

## A Thorough Analysis of the Safety Profile of St. John's Wort by the Natural Standard Research Collaboration

**Authors/Editors:** Catherine Ulbricht, PharmD (Massachusetts General Hospital); E-P Barrette, MD (MetroHealth Medical Center, Ohio); Ethan Basch, MD (Memorial Sloan-Kettering Cancer Center); Heather Boon, BScPhm, PhD (University of Toronto); Julie Conquer PhD (RGB Consulting); Cynthia Dacey, PharmD (Natural Standard Research Collaboration); Ivo Foppa, MD, ScD (Harvard School of Public Health); Jill M. Grimes Serrano, PhD (Natural Standard Research Collaboration); Paul Hammerness, MD (Harvard Medical School); Jenna Hollenstein, MS, RD (Natural Standard Research Collaboration); Ramon Iovin, PhD (Natural Standard Research Collaboration); Richard Isaac (Natural Standard Research Collaboration); Michael Smith, M.R.PharmS, ND (Canadian College of Naturopathic Medicine); Mamta Vora, PharmD (Northeastern University); Wendy Weissner, BA (Natural Standard Research Collaboration).

### Brief Background

Extracts of *Hypericum perforatum* L. (St. John's wort) have been used traditionally for a wide range of medical conditions.<sup>1</sup> The most common modern-day application of St. John's wort is in the treatment of depressive disorders.<sup>2,3</sup> Meta-analyses of heterogeneous studies conducted over the past two decades, as well as several subsequent randomized trials, have reported St. John's wort to be more effective than placebo and equally effective as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) in the short-term management of mild-to-moderate depression (1-3 months). Overall, the evidence supporting the efficacy of St. John's wort in mild-to-moderate major depression remains compelling. However, the evidence for severe major depression and other depressive disorders (e.g., seasonal affective disorder) remains equivocal.

While generally well-tolerated in clinical use, there is accumulating evidence of significant drug interactions with St. John's wort, particularly when used with medications metabolized by the cytochrome P450 system.<sup>4,5</sup> St. John's wort is not recommended in HIV/AIDS patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors, in patients receiving immunosuppressive therapy (particularly cyclosporine), or in users of oral contraceptives, warfarin, or digoxin.

St. John's wort may cause nausea, fatigue, allergic reactions, impotence, and photosensitivity. St. John's wort may induce mania in individuals with an underlying mood disorder, and may result in serotonin syndrome if used alone or with other serotonergic agents.

### Safety Summary

**Likely safe:** Extensive clinical trials of limited duration (<3 months) at recommended doses support the benign side effect profile and safety of St. John's wort in individuals not taking other drugs.

**Possibly unsafe:** When used in larger than recommended doses, or for extended duration (>3 months). When used with drugs metabolized by cytochrome P450 3A4 and 2E1, as decreased drug levels may occur.<sup>6,7,8,9,10,11,12,13,14</sup> When used in patients with diabetes or in those taking antidiabetic agents.<sup>15</sup> When used in renal transplant patients, due to potential to cause overdosage or fatal drug-herb interactions.<sup>5</sup> When taken by women on concomitant oral contraceptives.<sup>16,17</sup> When

used in patients with sensitive skin or those taking photosensitizing drugs.<sup>18,19</sup> When used in patients on monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs).<sup>20,21,22,23,24</sup> When used in patients with histories of mania, hypomania (as in bipolar disorder), or affective illness.<sup>25,26,27,28,29,30</sup>

**Likely unsafe:** When taken in patients with known allergies/hypersensitivities to St. John's wort or to any of its constituents. When taken by individuals with HIV or AIDS concomitantly with protease inhibitors or nonnucleoside reverse transcriptase inhibitors.<sup>9,31,32</sup> When taken by transplant recipients receiving immunosuppressive therapy, particularly cyclosporine.<sup>33,34,35,36,37,38,39,40,41,42,43,44,45,46</sup> When taken in patients with bleeding disorders or in those taking anticoagulants.<sup>9,16,47,48</sup> When used by individuals going through surgery, due to difficulty inducing relaxation and anesthesia.<sup>49</sup> When used in patients taking digoxin, due to reports of reduced efficacy or drug concentration.<sup>9,50,51</sup> When used in patients using chemotherapeutic agents, as concomitant use may result in reduced effectiveness of chemotherapeutic agents and treatment failure.<sup>52,53,54</sup> When used in patients with suicidal ideation.<sup>55</sup>

**Toxicology:** Toxicological research using St. John's wort extract LI 160 reports a no-effect dose to be above 5,000 mg/kg in mice and rats. Study of chronic toxicity in rats and dogs has found only nonspecific symptoms such as weight loss.<sup>56</sup> *In vivo* and *in vitro* studies have not demonstrated significant mutagenic properties of St. John's wort.<sup>57,58</sup> One study in bacteria reported genotoxicity in *Salmonella typhimurium* and reported that this effect was due to quercetin.<sup>59,60</sup> A case report described a patient who experienced hepatotoxicity associated with ingestion of St. John's wort.<sup>61</sup> The U.S. Cosmetic Ingredient Review Expert Panel recently concluded that there is insufficient data to support the safety of St. John's wort and its constituents in cosmetic formulations. No maximally allowed levels were found in EU or FDA regulations.

### Adverse Effects/Precautions/Contraindications

**Allergy:** Known allergy/hypersensitivity to St. John's wort or its constituents.<sup>62,63</sup> Infrequent allergic skin reactions, including rash, itching, and pruritus, have been reported in clinical trials.<sup>62,63</sup> In a drug monitoring study of 3,250 patients, there were 17 cases of allergic reactions and 10 cases of allergy-related discontinuation of treatment.<sup>64</sup>

**General:** In published studies, St. John's wort has been generally well tolerated at recommended doses for up to 1-3 months. The most common adverse effects include gastrointestinal symptoms, skin reactions, fatigue/sedation, restlessness or anxiety, photosensitivity, sexual dysfunction (including impotence), dizziness, headache, and dry mouth.<sup>63,64,65,66</sup> Several recent meta-analyses and one clinical trial conclude that adverse event rates are comparable to placebo<sup>67,68,69,70,71,72</sup> and less than standard antidepressant treatment.<sup>24,67,69,71,73,74</sup> Reported adverse effects from available clinical trials are variable and often depend on the dose and brand used in the study as well as the sample size. For instance, a review of adverse events under treatment with Jarsin300®/Jarsin® (LI 160; 900 mg extract=1.08 mg hypericin daily) from 1991-1999, involving approximately 8 million people, documented 95 adverse reports.<sup>63</sup> A European drug-monitoring study of 3,250 patients (Jarsin® 300, 900 mg daily) reported an overall adverse reaction rate of 2.4%.<sup>64</sup> A post-marketing study of Aristoforat® documented the incidence of adverse events to be 1% in 2,404 ambulatory patients over a period of 4-6 weeks.<sup>65</sup> In a study of 324 outpatients with mild-to-moderate depression, adverse events occurred in 39% subjects taking 250 mg *Hypericum* extract ZE 117 twice daily for 6 weeks and in 63% taking imipramine; 3% of subjects taking *Hypericum* withdrew because of adverse events compared with 16% taking imipramine.<sup>75</sup> Plasma levels up to 300 ng/mL have been tolerated.<sup>76</sup>

**Cardiovascular:** Hypertension, tachycardia, and palpitations have been reported with St. John's wort use.<sup>21,22,71,77,78</sup> In a telephone survey, one woman reported nausea, diaphoresis, muscle cramping, weakness, and elevated pulse and blood pressure after a single dose of combination St. John's wort, kava, and valerian.<sup>79</sup> No cardiac conduction abnormalities have been found with high doses of St. John's wort in clinical study.<sup>23</sup> No difference in blood pressure or heart rate was found in comparisons of St. John's wort and imipramine in adults.<sup>24,80</sup> A case report described a 70 year-old homebound patient who experienced new-onset orthostatic hypotension and lightheadedness while taking multiple prescription medications and herbal products, including St. John's wort.<sup>81</sup> When all herbal products were discontinued, these symptoms improved, and the patient experienced improvement in pain control.

**Cardiovascular (edema):** "Swelling" or edema has been noted in 19% of patients taking 900-1,500 mg of St. John's wort daily for 8 weeks, versus 8% of placebo patients and 8% of sertraline (Zoloft®) patients.<sup>82</sup>

**Dermatologic (allergy):** Infrequent allergic skin reactions, including rash, itching, and pruritus, have been reported in clinical trials. A review of adverse events under treatment with Jarsin®/Jarsin300® from 1991-1999, involving approximately 8 million people, documented 27 adverse skin reactions.<sup>63</sup>

**Dermatologic (alopecia):** Persistent scalp and eyebrow hair loss has been described in a 24-year-old woman with schizophrenia treated with the antipsychotic medication olanzapine (Zyprexa®), occurring 5 months following augmentation with 900 mg daily of St. John's wort.<sup>22</sup>

**Dermatologic (photosensitization):** Photosensitization has been reported since the early 1900s in grazing animals consuming St. John's wort flowering plants.<sup>83</sup> Several cases of reversible photosensitivity to St. John's wort have been reported.<sup>84</sup> One patient developed itchy erythematous lesions in light-exposed areas of skin after taking 240 mg of *Hypericum* extract daily for 3 years.<sup>85</sup> In another case, a burning, erythematous eruption occurred after 4 days of treatment with 333 mg of *Hypericum* extract.<sup>85,86</sup> Lane-Brown presented 3 cases of phototoxicity associated with topical and oral St. John's wort: erythematobullous dermatosis and facial bullae related to sun exposure, and UVB phototherapy-related follicular erythema and urticarial edema.<sup>87</sup> Phase I studies of intravenous and oral hypericin in HIV-infected adults observed severe cutaneous phototoxicity in 11 out of 23 subjects<sup>88</sup> and a variety of photosensitivity reactions in 14 of 19 subjects with hepatitis C.<sup>89</sup> However, another study did not find a correlation between photosensitivity and total plasma *Hypericum* concentrations in human

volunteers, after a single 900-3,600 mg oral dose of hypericin extract.<sup>90</sup> The same report noted a small but significant increase in solar and UVA light sensitivity over 15 days of 1,800 mg *Hypericum* extract daily. Another study did not find phototoxic potential with oral L160.<sup>91</sup> A recent study found peak hypericin levels in skin blister fluid following administration of an oral dose of 1,800 mg or steady-state administration (900 mg daily for 7 days) to be at least 20 times below the estimated phototoxic concentration of 100ug/mL.<sup>92</sup> An additional study found phototoxicity after irradiation with UVA and visible light only at high concentrations.<sup>93</sup> It has been suggested that the risk for significant photogenic damage incurred by the combination of *Hypericum* extracts and UVA phototherapy may be low in the majority of individuals.<sup>94</sup> In healthy volunteers, *Hypericum* extract LI 160 use in combination with solar simulated radiation was investigated.<sup>84</sup> After both single-dose and steady-state administration, no significant influence on the erythema index or melanin index could be detected, with the exception of a marginal influence on UVB-induced pigmentation ( $P=0.0471$ ) in the single-dose study. The results do not provide evidence for a phototoxic potential of the *Hypericum* extract LI 160 in humans when administered orally in typical clinical doses up to 1,800 mg daily.

