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Ethnobotany as a pharmacological research tool and recent developments in CNS-active natural products from ethnobotanical sources

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ABSTRACT

The science of ethnobotany is reviewed in light of its multi-disciplinary contributions to natural product research for the development of pharmaceuticals and pharmacological tools. Some of the issues reviewed involve ethical and cultural perspectives of healthcare and medicinal plants. While these are not usually part of the discussion of pharmacology, cultural concerns potentially provide both challenges and insight for field and laboratory researchers. Plant evolutionary issues are also considered as they relate to development of plant chemistry and accessing this through ethnobotanical methods. The discussion includes presentation of a range of CNS-active medicinal plants that have been recently examined in the field, laboratory and/or clinic. Each of these plants is used to illustrate one or more aspects about the valuable roles of ethnobotany in pharmacological research. We conclude with consideration of mutually beneficial future collaborations between field ethnobotanists and pharmacologists.

Contents

1. Introduction

We have two objectives for this review of plant-derived CNS compounds. First we examine the rationale, benefits, and challenges of an ethnobotanical approach to pharmacological research. Second, we discuss a range of CNS-active medicinal plants that have been recently examined in the field, laboratory or clinic following ethnobotanical leads. Our hope is that readers of this review will develop an appreciation for the importance of ethnobotany, "the science of survival" (Prance et al., 2007).

1.1. Ethnobotany and natural product research

Ethnobotany, the largest subdiscipline of ethnobiology, is generally defined as the "science of people's interaction with plants" (Turner, 1995). This circumscription includes the study of plants that have therapeutic applications. While the primary objectives of modern ethnobotany are neither to develop new pharmaceuticals, nor to discover new bioactive chemical moieties, elucidating the pharmacological activities of a particular plant is part of some ethnobotanists' research.

Although there are many mutual benefits of joint effort between ethnobotanists and pharmacologists, there are also challenges to overcome in order to foster successful partnerships. The difference in worldview underlying research objectives of both fields is complex. While bioprospecting (exploring biodiversity for new sources of natural products) is still the objective of some pharmacologists, the field of ethnobotany is generally more concerned about the cultural

Abbreviations: CNS, central nervous system; ICV, intracerebroventricular; SJW, St. John's wort.

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meaning of the relationship between humans and plants than in mining for plant pharmaceuticals and information about plants. While bioprospecting did guide ethnobotanical research in the past, today the goals of ethnobotany have shifted toward understanding the human study population and exploring the meaning behind the relationship among peoples and plants in a full spectrum of cultures. Providing benefit to human study populations and often their associated ecosystems has become a primary objective, largely changing the types of hypotheses being explored in modern versus colonial era-style ethnobotanical research (Salick et al., 2003; Cunningham, 2008). International legal frameworks have also been developed to safeguard the intellectual property of cultures and individuals with specialist knowledge about plant uses, as well as biological material native to a political region (Convention on Biological Diversity, 1992; Salick et al., 2003). These challenges to cultural prospecting and bioprospecting are issues of which both field ethnobotanists and pharmacologists must be aware. Ignorance does not safeguard bioprospecting researchers, as those attempting to patent turmeric (*Curcuma longa* L.), Basmati rice (*Oryza sativa* L.), and neem (*Azadirachta indica* A. Juss), and conduct genetic modification research on Hawaiian taro (*Colocasia esculenta* (L.) Schott) have learned (Kumar, 1997; Mashelkar et al., 2001; U.S. Patents for taro PP12,342, PP12,361 and PP12,772). Thus, specific training of ethnobotanists in these arenas is necessary and can greatly benefit pharmacological researchers with whom they collaborate. Because ethnobotany stands at a crossroad between social and biological sciences, ethnobotanists have both the opportunity and the responsibility to address a number of ethical and social issues that scientists working as only social or biological researchers may not always experience.

Specifically, ethnobotanical researchers and their collaborators need to consider the following issues:

- The positive and negative effects of medicinal plant research, plant collection, and other activities on local communities;
- Effects of increased use of medicinal plants on wild plant populations and possible conservation concerns for protection of biological diversity;
- Effects of exploitation of cultures and changing economic structures caused by those who use researchers' publications for other purposes such as ecotourism or economic development.

They must also actively encourage:

- Recognition of intellectual property rights and contributions made by local or indigenous communities and individuals who share specialist knowledge;
- Equitable distribution of benefits obtained from the use of resources, including genetic material or chemical structures;
- Assistance to local communities and the conservation of biodiversity in their environments;
- Technology transfer, infrastructure development, capacity building, community-based education programs, policy dialogue, and local organizations to better enable the development of crop varieties and natural products for the benefit of local and indigenous communities (Salick et al., 2003).

Another difference in perspective between many pharmacologists and ethnobotanists involves the concepts of disease and healing. While most pharmacologists consider only one model of health, the biomedical approach, ethnobotanists examining health care systems and medicinal plants work within both a medical anthropological (Hahn, 1995) and an ethnopharmacological (Etkin, 1993; Cox, 1994) research framework. The underlying research philosophies about culture are usually viewed from an evolutionary perspective (Alland, 1970; Rappaport, 1967; Harris, 1979), but are sometimes from either cultural (Sahlins, 1976) or economic (Morsy, 1990) perspectives. Most ethnobotanists, though not explicitly, take what may be called a utilitarian approach: How do cultures use plants to meet their needs? Irrespective of the philosophical approach, anthropologists and ethnobotanists typically differentiate disease and illness (Browner et al., 1988). Disease is a pathophysiological abnormality of the structure or function of the body. It is defined without respect to the patient. Illness, in contrast, is patient defined and is often culturally bound. While similar symptoms may characterize a particular case, the patient-centered illness concept may invoke far different etiologies and treatments. There is no biological assay that can test the efficacy of a medicinal plant against "susto" or "alligator sickness." These illnesses can only be evaluated within their cultural contexts. Modern medicine is slowly beginning to see the value of the illness-based approach in treating patients (e.g., Eisenberg, 1977; Green et al., 2002). Evaluating "efficacy" is therefore complex and requires a keen understanding of culture in order to distinguish between the many different human theories of "why" people become ill (Murdock, 1980) and diseases.

This is directly relevant to pharmacological laboratory research because it is important to consider how and why plants are selected by people for use as medicine. Because people may include plants and other organic material in remedies for reasons other than biochemical activity, merely reading lists of plants with their documented uses is not a sufficient way to select plants and form good hypotheses for ethnopharmacological research. Rather it is important to work closely with people who use plants and to understand the cultural context of the plant use. Ethnobotanists rely on often subtle evidence to determine likely hypotheses for some medicinal plant activities. Clues to bioactivity include prohibitions during treatment, side effects, adjuvant therapies, and over dosage which are known by competent healers. These clues, for example, can help identify toxidromes (in this case limited to toxic over dosage syndromes, e.g., opioid, anticholinergic, sympathomimetic), which can guide the laboratory pharmacologist into likely areas of analysis of pharmacological activity. These are particularly germane for identification of potential CNS-active plants.

While some plants are discussed in culture as "affecting the head" or "the mind" or functioning as hallucinogens or entheogens, other types of uses that have CNS potential may be less clear. For instance, analgesics and stimulants can act peripherally as well as centrally. There are also many plants that are used medicinally that may not have a pharmacological basis for their inclusion in a mixture. For example, a plant may be included for treatment of headache because the headache is caused by listening to one's mother-in-law and the particular plant (*Sansevieria trifasciata* Prain) is a symbol of a mother-in-law's tongue that needs to be silenced in the head. The plant may have a perfectly good cultural basis for inclusion in the remedy but that does not strictly imply that there will be a pharmacological basis for its inclusion.

Plant remedies, as with pharmaceuticals, may be used for general or specific indications. This may be the result of the active pharmacophores having general or specific mechanisms of action or more specifically, acting at early stages in event cascades versus late stages. For example, inhibition of cyclooxygenase by salicylic acid (found in many plants) affects many systems. Because of its general anti-inflammatory activity, it can be used to treat many types of inflammation, and also can affect other apparatus since it is widely used to enhance the bloodstream and prevent heart attacks. Colchicine (from autumn crocus, *Colchicum autumnale* L.) acts specifically as an anti-mitotic agent, binding tubulin. It, thereby, interferes with the function of mitotic spindles and thus causes depolymerization and lack of motility in granulocytes and other motile cells active in propagation of inflammatory processes such as gout. Although both drugs are useful in treatment of inflammation, colchicine has specific activity, while salicylic acid is more general in its effects. There are also many mechanisms of CNS activity which have not yet been elucidated and for which ethnobotanical research may provide insight.

Although ethnobotanists often collect data on the full range of cultural uses of medicinal plants, no single lab has the capacity to test all of the possible hypotheses regarding the use of a single species. Moreover, assays are not available to test all types of activity. Rather, plants are selected that are active within the range of assays already functioning within the laboratory partner's facilities. This is clearly the primary limiting factor in the ability of ethnobotanists to make new contributions. There is a very large backlog of plants with interesting traditions of cultural use, however, very few have received phytochemical tests of the general or specific medical hypotheses proposed by the cultures that have used them. These untested plants are not included in this review because they lack pharmacological analysis.

2. Reviews of central nervous system natural products from ethnobotanical and other sources

It is highly unusual for an ethnobotanical study to focus specifically on CNS activity of plants. Rodrigues and Carlini (2004) is a rare exception. Their study includes many features of a good ethnopharmacological project which include the following features:

- The work was conducted by a multi-disciplinary group including researchers applying techniques of anthropology and botany with literature evaluations (and presumably follow-up laboratory research) by pharmacologists.
- Scientific and community resident written ethics permission, including institutional review board (IRB) approval and intellectual property rights, were recognized and acknowledged in advance of the work.
- Access to information learned has been carefully managed with limitations placed on what is published and what is kept in confidence while research proceeds. (Note that this is similar to arrangements between many corporations and academic researchers.)
- Interpretation of the results is limited by differences between cultural disease categories in the culture of the researchers (pharmacology) and the cultural system being examined.

Rodrigues and Carlini (2004) worked in western Brazil within a small community of 300 people. Healers from the community shared with them information about 48 plants with therapeutic indications relating to the CNS of which 15 were cited exclusively for CNS uses (Table 1). This study demonstrates a fruitful collaboration between field ethnobotanists and pharmacological laboratory researchers in their attempts to develop logical laboratory hypotheses. As with other similar types of studies, however, generation of pharmacological hypotheses for laboratory testing that are homologous to cultural medicinal use hypotheses is difficult, because of cultural variation in disease circumscriptions. This can result in the generation of heterogeneous hypotheses due to differing theories of illness (Murdock, 1980). This is an area which should be improved upon for more valuable ethnopharmacological collaborations.

