1.1 DESCRIPTION

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. Mental health is one of the major concerns of health and the 14% of the global burden of disease is attributed due to problem associated with mental health. WHO has declared 10 October as World Mental Health Day (Smith et al., 2006). 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 (Sartorius, 2006; Taylor & Hawley, 2006; Insel &Wang, 2010). A nation's growth, in part, depends on mental health of its population. But due to competitive nature of today's world degradation of mental health is day by day worsening in many developing countries. Around the world, almost one million people die due to suicide every year and it is the third leading cause of death among young people.

Mental illness affects a substantial portion of the US population. Annual prevalence among adults is 18% for anxiety disorders, 7% for major depression, 3% for bipolar disorder, and 1% for schizophrenia (Kessler et al., 2005; Regier et al., 1993). Nearly 4% of adults have antisocial personality disorder (Compton et al., 2005) and 2% have borderline personality disorder (Swartz et al., 1990). Of further concern is that two-thirds of women with mental illness are mothers (Nicholson et al., 2001) and maternal mental illness can have negative consequences for children (Kohl et al., 2011). Persons with severe mental illness have a life expectancy 25 years shorter than the general population, their lives cut short more often by cardiovascular diseases and other health problems than by suicide and injuries (Shibusawa & Padgett, 2009). The most important causes of disability due to health-related conditions worldwide include unipolar depression, alcoholism, schizophrenia, bipolar

name is derived from Sanskrit words *ARSH* (Blood loss) and *GHNA* (killer or remover). Another method adopted by *Charaka*, is based on collection of three or more plants having identical properties in one group signifies as *Gana* means group (Singh, 2008). Based on the physical forms of the different botanical sources drug are grouped in different texts of *Ayurveda* are classified as:

Brahatpanchmula: It is combination of roots of five medicinal plants including *Bilva* (*Aegle marmelos*), *Agnimantha* (*Premna integrifolia*), *Shoynaka* (*Oroxylum indicum*), *Gambhari* (*Gmelina arborea*), and *Patla* (*Sterospermum suaveolens*).

Dashmula: It is combination of roots of ten medicinal plants including *Bilva* (*Aegle marmelos*), *Agnimantha* (*Premna integrifolia*), *Shoynaka* (*Oroxylum indicum*), *Gambhari* (*Gmelina arborea*), *Patla* (*Sterospermum suaveolens*), *Shalaparni* (*Desmodium gangeticum*), *Prishnaparni* (*Uraria picta*), *Brahati* (*Solanum indicum*), *Kantkari* (*Solanum xanthocarpum*), and *Gokshura* (*Tribulus terrestris*).

Triphala: It is combination of fruits of three medicinal plants including *Haritaki* (*Terminalia chebula*), *Vibithaka* (*Terminalia belerica*), and *Amalaki* (*Emblica officinalis*).

1.2.2 Controversial Name of Botanicals or Sandigdha dravays

India is a country having variety of languages and population dependent on different tribal and folklore medicine. The variation in the language sometimes is responsible for confusion in the nomenclature of different plants having similar name. Moreover the descriptions of a plant in the ancient literature are found in versus having ample use of synonym. These synonyms have caused controversy in the identification of plants and hence the correct source sometime is misleading with a fictious plant (Sethiya et al., 2009b; 2010c). Many of the traditional systems have records where one common vernacular name is applied to plants with two or more entirely different plant species (Kumar, 2007).

Ambiguity in Ayurveda is reflected in the interpretation of names and description of drugs found in the books like *Charaka Samhita* and *Sushruta Samhita,* etc. Ayurvedic treatises were also hand written before the establishment of British rule, like the other books. Western scientist of the nineteenth century were divided in

Table 1.1: List of some controversial drugs in Indian medicine (Dixit, 2011).

