



Published in final edited form as:

Cell. 2007 September 7; 130(5): 769–774.

Molecular Understanding and Modern Application of Traditional Medicines: Triumphs and Trials

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Abstract

Traditional medicines provide fertile ground for modern drug development, but first they must pass along a pathway of discovery, isolation, and mechanistic studies before eventual deployment in the clinic. Here, we highlight the challenges along this route, focusing on the compounds artemisinin, triptolide, celastrol, capsaicin, and curcumin.

Traditional medicines continue to provide front-line pharmacotherapy for many millions of people worldwide. Although their application is often viewed with skepticism by the Western medical establishment, medicinal extracts used in ancient medical traditions such as Ayurveda on the Indian subcontinent and traditional Chinese medicine (TCM) are a rich source of therapeutic leads for the pharmaceutical industry.

The transformation of traditional medicines into modern drugs has its origins in the archetypal examples of the antimalarial quinine and the antipyretic analgesic aspirin. The alkaloid quinine was isolated in 1820 from the bark of several species of *Cinchona*, thought to have been used by Peruvian Indians to suppress shivering and used since the 17th century in the treatment of malarial fevers (Greenwood, 1992). Similarly, aspirin was derived from salicylic acid in the bark of the willow tree (*Salix* species), used traditionally to treat fever and inflammation in many cultures worldwide for at least four millennia (Mahdi et al., 2006). The successes of these two early “blockbuster” drugs set the stage for ongoing drug discovery efforts from traditional medicines.

Compounds derived from medicinal extracts are appealing for several reasons (Schmidt et al., 2007). They are often stereochemically complex, multi- or macrocyclic molecules with limited likelihood of prior chemical synthesis, and they tend to have interesting biological properties. But perhaps most importantly, parent extracts have been “clinically” tested in their traditional milieu, in some cases over millennia.

Despite these advantages, the path from traditional medicine to Western pharmaceutical is fraught with challenges. Here, we discuss the challenges of each of the four steps in this pipeline (see Figure 1): Western “discovery” of a traditional medicine, isolation and/or synthesis of the active component, elucidation of the molecular mechanism, and development as a pharmaceutical. We focus on five interesting and timely examples derived from traditional medicines in varied therapeutic classes, each at a different stage in the development process, highlighting successes and roadblocks on the path to status as a Western drug.

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Artemisinin: Production Problems

The antimalarial artemisinin (and derivatives) represents one of the greatest recent clinical success stories arising from a traditional medicine, echoing the success of quinine two centuries earlier. Artemisinin (see Figure 1) is derived from *Artemisia annua* L., the sweet wormwood (*qinghao*), a shrub first documented in TCM in 168 BCE as a hemorrhoid treatment (Liu et al., 2006). Since at least the fourth century CE, it has been used in the treatment of fever attributed to malaria. This long history of use prompted Chinese researchers to seek the active antimalarial principle; artemisinin was isolated and its structure determined in the mid 1970s (Liu et al., 2006).

Artemisinin, an endoperoxide sesquiterpene lactone with a complex polycyclic ring structure, is modified by Fe^{2+} ions to structures containing carbon-centered free radicals. Given that the intracellular environment of the *Plasmodium* malaria parasite is rich in this ion from heme, these radicals are currently thought to be responsible for artemisinin's antimalarial activity. The classic method of cell fractionation after treatment with radiolabeled artemisinin has identified numerous cellular constituents alkylated by artemisinin (Asawamahesakda et al., 1994); the strongest validated target for artemisinin is PfATP6, the *Plasmodium* sarcoplasmic reticulum Ca^{2+} ATPase (SERCA), which is inhibited by artemisinin (Eckstein-Ludwig et al., 2003).

Clinical studies, initiated in the 1970s prior to any mechanistic insights into artemisinin function, demonstrated that artemisinin and its derivatives are powerful antimalarials. They have proved particularly effective for treating severe malaria and, in combination with traditional antimalarials, for combatting *Plasmodium* drug resistance. Combination therapies containing artemisinin are now considered the treatment of choice for malaria in Asia, with growing adoption in Africa (see Table 1 for information on clinical trials). Artemisinin may also have efficacy against other parasites and as an anticancer compound, possibly acting via antiangiogenic and proapoptotic mechanisms in the latter case (Efferth, 2007).