Table 1
Therapeutic indications from interviews with healers of the Sesmaria Mata-Cavalos and possible homologous indication in biomedicine from Rodrigues and Carlini (2004).

Therapeutic indication from interviews	Possible homologous indication in biomedicine
To fortify the brain	Adaptogen
For insomnia	Hypnotic
As a depurative	Blood thinner
For weight loss	Anoretic or thermogenic
As a sedative	Anxiolytic
For rejuvenation	Adaptogenic
For insanity	Neuroleptic
For headaches and body pain	Analgesic
For leg pain	Analgesic
To make the body pure and light	Hallucinogen
To alter the mind	Hallucinogen
For sexual attraction	Aphrodisiac
To enhance vision	Hallucinogen
To energize	Tonic/adaptogen
For muscle building	Anabolic
To stimulate the appetite	Orexigenic
To clarify the mind	Hallucinogen

Another CNS-oriented ethnobotanical study involved a review of Brazilian plants with possible action on the CNS as reported from historical sources (Giorgetti et al., 2007). Some general observations that can be made about historical ethnobotanical sources that are exemplified with this study include:

- Records of plant information are often too vague to be useful (reporting only common names that could refer to a large number of species and not referencing collected specimens).
- Individuals recording information about use of plants mix their own cultural perspectives into their interpretation of other cultures.
- Modern communities that are surveyed often do not use all of the same plants as are recorded in historical documents or have different uses for the same plants.
- Some plants in the pharmacopoeia will be widely distributed, and thus probably also well studied in the international pharmacological literature. Likewise, some plants will be of restricted distribution and probably will not have been previously studied in the laboratory. The exceptions to this pattern are the small number of plants that were readily adopted as medicinal remedies (or foods) before the 1900s and became distributed and incorporated into various international pharmacopoeia. Some of these subsequently received substantial laboratory analyses early in the pharmacological revolution.
- Specific locations where information was learned, where plants were growing, or where medicinal practices were conducted are often missing or vague to the level of country or region.
- Details of plant use are often overly simplistic and do not represent the conditions that are typically encountered in real cultural situations with real healing professionals.

Conversely, the kinds of information that contemporary healers frequently relate to ethnobotanists include:

- Detailed and internally consistent disease diagnosis, prognosis and etiology.
- Detailed knowledge of the biology (life history, anatomy and chemistry) of plant taxa used as well as in-depth knowledge of related taxa that are not used.
- Patient specific, compound therapies most often based upon multiple plant parts prepared in doses that are customized for an individual patient. These are rarely designed as one plant for the treatment of one disease (in contrast to the approach typically taken by pharmacologists).

2.1. Key examples of central nervous system-active natural products from ethnobotanical leads

The plant taxa presented at length in this paper represent those that we have become familiar with through our research in Africa, Southeast Asia, Europe, the Pacific Islands, Southeastern U.S. and South America. Those presented in Table 1 are based upon either synoptic pharmacology texts such as Brunton et al. (2005) or specific recent pharmacological literature cited in the table.

Sections of textbooks on pharmacology (Brunton et al., 2005; Katzung, 2006) discussing the early history of drugs acting on the CNS are a tour-de-force of ethnobotanical discoveries beginning with exploration of our own pharmacopoeia and expanding into those of our trading partners and peoples who became colonized. Table 2 illustrates common examples of CNS-active molecules discovered from ethnobotanical leads. Some of these have led to pharmaceuticals that are still in use. Some have become embedded in culture in

Table 2
Some CNS-active molecules from plants of cultural importance.

Compound number	CNS-active molecules	CNS pharmacology	Plant(s)/origin (SA = South America, NA = North America)
1	Arecoline	Stimulant (nicotinic receptor agonist causing a cortical arousal response)*	*Areca catechu* L. Malaysia
2	Atropine	Depressant and euphoric (anticholinergic–muscarinic receptor antagonist)* (Halpern, 2004)	*Atropa belladonna* L. Eurasia *Brugmansia aurea* Lagerh. SA *Datura stramonium* L. NA *Mandragora officinalis* L. Eurasia
3	Caffeine (and other methylxanthines)	Stimulant (increases norepinephrine secretion via competitive antagonism at adenosine receptors)* (Nehlig et al., 1992; Carrillo & Benitez, 2000; Daly, 2000; Kitagawa et al., 2007; Pardo Lozano et al., 2007; Shapiro, 2007)	*Camellia sinensis* (L.) Kuntze SE Asia *Coffea arabica* L. E. Africa *Coffea canephora* Pierre ex A Froehner W. Africa *Coffea liberica* W. Bull ex Hiern W. Africa *Cola acuminata* (P. Beauv.) Schott & Endl. W. Africa *Cola anomala* K. Schum. W. Africa *C. nitida* (Vent.) Schott & Endl. W. Africa *Ilex guayusa* Loes. SA *Ilex paraguariensis* A. St.-Hil. SA *Ilex vomitoria* Aiton NA *Paullinia cupana* Kunth SA *Paullinia yoco* R.E. Schult. et Killip SA *Theobroma cacao* L. NA and SA
4	Cathinone	Stimulant (amphetamine-like adrenergic agonist*: this has been questioned by Roth et al., 2004) (causes release and inhibits reuptake of dopamine (Zelger & Carlini, 1981)	*Catha edulis* Forssk. E. Africa
5	Cocaine	Stimulant (euphoria primarily due to inhibition of dopamine uptake)*	*Erythroxylum coca* Lam. SA *Erythroxylum novogranatense* (D. Morris) Hieron. SA
6	Codeine	Analgesic (μ- and κ-opioid receptor agonist via conversion to morphine)*	*Papaver somniferum* L. Asia
7	Dimethyltryptamine (DMT)	Hallucinogen (Schultes & Hofmann, 1992) (serotonin receptor agonist)*	*Anadenanthera peregrina* (L.) Speg. SA *Virola theiodora* (Spruce ex Benth.) Warb. SA
8	Ephedrine	Stimulant (agonist activation of adrenergic receptors)* (this is in question by Roth et al., 2004)	*Ephedra nevadensis* S. Watson NA *Ephedra sinica* Stapf Asia
9	Ergotamine	Migraine relief (persistent competitive α-adrenergic blockade)*	*Claviceps purpurea* (Fr.) Tul. Eurasia
10	Ethanol	Depressant (disruption of a wide range of ion channels, receptor mediated functions, and signaling pathways)*	*Hordeum vulgare* L. (1° beer/whiskey) Eurasia *Vitis vinifera* L. (1° wine) Asia Many other plant starch sources
11 Ginkgolide A 12 Bilobalide	Ginkgolides, bilobalide	Controversial 'nootropic' properties improving memory and enhancing concentration (see review in Kumar, 2006)	*Ginkgo biloba* L. Asia
13 Harmine	Harmine, harmaline	Hallucinogen (Schultes & Hofmann, 1992) (type A monoamine oxidase inhibition).	*Banisteriopsis caapi* (Spruce ex Griseb.) C.V. Morton SA *Banisteriopsis inebrians* C.V. Morton SA
14 Harmaline		Sedative (Carlini, 2003; Halpern, 2004; McKenna, 2004; Halpern & Sewell, 2005)	*Peganum harmala* L. Asia *Passiflora incarnata* L. NA
15	Hyoscyamine	Depressant and euphoric (anticholinergic–muscarinic receptor antagonist)*	*Atropa belladonna* L. Eurasia *Hyoscyamus niger* L. Eurasia *Mandragora officinalis* L. Eurasia
16	Ibogaine	Hallucinogen (Schultes & Hofmann, 1992), (α3β4 nicotinic receptor antagonist and other activities) (Carlini, 2003)	*Tabernanthe iboga* Baill. W. Africa
17	Ibotenic acid	Hallucinogen (activates glutamate receptors inducing delirium)* (Halpern & Sewell, 2005)	*Amanita muscaria* (L.) Lam. Eurasia and NA
18	Lysergic acid amide (ergine)	Hallucinogen (Schultes & Hofmann, 1992) (serotonin receptor agonist)*	*Argyreia nervosa* (Burm. f.) Bojer Pacific *Ipomoea violacea* L. *NA* *Turbina corymbosa* (L.) Raf. NA and SA
19	Mescaline	Hallucinogen (Schultes & Hofmann, 1992) (serotonin receptor agonist)*	*Lophophora williamsii* (Lem. ex Salm-Dyck) J.M. Coult. NA *Trichocereus pachanoi* Britton et Rose SA
20 Methysticin 21 Dihydromethysticin 22 Yangonin 23 Desmethoxyyangonin 24 Kavain 25 Dihydrokavain	Methysticin, dihydromethysticin, yangonin, desmethoxyyangonin, kavain, dihydrokavain	Anxiolytic (kavain inhibits reuptake of norepinephrine, desmethoxyyangonin is a reversible monoamine oxidase B inhibitor) (Singh & Singh, 2002). Analgesic and other reported activities lack clear pharmacological mechanisms of action (See Kumar, 2006)	*Piper methysticum* G. Forst. Pacific
26	Mitragynine	Analgesic (opioid receptor agonist) (Matsumoto et al., 2004, 2006)	*Mitragyna speciosa* (Roxb.) Korth. SE Asia
27	Morphine	Analgesic (μ- and κ-opioid receptor agonist)* (Calixto et al., 2000)	*Papaver somniferum* L. Asia
28	Muscarine	Dysphoria (muscarinic receptor agonist)* (Halpern, 2004)	*Amanita muscaria* (L.) Lam. Eurasia and NA
29	Muscimol	Sedative (γ-aminobutyric acid receptor agonist)* (Halpern & Sewell, 2005)	*Amanita muscaria* (L.) Lam. Eurasia and NA
30	Nicotine	Stimulant (cholinergic–nicotinic receptor agonist leading to pre-junctional release of excitatory transmitters)* (Mantle et al., 2000)	*Nicotiana tabacum* L. NA and SA *Duboisia hopwoodii* F. Muell. Australia

Table 2 (*continued*)