**Endocrine:** In healthy volunteers, St. John's wort did not significantly alter levels of various androgens. However, combined concentrations of 5-alpha-reduced steroids, AoS, and epiAoS declined in males, and the testosterone-to-DHT ratio was increased in men and women.<sup>95</sup> WS 5570 stimulated adrenocorticotrophic hormone (ACTH) secretion and growth hormone (GH) release in healthy volunteers. There was no effect on cortisol or prolactin.<sup>96</sup> *In vitro* evidence suggests that St. John's wort may alter glucose metabolism.<sup>15</sup>

**Gastrointestinal:** Infrequent dyspepsia, anorexia, diarrhea, nausea, and constipation have been reported in controlled trials;<sup>73,97</sup> 18 cases of gastrointestinal symptoms were reported in 3,250 adult subjects in clinical study.<sup>98</sup> Nausea, diarrhea, dry mouth, and abdominal pain have both been observed in clinical trials investigating the effects of St. John's wort in depression.<sup>78,99,100,101</sup> One case report showed mixed-type liver injury with prolonged cholestasis and features of vanishing bile duct syndrome following 10 weeks of treatment with St. John's wort.<sup>102</sup> A case report described a patient who experienced hepatotoxicity associated with ingestion of St. John's wort.<sup>61</sup>

**Genitourinary:** Sexual dysfunction and urinary problems including anorgasmia and frequent urination have been noted.<sup>78,82,103</sup> Anorgasmia was reported in 25% of patients taking 900-1,500 mg of St. John's wort daily for 8 weeks, versus 16% of placebo patients and 32% of sertraline (Zoloft®) patients.<sup>97</sup> In addition, there are 2 published reports of sexual dysfunction associated with St. John's wort. A 42-year-old man with mood and anxiety disorders experienced decreased libido after ingesting St. John's wort for 9 months. Notably, the subject had subsequent recurrent depressive symptoms. His sexual libido returned when St. John's wort was discontinued, and an SSRI, citalopram (Celexa®), was initiated.<sup>104</sup> A 49-year-old man with a 10-year history of recurrent depression experienced orgasmic delay, erectile dysfunction, and inhibited sexual desire when taking the SSRI sertraline (Zoloft®).<sup>103</sup> The SSRI was discontinued with resolution of symptoms; however, 1 week after beginning therapy with St. John's wort the patient developed erectile dysfunction and orgasmic delay. Co-administration of sildenafil (Viagra®), 25-50 mg prior to sexual activity, reversed the sexual dysfunction. Frequent urination was reported in 27% of patients taking 900-1,500 mg of St. John's wort daily for 8 weeks, versus 11% of placebo patients and 21% of sertraline (Zoloft®) patients.<sup>82</sup> Inhibition of sperm motility due to St. John's wort has been observed *in vitro*.<sup>105</sup> St. John's wort has been suggested to directly inhibit rat and human vas deferens contractility.<sup>106</sup> There have also been reports of altered menstrual flow, bleeding, and unwanted pregnancies with concomitant use of St. John's wort.<sup>16,17</sup>

**Neurologic/CNS (headache/dizziness):** In a large controlled trial, headache occurred more frequently in the St. John's wort group than

placebo ( $P < 0.02$ ): 40% versus 26% of respective samples (86). However, in other reports headache has been found rarely.<sup>63,65,66,78,99,100,101,107</sup> Dizziness, fatigue, and insomnia have also been noted.<sup>78,99,100,101</sup> A case report cited a patient who experienced convulsions associated with an overdose of St. John's wort.<sup>108</sup>

**Neurologic/CNS (neuropathy):** Isolated reports of paresthesia<sup>66</sup> and neuropathy have been reported. In a case report, a 35-year-old woman was noted as having developed a subacute toxic neuropathy after taking 500 mg daily St. John's wort for 4 weeks.<sup>109</sup> The subject experienced a stinging pain upon exposure to mechanical stimuli that worsened during and after exposure to sun on her face and dorsum of both hands. Her symptoms began to improve after St. John's wort was withdrawn and gradually disappeared over 2 months. St. John's wort has also been implicated in possible seizure events.<sup>110</sup>

**Psychiatric (anxiety):** Restlessness, insomnia, and anxiety have been noted; 15 psychiatric adverse events were reported in a World Health Organization database up to 1998;<sup>66</sup> 8 reports of anxiety occurred in a sample of 3,250 subjects;<sup>98</sup> 5 patients reported nervousness and anxiety in a postmarketing trial of 2,404 patients.<sup>65</sup> Anxiety has also been reported elsewhere.<sup>78</sup>

**Psychiatric (mania):** Possible St. John's wort-induced mania has been described in several case reports; a majority of these patients had histories of affective illness, including unipolar (major depression) and bipolar (major depression and mania or hypomania) disorder.<sup>25,26,27,28,30</sup> Barbenel et al. described a manic episode in a 28-year-old man, following 5 weeks of simultaneous ingestion of St. John's wort and 50 mg daily of sertraline (Zoloft®), an SSRI antidepressant.<sup>29</sup>

**Psychiatric (psychosis):** Lal and Iskandar reported psychotic decompensation in two schizophrenic patients, temporally associated with the consumption of St. John's wort. However, both patients had discontinued antipsychotic medication prior to relapse.<sup>111</sup> An additional case report described psychotic features and delirium in a 76-year-old female with Alzheimer's dementia, associated with 3 weeks of self-medication with St. John's wort.<sup>112</sup> First-episode psychosis has also been observed in a case report.<sup>113</sup> In a recent systematic review, 17 case reports associated the use of St. John's wort with psychotic events.<sup>114</sup> In 12 instances, the diagnosis was mania or hypomania.

**Psychiatric (serotonin syndrome):** Cases of possible "serotonin syndrome" have been reported with the use of St. John's wort. This syndrome is characterized by rigidity, hyperthermia, delirium, confusion, autonomic instability, and coma. There is a case report of possible serotonin syndrome associated with St. John's wort, manifested by transient flushing, diaphoresis, hypertension, disorientation, dyspnea, and tremors, in a 40-year-old man. The patient, who had a history of depression and SSRI-induced mania, was not taking other medications.<sup>22</sup> Another report described a 33-year-old woman with mild anxiety who experienced multiple anxiety episodes with autonomic arousal (blood pressure maximum 195/110) following 3 doses of St. John's wort.<sup>20</sup> In a telephone survey, one woman reported nausea, diaphoresis, muscle cramping, weakness, and elevated pulse and blood pressure after a single dose of combination St. John's wort, kava, and valerian.<sup>79</sup>

**Psychiatric (suicidal thoughts):** Suicidal thoughts for 9 months were associated with use of St. John's wort in a 55-year-old woman.<sup>115</sup> Thoughts discontinued about 3 weeks after discontinuing the supplement.

**Psychiatric (withdrawal):** A 58-year-old woman experienced withdrawal syndrome after discontinuing St. John's wort. After 32 days of treatment with St. John's wort (1,800 mg 3 times daily), the individual discontinued use of the herb due to photosensitivity reaction. She experienced nausea, anorexia, dry retching, dizziness, dry mouth, thirst, cold chills, and fatigue within 24 hours after discontinuing St. John's wort. The symptoms peaked on day 3 and gradually improved and recovered by day 8.<sup>116</sup>

**Other:** A 22-year-old man presented with severe hematologic toxicity with conditions involving bone marrow necrosis after 1,000 mg daily of St. John's wort for 3 weeks. Treatment with granulocyte colony-stimulating factor 48 IU daily, intravenous immunoglobulin 400 mg/kg, and amphotericin B 100 mg daily was initiated. The patient did not respond and died within 1 week of the diagnosis.<sup>117</sup> Another clinical trial reported side effects of muscle and joint stiffness, tremor, seating, muscle spasms, and pain.<sup>78</sup>

Avoid in patients with known allergies/hypersensitivities to St. John's wort or to any of its constituents.

Avoid in patients with HIV/AIDS who are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors, as suggested by the U.S. Food and Drug Administration (FDA), due to documented reductions in drug concentrations with concomitant St. John's wort.<sup>9,31,32</sup>

Avoid in transplant recipients taking immunosuppressants (particularly cyclosporine), due to numerous reports of significant reductions in drug levels and possible organ rejections with concomitant St. John's wort.<sup>33,34,35,36,37,38,39,40,41,42,43,44,45,46</sup>

Avoid in patients with suicidal ideation.<sup>55</sup>

Avoid prior to surgery due to difficulty inducing relaxation and anesthesia.<sup>49</sup>

Avoid in patients using chemotherapeutic agents as concomitant use may result in reduced effectiveness of chemotherapeutic agents and treatment failure.<sup>52,53,54</sup>

Avoid in patients taking digoxin, as concomitant use may result in reduced digoxin efficacy.<sup>9,50,51</sup>

Avoid use in patients with bleeding disorders or in those taking anticoagulants, as concomitant use may result in reduced anticoagulant effectiveness.<sup>9,16,47,48</sup>

Use with caution when using St. John's wort with drugs metabolized by cytochrome P450 3A4 and 2E1, as decreased drug levels may occur.<sup>6,7,8,9,10,11,12,13,14</sup>

Use cautiously in patients with sensitive skin or those taking photosensitizing drugs, due to risk of photosensitivity, documented in case reports.<sup>18,19</sup>

Use cautiously in patients on monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs), due to an increased risk of serotonin syndrome.<sup>20,21,22,23,24</sup>

Use cautiously in women taking oral contraceptives with concomitant St. John's wort, due to reports of altered menstrual flow, bleeding, and unwanted pregnancies.<sup>16,17</sup>

Use cautiously in patients with histories of mania, hypomania (as in bipolar disorder), or affective illness, due to case reports of possible St. John's wort-induced manic episodes, as has been observed with standard antidepressant medications.<sup>25,26,27,28,29,30</sup>

Use cautiously in patients with diabetes or in those taking antidiabetic agents, due to a potential to alter glucose metabolism.<sup>15</sup>

Use cautiously in renal transplant patients, due to a potential to cause overdosage or fatal drug-herb interactions.<sup>5</sup>

## Pregnancy and Lactation

Although case reports of human exposure to St. John's wort during pregnancy exist,<sup>118</sup> there is insufficient data available at this time to determine if it is safe in pregnant or lactating women.<sup>119</sup>

In a case report, breast milk samples were obtained from a woman with postnatal depression, taking St. John's wort (Jarsin300®, 3 times daily).<sup>120</sup> Only hyperforin was excreted into the breast milk at quantifiable levels. No adverse effects on mother or infant were noted.

In a small safety study, 33 breastfeeding women taking St. John's wort who reported to a teratogen/toxicology reporting service were matched with 101 breastfeeding women not taking St. John's wort.<sup>121</sup> The authors reported no significant differences in adverse effects or lactation duration between groups, although there were nonsignificant differences: there were 2 reports of colicky infants in the St. John's

wort group versus 1 in the group without St. John's wort, and 2 cases of "drowsiness" and 1 case of "lethargy" with St. John's wort versus none reported in the matched controls. Because of the small sample size and nature of the reporting mechanism (leading to possible bias and self-selection), it remains unclear if the excess adverse events were actually attributable to St. John's wort. None of the adverse events required medical treatment.

