

## PHYTOTHERAPY AND THE NEW PARADIGM OF DRUGS MODE OF ACTION.

### RESUMEN

La farmacología ha sido refractaria a las contribuciones del etnofarmacología en términos de paradigmas para el uso de las drogas o el modo de acción. Los patrones complejos encontrados a menudo en evaluaciones de los extractos de plantas medicinales, sugieren que los efectos de las drogas vegetales se pueden fundamentar a menudo en bases farmacodinámicas más complejas que las relaciones droga/ efecto más usuales. Las características farmacológicas de las hierbas pueden resultar de varios ingredientes activos, de las interacciones entre éstos, o de ingredientes que poseen múltiples mecanismos de acción. Este artículo se centra en la psicofarmacología de las hierbas a la luz de nuevos paradigmas de la acción drogas psicotrópicas. Se sugiere que la comprensión de conceptos y de prácticas médicos tradicionales puede conducir al desarrollo innovador de las drogas.

**PALABRAS CLAVES:** etnofarmacología, plantas medicinales, modo de acción de drogas

### ABSTRACT

*Pharmacology has been refractory to the contributions of ethnopharmacology in terms of paradigms for drugs use or mode of action. The complex patterns often found in evaluations of medicinal plant extracts suggest that the effects of plant drugs may often be based on a more complex pharmacodynamic basis than the more usual drug/effect relationships. Pharmacological properties of herbals may result from various active ingredients, interactions among those, or ingredients possessing multiple mechanisms of action. This paper focuses on the psychopharmacology of herbals in the light of newer paradigms of psychotropic drug action. It is suggested that understanding of traditional medical concepts and practices can lead to innovative drug development.*

**KEYWORDS:** ethnopharmacology, medicinal plants, drugs mode of action

### 1. INTRODUCTION

Traditional (indigenous) and modern (western biomedical) medical systems evolved from diverse definitions of reality, are related to different and cosmovisions, and are therefore based on different paradigms. In spite of these gaps peoples worldwide establish dialogues and make use of different systems to maintain or re-establish health (1-4). Interestingly, most traditional systems share the practice of utilizing raw material from nature processed into drugs or food, or more recently food supplements, for therapeutic purposes.

Within the context of drug development, interest in traditional medical systems is mostly focused on the use of plants processed as traditional medicines. The underlying understanding is that at least some of the plant species that constitute the basis of such preparations may contain therapeutically useful compounds, to be further developed into western type drugs (5). Nonetheless, the fact that traditional medical systems are organized as cultural systems (6-7), allows for profound differences in

meanings of health, disease, and disease etiologies (8-9). Accordingly, such differences result in a variety of therapeutic practices not easily accommodated in the bio-mechanical paradigm of modern medicine.

The purpose of this paper is to review some prevailing features of traditional medicines in the context of the current understanding of mechanisms of action of psychoactive drugs. Comparisons of folk and contemporary healing concepts have been thoroughly explored by social scientists and medical anthropologists, in the light of ethnomedicine and of ethnopharmacology (9), and are beyond the purpose of this paper. The scope of this discussion is limited to some of the features of traditional medicines that are of relevance for understanding the way traditional medical practices, including plant medicines, affect brain functions. Concepts such as diet, prevention, low dose/long term posologies, and complex mixtures, often central to traditional medical treatments, will be discussed in this context.

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## 2. DIET

Within the classical humoral systems (prevailing in Asian countries and several Central and South American ethnic groups), good health is perceived as a balance between physical elements and the body humors (10). Foods and disease conditions are assigned temperature and moisture qualities or attributes; accordingly, hot illnesses are treated by consuming cold foods, and a wet disease is treated by dry foods.

In line with the western-like context of drug/body interaction, there is the commonly found concept of foods as containing substances that interact with body functions. Observing a special diet, preventing or increasing consumption of certain food-medicines, is frequently requested or recommended in association with other therapeutic measures in various societies (11).

In the context of CNS, persisting deficits in nutrition can lead to neurologic diseases; conversely, in several genetically determined neurologic diseases, treatments include either elimination of certain foods or supplementation with specific vitamins (12). It has been shown that alterations in tryptophan consumption significantly alters mood and behavior in selected groups of individuals (13), and that phenolic antioxidants, such as those found in wine, have a protective effect against atherosclerosis (14).

