St. John's Wort

Botanical Name: *Hypericum perforatum* L.
Pharmacopoeial Name: Hyperici herba.
Common Names: St. John's wort, Klamath weed (historic: Fuga daemonum, herba solus).

Summary

Drug/Class Interaction Type	Mechanism and Significance	Management
Alprazolam Triazolobenzodiazepines ◈◈	Drug is 3A4 substrate. St. John's wort (SJW) lowers bioavailability by inducing 3A4 enzyme production. Interaction proved experimentally; no clinical reports. May be significant for intravenous midazolam preoperatively.	Coadministration usually contraindicated. Avoid.
Amitriptyline Tertiary tricyclic antidepressants ◈◈◈	Drug 3A4/P-glycoprotein (P-gp) cosubstrate. Herb lowers bioavailability. Interaction proved experimentally; no clinical reports.	Coadministration usually contraindicated. Avoid.
Anesthesia, general ✗/?	Potential pharmacokinetic and pharmacodynamic interactions with premedications and anesthetics. Reports scarce.	Cessation SJW 1 to 2 weeks before procedure suggested. Disclosure essential.
Antiretrovirals Indinavir, nevirapine Protease inhibitors NNRTIs ✗✗/✗✗✗/◈◈	Most antiretroviral agents are 3A4/P-gp cosubstrates. Decreased bioavailability demonstrated. No clinical reports.	Generally avoid. Coadministration requires specialist supervision and monitoring of drug levels.
Cyclosporine Immunosuppressive agents ✗✗✗/◈◈◈	Cyclosporine A is cosubstrate of 3A4/P-gp. Decreased bioavailability demonstrated. Numerous serious reports of graft rejection.	Avoid.
Digoxin Cardiac glycosides ✗✗/◈◈	Drug is P-gp substrate. Possible biphasic response, short-term increase, long-term decrease in bioavailability. Isolated report of bigeminy, short term.	If coadministered, ramp/taper the addition/cessation of herb, and monitor drug levels with vigilance during transition.
Etoposide Topoisomerase II inhibitors ✗✗/◈◈/?	Possible combination pharmacokinetic and pharmacodynamic interaction, decreased availability (drug is 3A4 substrate), and interference with therapeutic action by hypericin, blocking topo II inhibition.	Avoid.
Fexofenadine Histamine H1-receptor antagonist antihistamine ✗/◈	Drug is P-gp substrate. Decreased bioavailability demonstrated. No clinical reports; minimal significance.	Unlikely to cause problems.
Imatinib Tyrosine kinase inhibitors ◈◈◈	Gleevec is 3A4 substrate; decreased drug bioavailability demonstrated. Possible compromise to targeted anticancer therapy. No case reports.	Avoid.
Irinotecan Camptothecin analogs ✗/◈◈◈	Variable pharmacokinetic interaction probable. Significance unknown. Camptothecin-11 responses subject to high inherent variability.	Avoid.
Omeprazole Benzimidazole Proton pump inhibitors ✗/◈◈	Prilosec is 3A4/2C19 substrate; SJW reduces bioavailability, as experimentally demonstrated. No clinical reports, although large size of effect may be clinically significant.	Avoid, or monitor and increase dose drug.
Oral contraceptives (OCs) ✗/◈◈	Steroids hormones are 3A4 substrates. SJW increases breakthrough bleeding, may reduce OC compliance. OC failure not established despite theoretical risk.	Avoid, or adopt barrier methods during coadministration.
Paclitaxel, docetaxel Taxanes ?/◈◈◈	Theoretically, induction of CYP3A4 and P-gp could influence drug disposition. Significance not established. Drug mostly eliminated via CYP2C8.	Avoid.
Paroxetine, trazodone SSRI and SSRI/SNRI antidepressants ?	Herb may lead to varying combined pharmacokinetic and pharmacodynamic interactions, at least with some SSRI/NSRI drugs. Mild symptoms of serotonergic excess possible. Several reports of varying reliability. Significance not established.	Avoid, except with professional monitoring during drug taper.
Simvastatin HMG-CoA reductase inhibitors (statins) ◈	Some older statins are cosubstrates of 3A4/P-gp. Minimal significance; no reports available.	Consider newer statins if coadministration indicated.
Tacrolimus ✗✗✗/◈◈◈	Cyclosporine A is a cosubstrate of 3A4/P-gp. Experimental evidence that tacrolimus is also 3A4 substrate, but no interactions reports for tacrolimus.	Avoid.
Verapamil Calcium channel blockers ✗/◈◈	Verapamil (and all calcium channel blockers) are 3A4 substrates. SJW induces intestinal 3A4 and increases drug clearance. No reports. Interaction significance not established.	Monitored coadministration unlikely to be problematic.

Summary

Drug/Class Interaction Type	Mechanism and Significance	Management
Voriconazole Triazole antifungals ✗/◈◈	Drug is 3A4/2C19/2C9 substrate. SJW reduces bioavailability, as experimentally demonstrated. No clinical reports, although large size of effect may be clinically significant.	Avoid.
Warfarin, Phenprocoumon Oral vitamin K antagonist anticoagulants ✗✗	Mechanism not established. Possible pharmacokinetic effect; may lead to reduced INR. Significance minimal to moderate. Reliable clinical reports or trials unavailable.	Unlikely to cause problems. If coadministered, monitor INR once or twice weekly, and titrate anticoagulant dosage when starting or stopping SJW therapy, until INR stable.

NNRTIs, Nonnucleoside reverse-transcriptase inhibitors; *SSRI*, selective serotonin reuptake inhibitor; *SNRI*, serotonin-norepinephrine reuptake inhibitor; *HMG-CoA*, 3-hydroxy-3-methylglutaryl–coenzyme A; *INR*, international normalized ratio.

HERB DESCRIPTION

Family

Clusiaceae (Guttiferae, Hypericaceae).

Habitat and Cultivation

Perennial; native in Europe Asia and North Africa; naturalized in the United States and considered a noxious weed in many areas; widespread in temperate zones, favoring disturbed ground.

Parts Used

Flowering tops.

Common Forms

Dried Plant: Flowering tops.
Tincture: 60% ethanol, 1:2 to 1:5 weight/volume.
Standardized Extract: 0.3% hypericin, 2.0% to 4.5% hyperforin.
Infused Oil: Fresh flowers, for external use.

HERB IN CLINICAL PRACTICE

Overview

A well-documented botanical medicine since Greco-Roman times, St. John's wort (SJW) has a long history of folk and traditional use as a *vulnerary* ("wound healer") and for banishing mental afflictions, particularly melancholy. For example, Gerard[1] (1633) described its use as a balm for wounds, burns, ulcers, and bites as being without equal. The oil made from the macerated flowers was listed in the first *Pharmacopoeia Londinensis* (1618). *Hypericum perforatum* was proved and introduced into the homeopathic materia medica by Muller in the mid-1800s and has been included in the *Homeopathic Pharmacopoeia of the United States* since that era, with primary indications focusing on nerve pain and traumatic injuries (e.g., concussion, coccygeal impact, sequelae).

More recently, clinical trial evidence accumulated through the 1980s and 1990s established the efficacy and safety of standardized SJW extracts for treating mild to moderate depression, and the "natural antidepressant" label propelled the herb to second-best-selling supplement in the United States by the late 1990s. In 2000, reports of serious interactions with prescription drugs began to appear, and the resulting adverse publicity caused sales of the herb to fall significantly, although SJW remains one of the top-selling U.S. botanicals. It was approved by the German Commission E for "depressive moods" (internally) and "contused injuries" (externally) in 1984.[2] The pharmacology and clinical effects of the herb are currently the focus of considerable research interest and, because of rapid accumulation of data, relatively recent literature reviews (e.g., 1997 *American Herbal Pharmacopoeia* monograph) are in some respects dated.[3] More recent reviews of the extensive literature include the 2003 European Scientific Cooperative on Phytotherapy (ESCOP) monograph[4] and a comprehensive monograph by McKenna et al.[5]

Historical/Ethnomedicine Precedent

Traditionally, SJW was used as a calming herb for symptoms of nervous tension, including anxiety and insomnia, as well as a restorative for melancholic conditions that might currently be diagnosed as depression. Folk use attributed the herb with properties of protection against enchantments, including demonic possession, and it was used for warding off evil spirits. *Hypericum* was characterized as "hot and dry" in the Galenic humoral system of medicine and has classically been associated with the liver and spleen, as well as the Sun. Historically considered a "woundwort," SJW is still used both internally and externally for pain relief, particularly neuralgic pain, shingles, mild contusions, and burns to the skin. For external use, the fresh flowers, traditionally harvested on St. John's Day (immediately following Summer Solstice), are the basis of a macerated oil, which is usually red (by the dianthrone hypericin). This red color was considered an indication of its vulnerary nature (likened to blood) by the Doctrine of Signatures. Before the modern clinical trial–driven indications of the herb for "mild to moderate depression," the nervous system indications were less clearly defined and included "psychovegetative" disorders, as well as such conditions as nocturnal eneuresis and night terrors. Its psychological effects were considered much less pronounced than those of prescription medications; Weiss[6] classified the herb as a "mild (i.e., gentle) psychotropic" agent.

Known or Potential Therapeutic Uses

Analgesic, antiviral, anti-inflammatory, anxiety, coccygeal impact, concussion depression (mild to moderate), hepatoprotection, herpes simplex infection (orofacial and genital), herpes zoster (shingles and postherpetic neuralgia), menopause-related psychological symptoms, psychosomatic and somatiform disorders (mild), nervousness, neuralgia, nocturnal eneuresis, photodynamic antitumor activity, premenstrual syndrome, restlessness, sacral irritation and spinal injuries, sciatica, seasonal affective disorder, tissue healing and wound repair.

Key Constituents

Characteristic napthodianthrones, including hypericin; phloroglucinols, including hyperforin and adhyperforin.
Flavonoids, including proanthocyanidin polymers of catechin and epicatechin; flavonols; phenylpropanoids; essential oil; amino acids; xanthones.

Therapeutic Dosing Range

Dried Plant: 2 to 5 g/day.
Tincture and Fluid Extract: As 1:1 equivalents, 1 to 3 mL/day.
Standardized Extracts: 900 mg/day in divided doses.
Topical: *Oleum hyperici*, oily macerate from fresh flowering tops (applied as needed).
Also used in ultradilute succussed preparations based on homeopathic indications.

INTERACTIONS REVIEW

Strategic Considerations/Background

Although an old medicine, SJW has a pivotal place in the relatively recent field of herb-drug interactions. The publication of convincing reports of interactions between SJW and digoxin[7] in 1999 and cyclosporine[8] and indinavir[9] in 2000 was seminal, initiating a widespread reevaluation of the safety of this popular herb, previously considered to be benign, in the context of conventional medications.[10] It also propelled the issue of potential interactions between botanicals and pharmaceuticals into media prominence and research focus. The subsequent years have seen increased understanding of the pharmacology of SJW, and the herb is now known to be associated with a number of clinically significant pharmacokinetic interactions, as suggested by the original reports. These interactions are mediated by its effects on several key components of drug metabolism, including the cytochrome P450 (CYP450) mixed-oxidase system, various conjugases and transferases, as well as the transporter proteins that modulate drug efflux across intestinal, renal, and biliary epithelia. These systems compose what are now often referred to as phases (or stages) I, II, and III of drug metabolism/detoxification.

The initial reports of SJW interactions with narrow-therapeutic-range drugs prompted sweeping warnings in professional and consumer media about the dangers of SJW herb-drug interactions (and often of herb-drug interactions in general). At the time, however, the actual number of reports of documented SJW-related drug interactions was, and in fact remains, relatively small, with data of widely varying reliability. Surveying the available cases in 2001, Fugh-Berman and Ernst[11] found 54 published reports claiming SJW interactions. Of these, 29 were rejected as unclassifiable, and the remaining 25 were evaluated for reliability according to the authors' ''reliability rating score'' system. Of these, 12 were classified as ''unreliable,'' 11 as ''possible,'' and only two as ''likely.'' More recently, Meyer et al.[12] analyzed six documented potential herb-drug interactions, including SJW-cyclosporine and SJW-digoxin, across a wide range of ''tertiary sources'' and found high variability in the reporting of the data, with only three sources even mentioning all six known interactions. Interestingly, as recently reviewed by Izzo,[13] clinical reports of SJW-drug interactions seem to be decreasing rather than increasing in frequency.

Mills et al.[14] recently conducted a systematic review of trials investigating SJW pharmacokinetic interactions with conventional drugs. The authors found the methodological quality of the studies was limited; in particular lacking accepted controls such as correct randomization, observance of established blinding procedures, and allowance for time-dependent effects. They also found that only 15 of the 22 available studies assayed the SJW content of the preparations used, and that varied dosing regimens and duration of exposure to the herb were common, without presenting a rationale for the tested dosing patterns. These limitations mean that most trials on SJW interactions do not appear to conform to the U.S. Food and Drug Administration (FDA)–recommended standards for safeguards against bias in pharmacokinetic trials.[15] This in turn results in questions about the interpretation and applicability of the available data that can only be resolved by more and better-designed studies, as well as consistent application of necessary standards in pharmacovigilance.

