Title

Is neurogenesis relevant in depression and in the mechanism of antidepressant drug action? A critical review

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REVIEW ARTICLE

Herbal medicine for psychiatric disorders: Psychopharmacology and neuroscience-based nomenclature

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ABSTRACT

Objectives: Herbs are frequently and concurrently used with prescribed drugs by patients worldwide. While clinical trials have found some herbs to be as useful as standard psychiatric drugs, most clinicians are unaware of their pharmacological mechanisms.

Methods: We searched English language and other language literature with English abstracts listed in PubMed website, supplemented by additional through Google Scholar's free academic paper abstract website for publications on herbs, focussing on their clinical use in mental disorders, their neurobiology and their pharmacology.

Results: A major reason for herbs remaining outside of mainstream psychiatry is that the terminology and concepts in herbal medicine are not familiar to psychiatrists in general. Many publications regarding the use of herbal medicine for psychiatric disorders are deficient in details regarding diagnosis, criteria for response and the neurobiology details compared with publications on standard psychotropic drugs. Nomenclature for herbal medicine is usually confusing and is not conducive to an easy understanding of their mode of action in psychiatric disorders.

Conclusions: The recent neuroscience-based nomenclature (NbN) for psychotropics methodology would be a logical application to herbal medicine in facilitating a better understanding of the use of herbal medicine in psychiatry.

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Herbs; psychiatric disorders; neuroscience-based nomenclature; multi-target polypharmacy

Introduction

Most of the drugs we have nowadays either originated from plants or were developed on plant molecular scaffolds. Examples include classical compounds such as reserpine from snakeroot, salicylic acid from the willow tree and morphine from poppy pods. While the use of synthesised drugs has become a norm in modern clinical psychiatric practice, herbs are still commonly used in many developing countries. Herbs may even be the primary medicine available in poor communities around the world (WHO fact sheet N134, Revised May 2003; WHO 2008).

In the US, herbal use is largely outside standard medical practice. However, in a world of increasing international travel, many clinicians are beginning to encounter foreign patients who use a variety of foreign herbal medicines. While St John's Wort is well known to many psychiatrists (Kasper & Dienel 2002; Kasper et al. 2010; Kasper 2015), other herbal medicines such as *Valeriana officinalis*, *Lavandula angustifolia* (Kasper et al. 2017), Maca roots and many common traditional Chinese medicinal plants, may not be as familiar to most. This is because clinical information regarding many popular foreign herbs is rarely published in mainstream clinical psychiatric or clinical psychopharmacological journals (see below in 'results of search'). However, a variety of foreign herbs is now easily available in health food stores or can be obtained through mail order shops. Many patients self-prescribe such herbs together with prescribed standard psychiatric drugs nowadays and drug–drug interactions can be dangerous (Tang et al. 2017b). As stated in the American Psychiatric Association Task report on herbal medicine, 'clinical, research, and educational initiatives designed to focus on complementary and alternative medicine (CAM) treatments in psychiatry are clearly warranted due to the widespread use of CAM therapies' (Freeman et al. 2010).

Compared with standard psychotropic drugs, the mode of action and neurobiology related to herbal medicine is much more complex. Recent research data on many herbs employing modern scientific technology are accumulating at a fast pace, and the mode of action of many herbs can now be interpreted

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psychopharmacologically. Unfortunately, such data were, and continues to be, published in some highly technical, pure chemistry, biochemical or plant medicine journals, and sometimes in foreign languages (Choi et al. 2015). The information in these publications was presented in variable formats. In addition, the quality of such publications and the journals is difficult to judge. Consequently, a busy clinician may miss these publications, and those without the appropriate background may also find such publications hard to interpret. In addition, classification of mental disorders in the field of traditional herbal medicine has never reached the same stringency or refinement state of Western psychiatric diagnosis. Terms such as 'qi' (air or energy) or 'yang' (Liu et al. 1993), 'wetness', 'dryness' or 'heat' used in Chinese traditional medicine to describe symptoms of patients are not easy to understand for Western psychiatrists. It is often difficult if not impossible to deduce accurately from the traditional herbal medicine literature which herb or herbal combination could be useful for which psychiatric disorders under modern diagnostic terminology in the ICD (International Statistical Classification of Diseases and Related Health Problems by the WHO) or DSM (Diagnostic and Statistical Manual of Mental Disorders by the American Psychiatric Association). Furthermore, behavioural changes or subjective feelings of disturbed moods and thoughts are often regarded as part of a systemic disturbance of the whole body in traditional herbal medicine practice. Therefore, some herbs not known to possess significant central nervous system (CNS) action are also often used to target other organs, in combination with a primary herb with established neuroactive properties. Polypharmacy involving multiple herbs with varying quantities of each herb is a normal practice (Yeung et al. 2015). This macro or systemic approach for the treatment of CNS disorders is in sharp contrast to current psychiatric practice in which an accurate diagnosis must precede the selection of drugs.

In the West, many new psychiatric drugs have appeared since the synthesis of tricyclic anti-depressants, phenothiazine anti-psychotics and cholinesterase inhibitors. The search for new drug molecules mainly follows the tradition of developing compounds targeting neurotransmitters, such as serotonin (5HT), norepinephrine (NE), dopamine (DA), γ-aminobutyric acid (GABA), acetylcholine (Ach), glutamate (Glu), or the enzymes responsible for their metabolism, such as monoamine oxidase (MAO), and acetylcholinesterase (AchE). New drugs in development are tested against specific psychiatric disorders as described in standard psychiatric diagnostic nomenclature. However, the observation that current psychopharmacological nomenclature fails to reflect contemporary developments and knowledge does not help the practicing clinicians to select the best medication for a given patient and is also confusing for the patients. This has led to the neuroscience-based nomenclature (NbN) initiative (Zohar et al. 2014; Zohar & Kasper 2016).

The structure of the NbN (Zohar et al. 2014; Zohar & Kasper 2016; http://nbnomenclature.org) describes psychotropic medicine in terms of: (1) pharmacology and (2) mode of action. Pharmacology 'reflects current knowledge and understanding about the pharmacological domain – neurotransmitter/molecule/system being modified'. Mode of action 'reflects current knowledge and understanding about the mechanism of action'. There are four additional dimensions of relevant information regarding every drug in the nomenclature as follows: (3) approved indication, (4) efficacy and side effect, (5) practical notes and (6) neurobiology.

