Utility of Therapeutic Drug Monitoring in Identifying Clinically Significant Interactions Between St. John's Wort and Prescription Drugs

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ABSTRACT

Background: The general population widely uses herbal medicines, as they are regarded as effective and safe. St. John's wort, which is an effective herbal antidepressant, exhibits both pharmacokinetic and pharmacodynamic interactions with several drugs. The aim of this review was to highlight the clinically significant interactions of St. John's wort with drugs that require to be monitored to assess their therapeutic effect.

Methods: Published literature was searched using electronic databases, such as MEDLINE, PubMed, and Elsevier ScienceDirect using terms such as “herbal medicine,” “herbal toxicity,” “legislation herbal medicine,” “drug–herb interactions,” “St. John's wort,” and “St. John's wort–drug interactions.” Searches were limited to the English language, and there was no restriction on the date of publication.

Results: St. John's wort exhibits a number of pharmacokinetic and pharmacodynamic interactions with drugs. The most dangerous interactions occurred when used concurrently with the immunosuppressants, cyclosporine, and tacrolimus (treatment failure or organ rejection) or warfarin (treatment failure resulting in thromboembolic events) or antiretroviral agents (treatment failure and the emergence of new viral variants that are resistant to conventional drugs).

Conclusions: Patients should consult their health care providers before consuming herbal supplements, especially St. John's wort, to avoid potentially dangerous drug–herb interactions.

Keywords: antiretrovirals; drug interactions; immunosuppressants; St. John's wort; therapeutic drug monitoring; warfarin

INTRODUCTION

Medicinal plants (herbal medicines) are the oldest known products used in health care. Each culture or country has developed its pharmacy of locally grown plants.[1] Herbal medicine constitutes a major part of the traditional medical system in Japan, China, Africa, and India (Ayurveda). These herbal remedies are used by approximately 80% of the population in developing countries and are gaining popularity in developed countries.[2,3]

The regulation of the production and use of herbal medicines varies between countries. In Europe, the Committee on Herbal Medicinal Products issues scientific opinions on herbal substances and preparations along with information on recommended uses and safety conditions on behalf of the European Medicines Agency. This gives companies and national competent authorities a clear reference point when preparing or assessing an application for marketing authorization or registration of herbal medicinal products in the European Union Member States.[4] According to a US federal law (Dietary Supplement Health and Education Act of 1994),[5] herbal medicine is defined as a type of dietary supplement containing one or more herbs, plants (other than tobacco), algae, fungi, or lichen that is often used in addition to conventional medical treatments to preserve or recover health. The US Food and Drug Administration (FDA) prohibits herbal supplement manufacturers and distributors from marketing products that are adulterated or misbranded, providing limited regulation.[6] In China, The National Medical Products Administration (formerly called the China Food and Drug Administration) ensures that all herbal products undergo stringent technical evaluations and clinical trials to demonstrate their safety.[7] In Japan, an approval system ensures that herbal products adhere to the same regulations as conventional medicines.[7]

Several herbal medicines are used solely for general well-being and the prevention of common ailments. There is, however, the misconception that herbal medicines are safe for consumption and effective because they are natural. As some herbal products contain toxic phytochemicals, this misinformation may pose health threats. For example, Kratom, which is available as an herbal supplement in the United States, is prepared from the leaves of the Southeast Asian plant *Mitragyna speciosa* and contains alkaloids with opioid properties.[8] *M. speciosa* has been used for centuries in Southeast Asia for its stimulatory and analgesic effects. In the United States, *M. speciosa* is used to treat pain or mood disorders. However, this product is reported to exert toxic effects and has been associated with 4 fatalities.[8]

Approximately 20,000 herbal products are reported to be commercially available. The 10 most used herbal supplements are St. John's wort, echinacea, ginseng, *Ginkgo biloba*, garlic, peppermint, ginger, soy, chamomile, and kava.[9] Population surveys have indicated that approximately a third to half of the American population consumes dietary supplements on a regular basis.[10] The Natural Medicine Comprehensive Database has a list of 54,000 dietary supplements, of which approximately 12% have indicated safety concerns. In the United States, an estimated 23,000 annual emergency department visits are ascribed to toxicity related to the use of herbal supplements.[11]

Many patients are likely to consume herbal medicines concurrently with prescription drugs owing to the popularity of herbal medicines.[12] This is a threat to patient health as several clinically significant drug–herb interactions may cause treatment failure or drug toxicity. In the United States, 20%–30% of patients have been estimated to concurrently use herbal supplements and conventional drugs.[13] Furthermore, 94% and 83% of patients in Taiwan and Korea, respectively, simultaneously use prescription drugs and herbal supplements.[14] Thus, clinically significant drug–herb interactions are a growing problem in patient management.

