1. INTRODUCTION

Ever since the birth of mankind there has been a relationship between life, disease and plants. Primitive men started studying diseases and treatments. There is no record that people in prehistoric times used synthetic medicines for their ailments but they tried to make use of the things they could easily procure. They started using plants and found that majority of plants were suitable as food, where as other were either poisonous or medicinally useful. By their experience, this knowledge of herbal remedies was transferred to generation as folk medicine. So the history of herbal medicine is as old as human history.

Herbal medicine is still the mainstay of about 75–80% of the world’s population, mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. It is estimated that approximately one quarter of prescribed drugs contain plant extracts or active ingredients obtained from or modeled on plant substances. Modern medicines and herbal medicines are complimentarily being used in areas for health care program in several developing countries including India.¹-³

Of late, the interest in the plant products surface all over the world due to the belief that many herbal medicines are known to be free from side effects. It is the fact that the discovery of the new synthetic drug is time consuming & an expensive affair. The utility of the synthetic drug is always accompanied with its single or multiple adverse effects and in some cases the curatives are not available.

Herbs had been used by all cultures throughout history but India has one of the oldest, richest and most diverse cultural living traditions associated with the use of medicinal plants. In the present scenario, the demand for herbal products is growing exponentially throughout the world and major pharmaceutical companies are currently conducting extensive research on plant materials for their potential medicinal value.⁴,⁵
According to World Health Organization (WHO), health is defined as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity”. WHO also defines mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community. WHO has declared 10th October as World Mental Health Day.⁶

A mental disorder or mental illness is a psychological or behavioral pattern generally associated with subjective distress or disability that occurs in an individual, and which is not a part of normal development or culture. The recognition and understanding of mental health conditions has changed over time and across cultures, and there are still variations in the definition, assessment, and classification of mental disorders.⁷⁻⁹

Major known, as well as emerging research in large cohorts of non-indigenous populations internationally, point to key risk factors and transition points along the life-cycle impacting on neuro-cognitive growth and decline, and increased risk of neurodegenerative diseases such as Alzheimer’s disease (AD) and other dementias later in life. Furthermore, it is increasingly recognized that early life events, social and biological, may interact to influence the aging process across the lifespan.¹⁰

The global dementia population is predicted to reach 81.1 million by 2040. Almost half of people with dementia (46%) live in Asia, 30 percent in Europe, and 12 percent in North America.¹¹ In India, the total prevalence of dementia per 1000 people is 33.6, of which AD constitutes approximately 54 and vascular dementia constitutes approximately 39. This prevalence is projected to increase four times by 2050.¹² The rapid increase in the number of dementia patients urgently demands effective prevention and treatment. Current approaches to dementia-related neurodegenerative diseases still highly rely on relieving symptoms.
Positive results in scientific studies prove that herbs should not be overlooked as an option for treatment of mental health conditions. Over the past decade, much effort has been put to use herbs as treatment modalities for mental illness. Traditionally, for treatment of mental health related disorders herbs had been used and the same finds its way to the pharmacy shelves today also, stating their significance to the area. Herbal formulations have advantages over synthetic drugs that herbs can contain active compounds that produce actions similar to pharmaceutical drugs and often cause fewer side effects\textsuperscript{13,14}.

Various Natural modalities for treatment of mental illness, ayurveda - ‘rasayana’ concept of ‘ayurveda’, complimentary alternative medicine (cam), yoga, exploring the role of homeopathy in reducing the global mental health burden, traditional medicine, herbs in mental illness, pharmacological evidence of existing herbal formulation in mental illness, chemical structures and pharmacology of bioactive molecule for mental illness from plant sources, herb-drug interactions and adverse herb reaction\textsuperscript{15}.

### 1.1. Dementia

Dementia (taken from Latin) originally meaning madness, from de- (without) + ment, the root of mens (mind) is a serious loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal aging. It may be static, the result of a unique global brain injury, or progressive, resulting in long-term decline due to damage or disease in the body. Although dementia is far more common in the geriatric population, it can occur before the age of 65, in which case it is termed "early onset dementia"\textsuperscript{16}.

Dementia is not a single disease, but a non-specific illness syndrome (i.e., set of signs and symptoms). Affected cognitive areas can be memory, attention, language, and problem solving. Normally, symptoms must be present for at least six months to support a diagnosis\textsuperscript{17}. 

Cognitive dysfunction of shorter duration is called *delirium*. In all types of general cognitive dysfunction, higher mental functions are affected first in the process. Age, stress, emotions are conditions that may lead to memory loss, amnesia, anxiety, high blood pressure, dementia, to more ominous threat like schizophrenia and Alzheimer’s diseases. Dementia means loss of memory. Some of the most common forms of dementia are: Alzheimer’s disease, vascular dementia, frontotemporal dementia, semantic dementia and dementia with Lewy bodies. It is possible for a patient to exhibit two or more dementing processes at the same time, as none of the known types of dementia protects against the others. Indeed, about ten per cent of people with dementia have what is known as *mixed dementia*, which may be a combination of Alzheimer's disease and multi-infarct dementia.\(^{18,19}\)

The limitation of thinking, function of brain, its connection with other organ and cascade of events for dementia is summarized in Figure 1.1.
Figure 1.1 Function of brain, its connection with other organ and cascade of events for mental illness