The increasing attention and comprehensive analysis of data relevant to the effects of ingestion of chemicals from plants in the maintenance/improvement of body functions and/or disease prevention (15-17) may reveal data to further substantiate specific interactions between dietary restrictions (or impositions) and functionality of given organs or tissues. Perhaps the growing market and quick acceptance of nutraceuticals may be associated to a return to earlier forms of behavior, when various societies did not make evident distinctions between food and medicine (11).

## 3. PREVENTION

The concept of well-being varies among peoples. Besides the ingestion of curative or preventive foods, some types of remedies are used chronically "because it is good for health", to prevent the appearance of certain diseases, and/or easy to slow the process of aging. For the Matsigenka Indians (Perú), well-being embraces physical and psychological health, successful gardening and hunting, and harmonious social interaction. Accordingly, Matsigenka medicine includes treatments for various culture-specific emotional and psychological syndromes, with plant species that apparently may be psychoactive (18).

In Latin America the use of "tonics" or "nerve tonics" are widespread, especially by the elders, by patients recovering from CNS illnesses, and as a "general stimulant" to cope with high physical or psychological stress situations. The pharmacological meaning of such tonics has yet to be elucidated (19).

In this context, it is illustrative to the rekindled interest in adaptogens, a term coined in 1947 by the Russian scientist Lazarev, designating agents which allow organisms to counteract stressors, helping the organism to be "adapted" to intense demands (20-21). Relevant to this discussion is that the mode(s) of action of adaptogens have been associated with a variety of cellular and molecular mechanisms, including increased synthesis of proteins or nucleic acids, increased formation of glucose-6-phosphate, catecholaminergic synaptic modulation, antioxidant activity, immunostimulation, the prostaglandins, or even genetic expression (22).

We suggest that thorough scientific studies of non-western category of drug action may reveal not only new prototypic drugs, but extremely useful new drugs and strategies to beneficially interfere with, minimize or prevent multifactorial illnesses and age associated decline.

## 4. LOW DOSE, LONG TERM

As in western medication, posology (dose and regimen) is usually well defined by medicinal plant specialists (23). Traditional formulations of medicinal plants processed for therapeutic purposes (such as teas, syrups, concoctions, beverages, etc) are expected to be ingested over a given period of time, varying with the expected length of the condition to be treated, and the time required for the remedy to attain its curative goal. Often, remedies are recommended for a considerable length of time (weeks or months), or even maintained for several years; sometimes it is expected that it actually takes weeks or months for the efficacy of the treatment (either cure or significant amelioration) to become apparent. Such long term treatments are usually associated with diseases that are chronic and incurable, where the treatment aims to keep a given disorder under control (such as asthma, epilepsy, diabetes), or minimize diseases or processes (such as aging) over the course of several years. Considering the yield of active constituents usually obtained from the amount of plant material, and mode of preparation used to prepare home made remedies (24), it is arguable that more often than not, traditional therapies involve the repeated ingestion of low doses of active substance(s) over a significant period of time.

In pharmacodynamic terms it is expected that this pattern of intervention with molecular targets may be profoundly different than an acute (single administration) or sub-chronic (few administrations) challenge to any given

molecular target. Nevertheless, the traditional posology is rarely taken into consideration in evaluating medicinal plant extracts or substances in new drug screening/development programs. Failure in shaping the traditional uses associated with efficacy claims are in part related to practical matters: the research design needed to match the effects of such repeated interaction with tissues and/or molecular targets, requires greater quantities of testing materials and poses several other obstacles that are difficult to manage. In fact, several *in vitro* methodologies are, unfortunately, inadequate for these purposes (25). Nevertheless, the consequences of constant and repeated challenges to molecular targets have to be taken into consideration at least in interpreting results, especially when effects are to be integrated with those evaluated through the use of *in vivo* models.