The official NbN App is available for free downloading at http://nbnomenclature.org, either through Google Play or through the app store. The European College of Neuropsychopharmacology (ECNP) site (https://www.ecnp.eu/research-innovation/nomenclature.aspx) gives a detailed introduction to the history of the development of the NbN.

The current NbN application does not include herbal medicine. However, considering the highly inconsistent or variable ways that current research data on the pharmacology of herbs is reported, making the information hard to access by clinicians, it would appear that the available information can be well organised using the NbN methodology. In this paper, we reviewed the pharmacology of common herbs used in the treatment of mental ailments in traditional Chinese medicine and tested the application of the NbN (Zohar et al. 2014; Zohar & Kasper 2016) to organise the existing psychopharmacological data. We included several herbs used in the West (*Hypericum perforatum*, commonly known as St John's Wort, *Valeriana officinalis, Lavandula angustifolia,* commonly known in the form of Lavanda oil, *Lepidium meyenii,* commonly known as Maca root, *Gingko biloba and Matricaria chamomilla*, commonly known as chamomile tea) for comparison purposes.

Method

We first searched English language and other language literature with English abstracts listed in PubMed of the website www.ncbi.nlm.nih.gov up to 8 March 2017, crossing the key words 'herb, herbal medicine, plants' and then the names of the following herbs, *Valeriana officinalis, Ziziphus jujube, Zizyphi Spinosi semen, Platycladus orientalis semen, Albizia julibrissin, Paeonia lactiflora, Polygala tenuifolia, Ganoderma lucidum, Polygonum multiforum* and *Poria cocos*, gingko and St John's Wort, in turn, and in combination with the following key words: central nervous system (CNS), psychiatry, psychiatric disorders, brain, neuroscience, stress, depression, schizophrenia, dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, anxiety, sleep, dendrites, neurons, glutamatergic, serotonin, dopamine, neurotransmission, neurodegeneration, neuroprotection, anti-inflammatory, inflammation, immunological, immune system, anti-depressant, anti-psychotic, anti-dementia, herbal cognitive enhancers. Foreign language literature including book chapters without English translation or summaries in English was discarded. The above search was supplemented by additional search methods. The first method was through Google Scholar's free academic paper abstract website. This yielded papers outside the scope of PubMed. In addition, for papers that were full text and hosted on the author's websites on academic servers, an '.edu' search modifier was added to the end of a normal www.google.com query, yielding additional full text papers. All information obtained was cross-validated against that from university affiliated authors and published in journals indexed by Medline. Public health statistics and data were searched in the month of December 2016 and updated on 5 December 2016.

Amazingly, our search yielded less than 200 publications in total from all healthcare journals including foreign language journals with English language abstracts of reliable sources (search performed on 8 March 2017) after eliminating those with irrelevant titles and content. When St John's Wort was excluded from the search, the number of publications dropped to below 100. Less than five of these were published in the *American Journal of Psychiatry* and the *Archives of General Psychiatry*. Only one article appeared in the *British Journal of Psychiatry*. The other papers were published in journals not frequented by clinical psychiatrists, such as chemistry and technical journals, or in foreign language journals with English abstracts only. For example, our search yielded only five articles on the use of *Poria cocos* to treat depression and anxiety but none of these articles were published in psychiatry or mental health-related journals. For the few papers regarding the use of *Ganoderma lucidum* to treat depression and anxiety, three papers were published in the *International Journal of Medicinal Mushrooms*. Obviously, the data, even if they are clinically useful, would not be easily accessible to a busy clinical psychiatrist. In addition, ancient terminology and different concepts of illnesses from Chinese traditional medicine were used in many traditional medicine literature and textbooks. The abstract of a paper yielded from the PubMed search on *Poria cocos* titled 'Effect of improving memory and inhibiting acetylcholinesterase activity by invigorating qi and warming yang recipe' (Liu et al. 1993) appeared interesting as it mentioned Ach. However, the text is in Chinese and the concept of 'invigorating qi and warming yang' as described certainly may not be easy to understand for Western psychiatrists.

We also crossed the word 'herbs' or 'herbal medicine' with 'depression' and 'clinical trials', and only 31 articles were retrieved in PubMed. This is close to the number of 21 clinical trials cited in an earlier review (Sarris et al. 2013). None of these trials were published in common clinical psychiatric journals and confirmed our impression that information on herbal medicine is not easily available to Western psychiatrists.

Herbs with neuroactive properties and mode of action

Mode of action is an important parameter in NbN. The mode of action for many herbs is becoming clear with recent research using modern biochemical and pharmacological technology. The identification of active ingredients and the reported pharmacology offers us the opportunity to interpret the mode of action of many of these herbs.

In Chinese traditional medicine, herbs are often used in different combinations, depending on the patient's symptoms. One herb alone, *Polygala tenuifolia*, is consistently the main herb used in any formula for mental ailments (Wang et al. 2014). This herb is the main component in an ancient formula '*Kai Xin San*', used for the relief of what seemed to be the symptoms of depression since a thousand years ago (Zhu et al. 2012; Yan et al. 2016).

These herbs all possess multiple therapeutic actions, and many of their ingredients have been identified and studied (Tables 1 and 2). The same herb may be used for its anti-bacterial action on one occasion, while on other occasions it may be used for its anti-cancer, cardiopulmonary benefits, immunological modulation properties or for memory improvement, as well as for its sedative action. Although this could be related to the multiple active components in plants under certain circumstances, there is also a possibility that these herbs or their extracts act through novel or multiple mechanisms.

Data on herbal medicine with therapeutic effects on the CNS show that these herbs may act through one or

Table 1. Herbal ingredients and mode of action.

