

NATURAL HEALTH PRODUCT

ST. JOHN'S WORT – *HYPERICUM PERFORATUM* Oral

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

Notes

- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date December 18, 2018

Proper name(s), Common name(s), Source material(s)

Table 1. Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)		
		Proper name(s)	Part(s)	Preparation(s)
<i>Hypericum perforatum</i>	<ul style="list-style-type: none">► Goatweed► Hypericum► St. John's wort► St. John's-wort	<i>Hypericum perforatum</i>	Herb top	Dried

References: Proper name: USDA 2018; Common names: Anhelescu et al. 2006, Gastpar et al. 2006, Szegedi et al. 2005, Wichtl 2004, McGuffin et al. 2000; Source material: Bradley 2006; Mills and Bone 2005, Hoffmann 2003, Blumenthal et al. 2000, Felter and Lloyd 1983, Wren 1907.

Route of administration

Oral

Dosage form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

Acceptable dosage forms for the age category listed in this monograph and specified route of administration are indicated in the Compendium of Monographs Guidance Document.

Use(s) or Purpose(s)

- ▶ (Traditionally) used in Herbal Medicine to help relieve restlessness and/or nervousness (calmative) (Mills and Bone 2005; Hoffmann 2003; Blumenthal et al. 2000; Felter and Lloyd 1983; Grieve 1971).
- ▶ (Used in Herbal Medicine to) help(s) promote healthy mood balance (Brattström 2009; Anhelescu et al. 2006; Gastpar et al. 2006; Kasper et al. 2006; Fava et al. 2005; Mills and Bone 2005; Szegedi et al. 2005; Uebelhack et al. 2004; ESCOP 2003; Hoffmann 2003; Lecrubier et al. 2002; Volz et al. 2002; Kalb et al. 2001).
- ▶ (Used in Herbal Medicine to) help(s) relieve sleep disturbances associated with mood imbalance (Randløv et al. 2006; Wichtl 2004; Friede et al. 2001; Wheatley 1999; Schrader et al. 1998).

The following combined use(s) or purpose(s) is/are also acceptable:

(Used in Herbal Medicine to) help(s) promote healthy mood balance and relieve sleep disturbances associated with mood imbalance (Brattström 2009; Anhelescu et al. 2006; Gastpar et al. 2006; Kasper et al. 2006; Randløv et al. 2006; Fava et al. 2005; Mills and Bone 2005; Szegedi et al. 2005; Uebelhack et al. 2004; Wichtl 2004; ESCOP 2003; Hoffmann 2003; Lecrubier et al. 2002; Volz et al. 2002; Friede et al. 2001; Kalb et al. 2001; Wheatley 1999; Schrader et al. 1998).

Note

Claims for traditional use must include the term “Herbal Medicine”, “Traditional Chinese Medicine”, or “Ayurveda”.

Dose(s)

Subpopulation(s)

Adults 18 years and older

Quantity(ies)

Relief of restlessness and/or nervousness

Methods of preparation: Dry, Powder, Non-Standardised Extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)

2 - 12.6 grams of dried herb top, per day; Not to exceed 4.2 grams per single dose (Anhelescu et al. 20; Wichtl 2004; ESCOP 2003; Blumenthal et al. 2000).

All uses

Methods of preparation: Standardized extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)

600 - 1800 milligrams of extract, per day, standardized to 3-6% hyperforin and/or 0.12-0.28% hypericin; Not to exceed 600 milligrams of extract per single dose (Angelescu et al. 2006; Gastpar et al. 2006; Kasper et al. 2006; Fava et al. 2005; Szegedi et al. 2005; Uebelhack et al. 2004; Wichtl 2004; ESCOP 2003; Hoffmann 2003; Lecrubier et al. 2002; Volz et al. 2002; Kalb et al. 2001; Blumenthal et al. 2000; BHP 1983).

Direction(s) for use

No statement required.

Duration(s) of use

- ▶ Use for at least 1 week to see beneficial effects (Papakostas et al. 2007; Kalb et al. 2001).
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician for use beyond 18 weeks (Angelescu et al. 2006; Gastpar et al. 2006; Kasper et al. 2006; Fava et al. 2005; Mills and Bone 2005; Szegedi et al. 2005; Uebelhack et al. 2004; ESCOP 2003; Hypericum Depression Trial Study Group 2002; Lecrubier et al. 2002; Vloz et al. 2002; Kalb et al. 2001; BHP 1983).