Following cerebral ischemia, energy failure and subsequent events including inflammation, glutamate-mediated excitotoxicity, calcium overload, initiation of intracellular death pathways, oxidative stress, and structural and functional changes occur. Mediators of these events interact with each other and contribute to cellular damage, in which a cholinergic deficit is involved, and finally cause cognitive impairment or dementia. Interestingly, protective effects of cholinergic agents, especially AChE inhibitors, involve multiple mechanisms (1-7). If we visualize brain functions in situ interaction with five organs, the brain could be hypothetically located at the center of or above the pentagonal interactive location of five elemental organs and equally interacts with.20,21
1.2 Herbs in Dementia

Herbal medicines include a wide range of pharmacologically active compounds.\(^{22}\) The supports of herbal medicine believe that isolated ingredients in the majority of cases have weaker clinical effects than whole plant extracts, a claim that would obviously require proof in each case. Physicians need to understand the biochemical and evidential bases for the use of herbs and nutrients to diagnose and treat participants safely and effectively, to avoid interaction with standard medications, and to provide participants with the benefits of alternative treatments. There are well established herbal formulations for mental health related disorders in the market but mechanism of action of such formulations are not well elucidated and documented. Apart from counseling, required in some cases, treatment of mental health involves synthetic and herbal formulations which act on central nervous system. To understand the role of herb in mental illness and related disorders an insight is given in the following section.

1.2.1 Plants and Aging

Aging is a universal biological process that leads to progressive and deleterious changes in organisms. From ancient time, mankind has already interested in preventing and keeping ourselves young. Keeping our brain functions as in young age is an important task for neuroscientists to prevent aging-associated neurological disorders, such as Alzheimer’s diseases (AD) and Parkinson’s disease (PD). The causes of these diseases are not fully understood, but it is believed that these diseases are affected by multiple factors. Neurodegenerative diseases can be cross-linked with a number of aging-associated conditions. Herbal medicine has a long history in Asian countries. It is believed that many of the medicinal herbs have antiageing properties. Recent studies have shown that some medicinal herbs are effective in intervention or prevention of aging-associated neurological disorders.\(^{23}\)
In Western societies, there has been increasing interest in herbal medicines, which are often perceived as a more ‘natural’ and ‘soft’ treatments compared to synthetic drugs. Some herbs are regarded as ‘anti-aging herbs’ in Asian countries. These herbs usually have some common properties. (1) Effects: these herbs usually belong to the group of ‘tonifying’ herb, which means they can help boosting up the level of vital energy in body. As deficiency of vital energy is thought to be the cause of aging, this property is especially important. (2) Multi-stages intervention: in healthy stage, some of these herbs act as food to provide certain essential nutrients; in disease stage, they help intervening disease and relieving symptoms. (3) Multi-targets and holistic approach: anti-aging herbs are often multi-targets and can be used in a number of diseases. They also achieve their therapeutic effects through modulating multiple pathological aspects. Anti-aging herbs which are described to have general tonic functions are therefore being investigated for their actions in the brain as anti-dementia drugs.\(^{24}\)

### 1.2.2 Plants and Memory

In traditional practices of Ayurvedic and Chinese medicine, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer’s disease (AD). An ethnopharmacological approach may be useful in providing leads to identify plants and potential new drugs that are relevant for the treatment of cognitive disorders, including AD. Many drugs currently available in Western medicine were originally isolated from plants, or are derived from templates of compounds isolated from plants. Some anticholinesterase (anti-ChE) alkaloids isolated from plants have been investigated for their potential in the treatment of AD, and are now in clinical use. In traditional practices of medicine, plants have shown pharmacological activities relevant to the treatment of cognitive disorders, indicating potential for therapeutic use in disorders such as AD and to alleviate other symptoms associated with AD.\(^{25}\)
1.3 Remedies for Dementia

Although a multitude of pharmaceutical agents are available for the treatment of mental disorders, physicians often find many participants cannot tolerate the side effects, do not respond adequately, or eventually lose their response. In comparison, many therapeutic herbs have fewer side effects. They can provide an alternative treatment or be used to enhance the effect of prescription medications. The following remedies are generally used for mental illness:

- Summary of the effects of some drugs frequently used as cognitive enhancers (Table 1.1)
- Marketed Herbal formulations enhancing vitality and mental health (Table 1.2)
- Plants of Traditional system of medicine used in aging (Table 1.3a)
- Plants of Traditional system of medicine used in memory (Table 1.3b)
Table 1.1 Summary of the effects of some drugs frequently used as cognitive enhancers

<table>
<thead>
<tr>
<th>Cognitive enhancer</th>
<th>Neuromodulatory mechanism</th>
<th>Cognitive function improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate, amphetamine</td>
<td>Dopamine and noradrenalin reuptake inhibitors</td>
<td>Response inhibition, working memory, attention, vigilance</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Non-selective adenosine receptor antagonist</td>
<td>Vigilance, working memory, incidental learning</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicotinic cholinergic receptor Agonist</td>
<td>Working memory, episodic memory, attention</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Unknown, but effects on dopamine, noradrenalin and orexin systems proposed</td>
<td>Working memory, episodic memory, attention</td>
</tr>
<tr>
<td>Atomoxetine, reboxetine</td>
<td>Noradrenalin reuptake inhibitors</td>
<td>Response inhibition, working memory, attention</td>
</tr>
<tr>
<td>Donepezil, galantamine, rivastigmine (AChEI)</td>
<td>Blocks enzymatic breakdown of acetylcholine</td>
<td>Episodic memory, attention</td>
</tr>
<tr>
<td>Memantine</td>
<td>Noncompetitive, low-affinity, open channel blocker of the NMDA receptor</td>
<td>Episodic memory, attention</td>
</tr>
</tbody>
</table>
Table 1.2 Marketed herbal formulations for enhancing vitality and mental health $^{27, 28}$