Medicinal Plants	Applications	Drug targets/Mode of action	Some identified ingredients	References
Albizia julibrissin (flower and bark)	Sedation Insomnia Depression Memory Anti-tumour Anti-angiogenic Anti-inflammatory	$5HT_{1A}$ VEGF/VEGF NF-κB inhibition PPARα and PPARγ activating (Peroxisome proliferator-activated receptors)	Julibroside C1 Other julibrosides Quercetin Linalool	Jung et al. 2005 Zheng et al. 2006 Rozema et al. 2012 Jung et al. 2013 Sun et al 2014b Cai et al. 2015
Bacopa monnieri (root)	Cognitive decline Anti-inflammatory Asthma	AchE $5\text{-}HT_6$ and $5\text{-}HT_{2A}$ BDNF-CREB Inhibition of proinflammatory cytokines TNF-α and IL-6 Inhibition of caspases 1 and 3, and matrix metalloproteinase-3 inflammatory enzymes	Bacoside A Bacosides	Taur and Patil 2011 Rastogi et al. 2012 Kadali et al. 2014 Ramachandran et al. 2014 Ramasamy et al. 2015 Dethe et al. 2016 Liu et al. 2016 Preethi et al. 2016 Nemetchek et al. 2017
Ganoderma lucidum (whole fungi)	Cognitive decline Sedation Insomnia Anti-tumour Anti-Inflammatory Hepatitis	β-Amyloid Immune system Anti-angiogenic FGFR1-ERK-AKT	Amino acids Polysaccharides Ganoderic acid A Terpenes Ganederol Ganederiol Germanium Adenosine	Hsu et al. 2004 Lin and Zhang 2004 Lull et al. 2005 Lai et al. 2008 Zhou et al. 2010 Matsuzaki et al. 2013 Vazirian et al. 2014 Bhardwaj et al. 2014 Huang et al. 2017
Paeonia lactiflora/ Paeonia suffruticosa (root)	Depression Neuroprotective Anti-aging Cerebral ischaemia Memory Anti-tumour Anti-inflammatory Anti-thrombotic	BDNF-CREB 5HT MAOI-A MAOI-B Anti-oxidant Anti-coagulant Anti-inflammatory Anti-amyloid	Paeoniflorin Albiflorin Paeonol Pentagalloylglucose Protocatechuic acid	Kong et al. 2004 Wang et al. 2016b Zhou et al. 2016b Li et al. 2017b Xie et al. 2017 Zhang et al. 2017b Zhang et al. 2017c
Panax ginseng (root)	Adaptogen Neuroprotection Memory Anti-aging Angiogenesis	γ-Secretase inhibitor Anti-Aβ BDNF-Bcl-2 Neurogenesis Inhibition of apoptosis and calcium overload	Ginsenoside Rg1 Ginsenoside Rb1 Other ginsenosides Quinguenosides 20-Glucoginseanoside	Cheng et al. 2005 Jiang et al. 2012 Ahmed et al. 2016 Oh and Kim 2016 Wang et al. 2016c Zhou et al. 2016a
Platycladus orientalis (leaves and seed)	Memory Sedation Insomnia Anti-inflammatory Anti-tumour	Inflammatory factors Nitric oxide inhibition Ach receptor	Esculin, Amentoflavone Apigenin Capric acid Glabridin Afromosin α-Thujone Thujone Neocryptomerin	Fan et al. 2011, 2012 Cheng et al. 2013 Ren et al. 2017
Polygala tenuifolia (root and root skin)	Sedation Insomnia Anxiety Depression Memory Anti-convulsant Anti-bacterial	GABA BDNF/TrkB-ERK/PI3K-CREB Inflammatory factors DA neuroprotection AchE inhibition Anti-Aβ	Tenuigenin A,B Tenuifolin Onjisaponins Tenuifoliside A (TFSA) 3,4,5-Trimethoxycinnamic acid (TMCA) Onjisaponins 3,6′-Disinapoyl sucrose (DISS) Polygalasaponin	Park et al. 2002 Jia et al. 2004 Cheong et al. 2011 Yuan et al. 2012 Xie et al. 2012 Kim et al. 2013 Dong et al. 2014a Liu et al. 2016 Zhou et al. 2016b
Polygonum multiflorum (root)	Memory Anti-Aging Neuroprotection Angiogenesis Anti-atherosclerotic Anti-inflammatory	DA neurons Inflammatory factors Synaptogenesis Anti-Aβ	Emodin Chrysophanol Physcion Rhein Resveratrol Lecithin 2,3,5,4′-Tetrahydroxystilbene-2-*O*-β-D-glucoside (TSG) 2,3,5,4′-Tetrahydroxystilbene-2-*O*-β-D-glucopyranoside	Li et al. 2005 Wang et al. 2007 Park et al. 2016 Lee et al. 2017 Zhou et al. 2012

(*continued*)