Administration of St. John's wort to mice before and throughout gestation did not significantly impact cognitive tasks performed by their offspring.<sup>122</sup>

There is a lack on information for the use of St. John's wort in pregnant or lactating women on the National Library of Medicine's Drug and Lactation Database (LactMed).

## St. John's Wort/Drug Interactions

**General:** St. John's wort has the potential to reduce systemic bioavailability of many conventional drugs.<sup>4,123,124</sup> However, the majority of clinical trials used small numbers of subjects and contained few safeguards against bias (such as random and concealed allocation of participants, inclusion of controls, and blinding). Moreover, the methods in the studies varied widely, with inadequate use of widely accepted standards of research practice. Few studies reported assaying the St. John's wort content of the preparations used, and the duration of dosing in these trials was highly variable, with few studies reporting a rationale for the dosing regimen tested. The methodological quality of many studies was limited, lacking in controls, randomization, or order of administration. Thus, the variable effects of St. John's wort on different conventional drugs, and the mechanism by which these effects may operate, remain inconclusive. Better-designed pharmacokinetic studies are required to guide clinical practice.<sup>125</sup>

**5HT1 agonists (triptans):** Interaction with various triptan medications, via enhanced serotonergic activity, is possible in theory. Examples include naratriptan (Amerge<sup>®</sup>), rizatriptan (Maxalt<sup>®</sup>), sumatriptan (Imitrex<sup>®</sup>), and zolmitriptan (Zomig<sup>®</sup>).

**Alcohol:** Based on human study, St. John's wort (900 mg daily) did not significantly interact with alcohol, in terms of cognitive capacities.<sup>126</sup> However, St. John's wort extracts, ibogaine and an ibogaine analog, reduced intake of alcohol in animal study.<sup>127,128</sup>

**Anesthetics:** Based on human case reports, use of St. John's wort before anesthesia may cause complications, including cardiovascular collapse and delayed emergence.<sup>129,130</sup> There is one case report of cardiovascular collapse during anesthesia reported in a healthy 23-year-old woman who had been taking St. John's wort daily for 6 months prior to surgery. The patient had undergone uneventful general anesthesia 2 years earlier when she was not taking St. John's wort.<sup>131</sup>

**Antianxiety drugs:** Based on laboratory study, St. John's wort has been shown to act on various neurotransmitter receptors, including GABA and benzodiazepine receptors.<sup>132,133</sup> In clinical study, St. John's wort has been shown to reduce the effectiveness of benzodiazepines, due to the induction of CYP450 3A4 by St. John's wort.<sup>10,11,35,134,135</sup> In an isolated case report, the addition of St. John's wort and ginkgo led to buspirone-induced hypomania; however, the patient was also co-medicated with fluoxetine (a selective serotonin reuptake inhibitor), which may have caused the interaction.<sup>136</sup>

**Antibiotics:** Antibiotic agents that are transported by P-glycoprotein or metabolized by cytochrome P450 may be altered by concomitant use of St. John's wort, an inducer of P-glycoprotein and cytochrome P450 3A4.<sup>135,137,138</sup>

**Anticoagulants and antiplatelets:** Based on human study, St. John's wort may reduce effects of warfarin (lowered International Normalized Ratio [INR]).<sup>16,47</sup> In most cases, the patients had been stabilized on warfarin for some time prior to ingesting St. John's wort. None of the patients in these cases developed thromboembolic events; however, the decrease in INR was thought to be clinically significant.

Increases in warfarin dose or discontinuation of St. John's wort resulted in the INR returning to target values. Proposed mechanisms for this interaction are induction of cytochrome P450 and P-glycoprotein.<sup>9,47,48</sup> In contrast, St. John's wort administration in adult males for 21 days had no apparent clinically relevant impact on the single-dose pharmacokinetic parameters of S(+)- and R(-)-ibuprofen.<sup>139</sup>

**Antidepressant agents:** Based on human, animal, and laboratory study, St. John's wort is thought to inhibit monoamine oxidase and serotonin reuptake.<sup>132,140,141,142,143,144</sup>

**Antidepressant agents, monoamine oxidase inhibitors (MAOIs):** Based on laboratory study, hypericin may inhibit monoamine oxidase (MAO) A and B,<sup>140</sup> as well as other components, such as xanthone and flavonols<sup>145</sup> and catechol-o-methyltransferase (COMT).<sup>146</sup> Other studies similarly reported weak MAOI properties *in vitro*.<sup>132,141,142,143</sup> In theory, St. John's wort may potentiate the effects of MAOIs, possibly leading to clinical toxicity, such as serotonin syndrome or hypertensive crisis.<sup>147</sup>

**Antidepressant agents, selective serotonin reuptake inhibitors (SSRIs):** Based on animal study, St. John's wort may inhibit the reuptake of serotonin.<sup>144</sup> Based on human evidence, concomitant St. John's wort may lead to increased adverse effects typically associated with SSRI antidepressants, including serotonin syndrome or mania.<sup>29,148,149,150</sup>

**Antidepressant agents, tricyclic (TCAs):** Based on human study, St. John's wort may cause a significant reduction in amitriptyline concentration.<sup>151,152</sup> A number of CYP enzymes including 1A2, 2C19, 3A4, and 2D6 are involved in the metabolism of tricyclic antidepressants. Theoretically, concomitant use of St. John's wort and tricyclic antidepressants may increase the risk of serotonin syndrome, due to increased risk of serotonergic adverse effects. However, no difference in blood pressure or heart rate was found in comparisons of St. John's wort and imipramine in adults.<sup>24,80</sup>

**Antidiabetic agents:** Based on human study, concomitant use of St. John's wort with tolbutamide resulted in hypoglycemia, although the mechanism is not likely due to effects on cytochrome P450 2C9.<sup>11</sup> One study showed that St. John's wort significantly altered glimepiride pharmacokinetics in 17 out of 21 patients, and the interaction was independent of the individuals' cytochrome P450 2C9 (CYP2C9) genotype.<sup>153</sup> St. John's wort has also been shown to alter glucose metabolism in *in vitro* study.<sup>15</sup>

**Antifungals:** Based on human study, concomitant intake of St. John's wort may decrease plasma levels of voriconazole.<sup>154</sup>

**Antihistamines:** Clinical study has demonstrated increased clearance of fexofenadine in response to St. John's wort, presumed to be due to MDRI induction.<sup>35,155</sup>

**Antihypertensives:** St. John's wort has reportedly caused hypertension<sup>20</sup> and tachycardia, based on human case reports.<sup>21,22,71,77</sup> The effects of St. John's wort with antihypertensive agents are not well understood.

**Anti inflammatory agents:** Based on laboratory study, St. John's wort may result in proliferation of T-lymphocytes and of the mixed EC lymphocyte reaction after topical application.<sup>156</sup> *In vitro* inhibition of free radical production has been demonstrated in cell-free and human vascular tissue.<sup>157</sup> Based on *in vitro* study, St. John's wort may induce CYP450 2C9.<sup>158</sup> Some anti-inflammatory agents (e.g., piroxicam, ibuprofen) are metabolized by cytochrome P450 2C9, and concurrent use with St. John's wort may alter their effects. Human study, however, revealed no significant effect of St. John's wort 300 mg 3 times daily on ibuprofen.<sup>139</sup>

**Antilipemic agents, HMG-CoA reductase inhibitors:** St. John's wort has reportedly lowered concentrations of simvastatin and its metabolite, but not pravastatin.<sup>159,160</sup> **The mechanism for this interaction is likely induction of CYP450 3A4.**<sup>160</sup> St. John's wort significantly increased the serum level of LDL cholesterol and total cholesterol with no change in HDL cholesterol in hypercholesterolemic patients taking atorvastatin compared with those taking atorvastatin without St. John's wort.<sup>161</sup>

**Antineoplastic agents:** Based on *in vitro* study, St. John's wort reduced serum levels of etoposide (Etoposide<sup>®</sup>), a topoisomerase II inhibitor, presumably through induction of CYP3A4.<sup>54</sup> Theoretically, St. John's wort may antagonize other chemotherapeutic agents that are directed against topoisomerase II alpha, such as anthracyclines or cytotoxic agents, as has been demonstrated *in vitro*.<sup>54</sup> St. John's wort has also been shown to increase imatinib clearance in human study.<sup>162,163</sup> Concomitant use of St. John's wort with irinotecan has been shown to reduce the AUC of the active metabolite of irinotecan (SN-38) in human study, likely due to induction of CYP450 3A4.<sup>52,53</sup>

**Antiretroviral agents, non nucleoside reverse transcriptase inhibitors (NNRTIs):** Based on human evidence, St. John's wort has been shown to decrease plasma concentrations of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), possibly due to cytochrome P450 induction.<sup>31</sup>

**Antiretroviral agents, protease inhibitors:** Based on human evidence, St. John's wort has been shown to decrease plasma concentrations of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), possibly due to cytochrome P450 induction.<sup>9,31,32</sup>

**Antiviral agents:** *In vitro* studies have documented St. John's wort's antiviral properties.<sup>164,165,166,167,168,169,170,171,172,173</sup> The effects of St. John's wort with antiviral agents are not clear.

**Benzodiazepine:** In clinical study, St. John's wort has been shown to reduce the effectiveness of benzodiazepines, due to the induction of CYP450 3A4 by St. John's wort.<sup>10,11,35,134,135</sup> Based on clinical study, St. John's wort decreases plasma quazepam concentrations, probably by enhancing CYP3A4 activity, but does not influence the pharmacodynamic effects of the drug.<sup>134</sup> A human study reported reductions of midazolam concentrations, presumed to be due to CYP3A4 induction.<sup>10,11,35</sup>

**Calcium channel blockers:** St. John's wort has been shown to reduce the effectiveness of calcium channel blockers likely due to induction of cytochrome P450 3A4. Repeated administration of St. John's wort significantly decreased the bioavailability of R- and S-verapamil in humans.<sup>174</sup> Reductions have also been noted in nifedipine concentrations.<sup>10</sup>

**Carbamazepine:** Based on human study, St. John's wort was observed to have no effect on carbamazepine concentrations.<sup>175</sup> Hypericin and pseudohypericin pharmacokinetics were only marginally influenced by co-medication with the enzyme inhibitor cimetidine and the enzyme inducer carbamazepine.<sup>176</sup>

**Cardiac glycosides:** According to human study, treatment with *Hypericum* extract may decrease digoxin levels and increase digoxin clearance, possibly through induction of P-glycoprotein.<sup>9,50,51,152,177,178,179,180</sup> The interaction may vary within St. John's wort preparations and doses, particularly of hyperforin.<sup>181</sup> Low-hyperforin St. John's wort does not appear to have an effect on plasma digoxin.<sup>182</sup>

