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## St. John's Wort for the Treatment of Depression: An Update

*By E-P. Barrette, MD, FACP*

SINCE LAST REVIEWED IN THIS NEWSLETTER,[1] SEVERAL LONG-awaited trials of St. John's wort (SJW), an herbal therapy for depression, have been published. The growing literature on the efficacy, adverse effects, and drug interactions of SJW has greatly expanded. In spite of this, much controversy still exists and SJW remains one of the top selling supplements.

### History

St. John's wort was used by the ancient Greeks and by 19th century European physicians for mood disorders in addition to other conditions. Interest in herbal SJW was rekindled in the mid-20th century. In 1984 the Commission E of Germany published its first monograph supporting the use of this herb for "psychovegetative disturbances, depressive moods, anxiety, and/or nervous unrest."[2]

In Europe, SJW remains among the most commonly used antidepressants and continues to outsell fluoxetine (Prozac) widely. In the United States, annual sales of SJW have been estimated to exceed $400 million.

### Botany and Chemistry

St. John's wort (*Hypericum perforatum*) is a perennial shrub that grows well in dry sunny areas. Its bright yellow star-shaped flowers can be seen along many highways in the United States. The flowering parts are harvested, dried, and extracted with alcohol for the medicinal supplement. A group of purple naphthodianthrones comprise the supplement's principal ingredients. This group includes hypericin, pseudohypericin, protohypericin, protopseudohypericin, and cyclopseudohypericin.[3] Other components of the extract include quercetin, quercitrin, rutin, campherol, lureolin, and hyperforin.[4]

The amount of hypericin, originally thought to be the active component, found in SJW varies from 0.06% to 0.75%, depending on the time of harvest and the quality of the plants.

### Mechanism of Action

Early theories of a mechanism involving hypericin and MAO inhibition have been discounted. Notably, hypericin does not cross



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the blood-brain barrier. Extracts have been standardized to the hypericin content. Consequently, other content, such as hyperforin content, has varied and usually was not measured (or reported on the label). This variation may explain some of the differences seen in the trials.

Recent data support hyperforin as a potential active component of SJW,[5] and evidence from validated animal models of depression support hyperforin.[6] Hyperforin inhibits the uptake of serotonin, dopamine, norepinephrine, GABA (gamma-aminobutyric acid), and L-glutamate receptors in vitro. This broad range of affected receptors suggests a mechanism different than that of the selective serotonin reuptake inhibitors. Hyperforin, a phloroglucinol, and hypericin, a naphthodianthrone, are chemically unrelated and their plant content varies independently.

## Early Clinical Evidence

In 1996, a meta-analysis published in the *British Medical Journal* supported the use of SJW for depression and generated much attention.[7] This meta-analysis was updated for the Cochrane library in 1999.[8] A total of 2,291 patients were included in 27 studies. Twenty-four of 27 trials were double-blind studies. Standard definitions of treatment response were used, e.g., Hamilton Depression Scale (HAMD) score of less than 10 or less than 50% of the baseline score or "much improved" on the Clinical Global Impression Index.

The results from 14 of the 17 trials comparing SJW to placebo were combined. SJW response rate was 56% while the response rate for placebo was 25%. The pooled rate ratio confirmed a significant effect (2.47, 95% confidence interval [CI] 1.69-3.61). Eight trials compared SJW to a tricyclic antidepressant. Pooling of responder rates from these trials suggested an equivalent response (i.e., no significant difference between SJW and tricyclic antidepressants).

These early trials have been criticized for poorly defined entry criteria resulting in heterogeneous populations, inadequate blinding, use of nonstandard outcome scores, use of combination products or low doses of SJW, small enrollment size, short duration of follow-up, and low doses of tricyclic antidepressants. In addition, the variety of commercially produced products with different extraction processes lessens the generalizability of these studies.

## Recent Trials Comparing SJW to Placebo or Tricyclic Antidepressants

Since the publication of the Linde meta-analysis,[7] three multicenter trials in Germany have showed a benefit of SJW over placebo *(see Table 1)*.

Schrader et al enrolled 162 patients with mild-to-moderate depression (ICD-10 criteria) and compared 250 mg bid SJW vs. placebo over six weeks.[9] This trial demonstrated a 56% response rate with SJW compared to 15% with placebo. For the main outcome, change in HAMD score, placebo showed essentially no change.

In the first published three-arm study, 263 subjects were randomized to SJW (350 mg tid), imipramine (100 mg/d), or placebo for eight weeks.[10] Subjects with moderate depression (ICD-10 definition with HAMD > 17) were enrolled by general practitioners. SJW improved the mean HAMD score significantly more than placebo (-15.4 vs. -12.1) and to a similar extent as imipramine (-15.4 vs. -14.2). The trial had a high placebo response and only a trend to improvement of imipramine compared to placebo. The dose of SJW was higher than usual and the dose of imipramine was lower than recommended.

In an equivalence study, 324 subjects were randomized to SJW (250 mg bid) or imipramine (75 mg bid) for six weeks.[11] Both treatments equally improved HAMD scores significantly over time (P = 0.20).