Despite these dramatic findings, widespread deployment of artemisinin has been hindered by production difficulties. Although a dozen synthetic routes to artemisinin have been described, all are complex and low yielding, rendering them economically unfeasible (Liu et al., 2006). Synthetic chemistry has, however, offered semi-synthetic artemisinin derivatives with improved solubility (such as sodium artesunate) and stability (such as artemether) (Efferth, 2007). Even a totally synthetic trioxolane compound RBX11160 (OZ277), inspired by the trioxane endoperoxide moiety of artemisinin, has shown promise as an antimalarial (Vennerstrom et al., 2004).

Artemisinin for clinical use is predominantly produced naturally in *A. annua* plants. Despite efforts to maximize agricultural production, the artemisinin content in plant extracts varies widely due to environmental conditions: 0.01%–0.8% dry weight (Efferth, 2007). This in turn makes the drug itself expensive—particularly problematic for an antimalarial, which is needed in large quantities in many poorer countries. Cell and plantlet cultures are an appealing alternative source of this compound as they can be grown under much more closely controlled conditions than whole plants. Indeed, useful yields of the compound can be produced by feeding cultures artemisinin precursors (Liu et al., 2006). An alternative approach is the genetic engineering of *A. annua* itself. The plant has proven genetically tractable: Several of the isoprenoid biosynthetic enzymes necessary for artemisinin production have been cloned, and *A. annua* can be successfully transformed with *Agrobacterium tumefaciens* to over-express key biosynthetic genes (Liu et al., 2006).

Perhaps the most promising strategy is the use of microbes to produce artemisinin. In a triumph of genetic engineering, Ro et al. combined genetic activation of the endogenous mevalonate

isoprenoid synthesis pathway with introduction of *A. annua* genes to produce artemisinic acid in the budding yeast *Saccharomyces cerevisiae* (Ro et al., 2006). This precursor compound, which can be readily converted to artemisinin in the laboratory, is secreted in large quantities from the yeast. Such creative strategies, leveraging the power of genetics and in vivo biochemistry, can provide a valuable counterpart to synthetic chemistry and natural sources in the production of natural product medicines.

Triptolide and Celastrol: Harnessing the Power of the Thunder God Vine

Tripterygium wilfordii Hook F., the “thunder god vine” (*lei gong teng*), is another TCM. This vine has been used traditionally for the treatment of arthritis and other diseases, and it is the source of several biologically active secondary metabolites (Tao and Lipsky, 2000). Some of its TCM uses might rely on the presence of multiple active components, and clinical studies have been performed on extracts of the plant (Table 1), rather than on a single compound (Tao and Lipsky, 2000). However, substantial work has focused on two major bioactive constituent compounds: triptolide and celastrol (Figure 1).

Triptolide is a diterpenoid epoxide with a staggering variety of documented cellular effects. Along with anti-inflammatory activity, it shows anticancer, immunosuppressive, and antifertility effects (Qiu and Kao, 2003). It was isolated in 1972, and several synthetic routes have been described since then (Yang et al., 1998 and references therein). Like artemisinin, however, triptolide is currently derived from its plant of origin with low yield: 6–16 ng/g in one study (Brinker and Raskin, 2005). Little work has been done to investigate biotechnological routes to triptolide production, which are important to reduce reliance on the natural source. Moreover, continued development of derivatives of triptolide such as the succinyl sodium salt PG490-88 will be valuable to improving the solubility and side-effect profile of this compound (Tao and Lipsky, 2000).

Determination of triptolide’s cellular target has proven to be an even greater challenge. This is not unusual: Many a promising therapeutic natural product has faltered when no clear-cut mechanism of action could be identified. Although progression into the clinic without such knowledge is possible, as was the case with artemisinin, a solid knowledge of molecular mechanism (ideally at the structural, not just the molecular, level) allows medicinal chemists to perform rational derivatization to improve affinity, specificity, pharmacokinetics, and stability. Knowledge of mechanism can also potentially lead to more specific clinical trials and, in cases like triptolide, completely new insights.