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Company</th>
<th>Formulation</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chyawanprash</td>
<td>Baidyanath</td>
<td>Shankhpushpi syrup</td>
<td>Unjha Pharm</td>
</tr>
<tr>
<td>Sonachandi</td>
<td></td>
<td>Braintab</td>
<td>Baidyanath</td>
</tr>
<tr>
<td>Chyawanprash</td>
<td>Dabur India</td>
<td>Brento tablets</td>
<td>Zandu</td>
</tr>
<tr>
<td>Chyavanprash special</td>
<td>Sandu</td>
<td>Mentat tablets/syrup</td>
<td>Himalaya</td>
</tr>
<tr>
<td>Ashwagandha pills/ghrita/Arishta/churna</td>
<td>Baidyanath</td>
<td>Smaran capsules</td>
<td>Jamna</td>
</tr>
<tr>
<td>Manmath ras</td>
<td>Baidyanath</td>
<td>Brahmivita granules</td>
<td>Bajaj</td>
</tr>
<tr>
<td>Alpitone</td>
<td>Zandu</td>
<td>Saraswstarishta</td>
<td>Dabur</td>
</tr>
<tr>
<td>Kesarijivan</td>
<td>Zandu</td>
<td>Remem syrup/capsules</td>
<td>Zydus Cadila</td>
</tr>
<tr>
<td>Shankhpushpi syrup</td>
<td>Zandu</td>
<td>Brahmibati</td>
<td>Baidyanath</td>
</tr>
<tr>
<td>Saraswatarishta</td>
<td>Baidyanath</td>
<td>Alert syrup</td>
<td>Vasu Pharm</td>
</tr>
</tbody>
</table>
### Table 1.3 (a) Plants of traditional system of medicine used in aging

<table>
<thead>
<tr>
<th>Plants Name, Family</th>
<th>Traditional /Pharmacological Use</th>
<th>Bioactive Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lycium barbarum</em> (Wolfberry) Solanaceae</td>
<td>The fruit belongs to “Yin tonifying herb” and is believed to be effective in replenishing any deficient “Yin” (a kind of vital energy); hence balancing homeostasis in our body.</td>
<td>Polysaccharides, Betaine, and β-carotene.</td>
</tr>
<tr>
<td><em>Panax ginseng</em> (Ginseng) Araliaceae</td>
<td>Anti-aging herb in the United States. They are viewed as adaptogenic herbs, which mean they increase body’s resistance to stress, trauma, anxiety and fatigue.</td>
<td>Ginsenosides</td>
</tr>
<tr>
<td><em>Lavandula stoechas</em> L. (Lavender) Lamiaceae</td>
<td>To strengthen a “stupid” and dizzy brain</td>
<td>β-pinene, Eucalyptol, β-Terpineol, Menthone, Menthol, Pulegone.</td>
</tr>
<tr>
<td><em>Salvia officinalis</em> L. (Garden sage) Lamiaceae</td>
<td>Remedies help those who shiver and suffer the effects of stroke and strengthen weak minds and memories, for a sensitive stomach, general debility, irregular menstruation and dementia</td>
<td>The α-thujone, Salvene, Pinene, Cineol, Borneol, Some esters, Salviol, Dextro Camphor in trace, Vitamin A and C.</td>
</tr>
</tbody>
</table>
| **Capsicum annuum**  
(L. (Mississippi pepper)  
Solanaceae | Native healers blend these herbs assisting memory, as well as foreczema, emphysema, asthma and other ailments of aging | Capsaicin, dihydrocapsaicin, sterols (cholest-5-en-3-ol, ergost-5-en-3-ol, stigmast-5,22-dien-3-ol and stigmast-5-en-3-ol) |
| **Barbieria pinnata**  
(Pers.) Baill.  
(Barberry)  
Fabaceae | The Kubeos prepared a tea of the seeds for elderly men with various mental problems | Argmmme |
| **Lundia erionema**  
De Candolle  
(Schultes et Cabrera)  
Bignoniaceae | Crushed leaves mixed with Jessenis oil are given to elderly ‘who speak crazily without making sense’ | _ |
| **Mandevilla steyermarkii**  
Woodson  
(Periwinkle)  
Apocynaceae | Given to the aged and the sick person | _ |
| **Pagaea recurva**  
Benth. (Bentham et Hooker fil)  
Gentianaceae | A decoction of the whole plant was prepared for debilitating forgetfulness in the elderly | _ |
| **Schlegia macrophylla**  
Ducke  
Bignoniaceae | Leaves given to people who refuse to eat and lose appetite | _ |
| **Tabernaemontana heterophylla**  
Vahl.  
(Milkwood)  
Apocynaceae | Tukano Indians prepared a tea of the leaves for the old folks who are slow and forgetful | Indole and bisindole alkaloids |
<p>| <strong>Unonopsis veneficiorum</strong> (Mart.) R.E.Fries | Added to the food of elderly people who forgot how to talk | Azafluorenones and bisaporphinoids |
| <strong>Unonopsis stipitata</strong> Diels | Added to the food of elderly people who have difficulty speaking | Aporphine alkaloid, arginine, histidine, lysine and ornithine, diaminobutyric acid and citrulline, |
| <strong>Vismia tomentosa</strong> Ruiz and Pav. | Plant for the elderly who suffer difficulty in understanding instructions and have physical degeneration and difficulty in talking | Prenylated anthranoids |
| <strong>Huperzia serrata</strong> Lycopodiaceae | Enhance the memory and motor activity in aged persons | Huperzine A, 3-β-hydroxysandaracopimaraic acid, abietane type diterpenoids phlegramariurine, huperser-ratinine |
| <strong>Coptis chinensis</strong> Franch. | For several conditions including age related cognitive and memory decline | Isoquinoline alkaloids, berberine, palmatine, hydrastine, and coptisine among others. |
| <strong>Emblica officinalis</strong> Gaertn. | Recommended for a life span of 100 years, to preserve youth, full vigor and cognitive function | Tannoid; pyrogallol, tanins, alkaloids, phenolic compounds, amino acids, carbohydrates, vitamin C, flavonoids, ellagic acid, chebulinic acid, quercetin, chebulagic |</p>
<table>
<thead>
<tr>
<th><strong>Withania somnifera</strong> (L.) Dun.</th>
<th><strong>Used in cases of debility from old age</strong></th>
</tr>
</thead>
</table>