Table 1. Continued

Medicinal Plants	Applications	Drug targets/Mode of action	Some identified ingredients	References
Poria cocos (whole fungi)	Sedation Anxiety Anti-inflammatory Anti-tumour (anti-angiogenic)	Immune factors Phospholipase A inhibition NF-κB downregulation	Pachymic acid Tumulosic acid Pachyman Pachymaran Glucan H11	Kikuchi et al. 2011 Ríos 2011 Sun 2014a
Sophora flavescens (root)	Neuroprotective Anti-bacterial Anti-viral Anti-allergic Anti-tumour Liver protection	MAO-B BACE1 Anti-inflammatory Immune-regulatory	Matrine Oxymatrine Sophoridine Allomatrine Isomatrine Kuraridin	Hwang et al, 2005 Hwang et al. 2008 Quan et al. 2008 Bai et al. 2012 Lee et al. 2016a
Scutellaria baicalensis (root)	Sedation Neuroprotective Anti-neuroinflammation Anti-bacterial Liver protection Anti-tumour Anti-allergic Anti-oestrogen	GABA Anti-oxidant Anti-inflammatory Anti-pro-inflammatory cytokines Anti-tumour necrosis factor-alpha (TNF-α) Anti-interleukin-6 (IL-6) Anti-oestrogen receptor	Baicalein Baicalin Wogonin Apigetrin Wogonoside	Hui et al. 2002 Huen et al. 2003 Hanrahan et al. 2011 Lim et al. 2016
Valeriana officinalis (root)	Neuroprotective Sedation Insomnia	GABA SUR1 receptor GAD	Valerenic acids β-Sitosterol Ursolic acid 4,4′,8,8′-tetrahydroxy-3,3′-dimethoxyl-dibenzyl-ditetrahydrofuran Linarin	Eadie 2004 Fernández et al. 2004 Awad et al. 2007 Jiang et al. 2007b Salter and Brownie 2010 Sudati et al. 2013 Baek et al. 2014 Leach and Page 2015 Santos et al. 2016
Ziziphus jujuba (Ziziphi Spinosae Semen) (seed)	Sedation Insomnia Anti-convulsant Anxiety Memory	GABA 5HT1A Anti-oxidant Anti-inflammatory Anti-amyloid-β1-42 oligomer (AβO) Neurogenesis Anti-angiogenic	Jujubosides Jujubogenin Sanjoinine A (frangufoline) Sanjoinine E (nuciferine) Sanjoinine K (coclaurine) PI3K/Akt/mTOR signalling pathway Spinosin Lysicamine Betulinic acid	Ma et al. 2007 Han et al. 2009 Jiang et al. 2007a Cao et al. 2010 Zhao et al. 2012 Lin et al. 2014 Liu et al. 2015 Ko et al. 2015 Han et al. 2016 Lee et al. 2016b
Hypericum perforatum (St John's wort) (flower, stem)	Depression Anti-inflammatory Anti-viral Anti-parasitic Anti-bacterial	5HT, NE, DA, Glu DA β-hydroxylase inhibitor Weak MAOI (A,B) COX 1 inhibitor	Hypericin Hyperforin Naphthodianthrones, Phloroglucinols Flavonoids	Kaehler et al. 1999 Barnes et al. 2001 Müller et al. 2003 Linde et al. 2005 Vance et al. 2014 Agapouda et al. 2017
Gingko biloba (leaves, seed)	Memory Cardiac/ Cerebro-vascular circulation enhancement Anti-inflammatory Anti-tumour Anti-allergic	GABA Immuno-regulatory Anti-oxidant Apoptosis	Ginkgetin Isoginkgetin Bilobetin Amentoflavone Kinokiflavone Ginkgolides A,B,C Bilobalide Flavonol glycosides Biflavones Kaempferol Proanthocyanidins Polysaccharides Isorhamnetin Quercetin	van Beek 2002 van Beek and Montoro 2009 Ng et al. 2016 Zhou et al. 2016a Gschwind et al. 2017
Matricaria chamomilla (German chamomile) (flower)	Insomnia Anti-oxidant Anti-tumour	GABA Glu NMDA receptor Adenosine receptor Opioid receptors Inflammatory factors	Apigenin	Awad et al. 2007 Chang et al. 2015
Lavandula angustifolia (Flower, oil Silexan)	Anxiety Sedation	5HT1A GABA	Valerenic acid Linalool	Huang et al. 2008 Chioca et al. 2013 Baldinger et al. 2014 Kasper et al. 2017

(*continued*)

Table 1. Continued

Medicinal Plants	Applications	Drug targets/Mode of action	Some identified ingredients	References
Lepidium meyenii (Maca root)	Sexual dysfunction Anti-anxiety Anti-inflammatory Anti-tumour Adaptogen Anti-oxidant	Anti-oxidant Spermatogenesis CNS targets unclear	Polysaccharides (+)-meyeniin A Tricins Pinoresinol 4-hydroxycinnamic acid Glucotropaeolin Desulfoglucotropaeolin	Dording et al. 2008 Bai et al. 2015 Inoue et al. 2016 Zhou et al. 2017

more of the following mechanisms: (1) inhibition of MAO enzymes; (2) action on neurotransmitters and their receptors; (3) activation of neuro-hormones such as brain-derived neurotrophic factor (BDNF), neurogenesis or synaptogenesis; (4) anti-inflammation, immunoregulation or modulation; (5) anti-infectious (bacterial, viral, fungal and parasitic); (6) cardiovascular improvement, protection and or anti- or pro-angiogenesis; (7) anti-oxidation, anti-toxin and corrective effects on mitochondrial metabolic imbalance; (8) multi-actions, including one or more of the above mechanisms from multiple compounds in a single or multiple herb compound, or a single compound with multi-actions and overall health benefits leading to neuroprotection, neurogenesis or anti-apoptosis.

Inhibition of MAO enzymes

Many alkaloids, β-carbolines and other compounds of plant origin, such as the ingredients in the herb *Sophora flavescens*, are inhibitors of MAO-A and or MAO-B (Hwang et al. 2005; Jeong et al. 2006; Tang et al. 2017b). Plant MAO inhibitory compounds have been used as scaffolds for new MAOI development for depression, Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders (Matos et al. 2009, 2012; Patil et al. 2013; Lv et al. 2015; Margret et al. 2015; Zhang et al. 2017a). The inhibitory action of MAO-A may be responsible for the observed anti-depressant effect of some herbs, whereas the inhibitory action of MAO-B may be responsible for their neuroprotective function (Lee et al. 2016a; Tang et al. 2017b) similar to other MAO-B inhibiting drugs such as rasagiline (Chau et al. 2010; Youdim et al. 2001). The neuroprotective action of MAO-B inhibitors may be related to the elevation of DA or the removal of reactive toxic MAO-B metabolites (Zarmouh et al. 2016).

Enhancement or modulation of neurotransmitters, receptors and related enzymes

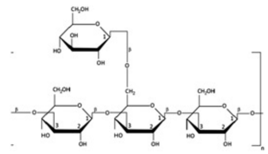
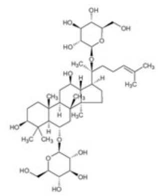
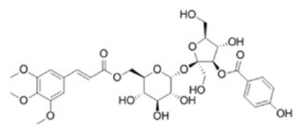
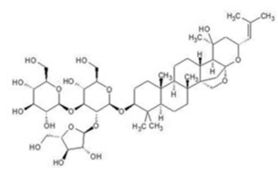
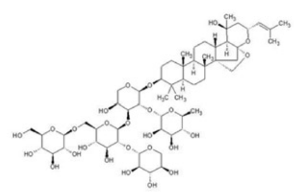
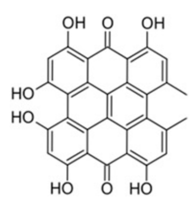
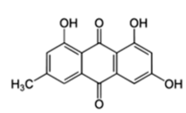
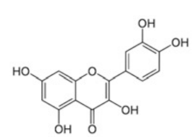
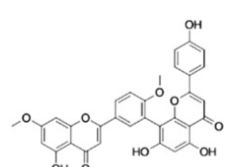
Many herbs used in the treatment of insomnia, anxiety and other non-specified symptoms of 'mental disturbances' in traditional medicine (Muszyńska et al. 2015) have now been found to exert direct action on one or more neurotransmitter systems (Farahani et al. 2015). For example, restoration of Ach neurotransmission can explain the memory-enhancement effect of the herb *Bacopa monnieri* (Calabrese et al. 2008; Ahirwar et al. 2012). Extract of the *Acacia catechu* leaf exhibits significant AchE-inhibiting activity (Saha et al. 2016). The seed of *Platycladus orientalis*, increases hippocampal α7nAChR (Ach receptor) protein expression in a rat model of Alzheimer's disease (Cheng et al. 2013).

