The Pharmacokinetics and Pharmacodynamics of Medicinal and Food Plants Medicine

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Health, Education & Research

outline

- Complex Chemistry of Plants
- PK
- PD
- Pharmacogenomics
- Dosing

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Unique Aspects of Herbal Whole System Research

Suzanna M. Zick, **Herbert Schwabl**, **Andrew Flower**, **Dip Lac**, **Bibhas Chakraborty**, and **Kristine Hirschkorn**

Abstract

Introduction—Whole systems of healthcare offer unique methodological and theoretical challenges for researchers. Herbalism has its own set of methodological and philosophical research issues, which are beyond those presented for whole system research, in general.

Methods—An International Society for Complementary Medicine Research (ISCMR) workshop was presented on, "Challenges in Herbal Whole Systems Research". Starting from a definition of herbalism the most important challenges to herbal whole system research (HWSR) were elicited with inputs from both the workshop presenters and the audience.

Results—Five major challenges unique to herbal whole systems research were identified: (1) Defining herbalists and herbalism; (2) role of natural products industry in herbal research; (3) designing placebos and delivering active herbal treatments as are given by herbalists; (4) researching the herb as a living entity; and (5) designing trials to investigate and develop multi-component herbal therapies.

Conclusions—To design studies of herbalism requires unique methods and theoretical frameworks. Solutions to these methodological challenges need to be addressed to conduct research that examines herbal systems of medicine versus conducting trials on individual herbs given out of their original therapeutic context.

Keywords

Whole Systems; Herbalism; Research Methodology

INTRODUCTION

Complementary and alternative medicine (CAM) is partially composed of systems of healthcare such as Traditional Chinese Medicine (TCM) and naturopathy. These systems of

The Plant

The advantages of plants is that they are naturally dilute and broad spectrum.

The disadvantage of plants is that they are naturally dilute and broad spectrum.

Michael Moore

Evolution

Boileau, T. W. M., Liao, Z., Kim, S., Lemeshow, S., Erdman, J. W., Jr., and Clinton, S. K. (2003). Prostate Carcinogenesis in N-methyl-N-nitrosourea (NMU)-Testosterone-Treated Rats Fed Tomato Powder, Lycopene, or Energy-Restricted Diets. *J Natl Cancer Inst %R 10.1093/jnci/djg081* 95, 1578-1586.

- Biochemical systems that appear to have evolved for a simple straightforward effect, such as toxins, are in fact quite complex
- Snakes, for example, which are ancient in comparison to most animals but are newly arrived by plant standards, have evolved venoms that are strikingly complex

Evolution

Firn, R. D., and Jones, C. G. (2003). Natural products--a simple model to explain chemical diversity. *Nat Prod Rep* 20, 382-91.

- A large body of experimental evidence supports the view that many alkaloids, cyanogenic glycosides, glucosinolates, terpenes, saponins, tannins, anthraquinones and polyacetylenes are allelochemicals
- They represent adaptive traits that have diversified during evolution by natural selection in order to protect against virus, bacteria, fungi, competing plants, and most importantly herbivores

Evolution

Spelman, K., Duke, J. A., and Bogenschutz-Godwin, M. J. (2006). The Synergy Principle in Plants, Pathogens, Insects, Herbivores and Humans. *In* "Natural products from plants" (P. B. Kaufman, ed.), Vol. Publication Forthcoming. CRC Press, Boca Raton, Fla.

Chemically diverse metabolites in plants, modified by natural selection during evolution, occur in diverse mixtures of several structural types

Evolution

Spelman K. 2005. Philosophy in Phytopharmacology: Ockham's Razor vs. Synergy. *J Herb Pharmacol* 5(2):31-47.

Slight variations in similar molecules, perhaps described as a protective chemical overlap, can be seen as the evolutionary development of a *chemical economy*; a network of protection

Evolution

Spelman K. 2005. Philosophy in Phytopharmacology: Ockham's Razor vs. Synergy. *J Herb Pharmacol* 5(2):31-47.

One study of sequiterpene synthesis in plants demonstrated that one enzyme produced 34 different compounds from a single substrate, and another enzyme produced 52 products from a single precursor

Evolution

Wink M. *Phytochem* 64:3-19, 2003.

Such "catalytic flexibility" is likely to yield products with multiple functionalities and bioactivities. And even if the individual interaction of a particular plant metabolite might be unspecific and weak, the sum of numerous metabolite interactions can lead to a substantial effect

Evolution

Dyer et al (2003) demonstrated this economy of chemistry by showing that three of the allelochemicals expressed by a Piper sp. act synergistically as allelochemicals and exhibit a broad spectrum protection against several species of pests

Evolution

Wu et al (2002) point out that allelopathic effects usually result from groups of constituents, often demonstrating synergy, rather than just one chemical.

Plant Chemistry

The phytochemical matrix is *selected* to be broad spectrum

Unique PK Properties

Selected over hundreds of millions of years

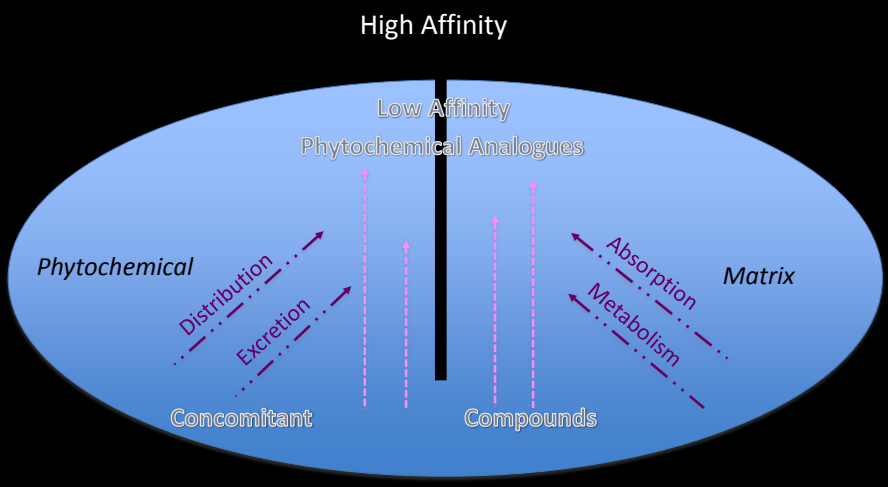
Two Types of Synergy

- Pharmacodynamic
  - Multiple modes of activity (biochemical convergence)
    - Engaging multiple genes/proteins/pathways
  - Multiple constituents working on one mode of activity
    - Multiple molecular species working on one gene/protein
    - One constituent multitasking
- Pharmacokinetic
  - Alterations in ADMET:
    - Absorption, Distribution, Metabolism, Excretion, Toxicology

Deductive Landscape

A Broad Perspective

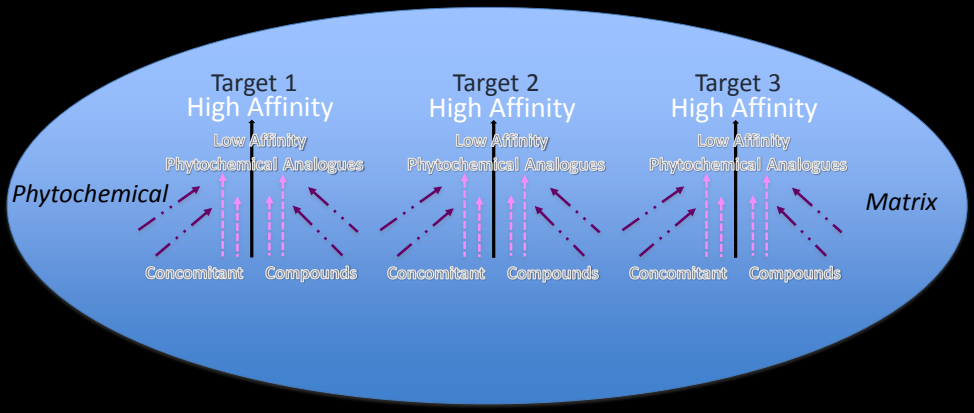
Spelman K. 2007. Ecological Pharmacology II: Molecular Details *UnifiedEnergetics* 3(6): 58-62.



Deductive Landscape

A Broader Perspective

Spelman K. 2007. Ecological Pharmacology II: Molecular Details *UnifiedEnergetics* 3(6): 58-62.



Pharmacokinetics

If pslant could not deliver their allelochemicals

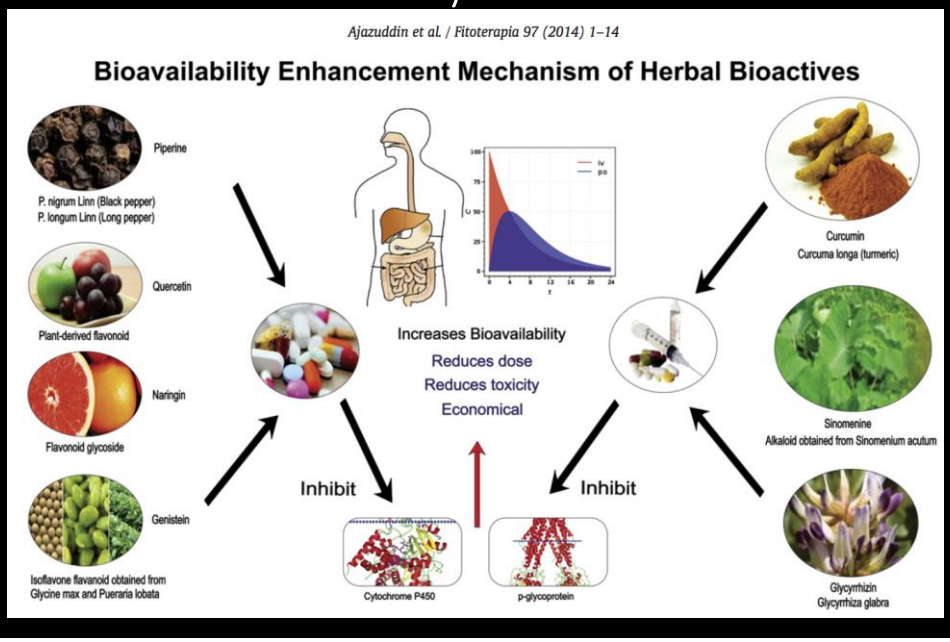
then production of these compounds was all for naught

Pharmacokinetics is the characterization of the time course of drug/metabolite concentrations in the body

Pharmacokinetic Processes

- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicology

Bioavailability Enhancement



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PLOS ONE

Dried Whole Plant *Artemisia annua* as an Antimalarial Therapy

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Abstract

Drugs are primary weapons for reducing malaria in human populations. However emergence of resistant parasites has repeatedly curtailed the lifespan of each drug that is developed and deployed. Currently the most effective anti-malarial is artemisinin, which is extracted from the leaves of *Artemisia annua*. Due to poor pharmacokinetic properties and prudent efforts to curtail resistance to monotherapies, artemisinin is prescribed only in combination with other anti-malarials composing an Artemisinin Combination Therapy (ACT). Low yield in the plant, and the added cost of secondary anti-malarials in the ACT, make artemisinin costly for the developing world. As an alternative, we compared the efficacy of oral delivery of the dried leaves of whole plant (WP) *A. annua* to a comparable dose of pure artemisinin in a rodent malaria model (*Plasmodium chabaudi*). We found that a single dose of WP (containing 24 mg/kg artemisinin) reduces parasitemia

…our experiments indicate that a dose of whole plant has a five-fold increase in anti-malarial activity over that of the corresponding amount of artemisinin. This increased efficacy may result from a documented 40-fold increase in the bioavailability of artemisinin in the blood of mice fed the whole plant, in comparison to those administered synthetic drug.

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Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Malaria is among the most prevalent infectious diseases in the developing world, imposing a vast burden of mortality and perpetuating cycles of poverty. In 2009, the World Health Organization (WHO) estimated that 225 million cases of malaria occurred, with >780,000 deaths [1]. In spite of recent advances in our understanding of this parasite, efforts to prevent transmission have remained largely unchanged for over a century. Though malaria vaccines hold future promise, vector control and chemotherapy remain the primary weapons for reducing the burden of disease in individuals and populations. Artemisinin, in the form of Artemisinin-based Combination Therapy (ACT), is currently the best treatment option against those malaria parasites that have evolved resistance to drugs such as chloroquine [2]. Moreover, artemisinin (AN) and its derivatives have also been shown to affect a number of viruses, a variety of human cancer cell lines [3,4], several neglected tropical parasitic diseases including schistosomiasis [5], leishmaniasis [6,7], New- and Old-World trypanosomiases [8], and some livestock diseases [9].

