PHYTOTHERAPY RESEARCH
Phytother. Res. **27**: 552–563 (2013)
Published online 7 June 2012 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.4749

Formulas Used by Tibetan Doctors at Men-Tsee-Khang in India for the Treatment of Neuropsychiatric Disorders and Their Correlation with Pharmacological Data

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The aim of the present study was to identify formulas used at Men-Tsee-Khang (Tibetan Medical and Astrological Institute), India, for the treatment of neuropsychiatric disorders and to compare the Tibetan usage of particular ingredients with pharmacological data from the scientific database. Using ethnographic methods, five doctors were selected and interviewed. A correlation was observed between central nervous system disorders and *rLung*, one of the three humors in Tibetan medicine, which imbalance is the source of mental disorders, and ten multi-ingredient formulas used to treat the imbalance of this particular humor were identified. These formulas utilize 61 ingredients; among them were 48 plant species. Each formula treats several symptoms related to *rLung* imbalance, so the plants may have therapeutic uses distinct from those of the formulas in which they are included. *Myristica fragrans*, nutmeg, is contained in 100% of the formulas, and its seeds exhibit stimulant and depressant actions affecting the central nervous system. Preclinical and clinical data from the scientific literature indicate that all of the formulas include ingredients with neuropsychiatric action and corroborate the therapeutic use of 75.6% of the plants. These findings indicate a level of congruence between the therapeutic uses of particular plant species in Tibetan and Western medicines. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: ethnopharmacology; medicinal plants; neuropsychiatric plants; Tibetan medicine; traditional medicine; Men-Tsee-Khang.

INTRODUCTION

In 1959, following the Chinese occupation of Tibet, the Dalai Lama and approximately 80 000 Tibetan refugees escaped to India in political exile. From this point, Dharamsala, a small city in the state of Himachal Pradesh in northern India, has been the site of the Tibetan Central Administration (Bhatia *et al*., 2002). In exile, Tibetans sought to maintain their cultural traditions, including the traditional medicine, which is currently taught and practiced at Men-Tsee-Khang, formally known as the Tibetan Medical and Astrological Institute of His Holiness the Dalai Lama.

A recent bibliographic search found that the majority of studies about Tibetan medicine pertain to pharmacological and phytochemical research and that few studies utilize an ethnopharmacological approach (Finckh, 1981, 1984; Begley, 1994; Ryan, 1997; Loizzo and Blackhall, 1998; Tokar, 1999; Zhen, 2000; Dakpa and Dodson-Lavelle, 2009a, 2009b; Loizzo *et al*., 2009). Among the ethnopharmacological studies, only a few described the plants used in Tibetan medicine, and the majority of these studies focused on Nepal, China, and the Ladakh region in India (Bhattarai *et al*., 2006; Ballabh and Chaurasia, 2007; Ballabh *et al*., 2008; Liu *et al*., 2009; Witt *et al*., 2009; Bhattarai *et al*., 2010).

Mental disorders affect a large portion of the world's population (Kessler *et al*., 2005). These disorders are components of comorbid conditions (Krueger, 1999) and a major cause of disability (Üstün, 1999). For example, major depressive disorder is the fourth-ranked cause of disability worldwide (Üstün *et al*., 2004) and is commonly identified in patients with chronic physical disorders (Moussavi *et al*., 2007). Individuals with mental disorders are frequently stigmatized, which impairs their social relationships and sometimes prevents them from seeking out treatment. With regard to neurological disorders, there are approximately 25 million people living with Alzheimer's disease, and this number is predicted to reach 81.1 million by the year 2040. Multiple sclerosis affects 2.5 million people worldwide and is one of the most common neurological disorders in young adults (WHO, 2006).

In this article, we present a survey of the medicinal formulas used at Men-Tsee-Khang in India for the treatment of neuropsychiatric disorders and compare the usage of medicinal plants with pharmacological data from the scientific literature.

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Received 22 December 2011
Revised 25 April 2012
Accepted 30 April 2012

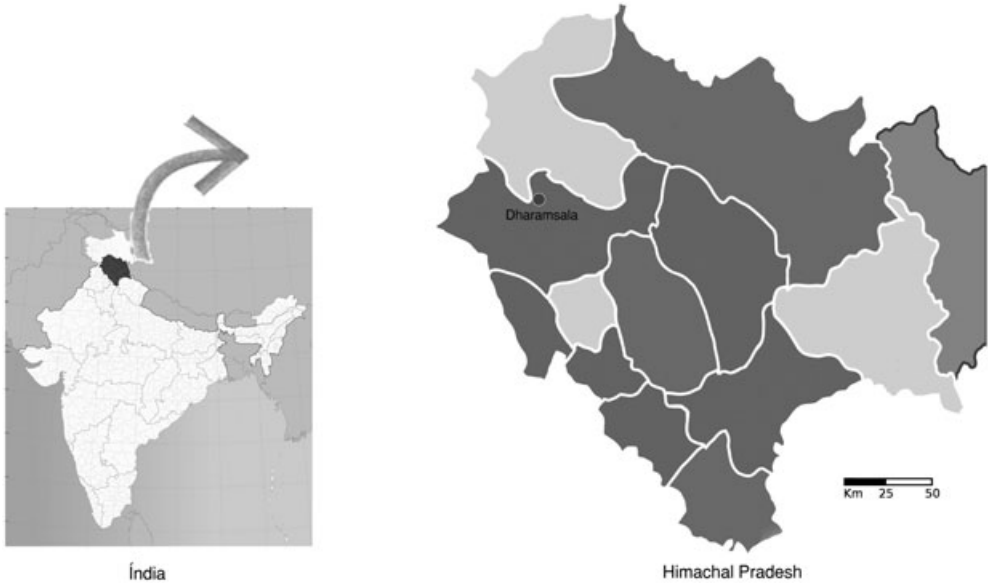

Figure 1. Localization of Dharamsala city, Himachal Pradesh state, India.