| Acid, emblicanin-A, gallic acid, emblicanin-B, puniglucosin, pedunculagin, citric acid, ellagotannin, trigallayl, glucose and pectin |

Table 1.3 (b) Plants of Traditional system of medicine used in memory

<table>
<thead>
<tr>
<th>Plants Name, Family</th>
<th>Traditional /Pharmacological Use</th>
<th>Bioactive Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celastrus paniculatus Wild. Celastraceae</td>
<td>Seeds and seed oil have been used in Ayurvedic medicine for stimulating intellect and sharpening the memory</td>
<td>Protein, carbohydrates, fats, Vitamin C, Sodium, Potassium, ash, Calcium, Iron, and Sesqiterpene polyesters.</td>
</tr>
<tr>
<td>Centella asiatica L. Umbelliferae</td>
<td>An ancient Ayurvedic remedy reputed to restore youth, memory and longevity</td>
<td>Terpenes, Asiaticoside and Asiatic acid</td>
</tr>
<tr>
<td>Clitoria ternatea L. Leguminosae</td>
<td>The roots of the plant have a reputation for promoting intellect</td>
<td>Scopoletin, β-sitosterol, Tro-pane alkaloids, Kaempferol, Taraxerol, Taraxerone, p-Hydroxycinnamic acid, Flavanol glycoside, Delphinidin, Kae-mpferol, Clitorin.</td>
</tr>
<tr>
<td>Curcuma longa L. Zingiberaceae</td>
<td>Regarded as a ‘rasayana’ herb in Ayurveda (to counteract ageing processes).</td>
<td>Curcumin, demethoxycurcumin, bisdemethoxycurcumin and calebin-A (and some of its synthetic analogues)</td>
</tr>
<tr>
<td>Ginkgo biloba L. Coniferae</td>
<td>In circulatory disorders, it has also been used in Traditional Chinese Medicine (TCM) for respiratory disorders and memory.</td>
<td>Ginkgolides A B C, Proanthocyanidins, ginkgolic acid, ascorbic acid, carotenoids, and Bilobalide</td>
</tr>
<tr>
<td>Huperzia serrata Lycopodiaceae</td>
<td>The prescription of the plant has been used in TCM to alleviate problems of memory</td>
<td>Huperzine A</td>
</tr>
<tr>
<td><strong>Lycoris radiata</strong> Herb</td>
<td>loss.</td>
<td><strong>Galantamine and lycoramine.</strong></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Amaryllidaceae</strong></td>
<td>It is reported to be more selective for AChE than BuChE, and provides complete oral bioavailability. Galantamine is licensed in Europe for AD treatment.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Magnolia officinalis</strong> Magnoliaceae</th>
<th>The bark of the root and stem has been used in TCM to treat anxiety and nervous disturbances.</th>
<th><strong>Biphenolic lignans (honokiol and magnolol).</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Polygala tenuifolia</strong> Willd</th>
<th>Root is used in TCM as a cardiotonic and cerebrotonic, as a sedative and tranquilliser, and for amnesia, neuritis and insomnia. According to the Chinese Materia Medica, the root is supposed to have a special effect upon the will and mental powers, improving understanding and strengthening the memory.</th>
<th><strong>Polygalasaponins, onjisapon-in F, the cinnamic acid derivative sinapinic acid.</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Salvia miltiorrhiza</strong> Bung. Lamiaceae</th>
<th>It is prescribed in TCM to stabilize the heart and calm nerves official indications for the root include treatment of</th>
<th><strong>Dihydrotanshinone, tanshinoneI, methylene, tanshin-quinone, cryptotanshinone, tanshinoneII, salvianolic</strong></th>
</tr>
</thead>
</table>
| **Biota orientalis**  
Coniferae | blood circulation disorders, insomnia, neurasthenia and alleviation of inflammation | acids A and B, rosmariquinone (also known as miltirone) and several other phenolic compounds |
|-----------------|--------------------------------------------------|--------------------------------------------------------------------------------------------------|
| **Codonopsis pilosula**  
Campanulaceae | It is used in TCM for insomnia and amnesia. | Quercetin and rutin, α-cedrol. |
| **Crocus sativus**  
Iridaceae | In TCM, root is used for various disorders including amnesia, and is believed to promote blood circulation and enhance vitality | Hesperidin, n-hexyl betasophoroside, atracylenolide, lobetyolin, lobetyolinin, tara-kerol, taraxeryl acetate, alpha-spinasterol, 9,10,13-trihydroxy-(E)-11-octadecenoic acid, β-sitosterol,β-daucosterol and sugar. |
| **Evodia rutaecarpa**  
Rutaceae | It was used in TCM to treat disorders of the nervous system. | Crocin |
| **Evolvulus alsinoids/Convolvulus pluricaulis/Convulvulaceae** | Used in TCM for cardiotonic, restorative and analgesic effects. | Rutaecarpine, rutaecarpine, limonin, dehydroevodiamine and dehydroevodiamine |
| **Canscora decussata**  
Gentianaceae | It is considered as ‘Medhya Rasayana’ in Ayurvedic texts. The drug finds use for its therapeutic effect on CNS disorders like insanity, epilepsy, nervous debility and memory enhancement | (EA)-Ergot alkaloids, Betaine, shankhapushpine and evolve -ine, Tropane alkaloids.  
(CP)-Scopoletin, β-sitosterol, Tropane alkaloids, Kaem-pferol.  
(CD)- Xanthone, Loliolides, Lanostane triterpenoids, Man-giferin and Scopoletin |
1.4 Chemical structures and pharmacology of bioactive molecule for mental illness from plant sources

