 2-4 mg thujone per drink, far below the level (10 mg/kg body weight or more) needed to induce neurological damage in chronic animal feeding experiments (21). This author also points out that research on thujone is generally quite weak and does not yet come close to explaining the neurotoxicity of any type of absinthe. It is unclear if the absinthe substitutes contained higher levels of thujone, and if these levels might have been sufficient to cause absinthism. Thujone levels in wormwood tincture have not been reported.

Other herbs reported to contain thujone include *Achillea millefolium*, *Boswellia spp* (olibanum), *Cistus ladanfier* (labdanum), *Juniperus communis* (juniper), *Lavandula officinalis* (lavender), *Nepeta cataria* (catnip), *Piper cubeb* (cubebs), *Piper nigrum* (black pepper), *Sasafras albidum* (sassafras), *Salvia officinalis* (sage), *Tanacetum vulgare* (tansy), and *Thuja occidentalis* (white cedar) (12, 22, 23). Thujone levels vary considerably among different varieties of yarrow and other Achillea species depending on the chromosome number or ploidy of the plant in question (23). The uses and toxicity of these herbs vary, providing evidence that the mere presence of thujone in a plant does not mean that it is invariably dangerous or will cause the symptoms of absinthism.

The other candidate constituents for causing absinthism are ethanol itself (24), copper sulfate, and antimony trichloride (25). The cheap absinthe substitutes contained up to 85% ethanol, compared to approximately 75% in true absinthe. Wormwood tincture contains only 45-50% ethanol in most cases. Some absinthe beverages contained sweet flag, as mentioned above. The European varieties of this herb contain asarone, a carcinogen (3). This compound may have other toxic effects that might have contributed to absinthism.

Essential oil of wormwood is a far more concentrated source of thujone than tincture, and hence has very different properties from tincture or absinthe. It has been reported that wormwood contains approximately 1.7% essential oil (18). Depending on growth and harvesting conditions, this essential oil contains 34-71% thujone (25). Therefore, it would take many pounds of wormwood herb to make even a small quantity of essential oil. A case has been reported of a patient who drank 10 ml wormwood essential oil and subsequently developed renal failure, rhabdomyolysis, and seizure (26). This dose is many magnitudes greater than the doses of wormwood tincture used clinically.

The authors have employed tincture of wormwood as part of a bitters formula for treating malabsorption and digestive complaints for years. It was theorized that tincture of wormwood in small doses, when combined with other bitter herbs, is safe for even long term use. No patient with any sign of absinthism, even those who have taken this bitters formula for years, has ever been seen in this clinic. Interestingly, some animal studies have shown that wormwood is hepatoprotective (25) and have confirmed its traditional use as an anthelmintic (26, 27). Therefore a retrospective review of patients given bitters formula was conducted to confirm the authors' suspicion that wormwood tincture appropriately prescribed and used in low doses is clinically safe.

METHODOLOGY

A list of all patients who purchased the bitters formula from 1/1/97 to 9/1/97 was generated by computer. Each patient's records were then compared to this list for accuracy. Each patient's basic data were recorded, including basic laboratory findings. Findings are presented in cases where laboratory data are available in the patient record and intake over the study period exceeds 32 oz to show before and after information related to bitters intake. If a patient bought under 32 oz, then such data were not recorded due to insufficient exposure. No attempt was made to verify if each patient took the entire amount of bitters that was purchased, though in most cases there was an indication in the chart notes suggesting the patients who bought large quantities fairly consistently took what they bought.

Given the retrospective nature of this study and the fact that it was conducted in the context of standard practice, bitters were not introduced when all other treatments were stable. Other supplements were sometimes introduced simultaneously with bitters, some were discontinued, and some doses were adjusted. There was no control group in this study due to its retrospective construction.