A recent French trial randomized 375 subjects to SJW (300 mg tid) or placebo for six weeks.[12] This trial used DSM-IV criteria and baseline HAMD score was

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**Table 1**

**Recent randomized double-blind controlled trials of St. John's wort vs. placebo**

| Study | Subjects | Duration | Dose | Hypericin | Hyperforin | HAMD Entry Criteria | Design | Statistically Significant |
|---|---|---|---|---|---|---|---|---|
| Schrader (1998)[9] | 162 | 6 weeks | ZE 117 250 mg bid | 0.5 mg/d | NS | 16-24 ICD10 | SJW vs. placebo | Yes |
| Philipp (1999)[10] | 263 | 8 weeks | STEI 300 350 mg tid | 0.2-0.3% | 2-3% | ≥ 18 ICD10 | SJW vs. imipramine vs. placebo | Yes for SJW vs. placebo |
| Woelk (2000)[11] | 324 | 6 weeks | ZE 117 250 mg bid | 0.2% | NS | ≥ 18 ICD10 | SJW vs. imipramine 75 mg bid | Treatments equivalent |
| Kalb (2001)[36] | 72 | 6 weeks | WS 5572 300 mg tid | NS | 1.5% | ≥ 16 DSM-IV | SJW vs. placebo | Yes |
| Shelton (2001)[13] | 200 | 8 weeks | Lichtwer Standardized Extract 300 mg tid, up to 1,200 mg/d | NS | NS | ≥ 20 DSM-IV | SJW vs. placebo | No |
| Lecrubier (2002)[12] | 375 | 6 weeks | WS 5570 300 mg tid | 0.12-0.28% | 3-6% | 18-25 DSM-IV | SJW vs. placebo | Yes |
| Duke Trial (2002)[14] | 340 | 8 weeks | LI 160 300 mg tid, up to 1,500 mg/d | 0.12-0.28% | 3.1% | ≥ 20 DSM-IV | SJW vs. sertraline vs. placebo | No |

NS = not stated

21.9. SJW improved HAMD scores more than placebo ($P = 0.037$), and responder rates were higher with SJW (52.5% vs. 42.3%, $P < 0.05$). A subgroup analysis of less depressed vs. more depressed subjects showed that those with higher HAMD scores (22, i.e., more depressed) improved significantly while those with HAMD scores of 17-21 did not differ from placebo. This contradicts all the earlier German trials, which demonstrated benefit for SJW in mildly depressed subjects.

### Clinical Studies—Negative U.S. Trials

In two U.S. trials, SJW failed to show a benefit over placebo. The Shelton trial compared SJW (300 mg tid) to placebo for eight weeks in 200 subjects.[13] Although there was significant improvement over eight weeks in both arms, SJW was not better than placebo in primary outcomes. A criticism of this trial is that the enrolled subjects had chronic depression (duration of the current depressive disorder 2.3-2.7 years). However, those with a history of failing to respond to an antidepressant in the current episode or failing more than one trial of antidepressants in the past were excluded.

The Duke trial compared SJW (300 mg tid titrated up to 1,500 mg/d), sertraline (50-100 mg/d), and placebo in 340 subjects over eight weeks.[14] In the primary analysis, neither SJW nor sertraline improved depression scores more than placebo. In a secondary endpoint, sertraline was better than placebo.

Why these two U.S. trials were negative and more than 25 randomized controlled trials in Germany have shown positive benefits remains controversial. The U.S. trials were performed at academic sites while the German studies generally used community physician practices. Most German trials enrolled patients with mild-to-moderate depression but few used DSM-IV criteria. The U.S. trials trained all raters extensively and tested for reliability (e.g., scoring videotaped vignettes). The U.S. trials used a higher cut-off for the depression scores, potentially enrolling more depressed subjects. Yet the Philipp trial, which showed a benefit of SJW over placebo, had subjects with a similar baseline HAMD score (22.6) to the U.S. trials.[10] Whether these or other systematic differences can explain the dichotomy of the results remains to be seen.

### Trials of SJW vs. SSRIs

The several trials comparing SJW with fluoxetine or sertraline suggest these treatments to be equivalent *(see Table 2)*. However, none of these trials included a placebo arm. The one U.S. trial was small and included a

**Table 2**

**Recent randomized double-blind controlled trials of St. John's wort vs. SSRIs**

| Study | Subjects | Duration | Dose | HAMD Entry Criteria | Design | Statistically Significant |
|---|---|---|---|---|---|---|
| Harrer (1999)[16] | 149 | 6 weeks | LoHyp-57, 400 mg bid | None | SJW vs. fluoxetine 10 mg bid | Treatments equivalent |
| Schrader (2000)[37] | 240 | 6 weeks | ZE 117 250 mg bid | 16-24 | SJW vs. fluoxetine 20 mg/d | Equivalent decreases in HAMD scores, but higher response rates with SJW |
| Brenner (2000)[15] | 30 | 7 weeks | LI 160 900 mg/d | ≥ 17 | SJW vs. sertraline 75 mg/d | Treatments equivalent |
| Van Gurp (2002)[38] | 87 | 12 weeks | 900-1,200 mg/d | ≥ 16 | SJW vs. sertraline 100 mg /d | Treatments equivalent |

heterogeneous group of patients.[15] The other trials included patients with mild depression. In one trial of elderly patients, the baseline HAMD scores were lower than in most trials, suggesting these subjects had very mild depression.[16]