Today, the principal chemical ingredients of most of the important herbal source materials are known and have been published. What is uncertain, however, is the identity of the chemical that is biologically relevant in a particular herb are becomes an important lead for new drug development\textsuperscript{75-76}. Some of the active constituents (Figure 1.2) obtained from several sources or native to one sources are promising against mental illness are:

1.4.1 Evolveine hydrochloride

The hydrochloride salt of alkaloid, evolveine was reported to exhibit lobeline-like action on the cardiovascular system. In cats, the drug demonstrated sympathomimetic activity. The blood pressure remained elevated for a longer duration as compared to adrenaline. Increase in peripheral pressure was observed on local injection of the drug\textsuperscript{77}.

1.4.2 Inositol

Inositol is a sugar alcohol and a structural isomer of glucose, ubiquitous in biologic organisms and located primarily within cell membranes. Of its nine different isomeric compositions, myo-inositol is the most abundant biologically active stereoisomer in the human body, comprising 95\% of total free inositol. It is present in a variety of foods, particularly beans, grains, nuts, and many fruits\textsuperscript{78}. Inositol is an important growth factor for human cells\textsuperscript{79}, acting in the synthesis of membrane phospholipids and as a precursor in the phosphatidylinositol (PI) cycle\textsuperscript{80}. The PI cycle is the second messenger system for numerous neurotransmitter receptors, including cholinergic muscarinic, alpha 1 noradrenergic, serotonergic 5-HT2A and 5-HT2C, and dopaminergic D1 receptors, which are involved in several psychiatric conditions. The potential importance of inositol in psychiatric disorders is thereby evident when
one considers the number of receptor types/ subtypes that interact with this signal transduction pathway.  

1.4.3 Convolvine

The specific pharmacological action of convolvine has been found to block M2 and M4 cholinergic muscarinic receptors. It was also found that convolvine potentiates the effects of arecoline, a muscarinic memory enhancer that ameliorates cognitive deficits in Alzheimer’s disease.  

1.4.4 Galantamine

Galantamine, an alkaloid obtained from the bulbs and flowers of the Caucasian snowdrop Galanthus woronowii (Amaryllidaceae), is a fine example of a plant secondary compound successfully used for the treatment of mild to moderate AD.
Figure 1.2 Chemical structures of plant metabolites used in mental illness\textsuperscript{54}

(Contd.)
Figure 1.2 Chemical structures of plant metabolites used in mental illness.
1.4.5 Huperzine A

An alkaloid from *Huperzia serrata*, was found to be a reversible AChE inhibitor and is neuroprotective. It was shown that, huperzine A has a neuroprotective effect against β-amyloid peptide fragment 25–53, oxygen glucose deprivation and against free radical-induced cytotoxicity. It also attenuates apoptosis by inhibiting the mitochondria-caspase pathway. Huperzine A facilitates cholinergic neurotransmission by increasing the concentration of acetylcholine in the CNS about 100 times more effectively than tacrine, a drug used for AD. \(^{85}\) In cell culture studies huperzine A decreased neuronal cell death caused by toxic levels of glutamate.\(^{86}\) In rat, huperzine A reversed β-amyloid-(1–40) induced deficit in learning in a water maze task, and reduced the loss of choline acetyltransferase activity in cerebral cortex, and the neuronal degeneration induced by β-amyloid protein (1–40). It was reported to be more selective for AChE than BuChE and was less toxic than the synthetic AChE inhibitors donepezil and tacrine.\(^{87}\)

1.4.6 Selegiline

Selegiline is a type B monoamine oxidase inhibitor (MAOI) that is metabolized to amphetamine and methamphetamine stimulant compounds that may be useful in the treatment of Attention deficit hyperactivity disorder (ADHD).\(^{88}\)

1.4.7 Acetylcholinesterase Inhibitors bioactive from plants

1.4.7.1. Steroidal alkaloid

Assoanine (*Narcissus assoanus*; Amaryllidaceae), Buxamine B (*Bucus hyrcana* and *Bucus papillosa*; Buxaceae), Epinor-galantamine (*Narcissus confuses, N. perezchiscanoi, Narcissus leonensis, N. legionensis* and *Narcissus poeticus*; Amaryllidaceae), Galantamine (*Galanthus nivalis, Narcissus confuses* and *Lycor us radiate*; Amaryllidaceae), 11-Hydroxygalantamine (*Narcissus poeticus*; Amaryllidaceae), Oxoassoanine (*Narcissus assoanus*; Amaryllidaceae) Sanguinine (*Eucharis grandiflora*; Amaryllidaceae),
Sarsalignone (*Sarcococca saligna*; Buxaceae), α-Solanine glycoalkaloids (*Solanum tuberosum*; Solanaceae), Vaganine (*Sarcococca saligna*, Buxaceae), N, N-dimethyl buxapapine (*Bucus papillosa*, Buxaceae).\(^{89-93}\)