Current artemisinin production requires its extraction from the cultivated herb *Artemisia annua* L., which is a "generally regarded as safe" (GRAS) herb suitable for human consumption [10]. However, considerable production costs and inadequate availability of artemisinin limit its present usefulness in the campaign against malaria [11]. Until very recently [12], *de novo* chemical synthesis of artemisinin was neither practical nor cost-effective. The best plant cultivars yield only ca. 1.5% artemisinin, and agricultural yields seldom exceed 20 kg/ha [13]. The drug is solvent-extracted from plant material, crystallized, and typically used for semi-synthesis of artemisinic derivatives. Although *A. annua* is relatively easy to grow in temperate and subtropical climates, low yields of artemisinin lead to relatively high costs for isolation and purification of the drug [14]. Because of this shortcoming, plant scientists have focused their efforts on producing cultivars of *A. annua* with higher artemisinin crop yield [15]. Transgenic production schemes are also underway [16,17]. Meanwhile, a worldwide shortage fails to meet the need to treat malaria, not to mention those other diseases against which artemisinin holds such promise [2].

One means of reducing the cost of production would be to limit the amount of post-harvest processing by using the whole plant (WP). We wondered whether omitting the extraction step, by using whole plant *A. annua* directly as the source of artemisinin, might prove efficacious in an experimental murine model. In a previous

Artemisinin content in tea preparations from *Artemisia annua*

Amount of material per litre water	Method of tea preparation	Artemisinin Concentration in the tea	Extraction efficiency
250 mg pure artemisinin	A	10.6 mg/1itre	-
5 g leaves	A	12.0 mg/1itre	41.4 %
10 g leaves	A	24.5 mg/1itre	42.2 %
20 g leaves	A	32.8 mg/1itre	28.3 %
40 g leaves	A	64.4 mg/1itre	27.8 %
5 g leaves	B	7.2 mg/litre	24.8 %

Mueller MS, *et al.* The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects. *J Ethnopharmacol*. 2000 Dec;73(3):487-93.

Pharmacodynamics

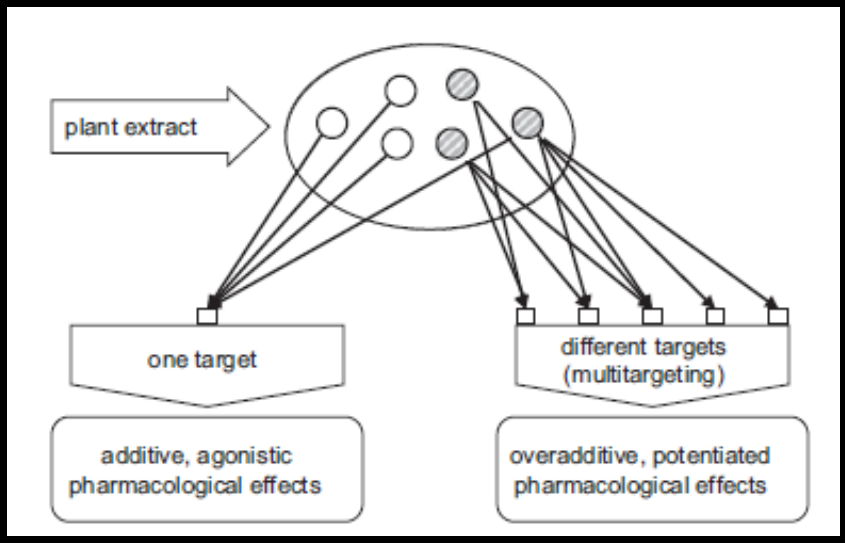
What the plant does to the body…

Pharmacodynamics

- Pharmacodynamic
  - Multiple modes of activity (biochemical convergence)
    - Engaging multiple genes/proteins/pathways
  - Multiple constituents working on one mode of activity
    - Multiple molecular species working on one gene/protein
    - One constituent multitasking

Multiple Targets

Wagner, H., Ulrich-Merzenich, G., Synergy research: Approaching a new generation of phytopharmaceuticals. Phytomedicine (2009), doi:10.1016/j.phymed.2008.12.018



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The role of the seven crude drug components in the sleep-promoting effect of Yokukansan

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ABSTRACT

Ethnopharmacological relevance: Yokukansan is a traditional Japanese "Kampo" medicine derived from Yi-Gan San in traditional Chinese medicine. Many studies have been published on its effects and mechanisms. In this study, we focused on the sleep-promoting effects of Yokukansan.

Aim of the study: Yokukansan composes of seven crude drugs: Uncaria Hook, Bupleurm Root, Cnidium Rhizome, Japanese Angelica Root, Poria Sclerotium, Atractylodes Lancea Rhizome, and Glycyrrhiza. Although each has distinctive effects in isolation, they combine to work as a sleep aid in the Yokukansan formula. We examined the roles of the seven crude drug components in the sleep-promoting effect of

The herbal formula Yokukansan causes a drop in body temperature which were responsible for promoting sleep. Those that did not drop body temp had no effect on sleep.

a drop in body temperature were responsible for promoting sleep, while those in the other group would have no such effect in isolation. To investigate whether the crude drugs that did not cause a decrease in body temperature might be unnecessary for the sleep-promoting effect of Yokukansan, a number of decoctions were prepared using only six of the seven crude drug components, excluding a different crude

Results of this study show that all crude drug components of Yokukansan contribute to its sleep-promoting effects.

crude drugs together was tested alongside extracts made by infusing the three crude drugs separately, the latter showed no effect and there were differences between the two in constituent analysis by HPLC. These results indicate that some reactions may occur during extraction.

Conclusions: Results of this study show that all crude drug components of Yokukansan contribute to its sleep-promoting effects. This is the first report to show the role of the seven clude drug components in the sleep-inducing effects of Yokukansan.

1. Introduction

Sleep is essential to life and has an intimate involvement in the nervous, immune and endocrine system. However, the trend of busy lifestyles taking precedence over regular sleep schedules has led to an increase in insomnia, with about one-third of the adult

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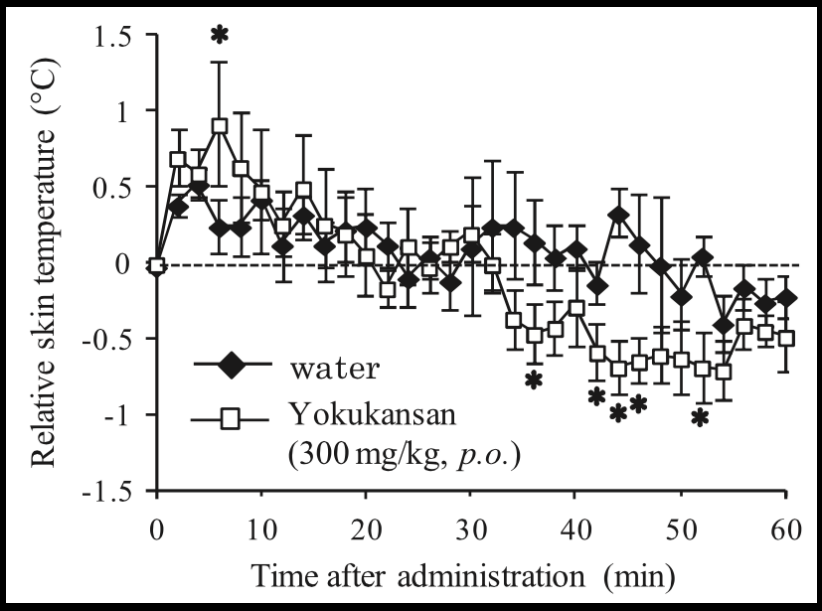
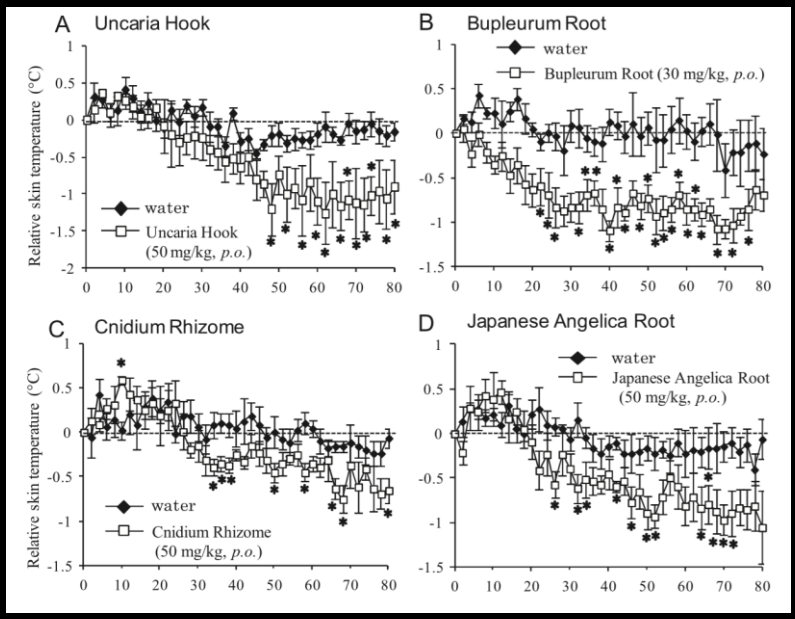
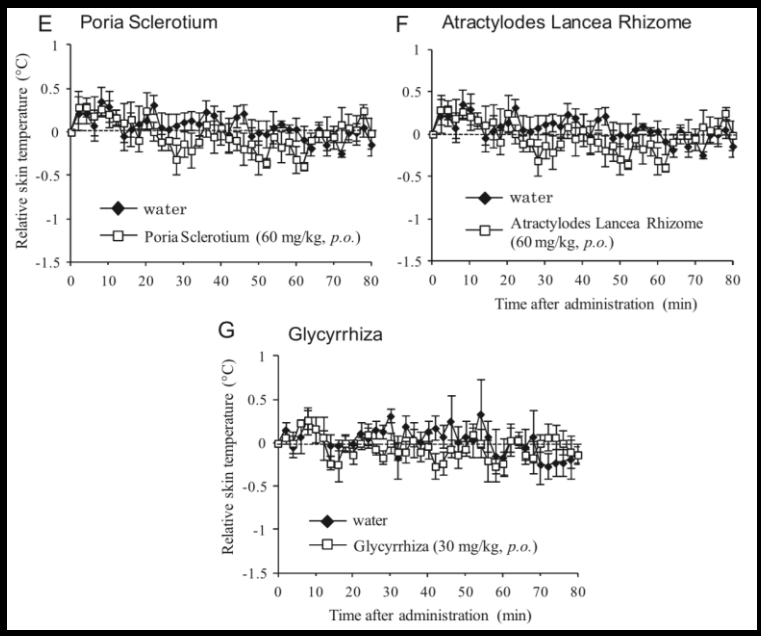
0378-8741/

Whole Extract





Ogawa Y, Fujii Y, Sugiyama R, Konishi T. 2016. The role of the seven crude drug components in the sleep-promoting effect of Yokukansan *J Ethnopharmacol*177:19-27.



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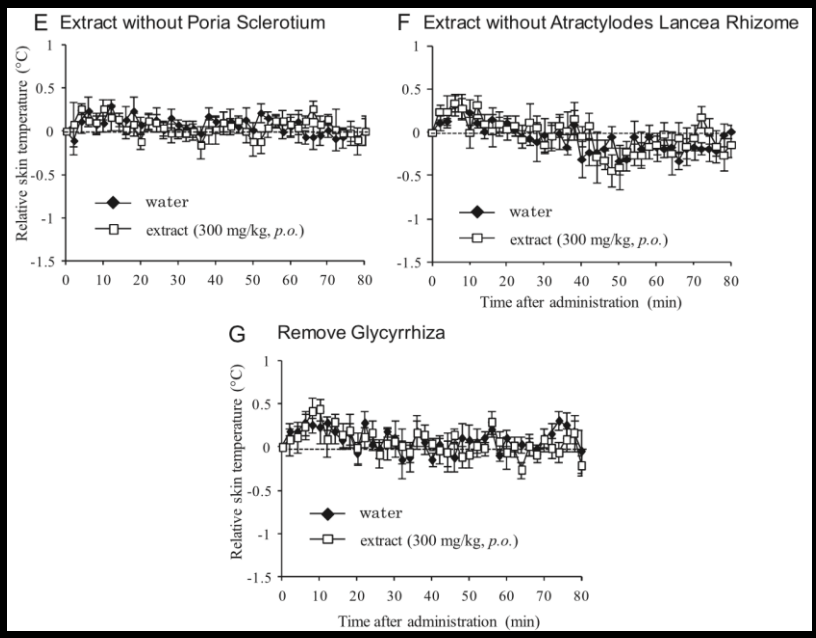
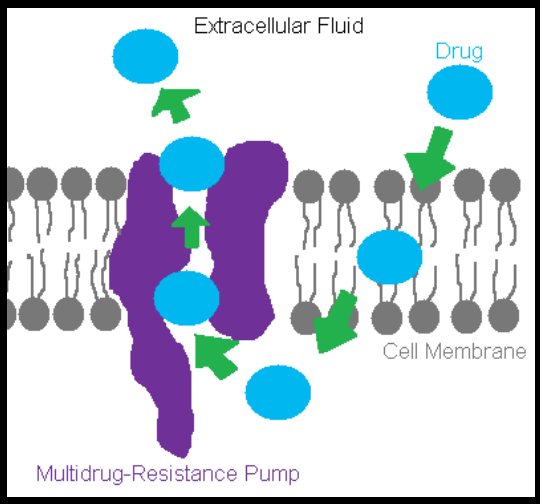


Ogawa Y, Fujii Y, Sugiyama R, Konishi T. 2016. The role of the seven crude drug components in the sleep-promoting effect of Yokukansan *J Ethnopharmacol*177:19-27.

