

St. John's Wort (*Hypericum perforatum*)

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General Features

St. John's wort is a perennial plant that is common to Europe and the United States (especially abundant in northern California and southern Oregon). It derives its unusual name from the fact that it tends to flower around the feast of St John. In Old English, a plant was known as a "wort", hence the name St. John's wort. The plant has a notable reputation throughout history as a treatment for emotional and nervous disorders. In the early 1900's, German researchers began studying St. John's wort, seeking to identify the physiological mechanisms through which it imparts its antidepressant effects.^{1,12,13} As such, it has received a great deal of attention from the research community during the last century, making it one of the best-documented herbal agents. In Germany, St. John's wort is the most commonly prescribed antidepressant, and is covered by the national health-care system for this application.¹² An abundance of evidence exists to support the use of St John's wort in cases of mild to moderate depression.^{1,12,13,14} Studies indicate that a standardized grade of this herbal product is at least as effective as any other type of antidepressant medication, and in general, produces fewer and milder side effects.¹² However, in cases of severe depression (major depression), where patients may feel suicidal, are unable to cope with daily life, or feel paralyzed by anxiety, and/or are incapable of getting out of bed, unable to sleep, uninterested in eating, St John's wort is not an appropriate intervention. These cases require the attention of a trained specialist, possibly hospitalization, and it should be noted that St. John's wort has been shown to be ineffective in trials involving this type of severely depressed patient. Furthermore, other medications (e.g., imipramine) have been shown to be effective in these cases, and may be required in order to save the person's life.^{12,15} In North America, the medical profession does not commonly recommend or prescribe St. John's wort for mild to moderate depression, but rather rely on a variety of other drugs such as serotonin reuptake inhibitors, tricyclic antidepressants and MAO-inhibitors. It should be acknowledged that it is unsafe to use St John's wort in conjunction with any other antidepressant drug, as St. John's wort may potentiate the action of these medications on brain neurotransmitter levels, and produce potentially life-threatening side effects such as serotonin syndrome. A number of adverse reactions of this nature have been reported, and often involve a person self-medicating with St. John's wort, without the knowledge of their attending physician, who has prescribed another antidepressant drug.^{16,17,18}

Principle Active Constituents

Possibly Hyperforin and Flavonoids: The active constituents of St. John's wort are found in the leaves and the flowers of the plant. For many years it was assumed that hypericin and pseudohypericin acted similar to monoamine oxidase inhibitor (MAO-inhibitors) drugs and were responsible for its antidepressant properties via this action.^{1,2} In recent years this has been shown to be invalid and evidence now exists to suggest that hyperforin and flavonoids from the leaves and flowers of the plant may be the real antidepressant agents.^{13, 19,20,21} Yet, two double-blind studies using St. John's wort extracts, containing low hyperforin content, found it to be effective in treating depression.^{22,23} Test tube studies indicate that the active constituents (although not completely identified) in St. John's wort extract act by inhibiting

the reuptake of the neurotransmitters serotonin, norepinephrine, and dopamine and thus, increase brain levels of these important chemical messengers.²⁴

Clinical Application and Mechanism of Action

1. Mild and Moderate Depression

The official German Commission E Monograph lists psychovegetative disturbances, depressive states, fear, and nervous disturbances as clinical indications for the use of St. John's wort extract. At least 26 studies demonstrate that St. John's wort is effective in the treatment of mild to moderate depression.^{1,6,7,8,9} Symptoms of mild to moderate depression include depressed mood, lack of energy, sleep problems, anxiety, appetite disturbance, difficulty concentrating, poor stress tolerance and chronic irritability. Studies on St. John's wort and other antidepressant drugs use the Hamilton Depression Index (HAM-D) to evaluate patient response. The HAM-D is a set of questions that can help establish the severity of depression and is a useful tool to track improvement through a rating scale system. An overview of all studies involving the use of St. John's wort extract for mild to moderate depression reveals that it is effective in approximately 55% of cases. As with other antidepressants it usually requires up to 4–6 weeks to show a significant improvement in the patient's symptoms.¹²