### 1.4.7.2 Indole alkaloid

Coronaridine (*Tabernaemontana australis*; Apocynaceae), Physostigmine (*Physostigma venenosum*; Leguminosae), Rupicoline (*Tabernaemontana australis*; Apocynaceae), Voacangine (*Tabernaemontana australis*; Apocynaceae), Voacangine hydroxyindolenine (*Tabernaemontana australis*; Apocynaceae).\(^{94,95}\)

### 1.4.7.3 Quinolizidine alkaloid

(-)-Huperzine A (*Huperzia serrata* and *Huperzia dalhousieana*; Lycopodiaceae)\(^{96,97}\)

### 1.4.7.4 Isoquinoline alkaloid

Palmatine (*Corydalis speciosa*; Papaveraceae), Corynoline (*Corydalis incisa*; Papaveraceae), Protopine (*Corydalis speciosa*; Papaveraceae).\(^{98,99}\)

### 1.4.7.5 Pregnane glycoside

Cynatroside A (*Cynanchum atratum*; Asclepiadaceae), Cynatroside B (*Cynanchum atratum*; Asclepiadaceae).\(^{100}\)

### 1.4.7.6 Bellidin 8-O-glucopyranoside

Norswertianolin (*Gentiana cambpestris*; Coniferae), Swertianolin (*Gentiana cambpestris*; Coniferae).\(^{101}\)

### 1.4.7.7 Flavonoids, Xanthones, Stilbene oligomers and others

Viniferin Stilbene oligomer (*Caragana chamlague*; Leguminosae), Bellidin Xanthone (*Gentiana cambpestris*; Coniferae), Bellidifolin Xanthone (*Gentiana cambpestris*; Coniferae), Ursolic acid and Hydroxy-...
heptamethylicosahydropicene carboxylic acid (*Origanum majorana*; Lamiaceae) \(^{102,103}\)

### 1.5 Pharmacological Screening Method

#### 1.5.1 Nootropic Activity

##### 1.5.1.1 Acetylcholinesterase enzyme (*AchE*) Inhibition assay

Acetylcholinesterase inhibition assay is carried out as below.

In brief, a preincubation volume of 250 µl of phosphate buffer (200 mM pH 7.7) in 96 flat bottom well plate with test samples of isolates, fractions and extracts of various botanicals and a reference standard galanthamine of various concentrations, 80µl of DTNB (3.96 mg of DTNB and 1.5 mg sodium bicarbonate dissolved in 10 ml phosphate buffer pH 7.7), and 10µl of enzyme (2 U/ml). The mixture is incubated for 5 min at 25 °C. Following preincubation, 15µl of the substrate (acetylthiocholine iodide: 10.85 mg in 5ml of phosphate buffer) is added and incubated again for 5 min. The colour developed is measured in a microwell plate reader at 412 nm. The percent inhibition is calculated using the formula:

\[
\text{Percent inhibition} = \left(\frac{\text{Control Absorbance} - \text{Sample Absorbance}}{\text{Control Absorbance}}\right) \times 100.
\]

The IC\(_{50}\) is calculated by log-probit analysis. Galanthamine is used as positive control.\(^ {104}\) AChE activity is measured using a 96-well microplate reader based on Ellman’s method.\(^ {105}\)

##### 1.5.1.2 β-amyloid induced neuroprotection on brain cell line

Neuro 2a cells isolated from neuroblastoma of mouse in the exponential phase of growth are exposed to a well reported neurotoxic compound β-amyloid. The duration of exposure is determined as the time required for maximal damage to occur. The compounds to be tested for protection against this damage were
added, and then the cells were allowed to proliferate for two to three population-doubling times (PDTs) in order to distinguish between cells that remain viable and are capable of proliferation and those that remain viable but cannot proliferate. The number of surviving cells is then determined indirectly by MTT dye reduction assay. The amount of MTT-formazan produced can be determined spectrophotometrically once the MTT formazan has been dissolved in a suitable solvent.\textsuperscript{106}

\subsection*{1.5.2 Screening for memory enhancement and learning behavior}

The following parameters are recorded\textsuperscript{107}:

\subsubsection*{1.5.2.1 Inhibitory (passive) avoidance tests}

a. Step down test

b. Scopolamine induced amnesia in rats

c. Elevated Plus Maze (Exteroceptive Behavior Model)

\subsubsection*{1.5.2.2 Active avoidance tests}

a. Assessment of Nootropic Activity

b. Hebb-Williams maze

c. Rectangular Maze Test

\subsubsection*{1.5.2.1 Inhibitory (Passive) Avoidance Tests}

The following parameters are used to assess effects on learning and memory.