Antibiotic Research

What is the MDR Efflux Pump?



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2002, p. 3133–3141 Vol. 46, No. 10
0066–4804/02/$04.00+0 DOI: 10.1128/AAC.46.10.3133–3141.2002

Multidrug Pump Inhibitors Uncover Remarkable Activity of Plant Antimicrobials

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Plant antimicrobials are not used as systemic antibiotics at present. The main reason for this is their low level of activity, especially against gram-negative bacteria. The reported MIC is often in the range of 100 to 1,000 μg/ml, orders of magnitude higher than those of common broad-spectrum antibiotics from bacteria or fungi. Major plant pathogens belong to the gram-negative bacteria, which makes the low level of activity of plant antimicrobials against this group of microorganisms puzzling. Gram-negative bacteria have an effective permeability barrier, comprised of the outer membrane, which restricts the penetration of amphipathic compounds, and multidrug resistance pumps (MDRs), which extrude toxins across this barrier. It is possible that the apparent ineffectiveness of plant antimicrobials is largely due to the permeability barrier. We tested

…the activity of rhein, the principal antimicrobial from rhubarb, was potentiated 100- to 2,000-fold (depending on the bacterial species) by disabling the MDRs. Comparable potentiation of activity was observed with plumbagin, resveratrol, gossypol, coumestrol, and berberine.

crobial, confirmed that disabling of the MDRs strongly increases the level of penetration of berberine into the cells of gram-negative bacteria. These results suggest that plants might have developed means of delivering their antimicrobials into bacterial cells. These findings also suggest that plant antimicrobials might be developed into effective, broad-spectrum antibiotics in combination with inhibitors of MDRs.

Plants produce an enormous array of secondary metabolites, and it is commonly accepted that a significant part of this chemical diversity serves to protect plants against microbial pathogens (10). These plant substances are classified as phytoanticipins, which are compounds that are present constitutively, or phytoalexins, whose levels increase strongly in response to microbial invasion. In several well-documented cases, mutant plants that lack the ability to produce a particular phytoalexin had considerably higher levels of sensitivity to microbial pathogens. For example, mutant oats that lack saponin avenacin A-1 became sensitive to a range of fungal pathogens (36). However, the only definitive test for a putative antimicrobial is activity. In this regard, the evidence is often unconvincing. In the example cited above, avenacin A-1 did not actually show antifungal activity in a direct susceptibility test in vitro (3). According to the influential review of Dixon cited above (10), there is only one documented case in which plant antimicrobials were present at a sufficient concentration in vivo to inhibit the growth of a bacterial pathogen (37). In that study, infection of cotton with *Xanthomonas campestris* remains puzzling is that one of the sesquiterpenoids, 2-hydroxy-7-methoxycadalene, had no antibacterial activity in vitro, yet its expression followed the same pattern as those of the other related phytoalexins.

Plant compounds are routinely classified as "antimicrobial" on the basis of susceptibility tests that produce MICs in the range of 100 to 1,000 μg/ml, orders of magnitude weaker than those of typical antibiotics produced by bacteria and fungi (MICs, 0.01 to 10 μg/ml). A compound that is synthesized in response to pathogen invasion and is required to protect the plant from a pathogen but that shows little activity in an in vitro susceptibility test is not necessarily an antimicrobial. Such a substance might have a regulatory function, indirectly increasing the level of resistance of the plant. This analysis suggests that we lack a solid rationale for making a functional assignment for the vast majority of plant compounds that have been classified as antimicrobials.

One helpful clue regarding the possible function of plant secondary metabolites is that these compounds often show considerable activity against gram-positive bacteria but not

JOURNAL OF NATURAL PRODUCTS

ARTICLE

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Synergy-Directed Fractionation of Botanical Medicines: A Case Study with Goldenseal (*Hydrastis canadensis*)

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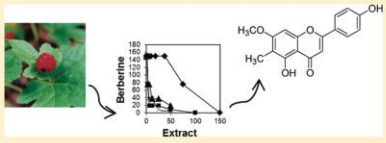
Supporting Information

ABSTRACT: It is often argued that the efficacy of herbal medicines is a result of the combined action of multiple constituents that work synergistically or additively. Determining the bioactive constituents in these mixtures poses a significant challenge. We have developed an approach to address this challenge, synergy-directed fractionation, which combines comprehensive mass spectrometry profiling with synergy assays and natural products isolation. The applicability of synergy-directed fractionation was demonstrated using the botanical medicine goldenseal (*Hydrastis canadensis*) as a case study. Three synergists from goldenseal were identified, sideroxylin (**1**), 8-desmethyl-sideroxylin (**2**), and 6-desmethyl-sideroxylin (**3**). These flavonoids synergistically enhance the antimicrobial activity of the alkaloid berberine (also a constituent of *H. canadensis*) against *Staphylococcus aureus* by inhibition of the NorA multidrug resistance pump. The flavonoids possess no inherent antimicrobial activity against *S. aureus*; therefore, they could have been missed using traditional bioactivity-directed fractionation. The flavonoid synergists are present at higher concentration in extracts from *H. canadensis* leaves, while the antimicrobial alkaloid berberine is present at higher levels in *H. canadensis* roots. Thus, it may be possible to produce an extract with optimal activity against *S. aureus* using a combination of goldenseal roots and leaves.



PNAS PNAS PNAS PNAS

Dried whole-plant *Artemisia annua* slows evolution of malaria drug resistance and overcomes resistance to artemisinin

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Edited* by Francisco J. Ayala, University of California, Irvine, CA, and approved December 5, 2014 (received for review July 10, 2014)

Pharmaceutical monotherapies against human malaria have proven effective, although ephemeral, owing to the inevitable evolution of resistant parasites. Resistance to two or more drugs delivered in combination will evolve more slowly; hence combination therapies have become the preferred norm in the fight against malaria. At the forefront of these efforts has been the promotion of Artemisinin Combination Therapy, but despite these efforts, resistance to artemisinin has begun to emerge. In 2012, we demonstrated the efficacy of the whole plant (WP)—not a tea, not an infusion—as a malaria therapy and found it to be more effective than a comparable dose of pure artemisinin in a rodent malaria model. Here we show that WP overcomes existing resistance to pure artemisinin in the rodent malaria *Plasmodium yoelii*. Moreover, in a long-term artificial selection for resistance in *Plasmodium chabaudi*, we tested resilience of WP against drug resistance in comparison with pure artemisinin (AN). Stable resistance to WP was achieved three times more slowly than stable resistance to AN. WP treatment proved even more resilient than the double dose of AN. The resilience of WP may be attributable to the evolutionary refinement of the plant's secondary metabolic products into a redundant, multicomponent defense system. Efficacy and resilience of WP treatment against rodent malaria provides compelling reasons to further explore the role of nonpharmaceutical forms of AN to treat human malaria.

malaria | drug resistance | artemisinin | *Plasmodium* | evolution

The fight against malaria predates the discovery of its causative agent, and for centuries malaria-associated fever was treated using herbal remedies. In the West, quinine (Cinchona bark extract) was the only affordable treatment against malaria until Paul Ehrlich's magic bullet concept was adopted and thousands of synthetic compounds were tested against malaria parasites. Very few of these compounds were effective and/or safe for human use, but in the 1930s chloroquine rose to ascendancy as a miracle cure for malaria (1). In the late 1950s, chloroquine was the main weapon used by the World Health Organization (WHO) in its Global Malaria Eradication Program (GMEP). Sadly, development of drug-resistant parasites and concomitant failure of chloroquine as the drug of choice led to the eventual demise of GMEP by the close of the 1960s. Following chloroquine's failure, various antimalarial compounds were serially deployed, and each in its turn failed as parasites evolved resistance, thus leaving millions of malaria patients without affordable treatment.

In the 1970s, artemisinin was discovered as a pure drug extracted from the plant *Artemisia annua*. In wide-scale clinical trials, pure artemisinin showed poor pharmacokinetic properties but nonetheless demonstrated potent antimalarial activity with a high safety profile (2). It was determined that artemisinin when modified to artesunate or artemether improved bioavailability and was more effective when used in combination with other antimalarial drugs, mainly mefloquine, which became known as Artemisinin Combination Therapy (ACT) (3). It was hoped that use of ACTs would minimize risk of drug resistance. However, in 2005 the earliest evidence of *P. falciparum* resistance to ACTs arose in Southeast Asia (4–8). The fight against malaria became critical once again when it became apparent that ACT might be following chloroquine's path toward obsolescences with no affordable replacement in sight.

We demonstrated the efficacy of the whole *A. annua* plant as a malaria therapy and found it to be more effective than a comparable dose of pure artemisinin in a rodent malaria model (9). WHO has cautioned against use of nonpharmaceutical sources of artemisinin because of the risk of delivering subtherapeutic doses that could exacerbate the resistance problem (10). This warning is valid given the low artemisinin content of juice extractions, teas, and infusion preparations of plant material used for most nonpharmaceutical plant-based therapies. However, the Whole Plant (WP) *A. annua* therapy that we have tested is not an extraction, a tea, or an infusion, but is based on oral consumption of the dried leaves of the whole plant. Based on our proof of principle in a rodent model, we postulate that with further development WP might provide a more abundant and affordable source of artemisinin-based therapy by eliminating the need for artemisinin extraction during manufacture.

WP may be more effective than monotherapeutic artemisinin because WP may constitute a naturally occurring combination therapy that augments artemisinin delivery and synergizes the drug's activity. This plant Artemisinin Combination Therapy (pACT) is the result of evolutionary refinement of the plant's secondary metabolic products into a resilient and multicomponent defense system. As was demonstrated for other combination therapies, we hypothesized that a WP-based pACT would (*i*) overcome existing resistance to monotherapeutic pure artemisinin and (*ii*) increase the longevity of this therapy by

Significance

Evolution of malaria parasite drug resistance has thwarted efforts to control this deadly disease. Use of drug combinations has been proposed to slow that evolution. Artemisinin is a favorite drug in the global war on malaria and is frequently used in combination therapies. Here we show that using the whole plant (*Artemisia annua*) from which artemisinin is derived can overcome parasite resistance and is actually more resilient to evolution of parasite resistance; i.e., parasites take longer to evolve resistance, thus increasing the effective life span of the therapy.

Author contributions: M.A.E. and S.M.R. designed research; M.A.E. performed research; M.A.E., M.J.T., and P.J.W. contributed new reagents/analytic tools; M.A.E., N.G.R., and S.M.R. analyzed data; and M.A.E., P.J.W., and S.M.R. wrote the paper.

The authors declare no conflict of interest.

*This Direct Submission article had a prearranged editor.

Freely available online through the PNAS open access option.

†To whom correspondence should be addressed. Email: smrich@umass.edu.

An Example…

An investigation into the use of *A. annua* tea (60 mg artemisinin) was as effective as the standard dose of 500 - 1000 mg of isolated artemisinin over the same time period

Mueller MS, *et al.* The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects. *J Ethnopharmacol.* 2000 Dec;73(3):487-93.