Official and regulatory reaction was also triggered by the initial SJW interaction reports. In 2000 the U.K. Committee on Safety of Medicines (CSM)[16] issued a general advisory letter on SJW interactions to all physicians and pharmacists. This included a fact sheet listing medications for which SJW might interact and advised patients to ''stop taking St John's Wort,'' while warning against immediate discontinuation in the event that drug levels might rise, causing serious adverse effects. Lists of drugs that might interact with SJW, causing ''serious adverse interactions,'' were provided, including selective serotonin reuptake inhibitors (SSRIs), anticonvulsants, and triptans. In 2001 the Irish Medical Board (IMB)[17] restricted SJW to physician prescription only, effectively removing the herb (along with ginkgo and several others) from general public access, citing the monoamine oxidase inhibitor (MAOI) activity of SJW as potentially interacting with tyramine foods and potentiating MAOI drugs, as well as claiming SJW caused phototoxicity and other (unspecified) adverse effects. The FDA issued an advisory to health care professionals warning about the SJW-indinavir interaction in 2000, also suggesting physicians alert patients about potential drug interactions involving ''any drug metabolized via the cytochrome P450 pathway.''[18]

Effects on Drug Metabolism and Bioavailability

Cytochrome P450

The complete spectrum of induction and inhibition effects of SJW on the CYP450 system in vivo in humans is not yet fully characterized. Possibly because of a number of differing investigative methodologies, as well as differences between the various types of extracts used, the available studies are inconclusive. In vitro evidence exists for *inhibition* effects by crude SJW extracts, its flavonoid components, and hypericin and hyperforin on CYP450 1A2, 2C9, 2C19, 2D6, and 3A4.[19,20] In vivo studies using single probe drugs that are specific CYP substrates have found *induction* effects by SJW on 3A4,[21] and with multiprobe drug ''cocktails,'' for 3A4, 2E1, 1A2, and 2D6[22] and 2C19.[23] By contrast, no significant effects on 2D6 and 3A4 were found by two other groups,[24,25] and a further probe cocktail study found no effect on 1A2, 2C9, or 2D6.[26] More recent studies have confirmed in vivo coordinate induction effects by SJW on hepatic and intestinal 3A4 and P-glycoprotein (P-gp).[27,28]

Summarizing the data available at this time, SJW definitely induces human 3A4; probably induces 1A2, 2C19, and 2E1; and probably does *not* significantly affect 2C9 or 2D6. It also induces P-gp and possibly other, related transporters. There is a degree of tissue specificity, with induction of both hepatic and intestinal 3A4, as well as a possible biphasic effect, at least on 3A4 and P-gp, with short-term *inhibition* followed by an *increasing induction* of enzymes over 7 to 10 days. However, evidence from isolated constituent studies suggests that hyperforin plays the main role in induction activity.[23,29-34] The initial inhibition may be caused by hypericin, but also by flavonoid constituents; a number of flavonoids are known to inhibit 3A4, with those from grapefruit and

other citrus-derived flavonoids being the best-known examples.[35,36] This "biphasic" effect of a short-term enzyme inhibition succeeded by longer-term induction has recently been demonstrated in a clinical study of voriconazole pharmacokinetics. This open-label study with 16 healthy male volunteers determined that that SJW coadministration with voriconazole (a substrate of CYP2C19) led to a short-term but clinically insignificant increase in the area under curve (AUC) of 22%, and after 15 days, AUC was reduced by 59% compared with controls.[37,38]

Pregnane X Receptor

The recent finding that hyperforin, an active phloroglucinol constituent compound of SJW, acts as a high-affinity ligand for the orphan nuclear receptor pregnane X receptor (PXR) is highly significant.[39,40] The PXR and related nuclear receptors, such as the constitutive androstane receptor (CAR) and the retinoid X receptor (RXR), have been described as "promiscuous" because of the unprecedented structural diversity of compounds that interact with their ligand-binding domain (LBD).[41-43] Activation of the PXR leads to upregulation of genes controlling multiple aspects of xenobiotic metabolism, including phase I (CYP450 1A1, 1A2, 2B6, 2C9, and 3A4) mixed oxidases, phase II conjugases (uridine diphosphate [UDP] glucuronosyltransferases, glutathione-*S*-transferases, sulfonyltransferases), and phase III drug transporters (MDR1/P-gp, MDR2, organic anion-transporting polypeptides [OATPs]).*

The implication is that the PXR and related nuclear receptors may effectively act to coordinate xenobiotic detoxification.[41-43,52-56] The PXR itself is subject to a degree of genetically determined polymorphism, the importance of which remains to be clarified, but pronounced interspecies differences are known to exist in activator compounds, with marked differences among rodent, rabbit, and human ligands.[41,57,58] Pascussi et al.[59] have aptly described expression of the genes controlling xenobiotic metabolism as a "tangle of networks of nuclear and steroid receptors, where receptors share partners, ligands, DNA response elements and target genes and where the different pathways exhibit cross-talk at several levels."

A broader view of SJW emerges from these recent developments. The herb can be conceptualized as a master inducer of detoxification, or more accurately as a *xenosensory activator,* capable of triggering the complex adaptive system evolved to metabolically eliminate toxic compounds, both endogenous and xenobiotic.[60,61] The downstream consequences of PXR activation on drug metabolism suggest that, to some extent, SJW interactions may be predicted (and thus managed) on the basis of whether a given coadministered drug is a substrate of the enzymes or transporters induced by PXR activation, particularly 3A4 and P-gp.[55,62]

P-Glycoprotein

Induction of P-gp by SJW further complicates the picture and may confound attempts to predict interactions. P-glycoprotein is a membrane-associated, adenosine triphosphate (ATP)–dependent "pumping" protein that ejects foreign or toxic compounds from cells and mediates "multidrug resistance" when induced in cancer cells. Durr et al.[28] estimated the induction of intestinal P-gp by SJW at a 1.5-fold increase in healthy human volunteers. Ernst[63] noted drugs that are dual substrates of both P-gp and CYP3A4 likely present an increased risk of pharmacokinetic interaction as a result of co-induction by SJW. However, the relative contributions of P-gp and 3A4 to drug efflux appear to be complex and differ for different agents that are dual substrates.[64]

The existence of several polymorphisms in P-gp phenotypes affects normal levels of expression of both hepatic and intestinal P-gp. These polymorphisms are known to exhibit variation with racial and gender characteristics.[65,66] As with P450 enzymes, dietary food ingredients may also affect P-gp expression; known examples include piperine from black pepper and some citrus flavonoids.[67,68] Alpha-tocopherol can also influence P-gp, probably through PXR activation.[52] Finally, the role of non–P-gp drug transporters, such as the OATP family, has recently emerged as another potential mechanism in controlling drug bioavailability, although modulating influences on OATP expression are not currently well characterized.

Overall, the interplay between CYP3A4 and P-gp (and other transporters) is not well understood, but this "drug-efflux metabolism alliance," as aptly named by Benet and Cummins,[69] remains of a crucial research area for future elucidation of drug interactions.[70,71]

Managing Pharmacokinetic Interactions

Numerous pharmaceuticals are metabolized by CYP3A4, which is a low-affinity, high-throughput P450 enzyme expressed primarily in the small intestinal mucosa and liver. This has led to suggestions that SJW may interact with more than 50% of all known drugs. Indeed, evidence is now rapidly accumulating from preclinical screening studies that confirms SJW induction effects on a range of drugs, particularly 3A4 substrates, often in the absence of any clinical interactions data. However, the magnitude of SJW induction effects is considerably less than that of other known PXR ligands, the best-known example being rifampin, a mainstay of conventional tuberculosis therapy. Rifampin is a coordinate inducer of P-gp and 3A4 with an induction effect on midazolam (a 3A4-specific substrate) that is 25 times that of SJW.[72] Red wine has similar order-of-magnitude effects as SJW on oral clearance of cyclosporine (a dual substrate).[73]

Theoretical predictions should be confirmed by clinical data before an interaction can be assumed inevitable. For example, carbamazepine is a well-known substrate and inducer of 3A4. When SJW was given for 14 days to patients previously stabilized on carbamazepine, no effect of SJW on carbamazepine kinetics or drug levels was observed.[74] This suggests that close attention must be paid to the precise metabolic pathways involved for each specific drug and to the associated effects on induction or inhibition of P450, enzymes, transferases, and transporters. Unfortunately, older drugs were not always well characterized by their manufacturers in terms of their interaction with the P450 metabolizing enzymes, leading to obvious problems for prediction and management of metabolic interactions.

Proposed coadministration should also consider different temporal patterns of combining herb and pharmaceutical agents. Three alternative scenarios are possible. First, adding an inducer (SJW) to a substrate (drug) will induce a lowering of previously stable drug levels over 1 to 2 weeks through increased drug metabolism, risking consequent loss of therapeutic efficacy. Moreover, in the case of SJW, initial inhibition may complicate this pattern, creating an apparent biphasic effect. Second, if the substrate (drug) is added to inducer (SJW), standard drug-dosing levels may be inadequate and may result in failure of therapy. Notably, this would not apply to drugs whose level is established by monitoring and

*References 19, 26, 29, 30, 32, 33, 44-51.

titration to a therapeutic endpoint (e.g., coumarin/INR value). Third, *withdrawal* of an inducer (SJW) from a regimen of previously stable coadministration with a substrate drug will reverse induction and possibly cause rebound toxicity from elevated drug levels. Theoretically, this series of patterns would be "reversed" if the drug concerned was a prodrug, depending on activation for the metabolic transformation by the CYP450 induced. Armstrong et al.[75] well describe this schema of possible pharmacokinetic interaction patterns among inducers, inhibitors, and substrates of CYP450 drug-metabolizing enzymes.

In summary, if appropriate data about metabolic pathways of a drug are available, the pharmacokinetics of any drug proposed for coadministration with SJW should be reviewed before prescription and, wherever possible, drugs metabolized by multiple routes selected. If this is not possible, and if compelling reasons exist for coadministration of the herb with the drug, precautionary measures should be adopted; this is mandatory for any drug with narrow therapeutic indices. Introduction or cessation of SJW should be ramped or tapered, respectively, and serum levels of the pharmaceutical need to be monitored to titrate drug levels and thus counter increased clearance rates. When factors such as financial cost or intermediate metabolite toxicity militate against compensatory increases in drug doses, avoidance of coadministration is the optimum management solution.

The literature on SJW interactions continues to expand, with persistent calls in secondary sources for large-scale in vitro screening of herbs to establish the "risk" of potential (pharmacokinetic) interactions with drugs. These calls ignore that drug disposition is unpredictably mediated by a wide variety of dietary[62] compounds, foods, herbs, beverages, and lifestyle products and also affected by a wide range of individual variables, from genomics through biological, lifestyle, and socioeconomic factors, all of which render meaningful screening virtually impossible.

One study analyzing responses of six different ethnic groups to SJW did not uncover significant differences in induction effects on CYP3A4 and P-gp.[76] However, Gurley et al.[77] examined CYP450 phenotypes in elderly versus younger subjects and found age-related differences in responsiveness to botanical agents regarding CYP3A4 induction, concluding that population vulnerabilities may exist in elders. The results of in vitro tests are often contradictory and may be at odds with clinical reality because of the inherent differences between experimental systems and the in vivo complexities of herbal administration; therefore these tests have limited predictive value. Butterweck et al. pointed out that logically, systematic screening for pharmacokinetic interactions should first be applied to narrow-therapeutic-index drugs.[78,79]

Some argue that understanding and managing variability in drug responses would be better than scaremongering about overstated adverse effects of herbs.[80,81] More recent mainstream papers suggest that the emphasis is beginning to shift in a more constructive direction.[62,82] Equally, the development of "low-hyperforin" extracts of SJW may provide efficacy in antidepressant indications without invoking PXR-mediated downstream effects on drug disposition.[34,83] However, hyperforin confers numerous other properties on SJW whole-plant extracts, including anti-inflammatory, antitumor, and antiangiogenic effects.[84]

Pharmacodynamic Interactions

In addition to pharmacokinetic interactions, pharmacodynamic interactions based on the antidepressant activity of SJW have been widely suggested, principally when combined with the SSRI antidepressants. The evidence for pharmacodynamic interactions is more problematic than that supporting the metabolic interactions, partly related to the general unreliability of SJW case reports, as previously noted.[11,14] Qualitative data sources such as postal surveys of psychiatrists have been used to suggest adverse reports and interactions that in effect are unassessable.[85] Safety and efficacy data from clinical trials of SJW suggest that adverse effects of the herb are an order of magnitude less (1%-3%) than those of pharmaceutical antidepressants.[86] Despite the known interactions issues, SJW remains a first-line treatment for mild to moderate depression in Europe.[87] Significantly, the adverse effect data from clinical trials of the herb suggest a completely different profile of adverse effects than with common antidepressant drugs. This correlates with current understanding of the underlying mechanisms of SJW's observed antidepressant effects. The herb is now believed to work through novel and apparently complex mechanisms, dissimilar to those of known pharmaceutical antidepressants.

Initial research presumed a typical druglike biogenic amine mechanism for SJW, but early in vitro data suggesting MAOI activity have not been substantiated by in vivo studies. Reports of hypertensive MAOI-SJW interactions are lacking, as are reliable reports of interactions between SJW and tyramine-containing food substances[88,89] (see also Theoretical, Speculative, and Preliminary Interactions Research later). Extensive research in vitro and on animals has examined the effects of both full-spectrum SJW extracts and isolated constituents on neurotransmitter uptake for serotonin, dopamine, noradrenaline, gamma-aminobutyric acid (GABA), and L-glutamate.[90-100] The emerging conclusion is that the phloroglucinol-derivative hyperforin acts as a synaptosomal uptake inhibitor for all five of these neurotransmitters. Müller[97] has described this effect as "broad-band" reuptake inhibition. The molecular mechanism of the "pseudo-nonselective reuptake" effect is thought to be related to activation by hyperforin of a sodium ion channel that causes an increase in intracellular sodium content, modifying the sodium gradient that is the common basis of all neuronal neurotransmitter transport proteins.[90,92,99,100]

Although hyperforin appears to be unique in having an approximately equal inhibitory effect on all five neurotransmitters, its effects also are at least an order of magnitude less than that of pharmaceutical antidepressants when quantified in vitro.[97] The improbability of achieving in vivo concentrations of hyperforin from oral SJW consumption that could correspond to effects of synthetic neurotransmitter uptake inhibitors is rarely considered when suggestions of "serotonin syndrome" are made relating to SJW interactions.[89] Serotonin syndrome, first characterized by Sternbach[101] in 1991, was initially described as the result of the adverse interaction of SSRIs with MAOI drugs. The clinical concept of serotonin syndrome has been overused and frequently misapplied in the drug interactions literature.[102] The concept has been reviewed and revised by Radomski et al.,[103] who found a high level of misdiagnosis and distinguished several subsets of the serotonin syndrome based on symptom severity, from transient mild symptoms to fatal toxic states. The latter must also be differentiated from neuroleptic malignant syndrome.[104]

Although hyperforin appears to be the only constituent that can affect uptake of all five neurotransmitters, it cannot be considered responsible for all the observed antidepressant effects of SJW. In some animal behavioral models of depression (e.g., the Porsolt test), hyperforin-free extracts exhibited significant activity, suggesting that other constituents have an effect. Clinical trials

with a low-hyperforin extract also demonstrated antidepressant activity against placebo, fluoxetine, and imipramine.[105,106] Furthermore, methodological controversy continues to surround clinical trials comparing SJW with placebo and pharmaceutical antidepressants, particularly because of the well-documented, powerful placebo responses associated with these trials.[107-109]

Despite the absence of definitive understanding of the mechanism of SJW antidepressant activity, caution regarding potential interactions with pharmaceutical antidepressants is more than warranted. Also, several classes of psychiatric drugs are substrates or inhibitors of CYP3A4 and P-gp, suggesting combined pharmacokinetic and pharmacodynamic interactions with SJW. Common agents likely to be encountered in general and psychiatric practice include triazolobenzodiazepines (alprazolam, estazolam, midazolam, triazolam), which are substrates of 3A4, as are the nonbenzodiazepine hypnotics zolpidem and zaleplon and the ''atypical'' anxiolytic buspirone.