### Adverse Effects

A systematic review in 1998 of the adverse effects of SJW collected data from published trials and drug monitoring agencies in several European countries. Generally, SJW was well tolerated with mild side effects, most commonly gastrointestinal symptoms, dizziness/confusion, tiredness/sedation, and dry mouth.[17]

Photosensitivity has been seen in animals grazing on SJW. Hypericin has been confirmed as the cause of photosensitivity. In a Phase I study of pure hypericin in HIV-positive adults, phototoxicity occurred in 26 of 30 subjects and was severe in 11 of 23 subjects.[18] The hypericin dose ranged from 0.25 mg/kg IV twice weekly to 0.5 mg/kg PO daily. In a 70-kg individual, the lower dose approximates 5 mg/d of hypericin. Lower doses were used in a Phase I study of oral pure hypericin in hepatitis C patients.[19] Phototoxic reactions were still seen in five of 12 subjects receiving 0.05 mg/kg/d and in six of seven subjects receiving 0.10 mg/kg/d (equivalent to 3.5 mg/d and 7.0 mg/d in a 70-kg subject, respectively). One case of subacute polyneuropathy occurred on sun-exposed areas after four weeks of hypericum.[20]

Induction of hypomania and mania are known complications of antidepressant therapy. Well-described cases of hypericum precipitating hypomania and mania have been reported.[21-24] There exists a report of cardiovascular collapse during anesthesia in a healthy 23-year-old woman who had been taking SJW for six months.[25]

### Drug Interactions

The serotonin syndrome (mental status changes, tremor, autonomic instability, gastrointestinal upset, headache, myalgias, and motor restlessness) was seen in five elderly patients who started SJW while on stable doses of sertraline (four patients) and nefazodone (one patient).[26] A similar interaction in younger patients with paroxetine has been reported.[27] Reports of a serotonin-like syndrome in those taking SJW alone also have been seen.[28]

The growing reports of significant drug drug interactions with SJW have generated much concern *(see Table 3)*. In all cases, SJW reduced the level of the second drug. Reports have noted reduced international normalized ratios in patients on chronic stable warfarin and breakthrough bleeding in women on oral contraceptives after starting SJW.[29] The changes resolved with discontinuation of the supplement.

Further reports of interactions between oral contraceptives, warfarin, digoxin, and theophylline were summarized by Ernst.[30] These cases suggest that SJW causes the induction of hepatic cytochrome P450 enzymes, which results in more rapid clearing of the drug. Human studies now confirm selective induction of the cytochrome P450 3A4 activity by SJW.[31] Hyperforin activates the pregnane X receptor, which activates hepatic cytochrome 3A4 activity. In addition, evidence suggests that SJW also induces the intestinal transport protein P-glycoprotein, which may further lower plasma levels of drugs.

The risk of rejection in transplant patients due to lowered levels of cyclosporin when combined with SJW is well documented. An early report of two cardiac transplant patients who developed rejection after starting hypericum[32] has been followed by multiple reports involving kidney, cardiac, liver, and pancreas transplants.

St. John's wort will lower the level of antiretroviral medications used for HIV infection. An open-labeled study measured the interaction between hypericum and indinavir, a protease inhibitor (PI), in eight healthy male subjects.[33] The mean indinavir serum level at eight hours

**Table 3**

**Drugs reported to interact with St. John's wort**

- Amitriptyline
- Cyclosporine
- Digoxin
- Indinavir
- Irinotecan
- Midazolam
- Nefazodone
- Neveripine
- Nifedipine
- Oral contraceptives
- Paroxetine
- Sertraline
- Simvastatin
- Tacrolimus
- Theophylline
- Trazodone
- Warfarin

after dosing fell 10-fold (0.493 vs. 0.048 µg/mL, P = 0.027). This report resulted in the release of an FDA health advisory letter in February 2000. Clearance of nevirapine, a nonnucleoside reverse transcriptor inhibitor (NNRTI), was increased when taken with SJW.[34] Other PIs and NNRTIs may be similarly affected.

## Dosage and Formulation

Most studies have used 300 mg given three times a day. But doses have ranged from 500 to 1,800 mg daily. Several standardized ethanol and methanol extracts exist. Most products were formulated to contain 0.3% hypericin providing 2.7 mg/d hypericin when 900 mg hypericum is taken. With the recent evidence supporting hyperforin as the active agent, some manufacturers are standardizing to this ingredient (usually 2-5%).

The continuing problem of standardization and purity was seen in a study of eight SJW products purchased in Germany (two are available in the United States).[35] The products were found to contain "widely differing amounts" of hypericin and hyperforin. Some even demonstrated pronounced interbatch variability.

## Conclusion

Since the original meta-analyses supporting SJW, some new studies continue to show a benefit in the treatment of depression. Concerns with generalizability of these trials remain. Also, the two U.S. trials in well-defined patients with major depression did not show a benefit with SJW. Unfortunately, no studies six months or longer in well-defined subjects with standardized extracts have been published to determine long-term efficacy. Numerous herb-drug interactions and adverse events have been reported. The only comparative trial with an SSRI, which included a placebo control arm, did not show benefit.