Among the many drug–herb interactions that have been reported, St. John's wort is an herbal supplement that has been demonstrated to have the most interactions with drugs. Supplements, such as curcumin, echinacea, garlic, Asian ginseng, green tea extract, and kava, have been reported to cause interactions, albeit with a limited number of medications. A low likelihood of drug interactions has been reported with other supplements, such as black cohosh, cranberry, milk thistle, American ginseng, and saw palmetto, as they are considered relatively safe to consume with most medications.[15] Sood et al[16] performed a 85 question survey on 1818 patients to determine the use of 52 complimentary alternative medicines. The study involved a cross-section, point-of-care survey of patients treated in 6 different specialty clinics (General Internal Medicine, Oncology, Physical Medicine, Fibromyalgia Clinic; Preoperative Clinic; Spine Center) at the Mayo Clinic in Rochester, Minnesota. The authors noted 107 drug–herb interactions of clinical significance.[16] The herbal supplements which resulted in the most adverse reactions (68%) were St. John's wort, ginkgo, garlic, valerian, and kava, whereas antidepressants, antidiabetic, sedatives, and anticoagulation medications accounted for 94% of all clinically significant interactions.[16]

This minireview highlights the clinically significant interactions of St. John's wort with drugs that require to be monitored to assess their therapeutic effect.

MATERIALS AND METHODS

A review of the literature was performed using electronic databases, such as MEDLINE, PubMed, and Elsevier Science Direct with various search terms, including “herbal medicine,” “herbal toxicity,” “legislation herbal medicine,” “drug–herb interactions,” “St. John's wort,” and “St. John's wort–drug interactions.” Searches were limited to the English language, and there were no restrictions on the date of publication. After reviewing the abstracts, only relevant papers were carefully analyzed.

ISSUES ASSOCIATED WITH HERBAL MEDICINES

Medicinal plant formulations are prepared in several ways depending on the plant and ailment being treated. These preparations vary from liquids (tinctures, macerations, infusions, and decoctions) to ointments and tablets. Irrespective of the formulation, the concentrations of active ingredients in the preparation may vary significantly from one brand to another. Furthermore, the concentrations of active ingredients may exhibit “intrabrand” variations, which can be attributed to seasonal variations of the active ingredient in the plant, harvesting conditions, processing, and storage of the product. An analysis of ginseng products revealed that the active compound

content varied by a factor of 10 between brands, whereas some brands contained no active compounds. Furthermore, adulteration of Chinese herbal medicines with synthetic drugs has been reported to be an additional problem.[17]

A major problem associated with the use of herbal supplements is poor manufacturing practices. In 2008, the FDA initiated a program to inspect the manufacturing processes of herbal supplements in the United States. Approximately 50% of the manufacturing facilities inspected between 2008 and 2012 violated good manufacturing practices.[18] The violations included a lack of standardized methods used to prepare the product, as well as the use of nonsterile conditions. Moreover, testing was not performed to verify the identity of active herbal ingredients. Genetic testing of commercial herbal products revealed DNA from 91% of the 44 herbal supplements manufactured by 12 companies. DNA barcoding analyses revealed that only 2 of the 12 companies provided products that contained DNA matching the plant listed as the active ingredient. In addition, 59% of the herbals contained plant species that were not listed on the product labels, whereas 33% of the herbals contained DNA that matched rice, soybeans, or wheat.[18]

ST. JOHN'S WORT: CLINICAL EFFICACY, ACTIVE INGREDIENTS, AND TOXICITY

St. John's wort is an herbal antidepressant that is sold in the form of an alcoholic or dried extract of *Hypericum*, a perennial aromatic shrub that grows in Europe and Asia. This shrub has bright yellow flowers, which bloom from June to September. The flowers are believed to be the most abundant and brightest around the 24th of June, the day that is traditionally believed to be the birthday of St. John the Baptist (hence the name St. John's wort).[19] St. John's wort is a popular herbal remedy recommended by traditional herbal practitioners primarily for the treatment of depression. Furthermore, St. John's wort is licensed and widely prescribed for the treatment of depression in some European countries. St. John's wort is also traditionally used for treating a diverse range of disorders, including bacterial and viral infections, respiratory tract infections, skin wounds, peptic ulcers, and inflammation.[20] The German Commission E designated St. John's wort as an approved herb in 1984. Currently, St. John's wort is one of the most widely consumed medicinal plants worldwide.[21] The importance of St. John's wort as a dietary supplement has significantly increased in the last few years. The annual market for St. John's wort has reached $210 million in the United States alone and more than $570 million worldwide.[22]

St. John's wort extracts contain several biologically active compounds, including naphthodianthrones (hypericin and pseudohypericin), phloroglucinol derivatives (hyperforin and adhyperforin), flavonoids (rutin, hyperoside, isoquercitrin, quercitrin, and quercetin), bioflavonoids, proanthocyanidins, and chlorogenic acids. The standardization of St. John's wort products is usually based on the content of hyperforin (3.0%) and hypericin (0.3%–0.5%).[23] Several authors have determined the concentrations of active components in various commercially available St. John's wort products. In a German study of 33 different St. John's wort products, the hyperforin content varied between <0.5 mg per dose (<0.2% of extract) to 13 mg per dose (approximately 4.3% of extract), whereas the hypericin content varied between