HERB-DRUG INTERACTIONS

Alprazolam, Midazolam, and Related Triazolobenzodiazepines

Evidence: Alprazolam (Xanax), midazolam (Hypnovel, Versed). Extrapolated based on similar properties: Adinazolam (Deracyn), brotizolam (Lendormin), estazolam (ProSom), triazolam (Halcion).

Interaction Type and Significance

◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

Probability: 2. Probable

Evidence Base: ◉ **Emerging**

Effect and Mechanism of Action

Alprazolam, midazolam, and related triazolobenzodiazepines are specific substrates of CYP450 3A4, which is induced by SJW. If the drug is added to SJW, standard dosing levels may be ineffectively low. Conversely, if SJW is added to the drug, plasma levels will be reduced after 7 to 10 days.

Research

Markowitz et al.[110] conducted an open-label preclinical study with 12 healthy volunteers using dextromethorphan and alprazolam probes as markers of CYP2D6 and CYP3A4 activity. Alprazolam was chosen because it is metabolized specifically by 3A4 and is not known to be a cosubstrate of P-gp. The oral preparation of SJW, LI60, was standardized to 0.3% hypericins and administered at 300 mg three times daily for 14 days; the probe was a single oral dose of 2 mg generic alprazolam. The measurements showed a twofold decrease in AUC for alprazolam versus time and shortening of mean half-life to 50% of the baseline. No significant differences were found between baseline and post-SJW maximum plasma levels or time taken to attain them. The kinetics of 2D6, as measured by urinary dextromethorphan, were unaffected by SJW. The study did not distinguish between intestinal mucosa and hepatic 3A4 effects. This result contrasted with an earlier study by the same group in 2000 that failed to demonstrate significant effects of SJW coadministration on alprazolam kinetics; however, the SJW administration period in that trial was only 3 days.[24]

Wang et al.[26] also studied midazolam, using both oral and intravenous doses of the drug before and after 14 days of SJW administration. They found a comparable 50% reduction in oral AUC, corresponding to a twofold clearance increase. Intravenous bioavailability was reduced 21%, suggesting significant intestinal as well as hepatic 3A4 effects.[26] Considerable interindividual variability in the level of 3A4 induction was noted in this study, and another study found a significant difference between healthy female and male subjects in the level of induction of 3A4 by SJW. This second study used a single time point, ''phenotypic ratio'' methodology and a drug cocktail probe that included midazolam, after 28 days of SJW administration.[22]

Although they did not find the same gender differences, Dresser et al.[64] established oral and parenteral values for midazolam kinetics after 12 days of pretreatment with SJW in 21 healthy subjects; however, interindividual differences were higher for oral than intravenous route. Their data confirmed the large decreases (55%) in oral bioavailability after SJW pretreatment reported by other investigators.

Clinical Implications and Adaptations

There are no clinical reports of this interaction, which was experimentally established by pharmacokinetic ''probe'' studies of P450 effects with the drug. Theoretically, the consequences of adding triazolobenzodiazepines to a stable SJW regimen are that normal drug-dosing levels will result in insufficient sedation. Conversely, inhibition rather than induction of 3A4 can cause enhanced effects, such as delirium and excessive sedation; for example, grapefruit juice with midazolam or triazolam.[111] In practice, the interaction is probably of minimal clinical significance. Intravenous midazolam is extensively used in preoperative sedation, and SJW use by elective surgical patients should be checked routinely.

Amitriptyline and Related Tertiary Tricyclic Antidepressants

Evidence: Amitriptyline (Elavil).
Extrapolated, based on similar properties: Amitriptyline combination drug: amitriptyline and perphenazine (Etrafon, Triavil, Triptazine), clomipramine (Anafranil), doxepin (Adapin, Sinequan), imipramine (Janimine, Tofranil), trimipramine (Surmontil).

Interaction Type and Significance

◈◈◈ **Impaired Drug Absorption and Bioavailability, Avoidance Appropriate**

Probability: 3. Possible

Evidence Base: ○ **Preliminary**

Effect and Mechanism of Action

A complex pharmacokinetic interaction occurs between the tertiary tricyclic amitriptyline and its metabolites, including the active secondary tricyclic metabolite nortriptyline, with involvement of P450 and P-gp, resulting in decreased oral bioavailability of the drug.

Research

One preclinical study examined the effect of adding SJW at 900 mg once daily for 14 days to 12 healthy subjects pretreated with 12 days of oral amitriptyline at 75 mg twice daily. The AUC values for amitriptyline were reduced by 22% and for nortriptyline by 41%. The reduction in nortriptyline was evident after only 3 days of SJW administration. Urinary and plasma amounts of amitriptyline and metabolites varied directly with administration of its SJW. The authors suggested a P450 and P-gp mechanism would explain the observed decreases in AUC.[112]

Clinical Implications and Adaptations

There are no clinical reports of this interaction. The metabolism of tricyclic antidepressants (TCAs) is rather complex; amitriptyline is initially hydroxylated by CYP2D6 to nortriptyline, a secondary TCA which is further demethylated by other P450 enzymes before conjugation. However, nortriptyline is also an inhibitor of 2D6, which is a high-affinity, low-capacity enzyme and the rate-limiting step in transformation of TCAs. SJW is not known to affect 2D6. CYP3A4 may play a secondary "backup" role in hydroxylation. Both amitriptyline and nortriptyline are also P-gp substrates, whereas amitriptyline is a P-gp inhibitor. Polymorphisms in 2D6 are well known, and the complexity of the metabolic picture suggests that clinical consequences of coadministration are unpredictable. The conventional drug-drug interactions literature has established the potential seriousness of 2D6 *inhibition* (e.g., by fluoxetine) as a potentially serious interaction with TCAs; however, there is no obvious drug-drug precedent for P-gp/3A4 *induction*-driven interactions with TCAs. Given the unpredictable outcome of coadministration, avoiding this interaction would be a prudent strategy.

Anesthesia, General

Anesthesia, General

Related but evidence lacking for extrapolation: Halogenated inhalational anesthetic agents: Desflurane (Suprane), enflurane (Ethrane), halothane (Fluothane), isoflurane (Forane), sevoflurane (Sevorane, Ultane).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**

? **Interaction Likely but Uncertain Occurrence and Unclear Implications**

Probability: 6. Unknown

Evidence Base: ☐ **Inadequate**

Effect and Mechanism of Action

Theoretically, variable pharmacokinetic and interactions with common preoperative and anesthetic agents are possible, depending on the particular agent and individual factors. Central pharmacodynamic effects have also been suggested, based on animal data for sedation times. The incidence, effects, and significance of the potential interactions are unknown.

Research

Evidence for pharmacokinetic interactions with anesthetic agents is mixed, but circumstantially compelling. The CYP3A4 probe midazolam (Versed) is used preoperatively, and its metabolism is significantly affected by SJW. The halogenated anesthetics are metabolized by CYP2E1, which has more recently been demonstrated subject to SJW induction.[22] Pharmacodynamic effects are not established, although an animal study suggested that ethanolic extracts of SJW prolong sleeping time induced by phenobarbital in rats.[113]

Reports

A patient experienced a severe episode of hypotension during a routine surgical procedure and was initially unresponsive to intravenous epinephrine, which the author attributed to SJW after the patient admitted to regular SJW use in the 6 months before the procedure (dose and preparation unspecified). The author suggested that adrenergic modulation by the herb had affected the sympathetic responsiveness to the drug, and that the herb was the only logical "offending agent," having failed to find alternative explanations for the mechanism of circulatory collapse.[114] This speculation does not appear to have any foundation in the known pharmacology of the herb, and attributing causation involves implausible logic. Further investigations in animal models would be appropriate.

Clinical Implications and Adaptations

Disclosure of all herbal and nutrient consumption is accepted as mandatory before elective surgery, the primary objective being to audit for possible disturbances in normal hemostasis induced by herbal medicines and similar agents before the procedure.

Induction effects of SJW on P450 and P-gp may be considered sufficiently complex by some anesthesiologists to mandate patient cessation of SJW before surgery, which would require at least 10 days for complete reversal of enzyme induction. This is arguably a judgment call that could be made on the basis of individual case history and indications for antidepressant therapy, as well as expert knowledge of the pharmacokinetics of the drugs to be used. Exaggeration of possible dangers from herbal consumption may be counterproductive by reinforcing patient reluctance to disclose usage. Pharmacodynamic interactions with central sedation from SJW seem improbable from the known pharmacology of the herb, and any minor effects would be unlikely to present untoward management issues in the context of high-profile inpatient clinical settings such as surgical procedures.

Antiretrovirals: Protease Inhibitors and Nonnucleoside Reverse-Transcriptase Inhibitors

Evidence: Indinavir (Crixivan); nevirapine (Viramune).

Similar properties but evidence lacking for extrapolation:

Protease inhibitors: Amprenavir (Agenerase), atazanavir (Reyataz), brecanavir, darunavir (Prezista), fosamprenavir (Lexiva), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Fortovase, Invirase), tipranavir (Aptivus); combination drugs: lopinavir and ritonavir (Aluvia, Kaletra), saquinavir and ritonavir (SQV/RTV).

Nonnucleoside reverse-transcriptase inhibitors (NNRTIs): Delavirdine (Rescriptor), efavirenz (Sustiva).

Interaction Type and Significance

✗✗ **Minimal to Mild Adverse Interaction—Vigilance Necessary**

✗✗✗ **Potentially Harmful or Serious Adverse Interaction—Avoid**

◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

Probability: **2. Probable**

Evidence Base: ○ **Preliminary** (although apparently ● **Consensus)**

Effect and Mechanism of Action

All known protease inhibitors and nonnucleoside reverse-transcriptase inhibitors (NNRTIs) are metabolized by CYP3A4 and are also probable cosubstrates of P-gp. It is established that SJW increases oral clearance of the typical representative of both classes of antiretrovirals (indinavir and nevirapine), although evidence for other drugs in either class is lacking. Theoretically, this may lead to decreased therapeutic efficacy; however, case reports are lacking.

Research

The first study to investigate this interaction remains the most quoted. Piscitelli et al.[9] reported a small, open-label "before and after" trial in 2000, in which eight healthy male volunteers were administered 800 mg oral indinavir for 2 days to establish baseline kinetics of the protease inhibitor. From day 3, participants were given SJW (0.3% hypericin) 300 mg three times daily for 14 days, then another 800 mg oral dose of indinavir was given, for which AUC of the drug decreased by 57% compared to baseline.[9] The authors did not comment on indinavir being both a highly potent inhibitor of 3A4, which it also moderately induces, and an inhibitor of intestinal P-gp.[115,116] These factors suggest that extrapolation from this study to in vivo steady-state coadministration is not possible.

A case-series analysis by de Maat et al.[117] used retrospective nonlinear analysis of variance on a cohort of human immunodeficiency virus (HIV) patients whose serum nevirapine had been checked routinely every 3 months. The authors reviewed five patients who admitted concomitant use of SJW (dose and preparation not specified), with at least one serum reading reflecting a period of SJW coadministration and one of nevirapine alone. These patients showed a significant increase in oral clearance (35%; $p = 0.02$) of nevirapine during SJW use. Nevirapine is also a moderate autoinducer of the two P450 enzymes of which it is a substrate, 3A4 and 2B6.

Clinical Implications and Adaptations

The interaction with indinavir was highly publicized, and advisories from regulatory bodies in the United Kingdom and United States recommended that coadministration of all antiretrovirals with SJW be avoided.[16,18] Management by avoidance may be an appropriate strategy to eliminate interaction, but this official consensus was based on a single preclinical study of one protease inhibitor. The authorities did not mention that the clinical pharmacology of HIV and acquired immunodeficiency syndrome (AIDS) is a field in which complex interactions are the norm. The antiretrovirals in particular display a wide range of highly volatile and variable interactions, both pharmacokinetic and pharmacodynamic, with other drugs as well as with each other. Pharmacogenomic factors also play a major but currently little-acknowledged role in treatment of individuals with HIV/AIDS.[118]

This interactivity of the antiretroviral drugs is well known among HIV/AIDS specialist providers and many HIV/AIDS patients. The pharmacokinetic effects of the drugs on P450 enzymes are extensive and vary considerably between different drugs; for example, indinavir potently inhibits and induces 3A4, whereas ritonavir is a powerful pan-inhibitor of most P450 enzymes and a specific inducer of 3A4, 1A2, 2C9, and 2C19. Pronounced interactions of antiretrovirals with each other and many drugs are well established, and prescribing regimens for HIV and AIDS patients often involve empirical antiretroviral drug cocktails. Additional polypharmacy with other drugs is also likely, depending on individual status. Viral load is invariably monitored as an indicator of antiviral therapeutic efficacy. Serum drug levels are often monitored directly, and serum dosage, timing of administration, and drug combinations may be adjusted accordingly and frequently. Extrapolation from the one available (and limited) study on one agent to all known antiretrovirals is at best an oversimplification, at worst a suspect (and potentially counterproductive) judgment call.

St. John's wort aroused interest in the late 1980s and early 1990s because of its potential as an antiretroviral agent, but preliminary studies with both the herb and synthetic hypericin (the purportedly active anti-HIV constituent) were disappointing. Nonetheless, patients may incorporate SJW by self-prescription into their treatment protocols for indications such as depression. Such cases would require vigilant attention to viral load monitoring or (preferably) serum drug levels before and after initiation of SJW. Theoretically, once a stable level of SJW administration was established, long-term management issues of coadministration would be routine for clinicians experienced in the field, although financial costs may also be a significant factor if substantial increases in drug dose were required to maintain therapeutic levels.

