HYPERICUM PERFORATUM INTERACTIONS WITH PHARMACEUTICALS DUE TO CYP450

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Abstract

A search and systematic review of current scientific evidence was performed to determine which specific pharmaceutical drugs interact with *Hypericum perforatum* aka: St.

John's wort (SJW) through the CYP450 metabolic pathway. Databases searched included Natural Standards Databases, Natural Medicine Comprehensive Database, PubMed, Google Scholar, The Cochran Review and various other search engines. The evidence points to most drug-herb interactions occurring in CYP3A4, CYP2E1, CYP2D6, CYP2C9 & CYP1A2 isoenzymes. Studies show 50% of all pharmaceutical drugs are metabolized via CYP3A4 and have the highest potential for interactions with SJW to varying degrees. Individuals taking SJW concurrently with narrow therapeutic index (NTI) drugs are at the highest risk for unfavorable consequences.

Key Words: Hypericum, Hypericum perforatum, St. John's wort, SJW, CYP450, CYP3A4 & drug interactions and pharmaceuticals.

Introduction

In today's modern world where pharmaceutical drugs are plentiful and access to self-prescribed or practitioner prescribed herbal medicine is readily available to the general public, there are some very important safety factors to consider when combining herbs and drugs concurrently. Not unlike herbal medicines, many pharmaceutical drugs have plant based origins. However, these drugs are usually in isolated or concentrated compounded forms, and usually synthesized in a lab. When mixed with other plant compounds, such as those found naturally in herbal medicines, healing outcomes can be affected.

Hypericum perforatum aka: St. John's wort (SJW) is a popular herb known best for its anti-depressant effects and is a leading treatment for depression in Germany. SJW has also been used as an anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, astringent, hepatoprotective,

nervine, sedative and vulnerary herb. The method or pathway that SJW is administered will also affect its outcome. Evidence indicating the therapeutic application of SJW dates back over 2,000 years - beginning with the early Greeks. (3)

The purpose of this review is to explore and compare the research on pharmaceutical interactions with SJW, focusing on the metabolism via CYP450. The intention is to clarify and explain which specific drug classes are indeed unsafe to use in combination with SJW, and to discuss the benefits of SJW as an herbal dietary supplement.

SJW is metabolized in the liver and the small intestines by a group of enzymes called cytochrome P450 (CYP450). Within the CYP450 family of enzymes, there are over 50 different known isoenzymes, in which possible metabolic pathways can occur. When it comes to potential drug interactions with SJW, studies confirm interactions taking place via CYP2E1, CYP2D6, CYP2C9, CYP1A2 and CYP3A4 isoenzymes. SJW is considered an inhibitor of CYP450 and can both induce and inhibit the metabolism of certain drugs. Studies show time and time again that SJW specifically induces CYP3A4.

Concurrent ingestion of herbs with certain medications can create a metabolic competition within the body. The danger mostly lies with those pharmaceuticals considered to have a narrow therapeutic index (NTI). A patient taking these types of medications relies on very specific dosaging. If not adequately dosed, the consequences may be dangerous and possibly life threatening.

The main classes of drugs to avoid taking with SJW include anti-viral drugs including protease inhibitors and non-nucleoside reverse transcriptase inhibitors, immunosuppressive

therapy aka: anti-rejection drugs, oral contraceptives, chemotherapeutic agents, anti-diabetic drugs, warfarin and digoxin.

Caution is also recommended for those patients with histories of mania, bipolar disorder, and those taking standard antidepressant medications, monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs), due to an increased risk of serotonin syndrome, which can result in death.

It is important to weed through the clinical studies and research available, making sure the sources and methods are credible. It would be unwise to base evidence merely on subject title headlines, as there are many factors that lead to study conclusions.

Individuals taking pharmaceutical medications and SJW concurrently should inform their healthcare professional that they are taking herbal medicines. Many patients withhold this important information from their physicians, possibly in fear of having their decision to take herbal dietary supplements rejected. Mutual education on this topic would be of great benefit to all parties involved.

Means and Methods

Search and Selection Criteria

The focus was to find the specific drugs that metabolize through CYP450, specifically CYP3A4, which interact with SJW. The terms used as search criteria on PubMed, Natural Standards Databases, Natural Medicine Comprehensive Database, Google Scholar, The Cochran Review and various other search engines were explored using key words Hypericum, Hypericum perforatum, St. John's wort, SJW, CYP450, CYP3A4 & drug interactions. The author attended a

Supplement-Drug Interactions webinar presented by Forrest Batz, PharmD from the University of Hawaii Department of Pharmacy. In addition, email correspondence and phone conversations were conducted between the author and Forrest Batz for further extrapolation.

A large number of articles were found using these terms in various combinations. To narrow the field, only reputable databases were used. Studies based on human trials were favored in leiu of those based on test tube or animal research. Literature reviews and meta-analysis of credible sources were evaluated.

Data Analysis

The remaining articles and reference materials were analyzed for consistency of specific drug interactions to determine if the research thesis was supported. Although there were some variations between the studies, a focus on CYP3A4 was chosen, due to the high herb-drug interaction rate with SJW.

Cases and Controls

The main reference information on specific drug-herb interactions with *Hypericum perforatum* (SJW) was based on Databases 1-3 and Tables 1-2. (See Addendum)

In evaluating and exploring those databases and tables, cross reference for consistency and drug reoccurrence was favored - NTI pharmaceuticals were of highest concern because of their potentially life threatening repercussions. Within the Natural Standards Database and Natural Medicines Comprehensive Database, any research based on theory vs. actual human study was noted along with grade levels and theoretical evidence. Only human based evidence was highlighted in the excerpts from Herbal Medicine: Biomolecular and Clinical Aspects. 2nd

edition. Benzie IFF, Wachtel-Galor S, editors. Chapter 11-Medical Attributes of St. John's Wort (*Hypericum perforatum*). Regarding A-Z Guide to Drug-Herb-Vitamin Interactions + website searches for up to date pharmaceutical info, specific drug classes include detailed pharmaceutical names for reference purposes, despite all listed drugs not having been used in the actual studies. The aforementioned being a prime example of when a warning for drug-herb interaction is based on theory vs. studies of other related drugs in the same drug category. Tables # 1 and 2, Inducers and Inhibitors of CYP450, as stated by Pharmacology Weekly, were used for cross-reference.

Discussion

SJW is metabolized in the liver and the small intestines by a group of enzymes called cytochrome P450 (CYP450). Enzymes are substances that allow for chemical reactions to occur, which would not otherwise under normal conditions. Chemicals coming into the body aka: substrates, attach themselves to the enzymes, and are converted into a form that can be utilized, transported easily through the blood or excreted by the body.

Within the CYP450 family of enzymes, there are over 50 different known isoenzymes, in which possible metabolic pathways can occur. Of these pathways, six of them metabolize 90% of pharmaceutical drugs, with the two most significant isoenzymes being CYP2D6 and CYP3A4; the latter of which metabolizes approximately 50% of all pharmaceuticals on the market today. (5, 6). When it comes to potential drug interactions with SJW, studies confirm interactions taking place via CYP2E1, CYP2D6, CYP2C9, CYP1A2 and CYP3A4 isoenzymes.

Enzymes either induce/increase or inhibit/decrease the therapeutic potential of the incoming pharmaceutical or herbal substrates. In the case of induction, a greater interaction can occur with the pharmaceutical drug or target, resulting in a decrease in blood serum drug levels

and a decreased therapeutic effect. In the case of inhibition, enzyme activity can be slowed down, making the drug or target less effective. This effect occurs due to increasing blood serum levels, which cause the pharmaceutical drug properties to also increase, leading to more side effects and possible toxicity.

Hypericum itself is considered an inhibitor of CYP450 and can both induce and inhibit the metabolism of certain drugs. Studies show time and time again that SJW specifically induces CYP3A4.

> *"...many herbs and natural compounds isolated from herbs have been identified as substrates, inhibitors, and/or inducers of various CYP enzymes. For example, St. John's wort is a potent inducer of CYP3A4, which is mediated by activating the orphan pregnane X receptor. It also contains ingredients that inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4"* (Zhou, Gao, Jiang, Huang, Xu, Paxton 2003)

Unfortunately, many physicians and pharmacists recommend total avoidance of herbs, in this case, SJW, while taking any pharmaceutical. It is smart to be cautious about the potential for herb-drug interactions, but essential to stay open to the possibility that some pharmaceuticals, in fact, may not interact with SJW. If there is interest in taking SJW while taking pharmaceuticals, discussing options with a prescribing physician is encouraged.