Compound number	CNS-active molecules	CNS pharmacology	Plant(s)/origin (SA = South America, NA = North America)
31	Physostigmine (aka eserine)	"Reversible" anticholinesterase (inhibition of acetylcholine esterase by greatly slowing its activity)*	*Physostigma venenosum* Balf.f.
32	Pilocarpine	Stimulant (muscarinic receptor agonist)*	*Pilocarpus microphyllus* Stapf.
32 Psilocin 33 Psilocybin	Psilocin, psilocybin	Hallucinogenic (Schultes & Hofmann, 1992) (serotonin receptor (5-HT1A and 5-HT2A/2C) agonist) (psilocybin is metabolized into psilocin which is active) (Halpern, 2004)	*Psilocybe* spp. Eurasia, NA, SA and Eurasia especially *Psilocybe cubensis* (Earle) Singer Asia
34	Reserpine	Anti-psychotic (depletion of vesicular stored monoamines)*	*Rauvolfia serpentina* (L.) Benth. ex Kurz Indomalasia
35 Salicin 36 Salicylic acid	Salicin, salicylic acid	Analgesic (non-selective inhibition of constitutive and induced cyclooxygenaze cyclooxygenase enzymes)* (Calixto et al., 2000)	*Salix alba* L. Europe *Spiraea* spp. Eurasia and NA
37	Salvinorin-A	Hallucinogen (κ-opioid receptor agonist) (Roth et al., 2002; Willmore-Fordham, 2007)	*Salvia divinorum* Epling et Játiva NA
38	Scopolamine	Depressant and euphoric (anticholinergic–muscarinic receptor antagonist)*	*Atropa belladonna* L. Eurasia *Brugmansia aurea* Lagerh. SA *Datura metal* L. Asia *Datura stramonium* L. NA *Hyoscyamus niger* L. Eurasia *Mandragora officinalis* L. Eurasia
39	Δ-9-tetrahydro cannabinol	Stimulant (euphoria due to agonist activity at cannabinoid receptors)* (Calixto, 2000)	*Cannabis sativa* L. Asia

All scientific names verified using Tropicos (Missouri Botanical Garden) and Index Fungorum (*CABI Bioscience*, *CBS* and *Landcare Research*) databases in December 2007. Plant origins verified with Mabberley (1997). Sources: Halpern (2004), Schultes and Hofmann (1992), Brunton et al. (2005)*, Carlini (2003).

religious, ceremonial, and other social roles. Some have become banned by modern society although they continue to play important roles in subcultures of modern society and in other parts of the world where knowledge of the plants was first developed. A recent review of plants and the CNS (Carlini, 2003) focused primarily on hallucinogenic plants and their potential roles in new therapies. Research on roles for traditional ceremonial plants (mostly hallucinogens) in treatment of drug addiction, mental illness, and other centrally mediated disorders is ongoing and has continued to be explored in this journal (see Halpern, 2004; McKenna, 2004; Roth et al., 2004).

A wide range of plants with resins and volatile oils (including species of Burseraceae, Dipterocarpaceae, Fabaceae, Lamiaceae, Pinaceae, Podocarpaceae, and Verbenaceae) are used in different traditions to treat headaches, improve mood, alter perceptions, and otherwise improve CNS health via inhalation or topical applications. These are such large topics that they deserve a discussion of their own and so have been excluded from here. Scores of recent publications show that crude plant extracts have CNS analgesic activity. Likewise, authors still publish results showing that a particular plant has the presence of "alkaloids" that might indicate potentially CNS-active chemistry. Neither of these is particularly remarkable. These types of publications are not considered in this paper.

One of the false assumptions about ethnobotany is that it is exclusively the study of "other" cultures. In fact, many ethnobotanists work within our own cultures (Vogl-Lukasser & Vogl, 2004; Estabrook, 2006; Price & Kindscher, 2007) or on subcultures (Reiff et al., 2002) nested within the modern world. Carl Linnaeus is not only considered to be the father of modern taxonomy but also the first practical ethnobotanist (Cox, 1999) who studied plants used in other cultures, as well as his own culture. One such plant that is still being explored today for new CNS activities is golden root (*Rhodiola rosea* L., Crassulaceae). An extensive review of the traditional Northern Eurasian and modern uses of golden root was published by Brown et al. (2002) while research on the efficacy of this plant for enhanced mental and physical performance (Perfumi & Mattioli, 2007), as well as the treatment of depression (Darbinyan et al., 2007) is currently ongoing. *R. rosea* roots are a source of a series of phenlypropane derivatives, most notably rosavin, and a set of phenylethane derivatives, most notably salindroside. An important note is that these ethnobotanical leads have been known for a long time, as have the molecules likely responsible for pharmacological activity. Because of this, there is little likelihood that a patentable pharmaceutical drug would be developed directly from a plant whose chemistry is well known. However, for a great many natural products, the mechanisms of action are unknown or merely assumed and specific structure activity relationships have rarely been determined. As these are examined it is likely that new relationships will be revealed including new classes of receptors, new binding sites, and potential new mechanisms for treating a wide range of illnesses that traditional medicines have been treating.

In ethnomedicine, *R. rosea* is primarily considered to be an 'adaptogen.' This is a plant or other substance that increases endurance, longevity, resistance, health or generally protects the body from stressful situations (Brekhman & Dardymov 1969). Other plants traditionally used as adaptogens include *Bacopa monnieri* (L.) Wettst., *Eleutherococcus senticosus* (Rupr. ex Maxim.) Maxim., *Panax ginseng* C.A. Mey, *Schisandra chinensis* (Turcz.) Baill., and *Withania somnifera* (L.) Dunal. This category, as with many others of traditional medicines, is inconsistent with the dominant paradigm of biomedicine, and is thus difficult to test as a pharmacological hypothesis. Categories, such as this, pose major challenges for both ethnobotanists and pharmacologists seeking to bridge research between the field and the laboratory.

Beginning with morphine, and moving through the various traditional plant medicines of Europe, chemists of the 1800s and early 1900s attempted to identify the molecule or molecules responsible for the pharmacological activity found in herbal medicines. Once these molecules were identified, they formed the basis of the modern pharmaceutical industry. However, some plants such as valerian (*Valeriana officinalis* L.) have been used to treat insomnia in Europe and Asia for centuries and yet it has long defied the chemists and pharmacologists abilities to determine its active constituent(s). A large number of molecules have been identified from the plant including valerienic acid (Houghton, 1999; Abourashed et al., 2004; Schellenberg et al., 2004; Yuan et al., 2004; Dietz et al., 2005; Khom et al., 2007), yet it has been difficult to pin down one or even a small number of molecules that are responsible for all of the reported pharmacological activity. Valerian is likely an example where a large number of active molecules are acting in concert, in this case probably as partial agonists at a variety of serotonin and melatonin receptors. Although not yet confirmed, valerienic acid has been proposed to act as a partial agonist of the serotonin receptor (5-HT5a) (Dietz et al., 2005). Finally, although valerian has long been used, there is conflicting data about its efficacy with two meta data studies giving

differing results but the same conclusion: a review of 16 studies, each with randomized placebo controlled trials (Bent et al., 2006) and a review of 37 studies with 29 controlled trials (Taibi et al., 2007), did not support its efficacy as a sleep aid in humans. The primary problem identified by Taibi et al. (2007) was that the plant material used by so many of the studies that had been conducted differed so dramatically from the traditionally developed products (dried versus fresh) that many of the more recent and best controlled research studies were fundamentally flawed.

2.2. Recent reviews of central nervous system-active natural products

During the last few years several reviews of CNS-active plants have been produced (Carlini, 2003; Halpern, 2004; McCurdy & Scully, 2005; Kumar, 2006). Carlini (2003) focused specifically on:

- Psychoanaleptic or stimulant plants used for weight loss (*Ephedra sinica* Stapf., other *Ephedra* spp., *Camellia sinensis* (L.) Kuntze, *Ilex paraguariensis* A. St.-Hil., *Paullinia cupana* Kunth, *E. senticosus* (Rupr. ex Maxim.) Maxim., *Bryonia alba* L., *S. chinensis* (Turcz.) Baill., *P. ginseng* C.A. Mey, *W. somnifera* (L.) Dunal., Rasayana herbs, *R. rosea* L., *Catha edulis* Forssk., *Erythroxylum coca* Lam., and *Hypericum perforatum* L.).
- Psychodysleptic, entheogenic or hallucinogenic plants (*Banisteriopsis (Spruce ex Griseb.) C.V. Morton, Psychotria viridis Ruíz and Pavón, and Tabernanthe iboga Baill.)*.
- Psycholeptic, including analgesic and anxiolytic plants (*Passiflora incarnata* L., *V. officinalis* L., and *Piper methysticum* G. Forst.).

Halpern (2004) reviewed hallucinogenic or entheogenic plants naturally growing within the United States (although most are not native to the United States territory), specifically focusing on plants containing:

- N,N-dimethytryptamine (DMT; *P. viridis*, *Desmanthus illinoensis* (Michx.) MacMillian ex Robinson & Fern, *Phalaris arundinacea* L., *Phalaris aquatica* L., and *Phalaris tuberosa* L.).
- Reversible monoamine oxidase A inhibitors (MAOI; *B. caapi, Peganum harmala* L., and *P. incarnata*).
- Psilocypin and psilocin (*Pilocybe cubensis* (Earle) Singer and other species).
- Mescaline (*Lophophora williamsii* (Lem. ex Salm-Dyck) J.M. Coult. and Trichocereus pachanoi Britton & Rose).
- Salvinorin-A (*Salvia divinorum* Epling & Játiva).
- Lysergic acid amide (*Argyreia nervosa* (Burm. f.) Bojer, *Ipomoea violacea* L., and *Stipa robusta* (Vasey) Scribn.).
- Atropine and scopolamine (*Datura stramonium* L., *Atropa belladonna* L., *Hyoscyamus niger* L., and *Mandragora officinalis* L.).
- Muscimol and ibotenic acid (*Amanita muscaria* (L.) Lam. and *Amanita pantherina* (DC.) Krombh.).

Kumar (2006) provided a very specific review of medicinal plants for CNS disorders and focused on a set of species considered to the most important medicinal plants (*Ginkgo biloba* L., *H. perforatum*, *P. methysticum*, *V. officinalis*, *B. monnieri*, and *Convolvulus pluricaulis* Choisy (=*Convolvulus prostrates* Forssk). McCurdy and Scully (2005) reviewed analgesic substances from natural products with their inclusion neither being restricted to plants nor to the CNS. Additional recent reviews that proved to be helpful were Beaubrun and Gray (2000), Calixto et al. (2000), Mantle et al. (2000), and Werneke et al. (2006). Although these are not specifically recent reviews of natural products, they do cover natural products used for CNS illnesses.