Cyclosporine

Cyclosporine (Ciclosporin, cyclosporin A, CsA; Neoral, Sandimmune, SangCya).

Interaction Type and Significance

✗✗✗ **Potentially Harmful or Serious Adverse Interaction—Avoid**

◈◈◈ **Impaired Drug Absorption and Bioavailability, Avoidance Necessary**

Probability:	Evidence Base:
1. Certain	● **Consensus**

Effect and Mechanism of Action

Cyclosporin A (CsA) is a dual substrate of both P-glycoprotein and of CYP450 3A4, both of which are induced by SJW. Addition of SJW to previously stable cyclosporine patients will result in significant reductions in drug levels and the possibility of therapeutic failure of immunosuppression. The interaction is well documented and considered established.

Research

The induction effects of SJW on 3A4 and P-gp are established. Cyclosporine is a cosubstrate whose disposition is controlled by both proteins, with P-gp (MDR1) affecting intestinal absorption and biliary excretion, and intestinal and hepatic 3A4 both contributing to first-pass metabolism.[119-121] Bauer et al.[122] recently described a case series of 11 renal graft patients maintained with immunosuppressive regimens incorporating CsA who were administered relatively low doses of SJW (600 mg once daily) for 14 days. Dose-corrected CsA levels decreased more than 40%, and CsA had to be increased from 2.7 to 4.1 mg/kg/day to maintain therapeutic levels. Interestingly, these figures correspond closely to the increase in clearance for cyclosporine found by Dresser et al.[27] in a preclinical study designed to quantify the relative levels of P-gp and 3A4 induction in the effects of SJW. They estimated induction effects of SJW on cyclosporine to be 1.6-fold after oral administration.[27] The authors note that unexplained discrepancies remain in data on the effects of coordinate induction on dual-substrate compounds. According to their results, increased cyclosporine clearance caused by SJW is not only less than that of a unique 3A4 substrate, such as midazolam, but also an order of magnitude less than that induced by pretreatment with rifampin, also a SXR/PXR ligand, as is hyperforin.[72] Dresser et al.[27] conclude that other, as yet undefined, mechanisms (e.g., OATPs) may be involved.

Reports

The multiple case reports of the cyclosporine-SJW interaction make it the best documented of the SJW pharmacokinetic interactions. The initial *Lancet* report in early 2000 by Ruschitzka et al.[8] described two cardiac transplant patients who developed acute rejection responses after starting SJW. Serum levels of cyclosporine were depressed, and after

intensification of immunosuppressive therapy and cessation of the herb, the acute rejection responses were reversed, and plasma cyclosporine levels returned to normal. Fugh-Berman and Ernst[11] rated this report as ''likely'' with a maximum score of 9/9 points on their reliability rating scale; however, other reports have been poorly documented, providing minimal data for evaluation. In a more recent review of 11 available reports, Ernst[63] concluded that the clinical evidence for actual decreases in cyclosporine levels in transplant patients was conclusive, and that the risk of acute rejection was significant. Several reports noted decreased serum levels of cyclosporine after SJW administration in renal and cardiac graft patients, fortunately before rejection episodes.[122-125] Since the original Ruschitzka report,[8] two other cases of acute rejection have been documented, one involving a renal-pancreatic graft and the other a hepatic graft patient.[126,127]

Clinical Implications and Adaptations

The addition of SJW to previously stable regimens of immunosuppression based on CsA will clearly cause serum levels of the drug to fall, approximately 1.5-fold according to the available data. This is considerably less than the effect of known pharmaceutical inducers and about equivalent to the effect of consuming red wine.[73] Cyclosporine levels are regularly monitored in transplant patients, so theoretically, coadministration with professional management does not present insurmountable problems. Upward adjustment in oral dosing of the drug sufficient to maintain effective plasma levels to compensate for the metabolic induction by the herb should, all other factors being equal, maintain immunosuppression if coadministration were to be adopted. However, because the metabolites of cyclosporine also exhibit nephrotoxicity, increased drug ingestion to maintain therapeutic levels may risk increased toxic effects; furthermore, because the drug is expensive, cost factors would not favor this approach.

In reality, risks from the cyclosporine interaction are most likely with undisclosed self-prescription of the herb by allograft patients unaware of the potential dangers; this has been the case with all the reported cases of graft rejection to date. The real risk of acute rejection in such patients has led to publicity emphasizing the need for disclosure and the counseling of transplant patients on potential dangers of adding SJW to immunosuppressive protocols. (See also Tacrolimus later.)

Digoxin, Digitoxin, and Related Cardiac Glycosides

Evidence: Digoxin (Digitek, Lanoxin, Lanoxicaps, purgoxin), digitoxin (Cystodigin).
Related but evidence lacking for extrapolation: Deslanoside (cedilanin-D), ouabain (g-strophanthin).

Interaction Type and Significance

✗✗ **Potentially Harmful or Serious Adverse Interaction—Vigilance Necessary**
◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

Probability:	Evidence Base:
1. Certain	▽ **Mixed**

Effect and Mechanism of Action

A pharmacokinetic interaction arises because digoxin is a specific substrate for P-gp, which is induced by SJW. The effects of coadministration may be biphasic, depending on the sequence and manner of combining herb and drug. The clinical significance of the interaction is not established.

Research:

The induction effects of SJW on intestinal P-gp are known (see Strategic Considerations earlier). Digoxin and related cardiac glycosides are substrates of P-gp, and the inhibition of P-gp by cardiac drugs such as verapamil and quinidine is the known mechanism of several well-established drug interactions involving digoxin that lead to increased cardiac glycoside toxicity. The original study by Johne et al.,[7] implicating SJW in a pharmacokinetic interaction with digoxin, found a 25% decrease in digoxin AUC after 10 days of treatment with oral SJW, 900 mg once daily, in healthy subjects with previously stabilized digoxin levels by serum monitoring. Importantly, a 10% increase in digoxin levels was found with single-dose addition of SJW, but this value was not statistically significant and is never reported in the secondary literature. A subsequent ''before and after'' study by Durr et al.[28] examined the induction effects of SJW on intestinal P-gp/MDR1 and intestinal and hepatic 3A4. After 14 days of SJW administration in healthy volunteers, SJW increased intestinal P-gp by 1.4-fold and decreased the AUC of a standard 0.5-mg digoxin dose by 18% compared with baseline.[28]

Although these two studies are in broad agreement about the long-term effects of SJW on digoxin kinetics, it is possible that the effect of SJW on digoxin may be biphasic, mirroring the behavior of fexofenadine (Allegra), another P-gp specific substrate that has been used as a probe in experimental investigations of P-gp. Wang et al.[26] investigated this hypothesis in a study that confirmed the biphasic effects of SJW on drug transporter kinetics. They found the effect of a single oral dose of SJW (900 mg) administered within 1 hour of 60 mg fexofenadine decreased the clearance of the drug by 20%, resulting in a 45% *increase* in serum drug level ($p < 0.05$). Long term, however, there was a 35% *decrease* in maximum plasma concentrations after 14 days of SJW administration at 900 mg once daily.[26]

A recent study by Mueller et al.[128] examined the effects of 10 forms of SJW preparation and different doses of several forms on digoxin kinetics. The preparations included SJW dried herb tea, powdered crude herb, fresh plant juice, standardized extracts with high and low hyperforin content (LI60, Ze 117), and infused oil, as well as a placebo control. Healthy volunteers (n = 93) were stabilized on digoxin at 0.2 to 0.3 mg three times daily for 1 week, followed by adding SJW concurrently for 14 days. Only two of the SJW preparations tested, the LI60 and high dose of *Hypericum* powder (4 g once daily, with comparable hyperforin content to LI60), produced comparable and significant reductions in digoxin maximum concentration (C_{max}) and $AUC_{0\text{-}24}$. The reductions in AUC were approximately 25% and in C_{max} approximately 37%, with 95% confidence interval (CI). The dose of the SJW preparations that failed to generate significant changes in digoxin pharmacokinetics correspond to dosage levels given for traditional use in therapeutic monographs, such as Commission E and ESCOP (2-4 g crude herb daily),[2,4] suggesting a probable difference in the capability to induce interaction effects between traditional herbal prescription and hyperforin/hypericin standardized concentrated extracts.

At present, data are insufficient to characterize fully the mechanisms of the interaction. However, the OATP family, in addition to P-gp, may be implicated. There is a specific transporter for digoxin (OATP-8),[129] and digoxin transport was shown to be more affected by naturally occurring

bioflavonoids operating on P-gp than on OATP in an in vitro model.[130] In a recent poster study, SJW completely abolished P-pg–mediated digoxin transport in vitro.[50] A recent immunohistochemical study identified another transporter, OATP-4C1, that mediates digoxin, ouabain, triiodothyronine, and methotrexate transport in a sodium-dependent manner and is located in the proximal tubule of the human nephron.[131] Further research is required to fully elucidate the various mechanisms of digoxin disposition.

Reports

Case reports of subtherapeutic digoxin levels after addition of SJW to previously stable digitalized patients are unavailable. A single report is available that describes the predicted pattern of cessation of an inducer (SJW) causing rebound drug toxicity. An 80-year-old man stable on digoxin consumed 2000 mL of SJW tea daily. On cessation of the tea, he developed nodal bradycardia and bigeminy, which was treated successfully with digoxin (FAB). The original report is in Serbian and unavailable for full evaluation.[132]

Clinical Implications and Adaptations

Addition of SJW to a stable digoxin level may result in a short-term increase in drug levels potentially capable of inducing classic digitalis toxicity. However, longer-term coadministration risks inducing a decline in drug levels after induction of transporter proteins. This could theoretically lead to therapeutic failure if not corrected.

Introduction of SJW to patients already stabilized on digoxin should therefore initially follow a ramped dose increase of the herb over several days, rather than starting at 100% of the target dose, to avoid possible short-term inhibitory effects on drug transport. Once stable therapeutic doses are attained, serum digoxin level monitoring should drive any adjustment in cardiac glycoside dosage to compensate for transporter induction. Discontinuation of the herb must also be tapered, to avoid rebound digitalis intoxication resulting from the reversal of induction.

Patients stable on cardiac glycoside therapy must be counseled on the potential risks of unsupervised addition or withdrawal of SJW. However, the order of magnitude of these effects is similar to that resulting from dietary ingredients, particularly citrus bioflavonoids and red wine,[35,51,130,133] and is not itself a compelling reason to avoid coadministration if clinically indicated.

Etoposide and Related Topoisomerase II Inhibitors

Evidence: Etoposide (Eposin, Etopophos, Vepesid, VP-16). Extrapolation based on similar properties: DNA topoisomerase II inhibitors: Daunorubicin (Cerubidine, DaunoXome), doxorubicin (Adriamycin, Rubex), doxorubicin, pegylated liposomal (Caelyx, Doxil, Myocet), epirubicin (Ellence, Pharmorubicin), idarubicin (Idamycin, Zavedos), mitoxantrone (Novantrone, Onkotrone), teniposide (Vumon).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**

◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

? **Interaction Likely but Uncertain Occurrence and Unclear Implications**

Probability: 4. Plausible

Evidence Base: ☐ **Inadequate**

Effect and Mechanism of Action

Combined pharmacokinetic and pharmacodynamic interaction is possible. Etoposide is partially metabolized through CYP3A4 and is therefore subject to SJW induction, while the naphthadianthrone constituent hypericin pharmacodynamically interferes with the etoposide-mediated cytotoxicity in vitro. The clinical significance of this plausible interaction is not established.

Research

Peebles et al.[134] investigated the mechanism of action by which hypericin interfered with the topoisomerase (topo) II poisons, using an HL-60 cell-line model. The study was partially motivated by the initial hypothesis that hypericin may exhibit leukemogenic toxicities, because these are known to be associated with topo II agents. The mechanism of action of hypericin was unlike that of etoposide (and amsacrine), resembling the effect of topo II catalytic inhibitors that operate upstream of etoposide to inhibit etoposide effects, protecting the HL-60 cells from etoposide-mediated damage.[134] Methodologically, extrapolations are not directly possible to in vivo situations with oncology patients, and the dose-response curves of the hypericin effects were not established. However, as Block and Gyllenhaal[135] noted in a review of herb-drug interactions in cancer chemotherapy, etoposide is also metabolized by 3A4 before renal elimination.

Clinical Implications and Adaptations

Cancer patients are likely candidates for self-prescription of SJW, and concurrent use of botanical and dietary agents during chemotherapy should be audited closely. Information about putative antitumor activity of hypericin is available on the Internet, and purified hypericin can currently be obtained as a "dietary supplement," suggesting the possibility of undisclosed self-prescription. At present, insufficient data are available to establish the in vivo effects of hypericin and SJW interactions with any chemotherapy agents (see also Irinotecan [CPT-11] discussion), although the potential clearly exists for a reduction of cytotoxic efficacy through several pharmacokinetic mechanisms, and in the case of etoposide, additional pharmacodynamic factors may be involved. Combining nutritional and botanical agents with chemotherapy is a specialist field, and professionals experienced in integrative oncology should be involved in any decisions on coadministration.

Fexofenadine

Fexofenadine (Allegra)

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**

◈ **Impaired Drug Absorption and Bioavailability, Negligible Effect**

Probability: 3. Possible

Evidence Base: ● **Consensus**

Effect and Mechanism of Action

The histamine H_1-receptor antagonist fexofenadine hydrochloride is a documented substrate of P-gp that is induced by SJW, and the herb is known to be capable of modifying fexofenadine levels. The clinical effect and significance are likely minimal because of the wide therapeutic index of the drug.

Research

Fexofenadine is a specific substrate of P-gp and is eliminated without undergoing significant metabolism. It has been used as

a probe drug in preclinical investigations of P-gp pharmacokinetics because of its high specificity for the transporter and because it is relatively well tolerated, with few adverse effects over a widely varying dose range. Notably, the manufacturer's information suggests an absence of effects on QT interval for doses ranging from 60 to 400 mg twice daily in healthy individuals. The innocuous characteristics of the drug have been used to analyze the behavior of P-gp substrates with a much narrower therapeutic index, such as digoxin (see previous SJW-digoxin section).[27,51,133,136]

Clinical Implications and Adaptations

Despite substantial evidence of the ability of SJW to affect fexofenadine levels, the interaction itself lacks case reports and is probably of minimal clinical significance. Given the wide therapeutic index of the drug in clinical practice, as well as the likelihood of patient self-adjustment of drug dosage levels to treat allergic symptoms as required, coadministration with SJW appears unproblematic. The inclusion of this interaction in lists of SJW interactions without qualification in the secondary literature is arguably a case of "overstatement." (See Theoretical, Speculative, and Preliminary Interactions Research later.)