## Recommendation

Scant evidence is available to support SJW use in moderate-to-severe depression; SJW should be avoided in these patients. Although many trials show a benefit in patients with milder depression, concerns about the methodology and generalizability of these trials remain. For those who elect to use SJW in the care of their patients, careful review of this new information, including that of drug-drug interaction, is well advised. ❖

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# What's the Buzz? Honey for Topical Wound Dressings

*By Susan T. Marcolina, MD, FACP*

PART II OF A SERIES ON APITHERAPY

ALTHOUGH WOUND SALVES CONTAINING HONEY WERE mentioned on Egyptian papyri dating back to 2500 BC, honey is not well recognized for its use as a topical medication in modern times.[1] There has been a resurgence of interest in honey for this purpose, however, with the emergence and proliferation of antibiotic resistant microbes, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus in non-healing wounds. Curiously, there appears to be something to it.

**Honey Production**

Bees gather nectar from flowering plants and transform it into honey with the addition of enzymes. One of these enzymes is invertase, which converts the sucrose in the nectar into glucose and fructose: The sucrose content of honey is generally just 1% of the total sugar content. Another enzyme is glucose oxidase, which is inactive in ripened honey and becomes activated with dilution to form hydrogen peroxide and gluconic acid from glucose. Hydrogen peroxide and gluconic acid impart antibacterial activity.

Bees store nectar in honeycomb cells and evaporate water from it by rapid wing ventilation. Once the water concentration is about 18%, the bees cap off the cells.[2,3] Table 1 delineates the nutritional constituents of honey.

**Table 1**
**Nutritional constituents of honey**

| Nutrient | Average Amount/ 1 Tbsp Serving (21 g) |
|---|---|
| Water | 3.62 g |
| Calories | 64 kcal |
| Total carbohydrate | 17.46 g |
| Fructose | 8.16 g |
| Glucose | 6.57 g |
| Maltose | 1.53 g |
| Sucrose | 0.32 g |
| Other carbohydrate | 0.85 g |
| Total protein | 0.06 g |
| Niacin | 0.03 mg |
| Folate | 0.42 mg |
| Vitamin C | 0.11 mg |
| Calcium | 1.27 mg |
| Phosphorus | 0.85 mg |
| Sodium | 0.85 mg |
| Potassium | 0.011 mg |
| Magnesium | 0.42 mg |

***Adapted from:*** U.S. Department of Agriculture; data obtained from Genesis R&D Nutrition Analysis Program. Version 7.01. Salem, OR: ESHA Research.

**Table 2**
**Therapeutic attributes of honey[2]**

| Attribute | Key Properties |
|---|---|
| Antimicrobial activity | Low Aw (water activity), high osmotic pressure, hydrogen peroxide production, high acidity/low pH, nonperoxide phytochemical components |
| Promotion of wound healing | Antimicrobial activity, stimulation of the immune system, high viscosity/ osmolarity, antioxidant activity |
| Antioxidant activity | Presence of ascorbic acid, enzymes (glucose oxidase, catalase) |

## Properties Responsible for Antibacterial Activity

Table 2 outlines the therapeutic attributes and key properties of honey.[2]

The major antibacterial effects exerted by honey result from its glucose oxidase enzyme content. This enzyme catalyses the reaction, which produces acid (primarily gluconic acid) and hydrogen peroxide from glucose, water, and oxygen.[4] In addition, several phytochemicals present in honey—including flavonoids, catalase, and ascorbic acid—perform antioxidant functions. They also function as nonperoxide antibacterial factors, which may account for honey's antibacterial activity, even after inactivation of the glucose oxidase enzyme.[5]

Honey itself is not easily subject to bacterial activity. As a supersaturated solution of sugars, honey has a high osmotic pressure and low water activity (Aw) values, which range from approximately 0.5 (16% water) to 0.6 (18.3% water); most bacteria grow with an Aw between 0.94-0.99. The pH of honey ranges from 3.2-4.5, and this acidity also inhibits many bacterial pathogens. If honey is diluted by body fluids, however, its pH will increase, the osmolarity will decrease, and the acidity and osmolarity alone will no longer inhibit bacterial growth.

## In Vitro Assessment of Antibacterial Potency

In vitro experiments show that honey stimulates peripheral proliferation of B lymphocytes and T lymphocytes at concentrations of 0.1%. Honey also stimulates monocytes to release cytokines, tumor necrosis factor-alpha, IL-1, and IL-6, which activate immune responses to infection.[6,7]

Allen et al analyzed 345 samples of New Zealand honeys from 26 different floral sources and found greater than a 30-fold difference in the range of antibacterial activity.[8] Differences in floral origin and seasonal conditions are responsible for some variability. Studies have shown high antibacterial levels exist in a specific type of honey derived from the nectar of *Leptospermum scoparium*, locally known as the manuka bush, which grows uncultivated throughout New Zealand.[9]

Willex et al performed in vitro testing of the activity of a standardized New Zealand manuka honey of median antibacterial activity against seven species of bacteria, including clinical isolates of *S. aureus*, and found the minimal inhibitory concentration (MIC) ranged from 2% to 4%.[10] Cooper et al tested the antibacterial activity of the median manuka honey against 20 infected wound isolates of Pseudomonas and found the MIC to range from 5.5% to 9.0%.[11]

## Clinical Studies

Al-Waili et al performed a randomized controlled trial of 50 patients who had postoperative wound infections with gram-positive and gram-negative bacteria following cesarean section and hysterectomy.[12] Twenty-six patients had honey dressings applied to their wounds and 24 had their wounds washed with 70% ethanol followed by application of povidone-iodine. The honey-

treated group had complete healing with eradication of infection in less than half the time required by the antiseptic-treated group.