Six categories of CNS-active plants of ethnobotanical origins that have been brought to the research forefront recently are discussed below. Some of these are very well known but our knowledge about their activities continues to develop. Others are not as well known but they may become issues in the near future. Each illustrates at least one important ethnobotanical principle that should be of importance for development of pharmacy and therapeutics.

3. Ethnobotanical leads with new pharmacological knowledge

3.1. Plants with methylxanthine alkaloids

The principle sources of methylxanthines are coffee, tea, and chocolate or cacao. Coffee is derived from the seeds of three species of *Coffea* (Rubiaceae), an Old World genus. *C. arabica* L. accounts for most of the world's coffee production, while *C. canephora* Pierre ex A. Froehner is used for instant coffee. Tea is made from the pulverized leaves of *C. sinensis* (L.) Kuntze (Theaceae) and also is native to the Old World. Cacao, the third major source of methylxanthines is made from the seeds of the New World species *Theobroma cacao* L. (Malvaceae).

Another important source of methylxanthines is the genus *Cola* (Malvaceae) from tropical Africa. *Cola acuminata* (P. Beauv.) Schott & Endl. is the principle source of cola nuts used to flavor carbonated beverages. The seeds of three other species (*C. anomala* K. Schum., *C. nitida* (Vent.) Schott & Endl., and *C. verticillata* (Thonn.) Stapf ex A. Chev.) are also commercial sources of cola nuts. Two species of the South American genus *Paullinia* (Sapindaceae) are regionally important caffeine sources. Guaraná (*P. cupana* Kunth) is a popular beverage in Brazil. Yoco (*Paullinia yoco* R.E. Schult. & Killip) is used by indigenous groups in the Amazon. The final source of methylxanthines is the genus *Ilex* (Aquifoliaceae). Yerba Mate (*I. paraguariensis* A. St.-Hil.) is the best known of the three commonly employed species. Native to southern South America, it is the national drink of Argentina and Uruguay and is gaining appeal elsewhere.

3.1.1. History of traditional usage

Two species of *Ilex* have remarkably similar uses in Amerindian cultures. Guayusa (*I. guayusa* Loes.) from Peru and Ecuador and *I. vomitoria* Aiton from the southeastern U.S. are employed similarly as both stimulants and purgatives (Bennett et al., 2002). *I. vomitoria*, known as cassina or yaupon, was the source of the ritual black drink beverage consumed by indigenous groups in the southeastern U.S. and was one of their defining cultural traits (Hudson, 1979). Some of the literature continues to refer to yaupon as *I. cassine* L. but the methylxanthine profiles strongly suggest that the error is based on confusion between common name and scientific epithet (Edwards & Bennett, 2005). Males drank a strong decoction made from the plant's leaves and twigs before going into battle and during the annual green corn dance. It also was consumed daily as a social beverage (Fairbanks, 1979). In certain contexts, imbibing yaupon produced emesis. The Shuar, Achuar, and related ethnic groups consume leaf decoctions of guayusa (*I. guayusa*) in a similar manner (Lewis et al., 1991; Bennett et al., 2002). Males consume guayusa for its stimulant properties in the predawn hours, especially before embarking on hunting treks. Subsequent vomiting reduces caffeine levels, preventing undesirable CNS effects. It also is employed medicinally by the Shuar to alleviate stomach aches, headaches, pain, and dizzy spells (Bennett et al., 2002).

Lewis et al. (1991) suggest that emesis, following the consumption of guayusa, is learned and not the result of emetic compounds in the decoction. A similar argument is made for yaupon. While emetic constituents have not been identified in either species, three points are germane. First, there is a strong cultural context and thus expectation of proper behavior in the traditional uses of the plants. The perception that both are emetics, no doubt contributes to their emetic potential, whether there is a pharmacological effect or not. Second, large amounts are consumed before emesis occurs. Merrill (1979) describes a 1579 account of yaupon, which noted that, “Each man drank until his stomach became distended.” While Merrill suggested that the use of salt water to prepare yaupon was responsible for the emetic effects the large quantities consumed (on empty stomachs)

probably played a key role. Caffeine in large quantities can produce emesis. Prepared as infusions similar to *C. sinensis*, both *Ilex* species provide a very palatable tea.

3.1.2. Primary central nervous system pharmacological activity and pharmacophores

Methylxanthines are used traditionally as stimulants and entheogens while they are widely used in global society as stimulants. The methylxanthine alkaloids caffeine, theobromine, and theophylline, are consumed in foods, drugs, and beverages throughout the world. Caffeine is the world's most widely employed CNS stimulant (Nehlig et al., 1992; Carrillo & Benitez, 2000; Shapiro, 2007). Of the three xanthine alkaloids, theophylline occurs in the smallest quantities in plants. Caffeine, theobromine, and theophylline differ structurally only in the number and position of methyl groups. Caffeine contains three methyl groups at positions 1, 3 and 7. Theophylline (1,3) and theobromine (3,7) are dimethyl xanthine isomers (Table 2). Methylxanthines are synthesized from purines. The two final steps of synthesis are successive methylation of N to produce theobromine and then caffeine (Kato et al., 2000). The half-life of caffeine is 3–7 h in adults. After ingestion, caffeine is metabolized by the hepatic cytochrome *P450* 1A2 enzymes (Pardo Lozano et al., 2007) into three primary metabolites: paraxanthine (ca. 82%), theobromine (ca. 11%), and theophylline (ca. 5%) (Gu et al., 1992).

3.1.3. Mechanism(s) of action

Methylxanthines have pronounced pharmacological effects; they act as adenosine-receptor antagonists. Caffeine is a nonspecific competitive blocker of adenosine A1 and A2A receptors (Daly, 2000; Pardo Lozano et al., 2007; Kitagawa et al., 2007). Theophylline also is a non specific adenosine antagonist, with equivalent activity on A1, A2 and A3 receptors. Theobromine appears less effective on A2 than A1-receptors (Daly et al., 1983). Adenosine antagonism by methylxanthines is responsible for their CNS stimulating activity. Adenosine modulation of dopamine transmission through A2A receptors has been implicated in the effects of caffeine (Cauli & Morelli, 2005).

Methylxanthines also inhibit phosphodiesterase, which increases intracellular cyclic AMP. However, inhibition occurs only at non-physiological concentrations of caffeine (Nehlig et al., 1992; Daly, 2000). A third pharmacological effect of these alkaloids is mobilization of intracellular calcium (Daly, 2000). Moderate methylxanthine concentrations stimulate the uptake and release of calcium by the endoplasmic reticulum. High concentrations inhibit uptake (Debry, 1994).

3.1.4. Recent modern use and issues

Methylxanthines have many therapeutic applications. A plethora of over-the-counter caffeine products are marketed for weight loss or treatments for drowsiness. The alkaloids effects as a stimulant are well established; however the evidence for caffeine's efficacy in weight loss is equivocal (e.g., Greenberg et al., 2005, 2006; Hackman et al., 2006).

Caffeine is a common component of headache remedies including those for migraine headaches. It is an effective analgesic for headache or an important adjuvant with other analgesics. However, chronic use is associated with an increased risk of analgesic overuse, headache and chronic daily headache and physical dependency (Shapiro, 2007). Antinociceptive action of caffeine includes blockade of adenosine receptors and inhibition of cyclooxygenase-2 enzyme synthesis (Zhang, 2001).

Another major use of caffeine is the treatment of respiratory diseases (Pardo Lozano et al., 2007). Caffeine is a weak bronchodilator and reduces respiratory muscle fatigue. In a review of six trials, Bara and Barley (2001) concluded that "caffeine appears to improve airways function modestly in people with asthma for up to 4 h." Theophylline, a more potent bronchodilator, relaxes bronchial smooth muscle. It is available in several forms including aminophylline (2:1 ratio of theophylline and ethylenediamine) and oxtriphylline (choline salt of theophylline). Theophylline has a narrow therapeutic index and can induce seizures (Gulati et al., 2005). Proposed mechanisms of action include inhibition of phosphodiesterase to increase intracellular cAMP levels. However, clinical effects can be seen at doses that do not significantly increase cAMP. Ito et al. (2005) suggested that the anti-asthma effects of low doses of theophylline are due, in part, to increased activation of histone deacetylases.

Methylxanthines have positive effects on cognitive function. Riedel et al. (1995) showed that caffeine reduced scopolamine-induced impairment of memory. Prediger et al. (2005) demonstrated that caffeine improves spatial learning deficits in an animal model of attention deficit hyperactivity disorder. Caffeine and theobromine from chocolate improve cognitive function (Smit et al., 2004). Caffeine might reduce cognitive decline in women without dementia, especially at higher ages (Ritchie et al., 2007) and may improve performance on cognitive tests (Norman et al., 2008).

Methylxanthines have a variety of other applications. Methylxanthine therapy is commonly used for apnea of prematurity (Schmidt et al., 2007). Caffeine is preferred over theophylline in neonates because of its ease of administration, high oral absorption, and its wider therapeutic window. Caffeine is the methylxanthine of choice for activation of intracellular calcium-sensitive calcium release channels (Daly, 2000). It can sustain regional brain activation patterns lost in acute hypoglycemia (Rosenthal et al., 2007). One hundred milligrams of caffeine per day improved "total akinesia" type of freezing of gait, but had no effect on "trembling in place" in patients with Parkinson's disease (Kitagawa et al., 2007). Theophylline might be effective in treating tardive dyskinesia (Bishnoi et al., 2007); methylxanthines from *I. paraguariensis* have antiparkinsonian effects in animal models (Milioli et al., 2007).

Methylxanthines consumption carries some risk. Therapeutic doses can cause alterations of blood glucose; anxiety; diarrhea, nausea and vomiting; headache; hypertension; insomnia; muscle twitches; sinus tachycardia, and tremor. Caffeine also interacts with other drugs. Overdoses can produce cardiac arrhythmias, seizures, and delirium (Carrillo & Benitez, 2000; Shapiro, 2007).

Modified methylxanthine alkaloids might be more effective and safer than caffeine, theobromine, or theophylline. Several synthetics have been developed that are more potent and more selective inhibitors of cyclic nucleotide phosphodiesterase than caffeine or theophylline (Daly, 2000). The analogs have been significant in elucidating the function of adenosine receptors, phosphodiesterases, and calcium release channels. Xanthine analogs also provide important research tools and potential therapeutic agents for treatment of Alzheimer's disease, asthma, cancer, diabetes, and Parkinson's disease (Daly, 2007). A recent study showed that theobromine suppressed capsaicin-induced cough and had no adverse effects suggesting it might form the basis for a new class of antitussive drugs (Usmani et al., 2005).