A large body of work describes triptolide’s inhibitory effects on transcription mediated through NF- κ B and NFAT (Qiu and Kao, 2003), but until recently, direct cellular targets were elusive. Nonetheless, careful cell fractionation with [³H]-triptolide enabled identification of the Ca²⁺ channel polycystin-2 (encoded by the *PKD2* gene) as a possible triptolidebinding protein (others also likely exist) (Leuenroth et al., 2007). *PKD2* or the gene encoding its activator, *PKD1*, causes polycystic kidney disease (PKD) when mutated because entry of Ca²⁺ ions is essential for growth arrest of epithelial cells forming the kidney tubule. Because triptolide activates opening of the polycystin-2 channel, it could potentially complement loss of *PKD1*. This is the case in a mouse model of polycystic kidney disease in which the mice lack *Pkd1* (Leuenroth et al., 2007). Thus, this calcium-dependent activity of triptolide, which is unrelated to its transcriptional repression activity (Leuenroth and Crews, 2005), opens a new therapeutic avenue for pursuing triptolide, in addition to its effects on the immune and reproductive systems and in cancer.

Highlighting the complexity of plant extracts, the pentacyclic triterpene celastrol (Figure 1) is structurally a very different component of *T. wilfordii* with a divergent therapeutic profile. Celastrol (also known as tripterine) is extracted in small quantities from *T. wilfordii* or other

members of the *Celastraceae* (bittersweet) family. To our knowledge, no total synthesis or alternative production routes have been reported.

Although not yet tested as a single agent in humans (Table 1), celastrol has shown promise as an anti-inflammatory compound in animal models of arthritis, lupus, amyotrophic lateral sclerosis, and Alzheimer's disease (Sethi et al., 2007 and references therein). It also has antiproliferative effects against numerous cancer cell lines. Several molecular mechanisms have been identified for these effects, including gene expression modulation likely mediated through inhibition of NF- κ B via TAK1 and I κ B α kinase (Sethi et al., 2007 and references therein), proteasome inhibition, topoisomerase II inhibition, and heat shock response activation (Hieronymus et al., 2006 and references therein). Nonetheless, direct targets remain elusive. As celastrol and triptolide move into human studies, it will be vital not only to better understand their mechanisms of action but also to investigate any potential synergistic effects of the two compounds, both at the cellular and organismal levels.

Capsaicin: Painless for Some?

Used worldwide, the alkaloid capsaicin is the main cause of the "hot" sensation associated with chili peppers, members of the genus *Capsicum*. Beyond their widespread use as a spice, chili peppers were used in the Americas by the Aztecs and Tarahumara Indians as a remedy for coughs and bronchitis. Similar uses plus anti-inflammatory and gastrointestinal applications were adopted in India after the Portuguese imported chili peppers in the late 15th century. In Africa, they are traditionally used internally and externally as antiseptics (Dasgupta and Fowler, 1997). However, modern usage of capsaicin is focused on the treatment of various types of pain (see below) and also in the treatment of detrusor hyperreflexia, a form of urinary incontinence (Dasgupta and Fowler, 1997). High-dose oral capsaicin also has anticancer properties in some animal model studies but seems to be a cancer promoter in others.

Compared with artemisinin, triptolide, and celastrol, capsaicin is chemically quite simple (Figure 1). It was purified and named in the 19th century and first synthesized in the 1920s (Dasgupta and Fowler, 1997). But the widespread cultivation of *Capsicum* makes synthesis unnecessary, as large quantities of capsaicin can easily be extracted from readily available peppers.

