The Importance of Pharmacological Synergy in Psychoactive Herbal Medicines

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Abstract

The therapeutic effects of many herbal medicines have been well established; however, definitive mechanisms of action remain to be elucidated for many psychoactive herbal medications. Although several mechanisms have been identified, they are often insufficient to account for the observed effects of the plant or its extracts. This review emphasizes that, in addition to searching for more potent mechanisms, one must consider the additive and supra-additive effects of a plant's multiple constituents. Synergy may occur through pharmacokinetic and/or pharmacodynamic interactions. Examples are given that illustrate synergistic actions in St. John's wort (*Hypericum perforatum*), kava kava (*Piper methysticum*), and valerian (*Valeriana officinalis*).

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Introduction

Determining the pharmacological mechanisms of herbal medicines presents certain challenges distinct from the study of synthetic drugs. For example, synthetic drugs are studied in isolation; whereas, herbal medicines often contain multiple active substances that act in combination.

A single drug may have several pharmacological actions, but it is only those that occur in concentrations reached by standard doses that are considered relevant. In many cases, it may be a single action that is believed to account for its effects. For example, caffeine has multiple actions, but only antagonism of adenosine receptors occurs at normally-reached concentrations.[1] Some psychoactive herbal medicines have had several of their chemical constituents identified. Although a plant may contain the appropriate constituents, they may be in insufficient amounts to account for the observed effects. Pharmacological synergy should also be investigated to explain the actions of an herbal medicine. Significant interactions may occur which are not evident when single constituents are studied in isolation. In other cases, a predominant mechanism may be potentiated by lesser mechanisms. Thus, some herbal medications may produce a more favorable response when an extract is given versus an isolated single constituent. However, the advantages of single constituents versus extracts should be considered on a case-by-case basis.

Mechanisms of Synergy

Two broad types of synergy can be distinguished, based on the nature of the interaction: pharmacodynamic or pharmacokinetic. Pharmacodynamic synergy results from two drugs directed at a similar receptor target or physiological system. For example, combinations of allosteric modifiers at the gamma-aminobutyric acidA ($GABA_A$) receptor create potent synergistic interactions.[2-4] Pharmacokinetic synergy results from the processes of drug absorption, distribution, biotransformation, or elimination. For example, combined administration of drugs which compete for albumin binding will elevate the free drug concentrations, and thus potentiate their actions.[5]

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St. John's Wort

St. John's wort (*Hypericum perforatum*) is traditionally known for treatment of depression, insomnia, and anxiety. A large body of animal and human clinical research supports its antidepressant effects.[6-10]