0.1% and 0.3%.[24] The wide variations in hyperforin content in commercially available St. John's wort preparations can be attributed to several factors. Environmental factors, such as temperature, light quality, light intensity, and nutrient availability, affect the levels of secondary metabolites in plant tissues, resulting in varied chemical profiles. The phytochemical composition of St. John's wort is dependent on the season, region, and temperature. Furthermore, controlling the quality of plants grown in the field is challenging.[25] Hyperforin and rutin contents of St. John's wort are reported to be significantly influenced by temperature (18°C–23°C) and light intensity (49–147 $\mu mol \cdot m^{-2} \cdot s^{-1}$ photosynthetic photon flux density).[26]

A meta-analysis of 27 clinical trials with a total of 3808 patients, revealed that St. John's wort exhibited a response and remission rate comparable with that of selective serotonin reuptake inhibitors (SSRIs) but with a significantly lower discontinuation/dropout rate,[27] as well as a decrease in the number and severity of side effects.[28] In contrast to tricyclic antidepressants, which exert cardiotoxic effects at higher doses, St. John's wort has no reported adverse cardiac effects. A European drug-monitoring study of 3250 patients reported an overall adverse event incidence of only 2.4% for the clinical use of a commercial St. John's wort extract in the treatment of depression. The most commonly reported side effects were gastrointestinal irritation (0.6%), allergic reactions (0.5%), fatigue (0.4%), and restlessness (0.3%).[29] Phototoxicity is another potential adverse effect of St. John's wort due to hypericin, which is a photosensitizer. A patient consuming St. John's wort was reported to develop a severe phototoxic reaction to laser light at 532 nm and an exaggerated and unexpectedly severe response to pulsed dye laser light at 585 nm.[30] St. John's wort appears to be a significant radiosensitizer for photon radiotherapy and can cause severe skin toxicity in patients receiving this therapy while taking this herbal supplement.[31] Therefore, herbalists prescribing St. John's wort to a patient must warn against direct sun exposure practices, such as sunbathing.

ST. JOHN'S WORT–DRUG INTERACTIONS: AN OVERVIEW

St. John's wort interacts with several common medications. The use of St. John's wort with oral contraceptives, anticoagulants, benzodiazepines, cancer chemotherapy medicines, digoxin, antiretrovirals, statins, immunosuppressants, SSRIs, or verapamil is not recommended as it can reduce the concentration of most of these drugs in the body, resulting in impaired efficacy and treatment failure.[32] Furthermore, serotonin syndrome (with possible mania) is the main concern with the use of St. John's with antidepressants, such as SSRIs. The National Center for Health Statistics conducts the National Ambulatory Medical Care Survey (NAMCS) annually to characterize the provision of ambulatory medical care in the United States. Davis et al[32] searched the 1993–2010 NAMCS for visits that mentioned St. John's wort. In the 18-year search period, St. John's wort was mentioned in 2,230,000 visits (120,000 visitors per year). Of these, 28% (620,000 visits over the 18-year study period) were related to interactions between St. John's wort and drugs not recommended for concurrent use.[32] Leading medications that interacted with St. John's wort included SSRIs (13.7% of visits), benzodiazepines (9.8% of visits), warfarin (4.2% of visits), statins (3.3% visits), verapamil (1.0% of visits), digoxin (1.0% of visits), and oral contraceptives (0.6% of visits).[32]

Clinically significant drug interactions with St. John's wort have been reported with anticancer (imatinib and irinotecan), antiretroviral (eg, indinavir, lamivudine, and nevirapine), anti-inflammatory (eg, ibuprofen and fexofenadine), antimicrobial (eg, erythromycin and voriconazole), cardiovascular (eg, digoxin, ivabradine, warfarin, verapamil, nifedipine, and talinolol), central nervous system (eg, amitriptyline, buspirone, phenytoin, methadone, midazolam, alprazolam, and sertraline), hypoglycemic (eg, tolbutamide and gliclazide) and immunomodulating drugs (eg, cyclosporine and tacrolimus), oral contraceptives, proton pump inhibitors (eg, omeprazole), respiratory system agents (eg, theophylline), and statins (eg, atorvastatin and pravastatin).

PHARMACOKINETIC INTERACTIONS

St. John's wort–drug interactions can be classified into the following 2 broad categories: pharmacokinetic and pharmacodynamic interactions. In pharmacokinetic interactions, St. John's wort is a potent inducer of CYP3A4 and P-glycoprotein (P-gp) and may inhibit or induce other CYPs depending on the dose, route, and duration of administration. This may cause treatment failure as St. John's wort decreases the blood concentrations of amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, methadone, midazolam, nevirapine, phenprocoumon, simvastatin, tacrolimus, theophylline, and warfarin.[33]

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions of St. John's wort occur mostly with psychoactive drugs, such as SSRIs, causing serotonin syndrome, a medical emergency. Hyperforin, a constituent of St. John's wort with antidepressant activity, is a potent ligand for the pregnane X receptor, an orphan nuclear receptor that regulates the expression of cytochrome (CYP) P450 3A4 drug-metabolizing enzyme (and other CYP enzymes).[34]