Historical reports of absinthism give a number of clues as to possible signs of toxic reactions to *Artemisia absinthium*. For acute intoxication, these were primarily aggressiveness and intoxication lasting longer than from ethanol abuse alone. Following this came a period of deep, prolonged depression and fatigue, indigestion, anorexia, intense polydipsia, constant uneasiness and anxiety, giddiness, paresthesias in the ears, hallucinations and aberrant behavior (17). Later, spasms of muscles in the face and extremities were reported along with severe paresthesias, occasionally alopecia, emaciation, jaundice, nightmares causing insomnia, headaches, delirium, speech impediments, complete loss of intellect, paralysis, and even death (17). One case of an overdose of *Artemisia absinthium* oil reported hypernatremia, hypokalemia, microscopic hematuria, renal failure, and rhabdomyolysis with elevated serum creatinine levels and a large anion

gap, all of which were reversible (24). Menorrhagia and spontaneous abortion were also considered theoretical signs of toxicity. Any of these symptoms reported by patients in our studies would have been considered as possible signs of *Artemisia absinthium* toxicity. All patients were given a baseline full physical examination. Since no patient developed any symptoms or signs of wormwood toxicity from the list above, and many in fact improved (including two patients who had elevated serum liver enzyme levels initially that improved during bitters therapy), no further physical examination was considered necessary to insure safety of the herbs.

The composition of the bitters formula is reported in table 1. *Gentiana lutea* and *Taraxacum officinale* radix were imported from England. The remaining three ingredients were obtained from wild sources in the U.S. and prepared on site. Voucher specimens were maintained of all three, and their authenticity was verified organoleptically by one of the authors (SH).

Briefly, each herb was lightly ground under ethanol and water, then left to sit in the remaining liquid, with glycerin, for a minimum of two weeks. The marc was then pressed and filtered through unbleached paper to remove particulate matter, and stored in dark glass in a room kept at 60 degrees F consistently. It was mixed in gallon lots as needed, along with the two imported tinctures, and shaken well before dispensing.

Patients were instructed to shake their bitters formula well before taking each dose. The typical dose was 5 ml (1 tsp) sipped slowly in water 15-30 minutes before eating a standard size meal. The dose of wormwood was therefore 0.5 ml three times per day on most days. For larger meals, a larger dose was recommended (7 ml or 1.25 tsp); for smaller meals the dose was decreased (3 ml or 0.5 tsp). Many patients reported they often did not manage to take bitters a full 15 min before eating. Though it has long been known that tasting bitters provides the strongest effect, they have since been shown to also stimulate hydrochloric acid production upon direct contact with the gastric mucosa (28).

Some people are unable to tolerate the taste of bitters, though many even come to like it (3). For those who absolutely can't stand the flavor, bitters can be taken in capsules and will still have some effect. Alternately, the bitter flavor can be masked with pungent flavors,

TABLE 1. BITTERS FORMULA

Latin binomial	Common name	Part Used in Formula	Amount (%)	Weight: Volume	Solvents
Gentiana lutea	yellow gentian	radix	52.5%	1:5	45% ethanol, 55% water
Taraxacum officinale	dandelion	herba	15.5%	1:2	30% ethanol, 60% water, 10% glycerin
Taraxacum officinale	dandelion	radix	11%	1:5	25% ethanol, 75% water
Achillea millefolium	yarrow	flos	11%	1:4	30% ethanol, 60% water, 10% glycerin
Artemisia absinthium	wormwood	herba	11%	1:3	45% ethanol, 45% water, 10% glycerin

TABLE 2. SUMMARY OF PATIENT DATA AND MAJOR LIVER/KIDNEY TESTS

Patient	DOB	Dose[1] (ml)	Test Date	AST (U/L)[2]	ALT (U/L)[3]	LDH (U/L)[4]	BUN (mg/dL)[5]	C (mg/dL)[6]
1	3/20/44	5,280	4/16/97	25	16	173	19	0.9
			1/22/99	19	11	148	14	1.0
2	6/11/33	2,670	1/21/97	19	15	128	20	0.9
			8/29/97	24	22	170	14	0.9
3	4/9/37	6,480	1/23/96	19	16	118	15	0.9
			11/4/97	19	21	123	17	0.9
4	12/4/33	4.08	11/14/96	74*	57*	170	18	0.9
			9/22/97	36	28	146	16	0.9
5	3/2/53	1,800	1/22/97	16	9	117	12	1.0
			11/10/97	21	12	121	14	1.0
6	7/8/39	1,920	5/19/97	39	64*	177	14	0.6*
			11/28/97	32	44	169	13	0.7
7	10/26/60	1,200	6/22/96	15	12	159	11	0.8
			11/26/97	20	17	144	13	0.9
8	9/23/21	1,440	11/21/96	20	34	180	16	0.8
9	7/20/62	1,440	7/9/97	31	50*	101*	8	0.6
			11/10/98	18	NP	NP	12	0.6

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, C = creatinine, NP = not performed. * indicates an abnormal value.