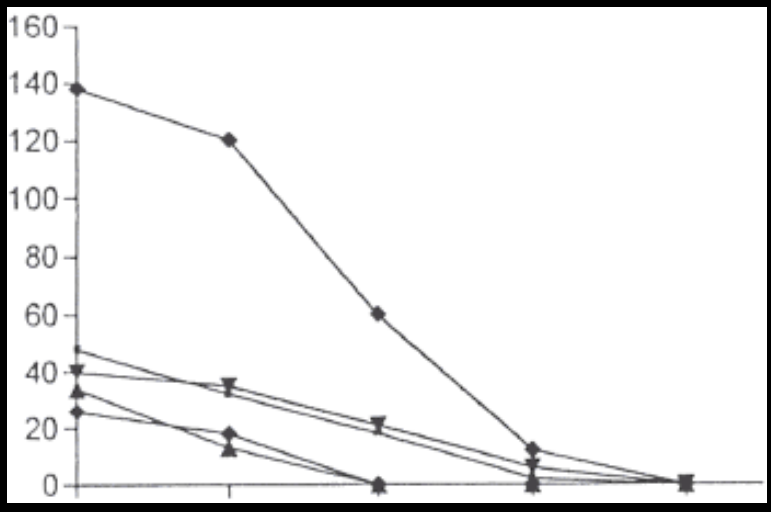
Artemisinin content in tea preparations from *Artemisia annua*

Amount of material per litre water	Method of tea preparation	Artemisinin Concentration in the tea	Extraction efficiency
250 mg pure artemisinin	A	10.6 mg/1itre	-
5 g leaves	A	12.0 mg/1itre	41.4 %
10 g leaves	A	24.5 mg/1itre	42.2 %
20 g leaves	A	32.8 mg/1itre	28.3 %
40 g leaves	A	64.4 mg/1itre	27.8 %
5 g leaves	B	7.2 mg/litre	24.8 %

Mueller MS, *et al.* The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects. *J Ethnopharmacol*. 2000 Dec;73(3):487-93.

Parasite counts in thick blood films of five malaria patients undergoing treatment with Artemisia annua tea.

Mueller MS, *et al*. The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects. *J Ethnopharmacol*. 2000 Dec;73(3):487-93.



Artemisia annua Against Malaria

Antihepatotoxic	oleanolic-acid ; quercetin ; scoparone ; scopoletin
Antimalarial	artemetin ; artemisinin ; ascaridole ; casticin ; chrysosplenetin ; chrysosplenol-d ; cirsilineol ; eupatorin ; oleanolic-acid ; quercetin
Antiplasmodial	chrysosplenetin ; chrysosplenol-d ; oleanolic-acid ; quercetin
Antipyretic	α-bisabolol ; borneol ; menthol
Antiseptic	1,8-cineole ; α -bisabolol ; α -terpineol ; arteannuin-b ; β-pinene ; camphor ; carvacrol ; carvone ; geraniol ; kaempferol ; limonene ; linalool ; menthol ; oleanolic-acid ; rhamnocitrin ; scopoletin ; terpinen-4-ol ; thymol
Hepatoprotective	borneol ; isorhamnetin ; kaempferol ; luteolin ; oleanolic-acid ; quercetin ; rhamnetin ; scoparone ; scopoletin
Immunostimulant	astragalin ; coumarin ; eupatorin
Larvicide	cuminaldehyde ; linalool ; thymol
MDR-Inhibitor	artemisinin ; chrysosplenetin ; chrysosplenol-d
Parasiticide	artemetin ; casticin ; chrysosplenetin ; chrysosplenol-d ; cirsilineol ; eupatorin
Protisticide	α -bisabolol ; artemetin ; casticin ; chrysosplenetin ; kaempferol

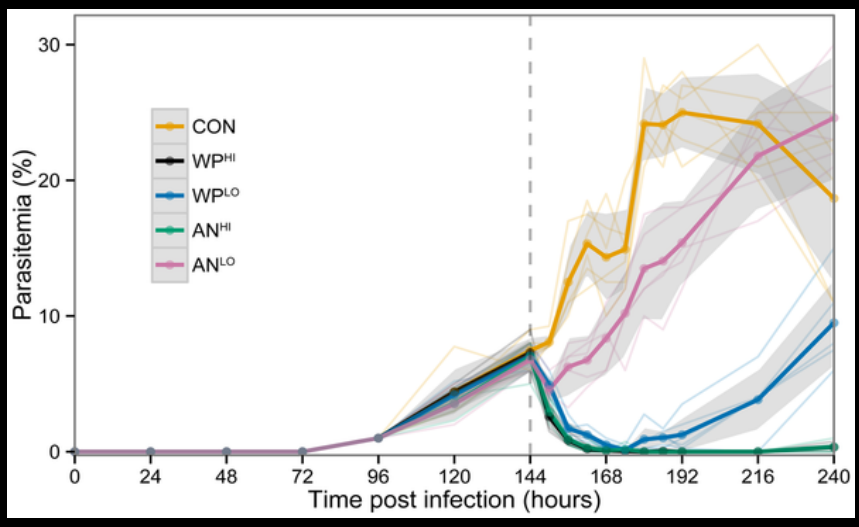
Spelman K, Duke J, Bogenschutz-Godwin M. The Synergy Principle with Plants, Pathogens, Insects, Herbivores and Humans. Chapter in: *Natural Products from Plants*. CRC Press.

Pharmacodynamic Synergy

Elford BC, Roberts MF, Phillipson JD, Wilson RJM. Potentiation of the antimalarial activity of qinghaosu by methoxylated flavoned. *Trans R Soc Trop Med Hyg* 1987; 81:434-6.

In vitro investigations of the extract of the plant have shown that other constituents, notably flavonoids, enhance the antiplasmodic activity of artemisinin

Figure 3. Dose comparisons of WP and AN treatments from the third replicate of data: WPLO



Elfawal MA, Towler MJ, Reich NG, Golenbock D, et al. (2012) Dried Whole Plant Artemisia annua as an Antimalarial Therapy. PLoS ONE 7(12): e52746. doi:10.1371/journal.pone.0052746

Pharmacodynamic Synergy

Wan Y, Zhang Q, Wang J: **Studies on the antimalarial action of gelatin capsule of *Artemisia annua*. .** *Chung Kuo Chi Sheng Chung Hsueh Yu Chi. Sheng Chung Ping Tsa Chih* 1992, **10:**290-294

In experiments with *P. berghei* infection a crude ethanolic extract of *A. annua* formulated with oil in a soft gel capsule, the ED_{50} value with respect to the *Artemisia* content was 35.1 mg/kg whereas the ED_{50} of artemisinin was 122 mg/kg.

Pharmacokinetic Potentiation

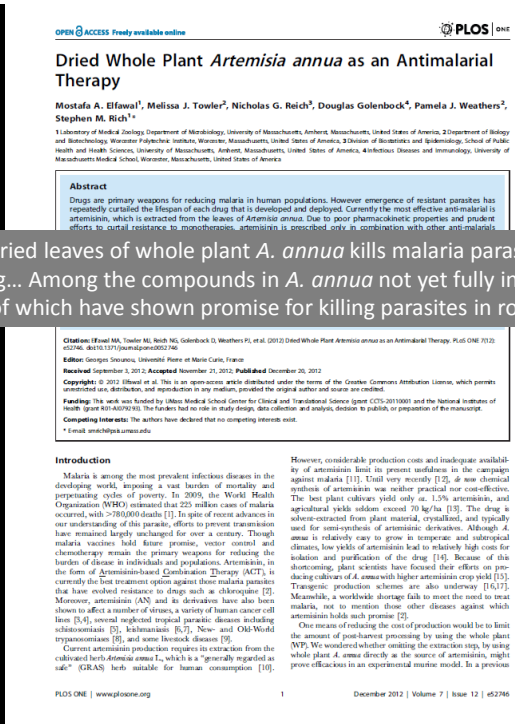
Rezelman D. 2010. Ethanolic extract of *Artemisia annua*: a promising new preparation. Unpublished data.

- A pilot phase I crossover clinical trial comparing 132 mg in extract to pure artemisinin (500 mg).
- The bioavailability relative to the dose received was 2.1x greater for the extract than for the pure compound

Pharmacodynamic Synergy

Sannella AR, Messori L, Casini A, Francesco Vincieri F, Bilia AR, Majori G, Severini C: **Antimalarial properties of green tea.** *Biochem Biophys Res Commun* 2007, **353:**177-181

- Epigallocatechin-3-gallate (EGCG), the most abundant tannin in green tea has antimalarial activity which is additive when combined with artemisinin
  - EGCG is an MDR inhibitor and



OPEN ACCESS Freely available online

PLOS ONE

Dried Whole Plant *Artemisia annua* as an Antimalarial Therapy

Mostafa A. Elfawal[1], Melissa J. Towler[2], Nicholas G. Reich[3], Douglas Golenbock[4], Pamela J. Weathers[2], Stephen M. Rich[1]*

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Abstract

Drugs are primary weapons for reducing malaria in human populations. However emergence of resistant parasites has repeatedly curtailed the lifespan of each drug that is developed and deployed. Currently the most effective anti-malarial is artemisinin, which is extracted from the leaves of *Artemisia annua*. Due to poor pharmacokinetic properties and prudent efforts to avoid resistance to monotherapies, artemisinin is prescribed only in combination with other anti-malarials

…orally ingested, powdered dried leaves of whole plant *A. annua* kills malaria parasites more effectively than a comparable dose of pure drug… Among the compounds in *A. annua* not yet fully investigated are more than a dozen other sesquiterpenes, some of which have shown promise for killing parasites in rodent models.

Citation: Elfawal MA, Towler MJ, Reich NG, Golenbock D, Weathers PJ, et al. (2012) Dried Whole Plant *Artemisia annua* as an Antimalarial Therapy. PLoS ONE 7(12): e52746. doi:10.1371/journal.pone.0052746

Editor: Georges Snounou, Université Pierre et Marie Curie, France

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Competing Interests: The authors have declared that no competing interests exist.

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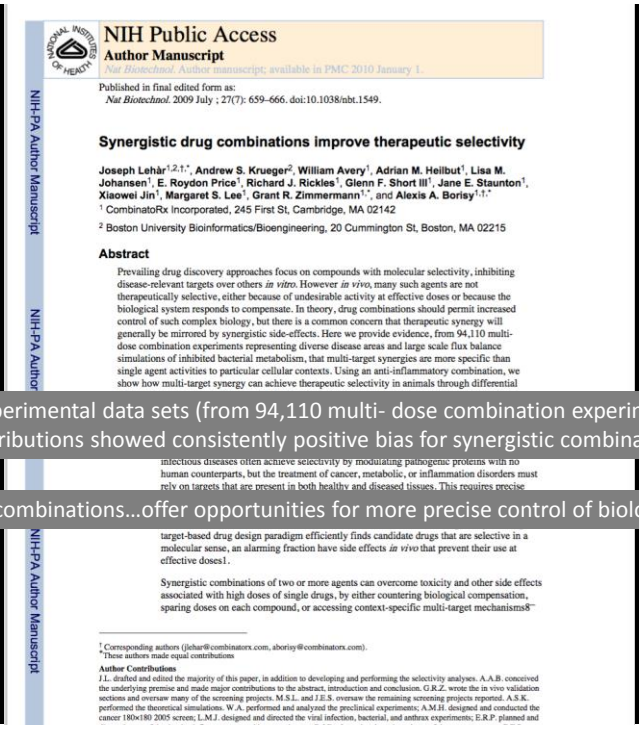
Introduction

Malaria is among the most prevalent infectious diseases in the developing world, imposing a vast burden of mortality and perpetuating cycles of poverty. In 2009, the World Health Organization (WHO) estimated that 225 million cases of malaria occurred, with >780,000 deaths [1]. In spite of recent advances in our understanding of this parasite, efforts to prevent transmission have remained largely unchanged for over a century. Though malaria vaccines hold future promise, vector control and chemotherapy remain the primary weapons for reducing the burden of disease in individuals and populations. Artemisinin, in the form of Artemisinin-based Combination Therapy (ACT), is currently the best treatment option against those malaria parasites that have evolved resistance to drugs such as chloroquine [2]. Moreover, artemisinin (AN) and its derivatives have also been shown to affect a number of viruses, a variety of human cancer cell lines [3,4], several neglected tropical parasitic diseases including schistosomiasis [5], leishmaniasis [6,7], New- and Old-World trypanosomiases [8], and some livestock diseases [9].

Current artemisinin production requires its extraction from the cultivated herb *Artemisia annua* L., which is a "generally regarded as safe" (GRAS) herb suitable for human consumption [10]. However, considerable production costs and inadequate availability of artemisinin limit its present usefulness in the campaign against malaria [11]. Until very recently [12], de novo chemical synthesis of artemisinin was neither practical nor cost-effective. The best plant cultivars yield only ca. 1.5% artemisinin, and agricultural yields seldom exceed 70 kg/ha [13]. The drug is solvent-extracted from plant material, crystallized, and typically used for semi-synthesis of artemisinic derivatives. Although *A. annua* is relatively easy to grow in temperate and subtropical climates, low yields of artemisinin lead to relatively high costs for isolation and purification of the drug [14]. Because of this shortcoming, plant scientists have focused their efforts on producing cultivars of *A. annua* with higher artemisinin crop yield [15]. Transgenic production schemes are also underway [16,17]. Meanwhile, a worldwide shortage fails to meet the need to treat malaria, not to mention those other diseases against which artemisinin holds such promise [2].