Daruharidra
Berberis aristata (Berberidaceae), *Coscinium fenestratum* (Menispermaceae),
Brahmi
Bacopa moniera (Scrophulariaceae), *Hydrocotyle asiatica* (Umbellifereae), *Moniera cuneate*
Amaravela
Cascutta reflexa (Convolvulaceae), *Cassyatha filiformis* (Lauraceae).
Punarnava
Trianthema partulacastrum (Ficoidaceae), *Boerhavia diffusa* (Nyctaginaceae)
Jivanti
Leptadenia reliculata (Asclepiadaceae), *Desmotrichun fimbritum* (Orchiaceae), *Cimicifuga*
foetida (Ranunculaceae)
Shankhapuspi
Convolvulus pluricaulis (Convulvulaceae), *Evolvulus alsinoides* (Convulvulaceae), *Canscora*
decussata (Gentianaceae), *Clitorea ternatea* (Papilonaceae).

1.3 BRAIN

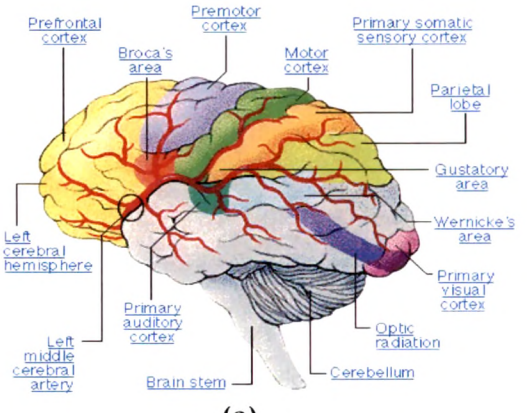
Brain is soft, whitish, large sized and slightly flattened structure present inside cranial cavity of cranium of skull. In human, it is about 1200-1400 gm in weight and forms about 98% of weight of Central Nervous System.

The brain is formed of three parts:

(A). Fore brain or Prosencephalon.

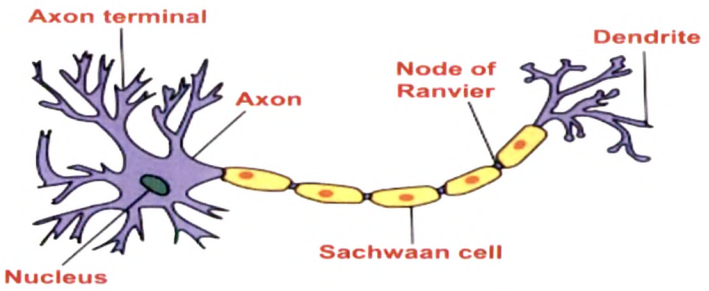
(B). Mid brain or Mesencephalon.

(C). Hind brain or Rhombencephalon.



(a)

Human brain has about 10,000 million neurons (with largest number of neurons). It is the busiest organ of body, which controls and coordinates the body functions (Arora & Sabharwal, 1998; Hendrickson & Robert, 2000). The typical structure of brain and neurons has been shown in figure 1.1



(b)

Figure 1.1 (a).Various brain parts; (b). Structure of a typical neuron

1.3.1 Cognition

Memory (Cognition) is a recollection of that which has been experienced once or learnt. Memory may be defined as mental information system consisting of encoding, storage and retrieval (Bharkatiya et al., 2006). Several additional classifications of memory are sometimes used by psychologists, particularly in reference to the content or use:

- ***Reference memory*** refers to a filing system that contains recent and remote information gained from previous experience.
- ***Working memory*** refers to an active process that is being updated continually by current experience.
- ***Episodic memory*** contains information about events occurring in a specific place and time.
- ***Semantic memory*** contains unchanging facts, principles, associations and rules.
- ***Declarative (explicit) memory*** refers to facts about the world and past personal events that must be consciously retrieved to be remembered.
- ***Procedural (implicit) memory*** is involved in learning and retaining a skill or procedure such as how to ride a bicycle, or drive a car.

The difference between episodic and declarative memory has been given in Table 1.2.