Specifically referring to the CNS, attention has been called to the fact that “it is the adaptive response of the nervous system to adequate repeated perturbations mediated through these initial targets that produces the therapeutic responses” (26). The authors suggest that chronic perturbations can lead to different types of adaptations (quantitatively and qualitatively), eventually resulting in a new functional state. Traditional remedies, more often than not, consisting of long term treatments with low to moderate doses of active ingredients (as those found in traditional preparations) are in line with the current paradigm of psychoactive drug action.

## 5. COMPLEX MIXTURES

In discussing the basis for the effectiveness of Kampō medicines, Ishihara (27) calls particular attention to the pharmacological antagonism and synergism found among the chemical components of the crude extracts that form Kampō infusions. Such drug interactions have been further substantiated in Kampō formulations (28). Complex chemical mixtures have the potential to generate interactions, pharmacokinetic benefits, pharmacodynamic synergisms or antagonisms, and/or combinatorial responses, and the proportion of different components in the mixture may determine efficacy and safety. Examples have proved that in fact, effects of plant based remedies may be due to one active compound with a single mechanism of action, to compound(s) that possess multiple mechanisms of action (eg., Huperzine A, to the combined activity of more than one active ingredient in a single species (eg., flavonol glycosides, phenolic compounds, bilobalide, ginkgolides in *Ginkgo biloba*), or the synergic interactions of different active ingredients from several plant species processed as a medicinal formula (eg, harmane alkaloids and d-MT-tryptamine in the ayahuasca drink).

It has been repeatedly demonstrated that a combination of at least 4 substances are responsible for the polyvalent pharmacological action and therapeutic properties of the

*Ginkgo biloba* extract Egb761, whose beneficial effects result from “the combination of its various protective, curative and modulating properties against the pathological process” (29). In other hand, a single alkaloid such as Huperzine A can have a diversity of complementary pharmacological properties, such as anticholinesterase activity and inhibition of different phases of the apoptotic process (30) that are complementary in counteracting the diseases processes found in Alzheimer disease.

The following are examples of ethnopharmacological investigations of medicinal plants with alleged psychopharmacological effects are useful to illustrate how these issues are of relevance in the context of CNS diseases and psychopharmacology.

### 5.1 Analgesia from *Psychotria* alkaloids

In the Brazilian Amazon “Perpétua do Mato”, *Psychotria colorata* (Willd R & S) Muell. Arg, is used to treat earache (a handful of cut up fresh flowers in packed in banana leaves, and left over warm ashes; the warmed flowers are mixed with milk, preferably “mother’s milk”, filtered through a piece of cloth and drops are topically applied to the ear). Abdominal pain can also be treated wit remedies based on this species (roots and fruits are mixed with water and left to boil; the decoction is taken orally) (31). We reported that alkaloids present in the leaves and flowers of *P. colorata* have marked analgesic activity, as evaluated through various pain models (31-33). Phytochemical analyses of *P. colorata* flowers identified pyrrolidinoindoline alkaloids (Figure 1) as major components, including hodgkinsine, psychotridine, chimonanthine (34-35).

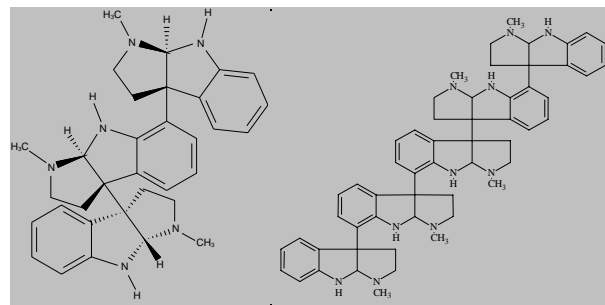


Figure1. Hodgkinsine and psychotridine isolated from *Psychotria colorata* (Willd R & S) Muell. Arg.

Pharmacological analyses revealed that hodgkinsine produces a dose-dependent naloxone reversible analgesic effect in thermal models of nociception, and acts as a potent dose-dependent analgesic in the capsaicin-induced pain (36); *in vivo* data complemented by binding studies demonstrate that the activation of opioid and blockade of glutamate NMDA receptors participate in the hodgkinsine mode of action. The analgesic properties of psychotridine

turned out to be associated with the modulation of NMDA receptors (37).