In two randomized clinical trials comparing the use of honey vs. silver sulfadiazine (SSD) gauze dressing in two groups of 52 patients[13] and SSD cream in two groups of 25 patients,[14] Subrahmanyam showed that honey was significantly superior to both SSD products in the treatment of superficial burn injuries with quicker wound sterilization, complete healing, and a lower incidence of hypertrophic scar and post-burn contracture. Allergic or other side effects were not observed. A major drawback of these studies was the lack of identification of floral source and antibacterial standardization of the honeys used.

Vardi et al performed an observational study of the effect of topical honey dressings in nine infants with large, infected, recalcitrant surgical wounds.[15] Marked improvement was seen in all cases within five days and all wounds were cleared within 21 days. Again, the study identified neither a floral source nor antibacterial standardization for the honey. In addition, the honey used was not sterilized with gamma-irradiation. This study reported no adverse effects in terms of electrolyte imbalances, hyperglycemia, local tissue irritation, or wound botulism.

**Formulation**

Since the glucose oxidase enzyme is both thermolabile and light-sensitive, the antibacterial properties of honey can be affected both by processing and storage conditions. Most commercial food honeys have not been standardized for antibacterial potency and, therefore, are not suitable for use as topical wound therapy.[16] Despite the fact that some unpasteurized floral types of honey in the United States have good antibacterial activity, commercial processing destroys this activity.

Honey intended for wound care is extracted and processed in facilities that use specialized machinery for filtering out small particulates such as pollen while exposing the honey to minimal heating to protect the heat-labile components. According to Molan et al, the honey is then gamma-irradiated, which effectively destroys any clostridial spores without compromising its antibacterial activity.[17]

**Safety Issues**

Like other natural products, the composition of honey is not constant. It often contains pollen particulates, bee parts, non-pathogenic *Bacillus* bacteria species, and, importantly, clostridial spores. Such spores, if ingested, can cause infant botulism or may be inoculated into a wound causing further damage.[18] The other particulates may cause granuloma formation if embedded in healing wounds. Honeys specifically formulated for wound care are commercially available and only these honeys should be used for this purpose.[19]

**Adverse Effects**

Both proteins derived from pharyngeal and salivary secretions of honeybees and pollen proteins contained in honey can cause allergic reactions. Therefore, persons with pollen and honey allergies should avoid the use of topical honey therapy for wounds.[20]

In papers describing the application of topical honey to open wounds, a few instances of a stinging sensation have been reported in a few instances, possibly secondary to the acidity of the honey after initial application. In general, however, the application of topical honey has been reported to be soothing and analgesic.[4] Honeys used for wound therapy should be gamma-irradiated to ensure sterilization of clostridial spores, which could, in theory, be responsible for wound botulism if inoculated into healing wounds.[15,17]

**Regulation**

In May 1999, the Therapeutic Goods Administration of Australia approved the use of Medihoney, which is 100% standardized manuka honey as a primary wound dressing.[21]

**Conclusion**

At the present time, in Australia and New Zealand, specific honey that has been found in laboratory testing to have high antibacterial potency is being marketed (in Australia, with medical approval) for topical wound care. Despite laboratory studies that document the bactericidal effects of a specific type of honey and favorable outcomes in several clinical studies in patients with recalcitrant wounds of various etiologies, the unselected, nonstandardized honeys used make the clinical data difficult to interpret and impossible to duplicate due to lack of documentation.

Though the laboratory investigations and the microbacteriologic sensitivities merit careful consideration of honey for use as a wound dressing, more clinical research with different honeys of standardized antibacterial potency needs to be performed to elucidate the patients and types of wounds that would benefit most from intervention with a particular honey.

**Recommendation**

Further in vitro testing is necessary to identify and standardize other types of honey with high antibacterial

and antioxidant potency. Such honey should be tested against currently used topical wound therapies in blinded, randomized, controlled trials in order to elucidate the most effective situations in which to use this dressing. Studies done to date do not support its general clinical use, but certain types of honey remain promising possibilities for future wound care treatment. ❖

*Dr. Marcolina is a board-certified internist and geriatrician in Issaquah, WA.*

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# Olive Leaf Extract for Hypertension

*By Georges Ramalanjaona, MD, DSc, MBA, FACEP*

OLIVE LEAF EXTRACT (OLE) HAS BEEN ASSOCIATED with many health-promoting benefits, including antihypertensive effects, for hundreds of years. However, successful identification of what appears to be the biological active component of OLE, oleuropein, has only been accomplished recently.[1] Recent development in clinical investigations of OLE was due to the structural changes to the molecule, which overcame the bioavailability problems seen earlier in humans.