Notes: All patients were by chance female. 1. Maximum, total dose possible of bitters formula the patient took. 2. Reference range is 0-41 U/L (9-34 for pt 2 on 8/29/97, 15-37 for pt 8 and 10-50 for pt 9). 3. Reference range is 0-45 U/L (4-37 for pt 2 on 8/29/97, 30-65 for pt 8 and 0-40 for pt 9). 4. Reference range is 100-230 U/L (102-172 for pt 2 on 8/29/97, 100-200 for pt 8 and 110-230 for pt 9). 5. Reference range is 10-26 mg/dL (7-18 for pt 2 on 8/29/97, 7-20 for pt 8 and 5-20 for pt 9). 6. Reference range is 0.7-1.5 mg/dL (0.6-1.2 for pt 2 on 8/29/97, 0.6-1.3 for pt 8 and 0.4-1 for pt 9).

whereas sweet flavors will not have a masking effect (3). *Zingiber officinale* Rosc (ginger) is ideal because it is a pungent digestive stimulant and will potentiate the benefits of bitters while hiding their flavor (2). It has been reported that some people develop nausea and a paradoxical appetite suppression when taking too much bitters (6); the authors have not encountered this in practice. In such a situation, the dose should be lowered until the patient tolerates the bitters.

Results

Nine patients were identified who had purchased more than 32 oz between 1/1/97 and 9/1/97. Eight of these nine had before and after laboratory information. Laboratory findings are summarized in table 2. The dose reported is a maximum possible dose. Each of these nine patients will be discussed in greater detail.

Patient 1: This 54 year old white woman purchased a total of 176 oz (5,280 ml) bitters formula during the study period. She had developed macrocytosis of unknown origin and bitters were prescribed in case the underlying problem was malabsorption. The macrocytosis had not responded to oral or intramuscular vitamin B12 and folic acid administration over a period of years. Ethanol avoidance also failed to have an impact. Her blood folate level was >20 ng/ml (reference range 3-17 ng/ml), blood cobalamin level >2,000 ng/ml (reference range 200-950 ng/ml) and her erythrocyte folate level >1,016 ng/ml (reference range 175-700 ng/ml) on 10/21/97 after many months of supplementation of these two nutrients. A sample of laboratory values showed her mean corpuscular volume (MCV) was 103 (reference range 80-98) and mean corpuscular hemoglobin 34.7 pg (reference range 26.8-34 pg) on 4/16/97, 104.5 and 35 on 7/24/97, 102 and 33.8 on 10/21/97, 101.2 and 33.7 on 4/4/98, and 102.2 and 34.4 on 1/22/99. On 4/16/97 there were 0.9% reticulocytes (reference range 0.5-1.5%).

Patient 1 had persistently elevated or near-elevated T3 uptake. For example, on 7/24/97, it was 35% (reference range 25-35%), 37% on 10/21/97, 36% on 4/4/98, and 36% on 1/22/99. Her thyroid stimulating hormone (TSH) level was 1.38 mIU/L (reference range 0.4-4.2 mIU/L) on 4/19/97. She was diagnosed with osteoporosis by dual electron absorptimetry (DEXA) on 4/16/97. N-telopeptide levels in the urine were 82 pmol BCE/micromol creatinine on 11/10/97.

Patient 1 also had symptoms of menopause and benign breast cysts. Her other supplements included calcium, magnesium, proanthocyanidins, vitamin B complex, multivitamin/multi-mineral without iron, lysine, a constitutional homeopathic remedy (baryta carbonica), an individualized botanical formula, *Allium sativum* (garlic) extract and vitamin E. She had been taking 5 mg dehydroepiandrosterone twice daily and 50 mg micronized progesterone twice daily by the sublingual route since 11/27/97. There was no indication of toxicity from her use of large amounts of bitters formula over a long period of time.