Treatment of primary human hepatocytes with *Hypericum* extract or hyperforin markedly induced CYP3A4 expression. As CYP3A4 is involved in the oxidative metabolism of >50% of all clinically used drugs, St. John's wort may interact with many drugs that are metabolized by this enzyme.[34] In general, St. John's wort is reported to induce CYP3A4, CYP2E1, and CYP2C19 but does not affect the expression of CYP1A2, CYP2D6, and CYP2C9. Generally, St. John wort–mediated induction of CYP enzymes takes almost 2 weeks, and maximum reductions in drug levels are observed after 14 days. The discontinuation of St. John's wort resulted in CYP enzymes regaining their activity within 2 weeks.[34] St. John's wort has also been reported to induce the clearance of drugs that are minimally metabolized by liver enzymes, such as digoxin and fexofenadine (approximately 5% hepatic metabolites), which are well-known P-gp substrates.[35] The components of St. John's wort may also modulate intestinal CYP enzymes, leading to the decreased bioavailability of some drugs and induction of intestinal P-gp drug efflux pumps.

St. John's wort extract is prepared from the aerial parts of the plants (fresh flowers and leaves). The common mode of extraction is ethyl alcohol extraction. The product is available in the form of capsules, tincture, or St. John's wort oil for skin application. The standard dosage of St. John's

wort in adults and children are 300 and 150 mg, respectively, with some dosage adjustments required in younger children and mature teenagers. Owing to the short half-life of hyperforin (approximately 9 hours), the herb should be taken 3 times per day. Standardized extracts with 0.3% hypericin are recommended.[36] The hyperforin content of St. John's wort contributes to the observed drug interactions. The magnitude of the interaction depends on the concentration of hyperforin in the preparation. No interaction has been observed when the concentration of hyperforin is low.

Several St. John's wort preparations are commercially available, and manufacturers use various methods to produce and maintain product uniformity. The composition of the final product depends on the extraction process. At the end of the 1990s, manufacturers modified the extraction method to obtain stable extracts with 4%–5% of hyperforin. This increase in hyperforin content coincided with the first reports of clinically relevant drug interactions with St. John's wort.[37] In one study, the concomitant administration of *Hypericum* extracts with 41 and 12 mg of hyperforin every day decreased midazolam bioavailability by 80% and 50%, respectively.[38] In another study, 20 volunteers ingested a single dose of midazolam (7.5 mg) after consuming a preparation of St. John's wort containing low doses of hyperforin (0.6 mg) for 2 weeks. No clinically significant interactions were observed between midazolam and St. John's wort.[39] The authors concluded that administration of a St. John's wort product with low hyperforin content results in a mild induction of CYP3A, which is not considered clinically relevant.[39] In another study, renal transplant recipients receiving a St. John's wort extract with a 7 mg/d dose of hyperforin exhibited a 45% lower cyclosporine bioavailability than recipients consuming an extract with 0.45 mg of hyperforin/day.[40]

MECHANISM OF ST. JOHN'S WORT–DRUG INTERACTION

Hyperforin, a constituent of St. John's wort with antidepressant activity, is a potent ligand for the pregnane X receptor, which promotes the transcriptional activation of genes that regulate the enzyme activities of CYP3A4, CYP2E1, and CYP2C19, causing clinically significant drug interactions with many drugs. Components of St. John's wort also regulate the activity of the P-gp pump, particularly hypericin and quercetin.[34] In addition, St. John's wort pharmacodynamically interacts with antidepressants, such as fluoxetine, sertraline, paroxetine, venlafaxine, and classical tricyclic antidepressants, causing serotonin syndrome.[13]

ROLE OF THERAPEUTIC DRUG MONITORING

To identify clinically significant St. John's wort–drug interactions, one approach is to determine the serum levels of hyperforin. To the best of our knowledge, no commercial laboratory offers this test although there are published reports on determining its concentrations using liquid chromatography combined with mass spectrometry. In addition, commercial immunoassays are not available. Therefore, these interactions can be identified only when a clinician notes decreased drug levels in a patient who previously exhibited therapeutic drug levels without changes in dose.

Treatment Failure/Organ Rejection due to Interaction of St. John's Wort With Immunosuppressants

One of the most clinically important pharmacokinetic drug interactions of St. John's wort is that with immunosuppressants. Transplant recipients consuming cyclosporine or tacrolimus may experience acute organ rejection due to self-medication with St. John's wort because it induces the metabolism of both drugs, reducing the whole blood concentrations of these drugs by more than 50%. The first clinically relevant reports of St. John's wort preparations interacting with other drugs and consequently altering their bioavailability and efficacy were published in 2000. This study reported that a pharmacokinetic interaction between St. John's wort and cyclosporine caused acute rejection in a 29-year-old White woman whose maintenance immunosuppression regimen consisted of 100 mg cyclosporine twice daily and 10 mg/d prednisone. The whole blood cyclosporine trough concentrations in the patient were within the therapeutic range (250–300 ng/mL) but decreased to 155 ng/mL 30 days after self-medication with St. John's wort.[41] Since then, various reports of clinically significant interactions of pharmaceutical drugs with this plant have been reported. Alschner and Klotz reported a case study in which a 57-year-old kidney transplant patient consuming cyclosporine (125–150 mg/d) and prednisolone (5 mg/d) exhibited a cyclosporine trough level of 100–130 ng/mL over 2 years.[42] This patient suddenly demonstrated a subtherapeutic cyclosporine concentration of 70 ng/mL despite increasing the daily cyclosporine dose to 250 mg when the patient started taking a tea containing St. John's wort. Five days after discontinuing the herbal tea, the cyclosporine level increased to 170 ng/mL, after which the cyclosporine dose was reduced to 175 mg per day to readjust the cyclosporine whole blood concentration. Subsequently, the trough cyclosporine level returned to 130 ng/mL.[42] It is well known that the hyperforin content of St. John's wort determines the magnitude of the interaction between St. John's wort and cyclosporine[40] and can endanger the success of organ transplantation, leading to several cases of organ rejection.[43]