This article reviews the available scientific evidence on the hypotensive role of OLE.

**Pharmacokinetics**

Oleuropein, the biologic active component responsible for the hypotensive action of OLE, is derived from the olive's leaves, buds, wood, fruit, and roots.[2,3] OLE contains 60-90 mg per gram (dry weight) of oleuropein, which in turn is hydrolyzed to the major biologically active molecules such as oleuropein aglycone and elenolic acid.

Oleuropein, a bitter glycoside that belongs to the iridoid group, is water soluble and unstable against acid. It appears that oleuropein has other cardiovascular effects unrelated to hypotensive action, including antioxidant

and antiarrhythmic properties, and improves coronary blood flow.[4]

**Mechanism of Action**

The specific pharmacological mechanisms of the cardiovascular effects of OLE remain unknown. Recently, Fehri et al demonstrated that OLE works on a biphasic mode (hypertensive and hypotensive) with two types of receptors: The first receptor has a high affinity for small concentrations of OLE, which leads to vasoconstriction, and the second receptor has a low affinity for high concentrations of OLE, which results in vasodilation.[5]

Phenolic compounds derived from leaves and olive trees have antioxidant properties. Recently, Le Tutour et al showed that extracts of olive tree leaf (containing 90% of oleuropein, 1.8 flavonoid glycosides) displayed more potent antioxidant activity than vitamin E.[6]

**Animal Studies**

Empirical data about the antihypertensive properties of OLE have been derived mainly from animal studies. This hypotensive action depends on the species of animal studied and dose of oleuropein used.

In a study of anesthetized cats, oleuropein at a dose of 30 mg/kg IV decreased blood pressure (BP) by an average of 36%; 20 mg/kg and 40 mg/kg doses decreased initial BP by 25% and 50%, respectively.[7] A hypotensive effect was seen at a dose of 30 mg/kg; initial BP decreased by 36% (average values from seven experiments). BP returned to its pretreatment value in 1-2 hours. The difference in rate of BP decrease between pretreatment and post-treatment at various doses was statistically significant.

In dogs with induced hypertension, oleuropein at a dose of 10 mg/kg IV decreased the systolic pressure by 62% and the diastolic pressure by 68%.[8] A three-fold increase in dose (30 mg/kg) decreased the systolic pressure by 61% and diastolic pressure by 73%. This difference in BP (systolic and diastolic) was statistically significant in both doses. Also, oleuropein given in successive days did not display any cumulative effect. Recovery of BP was seen in five hours.

Petkov et al observed that oleuropein at 3-50 mg/kg intraperitoneally (IP) caused a minimal increase in respiration rate in anesthetized cats.[7] In another study, the same authors were unable to determine oleuropein $LD_{50}$ in mice after a single dose ranging from 100 to 1,000 mg/kg IP; there were no deaths or side effects during seven days of post-treatment.

In conscious dogs with induced hypertension, a dose of 30 mg/kg IV of OLE for one month resulted in mild gastric irritation with gastric biopsy revealing small gastric erosion.[8]

**Clinical Studies**

Formal clinical trials of antihypertensive effects of OLE in humans are scarce. Most of the evidence of its clinical efficacy comes from case reports and clinical anecdotes provided by health practitioners and consumer letters received by manufacturers.[9] A limited number of open (uncontrolled) clinical trials have been conducted with OLE; however, results from these trials have not been published.

In a recent uncontrolled clinical trial of 30 primary hypertensive patients (ages 40-66 years; 16 males), Cherif et al used OLE (7.2% oleuropein) 400 mg qid for three months following a 15-day placebo period.[10] The investigators found a statistically significant decrease in both systolic and diastolic BP ($P < 0.001$) in the group with no prior treatment ($n = 12$) and the group with prior treatment ($n = 18$) when comparing initial values to post-treatment at days 30, 60, and 90. This effect began at 30 days post-treatment and BP steadily declined over a two-month period. Additionally, the authors did not report any side effect from OLE in either group.

**Adverse Effects**

In the sole clinical trial of OLE for hypertension treatment, authors did not find any side effects during a three-month period. Biological decrease of glycemia and calcemia were observed.

A "die-off" effect similar to the Herxheimer reaction is seen during OLE treatment of yeast infection.

**Contraindications and Precautions**

The effects of OLE in children and pregnant women are unknown. OLE can be irritating to the stomach and should be taken with meals. OLE can inactivate antibiotics and should not be taken concurrently with them. Patients who are taking warfarin should exercise caution when taking OLE since it may increase bleeding tendency.

**Formulation and Dosage**

Dried leaf extract containing 6-15% OLE is available commercially, but no standard formulation has been set. To make a tea infusion, 1 teaspoon of dry leaves is steeped in 1 cup of hot water for 10-15 minutes.

In the only human clinical trial for hypertension, OLE (7.2% oleuropein) was used at a dose of 400 mg qid for three months. The reported dosage of OLE in other unrelated trials was 500 mg PO tid.

## Conclusion

Animal studies demonstrate the hypotensive effectiveness of OLE.