For the 5HT system, St. John's Wort (Kasper & Dienel 2002; Kasper et al. 2010; Kasper 2015) has a 5HT-modulatory effect, while additional action on other neurotransmitters, including NE, DA and Glu, also has been proposed (Kaehler et al. 1999; Barnes et al. 2001; Müller 2003; Vance et al. 2014). Whether this herb has a true anti-depressant action been the subject of debate for years (Hypericum Depression Trial Study Group 2002; Linde et al. 2005, 2008), and the possibility of a placebo effect has also been studied (Chen et al. 2015). The flowering plant *Lavandula angustifolia* is well known for its sedative action. It has recently been shown, using brain imaging techniques, to act through the 5HT1A receptor (Baldinger et al. 2014; Kasper et al. 2017).

The herb *Bacopa monnieri* antagonises 5-HT_6 and 5-HT_{2A} receptors (Dethe et al. 2016). The herb *Bupleurum chinesis* (Chai Hu) is commonly included in many herbal formulae for the treatment of symptoms of depression and anxiety in Japan, China and Korea. It is now known that the herb acts through a 5HT and NE mechanism similar to other standard anti-depressant drugs, such as fluoxetine (Kwon et al. 2010).

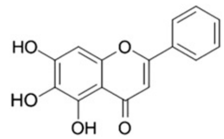
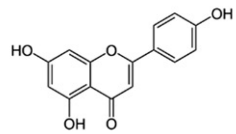
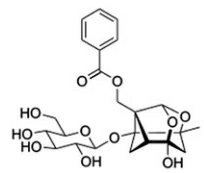
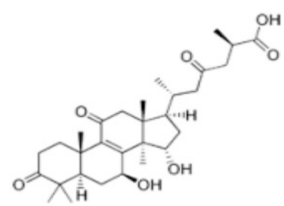
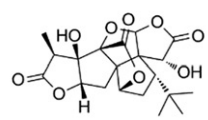
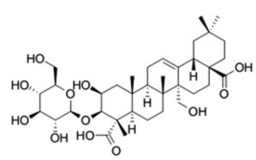
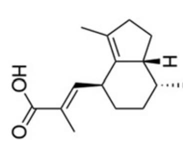
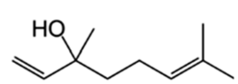
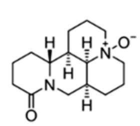
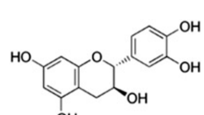
Other herbs are used for insomnia, anxiety or agitation. These include *Valeriana officinalis*s, which has been used in the West as well as in China for a long time (Eadie 2004; Salter & Brownie 2010; Baek et al. 2014; Leach & Page 2015), *Scutellaria baicalensis* (Hui et al. 2002; Huen et al. 2003) or *Matricaria recutita* (German chamomile) (Awad et al. 2007). These herbs or their ingredients have been discovered to be ligands of GABA receptors (Medina et al. 1997;

Table 2. Examples of ingredients in medicinal plants and their chemistry.

Type	Examples	Chemical Formula	Herbs
Polysaccharide	Mushroom Polysaccharides		*Poria cocos*
Glycosides	Ginsenoside Rg1		*Panax ginseng* (Ginseng)
	Tenuifoliside A		*Polygala tenuifolia*
	Bacoside A3		*Bacopa monnieri*
	Jujuboside A		*Ziziphus jujuba*
Quinone	Hypericin		*Hypericum perforatum* (St John's wort)
	Emodin		*Polygonum multiflorum*
Flavonoids	Quercetin		*Albizia julibrissin*
	Ginkgetin		*Ginkgo biloba*

(*continued*)

Table 2. Continued

Type	Examples	Chemical Formula	Herbs
	Baicalein		*Scutellaria baicalensis*
	Apigenin		*Matricaria chamomilla*
Terpenoids	Paeoniflorin		*Paeonia lactiflora*
	Ganoderic acid A		*Ganoderma lucidum*
	Ginkgolide A		*Ginkgo biloba*
	Tenuifolins		*Polygala tenuifolia*
	Valerenic acid		*Valeriana officinalis*
	Linalool		*Lavandula angustifolia*
Alkaloid	Oxymatrine		*Sophora flavescens*
Tannin	Polymeric catechin		*Tea, cacao, Uncaria rhynchophylla*

Hanrahan et al. 2011; Johnston 2015). A recent report identified the 5HT1A receptors as the drug target for the herb *Lavandula angustifolia* (Baldinger et al. 2014; Kasper et al. 2017), which has been known for its anti-anxiety action.

Activation of neurohormones

Many psychotropic drugs have been shown to activate the cAMP response element-binding protein brain-derived neurotrophic factor) CREB-BDNF pathways and enhance dendritogenesis, spinogenesis and neurogenesis in animals (Tang et al. 2012, 2017a). The herb *Polygala tenuifolia,* a main component of many herbal formulae and prescriptions for insomnia, anxiety, unstable mood and depressive symptoms, has been found to have a neuroprotective action via a CREB-BDNF-dependent pathway (Dong et al. 2014a; Liu et al. 2016; Zhu et al. 2012). Induction of BDNF has also been suggested as the mechanism behind the memory-enhancement property of *Bacopa monnieri* (Preethi et al. 2016), the anti-Parkinson function of herbal echinacoside, a compound from *Cistanches salsa* (Geng et al. 2007; Zhao et al. 2010), as well as the general anti-depressant and neuroprotective effect of *Paeonia lactiflora*, a herb commonly used in all formulae for treating all mental disorders (Mao et al. 2008).