A significant reduction in the area under the curve (AUC) for tacrolimus was also observed in 10 stable renal transplant patients receiving St. John's wort. The maximum concentration of tacrolimus decreased from a mean value of 29.0 ng/mL to 22.4 ng/mL after the coadministration of St. John's wort.[44] Interestingly, the pharmacokinetic parameters of mycophenolic acid, an immunosuppressant, were not affected by the coadministration of St. John's wort.[45] As immunosuppressants are routinely monitored, clinically significant interactions between St. John's wort and cyclosporine or tacrolimus can be recognized during therapeutic drug monitoring. The transplant team must advise organ recipients on the possibility of organ rejection with the use of herbal supplements, especially those containing St. John's wort.

Clinically Significant Interactions Between Warfarin and St. John's Wort: Role of International Normalized Ratio (INR) Monitoring

Warfarin (Coumadin), an anticoagulant drug, is used for treating among other heart diseases, such as atrial fibrillation, and preventing blood clots in lower extremities (deep vein thrombosis), stroke, and pulmonary embolism.[46] Warfarin therapy should be carefully controlled by measuring the clotting capacity of blood (INR monitoring). A patient undergoing Coumadin (anticoagulant) therapy must avoid St. John's wort because of the potential failure of warfarin

therapy owing to its increased clearance. Jiang et al[47] studied the interaction of warfarin and St. John's wort in 12 healthy subjects and concluded that St. John's wort significantly induced the clearance of both the S and R enantiomers of warfarin, thereby decreasing the pharmacological effect of racemic warfarin. Yue and Jansson reviewed 7 case reports in which the concomitant use of St. John's wort decreased the anticoagulant effect of warfarin (reduced INR). In one of these cases, a 70-year-old woman received warfarin therapy for 2.5 years and had a stable INR (2.5–3.8). However, self-medication with St. John's wort decreased the INR to 1.7. Thus, the warfarin dosage was increased from 18.5 mg/wk to 21.25 mg/wk[48] In another case involving a 76-year-old man, the INR decreased from 2.3 to 1.1 on consumption of St. John's wort. Although none of the patients developed thromboembolic complications, decreased INR levels were considered to be clinically significant. The INR returned to target values after the warfarin dose was increased or after St. John's wort was withdrawn. The reduced effect of warfarin is due to the induction of CYP2C9, which is the major liver enzyme responsible for warfarin metabolism.[48]

Interactions between St. John's wort and other anticoagulants have been reported. St. John's wort decreased the efficacy of clopidogrel, owing to the induction of CYP3A4 in healthy volunteers. However, St. John's wort effectively increased the efficacy of hyporesponders by increasing the enzymatic activity of CYP3A4. The authors concluded that St. John's wort may be a future therapeutic option to increase CYP metabolic activity as well as the antiplatelet effect of clopidogrel in hyporesponders.[49] St. John's wort also decreases the efficacy of direct anticoagulants, such as dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. Grześk et al[50] suggested that patients consuming direct oral anticoagulants should avoid St. John's wort.

St. John's Wort–Antiretroviral Drug Interactions

Interactions between antiretroviral agents and St. John's wort have also been documented. Patients with HIV infection/AIDS consuming amprenavir, atazanavir, zidovudine, efavirenz, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, and saquinavir must avoid the concomitant use of St. John's wort.[51] St. John's wort reduces the AUC of the HIV-1 protease inhibitor indinavir by approximately 57%.[52] In addition, the concomitant use of St. John's wort is reported to decrease the concentrations of nevirapine.[53] Another study also suggested that St. John's wort should be avoided by patients with HIV infection/AIDS who are consuming protease inhibitors and non-nucleoside reverse transcriptase inhibitors.[54] Thus, patients with AIDS undergoing highly active antiretroviral therapy (HAART) must not consume St. John's wort or any other herbal supplement because of the possibility of treatment failure as a result of drug–herb interactions. Therapeutic drug monitoring could be useful for detecting interactions between St. John's wort and antiretroviral treatment. Although the usefulness of therapeutic drug monitoring of protease inhibitors was reported as early as 2001,[55] the accessibility and availability of these facilities are limited.

