Hypericum perforatum (St. John's Wort) Indena photo

Hypericum perforatum

Description

Hypericum perforatum L. (St. John's wort) is a five-petalled, yellow-flowered perennial weed common to the western United States, Europe, and Asia.[1] Close examination of the flowers reveals small black dots that, when rubbed between the fingers, produce a red stain. This red pigment contains the constituent hypericin. Held up to light, the leaves of the plant display a number of bright, translucent dots. This perforated look led to the species name perforatum. The plant is currently cultivated in Europe, North and South America, Australia, and China.[2] The aerial parts of the plant are harvested during the flowering season and used in modern, standardized extracts.

Dioscorides, the foremost physician of ancient Greece, as well as Pliny and Hippocrates, recommended the herb for a host of ailments including sciatica and poisonous bites. The name St. John's wort has its origin in Christian folk tradition. St. John's wort has a long history of use in traditional European herbal medicine. It was, and continues to be, used as a topical treatment for wounds and burns. It has also been used as a folk remedy for kidney, stomach, and lung ailments, and was first noted as a remedy for melancholy and madness by Culpeper in 1652.[3]

Active Constituents

St. John's wort has a complex and diverse chemical makeup. Constituents include volatile oils (0.05 to 0.3%, including α-pinene, and cineole), anthraquinones, carotenoids, cumarine, flavonoids (0.5-1.0%, including hyperoside, quercetin, and rutin), naphthodianthrones (0.1-0.3% of which 80-90% are hypericin and pseudohypericin), carbolic acids, phloroglucins (up to 3% hyperforin), xanthones, and proanthocyanidins.[1] The naphthodianthrones hypericin and pseudohypericin previously received most of the attention in pharmacological studies. This is based on their contributions to the antiviral properties of the plant as well as speculation (based on early *in vitro* data) that they may also contribute to the plant's antidepressant actions.[4] This may partially explain why many extracts continue to be standardized to contain measured amounts of hypericin. Recent research, however, indicates that other constituents such as hyperforin,[5,6] and possibly flavonoid compounds, may also contribute to the antidepressant actions of the plant.

Mechanisms of Action

A number of proposed mechanisms exist for St. John's wort's antidepressant effect, involving several neurotransmitters and hormones. Initially, inhibition of monoamine oxidase (MAO) was believed to be the primary mode of action,[7] and was thought to be due primarily to hypericin.[8] More recent research indicates constituents of St. John's wort exert MAO inhibition only at concentrations higher than those typically found in commercially available extracts.[9,10]

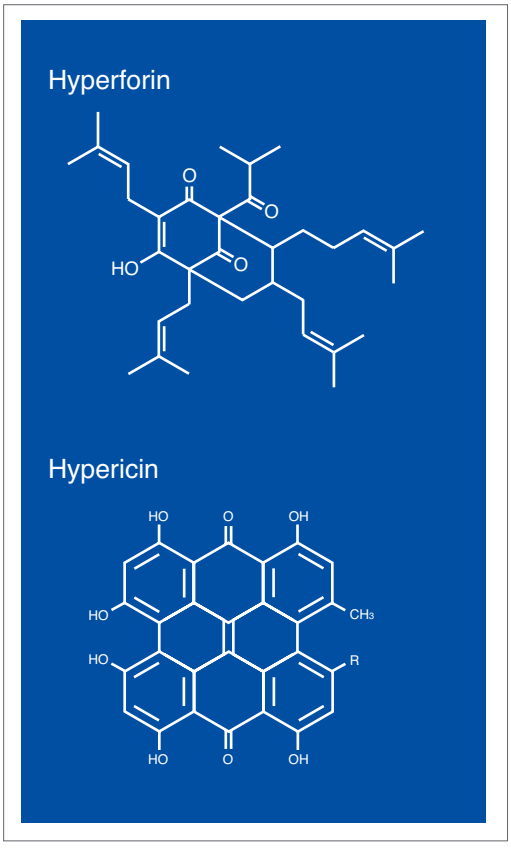
Attention over the past few years has shifted to the ability of St. John's wort and the constituent hyperforin to inhibit synaptosomal reuptake of serotonin, norepinephrine, and dopamine.[11,12] Two human pharmacological studies demonstrating an increase in cortisol levels following administration of two different St. John's wort extracts have recently been reported to support this proposed mechanism of action.[13,14] Although this has been the topic of much debate among European researchers, it has led to some commercial extracts providing standardized amounts (3-5%) of hyperforin.