Anti-inflammation and immunoregulation property of herbs

Chronic inflammation has been proposed as an important factor behind dementia and depression (Bortolato et al. 2015; Leonard 2014, 2015). Co-administration of anti-inflammation drugs such as COX-2 inhibitors have been examined as treatment for dementia, major depression and schizophrenia (Kotilinek et al. 2008; Müller et al. 2009), and is an active ongoing area of research. In fact, many herbs possess significant anti-inflammatory and immune-regulatory properties (Ye et al. 2016). Inhibition of inflammatory factors such as iNOS, COX-2, IL-6, IL-1β and TNF-α expression have been demonstrated by various herbs (Wang et al. 2012). Some herbs commonly used for the purpose of treating mental ailments in traditional medicine, such as acorus (*Acorus tatarinowii*) or poria (*Poria cocos*), have no significant action on neurotransmitters. Interestingly, their place in traditional medicine is for immune-regulation in treating tumours and inflammation such as hepatitis.

Some herbs are used for the treatment of diabetes and its complications. Diabetes impairs blood supply to the brain and triggers inflammation. Levels of neurotransmitter enzymes, such as AchE, choline acetyltransferase, MAO and receptors, nerve growth factor, BDNF and neuropeptides, may change as a result. The reduction of oxidative stress and/or inflammation by herbal compounds may modulate such damage (Patel & Udayabanu 2017). This indirect path to therapeutic action is not as unusual as it may seem. For example, simvastatin, a cholesterol-lowering drug, has been found to reduce activation of p21(ras), attenuated activation of nuclear factor-kappa B (NF-κB), inhibit expression of proinflammatory molecules and also suppress activation of glial cells in the substantia nigra. All these actions indirectly lead to the protection of DA neurons. Pravastatin, another cholesterol-lowering drug, was found to suppress microglial inflammatory responses as well protecting DA neurons in MPTP-treated mice (Ghosh et al. 2009).

Anti-bacterial, anti-viral and anti-parasitic property

Many herbs, including most of the ones we mentioned for the treatment of mental ailments in traditional medicine such as *Poria cocos* and *Ganoderma lucidum* (Vazirian et al. 2014), exhibit significant anti-bacterial, anti-viral (Zhao et al. 2012) and anti-parasitic properties, and even have anti-microbial properties against multi-drug-resistant bacterial infections (Miyasaki et al. 2013), These properties are probably an evolutionary defence mechanism that plants use against their natural enemies. Some other herbs with a primary indication in traditional medicine, but not for mental ailments, are anti-microbial. The herb *Sophora flavescens* (Ku shen) is used for the treatment of bacterial and fungal infections, skin rashes, parasites and jaundice, but is neuroprotective in models of brain ischaemia and Alzheimer's disease (Hwang et al. 2008; Jung et al. 2011; Ding et al. 2016; Zhao et al. 2015). Another herb, *Scutellaria baicalensis* (Huang Qin), has broad-spectrum anti-bacterial, anti-viral and anti-allergy actions. It is also neuroprotective in addition to its sedative action (Martin & Dusek 2002; Gasiorowski et al. 2011).

Infections may be the basis for inflammation and, as discussed above, inflammation may be the basis of mental disturbances in some patients. Thus, the anti-infectious properties of these herbs may be an important component of therapeutics in some patients suffering from mental disorders.

Cardiovascular improvement, protection and angiogenesis effects

Many medicinal plants exhibit significant effects on angiogenesis, both positive and negative. While the pro-angiogenesis action, coupled with the anti-oxidant properties, may contribute to promotion of neurogenesis, dendritogenesis, spinogenesis and synaptogenesis, or recovery from tissue damages, the anti-angiogenesis action may be responsible for their anti-tumour effects. Many herbs have an interesting bi-directional indication both for inhibiting clots by 'improving circulations' and 'dissipating blood clots'. This bi-directional property is regarded as one of the most unique properties of many herbs with regard to their health benefits (Lin 2011). Improvement in blood supply to the brain has also been proposed for herbs such as gingko (Zhou et al. 2016a), although the effect of gingko for treating dementia is still inconclusive (Birks & Grimley Evans 2009; Sarris et al. 2011). Ginseng and other adaptogens possess both anti-hypertensive and anti-hypotensive action (Chen et al. 2012). In this regard, it is similar to the action of partial agonists, such as aripiprazole.

Corrective effect on mitochondria and oxidative stress and damages and anti-toxin effects

Many glycosides and polysaccharides in plants serve to protect itself against oxidative stress and also as anti-toxins. Flavonoids such as apigenin possess anti-oxidant properties distinct from their well-known anti-inflammatory effect (Rezai-Zadeh et al. 2008). There has been much research and debate regarding the role of oxidative stress in chronic neuroinflammation (Mossakowski et al. 2016), which in turn has been proposed as the cause of some psychiatric disorders, in particular depression and dementia (Leonard 2014, 2015). Herbs such as *Polygonum multiflorum* and ginseng contain well-known glycosides, flavonoids, polysaccharides and other anti-oxidant compounds, which are also neuroprotective against oxidative stress in animal models. (Lee et al. 2017). The neuroprotective action of St John's Wort may also be related to an anti-oxidative mechanism as well (Oliveira et al. 2016). Chemical analysis of *Rhodiola* again revealed the presence of flavonoids, phenylpropanoids, phenylethanol/benzyl alcohol derivatives, cyanogenic glycosides and terpenoids, all of which are effective at scavenging reactive oxygen species (Li et al. 2017a). *Bacopa monnieri* is even effective against rotenone-induced oxidative stress and neurotoxicity (Hosamani & Muralidhara 2009; Hosamani et al. 2010). Hesperidin and linarin from *Valeriana officinalis* are known to possess significant anti-toxic and anti-oxidative stress actions. (Sudati et al. 2013; Santos et al. 2016). The herb *Huperzia squarrosa* (Forst.) *trevis*, which possesses a memory-enhancing effect, is also a potent anti-oxidant, in addition to having AchE-inhibitory activity (Tung et al. 2016).