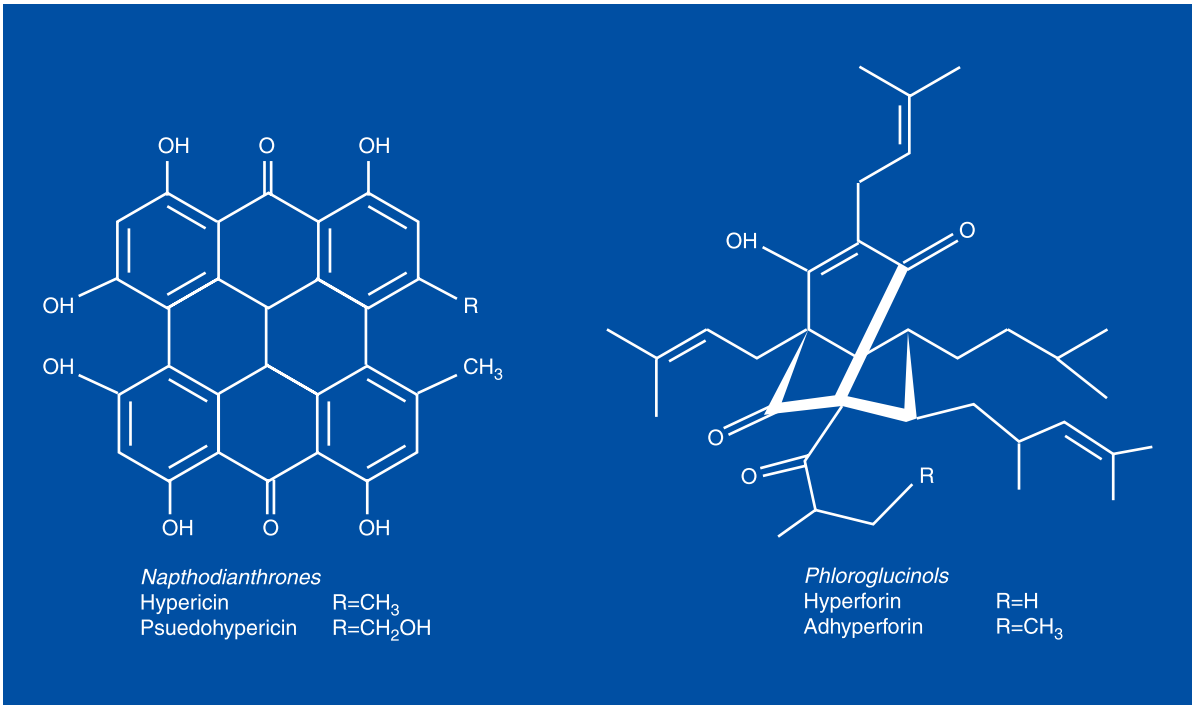
Pharmacodynamic Synergy

Several classes of chemical constituents of St. John's wort have been identified: naphtodianthrones, flavonoids, phloroglucinols, phenolic acids, xanthones, and terpenes (Figure 1).[11,12] The naphtodianthrone hypericin, flavonols, and xanthones have been shown to inhibit both monoamine oxidase (MAO) and/or catechol-o-methyltransferase (COMT).[13-16] While some pharmaceutical antidepressants significantly inhibit MAO, St. John's wort extracts only do so in millimolar concentrations; therefore, this mechanism appears inadequate to explain the full antidepressant effect of the herb.

The phloroglucinol hyperforin is a reuptake inhibitor of serotonin, norepinephrine, and dopamine in the nanomolar range.[17] Radiolabeled hyperforin crosses the blood-brain barrier and penetrates brain tissue.[18] Human and animal studies support hyperforin as an essential and perhaps sufficient element for antidepressant effects of St. John's wort.[6,7,19]

While hyperforin may be sufficient to explain the antidepressant effects of St. John's wort, synergistic effects on monoamines is possible.[20] Combined reuptake and enzyme inhibition can similarly be seen with conventional antidepressants drugs (MAO inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors) to potentiate each other's effects in cases of treatment-resistant depression.[21,22] This must be done with caution, selecting the appropriate drugs and doses, to avoid an overdose and serotonin syndrome. In the case of St. John's wort, however, effects which are individually sub-therapeutic (i.e., MAO and COMT inhibition) may combine to