MATERIALS AND METHODS

Study area. Men-Tsee-Khang is located in Dharamsala in the Kangra district of the state of Himachal Pradesh (Fig. 1) in the western Himalayan region.

Men-Tsee-Khang. Men-Tsee-Khang was first established in Lhasa, Tibet, in 1916 by the Dalai Lama XIII and in Dharamsala, India, in 1961 by the Dalai Lama XIV (Kala, 2005; Salick *et al.*, 2006). It is an institutional center for culture and education and promotes its activities at several universities around the globe. Men-Tsee-Khang has departments dedicated to research in *materia medica*, pharmacology, and clinical epidemiology. The *materia medica* department has had a herbarium since 1990, which contains hundreds of plant species used by Tibetan doctors.

Field research. The field research for the present study was conducted from July 2010 to February 2011 by R.L. Antonio. This study was approved by the Universidade Federal de São Paulo (UNIFESP) ethics committee under the process number 0427/10. In addition to the establishment of an agreement for scientific, academic, and technological collaboration between UNIFESP and Men-Tsee-Khang, other specific documents for this study were signed.

Selection of the respondents, interviews, and observations. Five doctors were designated as respondents for the study by the director of Men-Tsee-Khang, Dr Tsewang Tamdin, based on their extensive experience with the use of medicinal plants.

The personal information of the respondents and relevant ethnopharmacological information were obtained using anthropological methods and techniques for field research (Foote-Whyte, 1980; Bernard, 1988; Malinowski, 1990) in the form of informal interviews, nonstructured interviews, participant observation, and notes in the field diary. One month after gathering the information, the respondents were interviewed again using a checklist of questions to review the data previously provided. The interviews were carried out in English.

The initial interview focused on the following topics: emic[1] categorization, the basic principles of Tibetan medicine and its concepts of health and disease, comprehension of the elements equivalent to the central nervous system (CNS) and possible neuropsychoactive substances according to biomedicine. The respondents recommended the book *Fundamentals of Tibetan Medicine* (Men-Tsee-Khang, 2001) to the researcher. Considering the relationship between the *rLung* humor and the mind (see Section on Mind and *rLung*), some of the interview questions were about formulas having psychoactive and neurological effects, in other words, formulas used for the treatment of the neuropsychiatric disorders that were evocated during the interviews. The formulas were subsequently registered, and the ingredients were identified by their Tibetan and scientific names, with the latter according to the available material at the Men-Tsee-Khang herbarium. The doctors from the *materia medica* department were each interviewed about the therapeutic usage of each ingredient.

Literature search. Between February and May 2011, a literature review was performed using the PubMed, Web of Science, and Scopus databases to identify studies that investigated the pharmacological actions of the plant species contained in the formulas provided by the Tibetan doctors for the treatment of neuropsychiatric disorders.

RESULTS

All data presented in this section were obtained through the interviews.

[1]The attempt to discover and describe the behavior system of a certain culture using its own terms (D'Olne Campos, 2002).

Tibetan medicine as practiced at Men-Tsee-Khang, Dharamsala

In Tibetan medicine, the understanding of physiology utilizes a humoral principle that can ultimately be simplified to a dichotomy between hot and cold. The three humors, *rLung*, *mKhris-pa*, and *Bad-kan*, are contained in the human body and coordinate several organs and systems. The respondents explained that these humors, or energies, are normally balanced in the body and that the imbalance of these energies causes disease. Although the humors have distinct functions, they are interdependent and work together.

The general functions of *rLung* are to control breathing, excretions, movement, circulation, heartbeat, and operation of the sense organs. The sense organs, together with consciousness, form the mind. The general functions of *mKhris-pa* are to control sensations of hunger and thirst, digestion, nutrient absorption, production of body heat, and body complexion. Finally, the general functions of *Bad-kan* are to promote body strength, to facilitate the movement and connectivity of the body joints, to promote skin softness, and to control lubrication.

Diagnosis is done through observation of physical and mental aspects of the patient, palpation, and interrogation. Physical examinations of pulse and urine are extremely important, as they provide the most relevant information about the disease—whether it is hot or cold. The initial therapeutic approach addresses dietary needs and involves counseling for behavioral concerns, which may be sufficient to restore health if the disorder is mild. Nevertheless, the use of medicinal formulas is the most visible approach in the clinical setting. When prescribing a formula, several factors are taken into consideration, including the age of the patient, the stage of development of the disease, whether the disease conditions are chronic or acute, and whether the disease is a component of a comorbid condition. One specific formula is not applied to all instances of a disease; instead, the formula is selected specifically for the patient, with many factors taken into consideration.