Hyperforin has also been shown to have antimicrobial activity against gram-positive bacteria and numerous viruses. This property is likely attributed to the essential oils, phloroglucinols, and flavonoid constituents, and may involve a photoactivation process that disrupts certain components of the organism's cell membrane.[15,16] The antitumor properties of St. John's wort are attributed to hypericin, which is a powerful photosensitizer. Once taken up by tumor cells, hypericin reacts in the presence of oxygen and activates multiple apoptosis pathways that results in malignant cell death.[17,18]

Clinical Indications

Depression

A meta-analysis published in 1996 of 23 studies involving over 1,500 individuals found significantly positive responses to St. John's wort based on analysis of the Hamilton Depression Scale (HAMD) before and after treatment.[19] This was supported by a more recent meta-analysis covering clinical trials published through 2000.[20] In 2000, the *Annals of Internal Medicine* featured a two-part overview and critique of newer drug therapies for depression and dysthymia (a chronic but milder form of depression), and included St. John's wort as a potential treatment for both conditions.[21,22] Both reviews conclude St. John's wort is more effective than placebo for the treatment of mild-to-moderate depression and less likely to cause side effects than commonly prescribed antidepressants.



The 2000 meta-analysis of St. John's wort clinical trials lists 16 placebo-controlled trials on persons with mild-to-moderate depression.[20] These studies lasted from four to 12 weeks, with doses varying between 500-900 mg per day. Many of these trials were completed using 300 mg of the LI 160 extract (standardized to 0.3% hypericin) three times daily.[22-25] A significant decrease in HAMD scores compared to placebo was found in all trials. Similar results have been noted for an extract designated ZE 117,[26] as well as standardized Hypericum extracts with the designations WS 5570 and WS 5572.[27,28] A phase III clinical trial utilizing the WS 5570 extract included 375 patients with major depression, and demonstrated efficacy and safety superior to placebo when the extract was dosed at 900 mg daily for six weeks. This contradicts the results of an earlier well-known study published in *JAMA* that demonstrated 900-1200 mg St. John's wort daily was ineffective in treating severe depression.[29]

At least 12 clinical trials have compared St. John's wort directly to prescription antidepressants, including imipramine, amitriptyline, and fluoxetine, in persons with mild-to-moderate depression.[20] Earlier clinical trials comparing 900 mg St. John's wort daily with imipramine (75 mg daily) or amitriptyline (75 mg daily) in patients with mild-to-moderate depression found St. John's wort extract (LI 160) to be equally effective in lowering HAMD scores, with fewer side effects.[30,31] However, these trials have been criticized due to the low dose of the standard antidepressant and lack of a placebo group. One trial comparing 1,050 mg St. John's wort daily with 100 mg imipramine daily or placebo did find St. John's wort was safe and effective in treating mild-to-moderate depression.[32] More recently, in a six-week clinical trial (no placebo arm), 500 mg of the ZE 117 extract was as effective as 150 mg of imipramine.[33]

Two double-blind, randomized trials (with no placebo arm) suggest 500 mg[34] or 800 mg[35] St. John's wort daily is as effective as 20 mg/day of fluoxetine (Prozac®). Both trials lasted six weeks and found patients taking St. John's wort reported fewer side effects. More recently, two similar trials demonstrated Hypericum extract to be 83-percent as effective as fluoxetine therapy in one study[36] and equally effective (100%) as fluoxetine therapy in the other.[37] Dosages of Hypericum extract ranged from 300-500 mg daily; fluoxetine dosage in both studies was 20 mg daily. In these two studies adverse effects in the St. John's wort group were significantly fewer or equal to fluoxetine adverse effects.[36,37]