One means of reducing the cost of production would be to limit the amount of post-harvest processing by using the whole plant (WP). We wondered whether omitting the extraction step, by using whole plant *A. annua* directly as the source of artemisinin, might prove efficacious in an experimental murine model. In a previous



Published in final edited form as:
Nat Biotechnol. 2009 July ; 27(7): 659–666. doi:10.1038/nbt.1549.

Synergistic drug combinations improve therapeutic selectivity

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Abstract

Prevailing drug discovery approaches focus on compounds with molecular selectivity, inhibiting disease-relevant targets over others *in vitro*. However *in vivo*, many such agents are not therapeutically selective, either because of undesirable activity at effective doses or because the biological system responds to compensate. In theory, drug combinations should permit increased control of such complex biology, but there is a common concern that therapeutic synergy will generally be mirrored by synergistic side-effects. Here we provide evidence, from 94,110 multi-dose combination experiments representing diverse disease areas and large scale flux balance simulations of inhibited bacterial metabolism, that multi-target synergies are more specific than single agent activities to particular cellular contexts. Using an anti-inflammatory combination, we show how multi-target synergy can achieve therapeutic selectivity in animals through differential

Across all of our experimental data sets (from 94,110 multi- dose combination experiments), the selectivity distributions showed consistently positive bias for synergistic combinations

Synergistic combinations…offer opportunities for more precise control of biological systems

infectious diseases often achieve selectivity by modulating pathogenic proteins with no human counterparts, but the treatment of cancer, metabolic, or inflammation disorders must rely on targets that are present in both healthy and diseased tissues. This requires precise target-based drug design paradigm efficiently finds candidate drugs that are selective in a molecular sense, an alarming fraction have side effects *in vivo* that prevent their use at effective doses1.

Synergistic combinations of two or more agents can overcome toxicity and other side effects associated with high doses of single drugs, by either countering biological compensation, sparing doses on each compound, or accessing context-specific multi-target mechanisms8–

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* These authors made equal contributions

Author Contributions

J.L. drafted and edited the majority of this paper, in addition to developing and performing the selectivity analyses. A.A.B. conceived the underlying premise and made major contributions to the abstract, introduction and conclusion. G.R.Z. wrote the in vivo validation sections and oversaw many of the screening projects. M.S.L. and J.E.S. oversaw the remaining screening projects reported. A.S.K. performed the theoretical simulations. W.A. performed and analyzed the preclinical experiments; A.M.H. designed and conducted the cancer 180×180 2005 screen; L.M.J. designed and directed the viral infection, bacterial, and anthrax experiments; E.R.P. planned and

Network Pharmacology

Occam's Razor was Theology...

The Genome - Network Properties

Birney E, Stamatoyannopoulos JA, Dutta A, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature.* Jun 14 2007;447(7146):799-816.

Genes operate in complex networks!

Network Pharmacology

The recognition, informed by systems biology, that drugs for many disease states may require multiple activities to be efficacious, together with the observed promiscuity of old, small-molecule drugs, points strongly at the potential efficacy of medicinal plants as effective therapeutics

Asthma Targets

Hopkins AL. 2008. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 4:620-90.

aminergic GPCRs
- α-1a
- α-2a
- α-2c
- α-2c1
- β1
- β3
- H1
- H3
- H4
- M1
- M2
- M3

peptide GPCRs
- CCR3
- CXCR2
- NK1
- NK2
- NK3

lipophilic GPCRs
- CRTH2
- DP
- DP1
- EP1
- EP2
- EP4
- LTB4

ion channels
- P2X7

nuclear hormone receptors
- GR

enzymes
- 5-LO

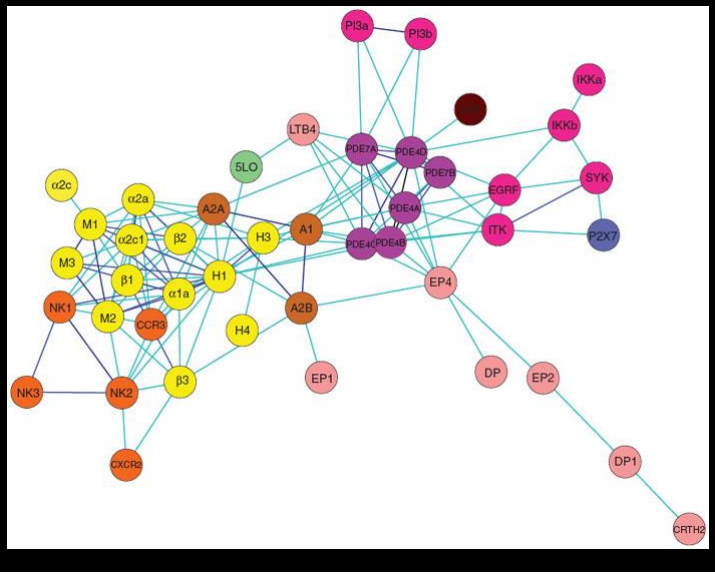
phosphodiesterases
- PDE4A
- PDE4B
- PDE4C
- PDE4D
- PDE7A
- PDE7C

protein kinases
- EGRF
- IKKa
- IKKb
- ITK
- PI3a
- PI3b
- SYK

adenosine receptors
- A1
- A2A
- A2B

Asthma Targets

Hopkins AL. 2008. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 4:620-90.



Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antiallergic

gallic acid
myricetin
ascorbic acid
caffeoyltartaric acid
calcium
ferulic acid
kaempferol
linalool
luteolin
niacin
oleanolic acid
opcs
pantothenic acid
procyanadins
quercetin
rutin

Antiasthmatic

α-tocopherol
ascorbic acid
β-carotene
gallic acid
limonene
magnesium
opcs
protocatechuic acid
quercetin
selenium

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antibronchitic

gallic acid

Antihistaminic

ascorbic acid
caffeic acid
catechin
chlorogenic acid
kaempferol
linalool
linoleic acid
luteolin
myricetin
niacin
opcs
procyanidins
quercetin
rutin
ursolic acid

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antileukotriene

(-) epicatechin
caffeic acid
caffeoyltartaric acid
chlorogenic acid
oleanolic acid
quercetin
resveratrol
selenium

Antipharyngitic

quercetin

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antioxidants

(+) catechin
(+) gallocatechin
(-) epicatechin
(-) epigallocatechin
alanine
alpha tocopherol
anthocyanidins
anthocyanins
ascrobic acid
beta carotene
beta sitosterol
caffeic acid
campesterol
chlorogenic acid
cholesterol
cyanidin
delphinidin
delphinidin 3 o beta d glucoside
ellagic acid
epicatechin
epicatechin 3 o gallate
ferulic acid
fumaric acid
gallic acid
gentisic acid
histidine
hyperoside
isochlorogenic acid
isoquercitrin
kaempferol
lupeol
lutein
luteolin
lycopene
malvidin
manganese
methionine
myricetin
myristic acid
oleanolic acid
opcs
p coumaric acid
p hydroxy benzoic acid
Palmitic acid
pelargonidin
peonidin 3 o beta glucoside
petunidin 3 o beta glucoside
piceid
procyanidin B 2 3' o-gallate
procyanidin B 2 3,3' DI o-gallate
procyanidins

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antioxidants

protocatechualdehyde
protocatechuic acid
pterostilbene
quercetin
resverotrol
riboflavin
rutin
salicylic acid
selenium
shikimic acid
sinapic acid
squalene
stigmasterol
syringaldehyde
syrigic acid
tannin
tryptophan
ursolic acid
vanillic acid
vanillin

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antiprostaglandin

(+) catechin
beta sitosterol
caffeic acid
catechin
coniferyl aldehyde
lupeol
resveratrol
tryptophan

Antispasmodic

ascorbic acid
caffeic acid
cinnmaldehyde
cinnamic acid
ferulic acid
geraniol
kaempferol
limonene
linalool
luteolin
magnesium
niacin
p coumaric acid
potassium
protocatechuic acid
quercetin
rutin
shikimic acid

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Asthma-preventative

ascorbic acid

Bronchodilator

gallic acid

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Bronchorelaxant

linalool

COX-Inhibitor

(+) catechin
catechin
cinnamaldehyde
gallic acid
kaempferol
oleanolic acid
pterostilbene
quercetin
resveratrol
salicylic acid
tannin
trans resveratrol
ursolic acid

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Expectorant

- acetic acid
- astragalin
- benzoic acid
- betaine
- geraniol
- limonene
- linalool

Immunomodulator

- alpha tocopherol
- ascorbic acid
- chromium
- copper
- gallic acid
- limonene
- linoleic acid
- magnesium
- oleanolic acid
- opcs
- rutin
- selenium
- ursolic acid
- zinc

Vitis vinifera

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Lipoxygenase Inhibitor

- (-) epicatechin
- caffeic acid
- catechin
- chlorogenic acid
- cinnamaldehyde
- cinnamic acid
- epicatechin
- kaempferol
- luteolin
- myricetin
- p coumaric acid
- quercetin
- rutin
- squalene
- tannin
- ursolic acid

Mast Cell Stabilizer

- quercetin

Network Pharmacology

- Compounds that selectively act on two or more targets of interest in theory should be more efficacious than single-target agents

Hopkins A. 2007. Network Pharmacology. Nature Biotechnology 25(10):1110-1111

Realities

Integrating drug data with genetic-disease associations, gene-expression information and protein-protein interaction data, researchers investigated the relationships between approved drugs and observed a rich network of polypharmacology interactions between drugs and their targets

Yıldırım, M.A., et al, 2007. *Nat. Biotechnol.* **25**, 1119–1126.

Realities

drugs acting on single targets appear to be the exception

Yıldırım, M.A., et al, 2007. *Nat. Biotechnol.* **25**, 1119–1126.

Network Pharmacology

Ágoston V, Csermely P, Pongor S. Multiple, weak hits confuse complex systems: A transcriptional regulatory network as an example. *Phys Rev E.* 2005;71(5):1-8.

- In comparisons of various pharmacological strategies, multiple but partial perturbations of selected targets in a network are almost always more efficient than the knockout of a single, well-selected target

Network Pharmacology

Csermely P, Agoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci*. Apr 2005;26(4):178-182.

- Redundant pathways of cellular networks are not generally inhibited by just one pharmacological agent

Network Pharmacology

Ágoston V, Csermely P, Pongor S. Multiple, weak hits confuse complex systems: A transcriptional regulatory network as an example. *Phys Rev E*. 2005;71(5):1-8.

- Robust living molecular networks are commonly resistant to high-affinity, high-selectivity single hits such as generated by the current pharmacological methodology

Network Pharmacology

Ágoston V, Csermely P, Pongor S. Multiple, weak hits confuse complex systems: A transcriptional regulatory network as an example. *Phys Rev E.* 2005;71(5):1-8.

- While a high-affinity compound can knock out a single interaction, a compound with less specificity can interact with more targets of a particular protein or operon

Network Pharmacology

Ágoston V, Csermely P, Pongor S. Multiple, weak hits confuse complex systems: A transcriptional regulatory network as an example. *Phys Rev E.* 2005;71(5):1-8.

- Such network activity is very similar to the interface between plant compounds and a human system when a person ingests a medicinal or food plants

Ensemble Properties

155 Chinese Journal of Traumatology 2010; 13(3):155-162

Effect of Xingnaojing injection on cerebral edema and blood-brain barrier in rats following traumatic brain injury

XU Miao 徐 妙+, SU Wei 苏 伟, XU Qiu-ping 徐秋萍 and HUANG Wei-dong 黄卫东

【Abstract】 Objective: To explore the effects of Xingnaojing injection on cerebral edema and blood-brain barrier (BBB) in rats following traumatic brain injury (TBI).

Methods: A total of 108 adult male Sprague-Dawley rats were used as subjects and randomly assigned to three groups: sham-operation, TBI and Xingnaojing injection groups (10 ml·kg^{-1}·d^{-1}, intraperitoneal injection). TBI in rats was set up by the improved device of Feeney's weight-dropping model with the impact of 600 g·cm. Brain water content and BBB permeability expressed as Evans blue content were measured at 1, 3, 5 and 7 days after surgery.

Result: In sham-operation group, brain water content and Evans blue content in brain tissue were 78.97%±1.22 % and 5.13 μg±0.71μg. Following TBI, water content in brain tissue was increased significantly at 1, 3, 5 and 7 days ±0.60%), being significantly higher than that in sham operation group (P<0.05). Evans blue content was increased in TBI group (16.54 μg±0.60 μg, 14.92 μg±0.71 μg, 12.44 μg ±0.92 μg, 10.14 μg±0.52 μg) as compared with sham-operation group(P<0.05). After treatment with Xingnaojing injection, brain water content decreased as compared with TBI group(81.91%±1.04%, 80.38%±0.72%, 79.54%±0.58%, 78.60%±0.77%, P<0.05). Xingnaojing injection also reduced the leakage of BBB as compared with TBI group (15.11 μg± 0.63 μg, 13.62 μg±0.85 μg, 10.06 μg±0.67 μg, 9.54 μg±0.41 μg, P<0.05).