Mind and *rLung*

According to the respondents, consciousness and the five sense organs comprise the mind. The sense organs process sensorial information through the action of *rLung*, and this information (sound, texture, vision, taste, and smell) stimulates or depresses mental activity. There is a normal state of mental activity, and there are unhealthy conditions, in which the mind becomes disturbed, resulting in excitement and/or depression caused by *rLung* imbalance. In other words, mental activity is affected when *rLung* is disturbed, along with other functions of the body related to this particular humor.

From the perspective of Tibetan medicine, medication treats *rLung* rather than the mind, and *rLung* imbalance is the source of mental disorders and other symptoms. Furthermore, it is possible to strengthen the nervous tissue, *sok tza karpo* (white vital channels), to prevent disease. In this regard, Parkinson's disease, Alzheimer's disease, and multiple sclerosis are especially related to *rLung* imbalance at the level of nervous tissue. For these types of diseases, accessory therapies are given, such as moxabustion, which involves stimulation using acupuncture points with burning herbs (Cardini and Huang, 1998), medicinal baths, acupuncture, and oil application at *rLung* trigger points. According to the respondents, patients report an improvement in concentration, memory, relaxation, and sleep after treatment for *rLung* imbalance, even if these symptoms were not part of the initial complaint.

Respondents—Tibetan doctors

Four respondents provided information about the formulas used for the treatment of neuropsychiatric disorders, with three of the respondents from the *materia medica* department and the other from the clinical department. All of the respondents are men, with their ages ranging from 40 to 53 years, and all were born outside of India: three from Tibet and one from Nepal. All of the respondents were trained at Men-Tsee-Khang, with two having graduated at Lhasa and the other two at Dharamsala. Their experience with Tibetan medicine ranges between 14 and 36 years of practice. The fifth respondent, from the pharmaceutical department, provided information regarding aspects of production and quality control of the formulas and not about the therapeutic use of the ingredients.

Medicinal ingredients

Tibetan medicine practiced at Men-Tsee-Khang and according to the classical texts includes over 2000 ingredients in its repertoire, which are utilized in hundreds of formulas. The main ingredients are plant materials, but minerals, salts, and animal products (pearl and pearl-shell) are also described. Please note that the formulas are in their classical composition, according to Tibetan medicine. Nowadays, Men-Tsee-Khang in Dharamsala is seeking to substitute animal products and some plants for different ingredients with similar properties due to ethical and ecological awareness.

Tibetan medicinal substances are typically multi-ingredient formulas, with limited use of single-ingredient treatments. Synergism is a quality of the former, and according to the respondents, it makes the action of each plant more "smooth," which allows the formula to be used for a longer period, to have fewer side effects, and to be used for a greater number of conditions.

Men-Tsee-Khang in Dharamsala produces approximately 170 different formulas utilizing 200 different ingredients. Ingredients may be used in multiple formulas, and a given multi-ingredient formula may have more than one usage. Each ingredient is associated with a particular use, and the formulas containing them may be used to treat others symptoms of humor imbalance beyond the primary usage of the formula itself. The imbalance of *rLung*, described as the underlying cause of neuropsychiatric disorders, provokes other symptoms, and the formulas are also intended to treat these symptoms. The plant species *Choerospondias axillaris* (Roxb.) B.L. Burtt & A.W. Hill is an ingredient in 80% of the formulas used for the treatment of *rLung* neuropsychiatric disorders. According to the respondents, this is one of the most commonly used plants for heart disorders, which are

common symptoms resulting from *rLung* imbalance. The number of ingredients in the formulas used by the doctors for the treatment of neuropsychiatric disorders ranges from 8 to 35 ingredients.

Of the 170 formulas produced at Men-Tsee-Khang for the treatment of a wide range of disorders, ten formulas were identified by the four doctors for the treatment of neuropsychiatric disorders. Some of these formulas were identified by all respondents for particular disorders, whereas others were cited by only one. For example, as shown in Table 1, *Sok zin 11* was identified by all four respondents for psychosis, whereas only one respondent prescribed this formula for memory disturbance. There are different pharmaceutical forms utilized in Tibetan medicine, with powder and pills, consumed orally, being the most common forms. Nine of the formulas identified in this study are pills, and *Agar 31* is incense. The pills are usually administered three times a day, and one dose typically corresponds to three pills.

Usage of plants in Tibetan medicine and pharmacological studies

The ten formulas utilize 61 ingredients, among them 53 plants. In this study, we present only the 48 vegetable species that could be identified. Although the animal products pearl and pearl-shell are included in some of the formulas, it was not possible to obtain their taxonomic classification. They are used for lesions in the nervous tissue (e.g., accidents in which the brain tissue is exposed), but studies describing this type of pharmacological action were not found for the generic names *pearl*, *pearl-shell*, or *nacre*.

The 48 vegetable species are listed in Table 2, along with the frequency of the use of these plants in formulas, their therapeutic neuropsychiatric uses, and other uses related to *rLung* imbalance. The latter uses—such as "to purify the blood," "to treat stomach disorders," and "to treat pain caused by inflammation,"—that were corroborated by pharmacological studies are also presented in Table 2. However, these references are not listed in this study, and only the references corroborating the neuropsychiatric treatments are shown.