A small, seven-week pilot study found St. John's wort (900 mg/day) to be as effective as 75 mg sertraline (Zoloft®) daily.[38] In a larger (340 participants) eight-week trial, St. John's wort was compared to sertraline or placebo for major depression. A high placebo response was observed, and neither St. John's wort extract nor sertraline were significantly more effective than placebo.[39] A randomized, double-blind study of 87 patients with major depression compared sertraline and St. John's wort at similar doses to previous trials, but was extended to 12 weeks. Despite the longer treatment period and slightly higher doses than used in the eight-week trial, researchers failed to demonstrate any significant differences in HAMD or Beck Depression Inventory scores between the drug and St. John's wort groups at the end of 12 weeks. As noted in other studies comparing St. John's wort to antidepressant drugs, fewer side effects were reported in the St. John's wort group.[40]

Treating depression in children often presents a significant challenge and, unfortunately, conventional antidepressants are often not well tolerated in this population due to myriad side effects involved. For this reason, St. John's wort has been investigated as a possible alternative to antidepressants because of its superior safety profile. In a study of 92 pediatric outpatients (ages 1-12 years) given 300-1800 mg (at physician's discretion) St. John's wort for 4-6 weeks, a significant improvement in symptomatology was observed. Independent physician and parental assessment of symptomatology in treated children revealed a perceived 72-percent improvement after two weeks and as high as 100-percent symptom improvement after six weeks.[41] A 2003, open-label pilot study of 33 children (ages 6-16) diagnosed with major depressive disorder demonstrated 450-900 mg St. John's wort for eight weeks was an effective treatment as evidenced by 75 percent of patients (n=25) meeting response criteria at the end of eight weeks. Few side effects were observed and were only mild in nature.[42]

Seasonal Affective Disorder

A small pilot study and a larger open-label study suggested patients suffering from seasonal affective disorder (SAD) may benefit from taking 300 mg St. John's wort extract three times daily for eight weeks.[43,44] Placebo-controlled trials are needed to confirm the efficacy of St. John's wort for SAD.

Cancer

In the development of new cancer therapies, significant antitumor activity without toxicity is the goal. In the case of plant-derived antitumor agents, an abundant supply of the plant is also a prerequisite. St. John's wort appears to satisfy both criteria, as it grows abundantly in

Europe, North America, North Africa, and Asia, and has an excellent safety profile with minimal side effects. The Hypericum constituent, hypericin, is a powerful photosensitizing agent and its use in photodynamic therapy for cancer patients has gained the attention of researchers for over a dozen years. Numerous *in vitro* studies[18,19,45,46] have investigated its effect on various cell lines. These studies all demonstrate hypericin's cytotoxic effect on tumor cells after photosensitization.

Hyperforin has also been investigated in animals and *in vitro* studies for its antitumor effects. Schempp et al found hyperforin dose-dependently inhibited the growth *in vitro* of rat and human mammary cancer, as well as squamous cell carcinoma, malignant melanoma, and lymphoma better than or equal to other cytostatic drugs tested, including camptothecin, paclitaxel, and vincristine. The data revealed hyperforin appears to induce tumor cell apoptosis via activation of mitochondria, release of cytochrome c, and caspase activation, which all in turn trigger cell death pathways. Further research in this area is indicated.[47]

Alcoholism

Because of its efficacy in treating depression and the fact that both depression and alcoholism have common neurochemical substrates, St. John's wort has been investigated for its potential therapeutic benefit in three rat models of alcoholism. In all three models Hypericum extract dose-dependently reduced voluntary alcohol intake to a significant degree. Due to its success in treating depression in humans, further research on Hypericum's use in treating alcoholism in humans seems warranted.[48]