**Chlorzoxazone (Paraflex<sup>®</sup>, Parafon Forte<sup>®</sup>, Relaxazone<sup>®</sup>, Remular-S<sup>®</sup>):** Chlorzoxazone, an antispasmodic skeletal muscle relaxant, has been used as a probe drug for CYP 2E1 function. In clinical study, St. John's wort has been shown to induce 2E1 *in vivo*.<sup>14</sup>

**Contraceptives:** Multiple human reports of reduced serum levels or half-lives of oral contraceptives in association with St. John's wort use—likely related to effects on P450 3A4—exist in the literature, along with concomitant alterations in hormone levels, increased breakthrough bleeding, unexpected pregnancies, and changes in menstrual flow.<sup>16,17,183,184,185,186,187</sup>

**Corticosteroids:** Concurrent administration of St. John's wort had no significant effect on the single-dose pharmacokinetics of prednisone or metabolic prednisolone in male subjects.<sup>188</sup>

**Cytochrome P450 metabolized agents:** In a systematic review of 19 trials with available plasma data, 3 reported no important interaction between St. John's wort and pharmaceutical drugs, and 17 described a decrease in systemic bioavailability of a conventional drug.<sup>125</sup> According to *in vitro*, animal, and human studies, concurrent

use of drugs metabolized via the CYP450 liver enzyme system may result in altered therapeutic levels of pharmacologic agents, due to induction or inhibition of enzymes by St. John's wort.<sup>5,6,7,8,9,10,11,12,135,158,189,190</sup> However, other studies have failed to show such induction or inhibition of enzymes.<sup>11,158,182,190,191</sup>

**Dextromethorphan:** High doses of dextromethorphan in conjunction with SSRIs have been associated with dextromethorphan-induced serotonin syndrome.<sup>192</sup> However, in clinical study, no effect on dextromethorphan metabolism was observed in response to St. John's wort.<sup>193</sup>

**Drugs that may lower seizure threshold:** There is concern that St. John's wort may cause seizure.<sup>110</sup> Caution is warranted when using St. John's wort with agents that lower the seizure threshold.

**Estrogens:** Multiple reports of reduced serum levels or half-lives of oral contraceptives in association with St. John's wort use—likely related to effects on P450 3A4—exist in the literature, along with concomitant alterations in hormone levels, increased breakthrough bleeding, unexpected pregnancies, and changes in menstrual flow.<sup>16,17,183,184,185,186</sup>

**Immunosuppressants:** Decreases in mycophenolic acid levels in association with St. John's wort use have been observed in human study.<sup>194</sup> There are several clinical reports of decreases in tacrolimus levels in association with St. John's wort use, likely due to induction of CYP450 3A4 and P-glycoprotein by St. John's wort.<sup>194,195,196</sup> There are numerous reports of significant reductions in cyclosporine drug levels and possible organ rejections with concomitant use of St. John's wort.<sup>33,34,35,36,37,38,39,40,41,42,43,44,45,197</sup> A significant drop in cyclosporine levels was observed in kidney transplant recipients,<sup>34,38,39,40,41,42,92,198</sup> in heart transplant recipients,<sup>43,45</sup> and in a liver transplant recipient<sup>44</sup> taking St. John's wort, a drop increased after St. John's wort was discontinued.<sup>36,37</sup> Many of these instances were also accompanied by organ rejection. Effects on cyclosporine levels may also be due to an induction of the drug pump P-glycoprotein.<sup>9,42</sup>

**Loperamide (Imodium<sup>®</sup>):** Delirium and agitation were reported in one patient taking loperamide (Imodium<sup>®</sup>), St. John's wort, and valerian.<sup>199</sup> The condition resolved rapidly with discontinuation of treatment.

**Mood stabilizers:** In theory, the effects of St. John's wort on mood may potentiate or negate the effects of other mood-stabilizing agents.

**Neurologic agents:** Mixed animal and *in vitro* evidence has suggested that the activity of St. John's wort may be related to its inhibition of serotonin, norepinephrine, and/or dopamine synaptic reuptake.<sup>200,201,202,203</sup>

**Omeprazole:** Clinical study has shown that St. John's wort induces both CYP3A4-catalyzed sulfoxidation and CYP2C19-dependent hydroxylation of omeprazole and enormously decreases the plasma concentrations of omeprazole.<sup>204</sup>

**Opiates:** A case of decreased methadone levels associated with St. John's wort in a chronic methadone user has been reported.<sup>205</sup> Interactions with oxycodone and fentanyl have also been proposed.

**P-glycoprotein-regulated drugs:** St. John's wort is considered an inducer of P-glycoprotein.<sup>179</sup> Human and *in vitro* studies have shown that hyperforin and hypericin inhibit the active efflux of fluorescent markers daunorubicin and calcein-AM.<sup>206,207</sup> Further *in vitro* study has provided evidence that St. John's wort and hyperforin, but not hypericin, increased the expression of P-glycoprotein and the efflux of digoxin in LS 180 cells; removal of St. John's wort resulted in restoration of levels within 48 hours. No acute effects on P-glycoprotein-mediated transport of digoxin in response to St. John's wort were observed.<sup>208</sup> St. John's wort increased the expression and enhanced the drug efflux function of P-glycoprotein in peripheral blood mononuclear cells of healthy volunteers.<sup>209</sup>

**Photosensitizing agents:** It has been suggested that concurrent use of St. John's wort and photosensitizing agents, including several antibiotics and oral contraceptives, may increase the risk of photosensitization.<sup>18</sup> A phototoxic reaction was observed in a patient experimentally treated with  $\delta$ -aminolaevulinic acid for breast cancer who also had been taking St. John's wort.<sup>19</sup>

**Sedatives:** Dizziness, fatigue, and insomnia have also been noted.<sup>78,99,100, 101</sup> *In vitro*, St. John's wort has been shown to act on various neurotransmitter receptors, some of which have been implicated as playing a role in sedation, including GABA and benzodiazepine receptors.<sup>132,133</sup>

**Theophylline (CYP 1A2):** It remains unclear if serum levels of theophylline or its metabolites are affected by St. John's wort.<sup>9</sup> One report describes a 42-year-old woman who experienced lowered serum theophylline levels upon concomitant ingestion of 300 mg daily of St. John's wort. The patient was on several other medications and smoked tobacco. Within 1 week of discontinuation of St. John's wort, her theophylline level rose from 9ug/mL to 19ug/mL.<sup>210</sup> However, in a 48-hour study in 12 healthy volunteers given both agents (theophylline 400 mg and St. John's wort 300 mg), no changes were observed in blood or serum levels of theophylline or its metabolites (13U, 1U, 3X). The duration of this study may not have been sufficient to adequately assess this interaction. In a 15-day open-label crossover study, it was determined that it is unlikely that treatment with St. John's wort on CYPs is sufficient to cause a change in plasma theophylline concentrations.<sup>211</sup>

**Thyroid hormones:** Based on a retrospective case-control study, elevated thyroid stimulating hormone levels may be associated with taking St. John's wort.<sup>212</sup> However, this small retrospective sample does not present a clear, significant relationship or imply causality.

## Other Interactions

St. John's wort has the potential to reduce systemic bioavailability of many agents.<sup>4,123,124</sup> However, the majority of clinical trials used small numbers of subjects and contained few safeguards against bias (such as random and concealed allocation of participants, inclusion of controls, and blinding). Moreover, the methods in the studies varied widely, with inadequate use of widely accepted standards of research practice. Few studies reported assaying the St. John's wort content of the preparations used, and the duration of dosing in these trials was highly variable, with few studies reporting a rationale for the dosing regimen tested. The methodological quality of many studies was limited, lacking in controls, randomization, or order of administration. Thus, the variable effects of St. John's wort on different herbs and supplements, and the mechanism by which these effects may operate, remain inconclusive. Better-designed pharmacokinetic studies are required to guide clinical practice.<sup>125</sup>

Weak monoamine oxidase inhibitor (MAOI) activity of St. John's wort has been observed *in vitro*.<sup>132,140,141,142,143,145,146</sup> Similar to warnings accompanying the use of MAOI antidepressants, consumption of tyramine-containing foods in combination with St. John's wort may pose an increased risk of a hypertensive crisis. In a telephone survey of 43 subjects who had taken St. John's wort, 39 persons reported ingesting tyramine-rich foods or products. Two persons taking 600-900 mg daily reported associated flushing and pounding headaches.<sup>21</sup>

Based on *in vitro* study, St. John's wort may affect glucose metabolism.<sup>15</sup>

## References

- Bent, S. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J.Gen.Intern.Med.* 2008;23(6):854-859.
- Hammerness, P., Basch, E., Ulbricht, C., Barrette, E. P., Foppa, I., Basch, S., Bent, S., Boon, H., and Ernst, E. St John's wort: a systematic review of adverse effects and drug interactions for the consultation psychiatrist. *Psychosomatics* 2003;44(4):271-282.
- van der Watt, G., Laugharne, J., and Janca, A. Complementary and alternative medicine in the treatment of anxiety and depression. *Curr.Opin.Psychiatry* 2008;21(1):37-42.
- Zhou, S. F. and Lai, X. An update on clinical drug interactions with the herbal antidepressant St. John's wort. *Curr.Drug Metab* 2008;9(5):394-409.
- Nowack, R. Review article: cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: grapefruit juice, St John's Wort - and beyond! *Nephrology*.(Carlton.) 2008;13(4):337-347.
- Budzinski, J. W., Foster, B. C., Vandenhoeck, S., and Arnason, J. T. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomedicine* 2000;7(4):273-282.
- Obach, R. S. Inhibition of human cytochrome P450 enzymes by constituents of St. John's Wort, an herbal preparation used in the treatment of depression. *J Pharmacol Exp Ther* 2000;294(1):88-95.
- Bray BJ, Perry NB, Menkes DB, and et al. St. John's wort extract induces CYP3A and CYP2E1 in the Swiss webster mouse. *Toxicol Sci* 2002;66(1):27-33.
- Cott JM. Herb-drug interactions. *CNS Spectrums: The International Journal of Neuropsychiatric Medicine* 2001;6:827-832.
- Smith M, Lin KM, and Zheng YP. PIII-89 an open trial of nifedipine-herb interactions: Nifedipine with St. John's wort, ginseng or ginkgo biloba. *Clin Pharm Ther* 2001;69:P86.
- Wang, Z., Gorski, J. C., Hamman, M. A., Huang, S. M., Lesko, L. J., and Hall, S. D. The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001;70(4):317-326.
- Roby, C. A., Anderson, G. D., Kantor, E., Dryer, D. A., and Burstein, A. H. St John's Wort: effect on CYP3A4 activity. *Clin Pharmacol Ther.* 2000;67(5):451-457.
- Moore, L. B., Goodwin, B., Jones, S. A., Wisely, G. B., Serabjit-Singh, C. J., Willson, T. M., Collins, J. L., and Kliewer, S. A. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Proc.Natl. Acad.Sci U.S.A* 6-20-2000;97(13):7500-7502.
- Gurley, B. J., Gardner, S. F., Hubbard, M. A., Williams, D. K., Gentry, W. B., Cui, Y., and Ang, C. Y. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, Panax ginseng and Ginkgo biloba. *Drugs Aging* 2005;22(6):525-539.
- Krusekopf, S. and Roots, I. St. John's wort and its constituent hyperforin concordantly regulate expression of genes encoding enzymes involved in basic cellular pathways. *Pharmacogenet.Genomics* 2005;15(11):817-829.
- Yue, Q. Y., Bergquist, C., and Gerden, B. Safety of St John's wort (*Hypericum perforatum*). *Lancet* 2-12-2000;355(9203):576-577.
- Ratz, A. E., von Moos, M., and Drewe, J. [St. John's wort: a pharmaceutical with potentially dangerous interactions]. *Schweiz Rundsch.Med Prax.* 5-10-2001;90(19):843-849.
- Miller LG. Drug interactions known or potentially associated with St. John's wort. *J Herbal Pharmacother* 2001;1(3):51-64.
- Ladner, D. P., Klein, S. D., Steiner, R. A., and Walt, H. Synergistic toxicity of delta-aminolaevulinic acid-induced protoporphyrin IX used for photo-diagnosis and hypericum extract, a herbal antidepressant. *Br J Dermatol.* 2001;144(4):916-918.
- Brown, T. M. Acute St. John's wort toxicity. *Am J Emerg.Med* 2000;18(2):231-232.
- Bachmann LM. *Hypericum* (St. John's Wort) is just as effective as low dose imipramine. *Schweizerische Rundschau fur Medizin Praxis* 2000;89(14):597.
- Parker, V., Wong, A. H., Boon, H. S., and Seeman, M. V. Adverse reactions to St John's Wort. *Can.J Psychiatry* 2001;46(1):77-79.
- Czekalla, J., Gastpar, M., Hubner, W. D., and Jager, D. The effect of hypericum extract on cardiac conduction as seen in the electrocardiogram compared to that of imipramine. *Pharmacopsychiatry* 1997;30 Suppl 2:86-88.
- Vorbach, E. U., Arnoldt, K. H., and Hubner, W. D. Efficacy and tolerability of St. John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD- 10. *Pharmacopsychiatry* 1997;30 Suppl 2:81-85.
- Schneck, C. St. John's wort and hypomania. *J Clin Psychiatry* 1998;59(12):689.
- Nierenberg, A. A., Burt, T., Matthews, J., and Weiss, A. P. Mania associated with St. John's wort. *Biol Psychiatry* 12-15-1999;46(12):1707-1708.
- Moses, E. L. and Malling, A. G. St. John's Wort: three cases of possible mania induction. *J Clin Psychopharmacol.* 2000;20(1):115-117.
- Guzelcan, Y., Scholte, W. F., Assies, J., and Becker, H. E. [Mania during the use of a combination preparation with St. John's wort (*Hypericum perforatum*)]. *Ned.Tijdschr.Geneeskd.* 10-6-2001;145(40):1943-1945.