Concurrent ingestion of herbs with certain medications can create a metabolic competition within the body. The danger mostly lies with those pharmaceuticals considered to have a narrow therapeutic index (NTI). A patient taking these types of medications relies on very specific dosaging. If not adequately dosed, the consequences may be dangerous and possibly life threatening. For example, if the proper dosages of oral contraceptives are not

absorbed by the body, there is a high risk for pregnancy; if blood serum levels of Cyclosporine, an immunosuppressant drug used to prevent transplanted organ rejection, are decreased, the risk could possibly lead to organ rejection and death. In contrast, if a patient is on pharmaceutical medication for seasonal allergies, the concern of the interactions decreasing the therapeutic dosage may result in a continuation of allergy symptoms, but not pose life threatening effects. Factors depend on the specific drug, the dosage, the individual's overall health and if the herb-drug interaction even share the same metabolic pathway.

The main classes of drugs to avoid taking with SJW include anti-viral drugs including protease inhibitors and non-nucleoside reverse transcriptase inhibitors, immunosuppressive therapy aka: anti-rejection drugs, oral contraceptives, chemotherapeutic agents, anti-diabetic drugs, warfarin and digoxin.

In addition, caution is recommended for those patients with histories of mania, bipolar disorder, and those taking standard antidepressant medications, monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs), due to an increased risk of serotonin syndrome, which can result in death.

> *"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.*** *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), and in users of oral contraceptives, warfarin, or digoxin."* (Mills 2004)

If the risk for drug-herb interactions is so high, why even bother with an herb like St. John's wort? SJW is best known for its ability to assist those with mild to moderate depression. According to the Natural Standard Database, SJW has earned a Grade "A" for possessing strong positive scientific evidence based on thorough review of studies. (3) Although other herbs may also be used to treat depression, studies consistently show the effectiveness of SJW for depression while exhibiting minimally reported side effects, in comparison to pharmaceutical antidepressants. This is partially due to the fact that SJW in pure plant or extraction forms is less potent than a single chemical pharmaceutical, which is both stronger and exhibits more side effects.

Dr. Duke's Phytochemical and Ethnobotanical Databases, *Hypericum perforatum* (SJW) has 637 distinct chemical activities, with hypericin and hyperforin being the main two active constituents researched for their antidepressant effects. Most studies involving SJW use the standardized extract form with concentrations of hypericin and hyperforin.

According to a 2003 article in The Journal of the American Medical Association, a study on the *Effect of St John's wort on drug metabolism by induction of Cytochrome P4503A4* was conducted by the Department of Pharmaceutical Sciences at the Medical University of South Carolina. Results indicate that "long term, chronic administration of St. John's wort may result in diminished clinical effectiveness or increased dosage requirements for all CYP3A4 substrates." (Markowitz, Donovan, DeVane, Taylor, Ruan, Wang, Chavin 2003)

In regards to relying on clinical studies as evidence, it is important to weed through the research and create standards for credibility. It would be unwise to base evidence merely on subject title headlines, as there are many factors that lead to study conclusions. For example, one

must evaluate questions like: Who is involved with the study? How many subjects participated? Was the study performed on either humans or animals (in vivo) or in a test tube (in vitro)? What dosage of herb or drug was administered? What plant part was used? Was the study cited? Inadequate standards may result in inconclusive results. It is important to cross reference the evidence, which is part of the intention of this review.

In a health field such as clinical herbalism, where practitioners are suggesting herbs and natural products to clients, the author feels it is a responsibility and duty to provide as much factual information, including the risk of drug-herb interactions, so that individuals can make the best educated choices available to them. Individuals are more likely to follow recommended protocol when given thorough information about why a specific herb is or is not suggested. It is especially helpful when this information, education and suggesting is made by an experienced and qualified practitioner. With proper education from all sides, SJW may in fact be a terrific alternative to taking anti-depressant medications for treating mild to moderate depression, but remains a conversation to have with the prescribing physician.

Conclusions and Recommendations

Over the last 30 years, *Hypericum spp*. aka: St. John's wort (SJW) has been one of the most thoroughly researched plant medicines regarding herb-drug interactions. The majority of clinical studies have shown with consistency that SJW is an effective antidepressant for mild to moderate depression, which makes it a highly valuable and in demand herbal medicine, especially when taken alone.

Numerous drug interactions with SJW have been reported and documented, mostly due to the metabolism by CYP450 and P-glycoprotien. When SJW is taken concurrently with specific

prescription medications, risks include either a decrease in the therapeutic effects from the drugs or the risk of increased side effects, which can prove to be potentially toxic.

Study findings appear to suggest that CYP3A4 is the metabolic pathway most often responsible for, although not completely exclusive to, many drug-herb interactions with SJW. Approximately 50% of all pharmaceutical drug interactions with SJW occur thorough CYP450 metabolism.

With this in mind, it's important to know exactly what drugs will interact if taken concurrently with SJW. Whether or not the pharmaceutical has a narrow therapeutic index should be known to both doctors and patients. If a drug has not been found to have interactions with SJW, this could be due the possibility of no serious drug-herb interaction or possibly due to lack of available research.

Although SJW is one of the most studied herbal dietary supplements on market, there is still a large gap of unknown information. It is extremely unlikely that individual studies on the metabolic influences for every single drug will ever be complete. Drugs that have found to be effected by herbs or other substances based on basic lab science do not always result in conclusive evidence.

With 50% of pharmaceuticals being metabolized via CYP3A4 proving to have some kind of interaction with SJW, this does not indicate lack of risk for the other 50% of undocumented drug interactions. This lack of information is not intended to give a false sense of security, yet indicates a need for continued research, further investigation and a willingness to explore the possible integration of SJW with the prescribing physician. It cannot be predicted which untested drugs will or will not be affected by SJW, so caution is still advised. It is imperative

that blood levels of medications be appropriately monitored by a health professional, especially with concurrent use of SJW.

Recommendations for further research with SJW includes studies focusing more on human trials, drugs not yet tested for interactions and drugs which are contraindicated based merely on theory vs. actual study. Many herbalists prefer to make medicine from fresh plant material. With that in mind, studies based on a variety of extraction methods using both fresh and dried non-standardized extracts in menstrums such as ethanol, glycerin or oil. In addition, topical application of SJW oil for nerve and muscle pain management would be an interesting topic to see researched.

It is the author's intention that this report may be utilized by physicians, nurses, pharmacists and other healthcare practitioners who prescribe and distribute pharmaceuticals, as well as any health care practitioners working with clients taking prescribed medications and herbs. This report can be used not only as reference for which specific drugs to avoid while taking SJW, but also to note which drug categories are not metabolized via specific metabolic pathways (CYP3A4, CYP2E1, CYP2D6, CYP2C9 & CYP1A2). The exclusion of information on specific drugs or studies showing interactions with SJW does not imply it is safe to take SJW while on medications. However, it is worth exploring with a prescribing physician, as SJW is a powerful plant medicine if used appropriately and under the right circumstances.

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ADDENDUM

DATABASE #1: Natural Medicines Comprehensive Database *Unbiased, Scientific Clinical Information on Complementary, Alternative, and Integrative Therapies.*

5-HT1 AGONISTS ("Triptans") <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = D

Theoretically, concomitant use of St. John's wort with selective serotonin agonists can increase the risk of serotonergic adverse effects and possibly serotonin syndrome. Concomitant use should be avoided (9204). The "triptans" include frovatriptan (Frova), naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex), and zolmitriptan (Zomig). Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome (8056).

ALPRAZOLAM (Xanax) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = Moderate • Occurrence = Likely • Level of Evidence = B

St. John's wort may decrease the effect of alprazolam. Alprazolam, which is used as a probe for cytochrome P450 3A4 (CYP3A4) activity, has a two-fold increase in clearance when given with St. John's wort. St. John's wort reduces the half-life of alprazolam from 12.4 hours to 6 hours (10830).

AMINOLEVULINIC ACID <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Concomitant use with St. John's wort extract may cause synergistic phototoxicity. Delta-aminolevulinic acid (an investigational drug used in oncologic diagnostic procedures) can cause a burning erythematous rash and severe swelling of the face, neck, and hands when taken with St. John's wort (9474).

AMITRIPTYLINE (Elavil) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = Moderate • Occurrence = Likely • Level of Evidence = B

Concomitant use can reduce serum concentrations of amitriptyline by 22% and its metabolite, nortriptyline, by 42% (1378,7808). St. John's wort induces intestinal and hepatic CYP3A4 and intestinal P-glycoprotein/MDR-1, a drug transporter, which increases amitriptyline clearance (1340).

