JCI The Journal of Clinical Investigation

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*J Clin Invest.* 2004;113(1):23-25. https://doi.org/10.1172/JCI20661.

**Commentary**

Jaundice, which is caused by accumulation of bilirubin, is extremely common in newborn infants. Phototherapy is an effective treatment, but a drug therapy would also be desirable. A Chinese herbal remedy for jaundice called Yin Zhi Huang is now shown to activate a liver receptor that enhances the clearance of bilirubin (see the related article beginning on page 137). This discovery could lead to improved pharmaceutical treatments for neonatal jaundice.



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# East meets West: an herbal tea finds a receptor

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**Jaundice, which is caused by accumulation of bilirubin, is extremely common in newborn infants. Phototherapy is an effective treatment, but a drug therapy would also be desirable. A Chinese herbal remedy for jaundice called Yin Zhi Huang is now shown to activate a liver receptor that enhances the clearance of bilirubin (see the related article beginning on page 137). This discovery could lead to improved pharmaceutical treatments for neonatal jaundice.**

*J. Clin. Invest.* **113**:23–25 (2004). doi:10.1172/JCI200420661.

Advances in Western medicine have dramatically increased health and life expectancy (1). Nevertheless, over $4 billion is spent per year on herbal remedies that are complementary or alternative to Western-style care (2). Prescription medicines are usually purified molecules whose biological target is established and whose efficacy is endorsed by regulatory agencies. By contrast, herbal medicines often contain many ingredients whose effects on biochemical pathways are unknown and whose efficacy is unproven in controlled studies. A report in the current issue of the *JCI* helps to bridge this gap. David Moore and colleagues (3) show the improvement of jaundice by a Chinese herbal tea called Yin Zhi Huang (YZH), "boiled down" to one component that regulates the activity of a nuclear receptor previously implicated in bilirubin clearance (4, 5). This discovery provides a mechanistic rationale for pursuing an ingredient in YZH as a lead to improve upon the standard Western treatment for fetal jaundice.

***While there's tea, there's hope.***
**—Sir Arthur Pinero**

Herbal remedies are often produced in the form of tea, that is, a decoction of dried plant leaves in boiling water. In today's Western world, teas serve as beverages for enjoyment as well as for herbal therapies. The former use has widespread acceptance, whereas the therapeutic use of tea is not espoused by mainstream Western medicine, largely because Western pharmacology has focused on purified chemical compounds, with defined mechanisms of action, whose effectiveness has been proven in controlled studies. By contrast, most teas used for medicinal purposes are admixtures of phytochemicals whose efficacy and biological target(s) are unproven by Western standards. This can threaten relationships between physicians guided by the Western medical literature and millions of their patients who opt to use teas preventively or therapeutically for cancer, inflammatory disease, and metabolic disease (6). At the same time, Eastern remedies may contain critical clues for disorders that have been refractory to Western medicine.

**Table 1**
Components of herbal remedies that target nuclear receptors

| Therapy | Indication | Compound | Receptor | Reference |
|---|---|---|---|---|
| *Rhei rhizoma*[A] | Prostate cancer | Lindleyin | ER | 17 |
| Ginseng | Stress | Ginsenoside-Rg1 | ER | 18 |
| Grapeseed/red wine | Cardiovascular | Resveratrol | ER | 9 |
| *Scutellaria baicalensis*[B] | Prostate cancer | Baicalein | AR | 19 |
| *Dioscorea villosa*[C] | Menopause | Diosgenin | PR | 20 |
| Longmu Zhuanggu Chongji | Rickets | Vitamin D2 | VDR | 21 |
| Xiao Chai Hu Tang | Leukemia | Retinoic acid | RAR | 22 |
| *Guggul* tree resin | Lipid disorder | Guggulsterone | FXR | 23 |
| *Pseudolarix kaempferi* | Fungal infection | Pseudolaric acid B | PPARα | 24 |
| *Hypericum perforatum*[D] | Depression[E] | Hyperforin | PXR | 25 |
| *Artemisia capillaris*[F] | Jaundice | Dimethylesculetin | CAR | 15 |
| Soy | Menopause | Genistein | ER, AR, PR | 26 |
| *Labiatae*[G] | Lipid disorders | Isoprenoids | PPARα/γ | 27 |