The mechanism of capsaicin in pain induction has been the topic of much neurophysiological research (Cortright et al., 2007). Capsaicin, along with thermal heat, directly activates nociceptors in the skin, the sensory neurons responsible for the sensation of pain, with the subsequent release of the neurotransmitter substance P. Capsaicin's therapeutic effect on pain is due to the desensitization and eventual destruction of nociceptors following repeated capsaicin exposure. In a classic example of expression cloning, Caterina et al. identified the capsaicin receptor (Caterina et al., 1997). Capsaicin was known to cause Ca²⁺ ion influx into nociceptors, so these authors transfected a nociceptor cDNA library into nonexcitable HEK293 cells and screened for capsaicin-dependent Ca²⁺ ion influx. The receptor they cloned, now known as TRPV1, is a Ca²⁺ ion channel that also responds to, and integrates, signals from piperine (the irritant in black pepper), protons, and other noxious stimuli (Caterina et al., 1997).

The cloning of *TRPV1* kick started the field of pain receptor pharmacology. Numerous pharmaceutical companies are developing both TRPV1 antagonists (to block nociception directly) and agonists (to desensitize nociceptors, as with capsaicin) (Immke and Gavva, 2006). Resiniferatoxin, another traditional medicine from the latex of *Euphorbia resinifera*, is one such agonist with higher potency than capsaicin (Immke and Gavva, 2006). Efforts continue to create TRPV1 agonists with better skin permeation and lacking the distinctive side effect of a burning sensation on application.

Capsaicin itself has been used clinically with moderate success as a topical treatment for the pain of rheumatoid and osteoarthritis, psoriasis, diabetic neuropathy, and postherpetic neuralgia (Table 1), but herein lies the particular challenge with this molecule: The chronic pain disorders are notoriously idiosyncratic, and not all patients or all pain syndromes respond to capsaicin (Immke and Gavva, 2006). The somewhat vague and diffuse traditional uses of this compound offer little assistance here, unlike artemisinin, for instance. Thus, testing for capsaicin efficacy is a matter of clinical trial and error, largely undermining the “tried and true” advantage of a traditional medicine. The major clinical advantage that capsaicin holds over other unrelated pain drugs under development is its approved status as a foodstuff.

Curcumin: Awaiting Targets and Outcomes

Like capsaicin, the polyphenol curcumin (Figure 1) is best known as a spice constituent: It is the yellow pigment component of the curry spice turmeric (*Curcuma longa*, known as *haldi* in Hindi). It is also, however, a drug used in Ayurveda and TCM in the treatment of diseases as diverse as rheumatism, fever, intestinal disorders, trauma, and amenorrhea (see the Analysis by S. Singh on page 765 of this issue). Modern research has attributed anti-inflammatory, immunomodulatory, antimalarial, and anticancer effects to this multitiered compound (Aggarwal et al., 2007).

Like capsaicin, synthesis of curcumin is trivial and was first reported in 1910, but sufficient quantities of curcumin for therapeutic use are available from the spice. This is particularly important as low bioavailability of the parent compound coupled with rapid intestinal metabolism dictates large doses for clinical use (Sharma et al., 2005); derivatization of the natural product is actively being pursued.

Given its pleiotropic clinical effects, it is perhaps not surprising that curcumin has documented effects on countless intracellular signaling pathways. Its anti-inflammatory action can be attributed largely to its inhibition of NF- κ B activity, COX-2 and 5-LOX expression, and cytokine release (Aggarwal et al., 2007). Curcumin may directly target I κ B α kinase to block NF- κ B. It also binds to a number of other proteins, including thioredoxin reductase, several kinases, and several receptors (Aggarwal et al., 2007). The challenge here, then, as with many other natural products, is deciphering which of these targets is mechanistically valid for which biological activity. With such a broad spectrum of potential targets and activities described for curcumin, this is no easy task. Synthesis of derivatives that selectively ablate certain cellular and/or therapeutic effects is one possible route to tease apart this mechanism-function conundrum, perhaps in concert with radiolabeled fractionation experiments (as described above) or affinity chromatography with immobilized curcumin.