ANTIDEPRESSANT DRUGS <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Concomitant use can lead to increased adverse effects and increase the risk of serotonergic side effects, including serotonin syndrome (166,542,3569). Although this effect has only been reported with nefazodone (Serzone), paroxetine (Paxil), and sertraline (Zoloft), it might also occur with other antidepressants. Use of St. John's wort with other antidepressants should only be done with close supervision. Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome (8056).

BARBITURATES <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = Moderate • Occurrence = Likely • Level of Evidence = D

St. John's wort can decrease barbiturate-induced sleep time (758). Some of these sedative medications include pentobarbital (Nebutal), phenobarbital (Luminal), secobarbital (Seconal), and others.

CLOPIDOGREL (Plavix) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = B

Taking St. John's wort with clopidogrel seems to increase the activity of clopidogrel. In clopidogrel non-responders, taking St. John's wort seems to induce clopidogrel metabolism to its active metabolite and therefore increase clopidogrel's antiplatelet activity (13038). Theoretically, in clopidogrel responders, this might lead to an increased risk of bleeding.

CONTRACEPTIVE DRUGS <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = B

St. John's wort can decrease norethindrone and ethinyl estradiol levels by 13% to 15%, resulting in breakthrough bleeding, irregular menstrual bleeding, or unplanned pregnancy (11886,11887,13099). Bleeding irregularities usually occur within a week of starting St. John's wort and regular cycles usually return when St. John's wort is discontinued. Unplanned pregnancy has occurred with concurrent use of oral contraceptives and St. John's wort extract (9880). St. John's wort is thought to induce the cytochrome P450 1A2 (CYP1A2), 2C9 (CYP2C9), and 3A4 (CYP3A4) enzymes, which are responsible for metabolism of progestins

and estrogens in contraceptives (1292,7809,9204). Women taking St. John's wort and oral contraceptives concurrently should use an additional or alternative form of birth control.

CYCLOSPORINE (Neoral, Sandimmune) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = D

Concomitant use can decrease plasma cyclosporine levels by 30-70% (1234,4826,4831,4834,7808,9596,10628). Using St. John's wort with cyclosporine in patients with heart, kidney, or liver transplants can cause subtherapeutic cyclosporine levels and acute transplant rejection (1234,1293,1301,6112,6435,7808,9596). This interaction has occurred with a St. John's wort extract standardized to 0.3% hypericin and dosed at 300-600 mg per day (6435,10628). Withdrawal of St. John's wort can result in increased cyclosporine levels by 64% (1234,4513,4826,4831,4834). St. John's wort induces cytochrome P450 3A4 (CYP3A4) and the multi-drug transporter, P-glycoprotein/MDR-1, which increases cyclosporine clearance (1293,1340,9204,9596).

CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = B

St. John's wort induces cytochrome P450 1A2, but to a lesser extent than CYP3A4 (9204,10848). Some substrates of CYP1A2 include clozapine (Clozaril), cyclobenzaprine (Flexeril), fluvoxamine (Luvox), haloperidol (Haldol), imipramine (Tofranil), mexiletine (Mexitil), olanzapine (Zyprexa), pentazocine (Talwin), propranolol (Inderal), tacrine (Cognex), zileuton (Zyflo), zolmitriptan (Zomig), and others.

CYTOCHROME P450 2C19 (CYP2C19) SUBSTRATES <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

Preliminary clinical research in healthy males shows that taking St. John's wort for 14 days induces cytochrome P450 2C19 (CYP2C19) and significantly increases metabolism of mephenytoin (Mesantoin). In patients with wild-genotype 2C19 (2C19*1/*1) metabolism was almost 4-fold greater in subjects who received St. John's wort compared to placebo. In contrast,

patients with 2C19*2/*2 and *2/*3 genotypes did not demonstrate a similar increase in metabolism (17405). Theoretically, St. John's wort might increase metabolism of other CYP2C19 substrates. Use St. John's wort cautiously in patients taking drugs metabolized by CYP2C19. Some drugs metabolized by CYP2C19 include amitriptyline (Elavil), carisoprodol (Soma), citalopram (Celexa), diazepam (Valium), lansoprazole (Prevacid), omeprazole (Prilosec), phenytoin (Dilantin), warfarin, and many others.

CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = B

There is contradictory research about the effect of St. John's wort on CYP2C9. Some in vitro research shows that St. John's wort induces CYP2C9, but to a lesser extent than CYP3A4 (9204,10848,11889). St. John's wort also induces metabolism of the S-warfarin isomer which is a CYP2C9 substrate (11890). Other research shows that St. John's wort 300 mg three times daily for 21 days does not significantly affect the pharmacokinetics of a single 400 mg dose of ibuprofen, which is also a CYP2C9 substrate (15546).Until more is known, use St. John's wort cautiously in patients who are taking CYP2C9 substrates. Some substrates of CYP2C9 include celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), and S-warfarin (Coumadin).

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = B

St. John's wort induces cytochrome P450 3A4 (9204,10830,10847,10848,11889). Use caution when considering concomitant use of St. John's wort and other drugs affected by these enzymes. Drugs that might be affected include some calcium channel blockers (diltiazem, nicardipine, verapamil), chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), glucocorticoids, cisapride (Propulsid), alfentanil (Alfenta), fentanyl (Sublimaze), losartan (Cozaar), fluoxetine (Prozac), midazolam (Versed), omeprazole (Prilosec), ondansetron (Zofran), propranolol (Inderal), fexofenadine (Allegra), and numerous others (1290,1292,1293,4835,6425,6473,7808,7810,9204,10830).

DEXTROMETHORPHAN (Robitussin DM, others) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = D

Theoretically, concurrent use might cause additive serotonergic effects and increase the risk of serotonin syndrome (763,6427,8936). Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome (8056).

DIGOXIN (Lanoxin) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

Concomitant use can reduce serum levels and the therapeutic effects of digoxin, requiring dosing adjustments when St. John's wort is started or stopped. St. John's wort extract 900 mg daily can reduce serum digoxin levels by 25% after 10 days in healthy people. St. John's wort is thought to affect the multidrug transporter, P-glycoprotein, which mediates the absorption and elimination of digoxin and other drugs (382,6473,7808,7810,9204).

FENFLURAMINE (Pondimin) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = B

Concomitant use with St. John's wort can increase the risk of serotonergic side effects and serotonin syndrome-like symptoms. St. John's wort 600 mg per day with fenfluramine can cause nausea, headache, and anxiety (3569).

FEXOFENADINE (Allegra) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = Mild • Occurrence = Probable • Level of Evidence = B

A single dose of St. John's wort can decrease the clearance of fexofenadine, resulting in increased plasma concentration of fexofenadine. However, with continued dosing, more than 2 weeks, St. John's wort does not appear to affect fexofenadine levels (9685). Patients taking fexofenadine and who start taking St. John's wort should be monitored for possible fexofenadine toxicity.

IMATINIB (Gleevec) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = A

Taking St. John's wort 900 mg/day decreases serum levels of imatinib by 30% in healthy volunteers. This is most likely due to St. John's wort's inducing effect on cytochrome P450 3A4 (CYP3A4) (11888). Advise patients not to take St. John's wort if they are taking imatinib.

IRINOTECAN (Camptosar) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = A

Concomitant use with St. John's wort can decrease serum levels of irinotecan by at least 50%. Clearance of the active metabolite of irinotecan, SN-38, is increased resulting in a 42% decrease in the area under the concentration curve (9206). St. John's wort is thought to lower drug levels by inducing cytochrome P450 3A4 (CYP3A4) (7092).

MEPERIDINE (Demerol) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Theoretically, concurrent use with meperidine might cause additive serotonergic effects and increase the risk of serotonin syndrome (763,6427,8936). Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome (8056).

MEPHENYTOIN (Mesantoin) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

Preliminary clinical research in healthy males shows that taking St. John's wort for 14 days induces cytochrome P450 2C19 (CYP2C19) and significantly increases metabolism of mephenytoin (Mesantoin). In patients with wild-genotype 2C19, metabolism was almost 4-fold

greater in subjects who received St. John's wort compared to placebo. In contrast, patients with 2C19*2/*2 and *2/*3 genotypes did not demonstrate a similar increase in metabolism (17405).

METHYLPHENIDATE (Concerta, Daytrana, Metadate, Ritalin) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Minor Be watchful with this combination.