Conclusion: Xingnaojing injection could alleviate cerebral edema following TBI via reducing permeability of BBB.

Key words: ***Medicine, Chinese traditional; Brain injuries; Brain edema; Blood-brain barrier***

Radix Curcumae formula: *Curcuma longa, Gardenia root, Moschus, Borneolum*

Reduces brain injury and enhances functional recovery after TBI.

key contributor to the morbidity and mortality associated with TBI. The cellular and molecular mechanisms contributing to the development or resolution of TBI-associated brain edema are poorly understood. Current treatments for brain edema such as hyperosmolar agents and surgical decompression have changed little

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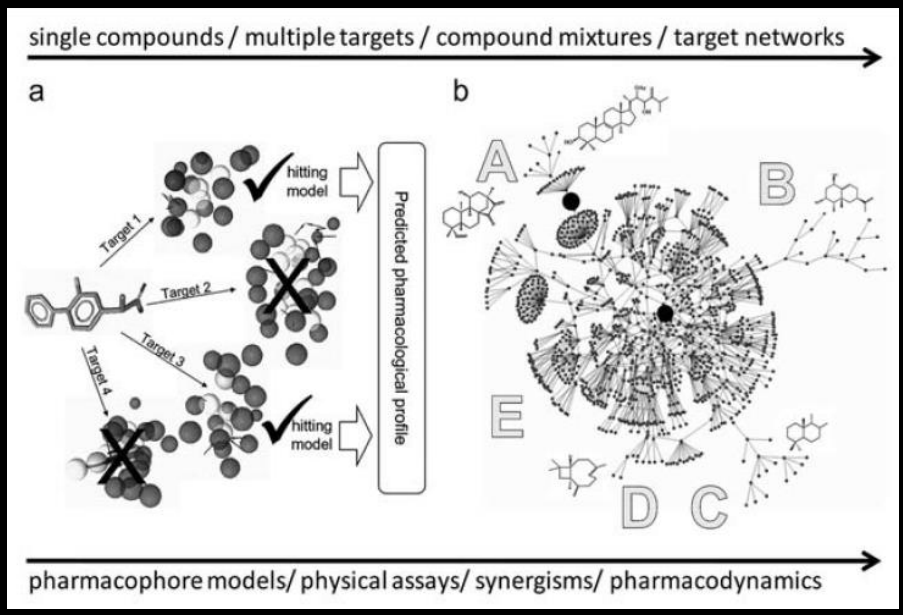
mediate and sustained reduction of cerebral edema, and recovery of cerebral function.

Xingnaojing injection (XNJ), consisting of Chinese herbs such as Moschus, Borneol, Radix Curcumae, Fructus Gardeniae, was extracted by modern biotechnology according to Chinese Traditional Medicine named An Gong Niu Huang Wan. Modern pharmacological studies confirmed that XNJ can directly act on the central nervous system through blood brain barrier (BBB). It is now well documented that XNJ can reduce brain injury and enhance functional recovery after TBI and stroke in different clinical trials and animal models of injury. Despite the demonstrated benefits of XNJ in treating TBI, little is known about how this medicine specifically produces its salutary effects at the cellular level after TBI. To elucidate further the mechanisms can help to prevent edema formation and inflammation. Therefore we studied the brain water content and permeability of BBB in response to TBI and then the effects of treatment with XNJ using a rodent brain injury model.



Journal of Ethnopharmacology 145 (2013) 1–10

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journal homepage: www.elsevier.com/locate/jep

Review

Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal *Radix Curcumae* formula for application to cardiovascular disease

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ARTICLE INFO

ABSTRACT

74 of 475 phytochemicals, 15.6%, show oral bioavailability and drug-likeness. 58 compounds interact with targets for cardio and cerebrovascular diseases. Each of 9 compounds hits more than 10 potential targets.

33 active compounds of *Curcuma* have 8 specific potential targets. 17 active compounds of *Gardenia* posses 5 specific targets. *Curcuma* & *Gardenia* have 15 common targets; *Curcuma* and *Moschus* have 8 common targets

According to our analysis this formula can be used for other diseases such as neoplasms and metabolic disorders.

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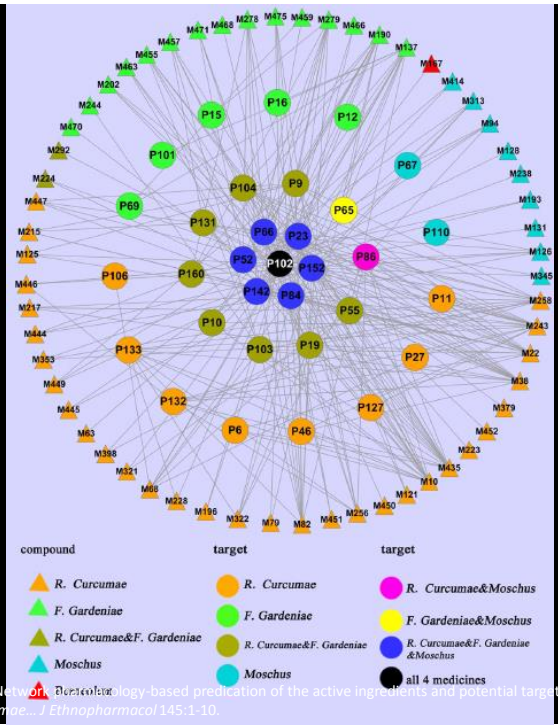
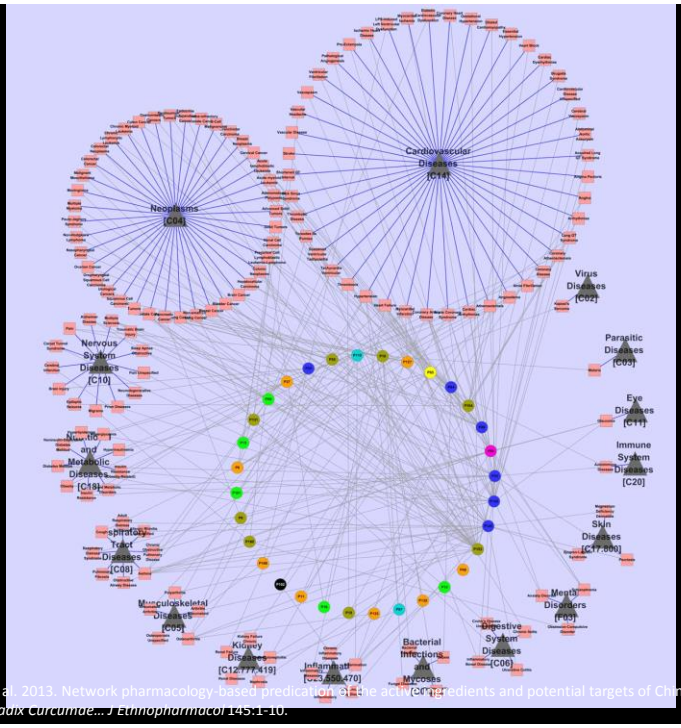
1 Contributed equally.

http://dx.doi.org/10.1016/j.jep.2012.09.051

No.	Compound	OB	DL	Medicine
M10*	(1E,4E,6E)-1,7-bis-(4-Hydroxyphenyl)-1,4,6- heptatrien-3-one	80.7	0.25	yujin
M22*	(E)-5-Hydroxy-7-(4-hydroxyphenyl)-1-phenyl-1-heptene	64.7	0.19	yujin
M38*	1,7-Diphenyl-3-acetoxy-4(E)-hepten	62.9	0.22	yujin
M63*	3,7-Dimethyl-5-indanecarboxylic acid	67.8	0.12	yujin
M68*	3-Hexadecenoic acid	67.4	0.12	yujin
M79*	4-Epi-curcumenol	89.6	0.27	yujin
M82*	4s-Dihydrocurcumenone	65.2	0.22	yujin
M117	a-Cadinol	64.8	0.18	yujin
M121*	Aerugidiol	67.2	0.22	yujin
M125*	Alismoxide	66.3	0.19	yujin
M135	Aromadendrene oxide	64.8	0.31	yujin
M179	Calarenepoxide	70.7	0.42	yujin
M196*	Cinnamic acid	79.8	0.15	yujin
M215*	Curcumanolide A	79.0	0.19	yujin
M217*	Curcumenol	91.1	0.27	yujin
M223*	Curcumol	109.8	0.27	yujin
M228*	Curzerenone	63.5	0.20	yujin
M243*	Dihydrocurcumin	65.5	0.44	yujin
M254	Endobornyl acetate	65.5	0.19	yujin
M255	Epicurcumenol	87.8	0.27	yujin
M256*	Epicurzerenone	63.0	0.20	yujin
M258*	Ethyl ferulate	87.8	0.11	yujin
M314	Isoaromadendrene epoxide	64.7	0.34	yujin
M317	Isocurcumenol	100.0	0.27	yujin
M321*	Isospathulenol	81.9	0.26	yujin
M322*	Isozedoarondiol	64.0	0.21	yujin
M329	Ledenoxide	80.5	0.40	yujin
M353*	Neocurcumenol	86.5	0.27	yujin
M376*	Oxycurcumenol	67.2	0.44	yujin
M398*	Procurcumadiol	68.3	0.23	yujin
M412	Spathulenol	79.6	0.26	yujin
M430*	Turmeronol A	67.6	0.12	yujin
M444*	Zedoalactone A	100.0	0.27	yujin
M445*	Zedoalactone B	100.0	0.34	yujin
M446*	Zedoalactone C	71.3	0.23	yujin
M447*	Zedoalactone D	100.0	0.34	yujin
M449*	Zedoarol	100.0	0.26	yujin
M450*	Zedoarolide A	87.2	0.52	yujin
M451*	Zedoarolide B	100.0	0.33	yujin
M452*	Zedoarondiol	60.3	0.21	yujin
M183	Camphor	68.9	0.17	yujinkhingpian
M315	Isoborneol	87.4	0.17	yujinkhingpian
M224*	Curdione	38.5	0.11	yujinkzhizi
M292*	Germacrone	41.1	0.10	yujinkzhizi
M354	Neocurdione	36.5	0.11	yujinkzhizi
M137*	Ascorbic acid	78.6	0.11	zhizi
M190*	Chlorogenic acid	39.0	0.39	zhizi
M202*	Crocetin	16.5	0.30	zhizi
M244*	Dimethoxydurene	63.4	0.12	zhizi
M276*	Gardenic acid	41.1	0.62	zhizi
M279*	GardeninA	40.1	0.56	zhizi
M438	Ursolic acid	19.4	0.88	zhizi
M455*	Asperuloside_DG	91.2	0.23	zhizi
M457*	6″-p-coumanoylgenipingentiobioside_DG	73.5	0.16	zhizi
M459*	6′-O-sinapoyljasminoside C_DG	60.5	0.10	zhizi
M461*	10-acetyl geniposide_DG	60.4	0.20	zhizi
M466*	Picracinicacid_DG	55.3	0.12	zhizi
M468*	Jasminoside I_DG	61.7	0.11	zhizi
M470*	Gardoside_DG	83.0	0.16	zhizi
M471*	Gardenoside_DG	100.0	0.20	zhizi
M475*	Caryptoside_DG	100.0	0.21	zhizi
M64	3-a-hydroxy-4-androsten-17-one	35.5	0.44	shexiang
M94*	5-cis-14-methyl-cyclopentadecenone	32.3	0.11	shexiang
M126*	Allantoin	98.7	0.10	shexiang
M128*	Androst-4-one-3,17-dione	47.2	0.49	shexiang
M131*	Androsterone	36.8	0.44	shexiang
M193*	Cholic acid	37.9	0.73	shexiang
M238*	Dehydroepiandrosterone	33.9	0.44	shexiang
M313*	Hydroxymuscopyridine	42.3	0.15	shexiang
M345*	Muscone	31.5	0.11	shexiang
M346	Muscopyridine	47.5	0.13	shexiang
M351	N-doxsane	63.5	0.28	shexiang
M414*	Stanolone	32.7	0.44	shexiang
M167*	Borneol	82.9	0.17	bingpian



Tai W, et al. 2013. Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal *Radix Curcumae*... *J Ethnopharmacol* 145:1-10.



Tai W, et al. 2013. Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal *Radix Curcumae*... *J Ethnopharmacol* 145:1-10.