As shown in Table 2, research studies describing the pharmacological use of 41 of the 48 plants species were identified, and no pharmacological studies were found for the remaining seven species. Of the 41 plants, the emic usage of 31 plants (75.6%)—uses related to *rLung* imbalance other than neuropsychiatric disorders—is coincident with the biological activity described in the studies, and neuropsychiatric action has been described for 24 of the plants in the list (58.5%). In addition, all ten formulas include at least one ingredient whose neuropsychiatric action has been described in the literature.

DISCUSSION

The use of multi-ingredient formulas is commonly observed in some traditional systems, as Chinese medicine and Ayurveda (Fabricant and Farnsworth, 2001) as well as Tibetan medicine. Williamson (2001) and Spinella (2002) have both described the synergism observed with the use of herbal medicine. In this context, *synergism* is defined as the effect derived from a combination of substances that is greater than the expected summation of its individual effects. Synergism may reflect the diversity of active compounds contained in a single plant (as opposed to an isolated compound) and the combination of ingredients in a particular formula. There are two types of synergism, pharmacodynamical and pharmacokinetical synergism, which describe different modes of interaction. Pharmacodynamical synergism is the effect of two different drugs directed at the same physiological system or receptor. Pharmacokinetical synergism, on the other hand, results from the metabolism of drugs, that is, the competition among different drugs that occurs at the levels of absorption, distribution, biotransformation, or elimination.

Synergism may also involve multitarget effects by acting on enzymes, metabolites, proteins, receptors, and ionic channels (Wagner and Ulrich-Merzenich, 2009). There are several examples of synergism in plants or formulations with psychoactive effects, including *Cannabis sativa* L., which is a therapeutic agent with analgesic, muscle relaxant, sedative, appetite enhancement, and

Table 1. Ten neuropsychiatric formulas and the number of respondents among four Men-Tsee-Khan's doctors that identified their therapeutic usage

Name of the formulas[a]	Parkinson's disease	Alzheimer's disease	Multiple sclerosis	Psychosis	Memory disorders	Sleep disorders	Anxiety	Depression	Sense organs disorders
Sem de	2	2	2	2	1	0	0	0	0
Sok zin 11	3	3	3	4	1	0	1	1	0
Shing kung 25	1	1	1	2	1	0	0	0	0
Bimala	1	1	1	1	1	0	1	1	0
Agar 8	1	1	1	1	2	2	0	0	1
Agar 15	0	0	0	0	1	1	0	0	1
Agar 20	1	1	1	2	1	1	0	0	1
Agar 31	0	0	0	0	0	1	0	0	0
Agar 35	2	2	2	2	2	4	0	2	1
Moe dik 25	1	1	1	1	1	0	0	0	0

[a]The number that follows the name of the formula indicates the quantity of ingredients contained on it.

Table 2. Forty-eight vegetable species utilized in ten neuropsychiatric formulas identified by four Tibetan doctors from Men-Tsee-Khang, the frequency of citation of the formulas, and the plants' individual usage and neuropsychiatric effects according to scientific literature

Botanical and popular names	Frequency of citation and name of the formulas in which it is utilized	Tibetan therapeutic usage[a]	Neuropsychiatric effects (scientific literature)
1. Aconitum violaceum Jacquem. ex Stapf (Ranunculaceae)—*pong nak*	10%—*Moe dik 25*		Anticonvulsant (Raza *et al.*, 2009)
2. Acorus calamus L. (Acoraceae)—*shu dak* (sweet flag)	10%—*Shing kung 25*	*Gak lok*[b]; to reduce *rLung*	Antiepileptic (Hazra *et al.*, 2007); anticonvulsant (Manis *et al.*, 1991); sedative (Bhattacharya, 1968); CNS depressant (Zaugg *et al.*, 2011); anticholinesterasic and memory enhancer (Mukherjee *et al.*, 2007); neuroprotective (Palani *et al.*, 2010); behavioral changes (Shukla *et al.*, 2006).
3. Adhatoda vasica Nees (Acanthaceae)—*ba sha ka* (Malabar nut tree)	20%—*Agar 31*; *Agar 35*	Fever[c] in the liver	
4. Allium sativum L. (Amaryllidaceae)—*gok thal* (garlic)	20%—*Bimala*; *Shing kung 25*	To combat microorganisms, food poisoning, and leprosy	Neuroprotective (Ray *et al.*, 2011); memory enhancer (Haider *et al.*, 2008).
5. Amomum tsaoko Crevost & Lemarié (Zingiberaceae)—*ka ko la*	40%—*Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*		
6. Aquilaria agallochum (Lour.) Roxb. ex Finl. (Thymelaeaceae)—*ar nak*	90%—*Agar 8*; *Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Sem de*; *Shing khung 25*; *Sok zin 11*	Different *rLung* disorders; important for brain/mind; diseases of the vital channels, mostly *sok tza karpo*[d], in which the person goes crazy and loses consciousness	CNS depressant (Okugawa *et al.*, 1993); anxiolytic and anticonvulsant (Alla *et al.*, 2007).
7. Aquilaria sinensis (Lour.) Spreng. (Thymelaeaceae)—*ar kya*	20%—*Agar 31*; *Agar 35*	*rLung* disorders; fever[c] in the *sok tza karpo*[d]	
8. Areca catechu L. (Arecaceae)—*gu yu karpo* (areca nut palm)	10%—*Sem de*	To enhance kidney's heat	Antidepressant (Dar & Khatoon, 2000); promotes tremors[e] (Hafeman *et al.*, 2006)
9. Bambusa textilis McClure (Poaceae)—*chu kang*	80%—*Agar 8*; *Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*; *Sok zin 11*		Without scientific studies for pharmacological activity
10. Bergenia purpurascens (Hook. f. & Thomson) Engl. (Saxifragaceae)—*li ga dur*	10%—*Bimala*	*Rim*[f] with fever[c]	
11. Bombax ceiba L. (Malvaceae)—*goe sar* (cotton tree)	50%—*Agar 8*; *Agar 20*; *Agar 31*; *Agar 35*; *Sok zin 11*		
12. Boswellia carteri Birdw. (Burseraceae)—*poe kar* (frankincense)	70%—*Agar 8*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Shing khung 25*; *Sok zin 11*	Reduces the increase of *chu ser*[g]	
13. Carthamus tinctorius L. (Asteraceae)—*gur ghum* (safflower)	60%—*Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*	*rLung* disorders	Neuroprotective (Tian *et al.*, 2008); neuromodulator (Zhao *et al.*, 2009b); memory enhancer (Huang *et al.*, 2007); antidepressant (Zhao *et al.*, 2009a)
14. Carum carvi L. (Apiaceae)—*go nye* (caraway)	30%—*Agar 31*; *Bimala*; *Shing khung 25*	*rLung* disorders; poisoning; used externally with *za ti* in the form of a bundle to restore consciousness and concentration in *rLung* unbalance, in cases of craziness	Adaptogen and nootropic (Koppula *et al.*, 2009)