Severity = Mild • Occurrence = Possible • Level of Evidence = D

St. John's wort might decrease the effectiveness of methylphenidate. In one report, an adult male, stabilized on methylphenidate for attention deficit-hyperactivity disorder (ADHD), experienced increased attention problems and ADHD symptoms after taking St. John's wort 600 mg daily for 4 months. ADHD symptoms improved when St. John's wort was discontinued (15544). The mechanism of this interaction is unknown. Until more is known, caution patients taking methylphenidate to avoid St. John's wort.

MONOAMINE OXIDASE INHIBITORS (MAOIs) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = D

Theoretically, because St. John's wort might affect serotonin similar to conventional antidepressants (763,3553). Concurrent use might cause additive adverse effects, including hypertension, hyperthermia, agitation, confusion, coma, etc. St. John's wort should be avoided in patients taking MAOIs and for 14 days after MAOI discontinuation.

NARCOTIC DRUGS <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

St. John's wort can increase narcotic-induced sleep time (758) and might also increase analgesic effects (1279).

NEFAZODONE (Serzone) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Concomitant use has been associated with serotonergic side effects, including nausea, vomiting, and restlessness (5074).

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

Concomitant use can decrease serum levels of NNRTIs. St. John's wort can increase the oral clearance of nevirapine (Viramune) by 35%. Subtherapeutic concentrations are associated with therapeutic failure, development of viral resistance, and development of drug class resistance. St. John's wort induces intestinal and hepatic cytochrome P450 3A4 (CYP3A4) and intestinal P-glycoprotein/MDR-1, a drug transporter (1290,1340,4837). Other NNRTIs include delavirdine (Rescriptor), and efavirenz (Sustiva).

NORTRIPTYLINE (Pamelor, Aventyl) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = Moderate • Occurrence = Likely • Level of Evidence = D

Concomitant use can reduce serum concentrations of amitriptyline by 22% and its metabolite, nortriptyline, by 42% (1378,7808).

PAROXETINE (Paxil) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Concomitant use with St. John's wort might increase the risk of adverse effects and serotonin syndrome-like symptoms. People taking St. John's wort and paroxetine together can experience nervousness, hyperactivity, diaphoresis, nausea, weakness, fatigue, lethargy, and incoherence (542,3569). Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome (8056).

PENTAZOCINE (Talwin) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Theoretically, concurrent use with pentazocine might cause additive serotonergic effects and increase the risk of serotonin syndrome (763,6427,8936). Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome (8056).

P-GLYCOPROTEIN SUBSTRATES <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = B

St. John's wort induces P-glycoprotein. P-glycoprotein is a carrier mechanism responsible for transporting drugs and other substances across cell membranes. When P-glycoprotein is induced in the gastrointestinal (GI) tract, it can prevent the absorption of some medications. In addition, induction of p-glycoprotein can decrease entry of drugs into the central nervous system (CNS) and decrease access to other sites of action. Drugs that might be affected include some chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), protease inhibitors (amprenavir, indinavir, nelfinavir, saquinavir), H2 antagonists (cimetidine, ranitidine), some calcium channel blockers (diltiazem, verapamil), corticosteroids, erythromycin, cisapride (Propulsid), fexofenadine (Allegra), cyclosporine, loperamide (Imodium), quinidine, and others (382,1340,7810,11722).

PHENOBARBITAL (Luminal) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

St. John's wort may increase the metabolism of phenobarbital, resulting in loss of seizure control. Plasma concentrations of phenobarbital should be monitored carefully. The dose of phenobarbital may need to be increased when St. John's wort is started and decreased when it is stopped (9204).

PHENPROCOUMON <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

St. John's wort appears to increase the metabolism of phenprocoumon (an anticoagulant that is not available in the US) by increasing the activity of the cytochrome P450 2C9 (CYP2C9) enzyme. This may result in decreases in the anticoagulant effect and international normalized ratio (INR) (9204).

PHENYTOIN (Dilantin) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

St. John's wort may increase the metabolism of phenytoin, resulting in the loss of seizure control. Plasma concentrations of phenytoin should be monitored carefully. The dose of phenytoin may need to be increased when St. John's wort is started and decreased when it is stopped (9204).

PHOTOSENSITIZING DRUGS <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Theoretically, concomitant use might increase the possibility of photosensitivity reactions (166). Some drugs that cause photosensitivity include amitriptyline, quinolones, sulfa drugs, and tetracycline.

PROCAINAMIDE <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = D

Preliminary research in an animal model shows that taking St. John's wort extract increases the bioavailability of procainamide, but does not increase its metabolism (14865). Whether this interaction is clinically significant in humans is not known.

PROTEASE INHIBITORS (PIs) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

Concomitant use can reduce serum concentrations of PIs. In healthy volunteers, St. John's wort can reduce the serum indinavir (Crixivan) area under the curve (AUC) by 57% and the extrapolated trough by 81%. Subtherapeutic concentrations are associated with therapeutic failure, development of viral resistance, and development of drug class resistance. St. John's wort induces cytochrome P450 enzymes and might also affect other PI-type antiretroviral drugs (1290,7808); including amprenavir (Agenerase), nelfinavir (Viracept), ritonavir (Norvir), and saquinavir (Fortovase, Invirase). St. John's wort also induces P-glycoprotein, which can result in decreased intracellular protease inhibitor concentrations and increased elimination (9204).

RESERPINE <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

St. John's wort can antagonize the effects of reserpine (758).

SERTRALINE (Zoloft) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Concomitant use can cause serotonergic side effects, including dizziness, nausea, vomiting, epigastric pain, headache, anxiety, confusion, and feelings of restlessness and irritability (5074).

SIMVASTATIN (Zocor) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Moderate Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = B

Concomitant use can reduce plasma concentrations of the simvastatin metabolite, simvastatin hydroxy acid, by 28%. St. John's wort induces intestinal and hepatic cytochrome P450 3A4 (CYP3A4) and intestinal P-glycoprotein/MDR-1, a drug transporter, which increases simvastatin clearance. St. John's wort does not appear to affect the plasma concentration of pravastatin (Pravachol) and fluvastatin (Lescol), which are not substrates of CYP3A4 or P-glycoprotein. Theoretically, St. John's wort could reduce the effectiveness of other HMG-CoA reductase

inhibitors that are CYP3A4 substrates such as atorvastatin (Lipitor) and lovastatin (Mevacor) (10627).

TACROLIMUS (Prograf, Protopic) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

A St. John's wort extract (Jarsin) 600 mg daily significantly decreases tacrolimus serum levels. Dose increases of 60% may be required to maintain therapeutic tacrolimus levels in patients taking St. John's wort concomitantly. St. John's wort is thought to lower tacrolimus levels due to cytochrome P450 3A4 (CYP3A4) enzyme induction (7095,10329).

THEOPHYLLINE <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Minor Be watchful with this combination.

Severity = Mild • Occurrence = Unlikely • Level of Evidence = D

St. John's wort doesn't seem to significantly affect theophylline pharmacokinetics (11802). There is a single case report of possible interaction with theophylline. A patient who smoked and was taking 11 other drugs experienced an increase in theophylline levels after discontinuation of St. John's wort. This increase has been attributed to a rebounding of theophylline serum levels after St. John's wort was no longer present to induce cytochrome P450 1A2 (CYP1A2) enzyme (3556,7808,9204). However, studies in healthy volunteers suggest that St. John's wort is unlikely to affect theophylline to any clinically significant degree (11802).

TRAMADOL (Ultram) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Probable • Level of Evidence = D

Theoretically, concurrent use with tramadol might cause additive serotonergic effects and increase the risk of serotonin syndrome (763,6427,8936). Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome (8056).

WARFARIN (Coumadin) <<interacts with>> ST. JOHN'S WORT

Interaction Rating = Major Do not take this combination.

Severity = High • Occurrence = Likely • Level of Evidence = B

St. John's wort can decrease the therapeutic effects of warfarin. Taking St. John's wort significantly increases clearance of warfarin, including both the R-isomer and S-isomer of warfarin (11890,15176). This suggests that St. John's wort induces CYP1A2 and CYP3A4, which metabolize R-warfarin and CYP2C9, which metabolizes S-warfarin (11890). St. John's wort can also significantly decrease International Normalized Ratio (INR) in people taking warfarin (1292). In addition, warfarin physically interacts with hypericin and pseudohypericin, active constituents of St. John's wort. When the dried extract is mixed with warfarin in an aqueous medium, up to 30% of warfarin is bound to particles, reducing its absorption (10448). Taking warfarin at the same time as St. John's wort might reduce warfarin bioavailability.

