SAFETY AND EFFICACY OF ST. JOHN'S WORT (HYPERICUM) DURING PREGNANCY AND LACTATION

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ABSTRACT

Background
There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbal medicines in pregnancy and lactation. This is one article in a series that systematically reviews the evidence for commonly used herbs during pregnancy and lactation.

Objectives
To systematically review the literature for evidence on the use, safety, and pharmacology of St. John's wort focusing on issues pertaining to pregnancy and lactation.

Methods
We searched 7 electronic databases and compiled data according to the grade of evidence found.

Results
There is very weak scientific evidence based on a case report that St Johns wort is of minimal risk when taken during pregnancy. There is *in vitro* evidence from animal studies that St John's wort during pregnancy does not affect cognitive development nor cause long-term behavioral defects, but may lower offspring birth weight. There is weak scientific evidence that St. John's wort use during lactation does not affect maternal milk production nor affect infant weight, but, in a few cases, may cause colic, drowsiness or lethargy. There is weak scientific evidence that St John's wort induces CYP450 enzymes, which may lower serum medication levels below therapeutic range; this may be of concern when administering medications during pregnancy and lactation.

Conclusions
Caution is warranted with the use of St John's wort during pregnancy until further high quality human research is conducted to determine its safety. St John's wort use during lactation appears to be of minimal risk, but may cause side effects. Caution is warranted when using medications along with St John's wort.

Key Words: *St. John's wort, hypericum perfoliatum, pregnancy, lactation, breastfeeding, systematic review*

Hypericum perforatum is an aromatic perennial herb that produces a star-shaped golden yellow flower. It is native to Europe, Northern Africa, and Western Asia but can be found growing throughout the world. The common name of the plant likely originates from "Saint John's Day", June 24, around which time the plants typically bloom. Hippocrates and Galen described the use of *Hypericum perforatum* as a treatment against demonic possession.[1]

Its Latin name is derived from "hyper" meaning "over" and "eikon" meaning "apparition": a clear reference to its historical use in treating demonic possession. Its use in treating depression

dates back to the time of Swiss physician Paracelsus (ca. 1493-1541), but many authorities believe that the ancient Greeks used it for treating psychiatric disease that they labeled as demonic possession. Throughout the ages it has been used for digestive disorders, worms, wound healing, fevers, and snakebites. It was very popular until the advent of synthetic medicines.

It was "rediscovered" in the late 1970s and early 1980s by German physicians who eventually had it approved as a prescription medication for depression by Commission E in 1984. It soon outsold every other anti-depressant drug in Germany and remains covered on the national health care plan. Even today, many German physicians save synthetic antidepressants until a treatment with St. John's wort has failed. Mood disorders are among the most common health problems in women and it is diagnosed twice as often in women than men.[2] Almost 10% of women experience depression during pregnancy and patients with a history of depression are at risk for puerperal worsening of mood.[3] A clinical dilemma often results during pregnancy and lactation due to the wish to avoid fetal and neonatal exposure to potential toxins while limiting the risks of untreated psychiatric disorders like depression. Some patients may turn to "natural" medicines such as St. John's wort that they may perceive to be a safer alternative.

However, data regarding the use of natural products in pregnancy and lactation is scarce. The Organization of Teratology Information Services (OTIS) reports in their statement on St. John's wort that "the limited data limits our ability to draw conclusions about whether there is an increased risk for birth defects or other problems associated with use of St. John's wort during pregnancy".[4] For this reason, a systematic review of the literature regarding the efficacy and safety of the use of St. John's wort by pregnant or breastfeeding women was conducted.

METHODS

The following databases were searched from inception to June 2005: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database, and Natural Standard. The common name and Latin name of the herb were used as keywords along with "pregnancy", "lactation", and "breastfeeding". In the case of a well-known active constituent of the herb, this term was also used in the search for its safety during pregnancy and lactation. In addition, the Complete German Commission E Monographs by the American Botanical Council were also searched.

Each relevant journal article was collected and referenced in a database. The nature of the findings and the grade of evidence were then abstracted and compiled in a final report. The grade of evidence for indications was evaluated as displayed in Table 1. Evidence of harm was rated as displayed in Table 2.

RESULTS

Synonyms/ Common Names/ Related Substances:[5] Amber, amber touch-and-heal, demon chaser, *fuga daemonum*, goatweed, hardhay, hypereikon, hyperici herba, hypericum, Johns wort, klamath weed, millepertuis, Rosin rose, Saint Johns wort, Saint John's wort, Saynt Johannes wort, SJW, St Johns wort, St John's wort, tipton weed.