Figure 1. *Chemical Structures of Hypericin and Hyperforin*

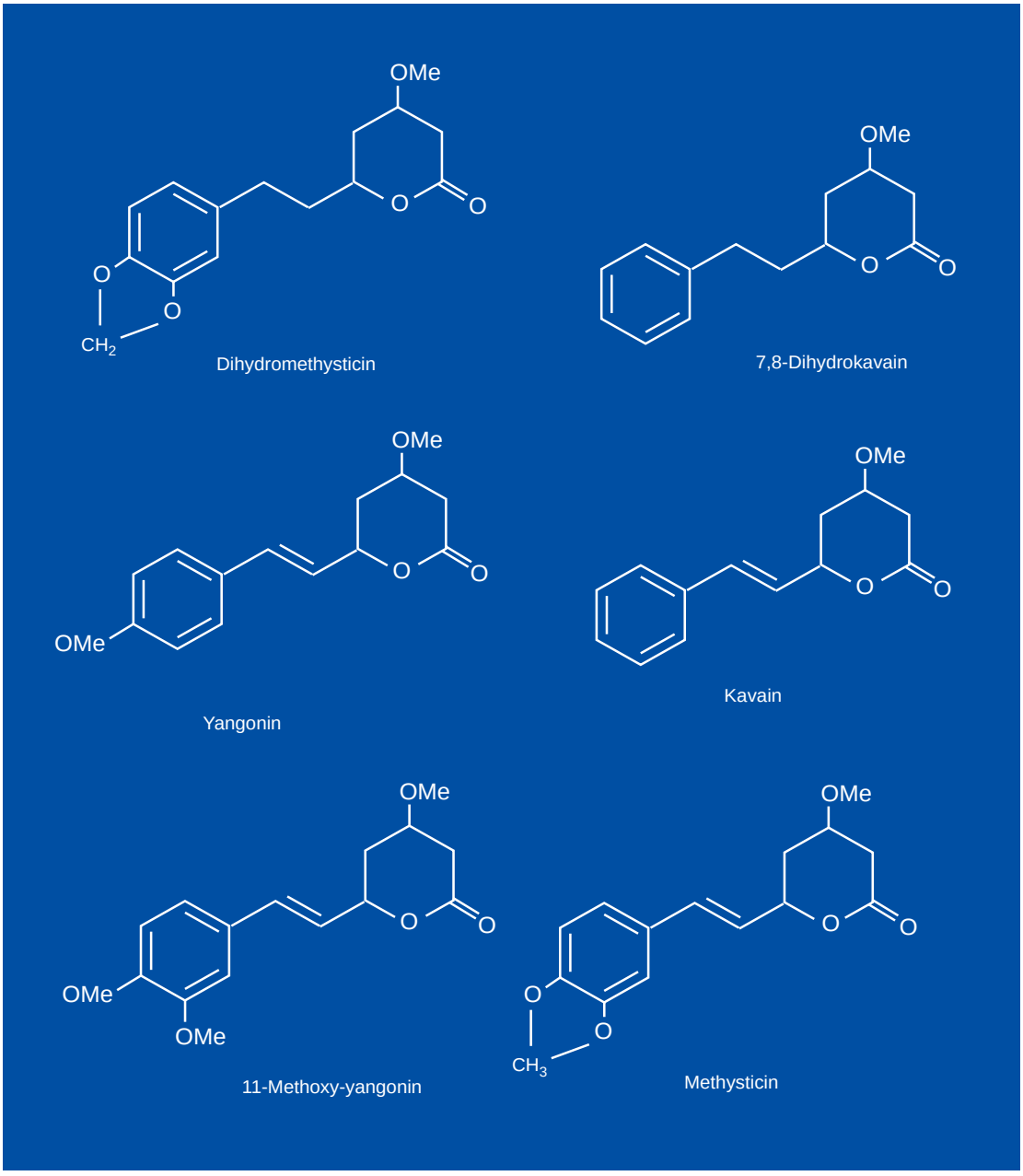


augment the primary pharmacological mechanism (monoamine reuptake inhibition).

Pharmacokinetic Synergy

Pharmacokinetic synergy may also occur with St. John's wort, where a combination of constituents improves its oral bioavailability. An extract containing naphtodianthrones is inactive in a water suspension, but very effective when another constituent, procyanidin, is present. Procyanidin increases the water solubility of naphtodianthrones, thus increasing their pharmacokinetic availability.[8]

Figure 2. *The Major Kava Lactones*



Kava Kava

Kava kava (*Piper methysticum*) is a plant native to the South Pacific islands with anxiolytic and sedative effects.[23] Controlled human clinical studies show it to be superior to placebo for treatment of anxiety, and equivalent in efficacy to the benzodiazepine oxazepam (Serax®).[24,25]

The active chemical constituents from kava are the kava lactones, principally kavain, dihydrokavain, yangonin, dimethoxyyangonin, methysticin, and dihydromethysticin (Figure 2).[23] Kava lactones pass the blood-brain barrier and behavioral effects occur at micromolar concentrations.[25,26]

Kava lactones enhance binding to the $GABA_A$ receptor in the low micromolar range, through a non-benzodiazepine mechanism.[27,28] Kava lactones also block voltage-gated Na^+ and Ca^{2+} channels in micromolar concentrations.[29-31] Further, kava lactones interact with monoamine systems by blocking the reuptake of norepinephrine and inhibiting MAO_B.[32,33]