St. John's Wort–Cardioactive Drug Interactions

The interaction between St. John's wort and digoxin is also clinically significant. St. John's wort usage for 10 days decreased the peak and trough serum digoxin concentrations by 33% and 26%,

respectively. The mean peak digoxin concentrations in the placebo and St. John's wort–treated groups were 1.9 and 1.4 ng/mL, respectively.[56] In a study involving 93 healthy volunteers (56 men and 37 women), the digoxin trough level (19%), digoxin peak level (Cmax) (37%), and digoxin AUC0–4 (37%) decreased after 14 days of coadministration with St. John's wort.[57] As digoxin is a P-gp substrate, and compounds in St. John's wort modulate the activity of P-gp, this is the mechanism in which digoxin concentrations are reduced.[57] As digoxin is routinely monitored, therapeutic drug monitoring can help identify such interactions.

Repeated administration of St. John's wort decreased the bioavailability of the R and S enantiomers of verapamil.[58] The AUC values for R-verapamil and S-verapamil decreased by 78% and 80%, respectively, whereas the maximum concentrations decreased by 76% and 78%, respectively. However, the terminal half-life did not significantly change for R-verapamil and S-verapamil. This effect is most likely caused by the induction of first-pass metabolism of CYP3A4 by St. John's wort in the gut.[58] Although therapeutic drug monitoring services are available in reference laboratories, verapamil is not routinely monitored.

In one study, 12 healthy volunteers received a single oral dose of ivabradine (10 mg), a heart rate–lowering agent with anti-ischemic efficacy, followed by oral St. John's wort administration (300 mg orally, 3 times a day) for 2 weeks. This treatment regimen significantly decreased the highest achieved plasma concentration (Cmax; 6.8 ± 3.7 versus 5.1 ± 2.0 ng/mL; $P < 0.05$) and the AUC (56.2 ± 23.4 versus 38.3 ± 25.1 ng·h/mL; $P < 0.01$) of ivabradine and its metabolite S18982. In addition, the time required to achieve Cmax was shorter, and the apparent terminal half-life values were lower.[59] As ivabradine is not subjected to therapeutic drug monitoring, it is difficult to identify such interactions. In a clinical trial of 9 volunteers, Schwarz et al reported that St. John's wort decreased oral talinolol (beta-blocker) bioavailability by 25% when compared with the control (water). In addition, a 93% increase in oral clearance and a 31% reduction in serum AUC were observed.[60]

St. John's Wort–Theophylline Interactions

Theophylline is metabolized by CYP1A2, CYP2E1, and CYP3A4. The plasma concentrations of theophylline decrease due to the intake of St. John's wort.[35] Theophylline is subjected to routine therapeutic drug monitoring, and interactions can be detected by observing changes in the levels of this drug in the patient.

St. John's Wort–Anticonvulsant Interactions

Anticonvulsants, such as phenytoin, phenobarbital, carbamazepine, and valproic acid, are routinely monitored. Therefore, drug–drug interactions or drug–herb interactions can be detected. Concurrent use of St. John's wort and phenytoin decreases the serum concentration of phenytoin.[61] However, interestingly, a clinically significant interaction between carbamazepine and St. John's wort has not been reported.[62] Brivaracetam, an antiepileptic drug that is indicated for the treatment of focal seizures, is associated with improved safety and tolerability when compared with first-generation antiepileptic drugs. St. John's wort may decrease brivaracetam

levels, as it inhibits CYP2C19. Therefore, caution should be exercised when including this herbal supplement in treatment of seizures.[63]

St. John's Wort–Anticancer Drug Interactions

The clearance of imatinib mesylate, an anticancer drug, increases when coadministered with St. John's wort, resulting in a decreased clinical efficacy of the drug. In a study involving 10 healthy volunteers, a 2-week treatment regimen with St. John's wort significantly reduced the maximum plasma imatinib concentration and AUC by 29% and 32%, respectively. Meanwhile, the half-life of the drug decreased by 21%.[64,65] St. John's wort also exhibits significant interactions with the anticancer drug irinotecan. In a study involving 5 patients, St. John's wort (900 mg per day) coadministration for 18 days, resulted in ~42% reduction in the concentration of SN-38 (the active metabolite of irinotecan). This reduction also decreased myelosuppression.[66] For both drugs, therapeutic drug monitoring can be used. Therapeutic drug monitoring of imatinib may provide additional information on efficacy, compliance, and safety when compared with clinical evaluation alone. Patients with suboptimal responses to treatment, treatment failure, rare adverse events, drug interactions, or suspected nonadherence will attain the best benefit from therapeutic drug monitoring.[67] Therapeutic drug monitoring of several anticancer drugs, including cyclophosphamide, ifosfamide, cisplatin, methotrexate, pemetrexed disodium, capecitabine, 5-fluorouracil, gemcitabine, doxorubicin, fulvestrant, tamoxifen, and irinotecan has clinical utility to minimize toxicity and improve the safety of these drugs.[68] An ultraperformance liquid chromatography–tandem mass spectrometry method is available for simultaneous monitoring of the abovementioned 12 anticancer drugs.[68]

St. John's Wort–Benzodiazepine Interactions

Most benzodiazepines are metabolized by CYP3A4. Thus, St. John's wort decreases the plasma concentrations of alprazolam, midazolam, and quazepam.[69] A 14-day course of St. John's wort administration significantly induced CYP3A4 activity as measured by changes in alprazolam pharmacokinetics. This indicates that the long-term administration of St. John's wort may result in diminished clinical efficacy or may increase the dosage requirements for all CYP3A4 substrates, which represent at least 50% of all marketed medications.[70]