Patient 2: This 65 year old white woman likely took 89 oz (2,670 ml) bitters formula between 2/11/97 and 5/11/98. She suffered intermittent headaches, arthritis, and hypertension, all of which improved during the time she took bitters. Bitters were prescribed to facilitate absorption of nutrients. Her other supplements included an individualized botanical formula that allowed her to reduce and then eliminate her anti-hypertensive medications, bromelain, coenzyme Q10, a constitutional homeopathic remedy, glucosamine sulfate, tincture of *Tanacetum parthenium* (feverfew), calcium, magnesium, vitamin C, vitamin B complex, a multivitamin/mineral, proanthocyanidins, and sea cucumber. There was no indication of any toxicity from her intake of bitters.

Patient 3: This 61 year old white woman bought 216 oz (6,480 ml) bitters formula from 1/3/97 through 7/13/98. It is unclear if she used this entire amount or possibly shared some with family members. She was healthy and bitters formula was given to improve nutrient absorption. Her other supplements included a constitutional homeopathic remedy (sepia), calcium, magnesium, vitamin C, folic acid, vitamin B12, *Scutellaria lateriflora* (skullcap) glycerite, spirulina, kelp, and antioxidants. No true post-therapy laboratory data were available on patient 3 but results from before and during (after a few months of intake) supplementation showed no problems. There were no clinical signs of toxicity from use of bitters formula.

Patient 4: This 65 year old white woman purchased 136 oz (4,080 ml) bitters formula and likely used the vast majority of them. Elevated liver enzyme levels of unknown origin were noted before she began taking bitters formula (see table 2). She was otherwise healthy. She had used oral and transdermal estrogens of various forms for years, though these were discontinued at least one year before the start of the study. At the time of her pre-study blood work (11/15/96), she also had an alkaline phosphatase level of 159 U/L (reference range 20-155 U/L), an erythrocyte sedimentation rate (ESR) of 32 mm (reference range 0-30 mm), and an MCH of 34.8 pg. Her major liver enzyme levels all improved while continuing to take bitters formula. By 9/22/97 her alkaline phosphatase was 78, ESR 10, and MCH 33.8 though her white blood cell count (WBC) was 3.6 (reference range 3.9-10.9 thousand/mm^3) and her MCV 98.9. She had previous low WBC values including 3.3 on 9/23/96 and 3.9 on 3/26/97; and her MCV was 4 on 3/9/95 (reference range 4.5-10.8 thousand/mm^3). She never reported any symptoms suggesting toxicity from the bitters formula. Her other supplements were *Ginkgo biloba* tincture, folic acid, vitamin B12, silymarin, digestive enzymes, a multivitamin/mineral, vitamin C, coenzyme Q10, a constitutional homeopathic remedy (sambucus nigra), spirulina, proanthocyanidins, predigested fish protein capsules, calcium, magnesium, *Fucus vesiculosus* (bladderwrack) tincture and borage oil.

Patient 5: This 45 year old white woman took a maximum of 60 oz (1,800 ml) bitters formula starting on 1/30/97. She had chronic iron-deficiency anemia, environmental sensitivities, and intestinal candidiasis at intake. Bitters were prescribed to enhance iron absorption and potentially reduce intestinal permeability to antigens. Her other supplements were spirulina, *Urtica dioica* (stinging nettles) tea, *Leonurus cardiaca* (motherwort) tea, probiotics, plant tannins (antifungal), grapefruit seed extract, bentonite clay, *Valeriana officinalis* (valerian) fluid extract, calcium, magnesium, borage oil, iron, a multi-nutrient supplement to promote appropriate intestinal permeability, fructooligosaccharides, chromium, niacin, vitamin B complex, vitamin E, proanthocyanidins, garlic extract, vitamin C, bromelain, folic acid and

vitamin B12. She developed no signs of toxicity from bitters formula.

Patient 6: This 59 year old white woman apparently took 64 oz (1,920 ml) of bitters formula starting on 6/23/97. She presented with a history of shingles and breast cancer, fatigue, fibromyalgia and a fear that she "didn't know what she was doing." She had abnormal liver enzyme levels prior to starting bitters (see table 2), particularly an elevated gamma glutamyltransferase (GGT) level of 165 U/L (reference range 0-65 U/L) on 5/19/97. Her GGT went down to 116 on 7/12/97, then up to 137 on 11/28/97 during and after her use of bitters. Her other abnormal liver enzyme levels normalized during treatment with bitters. Her total cholesterol level was 231 mg/dL (reference range <200 mg/dL) and low-density lipoprotein (LDL) cholesterol level 143 mg/dL (reference range <130 mg/dL) on 5/19/97; they went to 262 and 173 respectively on 11/28/97. Her WBC went from 3.7 (reference range 3.9-11.2 thousand/mm^3) on 5/19/97 to 3.8 on 11/28/97. Her basophil percent went from 2% to 3% (reference range <2%) in this same time frame.