29. Barbenel, D. M., Yusufi, B., O'Shea, D., and Bench, C. J. Mania in a patient receiving testosterone replacement postorchidectomy taking St John's wort and sertraline. *J Psychopharmacol* 2000;14(1):84-86.
30. Andreescu, C., Mulsant, B. H., and Emanuel, J. E. Complementary and alternative medicine in the treatment of bipolar disorder--a review of the evidence. *J.Affect.Disord.* 2008;110(1-2):16-26.
31. de Maat, M. M., Hoetelmans, R. M., Math t RA, van Gorp, E. C., Meenhorst, P. L., Mulder, J. W., and Beijnen, J. H. Drug interaction between St John's wort and nevirapine. *AIDS* 2-16-2001;15(3):420-421.
32. Piscitelli, S. C., Burstein, A. H., Chaitt, D., Alfaro, R. M., and Falloon, J. Indinavir concentrations and St John's wort. *Lancet* 2-12-2000;355(9203):547-548.
33. Alscher, D. M. and Klotz, U. Drug interaction of herbal tea containing St. John's wort with cyclosporine. *Transpl.Int* 2003;16(7):543-544.
34. Bauer, S., Stormer, E., Johne, A., Kruger, H., Budde, K., Neumayer, H. H., Roots, I., and Mai, I. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br J Clin Pharmacol* 2003;55(2):203-211.
35. Dresser, G. K., Schwarz, U. I., Wilkinson, G. R., and Kim, R. B. Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin Pharmacol Ther* 2003;73(1):41-50.
36. Breidenbach, T., Kliem, V., Burg, M., Radermacher, J., Hoffmann, M. W., and Klempnauer, J. Profound drop of cyclosporin A whole blood trough levels caused by St. John's wort (*Hypericum perforatum*). *Transplantation* 5-27-2000;69(10):2229-2232.
37. Breidenbach, T., Hoffmann, M. W., Becker, T., Schlitt, H., and Klempnauer, J. Drug interaction of St John's wort with ciclosporin. *Lancet* 5-27-2000;355(9218):1912.
38. Mai, I., Kruger, H., Budde, K., Johne, A., Brockmoller, J., Neumayer, H. H., and Roots, I. Hazardous pharmacokinetic interaction of Saint John's wort (*Hypericum perforatum*) with the immunosuppressant cyclosporin. *Int J Clin Pharmacol Ther* 2000;38(10):500-502.
39. Barone, G. W., Gurley, B. J., Ketel, B. L., and Abul-Ezz, S. R. Herbal supplements: a potential for drug interactions in transplant recipients. *Transplantation* 1-27-2001;71(2):239-241.
40. Beer, A. M. and Ostermann, T. [St. John's wort: interaction with cyclosporine increases risk of rejection for the kidney transplant and raises daily cost of medication]. *Med Klin* 8-15-2001;96(8):480-483.
41. Moschella, C. and Jaber, B. L. Interaction between cyclosporine and *Hypericum perforatum* (St. John's wort) after organ transplantation. *Am J Kidney Dis* 2001;38(5):1105-1107.
42. Turton-Weeks, SM, Barone GW, Gurley BJ, and et al. St. John's wort: a hidden risk for transplant patients. *Prog Transplant* 2001;11(2):116-120.
43. Ruschitzka, F., Meier, P. J., Turina, M., Luscher, T. F., and Noll, G. Acute heart transplant rejection due to Saint John's wort. *Lancet* 2-12-2000;355(9203):548-549.
44. Karliova, M., Treichel, U., Malago, M., Frilling, A., Gerken, G., and Broelsch, C. E. Interaction of *Hypericum perforatum* (St. John's wort) with cyclosporin A metabolism in a patient after liver transplantation. *J Hepatol.* 2000;33(5):853-855.
45. Ahmed, S. M., Banner, N. R., and Dubrey, S. W. Low cyclosporin-A level due to Saint-John's-wort in heart transplant patients. *J Heart Lung Transplant* 2001;20(7):795.
46. Ashar, B. H., Rice, T. N., and Sisson, S. D. Medical residents' knowledge of dietary supplements. *South.Med.J.* 2008;101(10):996-1000.
47. Jiang, X., Williams, K. M., Liauw, W. S., Ammit, A. J., Roufogalis, B. D., Duke, C. C., Day, R. O., and McLachlan, A. J. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br.J.Clin Pharmacol.* 2004;57(5):592-599.
48. Shalansky, S., Lynd, L., Richardson, K., Ingaszewski, A., and Kerr, C. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. *Pharmacotherapy* 2007;27(9):1237-1247.
49. Ciocon, J. O., Ciocon, D. G., and Galindo, D. J. Dietary supplements in primary care. Botanicals can affect surgical outcomes and follow-up. *Geriatrics* 2004;59(9):20-24.
50. Johne, A., Brockmoller, J., Bauer, S., Maurer, A., Langheinrich, M., and Roots, I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin Pharmacol.Ther.* 1999;66(4):338-345.
51. Johne A, Brockmoller J, Bauer S, and et al. Interaction of St.John's wort extract with digoxin. *Eur.J Clin Pharmacol.* 1999;55:a22.
52. Mathijssen RHJ, Verweij J, De Bruijn P, and et al. Modulation of irinotecan (CPT-11) metabolism by St. John's wort in cancer patients. American Association for Cancer Research, 93rd Annual Meeting, April 6-10, 2002, San Francisco, CA, USA.
53. Mathijssen, R. H., Verweij, J., de Bruijn, P., Loos, W. J., and Sparreboom, A. Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 8-21-2002;94(16):1247-1249.
54. Peebles, K. A., Baker, R. K., Kurz, E. U., Schneider, B. J., and Kroll, D. J. Catalytic inhibition of human DNA topoisomerase II alpha by hypericin, a naphthodianthrone from St. John's wort (*Hypericum perforatum*). *Biochem Pharmacol* 10-15-2001;62(8):1059-1070.
55. Bressler, R. Herb-drug interactions. St. John's wort and prescription medications. *Geriatrics* 2005;60(7):21-23.
56. Leuschner G. Preclinical toxicology profile of *Hypericum* extract LI 160. *Phytomedicine* 1996;supplement 1:104.
57. Okpanyi, S. N., Lidzba, H., Scholl, B. C., and Miltenburger, H. G. [Genotoxicity of a standardized *Hypericum* extract]. *Arzneimittelforschung.* 1990;40(8):851-855.
58. Greeson, J. M., Sanford, B., and Monti, D. A. St. John's wort (*Hypericum perforatum*): a review of the current pharmacological, toxicological, and clinical literature. *Psychopharmacology (Berl)* 2001;153(4):402-414.
59. Poginsky B, Westendorf J, Prosenic N, and et al. Johanniskraut (*Hypericum* toxicity associated with *Hypericum* (St. John's wort)]. *Deutsche Apotheker Zeitung* 1988;128:1364-1366.
60. Schimmer, O., Hafele, F., and Kruger, A. The mutagenic potencies of plant extracts containing quercetin in *Salmonella typhimurium* TA98 and TA100. *Mutat.Res* 1988;206(2):201-208.
61. Dominguez Jimenez, J. L., Pleguezuelo, Navarro M., Guiote, Malpartida S., Fraga, Rivas E., Montero Alvarez, J. L., and Poyato, Gonzalez A. [Hepatotoxicity associated with *Hypericum* (St. John's wort)]. *Gastroenterol.Hepatol.* 2007;30(1):54-55.
62. Ernst, E. Adverse effects of herbal drugs in dermatology. *Br.J.Dermatol.* 2000;143(5):923-929.
63. Schulz, V. Incidence and clinical relevance of the interactions and side effects of *Hypericum* preparations. *Phytomedicine* 2001;8(2):152-160.
64. Woelk, H., Burkard, G., and Grunwald, J. Benefits and risks of the hypericum extract LI 160: drug monitoring study with 3250 patients. *J Geriatr.Psychiatry Neurol.* 1994;7 Suppl 1:S34-S38.
65. Schakau D, Hiller K, Schultz-Zehden W, and et al. Risk/benefit profile of St.John's wort extract: STEI 300 in 2404 patients with various degrees of psychiatric disturbance. *Psychopharmakotherapie* 1996;3:116-122.
66. Ernst, E., Rand, J. I., Barnes, J., and Stevinson, C. Adverse effects profile of the herbal antidepressant St. John's wort (*Hypericum perforatum* L.). *Eur.J Clin Pharmacol.* 1998;54(8):589-594.
67. Linde, K., Ramirez, G., Mulrow, C. D., Pauls, A., Weidenhammer, W., and Melchart, D. St John's wort for depression--an overview and meta-analysis of randomised clinical trials. *BMJ* 8-3-1993;313(7052):253-258.
68. Shelton, R. C., Keller, M. B., Gelenberg, A., Dunner, D. L., Hirschfeld, R., Thase, M. E., Russell, J., Lydiard, R. B., Crits-Cristoph, P., Gallop, R., Todd, L., Hellerstein, D., Goodnick, P., Keitner, G., Stahl, S. M., and Halbreich, U. Effectiveness of St John's wort in major depression: a randomized controlled trial. *JAMA* 4-18-2001;285(15):1978-1986.
69. Kim, H. L., Streltzer, J., and Goebert, D. St. John's wort for depression: a meta-analysis of well-defined clinical trials. *J Nerv Ment Dis* 1999;187(9):532-539.
70. Gaster, B. and Holroyd, J. St John's wort for depression: a systematic review. *Arch Intern.Med* 1-24-2000;160(2):152-156.
71. Knuppel, L. and Linde, K. Adverse effects of St. John's Wort: a systematic review. *J Clin.Psychiatry* 2004;65(11):1470-1479.
72. Trautmann-Sponsel, R. D. and Dienel, A. Safety of *Hypericum* extract in mildly to moderately depressed outpatients: a review based on data from three randomized, placebo-controlled trials. *J Affect.Disord.* 10-15-2004;82(2):303-307.