St. John's wort has been tested against placebo and against standard antidepressant drugs in a significant number of clinical trials, involving patients with mild to moderate depression. In double-blind placebo-controlled trials totaling more than 1,000 patients, St. John's wort extract has shown that it can significantly reduce HAM-D scores when compared to placebo.²⁵ In one study HAM-D scores dropped by at least 50% in 70% of the subjects taking St. John's wort (and in 24% of patients in the placebo group).²⁶ Not all studies have shown success however, but the same is true for prescription antidepressants that are in use today, such as sertraline, which in some studies has not shown a benefit. This is common in the area of depression where no real precise method is available to measure the benefit of an intervention, such as a blood test for a proven biomarker of disease progression or improvement.^{27, 28} In general, the evidence to support the use of St. John's wort for the treatment of mild to moderate depression appears to be as substantial as the use of other prescription drugs.^{1,11,12,13,14}

Short-term double-blind studies (6 – 8 weeks) testing St. John's wort against fluoxetine (Prozac) demonstrated that St. John's wort is equally, or more effective, than fluoxetine in treating patients with mild to moderate depression, and produced fewer and less severe side effects.^{29,30} St. John's wort has also been shown to be as effective as sertraline (Zoloft) and imipramine in the treatment of moderate depression, in other head-to-head trials.^{31,32}

It should be noted once again that St. John's wort does not represent a treatment option for *severe depression*, and that a study testing St. John's wort against imipramine showed that imipramine was a more effective treatment for patients presenting with severe depression.¹⁵

2. Anxiety and Insomnia

In many of the studies testing St. John's wort as a treatment for depression, many patients reported an improvement in anxiety and insomnia, associated with their depression.^{12,14}

3. Seasonal Affective Disorder (SAD)

One small controlled trial showed that St. John's wort was effective in the treatment of SAD.³³ This may be due to its ability to raise brain levels of serotonin. Further studies are required to substantiate this preliminary report.³⁴

4. Viral Infections

St John's wort demonstrates antiviral activity against herpes simplex type 1 and 2, influenza A and B and vesicular stomatitis virus. Thus, it may have application for patients with these problems, although no concrete statements can be made at this time.^{4,5}

Dosage and Standardized Grade

The standardized grade of St. John's wort contains 0.3% hypericin content. A few new products on the market are standardized to 2 –3% hyperforin content instead of hypericin. These are taken at the same dosage as products standardized to 0.3% hypericin.^{11,12,13,14}

Depression (Mild to Moderate): 300 mgs, three times per day with meals for mild to moderate depression.^{1, 11,12,13,14}

Note that the use of 600 mgs, three times per day with meals for severe depression did prove to be effective in a single trial, but the use of St. John's wort in these cases is not widely accepted at this time.^{1,11,12,13,14}

Adverse Side Effects, Toxicity and Contraindications

Animal studies do not suggest that St. John's wort produces any significant toxicity, even when taken in large amounts.^{34,38} In two human trials designed to record adverse side effects from the use of St. John's wort, only 2.4% of the 3,250 study subjects reported side effects, which were primarily limited to mild stomach discomfort, allergic reactions-primarily rash, fatigue, and restlessness. The second study revealed similar findings in a group of 313 users of St. John's wort, over a one-year period.^{35,36} Other infrequently reported adverse side effects include dizziness and excess sedation.¹

St. John's wort has also been shown to speed up the detoxification of many drugs and thereby, alters dose requirement of these medications, as discussed below.¹² When taken alone (not concurrently with other antidepressants) St. John's wort is not reported to produce any frequently encountered side effects³⁹, however, the following precautionary statements should be acknowledged:

1. St. John's wort can produce a photosensitivity reaction resulting in skin rash upon exposure to sunlight. It is a rare side effect.¹⁰ This reaction is due to the presence of hypericin, a chemical that is a naphodianthrone compound. Patients using this product should avoid excessive exposure to direct sunlight, especially if they are fair-skinned.⁵⁹
2. Originally, it was thought that patients should avoid foods with a high tyramine content (cheese, beer, pickled herring, and yeast) and drugs such as L-dopa and 5-hydroxytryptophan, due to the fact that hypericin was considered a MAO-inhibitor, and would thus, permit a dangerous rise in blood pressure if these agents were present at significant concentrations in the blood stream. This was later shown to be invalid and therefore, these restrictions and precaution no longer apply.^{40,41,42} Note that if the tyramine ingested from these foods is not broken down in the intestinal tract by the MAO-A enzyme, then severe high blood pressure will result.^{40,41,42}