The very versatility that makes curcumin appealing has also limited its rigorous clinical testing: There are wide-ranging efficacy reports, but most are based on preclinical, anecdotal, or pilot studies rather than on randomized, placebo-controlled, double-blind trials (Hsu and Cheng, 2007). Activity has been reported in several inflammatory and autoimmune diseases and numerous cancers, both as a preventative agent and treatment, alone or in combination (Hsu and Cheng, 2007). The relative ease and rapid payoff of undertaking preclinical or pilot studies, compared to rigorous clinical trials, has slowed the formal validation of curcumin. This is confounded by limited pharmaceutical company interest because curcumin itself is not patentable (although synthetic methods, derivatives, and pharmaceutical formulations are) and by the perception that, as a foodstuff, curcumin is more a nutraceutical (perhaps a dietary cancer preventative) than a traditional drug. This perception can only be changed by clinical studies showing successful disease treatment with curcumin. Phase I studies have documented tolerance up to 8000 mg/day, allowing a large dose-response range to be tested in phase II studies, several of which are underway for the treatment of cancer, psoriasis, and Alzheimer's

disease (Table 1) (Hsu and Cheng, 2007). We must await the outcomes of these studies before curcumin can be validated as a pharmaceutical.

Ongoing Challenges

An effective drug should be facile and economical to produce and deliver, should display favorable absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics, and should treat the targeted disease with specificity and efficacy. Traditional medicines, as with other natural products, can offer powerful leads for therapeutic development because (unlike synthetic libraries) they already have documented effects on the organism. However, the process from plant to product is a slow one. Despite the oft-shared limitations noted here, these five examples of traditional medicines are exceptional in the extent to which they have been studied and the success they have achieved in the clinic; countless other promising compounds wallow in obscurity.

The challenges are formidable (Figure 1): Ethnopharmacologists must identify a medicine, its uses, and active components. These efforts are urgent, as traditional knowledge—and traditional plant species—are being lost at an alarming rate. Chemists must then synthesize the compound using a cost-effective method or develop alternative processes such as cell culture or transgenesis to enable useful-scale production. Despite continuing advances in synthetic chemistry, the very complexity of many natural products that is responsible for their desirable biological function can make production difficult.

With a reliable supply of compound available, biologists can then identify and validate cellular targets and mechanisms of action. New tools are sorely needed for this particularly daunting challenge, such as methods that compare the phenotypic or gene expression profiles induced by a small molecule to those induced by known compounds (Hieronymus et al., 2006) or chemical enhancer/suppressor screens. Development of *in silico* tools to “dock” small molecules with protein structures to provide models for testing *in vitro* will likely come into their own with advances in structural genomics, as sufficient computational power becomes available.

Ideally with a mechanism in hand, clinicians must then test the compound in the disease of interest (Table 1) while keeping an open mind for unexpected therapeutic activities and working with medicinal chemists to produce derivatives with improved ADMET properties. Finally, regulatory approval must be obtained, as with all drugs. This is particularly problematic if the active principle is an extract or mixture, rather than an isolated compound; the U.S. Food and Drug Administration has been understandably reluctant to approve multiple-agent drugs until recently (Schmidt et al., 2007). Only in 2006 was the first such drug approved: Polyphenon E (MediGene), a topical antiviral prepared from catechins extracted from green tea (*Camellia sinensis*).

Artemisinin, triptolide, celastrol, capsaicin, and curcumin are “poster children” for the power and promise of turning traditional medicines into modern drugs. However, their stories highlight the ongoing interdisciplinary research efforts that continue to be necessary to realize the pharmaceutical potential of traditional therapeutics.

ACKNOWLEDGMENTS

C.M.C. is supported by the US National Institutes of Health (AI055194 and GM062120). T.W.C. is supported by a Canadian Institutes of Health Research Fellowship.