Risk information

Caution(s) and warning(s)

- ▶ Avoid prolonged exposure to sunlight, ultraviolet light (UV) or UV therapy (Brinker 2010; Barnes et al. 2007; Mills and Bone 2005; ESCOP 2003; Hoffmann 2003; McGuffin et al. 1997).
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician if symptoms persist or worsen.
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are pregnant or breastfeeding (Brinker 2010; Barnes et al. 2007; Mills and Bone 2005).
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking antianxiety or seizure medications, antihistamines, bronchodilators, muscle relaxants and/or opiates (Brinker 2010; Barnes et al. 2007; Mills and Bone 2005; Kawaguchi et al. 2004; Morimoto et al. 2004; Eich-Höchli et al. 2003; Dresser et al. 2003; Hoffman 2003; Markowitz et al. 2003; Xie et al. 2003; Dannawi 2002; Gurley et al. 2002; Spinella and Eaton 2002; Wang et al. 2002; Parker et al. 2001; Wang et al. 2001; Burstein et al. 2000; Nebel et al. 1999).

Contraindication(s)

Do not use this product if you are taking anti-cancer, antidepressant [e.g. selective serotonin reuptake inhibitors (SSRI)], cardiovascular, contraceptive medications, blood thinners, anti-HIV agents and/or medications to suppress the immune system (immunosuppressive medications) (Brinker 2010; Barnes et al. 2007; Bradley 2006; Mills and Bone 2005; Murphy et al. 2005; Frye et al. 2004; Hebert et al. 2004; Jiang et al. 2004; Mueller et al. 2004; Smith et al. 2004; Sparreboom et al. 2004; Tannergren et al. 2004; Wichtl 2004; Alscher and Klotz 2003; Bauer et al. 2003; Dresser et al. 2003; ESCOP 2003; Hall et al. 2003; Hoffmann 2003; Pfrunder et al. 2003; Schwarz et al. 2003; Bolley 2002; Gorski et al. 2002; Mathijssen et al. 2002; Ahmed et al. 2001; De Maat et al. 2001; Moschella and Jaber 2001; Roby et al. 2001; Sugimoto et al. 2001; Turton-Weeks 2001; Wang et al. 2001; Barone et al. 2000; Durr et al. 2000; Karliova et al. 2000; Mai et al. 2000; Piscitelli et al. 2000; Ruschitzka et al. 2000; Ernst 1999; Johne et al. 1999; Maurer et al. 1999; Rey and Walter 1998).

Known adverse reaction(s)

- ▶ Stop use if hypersensitivity/allergy occurs (Barnes et al. 2007; ESCOP 2003).
- ▶ Some people may experience mild gastrointestinal disturbances, nausea, restlessness and/or headaches (Barnes et al. 2007; ESCOP 2003).

Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

Storage conditions

No statement required.

Specifications

- ▶ The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- ▶ The medicinal ingredient must comply with the requirements outlined in the NHPID.

References cited

- Ahmed SM, Banner NR, Dubrey SW. 2001. Low cyclosporin-A level due to Saint-John's-wort in heart transplant patients. *Journal of Heart and Lung Transplantation* 20(7):795.
- Alscher DM, Klotz U. 2003. Drug interaction of herbal tea containing St. John's wort with cyclosporine. *Transplant International* 16(7):543-544.
- Angelescu IG, Kohnen R, Szegedi A, Klement S, Kieser M. 2006. Comparisons of Hypericum extract WS 5570 and paroxetine in ongoing treatment after recovery from an episode of moderate to severe depression: results from a randomized multicenter study. *Pharmacopsychiatry* 39(6):213-219.
- Barnes J, Anderson LA, Philipson JD. 2007. *Herbal Medicines*, 3rd edition. London (GB): The Pharmaceutical Press.
- Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR. 2000. Drug interaction between St. John's wort and cyclosporine. *The Annals of Pharmacotherapy* 34(9):1013-1016.
- Bauer S, Störmer E, Johne A, Krüger H, Budde K, Neumayer HH, Roots I, Mai I. 2003. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *British Journal of Clinical Pharmacology* 55(2):203-211.
- BHP 1983: *British Herbal Pharmacopoeia*. Cowling (GB): British Herbal Medical Association.
- Blumenthal M, Goldberg A, Brinkmann J, editors. 2000. *Herbal Medicine: Expanded Commission E Monographs*. Boston (MA): Integrative Medicine Communications.
- Bolley R, Zülke C, Kammerl M, Fischereder M, Krämer BK. 2002. Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. *Transplantation* 73(6):1009.
- Bove M. 2001. *An Encyclopedia of Natural Healing for Children & Infants*, 2nd edition. Toronto (ON): McGraw-Hill.
- Bradley PR, editor. 2006. *British Herbal Compendium, Volume 1*. Bournemouth (GB): British Herbal Medicine Association.
- Brattström A. 2009. Long-term effects of St. John's wort (*Hypericum perforatum*) treatment: a 1 year safety study in mild to moderate depression.
- Brinker F. *Herb Contraindications and Drug Interactions*, 4th edition. Sandy (OR): Eclectic Medical Publications. 2010.