Imatinib

Imatinib (Gleevec, Glivec)

Interaction Type and Significance

◈◈◈ **Impaired Drug Absorption and Bioavailability, Avoidance Appropriate**

Probability: 3. Possible

Evidence Base: ☐ **Inadequate**

Effect and Mechanism of Action

A pharmacokinetic interaction in which SJW may reduce serum levels of the active metabolite of the tyrosine kinase inhibitor, causing possible decrease in drug exposure. Preliminary evidence supports the interaction, and imatinib is known to be metabolized by 3A4.

Research

A study recently reported by Frye et al.[137] investigated the possible interaction of SJW and the 3A4 substrate imatinib with 12 healthy volunteers, comparing single-dose oral clearance of the drug (400 mg) before and after 14 days of SJW (300 mg three times daily) pretreatment. Clearance was increased by 44%, AUC decreased by 30%, and the half-life and C_{max} were also decreased. Cytochrome P450 3A4 is the primary metabolic pathway that has been described for the drug, although individual variability in response to the drug (resistance) may result from pharmacogenomic mechanisms not yet adequately described. The 3A4-inducer phenytoin has also been shown to reduce AUC of imatinib to about 20% of the typical AUC_{24}, and this was reversed by ketaconazole.[138]

Clinical Implications and Adaptations

Given the serious indications for Gleevec, including chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST), accurate dosage levels should be confidently maintained for the clinical populations involved. Cancer patients are arguably likely to self-prescribe with SJW for depression and should be cautioned to avoid the herb during Gleevec treatment. Alternatively, if preexisting treatment with SJW has had significant positive impact on quality of life, and if alternative approaches have been poorly tolerated, higher doses of imatinib, with serum drug level monitoring, would be indicated.

Irinotecan

Irinotecan (Camptothecin-11, CPT-11; Campto, Camptosar).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**

◈◈◈ **Impaired Drug Absorption and Bioavailability, Avoidance Appropriate**

Probability: 4. Plausible

Evidence Base: ☐ **Inadequate**

Effect and Mechanism of Action

SJW may reduce serum levels of the active metabolite of the camptothecin analog CPT-110. The mechanism of interaction is complex, and pharmacogenetic factors can cause high individual variability in drug levels. A resultant decrease in tumor cytotoxic exposure is possible. Because of the known complexity of irinotecan metabolism and the wide variability in individual responses to the drug, the clinical significance of the interaction is not known.

Research

One small, unblended, crossover study involved five cancer patients treated with intravenous CPT-11 before and after SJW administration for 18 days at 900 mg once daily. Serum concentrations of the active cytotoxic metabolite SN38 (7-ethyl-10-hydroxy CPT) were reduced by a mean of 42% after SJW administration. Myelosuppression was less in the SJW phase, indicating a reduced chemotoxicity. This is significant because toxicity (NCI Common Toxicity Grading Criteria) often governs dose adjustment in irinotecan chemotherapy regimens. In fact, the statistical mean of this small sample of patients was derived from a range of 14% to 79%, typical of the wide interindividual variation in responses to the drug.

Clinical Implications and Adaptations

Irinotecan pharmacokinetics have been well documented and are known to be highly complex.[139-141] The prodrug is converted to the active compound SN38 by serum carboxylases; subsequent metabolism is through hepatic UGT1A1 glucuronidation and biliary excretion, which depends on a canalicular multispecific transporter (cMOATP). The conjugated form undergoes enterohepatic recirculation. The prodrug is secondarily transformed by 3A4 into two inactive metabolites, APC and ANC, which form 2% to 8% of the eliminated compounds. Finally, SN38 is 94% albumin bound in plasma. Considerable potential metabolic variability exists; hepatic microsomes display a thirteenfold variation in rate of SN38 formation, and genetically determined polymorphisms of UGT1A1 play a role in response variation. Significant pharmacokinetic interactions with conventional drugs have been observed with competitors and inducers of the glucuronidation process more than with 3A4-specific inducers, and P-gp induction (biliary) may also play a part in irinotecan interactions.[142]

More data are required before the effects of SJW on irinotecan metabolism can be accurately identified. Several authors have raised important questions about the possibility of SJW interactions with chemotherapeutic agents through induction of metabolism and transport.[135,143,144] The area is important, especially because of the possible effects of SJW on multidrug resistance through P-gp; oncologists, as well as integrative primary care providers supporting cancer patients undergoing

conventional chemotherapies, should be cognizant of the issues, despite the lack of definitive data. Dosing of these agents by body surface area seems a seriously outmoded practice, given the narrow therapeutic index of cytotoxic chemotherapy agents, the well-established wide variations in serum drug levels caused by genetic polymorphisms of drug-metabolizing enzymes, and the potential interactions with other drugs and dietary components as well as with herbal and nutritional agents (many as yet unknown), often unreported by patients to their oncologists.

The development of widely available clinical laboratory tests for cytotoxic chemotherapy drug levels and their routine utilization should be encouraged to enhance efficacy and reduce toxicity in the clinical practice of medical oncology. Such tests have been routinely used for decades with agents of much larger therapeutic indices, such as phenytoin (Dilantin) and digoxin. Development and utilization of serum chemotherapy drug levels tests would greatly simplify management of the underlying genetic polymorphisms affecting these levels and would help uncover covert use of self-prescribed herbal and nutritional agents, as well as allowing prescribers to compensate for such coadministration when indicated or reasonable.

Omeprazole and Related Proton Pump Inhibitors

Evidence: Omeprazole (Losec, Prilosec).
Extrapolated, based on similar properties: Esomeprazole (Nexium), lansoprazole (Prevacid, Zoton), pantoprazole (Protium, Protonix, Somac), rabeprazole (AcipHex, Pariet).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**
◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

Probability:	Evidence Base:
2. Probable	○ **Preliminary**

Effect and Mechanism of Action

A pharmacokinetic interaction occurs between SJW and omeprazole, and possibly with related benzimidazole drugs, which are metabolized by 3A4 and 2C19, resulting in a lowering of drug levels caused by enzyme induction by SJW. The interaction is experimentally confirmed, but clinical reports are lacking to date.

Research

A recent, randomized, crossover trial examined the effects of SJW pretreatment (300 mg three times daily) for 14 days on the single-dose kinetics of 20 mg oral omeprazole and its metabolites.[23] The 12 healthy volunteers were phenotyped for 2C19 polymorphisms because these are known to affect the metabolism of the substrate omeprazole. The drug is metabolized by two routes, involving sulfoxidation by 3A4 and hydroxylation by 2C19, so the separate metabolites (5-hydroxymeprazole and omeprazole sulfone) were measured in plasma by high-performance liquid chromatography (HPLC) along with the parent drug. Substantial decreases in omeprazole C_{max} (37.5%) and AUC (49.6%) [$p < 0.001$] were found with SJW pretreatment. The wild-type variants of 2C19 or "extensive metabolizers" (EMs) also displayed significant increases in 5-hydroxy metabolite levels, but "poor metabolizer" (PM) phenotypes showed lower effects. Xie[145] elaborated on the authors' interpretation of this study, noting that the 3A4 pathway is a minor metabolic route, and because omeprazole is also a competitive inhibitor of 2C19, as well as a substrate and inhibitor of the efflux transporter P-gp, that the disposition of the drug involves integrated effects of multiple pathways.

Clinical Implications and Adaptations

The authors of the previous study suggest that SJW induces 3A4 and also 2C19, the latter in a genotype-dependent manner, to the extent that significant increases in drug doses would be necessary during herb-drug coadministration to compensate for the induction effects by the herb.[23] The benzimidazoles do not have a narrow therapeutic index, and there are currently no clinical reports of this interaction; however, the size of the observed experimental effects suggests that the interaction could be clinically significant. Physicians prescribing proton pump inhibitors must consider the need for increased dose levels if there is prior stable usage of SJW, and adding SJW to omeprazole may significantly reduce previously stable drug levels.

Oral Contraceptives and Related Estrogen-Containing and Synthetic Estrogen and Progesterone Analog Medications

Evidence: Oral contraceptives: monophasic, biphasic, and triphasic estrogen preparations:
Ethinyl estradiol and desogestrel (Desogen, Ortho-TriCyclen).
Ethinyl estradiol and ethynodiol (Demulen 1/35, Demulen 1/50, Nelulen 1/25, Nelulen 1/50, Zovia).
Ethinyl estradiol and levonorgestrel (Alesse, Levlen, Levlite, Levora 0.15/30, Nordette, Tri-Levlen, Triphasil, Trivora).
Ethinyl estradiol and norethindrone/norethisterone (Brevicon, Estrostep, Genora 1/35, GenCept 1/35, Jenest-28, Loestrin 1.5/30, Loestrin1/20, Modicon, Necon 1/25, Necon 10/11, Necon 0.5/30, Necon 1/50, Nelova 1/35, Nelova 10/11, Norinyl 1/35, Norlestin 1/50, Ortho Novum 1/35, Ortho Novum 10/11, Ortho Novum 7/7/7, Ovcon-35, Ovcon-50, Tri-Norinyl, Trinovum).
Ethinyl estradiol and norgestrel (Lo/Ovral, Ovral).
Mestranol and norethindrone (Genora 1/50, Nelova 1/50, Norethin 1/50, Ortho-Novum 1/50).
Related, internal application: Etonogestrel/ethinyl estradiol vaginal ring (Nuvaring).
Related but evidence lacking for extrapolation:

Progestin-only oral contraceptives, implants, and postcoital contraceptives: Etonogestrel, implant (Implanon); levonorgestrel, implant (Jadelle, Norplant; Norplant-2); levonorgestrel, oral postcoital contraceptive (Duofem, Escapelle, Levonelle, Levonelle-2, Microlut, Microval, Norgeston, NorLevo, Plan B, Postinor-2, Vika, Vikela); medroxyprogesterone, injection (Depo-Provera, Depo-subQ Provera 104); medroxyprogesterone, oral (Cycrin, Provera); NES progestin, implant (ST-1435, Nestorone); norethindrone, oral (norethisterone; Aygestin, Camila, Errin, Jolivette, Micronor, Nor-QD, Ortho-Micronor); norethindrone, injectable (NET EN; Noristerat); norgestrel, oral (Ovrette).

Hormone replacement therapy (HRT), estrogens: Chlorotrianisene (Tace); conjugated equine estrogens (Premarin); conjugated synthetic estrogens (Cenestin); dienestrol (Ortho Dienestrol); esterified estrogens (Estratab, Menest, Neo-Estrone); estradiol, topical/transdermal/ring (Alora Transdermal, Climara Transdermal, Estrace, Estradot, Estring FemPatch, Vivelle-Dot, Vivelle Transdermal); estradiol cypionate (Dep-Gynogen, Depo-Estradiol, Depogen, Dura-Estrin, Estra-D, Estro-Cyp, Estroject-LA, Estronol-LA); estradiol hemihydrate (Estreva, Vagifem); estradiol valerate

(Delestrogen, Estra-L 40, Gynogen L.A. 20, Progynova, Valergen 20); estrone (Aquest, Estragyn 5, Estro-A, Estrone '5', Kestrone-5); estropipate (Ogen, Ortho-Est); ethinyl estradiol (Estinyl, Gynodiol, Lynoral).

HRT, estrogen/progestin combinations: Conjugated equine estrogens and medroxyprogesterone (Premelle cycle 5, Prempro); conjugated equine estrogens and norgestrel (Prempak-C); estradiol and dydrogesterone (Femoston); estradiol and norethindrone, patch (CombiPatch); estradiol and norethindrone/norethisterone, oral (Activella, Climagest, Climesse, FemHRT, Trisequens); estradiol valerate and cyproterone acetate (Climens); estradiol valerate and norgestrel (Progyluton); estradiol and norgestimate (Ortho-Prefest).

HRT, estrogen/testosterone combinations: Esterified estrogens and methyltestosterone (Estratest, Estratest HS).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**

◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

Probability:	Evidence Base:
3. Possible	○ **Preliminary**

Effect and Mechanism of Action

A pharmacokinetic interaction may theoretically result from SJW induction of estrogen and progestin metabolism, causing increased clearance and lowered serum drug levels, resulting in "breakthrough bleeding" and theoretically a risk of contraceptive failure, although failure is not established. Variability in oral contraceptive (OC) product formulations and known interindividual variability of responses to exogenous hormones confounds simple interpretation of the currently available data. Clinical significance of the interaction is not established.

Research

The metabolism of OCs is highly complex and incompletely characterized; the pharmacokinetics of steroidal hormones is subject to considerable interindividual variability because of the sheer complexity and number of metabolic pathways involved and the polymorphisms they exhibit. Also, significant differences in formulation exist between different OC products. By consensus, 3A4 is considered to the major P450 enzyme for metabolic transformation of both estrogens and progestins. However, the original OC estrogenic compound mestranol is in fact activated by 2C9 to ethinyl estradiol (EE). Similarly, the common progestin ingredient desogestrel is also a prodrug, metabolized by 2C9 to the active metabolite 3-ketodesogestrel. Glucuronidation and sulfation by the relevant transferase enzymes adds further variability because of polymorphisms in the transferase enzyme systems, which are also subject to induction and inhibition. Finally, conjugated EE is also hydrolyzed by bowel flora and undergoes enterohepatic recirculation, unlike the progestins. In turn, OCs themselves are mild inhibitors of 3A4 and more pronounced inhibitors of 1A2 and 2C19, although their effects on the clearance of other drug substrates of these enzymes are not well researched.

One pilot study has examined the effects of SJW on concentrations of circulating androgens by immunoassay after administration of the herb to healthy volunteers (six female, six male) for a 14-day period sufficient for CYP3A4 induction. No significant changes in androgen levels resulted from SJW administration, although there was a small reduction in the level of 5α-reduced androgens, more so in women than in men.[146]

Two recent controlled studies addressed the effects of SJW on combination OC therapy with regard to ovarian activity, the possibility of contraceptive failure, and the kinetics of the steroidal components of the OC products used.[147,148] The clinical findings of both trials were similar and confirmed that SJW coadministered with combination OCs increased breakthrough bleeding but did not result in ovulation (as recorded by endosonographic measurement). The studies differed significantly in other findings.