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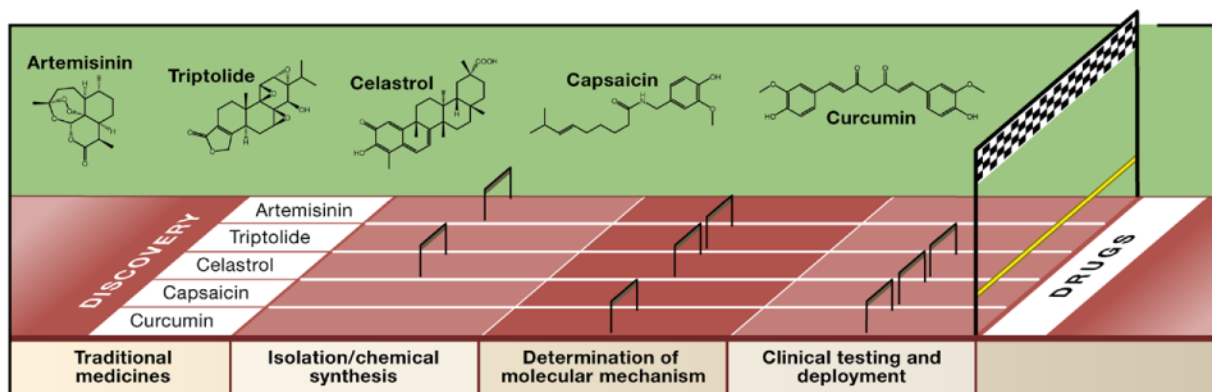


Figure 1. The Route from Traditional Medicine to Modern Drug

Shown are five traditional medicines—artemisinin, triptolide, celastrol, capsaicin, and curcumin—and the points in the pathway from ancient remedy to modern drug where they face the biggest hurdles.

Table 1

Five Traditional Medicines in Clinical Trials

Compound	Disease	Clinical Trials	
		Number	Principal Sponsors
Artemisinin	Malaria	81	31 charities, institutes, universities, and companies based in Australia, Austria, Belgium, Colombia, Ethiopia, France, Gambia, Germany, Ghana, Guinea-Bissau, the Netherlands, Papua New Guinea, South Africa, Sudan, Sweden, Switzerland, the United Kingdom, and the USA; and working in numerous Asian, African, and South American locations
	Cytomegalovirus infection	1	Hadassah Medical Organization, Israel
	Schistosomiasis	1	Dafra Pharma, Belgium
Triptolide & Celastrol (<i>T. wilfordii</i> extract)	Rheumatoid arthritis	1	National Institute of Arthritis and Musculoskeletal and Skin Diseases, MD, USA
Capsaicin	Chronic pain	13	NeurogesX, CA, USA; AlgoRx Pharmaceuticals, NJ, USA
	Postoperative pain	5	National Institute of Dental and Craniofacial Research, MD, USA; AlgoRx Pharmaceuticals, NJ, USA
	Radiation-induced mucositis	1	North Central Cancer Treatment Group, MN, USA
	Alopecia areata	1	University of Minnesota
	Morton's neuroma	1	AlgoRx Pharmaceuticals
	Osteoarthritis	1	Khon Kaen University
	Interstitial cystitis	1	National Institute of Diabetes and Digestive and Kidney Diseases, MD, USA
Curcumin	Colon cancer	6	Chao Family Comprehensive Cancer Center, CA, USA; Tel-Aviv Sourasky Medical Center, Israel; Johns Hopkins University, MD, USA; University of Michigan Comprehensive Cancer Center, USA; University of Pennsylvania, USA; University of Medicine and Dentistry, NJ, USA
	Pancreatic cancer	3	Rambam Medical Center, Israel; M.D. Anderson Cancer Center, TX, USA; Tel-Aviv Sourasky Medical Center, Israel
	Alzheimer's disease	2	John Douglas French Foundation, CA, USA; Chinese University of Hong Kong
	Chemotherapy-induced mucositis	1	Hadassah Medical Organization, Israel
	Multiple myeloma	1	M.D. Anderson Cancer Center, TX, USA
	Psoriasis	1	University of Pennsylvania, USA
	Cystic fibrosis	1	Seer Pharmaceuticals, CT, USA

Includes registered, open, closed, terminated, and completed trials of these compounds, parent extracts, or derivatives. For details see www.clinicaltrials.gov. Data current as of August 21, 2007.