3.2. Hypericum perforatum

3.2.1. History of traditional usage

Hypericum is a large genus comprising 370 species widely spread in temperate regions and tropical mountains (Bombardelli & Morazzoni, 1995; Mabberley, 2008). Many species of the genus *Hypericum* (Clusiaceae) have been utilized in traditional systems of medicine since ancient times, particularly *H. perforatum* L. for its effects on the CNS.

H. perforatum, commonly known as St. John's wort (SJW), is an herbaceous aromatic perennial plant native to Europe, Asia, Africa, and is naturalized in Africa, Australia and the Americas (Hobbs, 1989; Hahn, 1992; Bombardelli & Morazzoni, 1995; Blumenthal et al., 2000). The common name, St. John's wort, is thought to refer to John the Baptist, as the plant begins to flower around the 24th of June, the day of St. John feast (Hahn, 1992). In Europe and the United States the plant grows wild commonly near roads, ditches and in woodlands. Many of the modern medicinal uses of the plant, including its use to treat neurological disorders, come from its use in traditional Greek

medicine and were documented by ancient Greek physicians (Blumenthal et al., 2000). Hippocrates (ca. 460–377 B.C.), Euryphon (ca. 288 B.C.), Dioscordies (ca. 1st century A.D.) and Galen (ca. 130–200 A.D.) used SJW to treat a wide range of medical conditions including burns, wounds, pain, sciatica and depression (Hobbs, 1989; Hahn, 1992; Bombardelli & Morazzoni, 1995; Blumenthal et al., 2000; Osbaldeston & Wood, 2000). In the 16th century, Paracelsus, a Swiss physician, used SJW to treat psychological disorders, and in 1650, Culpepper employed it for the treatment of wounds and venomous stings (Osbaldeston & Wood, 2000). In the early 19th century, the Eclectic doctors used oily preparations of the plant for the treatment of ulcers, diarrhea, hysteria and nervous conditions, including depression (Hobbs, 1989). During the early part of the 20th century Madaus, a German physician, employed SJW preparations internally for the treatment of neuralgia, neuroses, neurasthenias, hysteria and insomnia, and externally for the treatment of wounds (Hobbs, 1989). Thus, extracts of the aerial parts of the plant have been used in Europe for centuries to treat anxiety, depression, neuralgia and other neuroses (Hahn, 1992; Osbaldeston & Wood, 2000).

3.2.2. Primary central nervous system pharmacological activity and pharmacophores

While the primary pharmacological activity attributed to SJW is antidepressant, multiple classes of compounds in SJW appear to contribute to its antidepressant activities and other CNS effects (Mahady et al., 2001; Choudhuri & Valerio, 2005; Butterweck & Schmidt, 2007). The concentration of these chemical compounds may vary among individual plant samples (and within botanical products) depending on numerous factors, including geographical origin, intra-species genetic variation, parts of plant used, growing conditions, time of harvesting, exposure to light, preparation, and processing of the plant material (Choudhuri & Valerio, 2005). The chemical constituents that appear to have biological activities that contribute to the overall CNS effects of SJW include the naphthodianthrones: hypericin and pseudohypericin, the flavonoids, and the phloroglucinols hyperforin and adhyperforin (Mahady et al., 2001). Hypericin, pseudohypericin and related naphthodianthrones represent approximately 0.05–0.3% w/w of the chemical constituents (Mahady et al., 2001; Choudhuri & Valerio, 2005). The flavonoids including hyperoside, quercitrin, isoquercitrin, and rutin make up approximately 2–4% w/w; the phloroglucinols including hyperforin and adhyperforin approximately 2–4% w/w; and the catechin tannins make up approximately 6.5–15% w/w (Bombardelli & Morazzoni, 1995; Osbaldeston & Wood, 2000; Mahady et al., 2001; Choudhuri & Valerio 2005).

3.2.3. Mechanism(s) of action

Due to its popularity, SJW has been the subject of many scientific investigations in an attempt to understand a rational scientific basis for its mechanisms of action at the molecular level (Cabrelle et al., 2008). Some of the more recent works on SJW and its active constituents provides support for the concept of pleotropic effects of the plant on the CNS to impact depression, anxiety, pain and inflammation. For example, hyperforin, one of the main compounds in SJW, inhibits interferon-gamma production, and down-regulates T-box (T-bet; marker of Th1 gene expression) and up-regulation of GATA-3 (marker gene of Th2) on interleukin-2/phorbol ester-activated T lymphocytes in vitro and shows efficacy against Th1-triggered CNS inflammatory-demyelinating disease when administered to animals (Cabrelle et al., 2008). These data suggest that SJW extracts containing hyperforin may be effective in treating autoimmune inflammatory diseases of the CNS (Cabrelle et al., 2008).

More recently high-throughput screening of the receptorome has also been used to determine the molecular mechanism of SJW, as part of an offshoot of the human genome project (Cabrelle et al., 2008). One of the discoveries of the human genome project is that a relatively large portion of the genome is dedicated to signal transduction, and that portion dedicated to encoding ligand reception has been described as the "receptorome" and encompasses more than 8% of the human genome (Kroeze et al., 2003; Roth et al., 2004; O'Connor & Roth, 2005). The receptorome is subdivided into multiple receptor superfamilies, the largest of which is G-protein coupled receptors (GPCRs), which are the most common molecular target for many CNS drugs (Roth et al., 2004). Various purified chemical constituents of SJW have been screened against a portion of the receptorome (O'Connor & Roth 2005). One example is amentoflavone, which has a high affinity for the GABA-benzodiazepine receptor complex and moderate affinity for δ-opioid receptors (Kroeze et al., 2003). Several other SJW compounds have affinities in the low nanomolar to micromolar range for several cloned receptors, including serotonin receptors (5-HT1B, 5-HT1D, 5-HT2C) and dopamine receptors for hypericin (D3 and D4) (Roth et al., 2004). Furthermore, hypericin and other chemical constituents of SJW have low micromolar affinities for various peptides (NPY-1, NPY-2), serotonin, and δ-opioid receptors. These results suggest that numerous chemical constituents in SJW interact with a wide range of biogenic amine and peptide receptors. Thus, it is likely that the antidepressant activities of SJW are mediated by classes of compounds, each with a complex pharmacological profile (Kroeze et al., 2003; Choudhuri & Valerio, 2005; Butterweck & Schmidt, 2007).

3.2.4. Recent modern use and issues

In Europe, SJW is currently prescribed by physicians as a treatment for depression, and has been recognized by the German Commission E as an approved medicinal herb for depression since 1984 (Volz, 1997). In addition, the World Health Organization's "Monographs on Selected Medicinal Plants", classifies SJW for the symptomatic treatment of mild to moderate depression (as defined by the International Classification of Diseases 10: F32.0 and F32.1; Mahady et al., 2001). These therapeutic uses and recommendations are based on systematic reviews and meta-analyses of the randomized controlled clinical trials that support the use of SJW for the symptomatic treatment of mild to moderate depression (Nahrstedt & Butterweck, 1997). The recommended dose of a standardized SJW extract (containing 0.3% hypericin or 5% hyperforin) is 900 mg/day in three divided doses (Mahady et al., 2001), and the therapeutic effects of SJW may require 4–6 weeks of therapy before a significant effect may be observed. Adverse events range from minor gastrointestinal disturbances and photosensitivity to acute neuropathy in sensitive patients (Mahady et al., 2001). Furthermore, there is considerable evidence that ingestion of SJW extracts induces the activities of hepatic enzymes responsible for drug metabolism, thereby reducing the serum levels of these drugs (Madabushi et al., 2006). Concomitant administration of SJW has been reported to reduce plasma and serum levels of many drugs including oral contraceptives, theophylline, digoxin, warfarin, cyclosporin, and protease inhibitors by inducing drug metabolism by cytochrome *P450* (Madabushi et al., 2006). As a consequence, the concomitant use of SJW and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended and may result in suboptimal antiretroviral drug concentrations, leading to a loss of virologic response and the development of resistance (Madabushi et al., 2006). Due to a lack of safety data, SJW should not be administered to patients allergic to the plant, or during pregnancy and nursing (Nahrstedt & Butterweck, 1997; Mahady et al., 2001).

Interestingly, there are numerous other *Hypericum* species used in ethnomedicine around the world to treat disorders of the CNS (Mukherjee et al., 2001). For example, *H. hookerianum* Wight & Arn. and *H. patulum* Thunb., both from India, are reported to have effects on the CNS in animal models (Mukherjee et al., 2001). Furthermore, *Hypericum* species from the Canary Islands, namely *Hypericum canariense* L., *H. glandulosum* Dryand., *H. grandifolium* Choisy and *H. reflexum* L. f. have also been shown to have antidepressant effects in mice when administered at doses of 500–1000 mg/kg body weight

(Sánchez-Mateo et al., 2002). Thus, there is potential for the development of new *Hypericum* extracts and the isolation of new chemical constituents from these plants for the treatment of CNS diseases, including anxiety, depression and autoimmune diseases of the CNS.

3.3. Hoodia spp

3.3.1. History of traditional usage

Several species of the plant genus *Hoodia* (Apocynaceae, subfamily Asclepiadoideae), especially *Hoodia gordonii* (Masson) Sweet ex Decne have a long history of usage by traditional societies in southern Africa, including the San, the Khoikhoi, and the Topnaar, as well as by more recent immigrants into the area. Reported medicinal applications of *Hoodia* spp. include reduction of hunger and thirst (Pappe, 1862; Marloth, 1932; Bruyns, 1993), treatment of coughs and colds (Chevallier, 1996), abdominal cramps, hemorrhoids, and tuberculosis (Rader et al., 2007), reduction of gastric secretions and prevention of aspirin induced gastric damage (Hakkinen et al., 2004), and for antidiabetic activity (Rubin et al., 2006; Rader et al., 2007).