Benzodiazepines are widely prescribed, and compliance of patients with benzodiazepine therapy is often monitored using immunoassays with urine specimens. However, immunoassays have limitations in monitoring benzodiazepines. Hence, patient compliance with benzodiazepine therapy should be monitored using chromatographic methods.[71]

St. John's Wort–Oral Contraceptive Interactions

St. John's wort exhibits significant interactions with oral contraceptives. The interaction between St. John's wort and oral contraceptives was investigated in 16 healthy women by evaluating the pharmacokinetics of norethindrone and ethinyl estradiol. Treatment with St. John's wort (300 mg 3 times a day for 28 days) resulted in a 13%–15% reduction in the dose exposure of oral contraceptives. Breakthrough bleeding increased during the treatment cycle along with follicle

growth and probable ovulation. Therefore, St. John's wort increases the metabolism of norethindrone and ethinyl estradiol, reducing the efficacy of its contraceptive activity.[72]

Other Clinically Significant Drug Interactions With St. John's Wort

The concomitant use of St. John's Wort downregulates the plasma levels of methadone. Long-term treatment with St. John's wort (900 mg/d) for a median period of 31 days (range 14–47 days) decreased the average trough concentrations of methadone by 47% in 4 patients. Two patients experienced withdrawal symptoms due to downregulated plasma levels of methadone.[73] A study conducted on healthy participants reported that consuming St. John's wort (300 mg) 3 times a day for 15 days and thereafter ingesting a single dose of oxycodone (15 mg) resulted in a 50% reduction in the elimination half-life and AUC of oxycodone. The concomitant use of St. John's wort and oxycodone must be carefully monitored owing to the risk of subtherapeutic concentrations of oxycodone.[74]

St. John's wort induces both CYP3A4-catalyzed sulfoxidation and CYP2C19-dependent hydroxylation of omeprazole.[75] Treatment with St. John's wort significantly increases the clearance of gliclazide, an oral hypoglycemic agent.[76] Glucose tolerance in healthy subjects who ingested metformin and St. John's wort was better than that of healthy subjects who ingested metformin alone. However, the mechanism of interaction has not been established. St. John's wort did not affect the steady-state pharmacokinetics of metformin, except for a minor reduction in renal clearance. The authors hypothesized that St. John's wort improves glucose tolerance by enhancing insulin secretion independent of insulin sensitivity in healthy male subjects consuming metformin.[77]

Previous studies have reported interactions between St. John's wort and the cholesterol-lowering drugs simvastatin and pravastatin. In a double-blind cross-over study involving 16 healthy male volunteers, the consumption of St. John's wort (900 mg per day) for 14 days decreased the peak serum concentration of simvastatin hydroxyl acid (the active metabolite of simvastatin) to 1.1 ng/mL in the St. John's wort–treated group as compared with the 2.3 ng/mL concentration in the placebo. In contrast to simvastatin, St. John's wort did not affect plasma pravastatin concentration.[78] St. John's wort has also been reported to reduce the efficacy of the cholesterol-lowering drug rosuvastatin.[79] The concomitant use of St. John's wort and clozapine, an antipsychotic drug metabolized by CYP450 enzymes, has been reported to reduce plasma clozapine levels, which may result in treatment failure.[80] In a study comprising 20 healthy volunteers, St. John's wort reduced exposure to ambrisentan irrespective of the drug having CYP2C19 genotype.[81]Table 1 provides a summary of pharmacokinetic drug interactions with St. John's wort.

Table 1. Clinically significant pharmacokinetic drug interactions with St. John's wort.

Class of drug	Specific	Clinical effect	Drug interaction detected by TDM (Y/N)
Immunosuppressant	Cyclosporine Tacrolimus	Possibility of organ rejection due to 30-50% reduction in trough due to CYP3A4 induction.	Yes, both cyclosporine and tacrolimus are routinely monitored.
Immunosuppressant	Mycophenolic acid (MPA)	MPA is metabolized by hepatic glucuronidation forming MPA-glucuronide (major pathway) and MPA-acyl glucuronide.	TDM is performed but no interaction.
Protease Inhibitors	Atazanavir Lopinavir Indinavir	Significantly reduced level, e.g., AUC of indinavir reduced by 57% due to induction of CYP3A4.	Not commonly monitored, but TDM is available in reference laboratories.
Non-nucleoside reverse transcription inhibitor (NNRTI)	Nevirapine	Reduced level due to induction of CYP3A4.	Not commonly monitored, but TDM is available in reference laboratories.
Anticoagulant	Warfarin	Reduced level due to induction of CYP2C9.	Yes, warfarin is routinely monitored through INR.
Anticoagulant	Clopidogrel	Reduced effect due to induction of CYP3A4.	No this drug is not monitored.
Direct oral anticoagulants	Dabigatran, Rivaroxaban, Apixaban, edoxaban and Betrixaban	Reduced effects due to induction of CYP3A4	No, these drugs are not monitored.
Cardioactive	Digoxin	Trough concentration reduced by 26% due to induction of P-glycoprotein	Yes, digoxin is routinely monitored.
Antianginal	Ivabradine	Reduced level due to induction of CYP2C9	No, this drug is not monitored.
Anticonvulsants	Phenytoin Carbamazepine Phenobarbital	Reduced efficacy due to induction of CYP3A4.	Yes, these drugs are routinely monitored.
Anticonvulsant	Brivaracetam	St. John's wort may reduce efficacy.	Not monitored.
Anticonvulsant	Carbamazepine	Although metabolized by CYP3A4, there is no interaction with St. John's wort.	Yes, this drug is routinely monitored.
Calcium Channel Blocker	Nifedipine Verapamil	Reduced level due to induction of CYP3A4.	Nifedipine is not monitored but sometimes verapamil is monitored.
Antihistamine	Fexofenadine	Decreased level due to induction of P-glycoprotein	No, this drug is not monitored.