Drug-Nutrient Interactions

1. Antidepressant drugs: St. John's wort acts in the body like many other antidepressant drugs, and has been shown to potentiate their effects, producing dangerous and severe side effects. It is therefore recommended that patients not take St. John's wort concurrently with any other antidepressants, including the following:

- 5-hydroxytryptophan ⁴³
- Serotonin re-uptake inhibitors (SSRIs) ⁴⁴⁻⁵⁰
- MAO-inhibitors ⁴⁴⁻⁵⁰
- Tricyclic antidepressants ⁴⁴⁻⁵⁰
- Resperine ⁵¹
- Barbituates and sedatives ⁵¹

Any attempt to combine the use of St' John's wort with an antidepressant medication should be supervised by a physician, trained in this area.¹¹

2. Medications that Cause Sun Sensitivity: St. John's wort may increase the potential for certain medications such as Sulfa drugs, Feldene and Prevacid to produce photosensitivity reactions, resulting in a severe skin rash. This is most important for fair-skinned individuals, who are most vulnerable. In these cases, sun light exposure to the skin must be limited. ¹²
3. Alters the Rate of Detoxification of Other Drugs: St. John's wort has been shown to alter the rate of detoxification of other drugs thereby altering their dose requirement and in cases where the therapeutic safety index is very narrow, as is the case with digitalis or digixon. These drug-nutrient interaction can potentially be very dangerous. Evidence of this nature exists to suggest that St. John's wort should not be taken concurrently with the following drugs:
 - Digoxin and digitalis ⁵²
 - Theophylline ⁵³
 - Immunosuppressive drugs (e.g., cyclosporin) ⁵⁴
 - Oral contraceptives- where it has caused breakthrough bleeding ^{55,56}
 - Anesthetic drugs- refrain form taking St. John's wort seven days prior to surgery ⁵⁷
 - Protease inhibitors ⁵⁸
 - Hormone replacement therapy ⁵⁵
 - Warfarin and Coumadin ⁵⁶

Pregnancy and Lactation

During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (e.g., magnesium and the treatment of preeclampsia.)

References: Pregnancy and Lactation

1. *Encyclopedia of Nutritional Supplements*. Murray M. Prima Publishing 1998.
2. *Reavley NM. The New Encyclopedia of Vitamins, Minerals, Supplements, and Herbs*. Evans and Company Inc. 1998.
3. *The Healing Power of Herbs (2nd edition)*. Murray M. Prima Publishing 1995.
4. *Boon H and Smith M. Health Care Professional Training Program in Complementary Medicine*. Institute of Applied Complementary Medicine Inc. 1997.