Seven months after she stopped using bitters (by 6/2/98), her AST was elevated at 51, her ALT was elevated at 52, her GGT 147, her total cholesterol level elevated at 267, her LDL cholesterol level elevated at 150, her WBC low at 3.6 and her neutrophils low at 37% (reference range 38-80%). Therefore, rather than any indication existing of toxicity from use of bitters formula, there was evidence that taking bitters helped normalize her liver enzyme levels, which deteriorated again when she stopped bitters.

Her other supplements included calcium, magnesium, silymarin, a multivitamin/mineral without iron, a constitutional homeopathic remedy (conium maculatum), an individualized botanical formula, *Silybum marianum* (milk thistle) seeds, probiotics and digestive enzymes.

Patient 7: This 38 year old white woman bought 40 oz (1,200 ml) bitters formula during the study period. She was given bitters to help improve nutrient absorption including iron to help combat iron-deficiency anemia related to chronic bleeding from uterine leiomyomata. She also had a history of thyroid nodules. There was no sign of bitters-related toxicity at any time during her course of treatment. Her other supplements included vitamin E, silymarin, antioxidants, magnesium, a constitutional homeopathic remedy (syphilinum), individualized botanical formulas, vitamin B complex, kelp, multivitamin/multi-mineral, *Angelica sinensis* (dong quai) tincture, *Urtica dioica* (stinging nettle) glycerite, *Fucus vesiculosus* (bladderwrack) glycerite, *Equisetum arvense* (horsetail) glycerite, spirulina, borage oil, fructooligosaccharides, and fish oil.

Patient 8: This 77 year old white female bought 48 oz (1,440 ml) bitters formula during the study period. She had a history of discoid lupus, hypertension, osteoarthritis, carpal tunnel syndrome, anxiety, and hypothyroidism. She had taken hydroxychloroquine (Plaquenil), alprazolam (Xanax), estradiol (Estrace) vaginal cream (temporarily), ipratropium (Atrovent) nasal spray, atenolol, calcium, vitamin C, fish oil, garlic extract, multivitamin/mineral, an individualized botanical formula and spirulina. No post-bitters laboratory values were available for patient 8 but no symptom of toxicity was encountered during her course of treatment.

Patient 9: This 36 year old white woman bought 48 oz (1,440 ml) bitters formula during the study period. She had a history of migraine headaches, thalassemia, hypothyroidism and depressed feelings. She was taking levothyroxine (Synthroid). Her supplements included fish oil, calcium, magnesium, lecithin, coenzyme Q10, taurine, vitamin C, bromelain, tyrosine, iodine, spirulina, a constitutional homeopathic remedy (cinchona officinalis), individualized botanical formulas, valerian fluid extract, and Echinacea angustifolia (echinacea) tincture. Though there was only incomplete post-bitters laboratory information, there was no sign of bitters-related toxicity. Her pre-bitters liver enzyme levels were elevated, possibly due to a week-long illness at the time the lab work was done. She reported no symptoms resembling any of those reported for wormwood toxicity.

Twenty additional patient records were studied, to provide some information on those who purchased fewer than 32 oz bitters formula during the study period. Two patients had been taking larger amounts of bitters prior to the study period. The first patient in this second group, patient 10, a 56 year old white woman with diabetes mellitus, diabetic retinopathy (treated surgically), mild diabetic neuropathy, atherosclerosis and arthritis, purchased exactly 32 oz bitters formula during the study. She was injecting insulin twice daily. Her latest laboratory values, serving as post-supplementation information, showed BUN 14, creatinine 0.8, AST 14, and ALT 13 (same reference ranges as table 2). There was no sign of toxicity from bitters formula.