Multicomponent Remedies

Wald NJ, Law MR. 2003. A strategy to reduce cardiovascular disease by more than 80% *BMJ* 326:1419

- The Polypill strategy, based on a single daily pill containing six components
  - A statin
  - Three blood pressure lowering drugs, each at half standard dose
  - Folic acid (800 mcg)
  - Aspirin (75 mg)
- would prevent 88% of heart attacks and 80% of strokes
- About 1 in 3 people would directly benefit, each on average gaining 11-12 years of life without a heart attack or stroke (20 years in those aged 55-64).

Garlic

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Cholesterol lowering agents

apigenin
adenosine
ajoene
allicin
alliin
campesterol
diallyl-disulfide
diallyl-trisulfide
inulin
lignin
methyl-ajoene
nicotinic-acid
phytic-acid
rutin
s-allyl-cysteine-sulfoxide
s-allyl-l-cysteine
s-methyl-l-cysteine-sulfoxide
taurine
trigonelline

Blood pressure lowering agents

ACEI	Ca^{2+} Channel Blockers	Diuretics
glutathione	allicin	apigenin
querceitin	caffeic acid	asparagine
	trans-ajoene	caffeic acid
		chlorogenic acid
		citrulline
		kaempferol
		myricetin
		oleanolic acid

Garlic

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antiinflammatory agents

COX Inhibs	Other
2-vinyl-4h-1,3-dithiin	α-linolenic-acid
caffeic-acid	chlorogenic-acid
kaempferol	ferulic-acid
oleanolic-acid	linalool
quercetin	myricetin
salicylic-acid	vanillic-acid

Antiaggregants

2-vinyl-4h-1,3-dithiin
adenosine
ajoene
allicin
alliin
allyl-methyl-trisulfide
allyl-trisulfide
α-linoleic acid
apigenin
caffeic acid
cycloalliin
ferulic acid
kaempferol
methyl-allyl-trisulfide
phytic-acid
quercetin
salicylates

Garlic spp.

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antioxidants

allicin
alliin
allixin
allyl-mercaptan
apigenin
campesterol
caffeic acid
chlorogenic acid
diallyl-disulfide
diallyl heptasulfide
diallyl hexasulfide
diallyl pentasulfide
diallyl sulfide
diallyl tetrasulfide
diallyl trisulfide
ferulic acid
glutathinone
ionol
kaempferol
lignin
myricetin
oleanolic acid
p-coumaric acid
p-hydroxy benzoic acid
pentadecanoic acid
phytic acid
quercetin
rutin
s-allyl-cysteine-sulfoxide
s-allyl-L-cysteine
s-allyl-mercaptocysteine
salicylic acid
sinapic acid
taurine
vanillic acid

Garlic, through another lense

for URIs?

Allium sativum

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Analgesic/Anesthetic/Antinociceptive

adenosine
allithiamin
caffeic acid
chlorogenic acid
ferulic acid
jinalool
quercetin
rutin
salicylic acid

Antiallergic

ajoene
apigenin
citral
ferulic acid
kaempferol
linalool
oleanolic acid
quercetin
rutin

Allium sativum

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Anti-flu

allicin
2-vinyl-4h-1,3-dithiin
caffeic acid
diallyl trisulfide
quercetin

Antihistaminic

apigenin
caffeic acid
chlorogenic acid
citral
kaempferol
linalool
myricetin
quercetin
rutin

Allium sativum

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antiinflammatory agents

COX Inhibs

2-vinyl-4h-1,3-dithiin
ajoene
apigenin
caffeic acid
kaempferol
oleonolic acid
quercetin
salicylic-acid

Other

ajoene
allicin
Alpha linolenic acid
apigenin
caffeic acid
chlorogenic acid
ferulic acid
kaempferol
myricetin
oleanolic acid
quercetin
quercetin 3 o beta d glucoside
rutin
salicylates
salicylic acid
vanillic-acid

Antiviral

ajoene
allicin
allyl alcohol
apigenin
caffeic acid
chlorogenic acid
diallyl disulfide
diallyl trisulfide
ferullic acid
kaempferol
lignin
linalool
myricetin
oleanolic acid
quercetin
rutin

Allium sativum

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antibacterial

ajoene
allicin
alliin
allistatin i
allistatin ii
alpha phellandrene
apigenin
caffeic acid
chlorogenic acid
citral
diallyl disulfide
diallyl sulfide
diallyl tetrasulfide
diallyl trisulfide
endolysin
ferulic acid
geraniol
kaempferol
lignin
linalool
muramidase
myricetin
oleanolic acid
p-coumaric acid
p-hydroxy benzoic acid
quercetin
rutin
aalicylic acid
sinapic acid
vanillic acid

Allium sativum

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Antipneumonic

diallyl trisulfide
2-vinyl-4h-1,3-dithiin

Antipyretic

Salicylates — Salicylic acid

Allium sativum

Duke J. 2014. Phytochemical Database and Ethnobotanical Databse. http://www.ars-grin.gov/duke/

Expectorant

beta phellandrene
2-vinyl-4H-1,3-dithiin
citral
geraniol
inulin
linalool

Immunostimulant

allicin
alliin
alpha linolenic acid
ascorbic acid
caffeic acid
chlorogenic acid
diallyl disulfide
inulin
oleanolic acid
S-allyl-L-cysteine

Multi-Targeting

Over 40% of drug targets that map with disease genes mapped to more that one disease

Hopkins A. 2007. Network Pharmacology. Nature Biotechnology 25(10):1110-1111.

Disease as Multi Factorial

- A network analysis of the OMIM database of genetic associations showed that the genetic origins of most diseases are shared with other diseases:
  - of 1,284 disorders catalogued in OMIM, 867 share at least one gene with another disorder

Goh, K.-I. *et al. Proc. Natl. Acad. Sci. USA* **104**, 8685–8690 (2007).

Systems Biology

Borisy AA, et al. (2003). Systematic discovery of multicomponent therapeutics. *Proc Natl Acad Sci U S A* 100, 7977-82.

A drug discovery approach consonant with a systems biology framework, and complementary to the target-based approach, entails identification of *combinations of small molecules* that perturb cellular signaling networks in a desired fashion

Systems Biology

Martin KR. 2006. Targeting apoptosis with dietary bioactive agents. *Exp Biol Med* 231(2):117-29

- It is clear that a large number of phytochemicals, often considered superfluous, directly or indirectly modulate gene expression

Intervening in a Network

Csermely, P., Agoston, V., and Pongor, S. (2005). The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci* 26, 178-82.

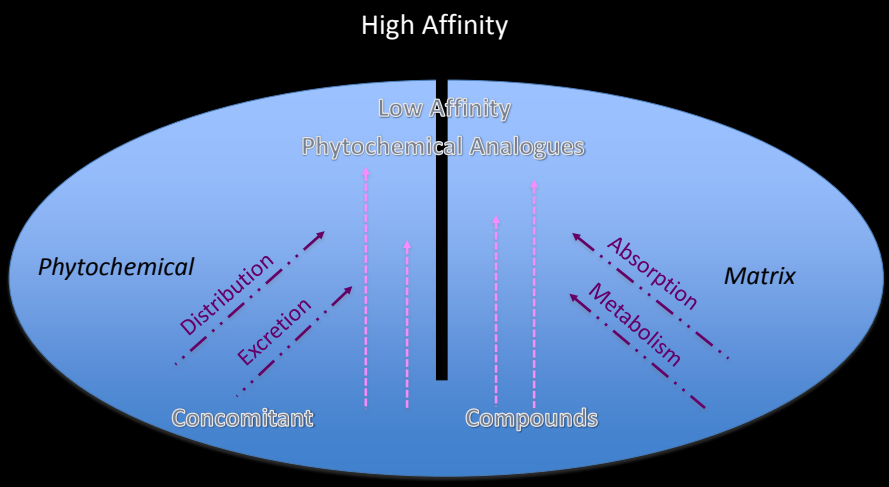
Pharmacological strategies with multiple targets might have a better chance of affecting the complex equilibrium of whole cellular networks than drugs that act on a single target

This also includes an enhanced safety profile

Deductive Landscape

A Broad Perspective

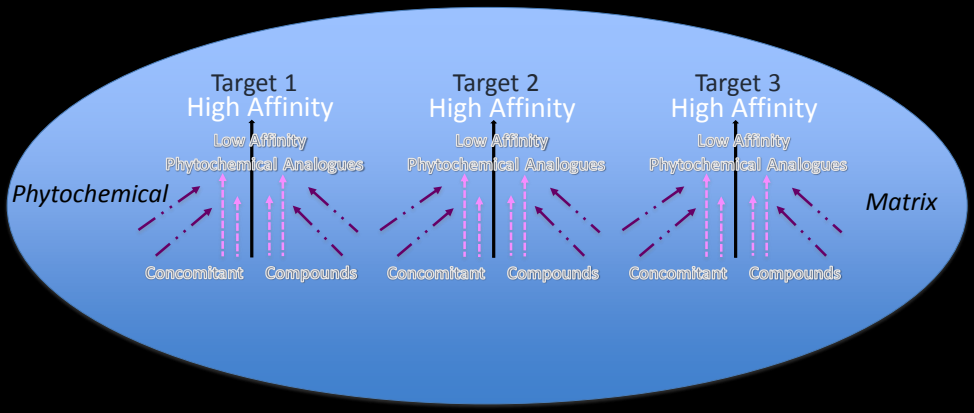
Spelman K. 2007. Ecological Pharmacology II: Molecular Details *UnifiedEnergetics* 3(6): 58-62.



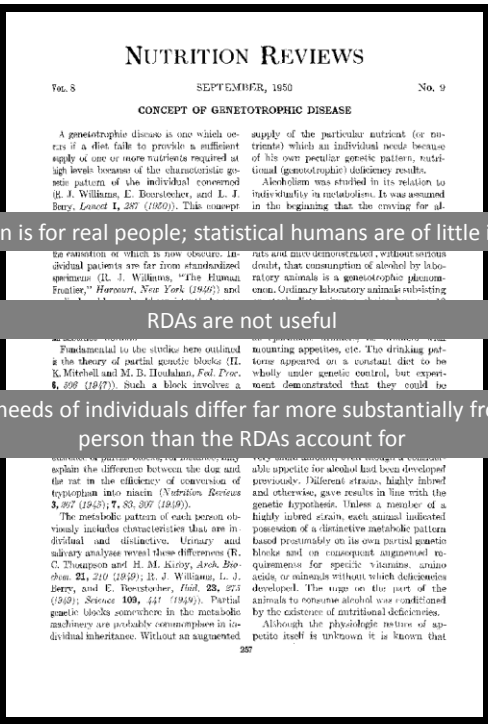
Deductive Landscape

A Broader Perspective

Spelman K. 2007. Ecological Pharmacology II: Molecular Details *UnifiedEnergetics* 3(6): 58-62.



Biochemical Individuality
Pharmacogenomics, Pharmacogenetics and Polymorphisms



NUTRITION REVIEWS

Vol. 8 SEPTEMBER, 1950 No. 9

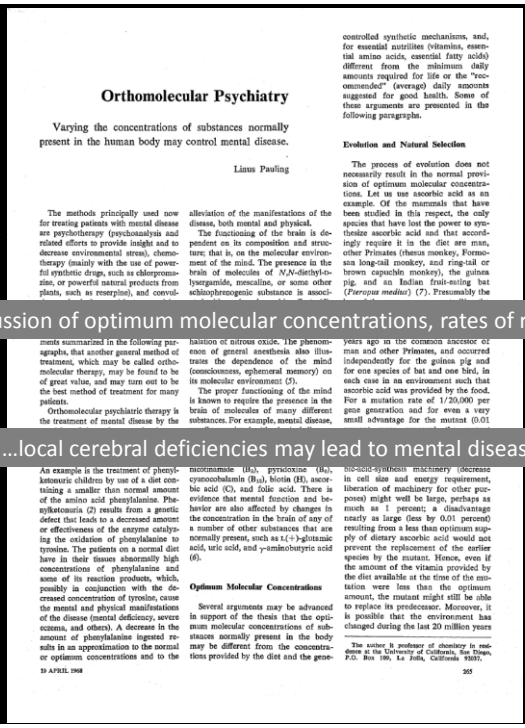
CONCEPT OF GENETOTROPHIC DISEASE

A genetotrophic disease is one which occurs if a diet fails to provide a sufficient supply of one or more nutrients required at high levels because of the characteristic genetic pattern of the individual concerned (R. J. Williams, E. Beerstecher, and L. J. Berry, *Lancet* **I**, 287 (1950)). This concept

Nutrition is for real people; statistical humans are of little interest

RDAs are not useful

The nutrient needs of individuals differ far more substantially from person to person than the RDAs account for



Orthomolecular Psychiatry

Varying the concentrations of substances normally present in the human body may control mental disease.