\subsubsection*{1.5.2.1a Step Down Test}

The test apparatus is a rectangular box (45 x 30 x 40 cm) with an electrified grid floor. It was made of transparent Plexiglass to permit observations. An 8 cm high wooden platform (17 x 12 cm) is fixed to the grid floor at the center of
the apparatus. A rat is placed on the platform and allows to step down. Twenty four hours later, on Day 1 of the experiment, the rat is again placed on the platform and foot shock (0.75 mA, 2 s) is delivered through the grid floor as soon as it steps down. The rat is given foot shock only when all the four paws are touching the grid floor. The rat is given three more trials until the latency of the step down has stabilized. The test is repeated on Day 15. Memory retention score for each animal is calculated by determining "inflexion ratio" by the formula:

\[ \text{Inflexion ratio} = \frac{L_{15} - L_1}{L_1} \]

Where \( L_1 \) is the step down latency on day 1 in seconds and \( L_{15} \) is the step down latency on day 15 in seconds.\(^{108,109}\) For this experiment, the animals are divided into different groups containing six animals in each group.

**1.5.2.1b Scopolamine Induced Amnesia in mice**

This activity is performed using the Cook and Weidley's pole climbing apparatus. The apparatus consists of a soundproof experimental chamber with a grid floor, which could be electrified and with a provision for a buzzer tone. The enclosure has a covering lid at the top, through which the animal could be introduced into the chamber. A wooden pole, screwed onto the inner surface of the lid of the chamber act as the shock-free zone. The stimulus provided is a foot shock of 6 mA given for a period of 10 s from the electrified grid floor. Mice are initially trained to escape the foot shock by climbing onto the pole, i.e. the shock free zone. This initial trial is carried out by having three trial sessions interspersed with an interval of 10 s. During each of the initial trials the mice are allowed to explore the apparatus for 10 s. This is followed by a foot shock for 10 s. Only those mice, which are sensitive to the foot shock and could climb the pole, are included in the study. The animals are divided into different groups with six animals per group. Twenty four hour later, on 8th day, a relearning trial is conducted and the number of ARs in the 10 trial sessions is noted. On day 9 of the experiment, after attaining complete training, all the
animals except the control, are treated with a single dose of scopolamine butyl bromide (SBB) (0.3 mg/kg i.p.), 30 minutes before the administration of the extracts. Control group receives the vehicle alone. Training schedule is continued further with daily dosing of the extracts till 15 days.  

1.5.2.1c Elevated Plus Maze (Exteroceptive Behavior Model)

Elevated plus maze is served as the exteroceptive behavior model to evaluate learning and memory in albino rats. It is so called exteroceptive behavior as the stimulus existed outside the body. The elevated plus maze (EPM) consists of two open arms (50×10 cm) crossed with two closed arms (50×10×40 cm). The arms are connected together with a central square (10×10 cm). The apparatus is elevated to a height of 70 cm in a dimly illuminated room. For the experiments rats are divided into different groups of six animals each. On the first day, each rat is placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) is taken as the time taken by the rat to move into any one of the covered arms with all its four legs. TL is recorded on the first day. If the rat does not enter into one of the covered arms within 90 s, it is assigned as 90 s. the rat is allowed to explore the maze for 10 s and then return to its home cage. Memory retention is examined 24 h after the first day trial on the second day.  

1.5.2.2 Active Avoidance Tests

1.5.2.2a Assessment of Nootropic Activity

The nootropic activity is assessed using the active avoidance paradigm. The apparatus consists of a soundproof experimental chamber with a grid floor which could be electrified and with a provision for a buzzer tone. The enclosure has a covering lid at the top, through which the animal could be introduced into the chamber. A wooden pole, screwed onto the inner surface of the lid of the chamber acted as the shock-free zone. In the assessment of nootropic activity, the stimulus is provided are a foot shock of 6 mA given for a
period of 10 s from the electrified grid floor. Rats are initially trained to escape the foot shock by climbing onto the pole, i.e. the shock free zone. This initial trial is carried out by having three trial sessions interspersed with an interval of 10 s. During each of the initial trials the rats are allowed to explore the apparatus for 10 s. This is followed by a foot shock for 10 s. Only those rats, which were sensitive to the foot shock and could climb the pole, are included in the study. The animals are divided into different groups, each group containing six animals. During each trial, the rats are allowed to explore the apparatus for 10 s, followed by a buzzer tone of 50 Hz (conditioned stimulus) for 10 s. This is followed by a foot shock for 10 s. The animal learned to associate the buzzer tone with the impeding foot shock and is capable of avoiding the foot shock on hearing the buzzer tone. Jumping onto the wooden pole, before the shock period, constituted an avoidance response (AR). The AR for 10 trials is noted. Twenty four hours later, a relearning trial (RT) is conducted and the number of ARs in the 10 trial sessions is noted. Piracetam (100 mg/kg, p.o.) is used as the standard reference drug for comparison.

1.5.2.2b Hebb-Williams maze

Hebb-Williams maze is an incentive-based Exteroceptive behavioral model useful for measuring spatial working memory of rats. It mainly consists of three components: animal chamber (or start box), which is attached to the middle chamber (or exploratory area), and a reward chamber at the other end of the maze in which the reward (food) is kept. All three components are provided with guillotine removable doors. On the first day (i.e., seventh day of drug treatment), the rat is placed in the animal chamber or start box and the door is opened to facilitate the entry of the animal into the next chamber. The door of the start box is closed immediately after the animal moved into the next chamber to prevent back-entry. Time taken by the animal to reach the reward chamber from the start box is recorded on the first day (training session) for each animal. Each animal is allowed to explore the maze for 3 min with all the doors are opened before returning to its home cage. Retention of this learned
task (memory) is examined 24 h after the first day trial (i.e., eighth day, 24 h after last dose).\textsuperscript{114}