Preliminary data from a single recent human trial on OLE's hypotensive action are encouraging. However, these results are insufficient to formulate a valid conclusion on its role as an antihypertensive agent at this time.

## Recommendation

OLE cannot be recommended as an antihypertensive agent. Final recommendations will await the results of future controlled trials. ❖

*Dr. Ramalanjaona is Associate Chairman for Academic Affairs, Department of Emergency Medicine, Seton Hall University, School of Graduate Medical Education, South Orange, NJ; and Director of Research, Division of Emergency Medicine, St. Michael's Hospital, Newark, NJ.*

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# *CME Questions*

**CME Instructions:** Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

**15. The current evidence suggests which of the following is the active component in St. John's wort?**
a. Hyperforin
b. Quercetin
c. Hypericin
d. Serotonin

**16. St. John's wort has been studied mostly for which condition?**
a. Psychotic depression
b. Seasonal affective disorder
c. Mild-to-moderate depression
d. Panic disorder
e. Anxious depression

**17. Which of the following drugs have been reported to have significant interactions with St. John's wort?**
a. Digoxin
b. Cyclosporine
c. Indinavir
d. Warfarin
e. All of the above

**18. Honey has been shown in clinical studies to:**
a. promote wound healing.
b. exacerbate wound healing in infants and children.
c. cause a buzzing sensation on application.
d. All of the above

**19. Honey contains clostridial spores.**
a. True
b. False

**20. The active compound in olive leaf extract (OLE) for hypertension is probably oleuropein.**
a. True
b. False

**Answer key:** 15. a, 16. c, 17. e, 18. a, 19. a, 20. a.

*With Comments from John La Puma, MD, FACP*

## Vitamin A and Fracture Risk

***Source:*** Michaelsson K et al. Serum retinol levels and the risk of fracture. *N Engl J Med* 2003;348:287-294.

ALTHOUGH STUDIES IN ANIMALS AND epidemiologic studies have indicated that a high vitamin A intake is associated with increased bone fragility, no biologic marker of vitamin A status has thus far been used to assess the risk of fractures in humans.

A total of 2,322 men, 49-51 years of age, were enrolled in a population-based, longitudinal cohort study. Serum retinol and beta-carotene were analyzed in samples obtained at enrollment. Fractures were documented in 266 men during 30 years of follow-up. Cox regression analysis was used to determine the risk of fracture according to the serum retinol level.

The risk of fracture was highest among men with the highest levels of serum retinol. Multivariate analysis of the risk of fracture in the highest quintile for serum retinol (> 75.62 micrograms per deciliter [2.64 micromoles per liter]) as compared with the middle quintile (62.16-67.60 micrograms per deciliter [2.17-2.36 micromoles per liter]) showed that the rate ratio was 1.64 (95% confidence interval, 1.12-2.41) for any fracture and 2.47 (95% confidence interval, 1.15-5.28) for hip fracture. The risk of fracture was further increased within the highest quintile for serum retinol. Men with retinol levels in the 99th percentile (> 103.12 micrograms per deciliter [3.60 micromoles per liter]) had an overall risk of fracture that exceeded the risk among men with lower levels by a factor of seven ($P < 0.001$). The level of serum beta-carotene was not associated with the risk of fracture.

These findings, which are consistent with the results of studies in animals, as well as in vitro and epidemiologic dietary studies, suggest that current levels of vitamin A supplementation and food fortification in many Western countries may need to be reassessed.

### COMMENT

In Sweden, hip fracture is more than twice as common among men than women. The authors postulate that serum retinol is a biological marker for fracture. Consuming more than 1.5 mg (4,500 IU) of vitamin A (retinyl palmitate) daily increased fracture risk.

What does vitamin A do? In premature and malnourished children it prevents some diseases of the eye, but in Western countries it appears to accelerate osteoporosis and promote bone fracture. The Harvard-based Nurses Health Study, of more than 70,000 nurses, found a similar association: Postmenopausal women whose daily intake of vitamin A exceeded 3,000 micrograms (about 10,000 IU) were 40% more likely to fracture a hip, compared with women whose daily intake was less than 1,250 micrograms (3,750 IU).

The therapeutic window of vitamin A is narrow and its serum levels increase with age. Editorialist Paul Lips writes, "One may conclude from such data that supplements containing vitamin A should not be routinely used by men or women and that fortification of cereals with vitamin A should be questioned."

Vitamin A is found in fatty fish, liver, kidney, and dairy products, and many are fortified with vitamin A, including milk and yogurt. Many processed cereals are augmented too. Beta-carotene and other carotenoids also are converted into vitamin A in the body, but these amounts are small relative to the direct intake and absorption of vitamin A.

How does fracture occur? Dietary vitamin A is converted to retinoic acid, which binds to specific receptors. In vitro, these receptors then curb osteoblast activity and encourage osteoclast formation. Osteoclasts take up old bone, and while this makes way for new bone, it also may cause susceptibility to fracture.

The Recommended Daily Intake for vitamin A is just 0.7 mg of vitamin A for women and 0.9 mg for men. Most multivitamins easily supply this—even twice this—on top of what people get from food.