73. 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(2):61-68.
74. Linde, K. and Mulrow, C. D. St John's wort for depression. *Cochrane Database Syst.Rev* 2000;(2):CD000448.
75. Woelk, H. Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. *BMJ* 9-2-2000;321(7260):536-539.
76. Biber, A., Fischer, H., Romer, A., and Chatterjee, S. S. Oral bioavailability of hyperforin from hypericum extracts in rats and human volunteers. *Pharmacopsychiatry* 1998;31 Suppl 1:36-43.
77. Zullino, D. and Borgeat, F. Hypertension induced by St. John's Wort - a case report. *Pharmacopsychiatry* 2003;36(1):32.
78. van Gurp, G., Meterissian, G. B., Haiek, L. N., McCusker, J., and Bellavance, F. St John's wort or sertraline? Randomized controlled trial in primary care. *Can Fam Physician* 2002;48:905-912.
79. Beckman, S. E., Sommi, R. W., and Switzer, J. Consumer use of St. John's wort: a survey on effectiveness, safety, and tolerability. *Pharmacotherapy* 2000;20(5):568-574.
80. Siepmann, M., Krause, S., Joraschky, P., Muck-Weymann, M., and Kirch, W. The effects of St John's wort extract on heart rate variability, cognitive function and quantitative EEG: a comparison with amitriptyline and placebo in healthy men. *Br J Clin Pharmacol* 2002;54(3):277-282.
81. Cappuzzo, K. A. Herbal product use in a patient with polypharmacy. *Consult Pharm.* 2006;21(11):911-915.
82. Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (St John's Wort) in Major Depressive Disorder: A Randomized Controlled Trial. *JAMA* 4-10-2002;287(14):1807-1814.
83. Araya, O. S. and Ford, E. J. An investigation of the type of photosensitization caused by the ingestion of St John's Wort (Hypericum perforatum) by calves. *J Comp Pathol* 1981;91(1):135-141.
84. Schempp, C. M., Winghofer, B., Muller, K., Schulte-Monting, J., Mannel, M., Schopf, E., and Simon, J. C. 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 simulated radiation. *Phytother Res* 2003;17(2):141-146.
85. Golsch, S., Vocks, E., Rakoski, J., Brockow, K., and Ring, J. [Reversible increase in photosensitivity to UV-B caused by St. John's wort extract]. *Hautarzt* 1997;48(4):249-252.
86. Holme, S. A. and Roberts, D. L. Erythroderma associated with St John's wort. *Br J Dermatol.* 2000;143(5):1127-1128.
87. Lane-Brown, M. M. Photosensitivity associated with herbal preparations of St John's wort (Hypericum perforatum). *Med J Aust.* 3-20-2000;172(6):302.
88. Gulick, R. M., McAuliffe, V., Holden-Wiltse, J., Crumacker, C., Liebes, L., Stein, D. S., Meehan, P., Hussey, S., Forcht, J., and Valentine, F. T. Phase I studies of hypericin, the active compound in St. John's Wort, as an antiretroviral agent in HIV-infected adults. *AIDS Clinical Trials Group Protocols* 150 and 258. *Ann Intern.Med* 3-16-1999;130(6):510-514.
89. Jacobson, J. M., Feinman, L., Liebes, L., Ostrow, N., Koslowski, V., Tobia, A., Cabana, B. E., Lee, D., Spritzler, J., and Prince, A. M. Pharmacokinetics, safety, and antiviral effects of hypericin, a derivative of St. John's wort plant, in patients with chronic hepatitis C virus infection. *Antimicrob.Agents Chemother.* 2001;45(2):517-524.
90. Brockmüller, J., Reum, T., Bauer, S., Kerb, R., Hubner, W. D., and Roots, I. Hypericin and pseudohypericin: pharmacokinetics and effects on photosensitivity in humans. *Pharmacopsychiatry* 1997;30 Suppl 2:94-101.
91. Schempp, C. M., Muller, K., Winghofer, B., Schulte-Monting, J., and Simon, J. C. Single-dose and steady-state administration of Hypericum perforatum extract (St John's Wort) does not influence skin sensitivity to UV radiation, visible light, and solar-simulated radiation. *Arch.Dermatol.* 2001;137(4):512-513.
92. Schempp, C. M., Pelz, K., Wittmer, A., Schopf, E., and Simon, J. C. Antibacterial activity of hyperforin from St John's wort, against multiresistant *Staphylococcus aureus* and gram-positive bacteria. *Lancet* 6-19-1999;353(9170):2129.
93. Bernd A, Ramirez-Bosca A, Kippenberger S, and et al. Phototoxic effects of Hypericum extract in cultures of human keratinocytes compared with those of psoralen. *Photochem Photobiol* 1999;2(69):218-221.
94. Traynor, N. J., Beattie, P. E., Ibbotson, S. H., Moseley, H., Ferguson, J., and Woods, J. A. Photogenotoxicity of hypericin in HaCaT keratinocytes: implications for St. John's Wort supplements and high dose UVA-1 therapy. *Toxicol.Lett.* 9-15-2005;158(3):220-224.
95. Donovan, J. L., DeVane, C. L., Lewis, J. G., Wang, J. S., Ruan, Y., Chavin, K. D., and Markowitz, J. S. Effects of St John's wort (Hypericum perforatum L.) extract on plasma androgen concentrations in healthy men and women: a pilot study. *Phytother Res* 2005;19(10):901-906.
96. Schule, C., Baghai, T., Sauer, N., and Laakmann, G. Endocrinological effects of high-dose Hypericum perforatum extract WS 5570 in healthy subjects. *Neuropsychobiology* 2004;49(2):58-63.
97. Schrader E, Meier B, and Brattstrom A. Hypericum treatment of mild-moderate depression in a placebo-controlled study. A prospective, double-blind, randomized, placebo-controlled, multicentre study. *Human Psychopharm* 1998;13:163-169.
98. Woelk H, Burkard G, and Grunwald J. Nutzen und Risikobewertung des Hypericum-extraktes LI 160 auf der Basis einer Drug-Monitoring-Studie mit 3250 patienten. *Nervenheilkunde* 1993;12:308-313.
99. Lecrubier, Y., Clerc, G., Didi, R., and 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(8):1361-1366.
100. Szegedi, A., Kohnen, R., Dienel, A., and Kieser, M. 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. *BMJ* 3-5-2005;330(7490):503.
101. Fava, M., Alpert, J., Nierenberg, A. A., Mischoulon, D., Otto, M. W., Zajecka, J., Murck, H., and Rosenbaum, J. F. A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *J Clin. Psychopharmacol.* 2005;25(5):441-447.
102. Etogo-Asse, F., Boemer, F., Sempoux, C., and Geubel, A. Acute hepatitis with prolonged cholestasis and disappearance of interlobular bile ducts following tibolone and Hypericum perforatum (St. John's wort). Case of drug interaction? *Acta Gastroenterol.Belg.* 2008;71(1):36-38.
103. Assalian, P. Sildenafil for St. John Wort-induced sexual dysfunction. *J Sex Marital Ther* 2000;26(4):357-358.
104. Bhopal, J. S. St John's wort-induced sexual dysfunction. *Can.J Psychiatry* 2001;46(5):456-457.
105. Ondrizek RR, Chan PJ, Patton WC, and et al. Inhibition of human sperm motility by specific herbs used in alternative medicine. *J Assisted Reproduct Genet* 1999;16(2):87-91.
106. Capasso, R., Borrelli, F., Montanaro, V., Altieri, V., Capasso, F., and Izzo, A. A. Effects of the antidepressant St. John's wort (Hypericum perforatum) on rat and human vas deferens contractility. *J Urol.* 2005;173(6):2194-2197.
107. Volz, H. P. [Somatoform disorders--what must the general practitioner know?]. *MMW.Fortschr.Med* 8-19-2004;146(33-34):27-8, 30.
108. Karalapillai, D. C. and Bellomo, R. Convulsions associated with an overdose of St John's wort. *Med.J.Aust.* 2-19-2007;186(4):213-214.
109. Bove, G. M. Acute neuropathy after exposure to sun in a patient treated with St John's Wort. *Lancet* 10-3-1998;352(9134):1121-1122.
110. Haller, C. A., Meier, K. H., and Olson, K. R. Seizures reported in association with use of dietary supplements. *Clin.Toxicol.(Phila)* 2005;43(1):23-30.
111. Lal, S. and Iskandar, H. St. John's wort and schizophrenia. *CMAJ.* 8-8-2000;163(3):262-263.
112. Laird RD and Webb M. Psychotic episode during use of St John's wort. *J Herbal Pharmacother* 2001;1(2):81-87.
113. Shimizu, K., Nakamura, M., Isse, K., and Nathan, P. J. First-episode psychosis after taking an extract of Hypericum perforatum (St John's Wort). *Hum. Psychopharmacol.* 2004;19(4):275-276.
114. Stevinson, C. and Ernst, E. Can St. John's wort trigger psychoses? *Int.J Clin. Pharmacol Ther.* 2004;42(9):473-480.
115. Nanayakkara, P. W., Meijboom, M., and Schouten, J. A. [Suicidal and aggressive thoughts as a result of taking a Hypericum preparation (St. John's wort)]. *Ned.Tijdschr.Geneeskd.* 6-11-2005;149(24):1347-1349.
116. Dean, A. J., Moses, G. M., and Vernon, J. M. Suspected withdrawal syndrome after cessation of St. John's wort. *Ann Pharmacother* 2003;37(1):151.