3.3.2. Primary central nervous system pharmacological activity and pharmacophores

Biomedical and herbal product CNS indication for *Hoodia* spp. is as an anorectic agent (MacLean & Luo, 2004; Van Heerden et al., 2007). Although further research is strongly advised on extracts of the various plant species, employing larger sample sizes and human subjects, recent studies demonstrate anorectic activity in rats from an "active ingredient" isolated from *H. gordonii* with a proposed CNS mechanism of activity. Appetite suppression has been induced by the patented compound trirhabinoside, 14-OH, 12-tigloyl pregnane steroidal glycoside named P57A53 (Van Heerden et al., 2007; P57A53 Fig. 1), through various routes of administration including oral, subcutaneous, intravenous, and third ventricle intracerebroventricular (ICV) injection (Tulp et al., 2001; MacLean & Luo, 2004; Van Heerden et al., 2007). Its empirical molecular formula is $C_{47}H_{74}O_{15}Na$, MW = 1008, and its structure is 3β-[β-d-thevetopyranosyl-(1→4)-β-d-cymaropyranosyl-(1→4)-β-d-cymaropyranosyloxy]-12β-tigloyloxy-14β-hydroxypregn-5-en-20-one (Van Heerden et al., 2007). This structure is quite similar to that of cardiac glycosides (cardinolides), such as those found in *Digitalis* spp. (i.e. foxglove). It has a similar steroidal core with a 14-OH substitution, but it lacks the D-ring lactone of the cardenolides, a key feature of activity (Gupta, 2000; Kren & Martinkova, 2001). Other steroidal glycosides have been isolated from *Hoodia* spp., but only P57A53 has demonstrated anorectic activity (MacLean & Luo, 2004; Dall'Acqua & Innocenti, 2007; Pawar et al., 2007a,b; Van Heerden et al., 2007).

3.3.3. Mechanism(s) of action

P57A53 may simultaneously act on multiple body systems. Hypotheses include impeding gastric secretions (Hakkinen et al., 2004) or gastric emptying (Van Heerden et al., 2007), which are likely actions on the peripheral nervous system, and different mechanisms of CNS activity affecting energy homeostasis sensing in the hypothalamus. ICV injection directly into rat brains reduces appetite, demonstrating a direct CNS mechanism (MacLean & Luo, 2004). It has been suggested that this action involves the melanocortin-4 receptor, regulating neuropeptide "Y" (which is negatively regulated by leptin) and increasing cholecystokinin, which inhibits gastric emptying (Van Heerden et al., 2007). Hypothalamic ATP content is altered by ICV injection of P57A53, elevating ATP in the hypothalami of rats fed a normal diet, and impeding the otherwise witnessed decrease in ATP in the hypothalami of underfed rats. It increases the concentration of K^+ in cells by acting as a non-binding antagonist to g-straphanthin/ouabain's effect of decreasing intracellular K^+ concentrations (shown by ^{86}RB proxy) through its action on Na^+,K^+-ATPase (the Na^+ pump). The specific mechanism of this action is not yet clear; although P57A53 does not bind to Na^+,K^+-ATPase as the cardenolides do, it is hypothesized to affect another ATPase regulating K^+ channels. P57A53 can clearly serve as a useful probe for further investigation into mechanisms of CNS energy sensing, which could lead to treatment of energy homeostasis disorders that can cause obesity and insulin resistance (Levin & Routh, 1996; MacLean & Luo, 2004).

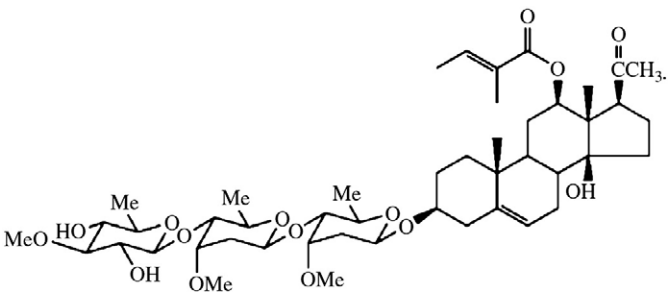

Fig. 1. Trirhabinoside, 14-OH, 12-tigloyl pregnane steroidal glycoside named P57A53A53 isolated from *Hoodia* (Van Heerden et al., 2007).

3.3.4. Recent modern use and issues

Dietary supplement products containing *Hoodia* spp. have been widely hyped through advertising, but concerns have been raised about product integrity and safety (Anonymous, 2006; Lee & Balick, 2007). Despite synthesis of "the active ingredient," over-harvest of the wild plants is also a concern, and the genus is listed as endangered by the Convention on the International Trade in Endangered Species of Wild Fauna and Flora (CITES). Intellectual property of the San (indigenous cultures originally using *Hoodia*) regarding uses of the plant has been legally, though problematically and belatedly (post-patent), recognized and benefit sharing has occurred with that cultural group following recommendations of the Convention on Biodiversity (Wynberg, 2004; Vermeylen, 2007). Such benefit sharing has only occurred with the San and only within the pharmaceutical realm however, and not with the natural products industry, which tends to exploit the story of local usage of the plant.

While the paradigm of Western herbal medicine recognizes the broad range of impacts on the body of plant compounds as part of the medicinal effect, the scientific pharmaceutical paradigm tends to recognize purposes other than what a drug is marketed for as "side effects" or "off-label" uses. Accordingly, the appetite suppressing properties of *Hoodia* extracts are likely not the only actions on the body. We strongly recommend research into the cardiac effects of *Hoodia*, given the similarity of structure and hypothesized mechanism of P57A53 to cardiac glycosides, as well as the incidence of heart complications caused by some appetite suppressants (Biswas et al., 1999).

3.4. Piper methysticum

3.4.1. History of traditional usage

P. methysticum G. Forst, Piperaceae (kava), is a multi-stemmed and multi-rooted shrub that grows in the humid tropics of the South and Central Pacific region. It is grown primarily for the production of a traditional beverage that is made exclusively from the roots and rhizomes of the plant. Across the Pacific, neither stems nor leaves are ever used for production of the traditional beverage. However, the leaves are occasionally applied as medicinal poultices or used in internal medicines. What makes these facts interesting is that even in a kava shortage, the people do not use any part other part of the plant to prepare the traditional beverage.

In 1990, Omi Managreve in the village of Saolei, Rotuma related the following story of the origin of kava. "Long ago the Rotumans had no kava and there was no peace between any people. A brother and sister

decided to leave the island to go in search of a way to find peace. They traveled to many places including Samoa, Tonga, and 'Uvea, but it was not until they came to Fiji that they found kava and realized that it was what they needed. When they returned they realized that the plant was already growing in Rotuma but that they had brought a different variety. They then began to use the roots to make kava and life began to be peaceful." Each Pacific Island culture has one or more stories of the origin of kava and these are testaments to the importance of this plant in the lives of these ancient civilizations (Lebot et al., 1992).

Most traditional tropical Pacific Island cultures do not dry foods or medicines before using them. There is little seasonal variation in availability of many plant resources and high humidity makes drying difficult. The most important reason is that by only harvesting what is actually needed for immediate use, what remains in the ground continues to grow and produce more material, thus increasing the harvest for next time.

When preparing kava for large groups, Pacific Islanders uproot whole plants and immediately replant the above ground tissues. If only a few people are to be served, only a portion of the root mass is harvested. The remainder is left in the ground for later use. Some plants are harvested in a rotating root-coppicing fashion, harvesting roots around the plant for years, but never taking more than a portion of the available roots at any one time.

The pounded, macerated or ground roots are mixed with an amount of water that varies among cultures to produce a beverage that ranges from a thick gelatin to a light tan watery suspension. The beverage is always consumed in a group, most often comprising only men and most often in the evening or at night. Depending on the concentration, the social status of the individuals involved and the importance of the ceremony involved, different amounts may be consumed. The beverage may be drunk for relaxation and socialization at the end of a hard day of work or it may be the focus of critical affairs of state. During each of the traditional roles of kava, its importance is in allowing clarity of thought, allowing users to focus upon their discussions and the ability to remember details of information (Pacific Island cultures had to remember all knowledge rather than use writing).

Although kava is sometimes used for medicinal purposes, these are rarely CNS purposes (except for headaches and treatments of hangovers). Rather, the "medicinal" role of kava is "pounded into the clothing" of traditional Pacific societies as firstly a social lubricant for bringing people together to discuss issues of the day and to maintain group cohesion, secondly as a mechanism for reducing group tension, and lastly, when all else fails, it serves as a mediator of conflicts.

3.4.2. Primary central nervous system pharmacological activity and pharmacophores

The primary traditional CNS indication of kava has been focused on increasing cognition while the modern CNS indication has been on relieving anxiety. Hänsel (1968) provided an excellent overview of the chemistry of *P. methysticum* which was largely resolved prior to the 1930s. Much of the basic pharmacology for these molecules was also resolved and reported by Hänsel (1968). Prior to the 1990s the active molecules consisted of kava lactones (or styryl α-pyrones) of which six have been considered to be of greatest pharmacological importance: methysticin, dihydromethysticin, yangonin, desmethoxyyangonin, kavain, and dihydrokavain.

Smith (1979) isolated the "pharmacophore," pipermethystine from kava leaves. Although this has been known and discussed for some time (Lebot et al., 1992), the compound was of little interest because it was a constituent of the leaves and had no known pharmacological activity. A major reason for inclusion of kava in this review is the recent turmoil over kava use in Europe and the likelihood that contamination with pipermethystine, whose pharmacology has recently been reported (Dragull et al., 2003), is the cause of the deaths and subsequent bans on use of kava in many countries.

3.4.3. Mechanism(s) of action

Kavain inhibits reuptake of norepinephrine and desmethoxyyangonin is a reversible monoamine oxidase B inhibitor. The other kava lactones likely have similar mechanisms of action that account for anxiolytic effects. Much of the research on kava lactone pharmacology is older and relies upon indirect evidence rather than on mechanism-specific assays. Recent pharmacological research has been summarized by Singh and Singh (2002) and Kumar (2006). Pipermethystine is cytotoxic (mitochondrial toxicity) to human liver cells (hepatoma, HepG2), and induction of apoptosis may be due to increased caspase-3 activity (Nerurkar et al., 2004).

3.4.4. Recent modern use and issues

After Europeans discovered Pacific Islanders using kava, they began to develop an industry that involved harvesting large amounts of kava roots, drying them, and shipping them to Europe and America. Outside of the Pacific, the dried roots were usually powdered and then either used in a capsule form or extracted and administered as tinctures. In the 20th century, with the advent of modern assays, root samples began to be checked for levels of kava lactones. Buyers then began to require that each shipment lot have a minimum level of lactones per unit weight. Increasing knowledge about the presence of kava lactones in stem peelings and leaves led to the inclusion of these parts in commercial preparations (Dragull et al., 2003). As stated above the stems and leaves of the plant were never used to prepare the traditional beverages, even in times of shortage. However, buyers who were only concerned about lactone levels and not contamination with other plant parts would probably have pulverized anything with the right concentration of lactones. No assays were being conducted for pipermethystine because no one knew that there were any problems with it or expected it to be present.