What are the study's limitations? It followed 2,322 middle-aged men over 30 years, but blood levels of vitamin A were taken once, at the beginning of the trial. Vitamin A is stored in fat cells, like the other fat-soluble vitamins (D, E, and K), but one time measurements are just that. A study of this duration and power is unlikely to be repeated prospectively.

**Recommendation**

Vitamin A toxicity has been well known for decades: Administration as a dietary supplement to adults should be avoided. For this vitamin, what patients get from food is enough. Advise your patients to take a multivitamin that derives all of its vitamin A from beta-carotene; patients also should avoid eating liver and reconsider fish oil supplements. ❖

**In Future Issues:**

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# Herb-Drug Interactions: How to Identify a Problem and What to Do

THE FOOD AND DRUG ADMINISTRATION (FDA), AS WELL AS HEALTH CARE PROFESSIONALS AND organizations, receives many inquiries each year from consumers seeking health-related information, especially about herbal supplements. Clearly, people choosing to supplement their diets (with herbals, vitamins, minerals, or other substances) want to know more about the products they choose so that they can make informed decisions about them. The choice to use an herb can be a wise decision that provides health benefits. However, under certain circumstances, these products may be unnecessary for good health or they may even create unexpected risks.

## Assessing the clinical data

Given the abundance and conflicting nature of information now available about herbal supplements, you may need help to sort the reliable information from the questionable. In 2001, Fugh-Berman and Ernst reviewed the medical literature for herb-drug interactions, identifying 108 suspected cases of herb-drug interactions *(see Table 1)*. These authors also developed a 10-point scale to evaluate the quality of a case report *(see Table 2)*.

## When to suspect an herb-drug interaction

Surveys of patients with chronic conditions indicate their willingness to explore alternative therapies. Unfortunately, because they usually take medication to treat their conditions,

**Table 1**

### Herb-drug interaction data

- 108 cases of suspected herb-drug interactions
- 68.5% did not contain enough information to be evaluated
- 13% were well documented and likely were interactions
- 18.5% were considered to be possible interactions
- Warfarin was the most commonly involved drug
- St. John's wort was the the most commonly involved herb
  - 85 case reports
  - 54 (63.5%) with cyclosporin
  - 12 with oral contraceptives
  - 7 with warfarin
  - 9 with antidepressants
  - 7 case reports were considered well documented

***Adapted from:*** Fugh-Berman A, Ernst E. Herb-drug interactions: Review and assessment of report reliability. *Br J Clin Pharmacol* 2001;52:587-595.

**Table 2**

### 10-point scale for reliable reporting of an herb-drug interaction

**Criteria:**

A point is given for each of the following criteria:

- Adequate patient history given
- Concurrent diseases, conditions, or medications associated with the adverse event
- Concomitant medications documented
- Adequate description of interactors
- Obvious alternative explanations have been excluded
- Chronology complete
- Time between taking herb and adverse event manifesting itself is reasonable
- Adverse event is adequately described
- Event ceases when herb stopped
- Event recurs upon rechallenge

**Scale:**

0-3 points: unevaluable—report contains insufficient information to determine the likelihood of an interaction

4-7 points: possible interaction—evidence points to an interaction, but other causes may be involved

8-10 points: likely interaction—report provides reliable evidence for an interaction

***Adapted from:*** Fugh-Berman A, Ernst E. Herb-drug interactions: Review and assessment of report reliability. *Br J Clin Pharmacol* 2001;52:587-595.

these patients are at increased risk of an adverse effect when taking herbal remedies. Tables 3 and 4 list common signs of an herb-drug interaction and the circumstances in which a serious interaction can occur.

**Table 3**

### When to suspect an herb-drug interaction

- When the condition of a previously stable patient suddenly changes (for better or for worse)
- When a new herb or herbal preparation is added to a regimen
- When previously effective medication becomes less effective
- When the dose of medication must be increased to maintain therapeutic effect

**Table 4**

### Circumstances in which a serious herb-drug interaction can occur

- When using a narrow therapeutic index drug such as digitalis or warfarin
- When treating any serious medical condition
- If the herb and the drug are both metabolized via the hepatic cytochrome P450 system
- If the patient has a medical condition, such as liver or kidney disease, that affects the utilization, absorption, metabolism, or elimination of drugs and pharmacologically active herbal constituents
- If the herb contains potent constituents such as alkaloids or cardioactive glycosides
- If the herb affects blood sugar
- If the herb affects platelet function

**Table 5**

### What to do if you suspect an herb-drug interaction

- Question the patient in a non-judgmental way
- Discontinue use of the herb
- Consider adjusting the dose of the drug and monitor the patient closely
- Collect a sample of the material the patient was taking
- Submit the material for analysis if possible
- Make a report to the Food and Drug Administration MedWatch program (www.fda.gov/medwatch/how.htm, or call (800-FDA-1088)

**Reporting adverse events**

If you believe an adverse event is related to the use of any dietary supplement product, contact the FDA's MedWatch program by phone (800) FDA-1088, fax (800) FDA-0178, or on-line : www.fda.gov/medwatch/how.htm.

Table 5 outlines several steps you should consider if you suspect an herb-drug interaction.

***Source:*** Food and Drug Administration. Available at: www.cfsan.fda.gov/~dms/ds-savvy.html.