Class of drug	Specific	Clinical effect	Drug interaction detected by TDM (Y/N)
Benzodiazepines	Alprazolam Midazolam Quazepam	Reduced blood level due to induction CYP3A4.	These drugs are infrequently monitored.
Anticancer	Irinotecan Imatinib	Reduced blood level due to induction CYP3A4.	Irinotecan and its active metabolite SN-38 are monitored infrequently.
Tricyclic antidepressant	Amitriptyline	Reduced blood level due to induction CYP3A4.	Yes, this drug is routinely monitored.
Antipsychotic	Clozapine		Infrequently monitored.
Statins	Atorvastatin Simvastatin	Reduced blood level due to induction CYP3A4.	No, these drugs are not routinely monitored.
Oral Contraceptives	Norethindrone Ethinyl Estradiol	Reduced blood level due to induction CYP3A4 and CYP1A2 causing contraception failure.	No, these drugs are not routinely monitored.
Antiasthmatic	Theophylline	Reduced blood level due to induction of CYP1A2.	Yes, this drug is routinely monitored.
Proton Pump Inhibitor	Omeprazole	Reduced level due to induction of CYP2C19.	No, this drug is not monitored.
Hypoglycemic agent	Gliclazide	Reduced level due to CYP2C9 induction	No, this drug is not monitored.
Opioid	Methadone	Trough concentration was reduced by 47% due to the induction of CYP3A4.	Yes, this drug is sometimes monitored.
Opioid	Oxycodone	AUC was reduced by 50% and the half-life was shortened from 3.8 h to 3 h.	Yes, this drug is sometimes monitored.
Endothelin-receptor antagonist	Ambrisentan	Reduced effect due to increased clearance.	No, this drug is not monitored.

PHARMACODYNAMIC DRUG INTERACTIONS WITH ST. JOHN'S WORT

St. John's wort exhibits pharmacodynamic interactions with antidepressant medications, such as fluoxetine, sertraline, paroxetine, and venlafaxine.[82] Adverse drug interactions between St. John's wort and fluoxetine are reported to be frequent in women.[83] The concurrent use of St. John's wort and buspirone causes serotonin syndrome.[84,85] Although St. John's wort is a weak inhibitor of serotonin, norepinephrine, and dopamine reuptake,[86] the side effects are due to an additive effect of St. John's wort and antidepressant medication as they have a similar mode of action. A case of prolonged orofacial dystonia was reported in a 58-year-old woman after combination therapy with bupropion and St. John's wort.[87] Important pharmacodynamic drug interactions with St. John's wort are listed in Table 2.

Table 2. Important pharmacodynamic interactions between St. John's wort and pharmaceutical drugs.

Class of drug	Specific drug	Clinical effect
Selective serotonin reuptake inhibitor (SSRI)	Fluoxetine Sertraline Paroxetine	Possibility of serotonin syndrome due to a synergistic effect.
Serotonin and norepinephrine reuptake inhibitor (SNRI)	Venlafaxine	Possibility of serotonin syndrome due to a synergistic effect
Other Antidepressant	Bupropion Buspirone	Possibility of serotonin syndrome due to a synergistic effect
Anti-migraine agent	Eletriptan	Possibility of serotonin syndrome due to a synergistic effect

DISCUSSION, GAP ANALYSIS, AND OUTLOOK

Clinically significant pharmacokinetic interactions between St. John's wort and various drugs may lead to treatment failure. Organ rejection resulting from failed immunosuppression therapy due to self-administration of St. John's wort has been discussed in detail in this review. St. John's wort preparations exhibit clinically important interactions with several classes of conventional drugs, such as immunosuppressants, anticancer agents, cardiovascular drugs, oral contraceptives, and lipid-lowering drugs, causing life-threatening events in several cases.[88] Therefore, we suggest that patients undergoing treatment for a chronic condition should avoid consuming St. John's wort.

CONCLUSIONS

Patients should consult their health care providers before consuming St. John's wort or any herbal supplement to avoid potentially dangerous drug–herb interactions. Furthermore, organ transplant recipients and patients undergoing HAART and anticoagulant therapy must avoid St. John's wort.

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