(Continues)

Table 2. (Continued)

Botanical and popular names	Frequency of citation and name of the formulas in which it is utilized	Tibetan therapeutic usage[a]	Neuropsychiatric effects (scientific literature)
15. Chaenomeles speciosa (Sweet) Nakai (Rosaceae)—*ce yap* (flowering quince)	10%—*Agar 20*		Inhibition of dopamine transport and antiparkinson (Zhao *et al.*, 2008)
16. Choerospondias axillaris (Roxb.) B.L. Burtt & A.W. Hill (Anacardiaceae)—*nying sho sha*	80%—*Agar 8*; *Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Sem de*; *Sok zin 11*	Main plant to heart disorders with fever[c]	
17. Chrysanthemum tatsienense Bureau & Franch. (Asteraceae)—*zen jom*	20%—*Agar 31*; *Agar 35*		Without scientific studies for pharmacological activity
18. Cinnamomum cassia (L.) D. Don (Lauraceae)—*sheng tsa* (cassia)	20%—*Shing khung 25*; *Moe dik 25*	*rLung* disorders; stops diarrhea; chronic lungs inflammation with pus	Anxiolytic (Yu *et al.*, 2007); antineuroinflammatory (Hwang *et al.*, 2011)
19. Cinnamomum parthenoxylon (Jack) Meisn. (Lauraceae)—*agar go nye* (selasian wood)	20%—*Agar 20*; *Agar 35*	*rLung* disorders	
20. Commiphora mukul (Hook. ex Stocks) Engl. (Burseraceae)—*gul nak*	20%—*Agar 35*; *Shing kung 25*	Pain caused by inflammation	
21. Crocus sativus L. (Iridaceae)—*kha che gur ghum* (saffron)	10%—*Moe dik 25*		Glutamatergic inhibition (Berger *et al.*, 2011); neuroprotective (Shati *et al.*, 2011); antidepressant (Wang *et al.*, 2010); antioxidant (Saleem *et al.*, 2006); antiparkinson (Ahmad *et al.*, 2005); anxiolytic (Hosseinzadeh & Noraei, 2009); hypnotic (Hosseinzadeh & Noraei, 2009); memory enhancer (Pitsikas *et al.*, 2007)
22. Cuminum cyminum L. (Apiaceae)—*zee ra karpo* (cumin)	10%—*Moe dik 25*	Infection of an *rLung* nature	Antiepileptic (Janahmadi *et al.*, 2006); anticonvulsant (Sayyah *et al.*, 2002); beneficial to morphine's conditioning (Khatibi *et al.*, 2008); sedative (Shams *et al.*, 2009)
23. Elettaria cardamomum (L.) Maton (Zingiberaceae)—*shuk mel* (cardamom)	50%—*Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*; *Shing khung 25*	Kidney disorders; enhances stomach heat	Sedative (Gilani *et al.*, 2007)
24. Ferula assa-foetida L. (Apiaceae)—*shing kung* (asafoetida)	40%—*Bimala*; *Sem de*; *Shing khung 25*; *Sok zin 11*	Virus infection	
25. Fragaria nubicola (Hook. f.) Lindl. ex Lacaita (Rosaceae)—*dreta sa zin*	20%—*Agar 20*; *Moe dik 25*	Inflammation in the *sok tza karpo*[d]	Without scientific studies for pharmacological activity
26. Inula racemosa Hook. f. (Asteraceae)—*ma nu*	50%—*Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Shing khung 25*	*rLung* and blood disorders	
27. Lygodium flexuosum (L.) Sw. (Lygodiaceae)—*ser ched*	10%—*Moe dik 25*		
28. Malva verticillata L. (Malvaceae)—*cham du* (Chinese mallow)	10%—*Moe dik 25*	Diarrhea; wounds	
29. Meconopsis horridula Hook. f. & Thomson (Papaveraceae)—*tser nyon* (blue poppy)	20%—*Agar 31*; *Agar 35*	*rLung* disorders with fever[c]	Without scientific studies for pharmacological activity