Somatoform Disorders

A multi-center, randomized, placebo-controlled trial compared the efficacy of St. John's wort to placebo in 151 outpatients suffering from somatization disorder or somatoform autonomic dysfunctions. Hypericum extract was dosed at 600 mg daily and outcome was measured with the Hamilton Anxiety Scale. The Hypericum extract LI 160 was significantly more effective than placebo at reducing anxiety and somatoform complaints. Eighty-one percent of patients in the treatment group were considered improved as compared to 50 percent in the placebo group. Tolerability was excellent.[49]

Wound Healing

St. John's wort has long been used successfully as a remedy for wound healing, and research in humans supports its effectiveness in this arena. A study of 24 female patients who recently had caesarean sections during childbirth examined the use of a combination oil-extract of Calendula and Hypericum oils in healing the incision site. Incisions of women in the treatment group were treated topically with an oily mixture of 70-percent Hypericum extract and 30-percent Calendula extract. The second group of patients acted as placebo and were given a wheat germ oil extract. All patients were treated twice daily for 16 days and Surface Perimeter Area (SPA) of the surgical wound was measured before and after treatment. Patients treated with the Hypericum/Calendula mixture exhibited a significant decrease (approximately 38%) in the SPA of the surgical wound compared to patients in the placebo group (approximately 16%).[50]

Drug-Botanical Interactions

Concomitant use of St. John's wort extract with selective serotonin reuptake inhibitors (SSRIs) has resulted in serotonin syndrome in two previous case reports[51,52] and was reported in two individuals in a report on the safety and efficacy of St. John's wort based on a local survey completed by the University of Missouri.[53]

Case reports and pharmacological and clinical studies have indicated St. John's wort may reduce serum levels of the following drugs: indinavir, cyclosporine, theophylline, digoxin, warfarin, and oral birth control pills.[54-61] The most direct effects on serum levels in patients taking St. John's wort have been found with cyclosporine[56-58] and indinavir.[54] Patients taking these medications should avoid concomitant use of St. John's wort. Research in humans has demonstrated St. John's wort causes induction of the cytochrome P450 isoenzyme CYP3A4 and may affect the metabolism of any drugs metabolized via this enzyme system.[61-63]

Clinical studies examining the effects of St. John's wort on drug metabolism have found it also affects the hepatic metabolism of the cholesterol-lowering drugs simvastatin and pravastatin,[64] omeprazole (a proton pump inhibitor),[65] irinotecan (a chemotherapeutic agent),[66] tacrolimus (an immunosuppressant prescribed to prevent transplant rejection),[67] verapamil (an anti-hypertensive agent),[68] and methadone[69] (used to modulate withdrawal symptoms in addicts). Additional studies support earlier information that St. John's wort induction of the CYP3A4 enzyme system affects the metabolism of theophylline[70] and oral contraceptives.[71,72]

Side Effects and Toxicity

In a drug-monitoring study of 3,250 patients taking 900 mg/day of St. John's wort, adverse events were reported in 2.4 percent of subjects, the most common being gastrointestinal irritation, restlessness, fatigue, and allergic skin reactions.[73]

St. John's wort may cause the skin and eyes to become photosensitive.[74] There is a case report of a woman experiencing neuropathy (nerve injury and pain) in sun-exposed skin areas after taking 500 mg of whole St. John's wort for four weeks.[75] However, one pharmacological study found doses as high as 3,600 mg (11.25 mg of hypericin) did not increase photosensitivity.[76] A later randomized trial of 72 patients also demonstrated a single dose (1,800 mg daily) of Hypericum extract LI 160 did not support evidence for a phototoxic effect.[77] Fair-skinned individuals should take precautions when exposed to the sun while taking St. John's wort. It is advisable that elderly people taking St. John's wort use protective eyewear when exposed to the sun. Although the German Commission E lists no contraindications to use of St. John's wort during pregnancy or lactation,[78] this statement appears to be based more on historical use than actual safety studies. One prospective study of 33 breast-feeding women and disease- and age-matched controls demonstrated taking St. John's wort did not affect milk production or infant weight or growth.[79]