Indications for Use

	Grade
Mild to moderate depression[8-12]	A
Anxiety (with valerian)[13]	B2
Acute otitis media (with *Verbascum thapsus, Calendula flores* and *Allium sativum*)[14]	B2
Obsessive compulsive disorder (OCD)[15]	C
Psychological menopause symptoms[16]	C
Premenstrual syndrome (PMS)[17]	C
Chronic colitis (with *Taraxacum officinale, Melissa officinalis, Calendula officinalis* and *Foeniculum vulgare*)[18]	C
Seasonal affective disorder (SAD)[19-21]	C

Safety of Consumption during Pregnancy

	Level
Normal healthy baby[22]	2
Does not affect cognitive development[23]	3
No long-term behavioural deficits[24]	3
Lowers offspring weight[24,25]	3
Does not affect long-term growth and physical maturation[26]	3
Conflicting evidence: Non mutagenic[27] / Teratogenic[28]	3
Increases uterine tone[29]	3
Emmenagogue[30]	4
Uterine stimulant[30]	4
Abortifacient[30]	4

A case of a 38-year-old women who started taking St. John's wort at 24 weeks gestation was reported in a letter to the editor.[22] The woman's pregnancy was unremarkable, with the exception of late onset of thrombocytopenia (the author did not attribute this to St. John's wort).[22] The offspring was born healthy, had a normal birth weight, normal APGAR scores, and physical examination and laboratory results were normal.[22] Behavioural assessment at 4 and 23 days was within normal.[22]

A study on the cognitive impact of prenatal exposure to St. John's wort in mice for 2 weeks before mating and throughout gestation found that prenatal exposure to a therapeutic dose of St. John's wort did not have a major impact on certain cognitive tasks in mice offspring.[23]

A study was conducted where Sprague-Dawley rats were exposed to dietary doses of St. John's wort 1-25 times the recommended human dose.[25] St. John's wort had no effect on maternal weight gain or duration of gestation.[25] Offspring body weights were similar to controls, but some treated groups, offspring weighed significantly less than the controls.[25] There were no St. John's wort-related behavioural alterations on any measure.[25] Whole and regional brain weights of offspring at adulthood indicated no significant effects of St. John's wort.[25] A behavioural study on mice offspring exposed antenatally to St. John's wort found that birth weights of male offspring were less in the St. John's wort group than in the placebo group.[24] Offspring in both treatment groups showed no long-term statistical differences in early developmental tasks, locomotor activity, and exploratory behaviour throughout development.[24] Performances on a depression task and on anxiety tasks revealed no differences between treatment groups.[24]

St. John's wort was administered to mice in order to determine whether prenatal exposure to the herb affects long-term growth and physical maturation of mouse offspring.[26] Maternal administration of St. John's wort before and throughout gestation did not affect long-term growth and physical maturation of exposed mouse offspring.[26]

A study on organogenesis found that hypericin induced teratogenic effects in whole rat embryo cultures.[28] A study on mammalian cells, however, showed that a standardized aqueous ethanolic extract of St. John's wort did not induce any mutagenic effects.[27] St. John's wort was shown to increase uterine tone in animals.[29]

A review article on the potential value of plants as sources of anti-fertility agents reported that St. John's wort is an abortifacient, emmenagogue, and uterine stimulant.[30] A homeopathic preparation of *Hypericum perforatu*m, called Hypericum, beyond the potency (dilution) of 12C, does not contain any molecules of the original substance. Although the principles of homeopathy are difficult to apply to evidence-based medicine research, a systematic review determined that homeopathic preparations do not significantly differ from placebo.[31]

Safety of Consumption during Lactation

	Level
Does not affect maternal milk production[32]	1b
Does not affect infant weight[32]	1b
May cause colic, drowsiness or lethargy[32]	1b
Crosses into breast milk[33]	2

A prospective observational cohort study was conducted on 33 breastfeeding women receiving St. John's wort (Group 1) and for comparison, 101 disease-matched (Group 2), and 33 age- and parity-matched non-disease controls (Group 3).[32] In the group receiving St. John's wort, there were 2 cases of colic, 2 cases of drowsiness, and 1 case of lethargy.[32] Specific medical treatment was not required for the infants.[32]

No significant difference was observed in the frequency of maternal reports of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life.[32] An analysis was performed on four breast-milk samples (fore and hind milk) during an 18-hour period from a mother with post-natal depression who had taken St. John's wort during pregnancy in order to measure concentration of hypericin and hyperforin.[33] Only hyperforin was excreted into breast milk at a low level.[33] No side effects were seen in the mother or infant.[33]

Part Used
Whole plant[7].

Constituents
- Napthodianthrones[6]: hypericin, pseudohypericin
- Flavonoids[6]: quercetin, quercetrin, amentoflavone, hyperin
- Phloroglucinols[6]: hyperforin, adhyperforin
- Essential oil[6].

Toxicity
St. John's wort may cause delayed hypersensitivity photodermatitis.[34-36] Hypericin is believed to be the photosensitizing agent present in St. John's wort.[37,38]

Pharmacology
St. John's wort effects on serotonin may be primarily responsible for its antidepressant activity.[39] Extracts of St. John's wort inhibit the reuptake of serotonin, norepinephrine, and dopamine in vitro.[39-41] Hyperforin and adhyperforin were shown to modulate the effects of serotonin, dopamine, and noradrenaline, and to act as serotonergic 5-HT3 and 5-HT4 receptor antagonists.[41-44] Hypericin inhibits *in vitro* almost irreversibly both type A and B monoamine oxidase (MAO) in rat brain mitochondria.[45] In human and animal cancer cells, hyperforin inhibited tumour cell growth by induction of apoptosis.[46] Topical application of St John's wort inhibits the proliferation of T lymphocytes in inflammatory skin disorders.[47] St. John's wort induces some of the cytochrome P450 (CYP) enzymes and may interfere with drug metabolism.[48] St. John's wort has antibacterial activity.[49]

Drug Interactions
St. John's wort has displayed consistent pharmacokinetic drug interactions in clinical trials resulting in reduced systemic exposure to many conventional drugs.