1. Boon H and Smith M, Health Care Professional Training Program in Complementary Medicine, Institute of Applied Complementary Medicine Inc., 1997.
2. Suzuki O, et.al., Inhibition of Monoamine Oxidase by Hypericin, *Planta Medica* 50, 1984, 272-274.
3. Holtz J, Demisch L, and Gollnick B, Investigations About Antidepressive and Mood Changing Effects of *Hypericum perforatum*, *Planta Medica* 55, 1989, 643.
4. Schmidt U and Sommer H, St. John's Wort Extract in the Ambulatory Therapy of Depression. Attention and Reaction Ability are Preserved, *Forsch Med* 111, 1993, 339-342.
5. Johnson D, Effects of St. John's Wort Extract Jarsin. Paper Presented at the 4th International Congress on Phytotherapy, Munich, Germany, September 10-13, 1992. [Abstract SL53]; Woelk H, Multicentric Practice – Study Analyzing the Functional Capacity in Depressive Patients, Paper Presented at the 4th International Congress on Phytotherapy, Munich, Germany, September 10-13, 1992 [Abstract SL54]; Sommer H, Improvement of Phychovegetative Complaints by Hypericum, Paper Presented at the 4th International Congress on Phytotherapy, Munich, Germany, September 10-13, 1992 [Abstract SL55]
6. Schlich D, Brauckmann F, and Schenk N, Treatment of Depressive Conditions with Hypericum, *Psychol* 13, 1987, 440-444
7. Harrer G and Sommer H, Treatment of Mild/Moderate Depressions with Hypericum, *Phytomed* 1, 1994, 3-8
8. Lavie D, Antiviral Pharmaceutical Compositions Containing Hypericin or Pseudohypericin, European Patent Application No. 87111467.4, filed 8/8/87, European Patent Office, Publ. No. 0 256 A2. 1987, 175-177
9. Someya H, Effect of a Constituent of Hypericin Erectum on Infection and Multiplication of Epstein-Barr Virus, *J Tokyo Med Coll* 43, 1985, 815-826
10. Gulick R, et.al., Human Hypericism: A Photosensitivity Reaction to Hypericin (St. John's Wort), *Int Conf AIDS* 8, B90, 1992. [Abstract PoB 3018]
11. Murray MT, *The Healing Power of Herbs* (2nd edition), Prima Publishing, 1995
12. Natural Products Encyclopedia. www.consumerslab.com:St John's Wort
13. Healthnotes, Inc. 2001. www.healthnotes.com:St. John's Wort
14. Dietary Supplement Information Bureau. www.content.intramedicine.com: St. John's Wort
15. Vorbach EU, Arnoldt KH, Hubner WD. Efficacy and tolerability of St. John's Wort extract LI 160 versus imipramine in patients with severe depressive episodes versus imipramine in patients with severe depressive episodes according to ICD-10. *Pharmacopsychiatry* 1997;30(suppl 2):81-5
16. DeMott K. St. John's wort tied to serotonin syndrome. *Clinical Psychiatry News* 1998;26:p28
17. Gordon JB. SSRIs and St. John's wort: Possible toxicity? *Am Fam Physician* 1998;57:p950, p953
18. Lantz MS, Buchalter E, Giambanco V. St John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol* 1999;12:7-10
19. Holzl J, Demisch L, Gollnik B. Investigations about antidepressive and mood changing effects of *Hypericum perforatum*. *Planta Med* 1989;55:643.
20. Chatterjee SS, Koch E, Noldner M, et al. Hyperforin with hypericum extract: Interactions with some neurotransmitter systems. *Quart Rev Nat Med* 1997;Summer:110.
21. Calapai G, Crupi A, Firenzuoli F, et al. Effects of *Hypericum perforatum* on levels of 5-hydroxytryptamine, noradrenaline and dopamine in the cortex, diencephalon and brainstem of the rat. *J Pharm Pharmacol* 1999;51:723-8.
22. Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol* 1999;15:61-8
23. Schrader E, Meier B, Brattstrom A. Hypericum treatment of mild-moderate depression in a placebo-controlled study: a prospective, double-blind, randomized, placebo-controlled, multicentre study. *Hum Psychopharmacol* 1998;13:163-9
24. Müller WE, Rolli M, Schäfer C, Hafner U. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. *Pharmacopsychiatry* 1997;30(suppl):102-7
25. 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
26. Hansgen KD, Vesper J. Antidepressant efficacy of a high-dose hypericum extract [translated from German]. *MMW Munch Med Wochenschr* 1996;138:29-33
27. Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St. John's wort in major depression: a randomized controlled trial. *JAMA* 2001;285:1978-86
28. Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St. John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002;287:1807-14