According to Database #1, interactions were determined by evidence based on an in-depth, systematic appraisal and evaluation of all of the scientific evidence. A large team of experts, researchers, and health professionals reviewed over 18,000 clinical trials and other studies. Each study was critically evaluated to determine the reliability and validity of the research based on rigorous evidence-based principles. Based on the relevance, validity, and consistency of research, an evidence-based Safety Rating and Effectiveness Rating was assigned to Hypericum perforatum. These ratings were then analyzed for each ingredient contained to calculate an objective rating.

Interaction Rating

Major: Do not take this combination; contraindicated; strongly discourage patients from using this combination; a serious adverse outcome could occur.

Moderate: Be cautious with this combination. Use cautiously or avoid combination; warn patients that a significant interaction or adverse outcome could occur

Minor: Be watchful of this combination. Be aware that there is a chance of an interaction; advise patients to watch for warning signs of a potential interaction.

Likelihood of Occurrence

Likely: Clinical research indicates that this interaction is likely to occur in most patients.

Probable: Clinical research or pharmacokinetic studies in humans suggests that this interaction will occur in a significant portion of patients.

Possible: Clinical research, pharmacokinetic data in humans or animals, or in vitro research suggest that this might occur in some patients.

Unlikely: Clinical research, pharmacokinetic data in humans or animals, or in vitro research suggest that this interaction can occur, but is not likely to occur in many patients.

Severity

High: Life threatening or severe impairment possible

Moderate: Moderate impairment or significant discomfort possible

Mild: Mild impairment or mild discomfort possible

Insignificant: Drug levels may be affected, but a clinically significant interaction is not likely.

DATABASE #2: Natural Standards Database

Interactions with Drugs

- **5HT1 agonists (triptans)**: Interaction with various triptan medications, via enhanced serotonergic activity, is possible in theory. Examples include **nartriptan (Amerge®), rizatriptan (Maxalt®), sumatriptan (Imitrex®), and zolmitriptan (Zomig®**).
- **Anesthetics:** Based on human case reports, use of St. John's wort before anesthesia may cause complications, including cardiovascular collapse and delayed emergence (180; 181). 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 six months prior to surgery. The patient had undergone uneventful general anesthesia two years earlier when she was not taking St. John's wort (182).
- **Antianxiety drugs:** Based on laboratory study, St. John's wort has been shown to act on various neurotransmitter receptors, including GABA and benzodiazepine receptors (183; 184). 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 (35;36;60;185; 186). 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 (187).
- **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 (186;188;189).
- **Anticoagulants and antiplatelets**: Based on human study, St. John's wort may reduce effects of **warfarin** (lowered International Normalized Ratio [INR]) (41;72). 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 (34;72;73). 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 (190).

- **Antidepressant agents:** Based on human, animal and laboratory study, St. John's wort is thought to inhibit monoamine oxidase and serotonin reuptake (183;191;192;193;194; 195).
- Antidepressant agents, selective serotonin reuptake inhibitors (**SSRIs**): Based on animal study, St. John's wort may inhibit the reuptake of serotonin (195). 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 (54;199; 200;201).
- Antidepressant agents, **tricyclic (TCAs**): Based on human study, St. John's wort may cause a significant reduction in amitriptyline concentration (202;203). A number of CYP enzymes including 1A2, 2C19, 3A4, and 2D6 are involved in the metabolism of tricyclic antidepressants (204). 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 (49;136).
- **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 (36). One study showed that St. John's wort significantly altered gliclazide pharmacokinetics in 17 out of 21 patients, and the interaction was independent of the individuals' cytochrome P450 2C9 (CYP2C9) genotype (205). St. John's wort has also been shown to alter glucose metabolism in in vitro study (40).
- **Antifungals**: Based on human study, concomitant intake of St. John's wort may decrease plasma levels of **voriconazole** (206).
- **Antihistamines:** Clinical study has demonstrated increased clearance of fexofenadine in response to St. John's wort, presumed to be due to MDRI induction (60;207).
- **Antihypertensives:** St. John's wort has reportedly caused hypertension (45) and tachycardia, based on human case reports (46;47;128;133). The effects of St. John's wort with antihypertensive agents are not well understood.
- **Antilipemic agents, HMG-CoA reductase inhibitors**: St. John's wort has reportedly lowered concentrations of **simvastatin and its metabolite**, but not pravastatin (210;211). The mechanism for this interaction is likely induction of CYP450 3A4 (211). 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 (212).
- **Antineoplastic agents**: Based on in vitro study, St. John's wort reduced serum levels of etoposide (Etoposide®), a topoisomerase II inhibitor, presumably through induction of CYP3A4 (79). 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 (79). St. John's wort has also been shown to increase **imatinib** clearance in human study (213;214). 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 (77;78).

- **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 (56).
- **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 (34;56;57).
- **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 (35;36;60;185;186). 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 (185). A human study reported reductions of **midazolam** concentrations, presumed to be due to CYP3A4 induction (35;36;60).
- **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 (225). Reductions have also been noted in **nifedipine** concentrations (35).
- **Carbamazepine:** Based on human study, St. John's wort was observed to *have no effect on carbamazepine concentrations* (226). Hypericin and pseudohypericin pharmacokinetics were *only marginally influenced* by co-medication with the enzyme inhibitor **cimetidine** and the enzyme inducer carbamazepine (227).
- **Cardiac glycosides:** According to human study, treatment with Hypericum extract may decrease **digoxin** levels and increase digoxin clearance, possibly through induction of P-glycoprotein (34;75;76;203;228;229;230;231). The interaction may vary within St. John's wort preparations and doses, particularly of hyperforin (232). *Low-hyperforin St. John's wort does not appear to have an effect on plasma digoxin* (233).
- **Chlorzoxazone (Paraflex®, Parafon Forte®, Relaxazone®, Remular-S®)**: 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 (39).
- **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 (41;42;234;235;236;237;238).
- **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 (239).
- **Cytochrome P450 metabolized agents**: In a systematic review of 19 trials with available plasma data, *three reported no important interaction between St. John's wort and pharmaceutical drugs*, and 17 described a decrease in systemic bioavailability of a conventional drug (176). 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 (5;31;32;33;34;35;36;37;186;209;240;241). However, other studies have failed to show such induction or inhibition of enzymes (36;209;233;241;242).

- **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 (41;42;234;235;236; 237)
- **Immunosuppressants:** Decreases in mycophenolic acid levels in association with St. John's wort use have been observed in human study (245). 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 (245;245;246; 246;247). There are numerous reports of significant reductions in cyclosporine drug levels and possible organ rejections with concomitant use of St. John's wort (58;59;60;61; 62;63;64;65;66;67;68;69;70;248). A significant drop in **cyclosporine** levels was observed in kidney transplant recipients (59;63;64;65;66;67;146;249), in heart transplant recipients (68;70), and in a liver transplant recipient (69) taking St. John's wort, a drop which increased after St. John's wort was discontinued (61;62). 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 (34;67).
- **Loperamide (Imodium®):** Delirium and agitation were reported in one patient taking loperamide (Imodium®), St. John's wort, and valerian (250). The condition resolved rapidly with discontinuation of treatment.
- **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 (255).
- **Opiates:** A case of decreased **methadone** levels associated with St. John's wort in a chronic methadone user has been reported (256). Interactions with **oxycodone** and **fentanyl** have also been proposed.
- **P-glycoprotein-regulated drugs**: St. John's wort is considered an inducer of P-glycoprotein (230). Human and in vitro studies have shown that hyperforin and hypericin inhibit the active efflux of fluorescent markers **daunorubicin** and **calcein-AM** (257;258). St. John's wort increased the expression and enhanced the drug efflux function of P-glycoprotein in peripheral blood mononuclear cells of healthy volunteers (260).
- **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 (43). A phototoxic reaction was observed in a patient experimentally treated with **δ-aminolaevulinic acid** for breast cancer who also had been taking St. John's wort (44).
- **Theophylline** (CYP 1A2): It remains unclear if serum levels of theophylline or its metabolites are affected by St. John's wort (34). One report describes a 42 year-old woman who experienced lowered serum theophylline levels upon concomitant ingestion of 300mg daily of St. John's wort. The patient was on several other medications and smoked tobacco. Within one week of discontinuation of St. John's wort, her theophylline

level rose from 9ug/mL to 19ug/mL (261). However, in a 48-hour study in 12 healthy volunteers given both agents (theophylline 400mg and St. John's wort 300mg), *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 (262).

- **Thyroid hormones:** Based on a retrospective case-control study, elevated thyroid stimulating hormone levels may be associated with taking St. John's wort (263). However, this small retrospective sample does not present a clear, significant relationship or imply causality.
- Evidence which was not based on human interactions was deleted from the above list, unless mixed in with human study reports in the same sentence.