Burstein AH, Horton RL, Dunn T, Alfaro RM, Piscitelli SC, Theodore W. 2000. Lack of effect of St John's Wort on carbazepine pharmacokinetics in healthy volunteers. *Clinical Pharmacology and Therapeutics* 68(6):605-612.

Dannawi M. 2002. Possible serotonin syndrome after combination of buspirone and St John's wort. *Journal of Psychopharmacology* 16(4):401.

De Maat MM, Hoetelmans RM, Math t RA, van Gorp EC, Meenhorst PL, Mulder JW, Beijnen JH. 2001. Drug interaction between St John's wort and nevirapine. *AIDS* 15(3):420-421.

Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. 2003. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clinical Pharmacology and Therapeutics* 73(1):41-50.

Dürr D, Steiger B, Kullak-Ublick GA, Rentsch KM, Steinert HC, Meier PJ, Fattinger K. 2000. St. John's wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clinical Pharmacology and Therapeutics* 68(6):598-604.

Eich-Höchli D, Oppliger R, Golay KP, Baumann P, Eap CB. 2003. Methadone maintenance treatment and St John's wort: a case report. *Pharmacopsychiatry* 36(1):35-37.

ESCOP 2003: ESCOP Monographs: The Scientific Foundation for Herbal Medicinal Products, 2nd edition. Exeter (GB): European Scientific Cooperative on Phytotherapy and Thieme.

Ernst E. 1999. Second thoughts about the safety of St. John's wort. *Lancet* 354(9195):20142016.

Fava M, Alpert J, Nierenberg AA, Mischoulon D, Otto MW, Zajecka J, Murck H, Rosenbaum JF. 2005. A double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *Journal of Clinical Psychopharmacology* 25(5):441-447.

Felter HW, Lloyd JU. 1983. King's American Dispensatory, Volume 1, 18th edition. Sandy (OR): Eclectic Medical Publications; [Reprint of 1898 original].

Friede M, von Zepelin H, Freudenstein J. 2001. Differential therapy of mild to moderate depressive episodes (ICD-10 F 32.0; F 32.1) with St. John's wort. *Pharmacopsychiatry* 34(Supplement 1):S38-S41.

Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, Egorin MJ. 2004. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clinical Pharmacology and Therapeutics* 76(4):323-329.

Gastpar M, Singer A, Zeller K. 2006. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a doubleblind, randomised, multicentre, placebo-controlled study. *Pharmacopsychiatry* 39(2):66-75.

Gorski JC, Hamman MA, Wang Z, Vasavada N, Huang S, Hall SD. 2002. The effect of St John's wort on the efficacy of oral contraception. *Clinical Pharmacology and Therapeutics* 71:P25.

Grieve M. 1971. A Modern Herbal, Volume 2. New York (NY): Dover Publications [Reprint of 1931 Harcourt, Brace & Company publication].

Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CY. 2002. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. *Clinical Pharmacology and Therapeutics* 72(3):276-287.

Hall SD, Wang Z, Huang SM, Hamman MA, Vasavada N, Adigun AQ, Hilligoss JK, Miller M, Gorski JC. 2003. The interaction between St. John's wort and an oral contraceptive. *Clinical Pharmacology and Therapeutics* 74(6):525-535.