(Continues)

Table 2. (Continued)

Botanical and popular names	Frequency of citation and name of the formulas in which it is utilized	Tibetan therapeutic usage[a]	Neuropsychiatric effects (scientific literature)
30. Myristica fragrans Houtt. (Myristicaceae)—*za ti* (nutmeg)	100%—*Agar 8*; *Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*; *Sem de*; *Shing khung 25*; *Sok zin 11*	Very important in *rLung* disorders; *rLung* unbalance affecting the heart; used externally in the form of a bundle to restore consciousness and concentration in *rLung* unbalance, in cases of craziness	Anxiogenic (Sonavane *et al.*, 2002); memory enhancer (Parle *et al.*, 2004); antidepressant (Dhingra & Sharma, 2006); sedative (Grover *et al.*, 2002); anticonvulsant (Wahab *et al.*, 2009); psychotropic (Beyer & Maurer, 2005)
31. Myrobalanus chebula (Retz.) Gaertn. (Combretaceae)—*a ru* (chebulic myrobalan)	90%—*Agar 8*; *Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*; *Shing khung 25*; *Sok zin 11*	Any disorder, known as "king of medicines"	Anticonvulsant (Debnath *et al.*, 2010)
32. Neopicrorhiza scrophulariiflora (Pennell) D.Y. Hong (Plantaginaceae)—*hong len*	20%—*Agar 31*; *Agar 35*		Neuroprotective (Li *et al.*, 2010); promotes neural growth (Li *et al.*, 2000)
33. Phyllanthus emblica L. (Phyllanthaceae)—*kyu ru* (Indian gooseberry)	60%—*Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*	Blood disorders as hypertension; cholesterol; diabetes; improve digestion; lungs disorders; initial state of liver disorders; rich in C vitamin	Memory enhancer (Wanasuntronwong, 2008)
34. Piper longum L. (Piperaceae)—*pi pi ling* (long pepper)	30%—*Moe dik 25*; *Sem de*; *Shing khung 25*	Lungs disorders	Neuroprotective (Subramanian *et al.*, 2010); antidepressant (Lee *et al.*, 2005); memory enhancer (Chonpathompikunlert *et al.*, 2010); hypnotic (Mujumdar *et al.*, 1990); GABA-A modulator (Zaugg *et al.*, 2010); antidepressant (Mao *et al.*, 2011); cognition enhancer (Wattanathorn *et al.*, 2008)
35. Piper nigrum L. (Piperaceae)—*pho wa ril* (black pepper)	20%—*Sem de*; *Shing khung 25*	Enhances appetite	Neuroprotective (Fu *et al.*, 2010); memory enhancer (Chonpathompikunlert *et al.*, 2010); hypnotic (Mujumdar *et al.*, 1990); GABA-A modulator (Zaugg *et al.*, 2010); antidepressant (Mao *et al.*, 2011); cognition enhancer (Wattanathorn *et al.*, 2008)
36. Pterocarpus santalinus L. f. (Fabaceae)—*tsen den marpo* (red sandalwood)	60%—*Agar 15*; *Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*	To treat thick blood; high cholesterol; a paste with water reduces swelling	
37. Pulicaria insignis Drumm. ex Dunn (Asteraceae)—*men chen serpo*	20%—*Agar 31*; *Agar 35*		Without scientific studies for pharmacological activity
38. Punica granatum L. (Lythraceae)—*se du* (pomegranate)	30%—*Agar 31*; *Agar 35*; *Shing khung 25*	Stomach disorders; one of the best medicines to increase digestive power	Neuroprotective (Hartman *et al.*, 2006); aphrodisiac (Türk *et al.*, 2008)
39. Rubus niveus Thunb. (Rosaceae)—*ken ta kari* (hill raspberry)	30%—*Agar 15*; *Agar 31*; *Agar 35*		
40. Saccharum sinense Roxb. (Poaceae)—*bu ram* (sugar cane)	10%—*Sem de*		
41. Santalum album L. (Santalaceae)—*tsen den karpo* (sandalwood)	50%—*Agar 15*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*	Heart disorders with fever[c] (caution if *rLung* is high; it may provoke headache or dizziness)	Memory enhancer (Azmathulla *et al.*, 2010)
42. Saxifraga umbellulata Hook. f. & Thomson (Saxifragaceae)—*sum tik*	10%—*Agar 35*		Without scientific studies for pharmacological activity

(Continues)

Table 2. (Continued)