Database # 3: Excerpts from Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. Benzie IFF, Wachtel-Galor S, editors. Chapter 11-Medical Attributes of St. John's Wort (Hypericum perforatum) (2011)

Fexofenadine is a nonsedating **antihistamine** used for treating allergic rhinitis and urticaria (Markham and Wagstaff 1998). Clinical studies have found that the effects of SJW on fexofenadine vary depending on dose and duration. A single treatment caused a 45% increase in the maximum plasma concentration, presumably by inhibiting P-gp (Wang et al. 2002). Conversely, a 12-day treatment caused a 35% decrease in Cmax (maximum plasma concentration; Wang et al. 2002) and a 60% increase in oral clearance of fexofenadine (Dresser et al. 2003), suggesting P-gp induction.

Digoxin and **other members of the digitalis family** of **cardioactive drugs** from the Digitalis (foxglove) plant also show side effects when used in conjunction with SJW. Whereas a single dose of SJW had no measureable impact on digoxin pharmokinetics, a 10-day treatment of SJW extract showed decreased Cmax and AUC (area under the plasma concentration-time curve) of digoxin compared to placebo (Johne et al. 1999). However, Mueller et al. (2004) and Arold et al. (2005) found that *patients who were administered low-hyperforin preparations of SJW had little in the way of decrease in digoxin AUC*. Thus, the pharmacokinetic effect is apparently due to the induction of intestinal P-gp caused by multiple doses of SJW high in hyperforin.

The **anticancer drug imatinib mesylate** (**Gleevec**) is a strong inhibitor of specific tyrosine kinases that promote tumor cell proliferation (Collins and Workman 2006). Imatinib is transported by P-gp and metabolized by CYP3A4 and CYP3A5 (Peng, Lloyd, and Schran 2005). Two studies have shown SJW interacts with **imatinib**. Frye et al. (2004) found that 2 weeks of SJW treatment on 10 healthy subjects decreased the AUC by 32%. When working with 12 healthy subjects receiving SJW extracts, Smith et al. (2004), likewise, found increased clearance and reduced **AUC** and **Cmax** for imatinib.

SJW has been shown to affect the pharmacokinetics of the drug **amitriptyline**, **a tertiary amine tricyclic antidepressant** metabolized in the liver by CYP3A4, CYP2C19, and CYP2D6 (Venkatakrishnan, von Moltke, and Greenblatt 1999). A clinical study of 12 patients taking both

SJW and amitriptyline exhibited a decrease in AUC as well as decreases in plasma concentrations (Johne et al. 2002).

Ivabradine is a **selective sinus node channel inhibitor** that decreases cardiac pacemaker activity, allowing for slower heart contractions and more time for blood flow. Intestinal and hepatic CYP3A4 metabolizes ivabradine (Zhou and Lai 2008). In 12 volunteers given SJW for 14 days, the AUC of ivabradine was lowered by 61.7%, while the maximum plasma concentration was lowered by 52.9% (Portoles et al. 2006).

Cyclosporin and **tacrolimus** are **immunosuppressants** commonly used to prevent the body from rejecting transplanted organs (Akhlaghi and Trull 2002; Zhou and Lai 2008). Cyclosporin and tacrolimus are metabolized by CYP3A4 and P-gp (Hebert 1997; Lown et al. 1997; Niwa et al. 2007; Zhou 2008). Concerns over the ability of SJW to interfere with cyclosporin first surfaced with clinical reports of patients receiving transplants (Barone et al. 2000; Mai et al. 2000; Ruschitzka et al. 2000; Ernst 2002). In those cases, patients demonstrated improved immunosuppression once SJW therapy was stopped. Larger studies involving 30 (Breidenbach et al. 2000) and 11 (Bauer et al. 2003) recently transplanted patients found that plasma levels of cyclosporin dropped when receiving SJW treatment, and that cyclosporin levels rose sharply when SJW was stopped. Mai et al. (2003) found that SJW extracts containing high levels of hyperforin induced lower plasma Cmax and AUC than extracts having low hyperforin content. Other studies indicate that patients on other immunosuppressants, such as tacrolimus, experience similar effects (Mai et al. 2003).

Antihypertensive agents have also been shown to interact with SJW. The **calcium channel blocker, verapamil**, is first-pass metabolized by CYP3A4 (Tannergren et al. 2004). Eight males administered SJW for 14 days showed a 78-80% decrease in AUC and a 76-78% decrease in the Cmax of verapamil, compared to the control (Tannergren et al. 2004). Clinical studies on **nifedipine** (Wang et al. 2007) and **talinolol** (Schwarz et al. 2007) revealed similar decreases in their AUC and Cmax values, although the latter may be attributed more to P-gp than CYP3A4 induction.

SJW has been shown to interact with **benzodiazepine sedatives**, including **quazepam, alprazolam**, and **midazolam** (Zhou and Lai 2008). All are metabolized by CYP3A4, although other CYPs play a role (Gorski et al. 1994; von Moltke et al. 1996; Miura and Ohkubo 2004). Studies conclude that interactions with SJW from a 14-day treatment decrease the AUC and Cmax values for the drugs as well as reduce oral clearance and bioavailability (Kawaguchi et al. 2004). The proposed mechanism for the decreased pharmacokinetics is CYP3A4 induction, although SJW did not reduce the sedative effect of quazepam.

The use of SJW may decrease concentrations and nullify the effect of **steroid contraceptives** that are substrates for—and inducers of—CYP3A4 (Thummel and Wilkinson 1998). Moreover, the major component of oral contraceptives, **ethinylestradiol**, is metabolized by CYP3A4 (Guengerich 1988). An analysis conducted by Hall et al. (2003) found that SJW administered concomitantly with a combination oral contraceptive pill containing **ethinylestradiol** and **norethindrone** to 12 healthy premenopausal women caused an increase in the oral clearance of norethindrone and a significant reduction in the half-life of ethinylestradiol, consistent with increased CYP3A activity. However, they found *that SJW did not affect the serum concentrations of follicle-stimulating hormones, luteinizing hormones, and progesterone*. The

authors noted a higher incidence of breakthrough bleeding during the SJW administration phase, a problem also observed by others (Ernst 1999; Yue, Bergquist, and Gerden 2000; Schwarz, Buschel, and Kirch 2003). Breakthrough bleeding often leads to the discontinuation of oral contraceptive use, occasionally resulting in unintended pregnancy (Rosenberg and Waugh 1998). Once SJW was discontinued, menstrual cycles returned to normal; however, alternate forms of birth control are suggested if the use of SJW is continued (Schwarz, Buschel, and Kirch 2003).

SJW can decrease the serum levels of two main classes of **anti-HIV compounds**: (1) **protease inhibitors** and (2) **nonnucleoside reverse transcriptase inhibitors (NNRTIs),** when taken concomitantly. In both cases, the effect is largely due to induction of CYP3A4 (Zhou 2008). An analysis of eight healthy subjects found a 57% decrease in the plasma concentration of the protease inhibitor **indinavir** (Piscitelli et al. 2000). A follow-up study by Ho et al. (2009) found that SJW extract administered to rats stimulated the ability of hepatic and intestinal CYP3A to lower indinavir plasma levels. Decreases in NNRTIs, particularly **nevirapine** and **lamivudine**, were also found when coadministered with SJW. In contrast, a study by L'Homme et al. (2006) found that *SJW did not lower the concentration of nevirapine* when administered to a small group of healthy women.

Warfarin and related compounds are widely used **anticoagulants** synthesized from **coumarin**, a **benzopyrone** found naturally in several plants (Runciman et al. 2002; Yarnell and Abascal 2009). Warfarin is a vitamin K inhibitor, and is used to treat clotting disorders like thrombosis and embolism, as well as myocardial infarction, atrial fibrillation, and stroke (Bovill, Fung, and Cushman 2004). Claims of interactions between SJW and coumarin-derived anticoagulants were first made in cases observed in Sweden (Ernst et al. 1998 Yue, Bergquist, and Gerden 2000). Subsequent controlled studies found that healthy males given SJW had higher clearances of anticoagulant than the control group (Jiang et al. 2004; Jiang, Blair, and McLachlan 2006). Since at least one enantiomer of warfarin is metabolized by CYP2C9, Zhou and Lai (2008) suggest the induction of that enzyme by either hyperforin or hypericin in SJW contributes to the clearance of warfarin.

The **antifungal agent, voriconazole**, is metabolized mainly by CYP2C19, and also by CYP3A4 and CYP2C9 (Hyland, Jones, and Smith 2003). In a study of 16 men, concomitant SJW treatment for 15 days was found to decrease the AUC of voriconazole by 59%, as well as increasing its oral clearance (Rengelshausen et al. 2005).