Hebert MF, Park JM, Chen YL, Akhatar S, Larson AM. 2004. Effects of St. John's wort (*Hypericum perforatum*) on tacrolimus pharmacokinetics in healthy volunteers. *Journal of Clinical Pharmacology* 44(1):89-94.

Hoffmann D. 2003. Medical Herbalism: The Science and Practice of Herbal Medicine. Rochester (VT): Healing Arts Press.

Hypericum Depression Trial Study Group. 2002. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. *The Journal of the American Medical Association* 287(14):1807-1814.

Isacchi B, Bergonzi MC, Carnevali F, van der Esch SA, Vincieri FF, Bilia AR. 2007. Analysis and stability of the constituents of St. John's wort oils prepared with different methods. *Journal of Pharmaceutical and Biomedical Analysis* September 7. doi:10.1016/j.jpba.2007.08.025.

Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. 2004. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *British Journal of Clinical Pharmacology* 57(5):592-599.

Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich, M, Roots I. 1999. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clinical Pharmacology and Therapeutics* 66(4):338-345.

Kalb R, Trautmann-Sponsel RD, Kieser M. 2001. Efficacy and tolerability of hypericum extract WS 5572 versus placebo in mildly to moderately depressed patients. A randomized double-blind multicenter clinical trial. *Pharmacopsychiatry* 34(3):96-103.

Karliova M, Treichel U, Malagò M, Frilling A, Gerken G, Broelsch CE. 2000. Interaction of Hypericum perforatum (St. John's wort) with cyclosporin A metabolism in a patient after liver transplantation. *Journal of Hepatology* 33(5):853-855.

Kasper S, Angelescu IG, Szegedi A, Dienel A, Kieser M. 2006. Superior efficacy of St John's wort extract WS 5570 compared to placebo in patients with major depression: a randomized, double-blind, placebo-controlled, multi-center trial [ISRCTN77277298]. *BMC Medicine* 4:14.

Kawaguchi A, Ohmori M, Tsuruoka S, Nishiki K, Harada K, Miyamori I, Yano R, Nakamura T, Masada M, Fujimura A. 2004. Drug interaction between St John's Wort and quazepam. *British Journal of Clinical Pharmacology* 58(4):403-410.

Lecrubier Y, Clerc G, Didi R, Kieser M. 2002. Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. *The American Journal of Psychiatry* 159(8):1361-1366.

Mai I, Krüger H, Budde K, Johne A, Brockmöller J, Neumayer HH, Roots I. 2000. Hazardous pharmacokinetic interaction of Saint John's wort (*Hypericum perforatum*) with the immunosuppressant cyclosporin. *International Journal of Clinical Pharmacology and Therapeutics* 38(10):500-502.

Maisenbacher P, Kovar KA. 1992. Analysis and stability of *Hyperici oleum*. *Planta Medica* 58(4):351-354.

Markowitz JS, Donovan JL, DeVane CL, Talor RM, Ruan Y, Wang J, Chavin KD. 2003. Effect of St. John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *The Journal of the American Medical Association*. 290(11):1500-1504.

Mathijssen RH, Verweij J, de Brujin P, Loos WJ, Sparreboom A. 2002. Effects of St John's wort on irinotecan metabolism. *Journal of the National Cancer Institute* 94(16):1247-1249.

Maurer A, Johne A, Bauer S, Brockmoller F, Conath I, Roots M, Langheinrich M, Hubner WD. 1999. Interaction of St. John's wort extract with phenprocoumon [Abstract]. *European Journal of Clinical Pharmacology* 55:A22.

McGuffin M, Kartesz JT, Leung AY, Tucker AO, editors. 2000. *Herbs of Commerce*, 2nd edition. Silver Spring (MD): American Herbal Products Association.

McGuffin M, Hobbs C, Upton R, Goldberg A, editors. 1997. *American Herbal Products Association's Botanical Safety Handbook*. Boca Raton (FL): CRC Press.

Mills S, Bone K. 2005. *The Essential Guide to Herbal Safety*. St. Louis (MO): Elsevier Churchill Livingstone.

Morimoto T, Kotegawa T, Tsutsumi K, Ohtani Y, Imai H, Nakano S. 2004. Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. *Journal of Clinical Pharmacology* 44(1):95-101.