The following drugs should be noted for potential interactions:

5-HT1 agonists[50, 51]
Alprozolam[52]
Aminolaevulinic acid[53]
Amitriptyline[54-56]
Analagesics with serotoneric activity[39-41, 51]
Antidepressants[51, 57-59]
Barbituates[60]
Carbamazepine[61]
Cyclosporine[50, 55, 56, 62-72]
Digoxin[50, 56, 73-75]
Dextromethorphan[39-41, 51]
Fenfluramine[59]
Fexofenadine[76]
Irinotecan[77, 78]
Monoamine Oxidase Inhibitors (MAOIs)[41, 43]
Mycophenolate mofetil[79]
Narcotics[60, 80]
Nelazodone[81]
Nonnucleoside Reverse Transcriptase Inhibitors[55, 82, 83]
Nortriptyline[54, 56]
Oral contraceptives[50, 84-86]
Paroxetine[51, 58, 59]
Phenobarbital[50]
Phenprocoumon[50]
Phenytoin[50]
Photosensitizing drugs[57]
Protease Inhibitors (PIs)[50, 56, 82]
Reserpine[60]
Sertraline[81]
Simvastatin[87]
Tacrolimus[79, 88]
Theophylline[50, 56, 89]
Warfarin[50, 84, 90]
Drugs metabolized by cytochrome P450 enzymes[48,50,52,56,65,74,75,82,84,91]

DISCUSSION

There is good evidence to support the use of St. John's wort for mild to moderate cases of depression. There is low-level evidence supporting the use of St. John's wort, alone or in combination with other medicinal herbs, for the following conditions: anxiety, acute otitis media, obsessive compulsive disorder (OCD), psychological menopause symptoms, premenstrual syndrome (PMS), chronic colitis, and seasonal affective disorder (SAD). With weak evidence as to the safety of consumption of St. John's wort during pregnancy, caution is warranted. One case was reported of the birth of a normal healthy baby following St. John's wort consumption during pregnancy. A small number of animal studies showed that St. John's wort:

1. does not affect cognitive development,
2. causes no long-term behavioural deficits, and
3. does not affect long-term growth and physical maturation.

However, other animal studies report lower birth weight in offspring's when St. John's wort is consumed during pregnancy and that it may increase uterine tone. There is also conflicting evidence as to the teratogenicity of hypericin, yet non-mutagenic activity of the whole plant.

During lactation, St. John's wort should be used with caution due to potential side effects of colic, drowsiness, and lethargy. Despite good scientific evidence that St. John's wort consumption during lactation does not affect maternal milk production nor affect infant weight, a few cases of colic, drowsiness, or lethargy were reported with its use. There is also evidence that St. John's wort constituents cross into breast milk.

While traditional and common use has not indicated any substantive risks of taking this herb during pregnancy and lactation, clearly more rigorous and well-controlled research is needed in this area. Clinicians and patients should also be concerned about the potential for interactions that may occur between St. John's wort and numerous prescription medications. This issue has greater significance when the possibility for increased exposure or toxicity to the developing fetus might result from altered drug metabolism due to interaction. Patients should also be vigilant about sun exposure as St. John's wort may cause photodermatitis.

TABLE 1 Grades for evidence for efficacy

GRADE	EVIDENCE
A	**VERY STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.
B1	**STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).
B2	**GOOD SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.
C	**FAIR SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more cohort studies OR outcome studies.
D	**WEAK SCIENTIFIC EVIDENCE** Evidence from case series.
E	**INDIRECT AND/OR CLINICAL EVIDENCE** Evidence from case reports OR expert opinion OR laboratory studies.
F	**HISTORICAL OR TRADITIONAL EVIDENCE** Historical or traditional use by medical professionals, herbalists, scientists, or aboriginal groups.

TABLE 2 Levels for evidence for harm

LEVEL	EVIDENCE
1a	**STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence from one or more systematic reviews or RCTs.
1b	**GOOD SCIENTIFIC EVIDENCE** Statistically significant evidence from one or more cohort studies OR control study.
1c	**WEAK SCIENTIFIC EVIDENCE** Evidence from one or more case series.
2	**VERY WEAK SCIENTIFIC EVIDENCE** Evidence based on case reports.
3	***IN VITRO* SCIENTIFIC EVIDENCE** Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.
4	**INDIRECT EVIDENCE** Evidence based on scientific theory OR expert opinion.
5	**UNKNOWN** No available information.

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