*"Since the 1980s, dozens of clinical studies have investigated the effectiveness of SJW. *Some of the studies compared study populations receiving SJW to those receiving placebo. *Compared study populations receiving SJW to those receiving standard antidepressants. *Three-armed, comparing study populations receiving SJW to a second study population receiving a standard antidepressant and a third receiving placebo.*Several meta-analyses of clinical studies have been conducted since the mid-1990s (Linde et al. 1996; Kim, Streltzer, and Goebert 1999; Linde and Mulrow 1998; Barnes, Anderson, and Phillipson 2001; Linde et al. 2005a, b; Clement et al. 2006; Linde, Berner, and Kriston 2009).* ***Perhaps the most comprehensive—and widely recognized—meta-analyses are the Cochrane Reviews*** *published by Linde and associates (Linde et al. 1996, 1998, 2005a; Linde, Berner, and Kriston 2009). *performed through computerized searches of several databases, based on published and unpublished trials*

conducted to that effect. Each review had specific inclusion criteria, with the criteria evolving over time.

Again, only studies highlighting human trials were included for validity.

Database #4: A-Z Guide to Drug-Herb-Vitamin Interactions + website searches for up to date pharmaceutical info.

Protease inhibitors are anti-viral drugs used to treat HIV/AIDS and Hepatitis caused by the Hepatitis C virus, help to prevent viral replication. Some of these include but are not limited to: Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Boceprevir and Telaprevir

Non-nucleoside reverse transcriptase inhibitors are antiretroviral drugs in patients with HIV and help control the genetic material of HIV. So far, only 4 have been approved by the FDA, and include: nevirapine, delavirdine and efavirenz and the next generation NNRTI etravirine.

Immunosuppressive therapy aka: **anti-rejection drugs**, used to help the body accept transplanted tissues. fall into 5 categories which include **1) Glucocorticoids** - Immunosuppressive mechanism, Antiinflammatory effects **2) Cytostatics**- Alkylating agents and Antimetabolites **3) Antibodies**- Polyclonal antibodies and Monoclonal antibodies **4) Drugs acting on immunophilins** – Ciclosporin, Tacrolimus, Sirolimus and 5) other such drugs as- **Interferons, Opioids, TNF binding proteins, Mycophenolate** and **small biological agents** (particularly cyclosporine).

Warfarin, used to thin the blood to prevent blood clots and strokes, are also known as Coumadin, Marevan, Warfilone and Phenoprocoumon (Jarsin, Marcumar).

Digoxin, a cardiac glycoside used to directly increase the force and velocity of myocardial contraction in both healthy and failing hearts, are also known as Lanoxicaps and Lanoxindigoxin.

Oral contraceptives, used to prevent pregnancy, include drugs such as **mini-pills**: estrogen or progesterone Lybrel Micronor, Nor-QD and Ovrette **combination birth control pills** are Alesse, Brevicon, Demulen, Desogen, Levlen, Loestrin, Loestrin Fe, Norinyl, Ortho-Cept, Ortho-Cyclen, Ortho-Novum, Yasmin, Yaz, Jenest-28, Mircette, Necon 10/11, Ortho-Novum 10/11, Ortho-Novum 7/7/7, Ortho Tri-Cyclen, Tri-Levlen, Tri-Norinyl, Triphasil, Apri, Aviane, Estrostep, Estrostep Fe, Genora, Levora, Lo/Ovra, Low-Ogestrel, Microgestin, Microgestin Fe, Modicon, Nordette, Nortrel, Ogestrel, Ovcon, Ovral, Trivora, Zovia and **extended cycle pills** including Lybrel, Seasonale and Seasonique.

Drugs which may contribute to serotonin syndrome when combined with St John's Wort include:

1)Antidepressants: MAOIs, TCAs, SSRIs, mirtazapine, venlafaxine, Opioids, tramadol, pethidine

2) CNS stimulants: phentermine, diethylpropion, amphetamines, sibutramine, cocaine, 5-HT, agonists triptans

3) Psychedelic drugs: methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD)

4) Others: selegiline, tryptophan, buspirone, lithium, linezolid, dextromethorphan, 5-HTP

Reference: Rossi, 2005

Selective serotonin reuptake inhibitors (SSRI) antidepressants, used to treat depression, anxiety, or panic disorder (among other less common uses) and **Serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants,** used for depression, anxiety, neuropathy, or fibromyalgia. These include Paroxetine aka: Paxil and Seroxat; Fluoxetine aka: Apo-Fluoxetime, Novo-Fluoxetine, Nu-Floxetime, PMS-Fluoxetine, Prozac; Nefazodone aka: Dutonin and Serzone and Sertraline aka: Lustral and Zoloft; Venlafaxine aka: Effexor.

Tricyclic Antidepressants, used to treat depression, include Adapin, Alti-Desipramine, Alti-Doxepin, Amitriptyline, Amoxapine, Apo-Amitriptyline, Apo-Desipramine, Apo-Doxepin, Apo-Impramine, Asendin, Clomipramine, Desipramine, Domical, Doxepin, Elavil, Imipramine, Janimine, Lentizol, Ludiomil, Maprotiline, Norpramin, Nortriptyline, Novo-Desipramine, Novo-Doxepin, Nu-Desipramine, Pamelor, Pertofrane, PMS-Desipramine, Protriptyline, Sinequan, Surmontil, Tofranil, Trimipramine Maleate, Tryptizol, Vivactil, Zonalon. Combination Drugs: Triavil, Etrafon

Monoamine Oxidase(MAO) Inhibitors, used to treat depression who do not respond to other anti-depressant therapies. Phenelzine aka: Nardil

Calcium Channel Blockers, antiarrhythmic agents to treat angina, hypertension, and supraventricular tachyarrhythmias, also known as Verapamil

Benzodiazepines, used to treat anxiety, panic attacks, muscle spasms and seizures, fall into five subcategories: 1) 2-keto compounds: chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, and others. 2) 3-hydroxy compounds: lorazepam, lormetazepam, oxazepam, temazepam 3) 7-nitro compounds: clonazepam, flunitrazepam, nimetazepam, nitrazepam 4) Triazolo compounds: adinazolam, alprazolam, estazolam, triazolam and 5) Imidazo compounds: climazolam, loprazolam, midazolam

Chemotherapy drugs, used to kill cancerous cells, include **Alktylating agents**: Busulfan (Myleran), Carboplatin (Paraplatin for Injection), Carmustine (BiCNU for Injections), Chlorambucil (Leukeran), Cisplatin (Platinol, Platinol-AQ Injection), Cyclophosphamide (Cytoxan, Neosar), Ifosfamide (Ifex for injection), Lomustine (CeeNu), Mechlorethamine (Mustargen for Injection), Melphalan (Alkeran), Pipobroman (Vercyte), Polifeprosan 20 with Carmustine (Gliadel Wafer), Streptozocin (Zanosar for Injection), Thiotepa (Thioplex for Injection), Uracil Mustard. Injection),Daunorubicin (Cerubidine for Injection, DaunoXome for Injection), Donorubicin (Adriamycin Injection, Ribex for Injection, Doxil Injection), Idarubicin (Idamycin), Mitomycin (Mutamycin for Injection), Mitoxantrone (Novantrone Injection), Pentostatin (Nipent), Plicamycin(Mithracin). **Antimetabolites:** Capecitabine (Xeloda), Cladribine (Leustatin Injection), Cytarabine (Cytosar-U for injection, Tarabine PFS Injection, DepoCyt Injection), Floxuridine (FUDR for Injection), Fludarabine (Fludara for Injection), Flurouacil (Adrucil for Injection, Efudex, Fluoroplex), Mercaptopurine ({urinethol), Methotrexate (Folex for Injection, Rheumatrex), Thioguanine (Tabloid). **Hormonal**

agonists/antagonists: Anastrozole (Arimidex), Bicalutamide (Casodex), Diethylstilbestrol (Stilphostrol), Estramustine (Emcy), Flutamide (Eulexin), Goserelin (Zoladex), Leuprolide (Lupron Injection), Megestrol (Megace), Nilutamide (Nilandron), Tamoxifen (Nolvadex), Testolactone (Teslac), Toremifene (Fareston). **Mitotic inhibitors:** Etoposide (VePesid), Teniposde (Vumon Injection), Vinblastine (Alkaban-AQ Injection, Velban for Injection, Velsar for Injection), Vincristine (Oncovin Injection, Vincasar PFS Injection). **Immunomodulators:** Aldesleukin (Proleukin for Injection) and Levamisole (Ergamisol). **Miscellaneous Antinoplastics:** Altretamine (Hexalen), Asparaginase (Elspar), Docetaxel (Taxotere for Injection), Hydroxyurea (Hydrea), Interferon alpha (Roferon-A Inection, Intron A for Injection, Alferon N Injection), Irinotecan, Mitotane (Lysodren), Paclitaxel (Paxene, Taxol), Procarbazine (Matulane)

Tyrosine Kinase Inhibitors, used for treating Chronic Myelogenous Leukemia (CML), includes Imatinib.