Linus Pauling

Discussion of optimum molecular concentrations, rates of reactions

…local cerebral deficiencies may lead to mental disease…

Pharmacogenomics and pharmacogenetics represent the study of a large number of genes that influence drug activity, toxicity, and metabolism

Genomics

The human genome contains 30,000 different genes, with a total of 3.12 billion nucleotides

Single nucleotide polymorphisms (SNPs) occur at a frequency about one in every 1250 base pairs

Thus we can expect to see more than three million genetic variations with the potential to influence response to a single substance

Pharmacogenetics

The study of genetic factors that influence an organism's reaction to a drug

Pharmacogenomics

Developing drug therapies to compensate for genetic differences in patients which cause varied responses to a single therapeutic regimen

Why?

The drug level in plasma can vary more than 1000-fold between two individuals of the same weight at the same drug dosage

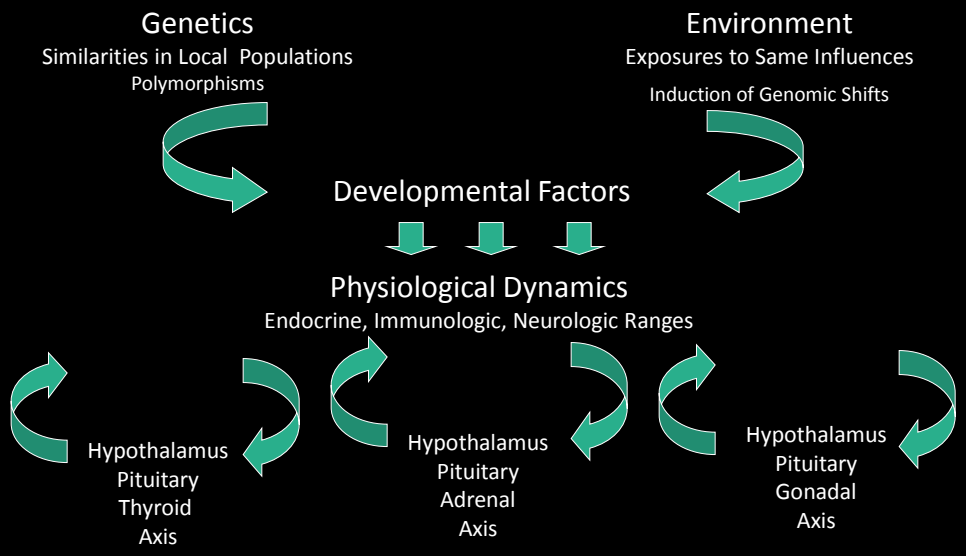
Constitution, An Old Idea

It is “more important to know what sort of patient has a disease than to know what sort of disease a patient has.”

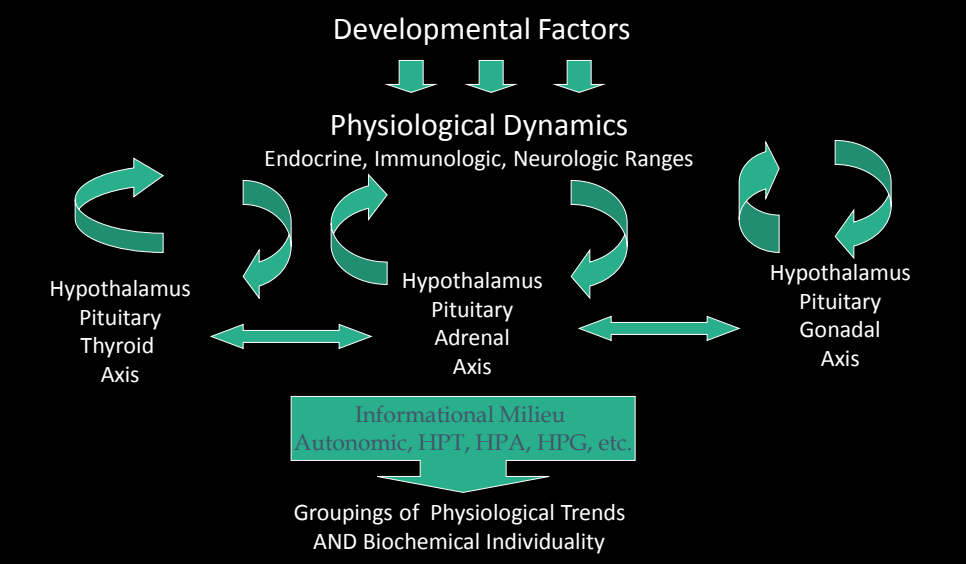
Sir William Osler

Originally Stated by Parry of Bath

Formation of Constitution



Formation of Constitution



Bhalerao et al. BMC Complementary and Alternative Medicine 2013, 13:248
http://www.biomedcentral.com/1472-6882/13/248

BMC Complementary & Alternative Medicine

RESEARCH ARTICLE Open Access

Prakriti (Ayurvedic concept of constitution) and variations in platelet aggregation

Supriya Bhalerao[1], Tejashree Deshpande[1] and Urmila Thatte[2*]

Abstract

Background: Ayurveda, the Indian traditional system of medicine describes a unique concept "*prakriti*" genetically

…in the study population of normal healthy participants, induced maximal platelet aggregation (MPA) was highest among the Vata-pitta types as compared to the other prakriti types and these individuals responded better to lower dose of aspirin compared to other prakriti types.

as compared to the other *prakriti* types and these individuals responded better to lower dose of aspirin compared to other *prakriti* types.

Conclusions: Our results suggest that identifying the *prakriti* may help in individualising therapy or predicting proneness to a disease.

Keywords: Adenosine diphosphate, Aspirin, *Pitta*, *Kapha*, *Vata*

Our results suggest that identifying the prakriti may help in individualizing therapy or predicting proneness to a disease.

concept is claimed to be useful in predicting an individual's susceptibility to a particular disease, prognosis of that illness and selection of therapy [3].

Ayurveda attributes these constitutional characteristics of an individual to the preponderance of certain "*doshas*". Three main *doshas* are described, viz *vata*, *pitta* and *kapha*. *Kapha dosha* is the "anabolic", synthetic *dosha*, responsible for growth and maintenance of structure [4]. The *pitta dosha* is the one responsible for

determined at the time of conception and is influenced by the *mileu interior* of the womb and the dietary habits and lifestyle of the mother [5]. These *prakritis* exhibit attributes of the dominant *Dosha* in physical, physiological and psychological characteristics. The disturbance in equilibrium of these *doshas* can lead to disease according to the *prakriti* of the person for example; a *pitta prakriti* person is described to be more prone to peptic ulcers, hypertension, and skin diseases, a *vata prakriti* person to backache, joint aches and crackling joints while individuals with *kapha prakriti* are prone to obesity, diabetes and atherosclerosis [6-8].

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Original Article

Traditional Medicine to Modern Pharmacogenomics: Ayurveda *Prakriti* Type and CYP2C19 Gene Polymorphism Associated with the Metabolic Variability

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DME) genotyping in 132 unrelated healthy subjects of either sex by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) technique. We observed significant association between *CYP2C19* genotype and major classes of *Prakriti* types. The extensive metabolizer (EM) genotype (**1/*1, *1/*2, *1/*3*) was found to be predominant in *Pitta Prakriti* (91%). Genotype (**1/*3*) specific for EM group was present only in *Pitta Prakriti*.

The extensive metabolizer (EM) genotype (*1/*1, *1/*2, *1/*3) was found to be predominant in Pitta Prakriti (91%). Genotype (*1/*3) specific for EM group was present only in Pitta Prakriti.

Poor metabolizer (PM) genotype (*2/*2, *2/*3, *3/*3) was highest (31%) in Kapha Prakriti when compared with Vata (12%) and Pitta Prakriti (9%).
Genotype (*2/*3) which is typical for a poor metabolizer was significant in Kapha Prakriti.

Introduction

tridosha theory that identifies principles of motion (*Vata*), metabolism (*Pitta*) and structure (*Kapha*) as dis-

These observations are likely to have significant impact on phenotype–genotype correlation, drug discovery, pharmacogenomics and personalized medicine.

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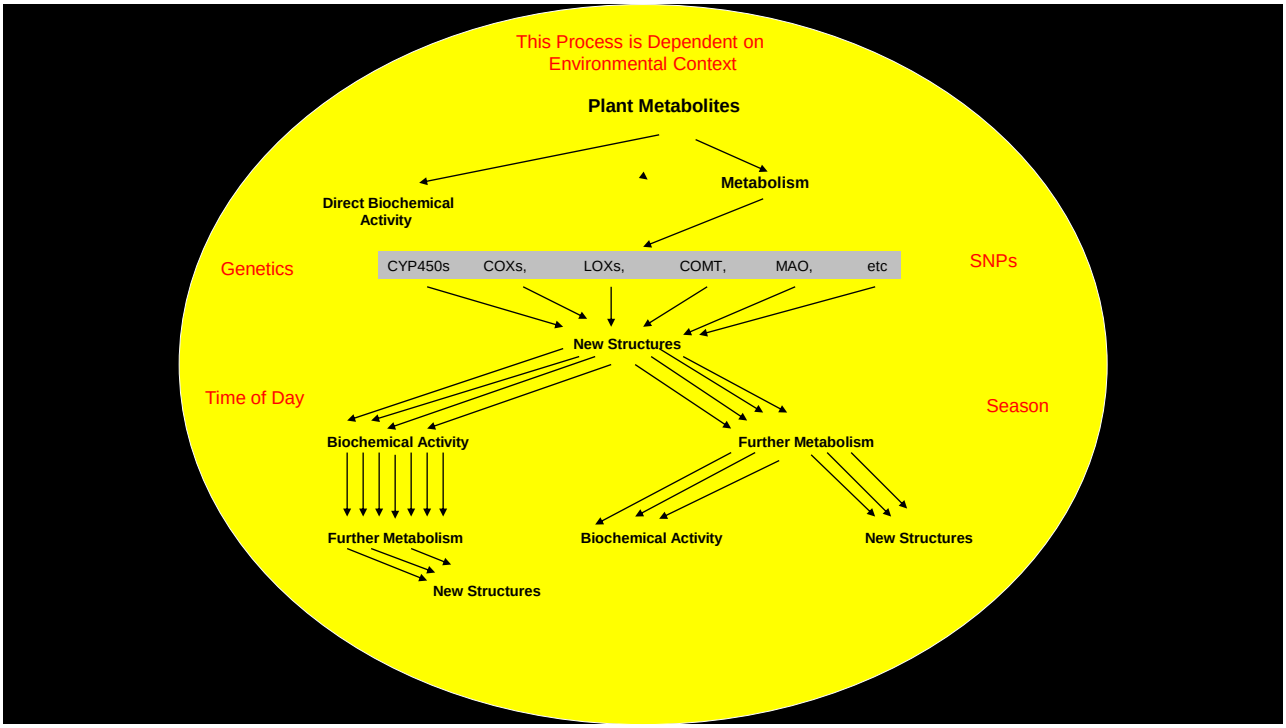
important basic principle rightly described hundreds of years ago as 'every individual is different from another and hence should be considered as a different entity; as many variations are there in the Universe, all are seen in



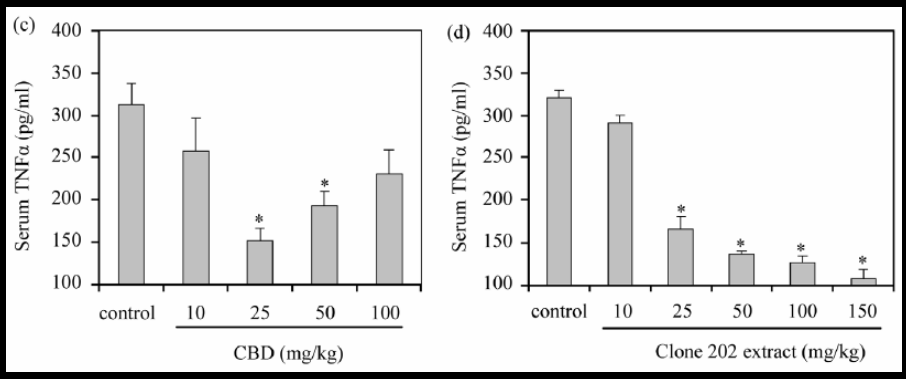
Dosing

An example from Cannabis

A Characterized CBD Extract

Phytocannabinoid	Content
Cannabidiol (CBD)	17.9%
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	1.1%
Cannabichromene (CBC)	1.1%
Cannabigerol (CBG)	0.2%
Cannabinol (CBN)	Traces
Cannabidivarol (CBDV)	Traces

Gallily, R., Zhannah Yekhtin, Z., & Hanuš, L. O. (2015). Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. *Pharmacol Pharm, 6*, 75-85.



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Questions?

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