Pfrunder et al.[148] found no changes in ethinyl estradiol AUC with SJW coadministration, at either 600 mg or 900 mg SJW daily doses with a combination OC (EE/desogestrel), but the progestin metabolite 3-ketodesogestrel decreased significantly at both these dosage levels. This metabolite is generated by 2C9 (and possibly 2C19), then further metabolized by 3A4. The authors suggested that 2C9 may be inhibited by hyperforin or apigenin constituents of SJW because of in vitro evidence for 2C9 inhibition,[19] or that 3A4 induction was responsible for the decrease, despite the apparent lack of effect on EE. This study did not examine hyperforin or hypericin levels, although the extract used (LI60) had high hypericin and hyperforin content.

Hall et al.[147] coadministered 900 mg SJW once daily for two cycles with Ortho-Novum (a combination OC containing EE/norethindrone) and examined a more comprehensive set of parameters. These included hyperforin levels, follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, pharmacokinetic parameters for norethindrone and EE, and oral and intravenous values for the 3A4 probe midazolam.[147] The clearance of EE was increased by 47% by SJW coadministration, but this was not deemed significant ($n = 12$). Norethindrone clearance increased by 16%. The midazolam probe data suggested that the changes were caused by intestinal rather than hepatic 3A4 induction, since systemic clearance was not changed but oral clearance increased by 50%. Hyperforin levels averaged a steady-state level of 20 ng/mL; however, a large (threefold) variation was noted between the subjects in hyperforin levels, which may reflect the variability in response rates. Breakthrough bleeding was positively correlated with significantly higher midazolam oral clearance. Larger studies are needed to confirm definitively whether SJW will permit ovulation during OC therapy, but both trials suggest that this is unlikely.

Reports

Despite media publicity, anecdotal reports of "miracle babies" born to women using SJW concurrently with OC therapy remain unsubstantiated.[149] Reports in the professional literature are sparse and contribute no useful data to establishing the incidence and significance of the possible SJW-OC interaction. The earliest report was in correspondence to the *Lancet* in 1999 that gave no details for three purported cases of breakthrough bleeding associated with combination OCs and SJW coadministration.[10] Another *Lancet* letter contained a report from Sweden by Yue et al.[150] (see also warfarin-SJW later) that mentioned "eight cases of intermenstrual bleeding and one report of changed menstrual bleeding from manufacturers of SJW products."[121] Patient history, details of the OC preparation, and SJW form and dose were not given. No contraceptive failure was mentioned. Fugh-Berman and Ernst[11] later classified the Yue reports as "unreliable."

A single case of contraceptive failure involved a 36-year-old patient with a history of depression and use of pharmaceutical antidepressants who stopped all pharmaceutical

treatment in favor of SJW (1700 mg once daily, a high dose). After 3 months, while still taking a combination OC (EE/dienogestrel), she conceived unexpectedly.[64] A midwifery magazine article also reports unwanted pregnancies as occurring while SJW was used, citing cases drawn from several government agency reports: from the U.K. Medicines Control Agency (MCA; seven cases) and from Sweden and Germany (four cases). None of these has been documented in professional literature, except the Swedish reports already mentioned, although the British MCA warned that the SJW-OC interaction would result in risk of unintended pregnancy in its advisory letter to practitioners and pharmacists.[16]

Clinical Implications and Adaptations

In the conventional drug interactions literature, induction of CYP450 3A4 and uridine glucuronosyltransferase (UGT) has been shown to increase EE and progestin clearance and is typically associated with increased symptoms of breakthrough bleeding. Ovulation parameters have not been well studied in this area, but ovulation with pharmaceutical 3A4/UGT inducers has not been reported.[151,152] The few reports of pregnancies resulting from combining conventional drugs with OCs are rare and almost impossible to evaluate. The situation appears similar with SJW-OC interactions. The risk of actual unwanted pregnancy seems small, but unquantifiable, at present.

Breakthrough bleeding, although associated with initial phases of OC therapy alone, appears to be increased by SJW coadministration. Bleeding is also associated with decreased compliance with OC therapy and thus indirectly with increased risk of contraceptive failure as other, less reliable alternative forms of contraception are adopted to avoid undesirable symptoms. Despite the lack of solid evidence for failure of contraception due to SJW, women using OCs concurrently with the herb should be advised about the risks and should consider the simultaneous use of barrier methods.

Given the contemporary trend toward ''ultra-low'' dosage of EE in commercial OC preparations because of concerns over adverse effects, the risks of contraception failure may be marginally higher than with the earlier, higher-dose products. Most available data relate only to combination products. Extrapolations to progestin-only minipills, to implants, and to postcoital ''morning-after'' pills cannot be drawn from current data.

The effect of SJW on hormone replacement therapy (HRT) has not been studied, although SJW is likely to have some impact on estrogen clearance in HRT. Because this population has no vulnerability to unwanted pregnancy, it would appear to be a lower priority for further research. The complex field of sex steroid molecular biology and metabolism will presumably yield more conclusive data in the future.

Paclitaxel, Docetaxel: Taxane Microtubule-Stabilizing Agents

Evidence: Docetaxel (Taxotere), paclitaxel (Paxene, Taxol).
Similar properties but evidence lacking for extrapolation: Paclitaxel, protein-bound (Abraxane).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**

◈◈◈ **Impaired Drug Absorption and Bioavailability, Avoidance Necessary**

Probability:
3. Possible

Evidence Base:
○ **Preliminary**

Effect and Mechanism of Action

This possible pharmacokinetic interaction could influence drug availability, although biotransformation of taxanes is primarily through CYP2C8. Multiple mechanisms are thought to underlie response variability and drug resistance to taxanes.

Research

Komoroski et al.[153] used a human hepatocyte model to test the effects of rifampin and hyperforin on the induction of docetaxel metabolism compared with controls. Hyperforin addition increased metabolism of the drug in a dose-dependent manner, with 1.5-micromolar hyperforin causing a sevenfold increase over control. The rifampin increased drug metabolism by a factor of 32. The authors concluded that chronic coadministration of SJW with docetaxel may reduce drug bioavailability to subtherapeutic levels. Wada et al.[154] used an MDR1-overexpressing line of HeLa cancer cell model and found that both hypericin and SJW lowered the antiproliferative activity of paclitaxel while inhibiting MDR1-mediated drug transport.

Clinical Implications and Adaptations

The taxanes are widely used in the treatment of breast, prostate, lung, and ovarian cancers. Body surface area (BSA) dosing is standard practice, but variability in responsiveness and resistance to the drugs is well documented. Paclitaxel is metabolized by CYP2C8, with minor CYP3A4 and CYP3A5 involvement, whereas docetaxel is primarily metabolized by 3A4 and 3A5. Administration of docetaxel with ketoconazole leads to a significant decrease in drug clearance (49%), suggesting that docetaxel disposition will be affected by 3A4 inducers and inhibitors in vivo.[155] Paclitaxel, although primarily metabolized by 2C8, has been shown to be influenced by 3A4 induction.[138] Further complexity arises when considering taxane resistance, which is thought to be at least partly caused by drug efflux pump mechanisms.

At present, avoidance of SJW with taxane administration is indicated. Modulation of taxane metabolism by induction of CYP450 by SJW has been emphasized as a problem (e.g., see Sparreboom et al.[144]). In context, however, there is considerable potential for improving the taxane-based pharmacotherapy by application of pharmacogenomics data to dosing.[156] Information about the difference, if any, between the traditional taxane drugs and the novel liposomal forms in terms of their metabolic degradation pathways is unavailable at this time.

Paroxetine and Related Selective Serotonin Reuptake Inhibitor and Serotonin-Norepinephrine Reuptake Inhibitor (SSRI and SSRI/SNRI) Antidepressants and Nonselective Serotonin Reuptake Inhibitors (NSRIs)

Evidence: Paroxetine (Aropax, Deroxat, Paxil, Seroxat); nefazodone (Serzone), trazodone (Desyrel).
Extrapolated, based on similar properties: Bupropion (Wellbutrin), citalopram (Celexa), duloxetine (Cymbalta), escitalopram (*S*-citalopram; Lexapro), fluoxetine (Prozac, Sarafem), fluvoxamine (Faurin, Luvox), mirtazapine (Remeron), sertraline (Zoloft), venlafaxine (Effexor).

Interaction Type and Significance

? **Interaction Likely but Uncertain Occurrence and Unclear Implications**

Probability:
3. Possible

Evidence Base:
○ **Preliminary** (arguably □ Inadequate)

Effect and Mechanism of Action

These complex, potential interactions involve variable pharmacokinetic and pharmacodynamic factors, depending on the specific serotonin uptake drug, the timing and manner of herb-drug coadministration, concurrent comedications, and individual factors. "Serotonin syndrome" has been suggested as a possible clinical outcome of the interaction, but this is controversial and poorly documented, and precise mechanisms for such effects are not consistent with known SJW pharmacology. Few clinical reports are available and are of variable quality. Overall, the clinical significance of the interaction may be overstated.

Research

This proposed interaction was originally based on early assumptions about SJW pharmacology that have not been confirmed by recent research. The first was the erroneous belief that SJW functions as a MAOI-like agent, and the interaction with SSRIs was simply an assumed extrapolation from the known drug-drug MAO-A inhibitors and serotonin reuptake agents. The in vitro findings of MAO inhibition have not been replicated and have been suggested by Cott[89] to be artifactual (see Theoretical, Speculative, and Preliminary Interactions Research later). The second assumption was that SJW exerts its antidepressant effects through a druglike serotonin uptake inhibition, thus leading to excessive serotonin levels, and the possibility of serotonin syndrome if combined with a pharmaceutical SSRI. As previously noted, the neurotransmitter effects of SJW do not appear to be homologous to any pharmaceutical drug action on specific neurotransmitter pathways; rather, this appears to be a "broad-band" effect on the reuptake of all five main central neurotransmitters.[94] Finally, "serotonin syndrome" may have been overenthusiastically reported; a significant proportion of cases probably resulted from misdiagnosis, according to Radomski et al.[103] (see Reports).

Given the likelihood that SJW extracts may act biphasically, inhibiting 3A4 in acute short-term doses, with progressive induction of P-gp and 3A4 at 7 to 10 days, adverse reactions caused by the addition of SJW to preexisting SSRI regimens may be the result of a short-term pharmacokinetic interaction, parallel to the digoxin-SJW interaction. This hypothesis might help explain the effects reported by Lantz (see Reports), which are more like enhanced adverse effects of the drug than "serotonin syndrome." Because each of the six principal SSRI drugs has different routes of metabolism, as well as different inhibitory profiles on P450 enzymes, the situation becomes more complex if the interaction is indeed pharmacokinetic. The respective CYP450 metabolic properties and pathways of the selective and nonselective serotonin uptake drugs are listed in the table.[157]

As data in the table show, none of the serotonin reuptake inhibitor (SRI) drugs is an exclusive substrate of 3A4; that nefazodone and norfluoxetine (the active metabolite of fluoxetine) are potent inhibitors of 3A4; and that nefazodone, trazodone, and venlafaxine also induce P-gp. It therefore seems unlikely that short-term inhibition would inevitably produce excessive serotonin levels, whereas the predominant effect of long-term coadministration should be for SSRI drug levels to be lowered by SJW induction, with a consequent decrease in serotonin levels. Further research is needed to clarify the precise extent and role of pharmacokinetic factors in different SJW-SRI drug combinations.

Reports

Reports of serotonin syndrome (SS) arising from the coadministration of SJW and SSRI/NSRI drugs are rare, particularly in Europe.[86] However, ominous warnings of the potentially fatal consequences of SS often accompany secondary accounts of SJW interactions in the United States. This appears unnecessarily alarmist because all six of the known fatalities in the toxicology literature for SS were caused by toxic encephalopathy (on postmortem examination), and five were deliberate drug overdoses involving the MAO-A inhibitor moclobemide with citalopram or clomipramine.[158] Other severe symptoms of toxic SS include disseminated intravascular coagulation (DIC), resulting in renal failure. These should be distinguished from the common symptoms of mild SS, which include myoclonus, tremor, diaphoresis, and restlessness, all of which are transient and self-limiting and do not usually require medication changes or supportive treatment.[103]

A frequently cited U.S. case series is from a geriatric care facility reported by Lantz in 1999; four elderly patients

Metabolism of Serotonin Reuptake Inhibitor Drugs

Drug	Major P450 Metabolism Site(s)	Inhibits	Induces
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram	2C19, 2D6, 3A4	2D6	
Escitalopram	2C19, 2D6, 3A4	2D6	
Fluoxetine	2C9, 2C19, 2D6, 3A4	1A2, 2B6, 2C9, **2C19**, **2D6**, 3A4 (+ norfluoxetine)	
Fluvoxamine	1A2, 2D6	**1A2**, 2B6, 2C9, **2C19**, 2D6, 3A4	
Paroxetine	2D6	1A2, **2B6**, 2C9, 2C19, **2D6**, 3A4	
Sertraline	2B6, 2C9, 2C19, 2D6, 3A4	1A2, 2B6, 2D6, glucuronidation	
Nonselective Serotonin Reuptake Inhibitors (NSRIs)			
Bupropion	2B6	**2D6**	
Mirtazapine	1A2, 2D6, 3A4		
Nefazodone	3A4, 2D6	**3A4**, P-gp (acute)	P-gp
Trazodone	3A4, 2D6		P-gp
Venlafaxine	2D6	2D6	P-gp

Modified from Cozza.[157]
Bold-face text denotes pronounced effects; *P-gp*, P-glycoprotein.

who were stable on sertraline commenced SJW and experienced symptoms diagnosed by the author as ''central serotonergic syndrome.'' However, the data for at least one of the four cases were inadequate, according to the Ernst and Fugh-Berman criteria (failure to list comedications), and in none of the cases was the herbal preparation fully identified.[11] The primary symptoms for all four were nausea and in three, vomiting. These symptoms alone are atypical of SS; according to a detailed review of all 62 published cases from 1982 to 1995 by Radmoski et al.,[103] nausea occurred in only 6%, and vomiting was never recorded. The fifth elderly woman in the same series was stable on nefazodone and experienced the same symptoms after adding SJW. The case presents problems of interpretation, even assuming a short-term pharmacokinetic inhibition of CYP 3A4. Nefazodone is a powerful 3A4 inhibitor and only likely to exhibit interactions with a more potent inhibitor than itself,[157] which rules out a SJW effect. Sertraline is cometabolized by multiple P450 CYPs (2B6, 2C9, 2C19, 2D6, *and* 3A4; see table), which suggests it would only be vulnerable to pharmacokinetic interactions with pan-inhibitors or pan-inducers, which excludes SJW. This suggests that the interaction may have been pharmacodynamic, but the antidepressant effects of SJW in vivo are mild, take several weeks to manifest, and are not equivalent to the pharmaceutical SSRI/NSRI drug mechanisms. Despite its frequent invocation as confirming the SJW-SSRI interaction, the Lantz report is inconclusive, and the authors' explanations are not consistent with the currently understood pharmacology of SJW.