Because some NMDA mediated painful events can be difficult to control with opioids alone (e.g., neuropathic pain states), it has been argued (38-39) that a combination of opioid and NMDA antagonism may be especially advantageous in specific clinical conditions. Interestingly enough, the combined (opioid and glutamatergic) mechanism of action of hodgekinsine alone or the alkaloid mixture in the traditional preparation, is in line with current strategies for managing severe pain states that respond poorly to conventional analgesics.

## 5.2 Linalool from *Aeollanthus suaveolens*

Other commonly used complex mixtures of compounds extensively used in traditional medicines are the essential oils. The anticonvulsant profile of linalool is an example.

Because epilepsy is an universal and ancient disease, it is reasonable to regard traditional treatments for epilepsy/seizures as potential sources of new anticonvulsant agents. In fact, dozens of species are reported to be used as antiepileptic home remedies, many of which have shown activity in preliminary evaluation (40). In the search for anticonvulsant plant derived compounds, ethnopharmacological surveys were conducted within Amazonian traditional communities. A widespread recipe that includes *Cissus sicyoides* (Vitaceae), *Aeollanthus suaveolens* (Lamiaceae), *Ruta graveolens* (Rutaceae) and *Sesamun indicum* (Pedaliaceae) was identified. Following the ethnopharmacological methodology, pharmacologically monitored chemical investigation lead to the identification of linalool as the major active ingredient.

*A. suaveolens* is one of the best known medicinal species in the Amazon, recognized as medicinal by 93% of the women interviewed in extractive reserves in the State of Acre (41). Because *A. suaveolens* is heavily aromatic, its essential oil was obtained, evaluated and proved active (42). The main components identified in the essential oil were E- $\beta$ -farnesen (37.75%),  $\delta$ -decen-2-lactone (20.6-44.3%), linalyl acetate (11.32%), linalool (10.49%) and  $\delta$ -decanolactone (0.37-3.02%) (Figure 2).

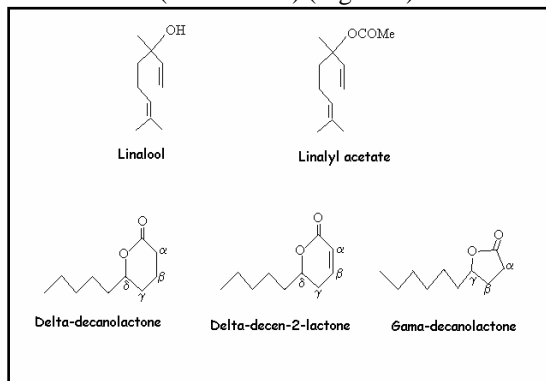


Figure 2. Main compounds of essential oils from *Aeollanthus suaveolens*

Although the study of E- $\beta$ -farnesen is still limited, we found that linalyl acetate (43),  $\delta$ -decen-2-lactone and  $\delta$ -decanolactone (44) were devoid of activity; linalool and  $\gamma$ -decanolactone (structurally related to  $\delta$ -decanolactone) proved to be active in several animal models (43-44). Moreover, it was found that linalool possesses an interesting mechanism of action, modulating the glutamatergic and gabaergic neurotransmission (45-46).

Interfering with multiple mechanisms that underlie seizures may be necessary to effectively counteract epileptic phenomena (47-48). Therefore, the fact the anticonvulsant profile of linalool deserves further investigation as a potentially novel strategy for developing new antiepileptic drugs.

## 6. CONCLUSIONS AND RECOMMENDATIONS

Determination, rather than causality, is the current extended interpretation of cause-effect relationships in physics, "cause" being substituted by "determining conditions", where all the conditions of a process or state are equally important. It has been suggested that some (if not all) diseases should be understood as processes, where an interplay of multiple factors (genetics, environmental exposures, psychic conditions, etc) have to be considered (49). In this context it becomes attractive to study complex plant extract that eventually can modulate more than one target simultaneously. Pharmacologists and phytochemists need to be open-minded and unprejudiced in order to understand traditional medical systems as such in order to truly profit from studying traditional medical systems rather than plant molecules. We suggest that a thorough understanding of traditional medical concepts of health and disease in general and traditional medical practices in particular, can lead to true innovation in paradigms of drug action and development.

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