In the late 1990s, a series of medical problems emerged in European countries with a number of reported cases of liver damage allegedly linked to medicinal use of kava products (Stoller, 2000). By 2002, Australia, Canada, Germany, France, and Switzerland had banned kava (Russmann et al., 2001; Schmidt et al., 2002; Clouatre, 2004). Subsequently, researchers discovered that the problem was likely due to the contaminant pipermethystine from poor quality kava that was adulterated with stem and leaf tissue (Dragull et al., 2003). While it is difficult to convince regulators to see this as a fairly clear case, it is important to consider that this is a typical rather than an unusual sort of problem that happens when plant medicines are taken from one culture and used in another culture without careful consideration of the parameters and traditional logic of use in the cultures of origin.

3.4.4.1. Kava as wine. Like grapes grown for wine, kava in its home cultures comes in many varieties with different tastes that are grown for different effects. Traditional drinkers may select a particular variety of kava for a desired taste and effect, and just as with wines, individual taste preferences vary. Kava is also consumed in social groups and it would be unusual for one person to drink kava alone and in fact would be an indication of a serious social problem. Finally, although kava is a social beverage, the parallel with wine continues in that kava is perceived as having a number of traditional medicinal qualities that are imparted with the normal consumption of the beverage within social settings (just as is the case with wine; Lebot et al., 1992).

American and European cultures regard kava very differently than do Pacific islands cultures. First, outside of the Pacific, kava is treated not as a beverage, but as a drug. Second, drinking kava is not considered to be a culturally-unifying ritual but rather it is employed as a medicinal therapy taken individually. For example the specific indications for use

of kava in the German Commission E Monographs (1998) are "conditions of nervous anxiety, stress, and restlessness" (and see Singh & Singh, 2002 for a U.S. version) which are distinctly different from the social contexts of use within the Pacific islands. Third, kava is bought and sold as a commodity largely based upon the kava lactone levels (a parallel would be if wine were purchased based upon alcohol or phenol levels) and not based upon the variety.

3.5. Salvia divinorum

3.5.1. History of traditional usage

In July, 1961, Mexican Mazatec healers Augustina Borja, Clementia Unda, Maria Sevastiana Carrera, and Sara Unda de la Hoz shared their traditional knowledge of the use of hojas de la Pastora (*S. divinorum* Epling et Játiva, Lamiaceae) with ethnobotanist R. Gordon Wasson. In October 1962, Consuelo Garcia, another Mazatec healer shared similar traditional knowledge with Wasson and Albert Hoffman. Although Wasson was not the first person to discover the use of hojas de la Pastora, he was the first scientist to collect botanical specimens and publish a description of its use (Wasson, 1962). He also included two brief elements of earlier publications that probably refer to the same plant but for which there is no clear evidence. He was working in Mexico studying traditional uses of psychoactive mushrooms used in healing divination ceremonies. He was told by many Mazatec informants that hojas de la Pastora was a common substitute when the mushrooms were unavailable. Although he had worked in the area for several years he was slow to realize that the plant was familiar to virtually all Mazatecs (Wasson, 1962).

The Mazatec healers and patients chew paired leaves of the plant as part of a healing ceremony intended to allow the healer to identify or divine the cause of illness as well as determine the best course of action to take for treatment. Chewing of the leaves is also healing for the patient allowing them to learn important insights.

During the 1960s, roads were opening up the mountains of Mexico and plants such as hojas de la Pastora moved out with Mexican immigrants and with those like Wasson exploring Mexico. They then became available in the U.S. and Europe just at the time that there was a growing interest in finding new psychoactive substances.

3.5.2. Primary central nervous system pharmacological activity and pharmacophores

S. divinorum is used for disease diagnosis in traditional communities and as a hallucinogen in globalized cultures. A non-nitrogenous neoclerodane diterpene salvinorin-A (Ortega et al., 1982; Valdes et al., 1984) is the only clearly described active agent from *S. divinorum*. Because of growing interest in this molecule and its unusual mechanism of action (see below), a number of research groups have been generating synthetic derivatives (Harding et al., 2006; Lee et al., 2006; Holden et al., 2007).

3.5.3. Mechanism(s) of action

Roth et al. (2002) determined that salvinorin-A is a selective κ-opioid receptor agonist. Numerous animal models have confirmed this mechanism (Willmore-Fordham et al., 2007). People who smoke *S. divinorum* leaves usually report a very quick onset of activity, in a few minutes, with effects being short-lived, lasting a few minutes to a few hours. When the leaves are chewed, and the drug adsorbed buccally, the onset is delayed, the duration is longer and the intensity is less pronounced.

3.5.4. Recent modern use and issues

Most of the recent reviews of CNS-active plants have included *S. divinorum* and for good reason. Although the plant has only relatively recently begun to be used in popular culture, it has rapidly become quite common. In many major U.S. cities, small bags of dried leaves can even be purchased in convenience stores. Whole plants are available for sale in garden shops and seeds (of questionable viability) and small plants (of much more likely botanical potential) can be purchased over the internet. It is probably one of the strangest of psychoactive plants. It is increasingly being used by university students (Lange et al., 2008) which may be an indication that it will spread to the rest of society.

4. Conclusions

The suite of recent research on plants elaborated above illustrates the kind of range of ethnobotanical possibilities for CNS-active leads.

- Methylxanthines are widely distributed in plants and represent a pharmacological class that is expected, predictable and reasonably well understood. Being well understood is what we would like to be able to say about each and every effective CNS-active pharmacophore, but this is simply not the current state of affairs. In fact, this is one of the best exceptional categories that should be the most well known to the average person who doses themselves with these CNS-active substances almost daily. Compare the cultural standard for consideration of this category with that of kava. In the cultures from which kava originates, it holds similar roles as the methylxanthine plant beverages, yet we have elected to treat kava quite differently. Consider that this may be more of a cultural and less of a pharmacological decision.
- SJW (*H. perforatum*), valerian and many other traditional remedies offer viable medical options that do not fit the mold of one-molecule to one-mechanism of action. If we do not wish to limit potentially important treatment options for patients, we need to develop better ways to deal with pharmaceuticals that do not fit into the rigid pharmaceutical model of the past.
- *Hoodia* spp. represents a large category of plants ethnobotanists have documented that are useful in local communities but are unlikely to be sustainable for global markets from wild plant populations. In fact this is seen so often that it is reasonable to assume that this is the case with almost all medicinal plants until proven otherwise. Wild harvest of medicinal plants for local use may or may not be sustainable, but it almost never is sustainable for a global market (Schippmann et al., 2002).
- Kava (*P. methysticum*) is a culturally important beverage of groups that has become twisted into a medication of individuals. In this process, critical information about its traditional pattern of use and preparation was ignored (the same may be happening for *Hoodia*) and has resulted in many adverse events, including death.
- Hojas de la Pastora (*S. divinorum*) is a plant recently emerging from a biodiversity hotspot (see discussion below) that is of interest to the general public in global society for its entheogenic/hallucinogenic activities. Hojas de la Pastora is still legal in most U.S. states. Salvinorum-A from hojas de la Pastora has been the target of drug development activities as researchers have attempted to modify it to develop new analgesic pharmacophores.

Each of the above has been the object of CNS pharmacological research with *S. divinorum* being particularly prominently pursued.

4.1. Need for central nervous system-active natural products in modern society

Table 2 is not a complete list of CNS-active plant-derived molecules, but it represents the major kinds of natural products from plants. It also illustrates that the known number of CNS receptors specifically targeted by natural products is severely limited. In fact, as new natural products are tested they are often examined in known assays and reported with known mechanisms of action. To some extent this has expanded the range of structure types known to have activity at certain receptors. For example, the finding that salvinorin-A (Roth et al., 2002) illustrated the first naturally occurring non-

nitrogenous κ-opioid receptor agonist. While this is useful information, in our opinion it is not very productive to use plant chemistry as a tool for expanding the repertoire of receptor types and mechanisms of action, since opioid receptors are well known and there are many κ-opioid receptor agonists.

An important question to be asked is: Are there any other mechanisms that have yet to be discovered? Perhaps the reason that few new receptors and mechanisms are identified is because almost all have been found. Roth et al. (2004) have addressed this question from the tact of the human genome and come to the conclusion that there is much more yet to be discovered. Furthermore, they discuss a set of mechanisms for approaching this problem using a bioinformatics approach.

Rather than a continued stream of new variations on old structures acting at known receptors, what is needed is a clear system for screening out, "de-replicating" those plants that are not going to lead to something really interesting and novel. Roth et al. (2004) propose screening the recepterome (the portion of the proteome encoding molecular receptors that represents 8% of the human genome) in order to identify new targets for CNS-active plants. However, we would propose that this be coupled with searches that employ a de-replication work flow as illustrated in Fig. 2.

Ethnobotany may be shedding light on the fundamental basis of CNS diseases such as amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC), through studies of plant-associated causes of the disease and through environmental dietary biomagnifications of cyanobacterial sources of β-methylaminoalanine (Murch et al., 2004). In this case, the molecule under study is not novel and its potential as a therapeutic is limited, but through study of the effects of long-term exposure of a traditional human population to a dietary toxin effective disease models may be developed.

4.2. Polypharmacy-synergistic actions

Two related issues that are important to this discussion but beyond the scope of this paper are compound remedies or polypharmacy (see conclusion of Carlini, 2003) and complexity of molecular effects on the CNS, either from one compound or a complex mixture. Together, these issues cause complications that are difficult to disentangle. Synergistic actions of multiple compounds and different actions caused by the same compound at different sites can both lead to complex pharmacology and in fact, this is what is typically seen from CNS-active plants.

One problem frequently encountered in pharmacological studies of medicinal plant efficacy is that the studies are not conducted on the sorts of preparations that have been used for generations and upon which the traditional belief in efficacy has been built. Rather, tests may be run on standardized commercial products that have been relatively recently developed for mass marketing and may or may not bear much chemical or therapeutic similarity to the traditional remedy. For laboratory pharmacologists whose research is sponsored by an herbal product company this is problematic. For an ethnobotanist whose research is based upon relationships of trust with communities this is unethical evaluation.