Another case report involved a woman who became lethargic, having discontinued paroxetine (40 mg once daily) after 8 months, and who began 600 mg of SJW powdered herb daily (preparation unspecified) 10 days later. On the second day of this regimen she also took a single dose of paroxetine (20 mg) to help with insomnia. The next day she was almost unable to rise from bed and was groggy and incoherent but arousable. Two hours later she still complained of fatigue, weakness, and nausea, although her vital signs and mini–mental status examination were normal. Twenty-four hours later she had no remaining ill effects.[159] The reporting physician described this as resembling a ''sedative/hypnotic syndrome'' intoxication. Interpretation of this case must account for paroxetine being a potent inhibitor of 2D6, the enzyme of which it is a substrate; the 10-day washout after the prolonged paroxetine therapy may have caused 2D6 to rebound, rendering the patient hypersensitive to a subsequent repeat dose of the SSRI. CYP2D6 is well known to exhibit ''slow'' and ''fast'' polymorphisms. This report is probably a case of excessive sedation resulting from enhanced effects of the drug, rather than a pharmacodynamic SJW interaction. Several in vivo studies have examined short-term and long-term effects of SJW on 2D6, the current consensus being a lack of observable effect for short-term inhibition or longer-term 2D6 induction.[24,26,31,29]

Nirenberg et al.[160] recorded mania in two depressive patients in temporal association with SJW consumption. Both patients had initially been diagnosed with major depression, and before initiating prescription psychiatric drugs, they had experimented with SJW. In an interesting conjecture, the authors suggested the resulting manic episodes were caused by an ''unmasking'' of rapid-cycling bipolar disorder, supported by both patients subsequently responding to lithium therapy. The authors advise that patients should be screened for episodes of hypomania and mania by their physician before the recommendation of SJW for depression.

A brief French report, drawn from the official Marseilles pharmacovigilance database, described a 32-year-old man with a history of depression who added SJW ''mother tincture'' to his regimen of venlaxafine.[161] In herbal pharmacy practice, ''mother tincture'' refers to 1:10 hydroethanolic extract of crude fresh herb. After 3 days of SJW at 200 drops three times daily, the patient developed symptoms of anxiety, hyperhydrosis, and tremor. These reversed on cessation of the SJW tincture. The authors note that the normal dose of this type of SJW preparation is 160 drops total per day, and the dose taken was 600 drops, more than triple the recommended level. The symptoms, however, do correspond to those described for mild SS. Venlafaxine is also a potent inhibitor not only of serotonin reuptake, but also of dopamine, which might make it more prone to interact with the pan-neurotransmitter reuptake inhibitor effects of SJW.

Integrative Therapeutics, Clinical Concerns, and Adaptations

The nature of the SJW-SRI interaction remains controversial, although enhanced serotonin effects appear probable under some circumstances. Further data are required before the mechanisms, incidence, and clinical significance can be adequately characterized. Physicians and psychiatrists experienced in psychopharmacology are usually aware of potential drug-drug interactions. The notoriety of SJW as a potential interactor with antidepressants is well known among mental health professionals, many of whom prescribe SJW alone as first-line therapy for mild depression, particularly in Europe.[85]

At a professional level, SJW coadministered for specific therapeutic goals does not present significant problems, given appropriate monitoring. Specifically, SJW may be used empirically before starting pharmaceutical antidepressant therapy, or it may be used to assist tapered withdrawal from antidepressant therapy, particularly with SSRIs, which are subject to withdrawal symptoms of varying severity. An alternative viewpoint adopted by some providers is to ''err on the side of caution,'' refrain from using SJW to support withdrawal, and only commence herbal therapy following a suitable washout period after cessation of the SRI, usually 3 weeks. Polypharmacy presents challenges that are unpredictable, as illustrated in the report by Spinella and Eaton[162] involving ginkgo, SJW, fluoxetine, and buspirone (see Buspirone later).

Simvastatin and Related HMG-COA Reductase Inhibitors (Statins)

Evidence: Simvastatin (Zocor).
Extrapolated, based on similar properties: Atorvastatin (Lipitor), lovastatin (Altocor, Altoprev, Mevacor); combination drug: lovastatin and niacin (Advicor); simvastatin combination drug: simvastatin and extended-release nicotinic acid (Niaspan).
Similar properties but evidence indicating no or reduced interaction effects: Fluvastatin (Lescol, Lescol XL), pravastatin (Pravachol), rosuvastatin (Crestor).

Interaction Type and Significance

◈ **Impaired Drug Absorption and Bioavailability, Negligible Effect**

Probability:	Evidence Base:
3. Possible	○ **Preliminary**

Effect and Mechanism of Action

Simvastatin is a prodrug and cosubstrate for 3A4 and P-gp. Serum levels of active metabolite may be lowered by concomitant administration with SJW because of the induction of drug

efflux and metabolism. Clinical effects of the interaction have not been established. Different statins are metabolized quite differently, and the interaction cannot be extrapolated to all 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors as a class.

Research

A single, small, double-blind crossover trial used two groups of eight healthy volunteers to investigate the effects of SJW versus placebo pretreatment on single-dose simvastatin (10 mg) and pravastatin (20 mg) kinetics. SJW was administered at 300 mg three times daily for 14 days and 24-hour blood samples taken. No changes were found for pravastatin, but the active metabolite simvastatin hydroxy acid (SVA) showed a significant decrease in AUC after SJW compared with placebo.[163] Simvastatin, lovastatin, and atorvastatin are all similar lactone prodrugs and cosubstrates of P-gp and 3A4, showing similar responses to 3A4/P-gp inhibitors such as itraconazole. CYP3A4 is probably only involved with a minor degree of transformation of pravastatin and fluvastatin, neither of which are prodrugs, and which do not appear to affect P-gp.[164]

Clinical Implications and Adaptations

Lowering of SVA levels by concomitant administration with SJW suggests theoretically that lipid-lowering targets may not be achieved because of underexposure to the drug. Clinical data are not available and would not necessarily be expected to emerge from case reports, given other known issues for statin therapy failure, such as poor long-term compliance. Duration of SJW administration, if taken for mild depression indications, can be many months, and statin therapy is often similarly continued for extended periods. If long-term coadministration is proposed, statins such as pravastatin or fluvastatin should be selected because these do not share the 3A4/P-gp characteristics of simvastatin and lovastatin. Newer statin drugs such as rosuvastatin have different P450/P-gp characteristics and may also be selected over simvastatin or lovastatin.

Tacrolimus

Tacrolimus (FK-506, fujimycin; Prograf).

Interaction Type and Significance

✗✗✗ **Potentially Harmful or Serious Adverse Interaction—Avoid**

◈◈◈ **Impaired Drug Absorption and Bioavailability, Avoidance Necessary**

Probability: 1. Certain

Evidence Base: ◉ **Emerging**

Effect and Mechanism of Action

Tacrolimus is a macrolide immunosuppressant that is a dual substrate of P-gp and 3A4, both of which are induced by SJW. Addition of SJW to previously stable tacrolimus regimens will result in significant reductions in serum drug levels and the risk of therapeutic failure and nephrotoxicity because of its narrow therapeutic and toxicological indices.

Reports

A single case report suggested that a renal graft patient previously stable on tacrolimus took SJW, 600 mg once daily for a month, and serum drug levels were depressed, reversing after cessation of the herb.[165]

Research

Two studies have confirmed this important interaction. A small preclinical "before and after" investigation on 10 healthy volunteers examined tacrolimus single oral doses before and after 18 days of SJW administration at 300 mg three times daily. Oral tacrolimus clearance was significantly increased by 59% and AUC significantly reduced by 50% after SJW administration.[166] Mai et al.[167] studied a case series of renal graft patients stable on a combination of tacrolimus and mycophenolic acid to examine the effects of adding SJW (300 mg twice daily, a lower-than-usual dose); after 14 days of SJW administration, tacrolimus levels decreased significantly from 180 to 75.9 ng/mL/hour. The median dose adjustment of tacrolimus to correct the herb induction effects was almost double, from 4.8 to 8.0 mg once daily.[167] Mycophenolic acid levels were unaffected.

Clinical Implications and Adaptations

The tacrolimus interaction is analogous to that of SJW-cyclosporine, as discussed earlier. Both agents are used in allograft patients for suppression of cell-mediated immunity, and the risks of therapeutic failure (acute graft rejection) are potentially fatal. Clinical case reports of rejection reactions caused by SJW interactions with tacrolimus are lacking. Whether this is caused by widespread avoidance of coadministration following publicity of the SJW-cyclosporine interaction is unknown.[63] The nephrotoxicity of tacrolimus is high, and upward adjustment of dose to compensate for pharmacokinetically induced increases on oral clearance will increase risks of toxicity.[165] This toxicity potential as well as the increased financial cost of higher dose regimens suggests that despite the theoretical possibility of steady-state coadministration with SJW being managed using routine serum monitoring of drug levels, in practice this is not a feasible option, and the combination should be avoided.

Verapamil and Related Calcium Channel Blockers

Evidence: Verapamil (Calan, Calan SR, Covera-HS, Isoptin, Isoptin SR, Verelan, Verelan PM).

Extrapolated, based on similar properties: Amlodipine (Norvasc); combination drug: amlodipine and benazepril (Lotrel); bepridil (Bapadin, Vascor), diltiazem (Cardizem, Cardizem CD, Cardizem SR, Cartia XT, Dilacor XR, Diltia XT, Tiamate, Tiazac), felodipine (Plendil), combination drugs: felodipine and enalapril (Lexxel), felodipine and ramipril (Triapin); gallopamil (D600), isradipine (DynaCirc, DynaCirc CR), lercanidipine (Zanidip), nicardipine (Cardene, Cardene I.V., Cardene SR), nifedipine (Adalat, Adalat CC, Nifedical XL, Procardia, Procardia XL); combination drug: nifedipine and atenolol (Beta-Adalat, Tenif); nimodipine (Nimotop), nisoldipine (Sular), nitrendipine (Cardif, Nitrepin); verapamil combination drug: verapamil and trandolapril (Tarka).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**

◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

Probability: 2. Probable

Evidence Base: ○ **Preliminary**

Effect and Mechanism of Action

A pharmacokinetic interaction between SJW and verapamil may be by induction of presystemic drug metabolism at the

intestinal mucosa by SJW. The interaction is experimentally confirmed with verapamil, but clinical reports are lacking to date. The interaction is likely to occur with related calcium channel blockers, most of which are substrates of CYP450 3A4.

Research

A pharmacokinetic study used a jejunal perfusion technique to examine the pharmacokinetics of racemic verapamil before and after SJW treatment (14 days, 300 mg three times daily) in eight healthy volunteers.[168] By comparing the levels of verapamil and its 3A4 metabolite norverapamil in perfusate and plasma, the investigators were able to localize the site and mechanism of the interaction. They concluded that the notable reduction in AUC (approximately 80%) of both *R*- and *S*-enantiomers of verapamil after pretreatment with the herb was caused by presystemic metabolism by 3A4, primarily at the intestinal wall.

Clinical Implications and Adaptations

Verapamil is a well-known substrate of 3A4, as are the majority of calcium channel blockers. *R-/S*-verapamil is also metabolized to some extent by 2C9 and by 2E1, unlike most other calcium channel blockers. Verapamil is also an inhibitor of 3A4, although not as potent as diltiazem. The related calcium channel blocker mibefradil was withdrawn because of the severity of its 3A4 and 2D6 inhibition-related adverse interaction effects. Verapamil is also an inhibitor of P-gp. The single available study does not illuminate the kinetics of sustained in vivo coadministration of SJW and the drug, and predicting the net results of combined autoinhibition of 3A4 and P-gp by the drug, with SJW induction of the same metabolic factors, is problematic.

Verapamil is well known in the conventional literature to exhibit metabolic interactions with digoxin, beta blockers, antineoplastic agents, and alcohol. Theoretically, coadministration with SJW may increase drug levels required for management of the condition, typically angina (including variant or Prinzmetal's angina), hypertension, atrial flutter or fibrillation, and supraventricular tachycardia. At present, given the lack of reports of the interaction, normal standards of vigilance and monitoring relating to calcium channel blocker polypharmacy are probably adequate until evidence to the contrary becomes available.

Voriconazole and Related Triazole Antifungal Agents

Evidence: Voriconazole (Vfend).
Extrapolated, based on similar properties: Fluconazole (Diflucan), itraconazole (Sporanox), posaconazole (Noxafil).

Interaction Type and Significance

✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**
◈◈ **Impaired Drug Absorption and Bioavailability, Precautions Appropriate**

Probability:	Evidence Base:
2. Probable	○ **Preliminary**

Effect and Mechanism of Action

A pharmacokinetic interaction between SJW and voriconazole, which are metabolized by CYP450 3A4, 2C9, and 2C19, resulting in a lowering of drug levels due to enzyme induction by SJW. The interaction is experimentally confirmed, but clinical reports are lacking to date.