Patients taking St. John's wort as an antidepressant should be closely questioned about any history of bipolar disorder. There have been several case reports of St. John's wort causing mania in patients with this history.[80-83] Case reports and clinical trials have linked St. John's wort to elevated blood pressure,[84] hypothyroidism (elevated TSH levels),[85] and stimulation of secretion of adrenal corticotropic hormone and growth hormone.[86]

Dosage

Typical daily dosages of standardized St. John's wort extracts range from 500 to 1,050 mg for the treatment of mild-to-moderate depression. The dose is typically divided into two or three doses throughout the day. It may take 2-4 weeks to notice clinical results.

References

1. Wichtl M. *Herbal Drugs and Phytopharmaceuticals*. Boca Raton, FL: CRC Press; 1994:273-275.
2. Blumenthal M, Goldberg A, Brinckmann J, eds. *Herbal Medicine: Expanded Commission E Monographs*. Newton, MA: Integrative Medicine Communications; 2000:359-366.
3. Culpeper N. *The English Physician, or an Astrologo-physical Discourse on the Vulgar Herbs of this Nation*. London, England: Nathanial Brook; 1652.
4. Schulz V, Hansel R, Tyler VE. *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine*. Berlin, Germany: Springer-Verlag; 2001:57-77.
5. Chatterjee SS, Bhattacharya SK, Wonnemann M, et al. Hyperforin as a possible antidepressant component of Hypericum extracts. *Life Sci* 1998;63:499-510.
6. Muller WE, Singer A, Wonnemann M. Hyperforin – antidepressant activity by a novel mechanism of action. *Pharmacopsychiatry* 2001;34:S98-S102.
7. Suzuki O, Katsumata Y, Oya M, et al. Inhibition of monoamine oxidase by hypericin. *Planta Med* 1984;50:272-274.
8. Holzl J, Demisch L, Gollnik B. Investigations about antidepressive and mood changing effects of *Hypericum perforatum*. *Planta Med* 1989;55:643.