Camptothecin Analogs, a potent anticancer drug with activity in a broad range of experimental tumor models for carcinomas of colon includes Irinotecan

Proton Pump Inhibitors, used for acid reflux, include Omeprazole
Benzimidazole.

Trizole Antifungal, an antifungal for resistant strains like Candida, includes Variconazole

Histamine H1-Receptor Antagonist Antihistamine, used to treat allergies and itching, include Fexofenadine also known as Allegra, Telfast and Combination Drug: Allegra-D

Theophylline/ Aminophylline, used both orally or intravenously in the treatment of asthma and bronchospasm, includes Amnivent 225 SR, Apo-Theo LA, Lasma, Norphyllin SR, Novo-Theophyl SR, Nuelin SA, Nuelin, Phyllocontin, Slo-Bid, Slo-Phyllin, Theo-24, Theo-Bid, Theo-Dur, Theo-SR, Theochron SR, Theocron, Theolair, Theophylline Ethylenediamine, Truphylline, Uni-Dur, Uniphyllin Continuous, Uniphyl. Combination Drug: Primatene Dual Action

Drug class categories include the most up to date pharmaceutical names for drug references.

Results

INDUCERS - CYTOCHROME P450 (CYP) ENZYMES DRUG TABLE
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CYP1A2	**CYP2B6**	**CYP2C8**	**CYP2C9**	**CYP2C19**	**CYP2D6**	**CYP2E1**	**CYP3A4**
Genetic Polymorphisms			Genetic Polymorphisms	Genetic Polymorphisms	Genetic Polymorphisms		
Carbamazepine **Clotrimazole** **Phenobarbital** **Phenytoin** **Primidone** **Psoralen** **Smoking**	Barbituates Mephenytoin Phenobarbital Phenytoin Primidone Roflumilast	Carbamazepine Phenytoin Rifabutin Rifampin	**Aprepitant** **Barbiturates** **Carbamazepine** **Primidone** **Rifampin** **Vigabatrin**	Barbiturates Norethindrone Phenytoin Rifampin	Carbamazepine Ethanol Phenobarbital Phenytoin Primidone Rifampin	4-methylpyrazole Ethanol Isoniazid	**Amprenavir** **Barbituates** **Carbamazepine** **Clotrimazole** **Dexamethasone** **Efavirenz** **Ethosuximide** **Griseofulvin** **Modafinil** **Nevirapine** **Oxcarbazepine** **Phenobarbital** **Phenytoin** **Prednisone** **Primidone** **Rifabutin** **Rifampin** **Rifapentine** **Ritonavir** **Topiramate**
Herbals **CYP1A2**	**Herbals** **CYP2B6**	**Herbals** **CYP2C8**	**Herbals** **CYP2C9**	**Herbals** **CYP2C19**	**Herbals** **CYP2D6**	**Herbals** **CYP2E1**	**Herbals** **CYP3A4**
			Genetic Polymorphisms	Genetic Polymorphisms			
Hypericum perforatum			*Eleutherococcus senticoccus* ***Hypericum perforatum*** *Panax ginseng* *Panax quinquefolius*				*Eleutherococcus senticoccus* ***Hypericum perforatum*** *Panax ginseng* *Panax quinquefolius*

INHIBITORS - CYTOCHROME P450 (CYP) ENZYMES DRUG TABLE
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CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4
Genetic Polymorphisms			Genetic Polymorphisms	Genetic Polymorphisms	Genetic Polymorphisms		
Amiodarone Atazanavir Cimetidine Ciprofloxacin Citalopram Clarithromycin Diltiazem Enoxacin Erythromycin Estradiol Fluvoxamine Interferon Isoniazid Ketoconazole Methoxsalen Mibefradil Tegaserod	Thiopeta Ticlodipine	Anastrozole Ezetimibe (p) Gemfibrozil Montelukast Nicardipine Sulfinpyrazone Trimethoprim	Amiodarone Atazanavir Cimetidine Clopidogrel Cotrimoxazole Delavirdine Disulfiram Efavirenz Fenofibrate Fluconazole Fluorouracil Fluoxetine Fluvastatin Fluvoxamine Gemfibrozil Imatinib Isoniazid Itraconazole Ketoconazole Leflunomide Lovastatin Methoxsalen Metronidazole Mexiletine Modafinil Nalidixic acid Norethindrone Norfloxacin Omeprazole Contraceptives Paroxetine Phenylbutazone Probenecid Sertraline Sulfamethoxazole Sulfaphenazole Sulfonamides Tacrine Teniposide Ticlodipine Tipranavir Troleandomycin Voriconazole Zafirlukast Zileutin	Cimetidine Citalopram Delavirdine Efavirenz Felbamate Fluconazole Fluoxetine Fluvastatin Fluvoxamine Indomethacin Isoniazid Ketoconazole Lansoprazole Modafinil Omperazole Oxcarbazepine Probenecid Ticlodipine Topiramate	Abiraterone Amiodarone Asenapine Buproprion Celecoxib Chloroquine Chlorphenirami ne Chlorpromazine Cimetidine Cinacalcet Citalopram Clemastine Clomipramine Cocaine Darifenacin Desipramine Diphenhydrami ne Doxepin Doxorubicin Duloxetine Escitalopram Febuxostat Fluoxetine Fluphenazine Halofantrine Haloperidol Hydroxychloroq uine Hydroxyzine Imatinib Levomepromazi ne Methadone Metoclopramide Mibefradil Midodrine Moclobemide Nefazodone Norfluoxetine Paroxetine Perphenazine Propafenone Propoxyphene Propranolol Quinacrine Quinidine Ranitidine Ranolazine Ritonavir Sertraline	Disulfiram	Amiodarone Amprenavir Aprepitant Atazanavir Boceprevir Cimetidine Ciprofloxacin Clarithromycin Cyclosporine Danazol Delavirdine Diltiazem Efavirenz Erythromycin Ethinyl Estradiol Ezetimibe (p) Fluconazole Fluoxetine Fluvoxamine Gestodene Imatinib Indinavir Isoniazid Itraconazole Ketoconazole Methylprednisolone Mibefradil Miconazole Mifepristone Nefazodone Nelfinavir Nicardipine Nifedipine Norethindrone Norfloxacin Norfluoxetine Oxiconazole Posaconazole Prednisone Quinine Ranolazine Ritonavir Roxithromycin Saquinavir Sertraline Telaprevir Telithromycin Troleandomycin Verapamil Voriconazole Zafirlukast Zileutin

					Tegaserod Terbinafine Thioridazine Ticlodipine Tipranavir Tripelennamine		
Herbals **CYP1A2**	**Herbal** **CYP2B6**	**Herbals** **CYP2C8**	**Herbals** **CYP2C9**	**Herbals** **CYP2C19**	**Herbals** **CYP2D6**	**Herbals** **CYP2E1**	**Herbals** **CYP3A4**
			Genetic Polymorphisms	Genetic Polymorphisms			
			Allium sativum *Bergamottin* *Harpagophytum Procumbens* *Lycium barbarum*	*Allium sativum* *Harpagophytum procumbens*	*Alpinia glanga* *Alstonia scholaris* *Andrographis paniculata* *Catharanthus roseus* *Cimicifuga racemosa* *Cinnamomum burmannii* *Eleutherococcus senticoccus* *Gycyrrhiza glabra* *Hydrastis canadensis* *Melaleuca leucadendron* *Panax ginseng* *Panax quinquefolius* *Piper nigrum* *Punica granatum* *Rheum palmatum* *Santalum album* *Strychnos ligustrina* *Syzygium aromaticum* *Tinospora crispa* *Zingiber aromaticum*	*Piper Methysticum*	*Allium sativum* *Ammi visnaga* *Azadirachta indica* *Cimicifuga racemosa* *Harpagphytum procumbens* *Hydrastis canadensis* *Naringenin compounds* *Panax ginseng* *Panax quinquefolius* *Strychnos ligustrina* *Uncaria tom*