Pharmacodynamic Synergy

The central nervous system depressant effects of kava lactones occur through actions on $GABA_A$ and Na^+ and Ca^{2+} channels, which occur at normally-reached concentrations. Combined kava lactones, kavain and dihydromethysticin, act in an additive manner to inhibit Ca^{2+} channels.[34] However, combined GABAergic and Na^+/ Ca^{2+} channel inhibition are likely to produce additive or synergistic depressant effects. For example, pharmaceutical Ca^{2+} channel blockers potentiate the sedative effects of benzodiazepines.[35] Ethanol and barbiturates are also noted to potentiate the sedative and cognitive-impairing effects of kava.[28,36,37]

The monoamine actions of kava may also contribute to its therapeutic effects. Monoamine mechanisms are more commonly associated with antidepressants, but they can be effective in treating generalized anxiety.[38,39] Kava lactone actions on norepinephrine reuptake and MAO_B are individually less potent than pharmaceutical antidepressants, but their combination may potentiate each other's effects.

Pharmacokinetic Synergy

Administering combined kava lactones allows for greater access to the brain than when they are given individually.[26] For example, yangonin given with other kava lactones (administered i.p.) reaches levels 20 times higher in the brain than when it is given alone. Similarly, kavain levels in the brain are doubled when given in combination with other kava lactones, compared to levels reached when given alone. The reason for this pharmacokinetic synergy is not certain. One possibility is that kava lactones are competing for plasma binding sites. Thus, giving them in combination occupies more plasma binding sites, allowing for greater free plasma concentrations of the remaining kava lactones. With higher plasma concentrations, there is greater access to the brain. Another possible reason for this pharmacokinetic synergy is that administering combined kava lactones improves intestinal absorption. While yangonin and desmethoxyyangonin are ineffective orally when given alone, they increase the potency of a combination of kava lactones.[40]

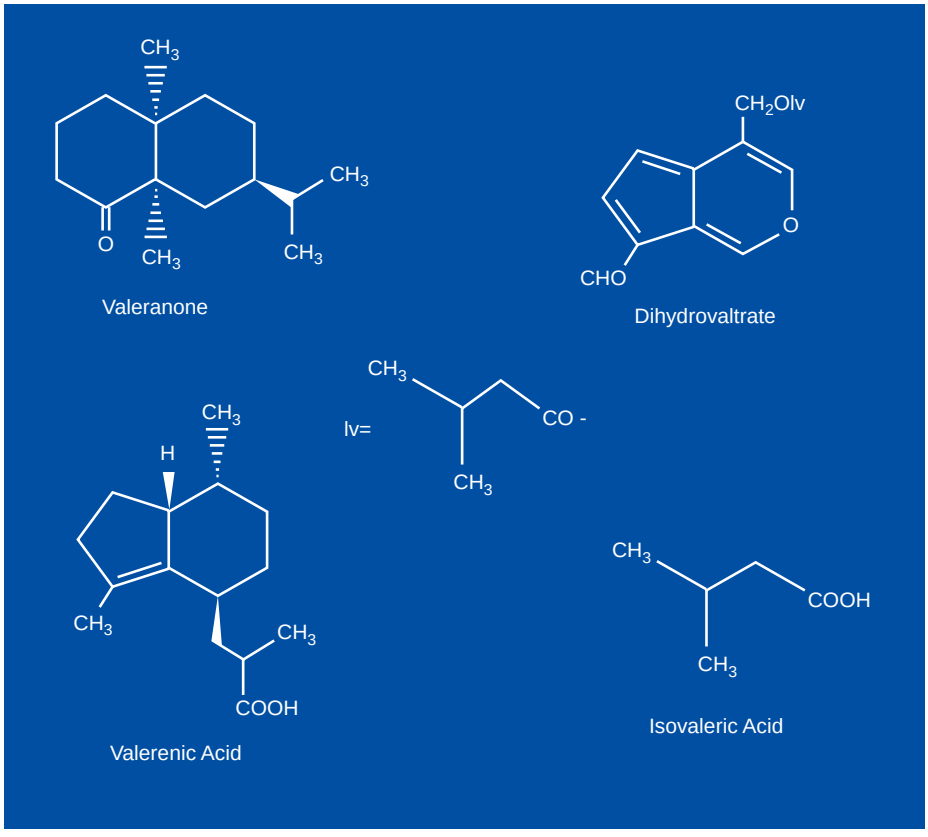
Valerian

Valerian (*Valeriana officinalis*) has a traditional reputation for treating anxiety, insomnia, and seizures.[41,42] Animal studies of valerian support it as a central nervous system depressant.[43-47] Studies in humans demonstrate that valerian extracts increase slow wave sleep, improve sleep quality, and decrease sleep latency.[48-52] Valerian's main chemical constituents are categorized as monoterpenes and sesquiterpenes (Figure 3).[43]