Moschella C, Jaber BL. 2001. Interaction between cyclosporine and *Hypericum perforatum* (St. John's wort) after organ transplantation. *American Journal of Kidney Diseases* 38(5):1105-1107.

Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, Hehl EM, Sievers H, Frank B, Riethling AK, Drewelow B. 2004. Effect of St. John's wort dose and preparations on the pharmacokinetics of digoxin. *Clinical Pharmacology and Therapeutics* 75(6):546-557.

Murphy A, Kern SE, Stanczyk FZ, Westhoff CL. 2005. Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 71(6):402-408.

Nebel A, Schneider BJ, Baker RK, Kroll DJ. 1999. Potential metabolic interaction between St. John's wort and theophylline. *The Annals of Pharmacotherapy* 33(4):502.

Papakostas GI, Crawford CM, Scalia MJ, Fava M. 2007. Timing of clinical improvement and symptom resolution in the treatment of major depressive disorder. A replication of findings with the use of a double-blind, placebo-controlled trial of *Hypericum perforatum* versus fluoxetine. *Neuropsychobiology* 56(2-3):132-137.

Parker V, Wong AH, Boon HS, Seeman MV. 2001. Adverse reactions to St John's wort. *Canadian Journal of Psychiatry* 46(1):77-79.

Pfrunder A, Schiesser M, Gerber S, Haschke M, Bitzer J, Drewe J. 2003. Interaction of St. John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *British Journal of Clinical Pharmacology* 56(6):683-690.

Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. 2000. Indinavir concentrations and St John's wort. *Lancet* 355(9203):547-548.

Randløv C, Mehlsen J, Thomsen CF, Hedman C, von Fircks H, Winther K. 2006. The efficacy of St. John's Wort in patients with minor depressive symptoms or dysthymia--a double-blind placebo-controlled study. *Phytomedicine* 13(4):215-221.

Rey JM, Walter G. 1998. *Hypericum perforatum* (St John's wort) in depression: pest or blessing? *The Medical Journal of Australia* 169(11-12):583-586.

Roby CA, Dryer DA, Burstein AH. 2001. St. John's wort: effect on CYP2D6 activity using dextromethorphan-dextrorphan ratios. *Journal of Clinical Psychopharmacology* 21(5):530-532.

Ruschitzka F, Meier PJ, Turina M, Lüscher TF, Noll G. 2000. Acute heart transplant rejection due to Saint John's wort. *Lancet* 355(9203):548-549.

Schrader E, Meier B, Brattström A. 1998. Hypericum treatment of mild-moderate depression in a placebo-controlled study: a prospective, double blind, randomised, placebo-controlled, multicenter study. *Human Psychopharmacology: Clinical and Experimental* 13:163-169.

Schwarz UI, Büschel B, Kirch W. 2003. Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. *British Journal of Clinical Pharmacology* 55(1):112-113.

Smith P, Bullock JM, Booker BM, Haas CE, Berenson CS, Jusko WJ. 2004. The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 24(11):1508-1514.

Sosa S, Pace R, Bornancin A, Morazzoni P, Riva A, Tubaro A, Della Loggia R. 2007. Topical anti-inflammatory activity of extracts and compounds from *Hypericum perforatum* L. The Journal of Pharmacy and Pharmacology 59(5):703-709.

Sparreboom A, Cox MC, Acharya MR, Figg WD. 2004. Herbal remedies in the United States: potential adverse interactions with anticancer agents. Journal of Clinical Oncology 22(12):2489-2503.

Spinella M, Eaton LA. 2002. Hypomania induced by herbal and pharmaceutical psychotropic medicines following mild traumatic brain injury. Brain Injury 16(4):359-367.

Sugimoto K, Ohmori M, Tsuruoka S, Nishiki K, Kawaguchi A, Harada K, Arakawa M, Sakamoto K, Masada M, Miyamori I, Fujimura A. 2001. Different effects of St John's Wort on the pharmacokinetics of simvastatin and pravastatin. Clinical Pharmacology and Therapeutics 70(6):518-524.

Szegedi A, Kohnen R, Dienel A, Kieser M. 2005. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. British Medical Journal 330(7490):503.

Tannergren C, Engman H, Knutson L, Hedeland M, Bondesson U, Lennernäs H. 2004. St. John's wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. Clinical Pharmacology and Therapeutics 75(4):298-309.