29. 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;15:61-8
30. Harrer G, Schmidt U, Kuhn U, et al. Comparison of equivalence between the St. John's wort extract LoHyp-57 and fluoxetine. *Arzneimittelforschung* 1999;49:289-96
31. Brenner R, Azbel V, Madhusoodanan S, et al. Comparison of an extract of hypericum (L1 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. *Clin Ther* 2000;22:411-9
32. Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomized multicentre study of treatment for eight weeks. *BMJ* 1999;319:1534-9
33. Martinez B, Kasper S, Ruhmann S, et al. hypericum in the treatment of seasonal affective disorders. *J Geriatr Psychiatr Neurol* 1994;7(suppl 1):S29-33
34. Muller WEG, et al. Effects of Hypericum Extract on the Expression of Serotonin Receptors. *J Geriatric Psychiatry and Neurology*. 1994;7:S63-S64
35. Rayburn WF, Gonzalez CL, Christensen HD, et al. Effect of prenatally administered hypericum (St John's wort) on growth and physical maturation of mouse offspring. *Am J Obstet Gynecol* 2001;184:191-5
36. Woelk H, Burkard G, Grunwald J. Benefits and risks of the hypericum extract LI 160: Drug monitoring study with 3,250 patients. *J Geriatr Psychiatr neurol* 1994;7(suppl 1):S34-8
37. Hubner WD, Arnoldt KH. St John's wort: a one year treatment study [in German; English abstract]. *Z Phytother* 2000;21:306-10
38. Schulz V, Hansel R, Tyler VE. Rational Thytotherapy: A Physicians' Guide to Herbal Medicine. 3rd ed. Berlin, Germany: Springer-Verlag 1998:p56
39. De Smet PA, Nolen WA. St. John's wort as an anti-depressant. *BMJ* 1996;3:241-2
40. Suzuki O, Katsumata Y, Oya M, et al. Inhibition of monoamine oxidase by hypericin. *Planta Med* 1984;50:272-4
41. Bladt S, Wagner H. Inhibition of MAO by fractions and constituents of hypericum extract. *J Geriatr Psychiatr Neurol* 1994;7(suppl 1):S57-9
42. Thiede HM, Walper A. Inhibition of MAO and COMT by hypericum extracts and hypericin. *J Geriatr Psychiatr Neurol* 1994;7(suppl 1):S54-6
43. Kahn RS, et al. L-5-hydroxytryptophan in the treatment of anxiety disorders. *J Affect Disord* Mar1985;8(2):197-200
44. Muller WE, et al. Effects of Hypericum Extract (LI 160) in Biochemical Models of Antidepressant Activity. *Pharmacopsychiatry*. 1997;30(Suppl 2):102-07
45. Linde K, et al. St. John's Wort for Depression--An Overview and Meta-analysis of Randomised Clinical Trials. *BMJ*. 1996;313m:253-58
46. Demott K. St. John's Wort Tied to Serotonin Syndrome. *Clin Psychiatry News* 1998;26:28.
47. Suzuki O, et al. Inhibition of Monoamine Oxidase by Hypericin. *Planta Medica* 1984;50:272-74.
48. Bladt S, et al. Inhibition of MAO by Fractions and Constituents of Hypericum Extract. *J Geriatric Psychiatry and Neurology* 1994;7:S57-S59
49. Gordon JB. SSRIs and St.John's Wort: possible toxicity? *Am Fam Physician* Mar1998;57(5):950,953
50. Lantz MS, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol* 1999;12(1):7-10.
51. Okpanyi SN, et al. Animal experiments on the psychotropic action of a hypericum extract. *Arzneimittelforschung* Jan1987;37(1):10-3
52. Johne A et al. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (Hypericum perforatum) *Clin Pharmacol Ther* Oct1999;66(4):338-45
53. Nebel A, et al. Potential metabolic interaction between St. John's wort and Theophylline. *Ann Pharmacother* Apr1999;33(4):p502
54. Ruschitzka F, et al. Acute heart transplant rejection due to St. John's wort. *Lancet* Feb2000;355(9203):548-9
55. Rey JM, et al. Hypericum perforatum (St John's Wort) in depression: Pest or blessing? *Med J Aust* Dec1998;169(11-12):583-6
56. Yue Qy, Bergquist C, Gerden B. Safety of St. John's wort (Hypericum perforatum), correspondence. *Lancet* 2000;355:576-7
57. Ernst E. Second thoughts about safety of St John's Wort. *Lancet* Dec1999;354(9195):2014-6
58. Piscitelli SC, et al. Indinavir concentrations and St. John's Wort. *Lancet* Feb2000;355(9203):547-8
59. Mills S, Bone K. Principles and Practice of Phytotherapy. Churchill Livingstone 2000:548-9