Pharmacodynamic Synergy

Several GABAergic mechanisms of action have been proposed for valerian. There is some debate whether oral valerian reverses uptake of GABA. In support of this, low microgram concentrations of an aqueous valerian extract inhibit uptake and stimulate release of GABA from synaptosomes.[53,54] This effect is Na^+-dependent and Ca^{2+}-independent, suggesting it is due to reversal of the neuronal GABA transporter. Some researchers report GABA is present in valerian, which

Figure 3. *Some Constituents of Valerian*



could account for these results.[55] If so, this does not explain the effects of oral valerian, since GABA does not readily cross the blood-brain barrier. However, other researchers have failed to find GABA in valerian preparations, so reversal of reuptake may still be considered a possible mechanism of valerian's sedative effects.[56]

There is additional evidence for other GABAergic effects of valerian. For example, valerenic acid inhibits enzymatic breakdown of GABA, and low concentrations of valerian extracts enhance benzodiazepine binding at the $GABA_A$ receptor ([^{3}H]flunitrazepam).[43,56,57] Ortiz and colleagues found there are at least two constituents of valerian acting at the $GABA_A$ receptor.[56] Valerian extracts also potentiate the behavioral actions of barbiturates.[47] It is not clear which of these GABA mechanisms account for valerian's effects, but additive or synergistic interactions are likely, especially since they all affect GABAergic transmission.

Conclusions

There are multiple examples of pharmacodynamic and pharmacokinetic synergy at work in psychoactive herbal medicines (Table 1). St. John's wort shows evidence of pharmacodynamic synergy through monoamine neurotransmitter systems, preventing neurotransmitter breakdown, and blocking reuptake. Pharmacokinetic synergy is evident in St. John's wort since procyanidin increases the bioavailability of the naphtodianthrones. Kava kava's effects on GABA and voltage-gated ion channels (and possible monoamine systems) create pharmacodynamic synergy. Kava kava also shows evidence of pharmacokinetic synergy since administration of combined kava lactones increases brain bioavailability of each, compared to individual administration. Valerian shows evidence of pharmacodynamic synergy since multiple constituents of the herb are acting on GABAergic systems, both pre- and post-synaptically. Pharmacokinetic synergy in valerian is possible, but has not yet been investigated.

The above examples of synergy are directly relevant to the therapeutic benefits of these herbal medicines. The synergistic effects of St. John's wort likely enhance its effects on monoamine neurotransmitter systems, the predominant mechanism of most antidepressant drugs. The synergistic interactions of kava kava occur through GABA, voltage-gated ion channel, and monoamine systems. All of these mechanisms help account for kava kava's demonstrated anti-anxiety effects. Finally, the synergistic effects of valerian's constituents on GABA transmission would explain its demonstrated effects on sleep.

Table 1. *Summary of Synergistic Mechanisms*

	Pharmacodynamic Synergy	Pharmacokinetic Synergy
St. John's Wort	Monoamine reuptake inhibition; MAO inhibition; COMT inhibition	Procyanidin increases bioavailability of hypericin
Kava kava	GABAA facilitation; Na+ and Ca2+channel inhibition; MAO inhibition; Reuptake inhibition of NE	Kavalactones increase each other's bioavailability
Valerian	Multiple GABA mechanisms	Not yet investigated

The above examples illustrate that synergistic mechanisms should at least be considered when searching for the mechanisms of action of a psychoactive herbal medication. In any given case, a sole mechanism may be in effect, or there may be complex interactions among active constituents. Since the effects of interest are often obtained by using the whole herb or extract, it is important to understand the effects of active constituents in combination as well as in isolation. Since herbal medicines are most commonly used as a whole-herb or extract, these are the preparations we should seek to explain.

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