9. Bladt S, Wagner H. Inhibition of MAO by fractions and constituents of Hypericum extract. *J Geriatr Psychiatry Neurol* 1994;7:S57-S59.
10. Thiede HM, Walper A. Inhibition of MAO and COMT by Hypericum extracts and hypericin. *J Geriatr Psychiatry Neurol* 1994;7:S54-S56.
11. Muller WE, Rolli M, Schafer C, Hafner U. Effects of Hypericum extract (LI 160) in biochemical models of antidepressant activity. *Pharmacopsychiatry* 1997;30:S102-S107.
12. Muller WE, Singer A, Wonnemann M, et al. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of Hypericum extract. *Pharmacopsychiatry* 1998;31:S16-S21.
13. Schule C, Baghai T, Ferrera A, Laakmann G. Neuroendocrine effects of Hypericum extract WS 5570 in 12 healthy male volunteers. *Pharmacopsychiatry* 2001;34:S127-S133.
14. Franklin M, Cowen PJ. Researching the antidepressant actions of *Hypericum perforatum* (St. John's wort) in animals and man. *Pharmacopsychiatry* 2001;34:S29-S37.
15. Weber ND, Murray BK, North JA, Wood SG. The antiviral agent hypericin has *in vitro* activity against HSV-1 through non-specific association with viral and cellular membranes. *Antivir Chem Chemother* 1994;5:83-90.
16. Lenard J, Rabson A, Vanderoef R. Photodynamic inactivation of infectivity of human immunodeficiency virus and other enveloped viruses using hypericin and rose Bengal: inhibition of fusion and syncytia formation. *Proc Natl Acad Sci U S A* 1993;90:158-162.
17. Thomas C, MacGill RS, Miller GC, Pardini RS. Photoactivation of hypericin generates singlet oxygen in mitochondria and inhibits succinoxidase. *Photochem Photobiol* 1992;55:47-53.
18. Hadjur C, Richard MJ, Parat MO, et al. Photodynamically induced cytotoxicity of hypericin dye on human fibroblast cell line MRC5. *J Photochem Photobiol Biol B* 1995;27:139-146.
19. Linde K, Ramirez G, Mulrow C, et al. St. John's wort for depression – an overview and meta-analysis of randomized clinical trials. *BMJ* 1996;313:253-261.
20. Kasper S. *Hypericum perforatum* – a review of clinical studies. *Pharmacopsychiatry* 2001;34:S51-S55.
21. Snow V, Lascher S, Mottur-Pilson C. Pharmacologic treatment of acute major depression and dysthymia. American College of Physicians-American Society of Internal Medicine. *Ann Intern Med* 2000;132:738-742.
22. Williams JW Jr, Mulrow CD, Chiquette E, et al. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. *Ann Intern Med* 2000;132:743-756.
23. Sommer H, Harrer G. Placebo-controlled double-blind study examining the effectiveness of a Hypericum preparation in 105 mildly depressed patients. *J Geriatr Psychiatry Neurol* 1994;7:S9-S11.
24. Hansgen KD, Vesper J, Ploch M. Multicenter double-blind study examining the antidepressant effectiveness of the Hypericum extract LI 160. *J Geriatr Psychiatry Neurol* 1994;7:S15-S18.
25. Montgomery SA, Hubner WD, Grigoleit HG. Efficacy and tolerability of St. John's wort extract compared with placebo in patients with mild to moderate depressive disorder. *Phytomedicine* 2000;7:S107.
26. Schrader E, Meier B, Brattsrom A. Hypercium treatment of mild-moderate depression in a placebo-controlled study. A prospective, double-blind, randomized, placebo-controlled, multicenter study. *Hum Psychopharmacol* 1998;13:163-169.
27. Lecrubier Y, Clerc G, Didi R, Kieser M. Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. *Am J Psychiatry* 2002;159:1361-1366.
28. Kalb R, Trautmann-Sponsel RD, Kieser M. Efficacy and tolerability of Hypericum extract WS 5572 versus placebo in mildly to moderately depressed patients. A randomized double-blind multicenter clinical trial. *Pharmacopsychiatry* 2001;34:96-103.
29. Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St. John's wort in major depression: a randomized controlled trial. *JAMA* 2001;285:1978-1986.
30. Vorbach EU, Hubner WD, Arnoldt KH. Effectiveness and tolerance of the Hypericum extract LI 160 in comparison with imipramine: randomized double-blind study with 135 outpatients. *J Geriatr Psychiatry Neurol* 1994;7:S19-S23.
31. Wheatley D. LI 160, an extract of St. John's wort, versus amitriptyline in mildly to moderately depressed outpatients – a controlled 6-week clinical trial. *Pharmacopsychiatry* 1997;30:S77-S80.
32. Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *BMJ* 1999;319:1534-1538.