1.5.2.2c Rectangular Maze Test

Assessment of learning and memory can be effectively done by this method. The maze consists of completely enclosed rectangular box with an entry and reward chamber appended at opposite ends. The box is partitioned with wooden slats into blind passages leaving just twisting corridor leading from the entry to the reward chamber. Animals were trained prior to the experiment by familiarizing with the rectangular maze for a period of 10 min for 2 h. Well-trained animals were taken for the experiment. Transfer latency (time taken to reach the reward chamber) was recorded. For each animal, four readings were taken and the average is taken as learning score (transfer latency) for that animal. Lower scores of assessment indicate efficient learning while higher scores indicate poor learning in animals. The time taken by the animals to reach the reward chamber from the entry chamber was noted on day 1, 3, 5, 7, and 9.\textsuperscript{115}

1.6 Standardization and Quality Control of Herbal Crude Drugs\textsuperscript{116-118}

Accounting to WHO it is the process involving the physicochemical evaluation of crude drug covering the aspects, as selection and handling of crude material, safety, efficacy and stability assessment of finished product, documentation of safety and risk based on experience, provision of product information to consumer and product promotion.

1.6.1 Physical evaluation

Each monograph contains detailed botanical, macroscopic and microscopic descriptions of the physical characteristics of each plant that can be used to insure both identity and purity. Each description is accompanied by detailed
illustrations and photographic images which provide visual documentation of accurately identified material.

1.6.2 Microscopic evaluation

Full and accurate characterization of plant material requires a combination of physical and chemical tests. Microscopic analyses of plants are invaluable for assuring the identity of the material and as an initial screening test for impurities.

1.6.3 Chemical evaluation

A chemical method for evaluation covers the isolation, identification and purification. Chemical analysis of the drug is done to assess the potency of vegetable and animal source material in terms of their active principles. The chemical tests include colour reaction test, these tests help to determine the identity of the drug substance and possible adulteration.

1.6.4 Biological evaluation

Pharmacological activity of certain drugs has been applied to evaluate and standardize them. The assays on living animal and on their intact or isolated organs can indicate the strength of the drug or their preparations. All living organism are used, these assays are known as Biological assays or Bioassay.

1.6.5 Analytical Methods

Critical to compliance with any monograph standard is the need for appropriate analytical methods for determining identity, quality, and relative potency. There are a plethora of analytical methods available. However, it is often difficult to know which the most appropriate to use is. The primary goal of AHP is to provide multiple methods of identification and testing by which all aspects of the botanical can be appropriately assayed.
1.6.6 Chromatographic Characterization

Chromatography is the science which is studies the separation of molecules based on differences in their structure and/or composition. In general, chromatography involves moving a preparation of the materials to be separated the "test preparation” over a stationary support. The molecules in the test preparation will have different interactions with the stationary support leading to separation of similar molecules. Test molecules which display tighter interactions with the support will tend to move more slowly through the support than those molecules with weaker interactions. In this way, different types of molecules can be separated from each other as they move over the support material.

Chromatographic separations can be carried out using a variety of supports, including immobilized silica on glass plates (thin layer chromatography), very sensitive High Performance Thin Layer Chromatography (HPTLC), volatile gases (gas chromatography), paper (paper chromatography), and liquids which may incorporate hydrophilic, insoluble molecules (liquid chromatography).

1.6.7 Purity Determination

Each monograph includes standards of purity and other qualitative assessments which include when appropriate: foreign matter, ash, acid-insoluble ash, moisture content, loss of moisture on drying, and extractives. High performance thin layer chromatography (HPTLC) is valuable quality assessment tool for the evaluation of botanical materials. It allows for the analysis of a broad number of compounds both efficiently and cost effectively. Additionally, numerous samples can be run in a single analysis thereby dramatically reducing analytical time. With HPTLC, the same analysis can be viewed sing different wavelengths of light thereby providing a more complete profile of the plant than is typically observed with more specific types of analyses.
1.6.8 Quantitative Analysis

When applicable, the most appropriate quantitative analytical method with accompanying chromatograms shall be provided. The primary goal of the method(s) is to provide validated methods to be used for the quantization of the compound(s) most correlated with pharmacological activity or qualitative markers as determined by the primary pharmacological literature, constituent declaration in product labeling, and a survey of experts. The method(s) will be selected from the primary analytical literature by a Methods Selection Committee with priority given to compendial methods when available. In this context, validation consists minimally of a two-lab validation using the same procedures, samples, and reference standards. Primary factors for considering a method as appropriate include accuracy of the findings, speed, basic ruggedness, applicability to a large segment of the manufacturing community and avoidance of the use of toxic reagents and solvents. When necessary, comparative tests shall be conducted to determine which of the available method(s) is most appropriate. The validation process minimally includes: standard precision, linearity, sample precision using replicate samples, sample linearity, selectivity (co-elution, sensitivity to analyte degradation), retention times, and limits of detection. Other methods which may be of value to the industry may be included or cited in the monograph but are not required for compliance with the monograph.

The guidelines set by WHO can be summarized as follows:


b. Reference to the physiochemical character of the drug. Chromatographic profiles, ash values, extractive values, refractive index, polarimetric readings, moisture content, volatile oil content, etc.
c. Reference to the pharmacological parameters. Biological activity profiles, bitterness values, haemolytic index, astringency, swelling factor, foaming index, etc.

d. Toxicity details – heavy metals like cadmium, lead, arsenic, mercury, etc. Pesticide residues.

e. Microbial contamination – Total viable aerobic count, pathogenic bacteria like Enterobacteria, E.coli, Salmonella, Pseudomonous aeruginosa, Staphylococcus aureus, etc. and presence of aflatoxins etc.