Turton-Weeks SM, Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR. 2001. St John's wort: a hidden risk for transplant patients. Progress in Transplantation 11(2):116-120.

Uebelhack R, Gruenwald J, Graubaum HJ, Busch R. 2004. Efficacy and tolerability of Hypericum extract STW 3-VI in patients with moderate depression: a double-blind, randomized, placebo-controlled clinical trial. Advances in Therapy 21(4):265-275.

USDA 2018: United States Department of Agriculture, Agricultural Research Service, National Genetic Resources Program. Germplasm Resources Information Network (GRIN) [online database]. *Hypericum perforatum* L. Beltsville (MD): National Germplasm Resources Laboratory. [Accessed 18 March 2008]. Available from: <https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=19600>

Volz HP, Murck H, Kasper S, Möller HJ. 2002. St John's wort extract (LI 160) in somatoform disorders: results of a placebo-controlled trial. Psychopharmacology 164(3):294-300.

Wang ZQ, Hamman MA, Huang SM, Lesko LJ, Hall SD. 2002. Effect of St John's wort on the pharmacokinetics of fexofenadine. Clinical Pharmacology and Therapeutics 71(6):414-420.

Wang ZQ, Gorski C, Hamman MA, Huang S, Lesko LJ, Hall SD. 2001. The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. Clinical Pharmacology and Therapeutics 70(4):317-326.

Wheatley D. 1999. Hypericum in Seasonal Affective Disorder (SAD). Current Medical Research and Opinion 15(1):33-37.

Wichtl M, editor. 2004. Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis, 3rd edition. Stuttgart (D): Medpharm GmbH Scientific Publishers.

Wren RC. 1907. Potter's Cyclopedic of Botanical Drugs and Preparations. London (GB): Potter and Clark.

Xie R, Tan L, Polasek EC, Hong C, Teillol-Foo M, Gordi T, Sharma A, Nickens DJ, Arakawa T, Knuth DW, Antal EJ. 2003. CYP3A and P-glycoprotein induction with St. John's wort in healthy volunteers of selected ethnic populations. Journal of Clinical Pharmacology 45(3):352-356.

References reviewed

Arold G, Donath F, Maurer A, Diefenbach K, Bauer S, Henneicke-von Zepelin HH, Friede M, Roots I. 2005. No relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract. Planta Medica 71(4):331-337.

Bjerkenedt L, Edman GV, Alken RG, Mannel M. 2005. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. European Archives of Psychiatry and Clinical Neuroscience 255(1):40-47.

Brenner R, Azbel V, Madhusoodanan S, Pawlowska M. 2000. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clinical Therapeutics 22(4):411-419.

Cosmetic Ingredient Review Expert Panel. 2001. Final report on the safety assessment of Hypericum Perforatum extract and Hypericum perforatum oil. International Journal of Toxicology 20 (Suppl 2):31-39.

Crowe S, McKeating K. 2002. Delayed emergence and St. John's wort. Anesthesiology 96(4):1025-1027.

Findling RL, McNamara NK, O'Riordan MA, Reed MD, Demeter CA, Branicky LA, Blumer JL. 2003. An open-label pilot study of St. John's wort in juvenile depression. Journal of the American Academy of Child and Adolescent Psychiatry 42(8):908-914.

Gastpar M, Singer A, Zeller K. 2005. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry 38(2):78-86.

Irefin S, Sprung J. 2000. A possible cause of cardiovascular collapse during anesthesia: longterm use of St. John's Wort. Journal of Clinical Anesthesia 12(6):498-499.

Johne A, Schmider J, Brockmöller J, Stadelmann AM, Störmer E, Bauer S, Scholler G, Langheinrich M, Roots I.. 2002. Decreased plasma levels of amitriptyline and its metabolites on comedication with an extract from St John's wort (*Hypericum perforatum*). *Journal of Clinical Psychopharmacology* 22(1):46-54.

Kasper S, Angelescu IG, Szegedi A, Dienel A, Kieser M. 2007. Placebo controlled continuation treatment with Hypericum extract WS 5570 after recovery from a mild or moderate depressive episode. *Wiener Medizinische Wochenschrift* 157(13-14):362-366.