33. Woelk H. Comparison of St. John's wort and imipramine for treating depression: randomised controlled trial. *BMJ* 2000;321:536-539.
34. Schrader E. Equivalence of St. John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol* 2000;15:61-68.
35. Harrer G, Schmidt U, Kuhn U, Biller A. Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. *Arzneimittelforschung* 1999;49:289-296.
36. Behnke K, Jensen GS, Graubaum HJ, Gruenwald J. *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression. *Adv Ther* 2002;19:43-52.
37. Friede M, Henneicke von Zepelin HH, Freudenstein J. Differential therapy of mild to moderate depressive episodes (ICD-10 F 32.0; F 32.1) with St. John's wort. *Pharmacopsychiatry* 2001;34:S38-S41.
38. Brenner R, Azbel V, Madhusoodanan S, Pawlowska M. Comparison of an extract of Hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. *Clin Ther* 2000;22:411-419.
39. Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St. John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002;287:1807-1814.
40. van Gurp G, Meterissian GB, Haiek LN, et al. St. John's wort or sertraline? Randomized controlled trial in primary care. *Can Fam Physician* 2002;48:905-912.
41. Hubner WD, Kirste T. Experience with St. John's wort (*Hypericum perforatum*) in children under 12 years with symptoms of depression and psychovegetative disturbances. *Phytother Res* 2001;15:367-370.
42. Findling RL, McNamara NK, O'Riordan MA, et al. An open-label pilot study of St. John's wort in juvenile depression. *J Am Acad Child Adolesc Psychiatry* 2003;42:908-914.
43. Kasper S. Treatment of seasonal affective disorder (SAD) with Hypericum extract. *Pharmacopsychiatry* 1997;30:S89-S93.
44. Wheatley D. Hypericum in seasonal affective disorder (SAD). *Curr Med Res Opin* 1999;15:33-37.
45. Thomas C, Pardini RS. Oxygen dependence of hypericin-induced phototoxicity to EMT6 mouse mammary carcinoma cells. *Photochem Photobiol* 1992;55:831-837.
46. Vandenbogaerde AL, Delaey EM, Vantieghem AM, et al. Cytotoxicity and antiproliferative effect of hypericin and derivatives after photosensitization. *Photochem Photobiol* 1998;67:119-125.
47. Schempp CM, Kirkin V, Simon-Haarhaus B, et al. Inhibition of tumour cell growth by hyperforin, a novel anticancer drug from St. John's wort that acts by induction of apoptosis. *Oncogene* 2002;21:1242-1250.
48. Overstreet DH, Keung WM, Rezvani AH, et al. Herbal remedies for alcoholism: promises and possible pitfalls. *Alcohol Clin Exp Res* 2003;27:177-185.
49. Volz HP, Murck H, Kasper S, Moller HJ. St. John's wort extract (LI 160) in somatoform disorders: results of a placebo-controlled trial. *Psychopharmacology (Berl)* 2002;164:294-300.
50. Lavagna SM, Secci D, Chimenti P, et al. Efficacy of Hypericum and Calendula oils in the epithelial reconstruction of surgical wounds in childbirth with caesarean section. *Farmaco* 2001;56:451-453.
51. Demott K. St. John's wort tied to serotonin syndrome. *Clin Psychiatry News* 1998;26:28.
52. Gordon JB. SSRIs and St. John's wort: possible toxicity? *Am Fam Physician* 1998;57:950,953.
53. Beckman SE, Sommi RW, Switzer J. Consumer use of St. John's wort: a survey on effectiveness, safety, and tolerability. *Pharmacotherapy* 2000;20:568-574.
54. Piscitelli SC, Burstein AH, Chaitt D, et al. Indinavir concentrations and St. John's wort. *Lancet* 2000;355:547-548.
55. Ruschitzka F, Meier PJ, Turina M, et al. Acute heart transplant rejection due to Saint John's wort. *Lancet* 2000;355:548-549.
56. Breidenbach T, Hoffmann MW, Becker T, et al. Drug interaction of St. John's wort with cyclosporin. *Lancet* 2000;355:1912.
57. Karliova M, Treichel U, Malago M, et al. Interaction of *Hypericum perforatum* (St. John's wort) with cyclosporin A metabolism in a patient after liver transplantation. *J Hepatol* 2000;33:853-855.
58. Barone GW, Gurley BJ, Ketel BL, et al. Drug interaction between St. John's wort and cyclosporine. *Ann Pharmacother* 2000;34:1013-1016.
59. Johne A, Brockmoller J, Bauer S, et al. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther* 1999;66:338-345.
60. Roby CA, Anderson GD, Kantor E, et al. St. John's wort: effect on CYP3A4 activity. *Clin Pharmacol Ther* 2000;67:451-457.