All examples are from traditional Chinese medicine except *Guggul* gum (Indian Ayurvedic), *Dioscorea villosa* (Mexican), and red wine. Note that not all examples could be listed, due to space constraints. Although several illustrative estrogen receptor compounds are shown, there are many environmental estrogens, which are reviewed elsewhere (27). [A]Rhubarb. [B]One of eight Chinese herbs in the herbal mixture PC-SPES (whose name is derived from PC, prostate cancer, and Latin *spes*, meaning "hope"): *Isatis indigotica*; *Glycyrrhiza glabra* and *Glycyrrhiza uralensis* (licorice); *Panax pseudo-ginseng* (ginseng); *Ganoderma lucidum*; *Scutellaria baicalensis* (skull cap); *Dendranthema morifolium* Tzvel (chrysanthemum); *Rabdosia rubescens*; and *Serenoa repens* (saw palmetto). [C]Yam. [D]St. John's wort. [E]Nuclear receptor likely involved in toxicity rather than antidepression. [F]Wormwood (component of Yin Zhi Huang and Yin Chin). [G]Herb family including basil, rosemary, oregano, and sage. ER, estrogen receptor; AR, androgen receptor; PR, progesterone receptor; VDR, vitamin D receptor; RAR, retinoic acid receptor; FXR, farnesyl X receptor (bile acid receptor); PXR, pregnane X receptor; CAR, constitutive androstane receptor.

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**Conflict of interest:** The author has declared that no conflict of interest exists.

**Nonstandard abbreviations used:** Yin Zhi Huang (YZH); constitutive androstane receptor (CAR).

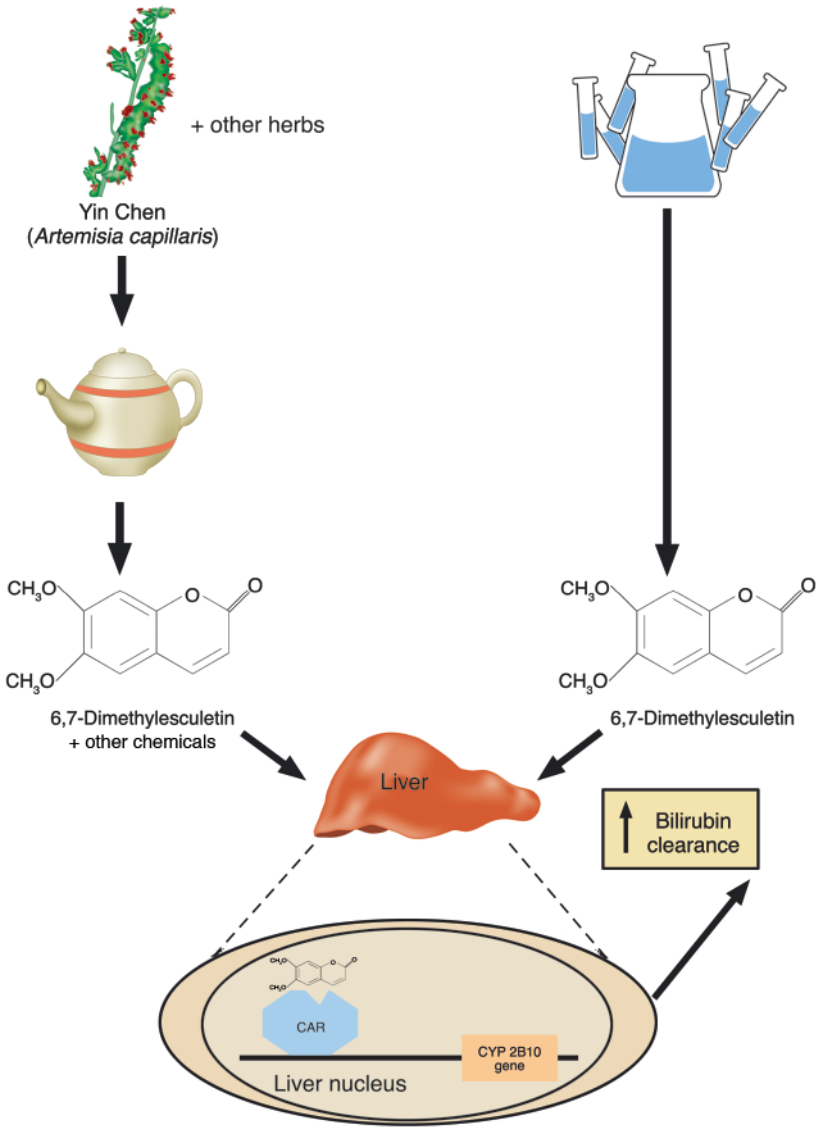


**Figure 1**
Eastern and Western paths to medicine. 6,7-Dimethylesculetin, in a wormwood tea or as a purified chemical, binds to and activates the hepatic nuclear receptor CAR and its target genes including CYP 2B10, leading to increased bilirubin clearance. Brewing of wormwood yields a tea that contains other chemicals, with potential for additional benefit or toxicity, or both.