Anti-amyloid properties, or the prevention of the damaging effects of toxic Aβ oligomers, have been reported for a number of herbs used for cognitive decline in traditional medicine, including *Ganoderm lucidum, Paeonia lactiflora, Ziziphus jujube* and *Panax ginseng*. Interestingly, fluoxetine has recently been reported to prevent Aβ-induced toxicity as well (Caraci et al. 2016).

Multi-target and multi-dimensional properties of herbal drugs and overall health benefits

In summary, all herbs for the treatment of mental ailments in traditional medicine appear to possess multi-target and multi-dimensional therapeutic properties. The multiple ingredients in these herbs distinguish them from standard psychotropics that are single molecules. Whether these combined anti-oxidative, anti-microbial, anti-inflammatory, immune-regulatory, neurovascular, and neurohormonal properties, combined with their neurotransmitter action, offers a comprehensive coverage of all potential, overt and covert pathological factors in mental disorders, will have to be further explored.

Some herbs appear to possess neuroactive properties but have not been clearly shown to have a dominant specific neurotransmitter action. The term 'adaptogens' refers to these herbs (Panossian 2013; Levin 2015). *Rhodiola rosea, Eleutherococcus senticosus, Schisandra chinensis* and *Panax ginseng* are all within this category. They have been used for centuries for general health enhancement, such as the relief of chronic fatigue (Choi 2016), and also for some specific CNS disorders such as Alzheimer's disease (Wang et al. 2016a).

Recent research has shown that some of the ingredients in these 'adaptogens' in fact also possess some or most of the properties listed above and there is no myth to their mode of action. Thus, there are two important research issues pertaining to the psychopharmacology of these herbs used in traditional medicine for mental ailments: can the combined pharmacological properties of the various ingredients in these herbs explain their therapeutic properties, or is it because some of the active ingredients have a multi-target profile pharmacologically.

Application of the NbN in herbal medicine

From the above, it can be seen that the NbN methodology should be useful for organising the accumulating research data and psychopharmacological knowledge on herbs with CNS properties, as well as for the identification of critical and missing data. This will make the much-needed information accessible for the busy practicing psychiatrists through an App similar to the NbN, especially when they are facing foreign patients and international travellers, many of whom are taking herbal medicine.

We use the herb *Ziziphus jujube (Zizyphi spinosi semen)* as an example. This herb contains multiple ingredients with CNS properties, including sedative and anti-arrhythmia action, anti-bacterial/anti-parasitic action, anti-cancer action, and anti-angiogenic and anti-inflammatory action. Under the NbN, this herb would be regarded as a 'GABA-5HT' compound and, under 'Mode of action' would be a 'GABA and 5HT1A agonist' (Ma et al. 2007; Han et al. 2009). For neurobiology, the ingredient sanjoinine E (nuciferine) has been shown to possess actions on multiple neurotransmitter targets. It is a D_2D_5 partial agonist, an antagonist at 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{2B}, an inverse agonist at 5-HT_7, a 5-HT_6 partial agonist, an agonist at 5-HT_{1A} and D_4 receptors, and it inhibits the DA transporter (Farrell et al. 2016). It also acts on the ERK-CREB-BDNF signalling pathway to increase hippocampal neurogenesis and cognitive performance in animal models (Lee et al. 2016b). Its anti-dementia property may also stem from its anti-amyloid-β1-42 oligomer (AβO) action through the reduction of AβO-activated microglia and astrocytes and AβO-induced decrease in Ach transferase expression levels (Ko et al. 2015). In addition, spinosin targets the GABA and 5HT pathways, which explains its anxiolytic effect, an effect blocked by GABA and 5HT_{1A} antagonists (Liu et al. 2015). The glycoside jujuboside A has sedative actions, which have been attributed to its inhibitory actions on the Glu and 5HT pathways (Zhang et al. 2003; Cao et al. 2010; Fang et al. 2010). Jujuboside B, on the other hand, has anti-tumour properties through the induction of apoptosis and autophagy (Xu et al. 2014).

The multi-dimensional multi-target claims for this herb can be explained by the combined effect of its multiple ingredients on the various neurotransmitter and hormonal targets. Using the NbN, each identified ingredient of *Ziziphus jujube,* may also be qualified accordingly. For example, sanjoinine E (nuciferine), is qualified according to its primary target, which, in this case, would be DA and 5HT. There is no known significant side effect. The application of the NbN to this herb is shown in Figure 1.

Another important herb, *Polygala tenuifolia*, is commonly used together with *Ziziphus jujube* for the purpose of sedation, symptoms of depression and anxiety, excessive dreams, low mood and mental exhaustion, forgetfulness and cognitive enhancement (Hong et al. 2016). The ingredients identified are numerous. Under the NbN, the pharmacology of this herb would be 'BDNF-CREB modifier and GABA'. The mode of action is 'GABA and neuroprotective' (Liang et al. 2011), including 'DA neurons protection (Yuan et al. 2012), anti-apoptotic and anti-oxidative'. It increases Glu