61. Markowitz JS, DeVane CL, Boulton DW, et al. Effect of St. John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. *Life Sci* 2000;66:PL133-PL139.
62. Wang Z, Gorski JC, Hamman MA, et al. The effects of St. John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001;70:317-326.
63. Bauer S, Stormer E, Kerb R, et al. Differential effects of Saint John's wort (*Hypericum perforatum*) on the urinary excretion of D-glucaric acid and 6beta-hydroxycortisol in healthy volunteers. *Eur J Clin Pharmacol* 2002;58:581-585.
64. Sugimoto K, Ohmori M, Tsuruoka S, et al. Differential effects of St. John's wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* 2001;70:518-524.
65. Wang LS, Zhou G, Zhu B, et al. St. John's wort induces both cytochrome P450 3A4 – catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. *Clin Pharmacol Ther* 2004;75:191-197.
66. Mathijssen RH, Verweij J, de Bruijn P, et al. Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002;94:1247-1249.
67. Hebert MF, Park JM, Chen YL, et al. Effects of St. John's wort (*Hypericum perforatum)* on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2004;44:89-94.
68. Tannergren C, Engman H, Knutson L, et al. St. John's wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. *Clin Pharmacol Ther* 2004;75:298-309.
69. Eich-Hochli D, Oppliger R, Golay KP, et al. Methadone maintenance treatment and St. John's wort – a case report. *Pharmacopsychiatry* 2003;36:35-37.
70. Morimoto T, Kotegawa T, Tsutsumi K, et al. Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. *J Clin Pharmacol* 2004;44:95-101.
71. Pfrunder A, Schiesser M, Gerber S, et al. Interaction of St. John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br J Clin Pharmacol* 2003;56:683-690.
72. Hall SD, Wang Z, Huang SM, et al. The interaction between St. John's wort and an oral contraceptive. *Clin Pharmacol Ther* 2003;74:525-535.
73. Woelk H, Burkhard G, Grunwald J. Benefits and risks of the Hypericum extract LI 160: drug monitoring study with 3250 patients. *J Geriatr Psychiatry Neurol* 1994;7:S34-S38.
74. Lane-Brown MM. Photosensitivity associated with herbal preparations of St. John's wort *(Hypericum perforatum). Med J Aust* 2000;172:302.
75. Bove GM. Acute neuropathy after exposure to sun in a patient treated with St John's wort. *Lancet* 1998;352:1121-1122.
76. Brockmoller J, Reum T, Bauer S, et al. Hypericin and pseudohypericin: pharmacokinetics and effects on photosensitivity in humans. *Pharmacopsychiatry* 1997;30:S94-S101.
77. Schempp CM, Winghofer B, Muller K, et al. Effect of oral administration of *Hypericum perforatum* extract (St. John's wort) on skin erythema and pigmentation induced by UVB, UVA, visible light and solar stimulated radiation. *Phytother Res* 2003;17:141-146.
78. Blumenthal M, Busse WR, Goldberg A, et al, eds. *The Complete Commission E Monographs*. Boston, MA: Integrative Medicine Communications; 1998:214-215.
79. Lee A, Minhas R, Matsuda N, et al. The safety of St. John's wort (*Hypericum perforatum*) during breastfeeding. *J Clin Psychiatry* 2003;64:966-968.
80. Nierenberg AA, Burt T, Matthews J, Weiss AP. Mania associated with St. John's wort. *Biol Psychiatry* 1999;46:1707-1708.
81. Moses EL, Mallinger AG. St. John's wort: three cases of possible mania induction. *J Clin Psychopharmacol* 2000;20:115-117.
82. O'Breasail AM, Argouarch S. Hypomania and St. John's wort. *Can J Psychiatry* 1998;43:746-747.
83. Schneck C. St. John's wort and hypomania. *J Clin Psychiatry* 1998;59:689.
84. Zullino D, Borgeat F. Hypertension induced by St. John's wort – a case report. *Pharmacopsychiatry* 2003;36:32.
85. Ferko N, Levine MA. Evaluation of the association between St. John's wort and elevated thyroid-stimulating hormone. *Pharmacotherapy* 2001;21:1574-1578.
86. Schule C, Baghai T, Sauer N, Laakmann G. Endocrinological effects of high-dose *Hypericum perforatum* extract WS 5570 in healthy subjects. *Neuropsychobiology* 2004;49:58-63.