## Nuclear receptors as targets of herbal remedies

Holistic medicine holds that herbal remedies work better when the whole complex of plant phytochemicals is kept together than when these chemicals are purified and administered singly or in combination. This hypothesis is difficult to put to stringent experimental test and remains a divisive point between Eastern and Western approaches. On the other hand, investigation of herbal remedies has revealed individual components that target nearly all classes of signaling molecules.

For mechanism-based scientists and physicians, including myself (and presumably much of the *JCI* readership), it is both satisfying and reassuring when a single component of an herbal remedy turns out to function via a defined mechanism. Members of the nuclear receptor superfamily of ligand-regulated transcription factors are frequent biological targets of active compounds contained in herbal remedies. This is perhaps not surprising, since nuclear receptors evolved to be regulated by lipophilic molecules derived from diet and the environment (7, 8).

There are 48 nuclear receptors, some of which are "orphans," meaning that no endogenous ligand has yet been found (9). At least ten of these receptors have been shown to be directly activated by compounds purified from herbal remedies (Table 1). Some compounds have a complex pharmacology; for example, grapeseed-derived resveratrol is an estrogen receptor ligand (10) but has also been suggested to activate a histone deacetylase enzyme implicated in the biology of aging (11). Other phytochemicals target multiple nuclear receptors (see Table 1 for examples). The pharmaceutical industry is now exploiting similar, less specific compounds, such as antidiabetic drugs that activate both PPARα and PPARγ (12). Indeed, although purified hormones have mostly replaced glandular extracts in Western medicine (13), a natural extract of pregnant mare's urine containing at least ten estrogenic compounds is a widely prescribed treatment for menopausal symptoms (14).

***When things are investigated, then true knowledge is achieved.***
**—Confucius**

Neonatal jaundice is extremely common and may lead to neurotoxicity (15). The treatment of choice for this condition in Western medicine is ultraviolet light therapy; pharmaceutical treatments have not been popular. Two groups have recently noted that the nuclear receptor constitutive androstane receptor (CAR) enhances bilirubin clearance (3, 4). In the present issue of the *JCI*, noting that Chinese medicine uses YZH and a tea called Yin Chin for the treatment of jaundice, Huang et al. test the hypothesis that the Chinese remedies exert their effects via this mechanism (3). YZH and Yin Chin were obtained not from a chemical supplier but from a Chinese-herb store, were prepared as teas, and then were administered to mice (Figure 1). The herbal teas accelerated the clearance of bilirubin in normal mice, but not in mice that had been genetically engineered to lack CAR, demonstrating a critical role for this nuclear receptor. But that is only half of the story — the teas contain many ingredients, including one component (*Scutellaria*) that has been

shown to contain an androgen receptor ligand (Table 1). However, the systematic study by Huang et al. reveals that a single compound found in both YZH and Yin Chin (6,7-dimethylesculetin) is sufficient to activate CAR and induce bilirubin clearance. This is a wonderful example of knowledge gained by applying the Western scientific method to an Eastern herbal remedy. It will be very exciting if a pure compound emerges from the tea leaves as a pharmacological therapy for neonatal jaundice that is complementary or alternative to the current Western practice of phototherapy (16).


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# The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity


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**IGF-1 and growth hormone (GH) interact with insulin to modulate its control of carbohydrate metabolism. A new study (see the related article beginning on page 96) shows that blocking the effect of GH in the presence of low serum IGF-1 concentrations enhances insulin sensitivity.**



*J. Clin. Invest.* **113**:25–27 (2004). doi:10.1172/JCI200420660.



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**Conflict of interest:** The author has declared that no conflict of interest exists.

**Nonstandard abbreviations used:** growth hormone (GH).

Understanding the relative roles of peptide hormones in modulating responsiveness to insulin presents a major challenge because of the adaptability of the growth hormone/IGF-1/insulin system. Changes in glucose and insulin secretion result in counter-regulatory responses, and modifications in growth hormone (GH) and IGF-1 function alter insulin's ability to maintain normal carbohydrate homeostasis. Historically, this problem has been analyzed in both human and rodent hormone-deficiency models (e.g., GH deficiency) in which the hormone of interest is replaced and the metabolic consequences are determined (1). The recent development of tissue-selective knockout animal models has brought new insights to our understanding of the relative roles of these hormones in carbohydrate homeostasis. In this issue of the *JCI*, Yakar et al. address the relative roles of GH and IGF-1 in regulating insulin sensitivity in mice (2). The authors created an animal model in which IGF-1 synthesis in the liver is eliminated and then crossed these animals with mice that overexpress a mutant form of GH that prevents GH activation of its receptor. The authors conclude that GH is a major determinant of insulin resistance in these IGF-1–deficient animals, since, in the presence of low concentrations of serum IGF-1, blocking