The second patient in this group, number 11, a 38 year old white woman, bought 16 oz bitters formula during the study period. This patient had Gilbert's syndrome prior to ever having taken bitters. An abdominal ultrasound showed no

Table 3. Patients Exposed to Low Levels of Bitters Formula

Patient	Sex	Date of Birth	Dose (ml)[1]
12	M	6/8/56	600
13	F	3/23/47	480
14	F	4/8/49	120
15	F	2/25/60	120
16	M	12/3/19	480
17	F	2/17/52	240
18	M	12/13/39	240
19	F	3/25/55	120
20	M	6/13/57	240
21	F	9/10/60	480
22	F	11/10/48	150
23	F	2/5/49	960
24	F	3/25/53	510
25	F	7/3/53	960
26	F	8/6/57	480
27	M	7/20/74	120
28	M	3/21/45	480
29	M	4/22/56	480

Note: 1. Total maximum possible dose taken.

sign of organ damage. On 3/89, her total bilirubin level was 2.7 (reference range 0-1.2), the highest level seen on any of her blood panels. This was prior to any use of bitters. Her post-supplementation laboratory work on 11/28/97 showed BUN 13, creatinine 0.7, AST 16, ALT 14 (same reference ranges as table 2), direct bilirubin 0.4 mg/dL (reference range 0-0.3 mg/dL), and indirect bilirubin 1.6 mg/dL (0-1.1 mg/dL normal). The patient never developed jaundice and it is unclear if bitters were related to the Gilbert's syndrome other than possibly to lessen her bilirubin levels.

All 18 remaining patients from the second group took less than 32 oz bitters formula during the entire time they were seen at the clinic. Basically all these patients started and terminated their use of bitters during the study period. None of them developed signs or symptoms of toxicity related to bitters formula. Table 3 summarizes data on these 18 patients.

Discussion

This retrospective review has investigated the safety of a bitters formula containing wormwood in a clinical setting. Over a period of nine months, a number of patients who had taken a wide variation in total doses of the formula were identified. No patient showed any signs of toxicity that could be attributed to any level of intake.

One patient who had Gilbert's syndrome prior to bitters supplementation showed no sign of aggravation of this condition while taking bitters; on the contrary, her serum bilirubin levels actually seemed to decline while taking bitters. Gilbert's syndrome is considered by most a genetic condition (29). This extremely preliminary finding warrants further study of bitters as a possible therapy for people with Gilbert's syndrome. Due to the problems with retrospective analysis, no attempt was made to determine the efficacy of bitters for this or any other problem in our study.

Some of the patients investigated had taken bitters for more than two years. There was insufficient data to truly determine how long bitters containing wormwood could be taken without harm. It would seem on the basis of this study, however, that bitters can safely be taken at a dose of 5 ml three times daily (providing less than 1 ml of wormwood tincture three times daily) for many months without causing adverse effects in adults. It appears that wormwood tincture used medicinally in low doses does not share the toxicity of any form of the now-banned absinthe liqueurs. The contraindications to use of bitters are hyperchlorhydria, though this is not absolute, and gut hyperactivity disorders such as acute colitis and diarrhea (3). Bile duct obstruction is an absolute contraindication for use of bitters. A patient with a duodenal ulcer and hyperchlorhydria is likely to be worsened by bitters in particular. Those with gastroesophageal reflux disease (GERD) may benefit from bitters but need to be closely managed so as to avoid possible worsening. Though this has not been documented in research publications, many practitioners of natural medicine report, based on clinical observation, that persons with GERD actually tend to have hypochlorhydria. Bitters might help with GERD by correcting this problem, or theoretically by acting on the lower esophageal sphincter.

Our research involved patients with a variety of disorder, taking a large number of different herbs and nutritional supplements. The goal of the study was to provide preliminary documentation of the safety of bitters containing wormwood in clinical practice as opposed to the artificial setting of a controlled clinical trial. This type of outcomes research is often considered to provide less definitive information. However, from the perspective of clinicians, it is important to know what happens in real-life settings when multiple agents are used in combination in patients presenting with myriad concerns. That no ill effects were experienced by different patients on different treatments and medications can itself be seen to support the general safeness of the bitters formula used. Data from clinical trials on single herbs is useful in establishing more clearly the effects of each agent in isolation, but is less relevant to the everyday practice of combining many agents.