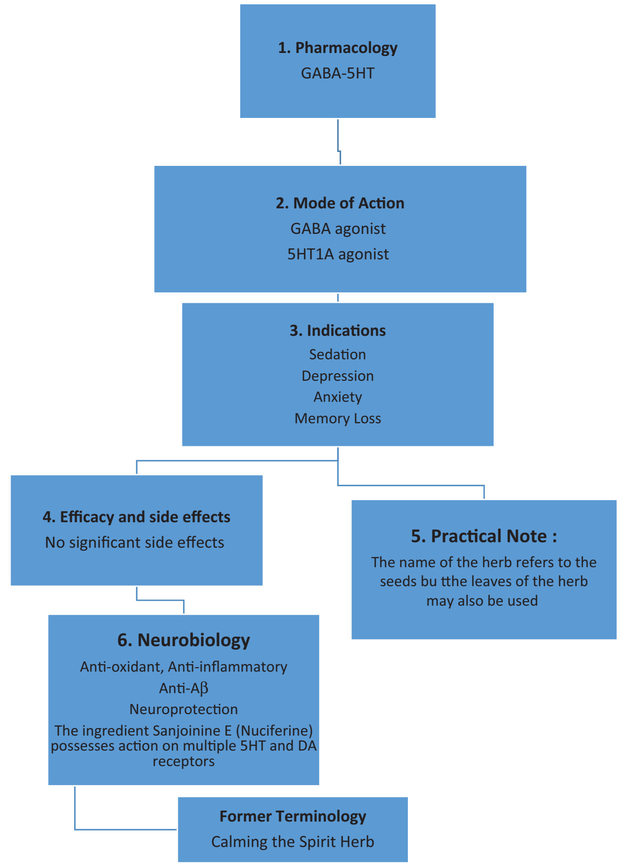


Figure 1. *Zizyphi spinosi semen.*

NR2B expression in the rat hippocampus. It is an anti-amyloid β (Jia et al. 2004), which explains its anti-dementia property (Xie et al. 2012). Tenuifolin exhibits a fast anti-depressant action with a mechanism similar to ketamine, through activation of the mTOR pathway and modulation of glutamatergic synapses (Shin et al, 2014). Polygalasaponin in the herb antagonises scopolamine-induced cognitive impairment (Zhou et al. 2016b) and improves hippocampal learning and memory (Xue et al. 2009). Tenuifoliside may exert its neuroprotective effect through a BDNF/TrkB-ERK/PI3K-CREB signalling pathway (Dong et al. 2014a) and shows a synergistic action together with another ingredient: 3,6′-disinapoyl sucrose, which also acts on this same pathway (Liu et al. 2016). It has a strong anti-inflammatory action through the inhibition of the NF-κB and mitogen-activated protein kinase pathways (Kim et al. 2013). The application of the NbN to this herb is shown in Figure 2.

From these two examples, it is clear that the multi-dimensional multi-target therapeutic properties of these herbs can be explained by the summation of the individual action of the multiple ingredients that the herb contains, while some of the ingredients also possess multi-target modes of action. The complex

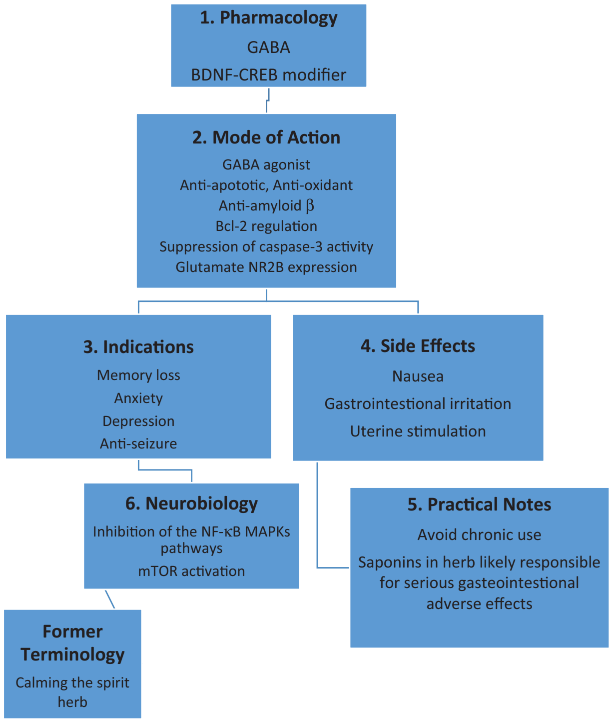


Figure 2. *Polygala tenuifolia*.

properties of the herb and the wealth of information and research data would be well organised and interpretable.

The important missing link: Affinity constant (K_i) of molecules of herbal origin

The NbN at present does not give the affinity constant (K_i) of the drugs. The K_i, however, is the most important parameter for the characterisation of any drug, particularly when the drug is used with other drugs in polypharmacy. A traditional approach in drug development is the search for new molecules that possess a high potency (a strong K_i for the intended target) and selectivity (a low K_i for unwanted targets) to the intended target, like the anti-depressant, escitalopram (Sanchez et al. 2014). An alternate approach is the synthesis of new molecules with high affinity to multiple targets, such as the anti-depressants vortioxetine (Pehrson & Sanchez 2014, 2015) and vilazodone. In both approaches, the K_i to the different targets constitutes the pharmacological as well as the clinical profile of the drug.

All herbs contain multiple ingredients. Some of these ingredients are responsible for their therapeutic benefits, while others may be responsible for their toxicity. The quantity as well as the K_i of each ingredient in the herb determines their contribution to the final therapeutic action and side effects. However, except for a few MAO-A and MAO-B inhibitory actions of isolated herbs (Kong et al. 2004), the K_i data for drug targets of the herbal ingredients for most herbs are still missing in almost all research reports on neurotransmitter receptor action of herbal ingredients. This makes the interpretation of the data on the herbal action on neurotransmitter receptors very difficult. Existing technology allows for the large-scale screening of neurotransmitter receptor profiles, but such data are generally unavailable for most herbs. The K_i data also determine the side effects. Numerous cases of liver damage have been reported for the popular herb *Polygonum multiflorum* (Jung et al. 2011; Dong et al. 2014b; Lei et al. 2015), which is generally used chronically, for example, in the promotion of black hair growth. The K_i data for the ingredients towards their therapeutic targets as well as the unwanted targets would make the data much more useful for the practicing clinicians.

Conclusion

Plant-based medicines have served humans for centuries and benefited many people suffering from mild to serious ailments. There is a wealth of experience and records available regarding the use of these herbs dating back to ancient times. However, much of this valuable information is not easily accessible. The NbN for herbs would provide a useful guide to a practicing psychiatrist when they face patients self-medicated with herbal products. The NbN would also facilitate future herbal medicine research to identify drug targets, primary site and mode of action, their pharmacology, side effects and associated neurobiology in a systematic manner. Future research data reporting under the NbN system would also be more interpretable and therefore more useful to the clinicians.

In addition, most research on herbs has been focussed on finding another new molecule with anti-depressant, anti-anxiety or anti-dementia properties comparable with or more potent than existing psychotropic drugs. In this process, the polypharmacy and multi-target benefits of herbal medicine may be missed. Many herbal drugs do not only have a single action and therefore they are not simply another choice of anti-depressant, anti-insomnia or anti-dementia drugs. The contribution of the herbs' combined anti-oxidant, anti-inflammatory, immunoregulatory, neurotransmitter, neurovascular, neurohormonal and neuroprotective properties is speculative at present but should be examined under stringent experimental conditions and clinical trial designs which address this multi-dimensional approach of herbal medicine in future research.

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None.

Statement of interest

None to declare.

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