

Warding off Evil in the 21st Century: *St John's Wort as a Xenosensory Activator?*

Jonathan Treasure

According to folklore St. John's wort (SJW) was once known for its special ability to ward off evil spirits and protect against magic spells. For herbalists, such uses are typically regarded as non-trivial.¹ Fast-forward to the late 1990s, and SJW in the guise of a standardized phytopharmaceutical with a slew of controlled clinical trials supporting its efficacy, is celebrated as a remedy for "mild to moderate depression". By most accounts the herb appeared to be at least as effective for this condition as pharmaceutical anti-depressants, and standardized SJW supplements became an enormously popular best-seller. If its efficacy for depression compared to pharmaceuticals was debatable, the safety of the herb - particularly in comparison to prescription antidepressants - was uncontroversial. Prior to 1999, SJW was considered benign: natural was safe.

The publication of convincing reports of interactions between St. John's wort and digoxin,² cyclosporine,³ and indinavir⁴ was a decisive turning point. St. John's wort was transformed almost overnight from a benign herbal remedy into public enemy number one, with authorities such

as Professor Ernst heading the *volte face*.⁵ Although regulatory and official bodies acted swiftly, a longer term consequence was to provide the status quo with a much needed gift horse - SJW's fall from grace

was the Achilles heel that the mainstream had desperately needed to counter the hitherto seemingly inexorable rise in public popularity of herbal medicines.

The subsequent five years has seen increased understanding of the pharmacology of SJW and its constituents, and the herb is now known to be associated with a number of clinically significant pharmacokinetic interactions as suggested by the original reports.⁶ These interactions are mediated by its effects on several key components of drug metabolism, including the P450 mixed oxidase system, various conjugases and transferases, as well as the transporter proteins that modulate drug efflux across intestinal, renal, and biliary epithelia. Taken together these systems comprise what are often referred to as Phases 1, 2 and 3 respectively of the detoxification system. Phylogenetically ancient, this system is present in lower animals and has been conserved during evolution; it has the dual function of metabolizing endogenous compounds (such as steroid hormones) and protecting the organism against the damaging effects of potentially harmful environmental xenobiotics.

During the same five year period, the mainstream medical literature generated a minor industry of publishing secondary articles containing hyperbolic warnings of the dire dangers of herb-drug interactions,

often coupled with strident demands for increased regulation and restriction of availability of herbs and dietary supplements. The quantity of this derivative literature may have been growing but the scientific quality of publications is generally low and in some notable instances, such as the notorious 1998 review by Lucinda Miller, overwhelmingly erroneous and ill-informed.⁷ Essentially by means of the process best described as the *mainstream manufacture of misinformation** potential drug interactions associated with botanicals have been promoted as the most significant safety concern about herbs for consumers and healthcare providers alike. In the face of this, the reaction of many herbalists, rear-footed by their obligation to demonstrate responsible regard for patient safety, has been unnecessarily defensive, which tends by default to concede the terms of debate to the mainstream.

In fact, the mainstream spin on interactions is deeply flawed for several reasons, foremost among which are some basic conceptual issues. Most importantly, the meaning of "interaction" is rarely defined, and the term is used inconsistently to cover a variety of situations which are not strictly interactions at all.⁸ Logically, a true interaction is properly an "unpredictable" or unexpected result of combining two

agents. The result is a non-linear (synergistic or antagonistic) departure from the expected combined effect, and is logically required to be independent of underlying mechanism (although in practice may not necessarily be so).⁹

Many so-called adverse pharmacodynamic herb-drug interactions suggested in the secondary literature are in fact simply additive combinations. If such a herb-drug pair is coadministered unknowingly or inappropriately due to ignorance (or negligence) it is possible that excessive effects may result but this is logically equivalent to an overdose rather than interaction. Administration of kava with benzodiazepines is a good example – an additive sedative effect is not an interaction but a predictable consequence of combining of two CNS depressants. (This is quite apart from the drug-herb combination violating standards of botanical practice which would consider this kind of combination at best redundant, at worst contraindicated.) Other additive "interactions" simply do not exist at all, but are speculatively extrapolated by arguing "in reverse" from in vitro pharmacological observations backwards, without a single supporting clinical or experimental datum on the combination. This is clearly a specious form of logic, but is nonetheless used regularly in the secondary literature: the commonest example is the extrapolation of an interaction with anticoagulant drugs from in vitro platelet aggregometry data of a given herb in the absence of any evidence whatsoever of the effects of the herb-drug combination either in vitro or in vivo.