117. Demiroglu, Y. Z., Yeter, T. T., Boga, C., Ozdogu, H., Kizilkilic, E., Bal, N., Tuncer, I., and Arslan, H. Bone marrow necrosis: a rare complication of herbal treatment with *Hypericum perforatum* (St. John's wort). *Acta Medica*. (Hradec.Kralove) 2005;48(2):91-94.
118. Grush, L. R., Nierenberg, A., Keefe, B., and Cohen, L. S. St John's wort during pregnancy. *JAMA* 11-11-1998;280(18):1566.
119. Goldman, R. D. and Koren, G. Taking St John's wort during pregnancy. *Can Fam.Physician* 2003;49:29-30.
120. Klier, C. M., Schafer, M. R., Schmid-Siegel, B., Lenz, G., and Mannel, M. St. John's Wort (*Hypericum Perforatum*) - Is it Safe during Breastfeeding? *Pharmacopsychiatry* 2002;35(1):29-30.
121. Lee, A., Minhas, R., Matsuda, N., Lam, M., and Ito, S. The safety of St. John's wort (*Hypericum perforatum*) during breastfeeding. *J Clin Psychiatry* 2003;64(8):966-968.
122. Rayburn, W. F., Gonzalez, C. L., Christensen, H. D., and Stewart, J. D. Effect of prenatally administered hypericum (St John's wort) on growth and physical maturation of mouse offspring. *Am.J Obstet.Gynecol.* 2001;184(2):191-195.
123. Dasgupta, A. Herbal supplements and therapeutic drug monitoring: focus on digoxin immunoassays and interactions with St. John's wort. *Ther.Drug Monit.* 2008;30(2):212-217.
124. Gardiner, P., Phillips, R., and Shaughnessy, A. F. Herbal and dietary supplement--drug interactions in patients with chronic illnesses. *Am.Fam.Physician* 1-1-2008;77(1):73-78.
125. Mills, E., Montori, V. M., Wu, P., Gallicano, K., Clarke, M., and Guyatt, G. Interaction of St John's wort with conventional drugs: systematic review of clinical trials. *BMJ* 7-3-2004;329(7456):27-30.
126. Schmidt U, Harrer U, Kuhn W, and et al. Interaction of *Hypericum extract* with alcohol. Placebo controlled study with 32 volunteers. *Nervenheilkunde* 1993;12(6):314-319.
127. Rezvani, A. H., Overstreet, D. H., Perfumi, M., and Massi, M. Plant derivatives in the treatment of alcohol dependency. *Pharmacol.Biochem.Behav.* 2003;75(3):593-606.
128. Rezvani, A. H., Overstreet, D. H., Yang, Y., and Clark E Jr. Attenuation of alcohol intake by extract of *Hypericum perforatum* (St. John's Wort) in two different strains of alcohol-preferring rats. *Alcohol Alcohol* 1999;34(5):699-705.
129. Koupparis, L. S. Harmless herbs: a cause for concern? *Anaesthesia* 2000;55(1):101-102.
130. Crowe, S. and McKeating, K. Delayed emergence and St. John's wort. *Anesthesiology* 2002;96(4):1025-1027.
131. Irefin, S. and Sprung, J. A possible cause of cardiovascular collapse during anesthesia: long- term use of St. John's Wort. *J Clin Anesth.* 2000;12(6):498-499.
132. Cott, J. M. In vitro receptor binding and enzyme inhibition by *Hypericum perforatum* extract. *Pharmacopsychiatry* 1997;30 Suppl 2:108-112.
133. Hansen, R. S., Paulsen, I., and Davies, M. Determinants of amentoflavone interaction at the GABA(A) receptor. *Eur.J Pharmacol* 9-20-2005;519(3):199-207.
134. Kawaguchi, A., Ohmori, M., Tsuruoka, S., Nishiki, K., Harada, K., Miyamori, I., Yano, R., Nakamura, T., Masada, M., and Fujimura, A. Drug interaction between St John's Wort and quazepam. *Br.J.Clin Pharmacol.* 2004;58(4):403-410.
135. Markowitz, J. S., Donovan, J. L., DeVane, C. L., Taylor, R. M., Ruan, Y., Wang, J. S., and Chavin, K. D. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* 9-17-2003;290(11):1500-1504.
136. Spinella, M. and Eaton, L. A. Hypomania induced by herbal and pharmaceutical psychotropic medicines following mild traumatic brain injury. *Brain Inj.* 2002;16(4):359-367.
137. Henderson, L., Yue, Q. Y., Bergquist, C., Gerden, B., and Arlett, P. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br.J.Clin.Pharmacol.* 2002;54(4):349-356.
138. Patel, J., Buddha, B., Dey, S., Pal, D., and Mitra, A. K. In vitro interaction of the HIV protease inhibitor ritonavir with herbal constituents: changes in P-gp and CYP3A4 activity. *Am.J.Ther.* 2004;11(4):262-277.
139. Bell, E. C., Ravis, W. R., Lloyd, K. B., and Stokes, T. J. Effects of St. John's wort supplementation on ibuprofen pharmacokinetics. *Ann.Pharmacother.* 2007;41(2):229-234.
140. Suzuki, O., Katsumata, Y., Oya, M., Bladt, S., and Wagner, H. Inhibition of monoamine oxidase by hypericin. *Planta Med* 1984;50(3):272-274.
141. Bladt, S. and Wagner, H. Inhibition of MAO by fractions and constituents of hypericum extract. *J Geriatr.Psychiatry Neurol.* 1994;7 Suppl 1:S57-S59.
142. Cott, J. NCDEU update. Natural product formulations available in Europe for psychotropic indications. *Psychopharmacol.Bull.* 1995;31(4):745-751.
143. Miller AL. St. John's wort (*Hypericum perforatum*): clinical effects on depression and other conditions. *Alt Med Rev* 1998;3(1):18-26.
144. Singer, A., Wonnemann, M., and Muller, W. E. Hyperforin, a major antidepressant constituent of St. John's Wort, inhibits serotonin uptake by elevating free intracellular Na+1. *J Pharmacol Exp.Ther.* 1999;290(3):1363-1368.
145. Demisch L, Holzl J, Gollnik B, and et al. Identification of selective MAO-type-A inhibitors in *Hypericum perforatum* L. (Hyperforat). *Pharmacopsychiat.* 1989;22:194.
146. Thiede, H. M. and Walper, A. Inhibition of MAO and COMT by hypericum extracts and hypericin. *J Geriatr.Psychiatry Neurol.* 1994;7 Suppl 1:S54-S56.
147. DeVane CL and Nemeroff CB. 2000 Guide to psychotropic drug interactions. *Primary Psych* 2000;7(10):40-68.
148. Gordon, J. B. SSRIs and St.John's Wort: possible toxicity? *Am Fam.Physician* 3-1-1998;57(5):950, 953.
149. Lantz, M. S., Buchalter, E., and Giambanco, V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr.Psychiatry Neurol.* 1999;12(1):7-10.
150. Waksman JC, Hard K, Jolliff H, and et al. Serotonin syndrome associated with the use of St. John's wort (hypericum perforatum) and paroxetine. *J Toxicol Clin Toxicol* 2000;38(5):521.
151. Roots I, Johne A, Schmider J, and et al. Interaction of a herbal extract from St.John's wort with amitriptyline and its metabolites. *Clin Pharm Ther* 2000;67(2):159.
152. Johne, A., Schmider, J., Brockmoller, J., Stadelmann, A. M., Stormer, E., Bauer, S., Scholler, G., Langheinrich, M., and Roots, I. Decreased Plasma Levels of Amitriptyline and Its Metabolites on Comedication With an Extract From St. John's Wort ( *Hypericum perforatum* ). *J Clin Psychopharmacol.* 2002;22(1):46-54.
153. Xu, H., Williams, K. M., Liauw, W. S., Murray, M., Day, R. O., and McLachlan, A. J. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. *Br.J.Pharmacol.* 2008;153(7):1579-1586.
154. Rengelshausen, J., Banfield, M., Riedel, K. D., Burhenne, J., Weiss, J., Thomsen, T., Walter-Sack, L., Haefeli, W. E., and Mikus, G. Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics. *Clin.Pharmacol Ther.* 2005;78(1):25-33.
155. Wang, Z., Hamman, M. A., Huang, S. M., Lesko, L. J., and Hall, S. D. Effect of St John's wort on the pharmacokinetics of fexofenadine. *Clin Pharmacol Ther* 2002;71(6):414-420.
156. Schempp, C. M., Winghofer, B., Ludtke, R., Simon-Haarhaus, B., Schopf, E., and Simon, J. C. Topical application of St John's wort (*Hypericum perforatum* L.) and of its metabolite hyperforin inhibits the allostimulatory capacity of epidermal cells. *Br J Dermatol* 2000;142(5):979-984.
157. Hunt, E. J., Lester, C. E., Lester, E. A., and Tackett, R. L. Effect of St. John's wort on free radical production. *Life Sci* 6-1-2001;69(2):181-190.
158. Komoroski, B. J., Zhang, S., Cai, H., Hutzler, J. M., Frye, R., Tracy, T. S., Strom, S. C., Lehmann, T., Ang, C. Y., Cui, Y. Y., and Venkataramanan, R. Induction and inhibition of cytochromes P450 by the St. John's wort constituent hyperforin in human hepatocyte cultures. *Drug Metab Dispos.* 2004;32(5):512-518.
159. Eggertsen, R., Andreasson, A., and Andren, L. Effects of treatment with a commercially available St John's Wort product (Movina) on cholesterol levels in patients with hypercholesterolemia treated with simvastatin. *Scand.J.Prim. Health Care* 2007;25(3):154-159.
160. Sugimoto, K., Ohmori, M., Tsuruoka, S., Nishiki, K., Kawaguchi, A., Harada, K., Arakawa, M., Sakamoto, K., Masada, M., Miyamori, I., and Fujimura, A. Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* 2001;70(6):518-524.
161. Andren, L., Andreasson, A., and Eggertsen, R. Interaction between a commercially available St. John's wort product (Movina) and atorvastatin in patients with hypercholesterolemia. *Eur.J.Clin.Pharmacol.* 2007;63(10):913-916.