Traditional medicinal systems are complex in that remedies typically involve incorporation of multiple plants for the treatment of a simple problem. It is unlikely that the traditions evolved as whole units but probably developed over time with elements being added creating ever more complicated formulations presumably adding to perceived efficacy through synergy of additional botanical elements. The major disjunction between traditional medicinal practices in many societies and the necessary evaluative paradigm of biomedicine is that traditional medicines are the result of complex systems that have built up over time whereas the pharmacological evaluation process usually requires that a fraction of a remedy (a solvent extract of one plant) be examined.

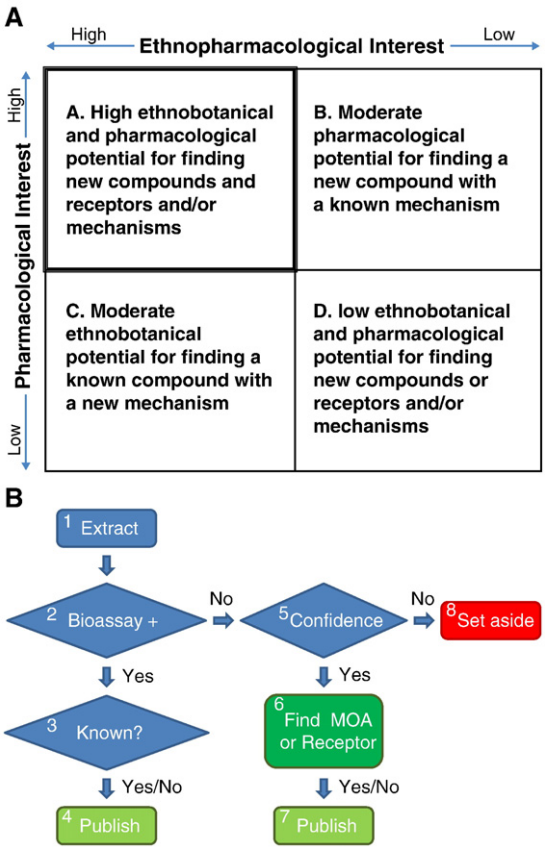

Fig. 2. A. Conceptualized de-replication work matrix illustrating that an ideal goal for ethnobotanists and pharmacologists should be to identify new pharmacophores with new receptors or mechanisms of action. **B**. De-replication work flow chart. The process of analysis of a traditional medicinal remedy typically begins with production of one or more solvent extracts (1) that are then tested in biological assays (2). Commonly the mechanism of action of the assay is known therefore if there is a positive find in the assay then the mechanism of action of one or more molecules within the extract is implied. De-replication (3) will help to determine if the sample likely contains a known molecule with known activity or if there could be an unknown molecule with now known activity. Through bioassay guided fractionation one or more purified molecules may be isolated. If these are known or unknown then they may be published (4) although unknown molecules are of more interest. Extracts that are not determined to be active in the bioassay may still have efficacy. The researchers determine the level of "confidence" in the traditional efficacy of the plant/remedy (5) through i) cross cultural comparison of use of plant, ii) analysis of within culture use (number of independent recommendations, number of similar uses, relative importance ranking by informants, etc.), or iii) recognition of the esteem of the information source (healer) by their home community (basically a relative show of confidence for the particular practitioners effectiveness). Based upon these results, the extract is either set aside (8) as being of lower interest both culturally and pharmacologically, or may be determined to be of higher interest both culturally and pharmacologically. If an extract is of interest then further attempts may be made to find new receptors or new mechanisms of action through testing in other assays (6). Although finding a new receptor or mechanism is ideal, identification of a cultural lead with high confidence is just as important and may eventually result in a new pharmacological finding. Publication in the biological or social science literature (7) is equality valuable.

4.3. Conservation issues

Ethnobotanists face responsibilities to not only the people, but also the plants and ecosystems with which they work. Beyond protecting resources from harm, creative application of ethnobotanical research may assist ecosystem protection and recovery through aiding sustainable development and providing alternatives to destructive land use practices. Although it cannot be taken for granted as true in all cases, income generated from natural products development may drastically alter the fate of landscapes and plant species.

4.4. Biodiversity hotspots

Conservation International maintains a list of locations on the planet that are considered to be biodiversity hotspots (Myers et al., 2000). These are locations that are defined by being botanically rich in species and those species are highly threatened with extinction. Thirty-four biodiversity hotspots have been identified, each with at least 1500 endemic plant species and having lost at least 70% of its original habitat extent. Together the thirty-four hotspots once covered almost 16% of the Earth's land surface. Biological researchers have become acutely aware of the fact that we cannot save all life of Earth and that prioritization must be done. These sites have been determined to be the highest priority and because of this, funding for many kinds of work is specifically earmarked for work within these sites.

Anthropologically these sites are of great interest because the distribution of global biodiversity hotspots very nearly matches similar concentrations of high cultural and language diversity (Nettle & Romaine, 2000; Harrison, 2007). Today there are almost 7000 known living languages (Gordon, 2005) most of which are clustered as very small communities in and around the biodiversity hotspots. Each culture and its language can be seen to some extent as a different historical experimental pathway taken by humans, with a different record of success and failure. Each time that a culture/language goes extinct, and this is happening quite rapidly (up to 4000 of the 7000 have or will become extinct by 2100), we lose thousands of years of wisdom, data, and much more. We do recognize that all of humanity has a shared-derived history implying that at least minimally some features of human experiences overlap with each other and that some of these, in the form of languages, are similar to each other. However, who can predict which one culture (language) has made the unique break through that could be most important in the future and who is willing to risk casting that culture (language) aside because it is so similar to another.

As plants diverge evolutionarily they diverge chemically creating new opportunities in the grand experiment of life. As cultures diverge linguistically they develop new vocabularies. This is particularly true because of close encounters with divergent plants in a biodiversity hotspot where we expect that knowledge will develop about that plant diversity and its chemistry that will be unique. Therefore, biodiversity hotspots should be focal points for research on natural products research of any sort, but particularly, ethnobotanical guided research, such as focused efforts to find new CNS-active plants. It is well worth noting that four of the five plants selected for longer examination in this paper were learned from small cultures in biodiversity hotspots: *Hoodia*, *P. methysticum*, and *S. divinorum* and the fourth, *H. perforatum*, possibly has its origin in the distant past (Robinson, 1981) in a biodiversity hotspot.

4.5. Marine ethnobotany

Marine natural product chemistry continues to be an area blossoming with new molecules yet few new drugs have emerged. An area not addressed in this paper that will hopefully begin to emerge in the near future is marine ethnopharmacology. There are many cultures around the world wherein traditional medicinal practices include a variety of marine plants and animals. An example can be seen in the thesis work of Hawaiian ethnobotanist Kaleleonalani Napoleon who learned from Papa Henry Allen Auwae on the Island of Hawai`i. Within this research Napoleon (2004) learned knowledge about 31 medicinally important algae. None of these species have been tested pharmacologically for any of the indications for which Hawaiians are employing them today. Ethnobotanical research has only just begun to take place in other parts of the world as scholars are beginning to realize that people in local communities have long used marine resources (Abbott, 1992; Turner, 1999; Ostraff, 2006) for food and medicines.

4.6. Future ethnobotanical research directions

Although thousands of new molecules have been described from plants, including plants used medicinally in hundreds of cultures, none of the recent ethnobotanical leads that we can identify have become pharmaceuticals in the United States in at least the last forty years (McClatchey, 2005). This may seem surprising given the amount of effort invested in exploration during this period of time. However, ethnobotanical leads are still considered by pharmacognocists to be good sources of new chemical structures (see Do & Bernard, 2006) that can serve as the basis for development of pharmacophores.

The task for ethnobotanists has become more complex now than it was in the past. We do not really have new cultures to find; rather we are focused upon developing depth of knowledge about the more than 4000 culture-language groups that are rapidly disappearing.

A fundamental problem faced by ethnobotanists is that research on plant medicines may not always result in clear discernment of mechanisms of action, rather only implications of generalized mechanisms “showing activity” or “involvement in” one system or another, or “suggesting activity in”, etc. What is clearly needed is a closer link between ethnobotanical field researchers (those who conduct the ethnographic interviews with people who actually use medicinal plants within cultures) and the laboratory pharmacologists (those who are designing and conducting the analyses of biological activity of medicinal plants based on hypotheses generated from cultures).

Many ethnobotanists are shifting their research efforts to focus on biodiversity hotspots. As we do, the need for collaborations with laboratory biologists will intensify because the encounters with new (to science) and previously unencountered plants and plant chemistry will increase. The same will be true as marine ethnopharmacology emerges as a focus of study.

4.7. A bucket of pills

One of the points of this paper is to show that practitioners of modern pharmaceutical medicine approach their problems from the opposite perspective of many other cultures. This difference is shown clearly in an example from an encounter that occurred in Madagascar while doing field research with the staff of the Missouri Botanical Garden. Dr. Lisa Gollin and the first author observed a sight that is sadly common in many developing nations. A vendor in the marketplace had a bucket full of loose unit dose pharmaceuticals. She sold the pills to any person who wanted to purchase them. No package inserts were available to the purchasers or the vendor and neither had any idea what the approved indications were for any of the medications for sale. When the vendor was asked how customers made a selection, she said they made their choices based on the color or taste of the tablet or capsule. The vendor had apparently tasted each of the tablets and capsules and knew which were bitter; the colors were obvious. The purchasers used traditional logic about the meaning of color and taste as indicators of the medicinal qualities. They also applied traditional dosing logic to determine how many units should be purchased, how they should be used (e.g., a capsule might be dissolved in water and drunk over a period of time, or a tablet might be ground into a paste and applied externally), and the period of use. As people trained in the practice of using modern pharmaceuticals, where medicines must be accompanied with information, we found this situation shocking.

On reflection, however, we can see that this practice is even common in our society. Consider that there is an array of herbal products that are for sale to the general public in forms, dosages, and

with directions that are alien to their cultures of origin, yet their efficacy is often based on "tradition of use."

We also do the same thing when we bring plant materials into the laboratory and examine them for potential uses without also bringing in the ethnobotanical data. This is akin to having the tablet in hand and leaving behind the information that is known about its use. We begin our laboratory studies much in the same way as the vendor in Madagascar; we guess at its use by examining its taste and color. Are there not then some parallels between a "bucket of pills" and natural products in that their intended use by one culture may not reflect the actual use in another culture?

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