Retrospective studies in real clinical settings have limitations. It is not possible to isolate wormwood and state without reservation it is safe in the doses prescribed from the data presented here. However, it does provide initial evidence suggesting this conclusion. No two patients in this study were taking the same set of supplements and herbs, thus any protective effect of a particular nutrient or botanical against wormwood toxicity is less likely to cloud these results.

An example of research on complex herbal formulae rather than single herbs comes from China. There, classic formulae known as patent medicines have developed over several millennia and in Asia are the subject of clinical trials too numerous to list documenting their safety and efficacy. This provides one instance proving the scientific validity of using and studying mixtures of rather than single herbs.

While there is no documentation regarding the use of bitters or wormwood in pregnancy, the authors suggest it would be wise to avoid them. *Artemisia absinthium* has been reported to have emmenagogue properties (11). If a pregnant woman was depleted or suffering digestive upsets, a safer bitters mix has been formulated by the second author. This formula contains *Silybum marianum* Gaertn (milk thistle), *Cnicus benedictus* L (blessed thistle), dandelion and *Marrubium vulgare* L (white horehound), all preferably as glycerin extracts or teas.

Future research should now attempt to document the efficacy of bitters, as they are generally safe for human consumption in moderate doses. Though all four herbs in the bitters formula are regarded as effective by the German Commission E monographs for digestive disturbances (2), independent, double-blind studies are indicated to confirm this, as well as to confirm the efficacy of the combination formula. Additionally, bitters should be studied as a way to counteract nonspecific malabsorption syndromes, mild liver damage causing elevated serum liver enzyme levels, and possibly even selective intestinal hyperpermeability (the so-called "leaky gut" syndrome). Some patients with gastric ulcers and GERD, as mentioned above, may have hypochlorhydria and thus may benefit from bitters. It would be crucial to document the presence of hypochlorhydria and carefully monitor any patient with peptic ulcer or GERD before giving bitters. Our results also indicated on a preliminary basis that bitters may lower elevated serum liver enzyme levels, a conclusion needing to be confirmed in future studies.

To more definitively show that *Artemisia absinthium* tincture is safe

at a dose of 1 ml three times per day or less, a randomized, double-blind study should now be performed. The authors believe that ideally this study would be undertaken in patients with non-ulcer dyspepsia or similar benign forms of indigestion not due to identifiable pathologic conditions. That way the potential efficacy of wormwood could be evaluated simultaneously with the safety. Such a study should run at least six months to help confirm long-term safety and efficacy of wormwood.

The authors urge other naturopathic physicians or clinicians using botanicals in practice to publish their own experiences about the safety of botanicals. There is little information available in print documenting the safety of botanical medicines, though many centuries of observation affirm the general safety of herbs. In the current climate of expanding use of botanicals by untrained lay persons and medical professionals, it is important to continue the tradition of scientific documentation of the safety and efficacy of natural approaches. This would improve everyone's ability to use herbs safely, and help to show that there are physicians actively, effectively and safely prescribing traditional extracts of botanical medicines. These physicians can then serve as resources to those seeking expert support in using herbs.

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Biographies

Silena Heron is a naturopathic physician with a family practice in Sedona, Arizona. She is a nationally-recognized specialist in botanical medicine, having taught throughout the West and Canada since 1974. Dr. Heron began her medical career more than 25 years ago as an R.N. in emergency medicine and psychiatry. She was on the faculty of Bastyr University for six years, founding their Department of Botanical Medicine, and is now adjunct faculty at Southwest College of Naturopathic Medicine. She is a founding member and vice president of the Botanical Medicine Academy, a clinical specialty board. She continues to educate fellow practitioners in the application of plants in medicine.

Eric Yarnell is a naturopathic physician and chair of the Department of Botanical Medicine at the Southwest College of Naturopathic Medicine. He is co-author of The A-Z Guide to Drug-Herb-Vitamin Interactions (Prima Health, 1999) and the Phytotherapy Research Compendium (NPRC, 1996) as well as being a major contributor to the HealthNotes Online software (HealthNotes Inc, 1998). He is a founding member and president of the Botanical Medicine Academy.

Personal Conflict of Interest Statement

Dr. Heron is technical director of Élan Botanicals, a small herbal extract company that markets to health care practitioners. This company produces the bitters formula mentioned in this study.