Pharmacokinetic interactions result in alterations in drug bioavailability and hence modify the magnitude of dose-response relations as opposed to intrinsically synergistic or antagonistic pharmacodynamic effects. Pharmaco-

* "*mainstream manufacture of misinformation*" characterizes the process whereby inaccurate negative information about herb safety, adverse effects and herb-drug interactions in the mainstream medical literature is propitiated as an artifact of the MEDLINE indexing system, which logically equates miscellaneous editorial correspondence with peer reviewed articles via the database <title> field. The whole exercise ultimately results in the curious phenomenon of the apparent existence of a self-referential body of ostensibly peer-reviewed negative literature on herb safety, which is in reality a smoke and mirrors chimera bearing little connection to clinical or indeed any other reality at all.

kinetic interactions are considered by some to be theoretically “predictable” if the specific metabolic pathways of the drug are known, together with likely effects of the herb upon those pathways. This has led to persistent mainstream calls for in vitro screening of herbs of to establish the “risk” of potential (pharmacokinetic) interactions with drugs. Such demands for systematic screening of herbs for potential (pharmacokinetic) interactions, ignore the fact that drug disposition is actually unpredictably mediated by a wide variety of dietary compounds, foods, herbs, beverages and life style products, and is also affected by a wide range of individual variables from genomics (SNPs = single nucleotide polymorphisms) through biological, lifestyle and socioeconomic factors, all of which render meaningful screening virtually impossible. Additionally, the results of in vitro tests are often contradictory and quite at odds with clinical reality, due to the inherent differences between experimental systems and the in vivo complexities of herbal administration; therefore they have limited predictive value.¹⁰

Secondly, the scale of the herb/drug interaction problem is not only overexaggerated but more importantly its underlying causes are conveniently “inverted”. This is due to the collective delusion of the medical establishment of the inviolable identification of medicine with pharmacotherapeutics. Medicinal herbs, certainly those that are commonly available to consumers, generally have a wide spectrum of therapeutic effects with broad safety and toxicity margins with considerable latitude in effective dose range. The opposite is generally the case for drugs. Although the interactions issue is typically presented in mainstream medical literature as being a problem of herbs interfering with drug efficacy, it is perfectly obvious that the primary

problem is caused by narrow therapeutic index drugs, their associated toxicities and their side-effects. It is clearly more sensible and necessary that pharmaceuticals should be the initial subject of more rigorous screening and tighter regulatory controls. Officially, testing and screening procedures for new drugs are claimed to be improving, but the recent fiasco over COX-2 inhibitors would suggest otherwise. Prescription pharmaceuticals continue to be a leading cause of death in the USA,¹¹ and enormous safety problems are by non-prescription OTC medications such aspirin and acetaminophen.¹²

Perhaps these are obvious points, and probably more than familiar to many herbalists and practitioners of natural medicine but to date they have not been clearly articulated in a way that pointedly enables the mainstream case against herbs generated from herb-drug interactions to be effectively challenged. Given the defining role of SJW as centerpiece of the interactions narrative, a review of the recent scientific data on the mechanisms underlying the pharmacokinetic interactions of SJW from a conceptually pro-herbal medicine perspective is a mandatory strategic element of any riposte to the mainstream position.

Recent research suggesting that hyperforin, an active phloroglucinol constituent compound of SJW, acts as a uniquely high affinity ligand for the orphan nuclear receptor PXR (pregnane X receptor) is highly significant.^{13, 14} Activation of the PXR leads to upregulation of a battery of genes controlling multiple aspects of xenobiotic metabolism, including Phase 1 (CYP 1A1, 1A2, 2B6, 2C9, 3A4) mixed oxidases, Phase 2 conjugases (UDP-glucuronosyltransferases, glutathione-S-transferases, sulfanyltransferases) and Phase 3 drug transporters (MDR1/P-glycoprotein, MDR2, organic ion transporter peptide

(OATPs).¹⁵⁻¹⁷ The implication is that the PXR and related nuclear receptors such as CAR (constitutive androstene receptor) and AHR (aryl hydrocarbon receptor) effectively act as high-level co-ordinators of a xenobiotic detoxification system.^{18, 19} This system was described by Pascussi and colleagues 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.”²⁰ In fact this network constitutes a sophisticated “pharmacosurveillance” system, capable of detecting and responding to an enormous number of potential xenobiotic insults. In this sense the nuclear receptors can be described as “xenosensors”, capable of downstream regulation of the detoxification pathways.