Kobak KA, Taylor LV, Bystritsky A, Kohlenberg CJ, Greist JH, Tucker P, Warner G, Futterer R, Vapnik T. 2005. St John's wort versus placebo in obsessive-compulsive disorder: results from a double-blind study. *International Clinical Psychopharmacology* 20(6):299-304.

Khawaja IS, Marotta RF, Lippmann S. 1999. Herbal medicines as a factor in delirium. *Psychiatric Services* 50(7):969-970.

Linde K, Mulrow CD, Berner M, Egger M. 2005. St John's wort for depression. *Cochrane Database of Systematic Reviews* Issue 2. Art. No.:CD000448. DOI: 10.1002/14651858.CD000448.pub2.

Mannel M. 2004. Drug interactions with St. John's wort: Mechanisms and clinical implications. *Drug Safety* 27(11):773-797.

Moreno RA, Teng CT, Almeida KM, Tavares Junior H. 2006. *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. *Revista Brasileira de Psiquiatria* 28(1):29-32.

Müller T, Mannel M, Murck H, Rahlf VW. 2004. Treatment of somatoform disorders with St. John's wort: a randomized, double-blind and placebo-controlled trial. *Psychosomatic Medicine* 66(4):538-547.

Philipp M, Kohnen R, Hiller KO. 1999. *Hypericum extract* versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *British Medical Journal* 319(7224):1534-1538.

Schempp CM, Hezel S, Simon JC. 2003. Topical treatment of atopic dermatitis with *Hypericum* cream. A randomised, placebo-controlled, double-blind half-side comparison study. *Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und Verwandte Gebiete* 54(3):248-253.

Schempp CM, Ludtke R, Winghofer B, Simon JC. 2000. Effect of topical application of *hypericum perforatum* extract (St. John's wort) on skin sensitivity to solar simulated radiation. *Photodermatology, Photoimmunology and Photomedicine* 16(3):125-128.

Schulz H, Jobert M. 1994. Effects of hypericum extract on the sleep EEG in older volunteers. *Journal of Geriatric Psychiatry and Neurology* 7(Suppl 1):S39-S43.

Shelton RC, Keller MB, Gelenberg A, Dunner DL, Hirschfeld R, Thase ME, Russell J, Lydiard RB, Crits-Cristoph P, Gallop R, Todd L, Hellerstein D, Goodnick P, Keitner G, Stahl SM, Halbreich U. 2001. Effectiveness of St John's wort in major depression: a randomized controlled trial. *The Journal of the American Medical Association* 285(15):1978-1986.

Simeon J, Nixon MK, Milin R, Jovanovic R, Walker S. 2005. Open-label pilot study of St. John's wort in adolescent depression. *Journal of Child and Adolescent Psychopharmacology* 15(2):293-301.

van Gurp G, Meterissian GB, Haiiek LN, McCusker J, Bellavance F. 2002. St John's wort or sertraline? Randomized controlled trial in primary care. *Canadian Family Physician* 48:905-912.

Vorbach EU, Arnoldt KH, Hübner WD. 1997. Efficacy and tolerability of St. John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD-10. *Pharmacopsychiatry* 30(Suppl 2):81-85.

Wang LS, Zhou G, Zhu B, Wu J, Wang JG, Abd El-Aty AM, Li T, Liu J, Yang TL, Wang D, Zhong XY, Zhou HH. 2004. St. John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. *Clinical Pharmacology and Therapeutics* 75(3):191-197.

Weber W, Vander Stoep A, McCarty RL, Weiss NS, Biederman J, McClellan J. 2008. Hypericum perforatum (St John's wort) for attention-deficit/hyperactivity disorder in children and adolescents: a randomized controlled trial. *The Journal of the American Medical Association* 299(22):2633-2641.

Wenk M, Todesco L, Krähenbühl S. 2004. Effect of St John's Wort on the activities of CYP1A2, CYP3A4, N-acetyltransferase 2, and xanthine oxidase in healthy males and females. *British Journal of Clinical Pharmacology* 57(4):495-499.

Wiersema J, Léon B. 1999. World Economic Plants: A Standard Reference. Boca Raton (FL): CRC Press LLC.

Woelk H. 2000. Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. *British Medical Journal* 321(7260):536-539.

Yue QY, Bergquist C, Gerdén B. 2000. Safety of St John's wort (*Hypericum perforatum*). *Lancet* 355(9203):576-577.