162. Frye, R. F., Fitzgerald, S. M., Lagattuta, T. F., Hruska, M. W., and Egorin, M. J. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol. Ther.* 2004;76(4):323-329.
163. Smith, P., Bullock, J. M., Booker, B. M., Haas, C. E., Berenson, C. S., and Jusko, W. J. The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 2004;24(11):1508-1514.
164. Meruelo, D., Lavie, G., and Lavie, D. Therapeutic agents with dramatic antiretroviral activity and little toxicity at effective doses: aromatic polycyclic diones hypericin and pseudohypericin. *Proc.Natl.Acad.Sci U.S.A* 1988;85(14):5230-5234.
165. Lavie, G., Valentine, F., Levin, B., Mazur, Y., Gallo, G., Lavie, D., Weiner, D., and Meruelo, D. Studies of the mechanisms of action of the antiretroviral agents hypericin and pseudohypericin. *Proc Natl.Acad.Sci U.S.A* 1989;86(15):5963-5967.
166. Schinazi, R. F., Chu, C. K., Babu, J. R., Oswald, B. J., Saalman, V., Cannon, D. L., Eriksson, B. E., and Nasr, M. Anthraquinones as a new class of antiviral agents against human immunodeficiency virus. *Antiviral Res* 1990;13(5):265-272.
167. Tang, J., Colacino, J. M., Larsen, S. H., and Spitzer, W. Virucidal activity of hypericin against enveloped and non-enveloped DNA and RNA viruses. *Antiviral Res* 1990;13(6):313-325.
167. Wood S, Huffman J, Weber N, and et al. Antiviral activity of naturally occurring anthraquinones and anthraquinone derivatives. *Planta Med* 1990;56:651-652.
169. Carpenter, S. and Kraus, G. A. Photosensitization is required for inactivation of equine infectious anemia virus by hypericin. *Photochem.Photobiol.* 1991;53(2):169-174.
170. Hudson, J. B., Lopez-Bazzocchi, I., and Towers, G. H. Antiviral activities of hypericin. *Antiviral Res* 1991;15(2):101-112.
171. Lopez-Bazzocchi, I., Hudson, J. B., and Towers, G. H. Antiviral activity of the photoactive plant pigment hypericin. *Photochem.Photobiol.* 1991;54(1):95-98.
172. Degar, S., Prince, A. M., Pascual, D., Lavie, G., Levin, B., Mazur, Y., Lavie, D., Ehrlich, L. S., Carter, C., and Meruelo, D. Inactivation of the human immunodeficiency virus by hypericin: evidence for photochemical alterations of p24 and a block in uncoating. *AIDS Research and Human Retroviruses* 1992;8(11):1929-1936.
173. Cohen, P. A., Hudson, J. B., and Towers, G. H. Antiviral activities of anthraquinones, bianthrone and hypericin derivatives from lichens. *Experientia* 2-15-1996;52(3):180-183.
174. Tannergren, C., Engman, H., Knutson, L., Hedeland, M., Bondesson, U., and Lennernas, H. St John's wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. *Clin Pharmacol. Ther.* 2004;75(4):298-309.
175. Burstein, A. H., Horton, R. L., Dunn, T., Alfaro, R. M., Piscitelli, S. C., and Theodore, W. Lack of effect of St John's Wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol. Ther.* 2000;68(6):605-612.
176. Johne, A., Perloff, E. S., Bauer, S., Schmider, J., Mai, I., Brockmoller, J., and Roots, I. Impact of cytochrome P-450 inhibition by cimetidine and induction by carbamazepine on the kinetics of hypericin and pseudohypericin in healthy volunteers. *Eur.J.Clin Pharmacol.* 2004;60(9):617-622.
177. Perloff, M. D., von Moltke, L. L., Stormer, E., Shader, R. I., and Greenblatt, D. J. Saint John's wort: an in vitro analysis of P-glycoprotein induction due to extended exposure. *Br J Pharmacol* 2001;134(8):1601-1608.
178. Cheng, T. O. St John's wort interaction with digoxin. *Arch Intern.Med* 9-11-2000;160(16):2548.
179. Durr, D., Stieger, B., Kullak-Ublick, G. A., Rentsch, K. M., Steinert, H. C., Meier, P. J., and Fattinger, K. St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol. Ther.* 2000;68(6):598-604.
180. Troutman MD, Thakker DR, Carson SW, and et al. Activation and inhibition of P-glycoprotein (P-gp) mediated efflux of digoxin by St John's Wort extract [abstract]. *AAPS Pharm Sci* 2000;2(4 suppl)
181. Mueller, S. C., Uehleke, B., Woehling, H., Petzsch, M., Majcher-Peszynska, J., Hehl, E. M., Sievers, H., Frank, B., Riethling, A. K., and Drewelow, B. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. *Clin Pharmacol. Ther.* 2004;75(6):546-557.
182. Arold, G., Donath, F., Maurer, A., Diefenbach, K., Bauer, S., Henneicke-von Zepelin, H. H., Friede, M., and Roots, I. No relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract. *Planta Med.* 2005;71(4):331-337.
183. Hall, S. D., Wang, Z., Huang, S. M., Hamman, M. A., Vasavada, N., Adigun, A. Q., Hilligoss, J. K., Miller, M., and Gorski, J. C. The interaction between St John's wort and an oral contraceptive. *Clin Pharmacol Ther* 2003;74(6):525-535.
184. Pfrunder, A., Schiesser, M., Gerber, S., Haschke, M., Bitzer, J., and Drewe, J. Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br.J.Clin Pharmacol.* 2003;56(6):683-690.
185. Schwarz, D., Kisselev, P., and Roots, I. St. John's wort extracts and some of their constituents potentially inhibit ultimate carcinogen formation from benzo[a]pyrene-7,8-dihydrodiol by human CYP1A1. *Cancer Res* 11-15-2003;63(22):8062-8068.
186. Baede-van Dijk, P. A., van Galen, E., and Lekkerkerker, J. F. [Drug interactions of *Hypericum perforatum* (St. John's wort) are potentially hazardous]. *Ned. Tijdschr.Geneeskd.* 4-22-2000;144(17):811-812.
187. Murphy, P. A., Kern, S. E., Stanczyk, F. Z., and Westhoff, C. L. Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* 2005;71(6):402-408.
188. Bell, E. C., Ravis, W. R., Chan, H. M., and Lin, Y. J. Lack of pharmacokinetic interaction between St. John's wort and prednisone. *Ann.Pharmacother.* 2007;41(11):1819-1824.
189. Bauer, S., Stormer, E., Kerb, R., Johne, A., Brockmoller, J., and Roots, I. Differential effects of Saint John's Wort ( *hypericum perforatum*) on the urinary excretion of D-glucuronic acid and 6beta-hydroxycortisol in healthy volunteers. *Eur J Clin Pharmacol* 2002;58(9):581-585.
190. Wenk, M., Todesco, L., and Krahenbuhl, S. Effect of St John's wort on the activities of CYP1A2, CYP3A4, CYP2D6, N-acetyltransferase 2, and xanthine oxidase in healthy males and females. *Br.J.Clin Pharmacol.* 2004;57(4):495-499.
191. Markowitz, J. S., DeVane, C. L., Boulton, D. W., Carson, S. W., Nahas, Z., and Risch, S. C. Effect of St. John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. *Life Sci* 1-21-2000;66(9):L133-L139.
192. Schwartz, A. R., Pizon, A. F., and Brooks, D. E. Dextromethorphan-induced serotonin syndrome. *Clin.Toxicol.(Phila)* 3-27-2008;1-3.
193. Roby, C. A., Dryer, D. A., and Burstein, A. H. St. John's wort: effect on CYP2D6 activity using dextromethorphan-dextrorphan ratios. *J.Clin Psychopharmacol.* 2001;21(5):530-532.
194. Mai, I., Stormer, E., Bauer, S., Kruger, H., Budde, K., and Roots, I. Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients. *Nephrol.Dial.Transplant.* 2003;18(4):819-822.
195. Hebert, M. F., Park, J. M., Chen, Y. L., Akhtar, S., and Larson, A. M. Effects of St. John's wort (*Hypericum perforatum*) on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2004;44(1):89-94.
196. Bolley, R., Zulke, C., Kammerl, M., Fischereider, M., and Kramer, B. K. Tacrolimus-induced nephrotoxicity unmasked by induction of the CYP3A4 system with St John's wort. *Transplantation* 3-27-2002;73(6):1009.
197. Mai, I., Bauer, S., Perloff, E. S., Johne, A., Uehleke, B., Frank, B., Budde, K., and Roots, I. Hyperforin content determines the magnitude of the St John's wort-cyclosporine drug interaction. *Clin Pharmacol. Ther.* 2004;76(4):330-340.
198. Schimmer, O., Kruger, A., Paulini, H., and Haefele, F. An evaluation of 55 commercial plant extracts in the Ames mutagenicity test. *Pharmazie* 1994;49(6):448-451.
199. Khawaja, I. S., Marotta, R. F., and Lippmann, S. Herbal medicines as a factor in delirium. *Psychiatr.Serv.* 1999;50(7):969-970.
200. Müller WE, Rolli, M., Schafer, C., and Hafner, U. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. *Pharmacopsychiatry* 1997;30 Suppl 2:102-107.
201. Chatterjee SS, Bhattacharya SK, Singer A, and et al. Hyperforin inhibits synaptosomal uptake of neurotransmitters in vitro and shows antidepressant activity in vivo. *Pharmazie* 1998;53(3):9.
202. Neary, J. T. and Bu, Y. Hypericum LI 160 inhibits uptake of serotonin and norepinephrine in astrocytes. *Brain Res* 1-23-1999;816(2):358-363.

203. Franklin, M. Sub-chronic treatment effects of an extract of *Hypericum perforatum* (St. John's Wort, Li 160) on neuroendocrine responses to the 5-T2A agonist, DOI in the rat. *Pharmacopsychiatry* 2003;36(4):161-164.
204. Wang, L. S., Zhou, G., Zhu, B., Wu, J., Wang, J. G., Abd El-Aty, A. M., Li, T., Liu, J., Yang, T. L., Wang, D., Zhong, X. Y., and Zhou, H. H. St John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. *Clin Pharmacol. Ther.* 2004;75(3):191-197.
205. Eich-Hochli, D., Oppliger, R., Golay, K. P., Baumann, P., and Eap, C. B. Methadone maintenance treatment and St. John's Wort - a case report. *Pharmacopsychiatry* 2003;36(1):35-37.
206. Wang, L. S., Zhu, B., El Aty, A. M., Zhou, G., Li, Z., Wu, J., Chen, G. L., Liu, J., Tang, Z. R., An, W., Li, Q., Wang, D., and Zhou, H. H. The influence of St John's Wort on CYP2C19 activity with respect to genotype. *J. Clin Pharmacol.* 2004;44(6):577-581.
207. Weber, C. C., Kressmann, S., Fricker, G., and Muller, W. E. Modulation of P-glycoprotein function by St John's wort extract and its major constituents. *Pharmacopsychiatry* 2004;37(6):292-298.
208. Tian, R., Koyabu, N., Morimoto, S., Shoyama, Y., Ohtani, H., and Sawada, Y. Functional induction and de-induction of P-glycoprotein by St. John's wort and its ingredients in a human colon adenocarcinoma cell line. *Drug Metab Dispos.* 2005;33(4):547-554.
209. Hennessy, M., Kelleher, D., Spiers, J. P., Barry, M., Kavanagh, P., Back, D., Mulcahy, F., and Feely, J. St John's wort increases expression of P-glycoprotein: implications for drug interactions. *Br J Clin Pharmacol* 2002;53(1):75-82.
210. Nebel, A., Schneider, B. J., Baker, R. K., and Kroll, D. J. Potential metabolic interaction between St. John's wort and theophylline. *Ann. Pharmacother.* 1999;33(4):502.
211. Morimoto, T., Kotegawa, T., Tsutsumi, K., Ohtani, Y., Imai, H., and Nakano, S. Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers. *J Clin Pharmacol* 2004;44(1):95-101.
212. Ferko, N. and Levine, M. A. Evaluation of the association between St. John's wort and elevated thyroid-stimulating hormone. *Pharmacotherapy* 2001;21(12):1574-1578.