Different nuclear xenosensor/receptors exhibit varying degrees of “fine tuning” (ie substrate specificity). For example, the nuclear aryl hydrocarbon receptor complex (AHR) is tightly linked to metabolism of polycyclic aromatic hydrocarbons via several narrow-band low-throughput CYP450 enzymes including 1A1, 1A2 and 1B1, enzymes which primarily metabolize environmental carcinogens.^{21, 22} Before its polymorphous nature was properly understood, the PXR was described as “promiscuous”, due to the wide range of compounds that appeared to serve as its ligands. This lack of specificity means that a wide range of lipophilic compounds can bind to the receptor independently of any unique structure-function characteristic. CYP3A4 which is upregulated by PXR activation, is itself well known as a broad band high throughput drug metabolizing enzyme (in contrast to 1A1 and 1A2 for example) and is heavily concentrated in human intestinal wall and hepatic microsomes.

Hyperforin is to date the most potent

known ligand for PXR, and this confers upon SJW the ability to act as a unique xenosensory activator. The downstream effect of PXR activation includes induction of CYP450 3A4. Therefore SJW triggers a concerted xenosensory upregulation of the most generic and broad spectrum aspects of all phases of the xenobiotic detoxification system, intended to eliminate the maximum number of potentially toxic environmental insults. Put another way, SJW will obviously “interfere with more than 50% of pharmaceuticals”, by ensuring their elimination from the body is promoted.

The hypothesis that SJW is a xenosensory activator generates novel therapeutic applications for the herb that are testable. Detoxification has not been synonymous with “puking and purging” for some time. Recently, heroic herbal medicines have taken a second place to accessory nutrients in contemporary therapeutic interventions targeting the molecular level of hepatic detoxification. These important approaches were originally developed by the Functional Medicine Group.²³ Diagnostic tests used probe drug evaluation of Phase 1 and Phase 2 hepatic pathways to generate assay-driven nutritional supplement protocols to balance and facilitate detoxification. Essentially, this approach focuses only on the “effector” side of the system. The emerging understanding of nuclear receptors as xenosensors of the pharmacosurveillance network enables botanicals that are ligands of these receptors to be conceived of as exerting an overarching sensory side “gain control” that genetically upregulates functionality of all three phases of detoxification. Therapeutically this approach could be used, for example, both in case of acute toxic exposures to environmental xenobiotics, or chronically in functional imbalances such as estrogen dominance, to facilitate clearance of endogenous

steroid hormones. Novel targeted actions in integrative settings are possible, such as combining SJW with prescription aromatase inhibitors in adjuvant treatment of post-menopausal endocrine positive breast cancer patients to decrease exposure to peripheral estrogen. Induction of detoxification enzymes is also an important aspect of cancer chemoprevention, not only through carcinogen metabolism, but also through induction of cytoprotective antioxidant mechanisms; reactive oxygen species and xenobiotics are cellular level stressors both capable of triggering adaptive responses via genes encoding detoxifying enzymes.²⁴ Compounds that induce Phase I enzymes have been termed mono-functional inducers, those inducing Phase I and II enzymes have been termed bifunctional inducers.²⁵ In this terminology, PXR ligands would be described as multifunctional inducers.

To date there are very few natural compounds besides hyperforin that have been shown to have potent PXR ligand activity. CYP3A4 may also be induced, activated or inhibited without PXR involvement, and a number of natural compounds display induction of this enzyme and other PXR controlled proteins without mediation of the nuclear receptor. A luciferase methodology has recently been developed that enables PXR activation to be measured in vitro, and positive results were found for kava extracts using this method.²⁶ Recent data also suggests that forskolin from *Coleus forskolii* (which can already be considered as a “meta-regulatory compound” due to its cyclic-AMP modulatory effects) and the sesquiterpene lactone artemisinin from *Artemisia annua*, both act as PXR ligands.^{27, 28} The non-botanical alpha tocopherol (Vitamin E) also may operate in this way.²⁹ It should be added that the PXR receptor itself is subject to polymorphisms, although the clinical

significance of such genomic variations remains to be established. However, they will likely alter xenosensory sensitivity to specific subsets of xenobiotic compounds.³⁰

For most herbalists, the conceptual leap from *warding off evil* to the detoxification of pharmaceuticals is unlikely to overstrain the imagination. For those uncomfortable with the ‘shamanistic’ implication that pharmaceuticals could possibly be malefic, perhaps designating St. John’s wort as a “pharmacovigilante” may be scientifically, if not politically, more correct.

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Contact jtreaure@herbological.com