Botanical and popular names	Frequency of citation and name of the formulas in which it is utilized	Tibetan therapeutic usage[a]	Neuropsychiatric effects (scientific literature)
43. Solms-laubachia pulcherrima Muschl. ex Diels (Brassicaceae)—*soo loo karpo*	30%—*Agar 15*; *Agar 31*; *Agar 35*	*rLung* disorders	Without scientific studies for pharmacological activity
44. Strychnos nux-vomica L. (Loganiaceae)—*ko chi lha* (strychnine tree)	30%—*Agar 20*; *Agar 31*; *Agar 35*	Back pain due to hypertension of an *rLung* nature; poisoning with fever[c]	Anticonvulsant (Parida *et al.*, 2010); antiepileptic (Katiyar *et al.*, 2010); nicotinic antagonist (Daly, 2005); reduces alcohol consumption (Sukul *et al.*, 2001)
45. Syzygium aromaticum (L.) Merr. & L.M. Perry (Myrtaceae)—*li shi* (clove)	80%—*Agar 20*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*; *Sem de*; Shing khun 25; *Sok zin 11*	*Sok tza karpo*[d] affected by *rLung*; to treat excess of heat in the stomach	Neuropathic pain (Lionnet *et al.*, 2010); aphrodisiac (Tajuddin *et al.*, 2004); memory enhancer (Halder *et al.*, 2011); anticonvulsant (Pourgholami *et al.*, 1999)
46. Terminalia bellirica (Gaertn.) Roxb. (Combretaceae)—*ba ru* (bastard myrobalan)	50%—*Agar 15*; *Agar 31*; *Agar 35*; *Bimala*; *Moe dik 25*	*rLung* disorders; *tsa tu*[h]	Antidepressant (Dhingra & Valecha, 2007)
47. Tinospora sinensis (Lour.) Merr. (Menispermaceae)—*le tay*	40%—*Agar 15*; *Agar 31*; *Agar 35*; *Shing khung 25*	To restore balance of the three humors; strengthens the elderly	
48. Zingiber officinale Roscoe (Zingiberaceae)—*ga kya* (ginger)	50%—*Agar 15*; *Agar 31*; *Agar 35*; *Sem de*; *Shing khung 25*	Enhances digestive power; *rLung* disorders; improves blood circulation; purifies the blood	Neuroprotective (Wattanathorn *et al.*, 2011); nootropic (Joshi & Parle, 2006); memory enhancer (Wattanathorn *et al.*, 2011); anxiolytic (Vishwakarma *et al.*, 2002)

[a]Uses referred to *rLung* imbalance, other than neuropsychiatric disorders, which were corroborated by pharmacological studies; and uses referred to neuropsychiatric disorders, corroborated or not by pharmacological studies.
[b]Inflammation with swelling in the neck region.
[c]Increased body heat, not necessarily temperature.
[d]Nerves.
[e]Effect related with the chronic chewing of the nut.
[f]Infectious diseases.
[g]Plasma.
[h]Hot diarrhea.

antiemetic properties, among others (Grotenhermen, 2003). The levels of tetrahydrocannabinol, one of the molecules responsible for the therapeutic effects, are elevated by the presence of another molecule known as cannabidiol; at the same time, some unwanted effects of tetrahydrocannabinol, such as anxiety, may be reduced by cannabidiol (Zuardi *et al.*, 1982).

Some spice plants exhibit the synergistic effect of facilitating absorption and/or the metabolism of other compounds. These species can simultaneously affect transit time, bile secretion, and enzymes of the pancreas and small intestine (Platel and Srinivasan, 2004). Piperine, for example, is a compound contained in some peppers that enhances the bioavailability of other substances and acts on the intestinal cells (Johri *et al.*, 1992; Srinivasan, 2007). *Piper longum* L., a plant with high levels of the piperine compound, is contained in 30% of the formulas used by Tibetan doctors to treat neuropsychiatric disorders. Piperine modulates the GABA-A receptor (Zaugg *et al.*, 2010), thereby allowing the entrance of chloride molecules, and its activity is similar to the anxiolitic effects of the benzodiazepines (Rudolph *et al.*, 1999). Moreover, as mentioned, piperine may enhance the bioavailability of other substances in the formula in which it is contained; examples in this study include *Moe dik 25*, *Sem de*, and *Shing khung 25* (Table 2).

The fact that each formula was prescribed for different usages by the respondents (Table 1) could be due to the result of the synergistic effects of these formulas, which act on distinct systems (Sarris *et al.*, 2011). These formulas may also have adaptogenic effects, which are described as "increased attention and endurance in fatigue, and reduced stress-induced impairments and disorders related to the neuro-endocrine and immune systems" (Panossian and Wikman, 2010).

Table 2 shows that some plants occur in great frequency in the formulas used for neuropsychiatric disorders, and we could assume that in Tibetan medicine they are more relevant to these disorders.

Myristica fragrans Houtt. (nutmeg) is contained in 100% of the formulas. Its seeds have psychotomimetic actions and also exhibit stimulant and depressant actions affecting the CNS (Sonavane *et al.*, 2002). El-Alfy *et al.* (2009) compared the effects of oral and intraperitoneal administration of this species; oral

administration of different nutmeg extracts stimulates locomotor activity, whereas intraperitoneal administration of the oily metanolic extract depresses this activity. The U-shaped curve characterizing the locomotor activity resulting from oral administration and the antinociceptive effect of one particular extract suggest a behavioral profile similar to that of amphetamine. The results of the El-Alfy *et al.* (2009) study indicated that the activity of nutmeg extracts is not of the cannabinoid type, based on the results of a tetrad assay; on the other hand, the CNS depressant, analgesic, and hypothermic effects were observed. The antidepressant activity has also been shown experimentally in mice, using forced swimming and tail suspension tests (Dhingra and Sharma, 2006); in this study, 10 mg/kg of the *n*-hexane extract from nutmeg seeds was found to have a greater effect than fluoxetine and imipramine. In Tibetan medicine, nutmeg is used to *rLung* imbalance, mostly to restore consciousness.