Research

Rengelshausen et al.[37] examined the disposition of single doses of voriconazole in 16 healthy male volunteers stratified by CYP2C19 genotype on day 1 and day 15 of concomitant SJW administration (300 mg three times daily, extract LI160). They found an overall decrease in AUC at day 15 of up to 59%, broadly equivalent to the effect of SJW on tacrolimus and cyclosporine. In addition, they found that 2C19 wild type (extensive metabolizer) exhibited the lowest exposure to the antifungal drug. The clearance data revealed an initial but insignificant increase in plasma levels of the drug after onset of SJW administration. This is a predictable result of the "biphasic" effect of SJW flavonoids mechanistically inhibiting CYP450, followed by a more potent effect of induction (see Effects on Drug Metabolism and Bioavailability).[38]

Clinical Implications and Adaptations

The novel antifungal voriconazole is used in patients with invasive aspergillosis and other serious fungal invasions. Therapeutic dosing is critical and, in SJW coadministration, should be avoided. The manufacturer's data on voriconazole do not recommend 2C19 phenotyping, although the wild-type polymorphism would appear to be at risk for lowered drug exposure.

Warfarin and Oral Vitamin K Antagonist Anticoagulants

Evidence: Phenprocoumon (Jarsin, Marcumar), warfarin (Coumadin, Marevan, Warfilone).
Extrapolated, based on similar properties: Anisindione (Miradon), dicumarol, ethyl biscoumacetate (Tromexan), nicoumalone (acenocoumarol; Acitrom, Sintrom), phenindione (Dindevan).

Interaction Type and Significance

✗✗ **Minimal to Mild Adverse Interaction—Vigilance Necessary**

Probability:	Evidence Base:
5. Improbable	▽ **Mixed**

Effect and Mechanism of Action

This suggested pharmacokinetic interaction could result in a pharmacodynamic decrease in the international normalized ratio (INR) because of lowered drug levels. Theoretically, the risk is decreased anticoagulation, but clinical reports of thrombosis caused by coadministration are lacking. The incidence and significance of the interaction are not established.

Research

A poster study examined the kinetics of single-dose oral phenprocoumon after SJW administration in 10 healthy males age 18 to 50 years.[169] SJW was given at 300 mg three times daily for 10 days, and the dose of phenprocoumon was 12 mg on day 11. AUC of phenprocoumon was significantly decreased ($p = 0.0007$) in the SJW group. Phenprocoumon is a warfarin analog unavailable in the United States but widely used in Europe. It is pharmacodynamically identical in action to warfarin but is well known to have different pharmacokinetics, its half-life being considerably longer than that of warfarin.[170] As with *S*-warfarin, it is metabolized by 2C9, but evidence indicates that the active sites on the 2C9 enzyme are different for warfarin and phenprocoumon, which may account for the difference in kinetics.[171] Currently available direct evidence suggests SJW in vivo lacks effect on either 1A2 or 2C9.[26] Cott[89] suggested that P-gp effects may cause a reduction in absorption at the enterocyte level, resulting in reduced drug levels. Circumstantial support for this hypothesis comes from a rodent model in which oral warfarin levels were reduced after

SJW treatment, but hepatic microsomal levels of CYP450 were unaltered.[172]

A human study examining warfarin pharmacogenomics showed that a specific haplotype for ABC1 (the *mdr*1 gene encoding for P-gp) was consistently overexpressed in a "low-dose" warfarin group; at present, however, it is not clear whether warfarin isomers are substrates of P-gp transporters or other, as-yet uncharacterized transporters.[173] It is known that the principal pharmacogenetic determinants of variability in warfarin kinetics are older age and the common 2C9 polymorphisms, 2C9*2 and 2C9*3.[174-177] A subsequent open-label trial examined the effects of ginseng and SJW pretreatment on warfarin kinetics in 12 healthy volunteers, using laboratory parameters (INR, derived from prothrombin time) and pharmacokinetic data (plasma levels of *S*- and *R*-enantiomers of warfarin and urinary *S*-7-hydroxywarfarin levels). Pretreatment with SJW resulted in significant effects on clearance of warfarin and reduction in INR.[178] However, the INR changes were a mean of 21%, well below the value suggested by Wells et al.[179] for "level 1 evidence" of a substantive interaction between warfarin and another agent. The ginseng pretreatment had no effect.

Reports

The only available and often-cited report of warfarin-SJW interaction is a case series summarized in a 2000 letter to the *Lancet* from Yue and colleagures[150] of the Swedish Medical Products Agency in a correspondence generated by the commentary on SJW safety by Ernst.[10] The series involved seven patients (six elderly, three male and four female) who apparently experienced reductions in previously stable INR after starting SJW (preparation, dose, and duration unspecified). None of the patients experienced thromboembolic episodes, and dose adjustment or cessation of herb apparently restabilized INR in all cases, although details were not given. Fugh-Berman and Ernst[11] later reviewed this report in their survey of interaction report reliability and found the Swedish reports scored "unreliable" and were effectively unevaluable. In an original and rigorous literature survey of warfarin drug-food interactions, Wells et al.[179] suggested that because of the variability of warfarin responses, only twofold INR changes (i.e., 50% or 200% stable value) should be admitted as "level 1 evidence" of an interaction on warfarin induced by another agent. In fact, three of seven INR values in the Swedish series met this criterion. However, comedications, comorbidities, and patient histories, as well as dose, preparation form, and duration of SJW administration, were not recorded, and the report must remain classified as unreliable.[11]

Clinical Implications and Adaptations

The absence of reliable reports of the interaction, especially given that warfarin is the most widely prescribed anticoagulant in the Western world and SJW remains a popular herbal medication, suggests that the interaction has minimal clinical significance, if it indeed exists. The phenprocoumon trial indicates some effect in younger healthy patients, but the use of this drug in Germany (Jarsin) has not been associated with adverse reports in combination with SJW, at an incidence level of two cases per million prescriptions of Jarsin, according to figures given at a recent ESCOP symposium.[180] If SJW has an induction effect on warfarin pharmacokinetics, there may be some reduction in drug levels if SJW is added to stably warfarinized patients. The degree of INR change is probably relatively small, about 20%, according to available preclinical data (males). Because INR monitoring is essential as a concomitant of warfarin therapy, however, management of coadministration should theoretically present no problems if monitoring procedures are maintained or increased, with dose-adjustment corrections made accordingly. Discontinuation of SJW from a stable regimen of coadministration would be more critical, potentially resulting in excessive anticoagulation and the risk of bleeds. However, this appears to be a theoretical concern at present, particularly compared to the many known determinants of anticoagulation variability in response to warfarin, from 2C9 polymorphisms through dietary factors and numerous drug-drug interactions.

THEORETICAL, SPECULATIVE, AND PRELIMINARY INTERACTIONS RESEARCH, INCLUDING OVERSTATED INTERACTIONS CLAIMS

Buspirone

Buspirone (Buspar).

In a survey of SJW interactions by Izzo,[13] buspirone-SJW was listed as an interaction. This was based on an isolated case report by Spinella and Eaton,[162] reporting "hypomania" after the addition of both SJW and ginkgo to buspirone. The patient was in fact comedicated with fluoxetine, and paradoxical interactions between fluoxetine and buspirone have been recorded in the conventional drug literature, including adverse reactions, the mechanism of which is not understood.[111] Although buspirone is metabolized by CYP3A4, the interaction cannot be reliably deduced from this report. Fluoxetine is also well known to precipitate manic episodes in patients with bipolar disorders misdiagnosed as unipolar depressive disorders.

Chlorzoxazone

Chlorzoxazone (Paraflex, Parafon Forte, Relaxazone, Remular-S).

The antispasmodic skeletal muscle relaxant chlorzoxazone is metabolized exclusively by CYP2E1 and used experimentally as a probe for phenotyping poor and fast metabolizing expressions of this enzyme. The recent investigation of the effect of several herbs on P450 phenotyping probes by Gurley et al.[22] was the first demonstration of a possible in vivo induction of 2E1 by SJW using chlorzoxazone as a probe drug. Interactions of the drug are rare, and human case reports are lacking. The induction of 2E1 by SJW appears unlikely to constitute a clinically significant interaction. The effect of SJW is probably no greater than induction of 2E1 by chronic ethanol consumption or tobacco use. The most significant established interaction involving induction of 2E1 is in the production of *N*-acetyl-*p*-benzoquinone imine (NAPQI), the hepatotoxic metabolite of acetaminophen. NAPQI is produced when acetaminophen intoxication exceeds available glutathione stores and is metabolized by 2E1 instead of glutathione-*S*-transferase, resulting in fulminant hepatic failure. At present, however, the SJW-chlorzoxazone interaction is overstated, and potential for SJW involvement in acetaminophen hepatotoxicity remains conjectural.

Loperamide

Loperamide (Imodium A-D, Imodium A-D Caplets, Kaopectate 1-D, Maalox Anti-Diarrheal, Pepto Diarrhea Control).

Loperamide is an opioid derivative lacking central nervous system (CNS) effects that is used for treatment of diarrhea. It is metabolized by CYP3A4 and is a substrate of P-gp (thus does not cross the blood-brain barrier). A letter described a single case of delirium in a 39-year-old woman with a history of migraines and depression, apparently stable on a regimen of "two tablets of St. John's wort and a valerian tablet daily" (preparation and dose not specified) for 6 months. She was admitted to the emergency room in a confused, disoriented state. She was

afebrile and tachycardic with elevated blood pressure, and a toxicology screen was positive for opioids. Subsequent history revealed she had taken loperamide for diarrhea. The patient had a previous history of admission because of Demerol (meperidine) intoxication. The authors suggested that the interaction was a MAOI type between SJW and loperamide.[181] This is speculation unsupported by the known pharmacology of SJW; further aspects of the report are "unreliable" in that doses of SJW and loperamide were not given, and the access of the patient to Demerol and her history of drug use increase the possibility of covert meperidine use. Pharmacokinetic interaction with SJW can be ruled out; it would have decreased rather than increased drug toxicity. Nonetheless, this speculative interaction is usually included without comment in secondary reviews.[78]

Monoamine Oxidase (MAO) Inhibitors

MAO-A inhibitors: Isocarboxazid (Marplan), moclobemide (Aurorix, Manerix), phenelzine (Nardil), procarbazine (Matulane), tranylcypromine (Parnate).
MAO-B inhibitors: Selegiline (deprenyl, L-deprenil, L-deprenyl; Atapryl, Carbex, Eldepryl, Jumex, Movergan, Selpak); pargyline (Eutonyl), rasagiline (Azilect).

Early recommendations that SJW should not be coadministered with MAO inhibitors were based on extrapolation of putative MAOI and catechol-*O*-methyltransferase (COMT) activity from in vitro studies, which have not been substantiated experimentally or demonstrated in vivo (see Strategic Considerations earlier). In a survey, 862 psychiatrists in Australia and New Zealand were questioned about SJW use and adverse effects. No cases of hypertension were noted, although two (<1%) claimed reports of palpitations as an adverse effect of SJW alone. Five reports of interaction with moclobemide were noted, but these could not be evaluated due to lack of details.[85]

There is a brief report of otherwise-unexplainable hypertension associated with prescribed SJW alone (Ze 1117, 250 mg twice daily for 1 week) that reversed on cessation of the herb. The herb was self-prescribed for stress, and the patient lacked previous cardiovascular history and took no other drugs.[182] The correspondent speculatively attributed this episode to norepinephrine uptake inhibition by SJW. Another case described a 41-year-old man admitted to the emergency room with confusion, disorientation, tachycardia, and hypertension (blood pressure, 210/140) who was negative for toxicology screen and numerous other laboratory and diagnostic tests, which ruled out pathological causes. He apparently took no concurrent medications or nutritional supplements. History revealed use of SJW (dose and preparation not specified) and consumption of cheese and red wine immediately before the episode.[183] This report is the only one suggesting a tyramine food interaction with SJW, but unfortunately the dose and preparation of the herb (and possible other ingredients) were not identified, and thus the report is not evaluable. At this time, advice to avoid tyramine-containing foods with SJW seems unnecessary.

Photosensitizing Agents

Delta-aminolevulinic acid (d-ALA)

Phototoxicity is frequently suggested as a possible adverse effect of SJW, although published human case reports are lacking. According to official German adverse drug interaction (ADR) data reviewed by Schulz,[86] reversible skin photosensitization responses have been reported at a rate of less than one per 300,000 doses of SJW between October 1991 and December 1999, during which an estimated 8 million patients were treated with SJW. Hypericin, the naphthodianthrone constituent of SJW, in fact exhibits photodynamic properties, and it has been used in oncological research as an investigational cytotoxic agent in photodynamic therapy (PDT) and as an imaging agent in photodiagnosis (PD).[184]

Delta-aminolevulinic acid (d-ALA) is a precursor compound used to enhance endogenous synthesis of the photosensitizer protoporphyrin IX through the heme pathway. There is one report of a possible interaction between d-ALA and SJW in a dermatological case in which excessive skin erythema occurred after topical irradiation.[185] Currently, these uses of ALA are confined to specialized clinical environments.[186] If the photosensitizer d-ALA becomes more generally used in photodynamic imaging studies, potential interactions with SJW should be considered, and avoidance may be prudent pending further data.

Theophylline/Aminophylline

Theophylline/aminophylline (Phyllocontin, Slo-Bid, Slo-Phyllin, Theo-24, Theo-Bid, Theocron, Theo-Dur, Theolair, Truphylline, Uni-Dur, Uniphyl); combination drug: ephedrine, guaifenesin, and theophylline (Primatene Dual Action).

Several secondary sources have repeated a suggested interaction between theophylline and SJW. However, the suggestion is derived from a single case reported in a letter from Nebel et al.[187] in 1999. Theophylline is metabolized by CYP1A2 and has a relatively narrow therapeutic index in that toxicity can arise from marginally supranormal plasma levels. The patient in the case report smoked half a pack of cigarettes daily (tobacco smoke induces 1A2 via the arylcarbon receptor) and was taking 11 concurrent prescription medications, including the leukotriene antagonist zafirlukast, which is a 1A2 inhibitor and interacts with theophylline.[111] Other medications included morphine, amitriptyline, valproate, and zolpidem. With a polypharmaceutical regimen that includes multiple substrates, inducers, and inhibitors of multiple metabolic enzymes and transporters, several of which are known to interact with each other, the report is unevaluable as evidence of a putative SJW-theophylline interaction, despite the authors' suggestion that theophylline levels increased after cessation of SJW (dose and preparation unrecorded).

A recent study by Morimoto et al.[188] has confirmed the lack of clinically significant interaction with theophylline. After 15 days of pretreatment with 300 mg SJW three times daily, healthy Japanese male volunteers showed no significant change in urinary concentrations of theophylline or its metabolites after a single 400-mg oral dose.

The 188 citations for this monograph are located under St. John's Wort on the CD at the back of the book.

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