Although *Aquilaria agallochum* (Lour.) Roxb. ex Finl. is present in 90% of the formulas and its depressant actions affecting the CNS have been demonstrated (Okugawa *et al.*, 1993; Alla *et al.*, 2007), there are few psychopharmacological studies regarding this species. In Tibetan medicine, this species is directly related to neuropsychiatric disorders, especially those involving the nervous tissue. *Bambusa textilis* McClure, which is present in 80% of the formulas, has never been investigated, to our knowledge, from a pharmacological perspective. After it is burned, the liquid contained in its stalk solidifies and is used for lung infection. For the plant *C. axillaris*, despite its importance in Tibetan medicine, because it is present in 80% of the formulas as previously mentioned, there were no pharmacological studies, and considering its Tibetan uses for neuropsychiatric disorders it should be a strong candidate for future investigations.

In the same Table 2, we can also find plants that occur in low frequency in the formulas, but differently from the plants earlier discussed, they have been broadly investigated in pharmacological trials. Hereafter, we will describe the three of them, which are present in only 10% of the formulas.

In both pentylenetetrazole and electroconvulsive shock models, the essential oil from cumin fruits (*Cuminum cyminum* L.), administered between 0.05 and 0.5 mL/kg at concentration 4% v/w, showed dose-dependent anticonvulsant activity in mice (Sayyah *et al.*, 2002). In a different study (Janahmadi *et al.*, 2006), the same oil at concentration 1% and 3% also suppressed epileptic activity of snail F1 neurons in a model that also used pentylenetetrazole. Yet, 0.001% to 2% (5ml/kg; ip) of the oil reduced the rewarding properties of morphine in mice, both in conditioning and post-conditioning phases (Khatibi *et al.*, 2008), when administered 60 min before the drug injection in a place-preference model, suggesting a memory-related mechanism through GABAergic system. Cumin is used in Tibetan medicine for the treatment of infection due to *rLung* imbalance.

Although *Crocus sativus* L., saffron, is not specially used for *rLung* imbalance in Tibetan medicine, its antidepressant activity has been demonstrated both in preclinical and clinical trials. Akhondzadeh *et al.* (2004, 2005, 2007) showed the therapeutic effect of saffron's ethanolic extract therapeutic effect in clinical randomized, double-blind trials with placebo and positive controls (imipramine and fluoxetine). Its aqueous extract has been evaluated by Hosseinzadeh and Noraei (2009) at 80, 320, and 560 mg/kg in an open-field test, demonstrating anxiolitic effect in mice (reduced grooming, leaning, and rearing behaviors). Neuroprotective effect of saffron has also been demonstrated in preclinical trials (Ahmad *et al.*, 2005; Shati *et al.*, 2011). It is possible that *C. sativus* L. acts through inhibition of glutamatergic NMDA receptors (Berger *et al.*, 2011).

Differently from the previous two species, sweet flag (*Acorus calamus* L.) is specifically used to treat *rLung* disorders. Indeed, Zaugg *et al.* (2011) tested several compounds derived from a petroleum ether extract of this plant, and all of them showed potentiation of the GABA-A receptor chloride current. Its protective effect has been demonstrated in different rat models, as acetaminophen induced nephrotoxicity (Palani *et al.*, 2010) and middle cerebral artery occlusion (Shukla *et al.*, 2006).

Although there are reports in the literature describing the psychopharmacological activities of *M. fragrans* Houtt., other species frequently included in the formulas used for neuropsychiatric disorders have not been substantially studied pharmacologically. On the other hand, some plants that are less frequent in the formulas have been extensively studied for their neuropsychiatric effect, having some neurotransmission systems proposed, such as GABAergic for cumin and sweet flag and glutamatergic for saffron.

Although the medical practices of Tibetan medicine and biomedicine are distinct, they are congruent regarding the use of medicinal plants. More specifically, there is a high degree of conformity between Tibetan therapeutic usage and pharmacological studies in the scientific literature. Nevertheless, for many of the ingredients used for the treatment of *rLung* disorders or *sok tza karpo* (nervous tissue), there are no scientific studies regarding the potential neuropsychoactivity of these ingredients. The study of these plants may be of great value, considering the prevalence of mental and neurological diseases worldwide and the damage they cause to individuals. Future studies will require the development appropriate methodologies for studying multi-ingredient formulations in a controlled experimental context, and the findings of these studies may contribute significantly to drug development research.

Acknowledgements

Financial and structural support was provided by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FAP (Fundação de Apoio à Universidade Federal de São Paulo), and AFIP (Associação Fundo de Incentivo à Pesquisa). The authors acknowledge the UNIFESP International Affairs Office, Lia Diskin, and Dr Luiz Eugenio Araujo de Moraes Mello for promoting the collaboration between UNIFESP and Men-Tsee-Khang. They also thank Geshe Lhakdor from the Library of Tibetan Works and Archives. They also acknowledge the anonymous referee for his helpful suggestions in improving this article. Finally, they express their sincere thanks to Tseten Dorjee and Dr Tsewang Tamdin from Men-Tsee-Khang.

Conflict of Interest

The authors declare no conflict of interest.

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