Table 1.2 Episodic and declarative memory: defining features (Tulving & Markowitsch, 1998; Griffiths et al., 1999)

Declarative memory (episodic and semantic common features)	*Episodic memory: unique features*
✓ Large, complex and highly structured, with fast encoding operations	✓ Concerned with conscious recollection of specific past experiences
✓ Can receive factual information through different sensory modalities and internally generated sources	✓ Oriented, at the time of retrieval, to the past
✓ Stored information is representational (isomorphic with what is in the world) and propositional (can be described symbolically)	✓ Accompanied by 'autonoetic' consciousness, which enables 'remembering' (relating to personal experience) as opposed to 'knowing'
✓ Information has truth value, can be accessed and expressed flexibly, and can be used as a basis for inferences	✓ Embedded relationship with semantic ('knowing') memory: episodic remembering always implies semantic knowing, whereas knowing does not imply remembering
✓ Processing is highly sensitive to context	✓ Development occurs later than semantic abilities in children
✓ System is cognitive (as opposed to behavioural):	✓ More vulnerable to a number of brain pathologies and aging
✓ information can be 'thought about'	
✓ Behavioural expression of retrieval products is optional rather than obligatory	✓ Dependent on frontal lobes in a way that declarative memory is not: episodic retrieval is associated with changes in regional cerebral blood flow in right prefrontal cortex, which is rarely caused by semantic recall
✓ System interacts closely with other brain/behaviour systems, such as language, emotion, affect and reasoning	✓ Unique to humans.
✓ Dependent on MTL and diencephalic structures such as the thalamic nuclei	

1.3.2 Mental fitness

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. Amnesia means loss of memory. There are many different types of amnesias according to their cause. *Functional amnesia* refers to memory disorders that seem to result from psychological trauma, not an injury. *Organic amnesia* involves memory loss caused by specific malfunctions in the brain. Another is *infantile amnesia*, which refers to the fact that most people lack specific memories of the first few years of their life. The limitation of thinking, function of brain, its connection with other organ and cascade of events for mental illness are summarized in figure 1.2 and figure 1.3.

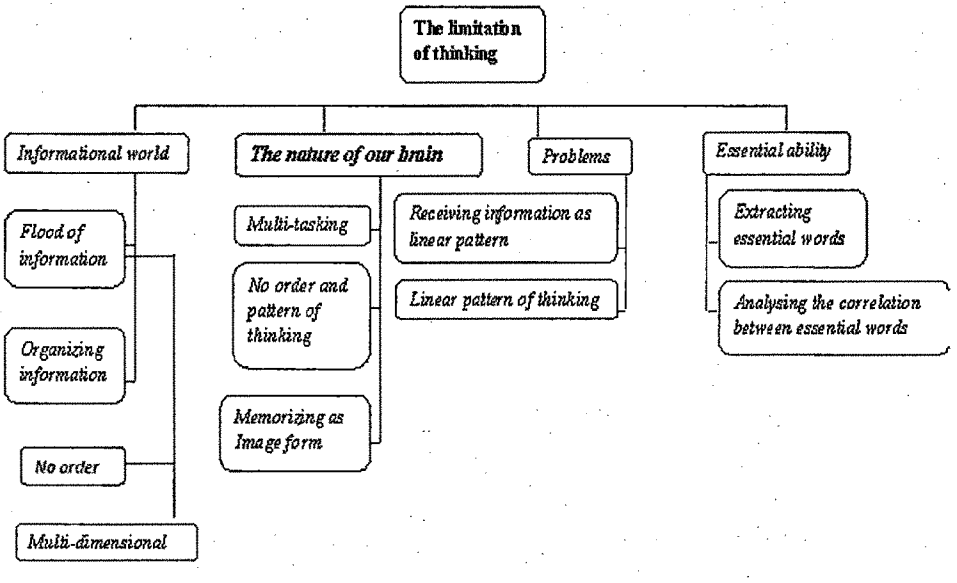


Figure 1.2 Limitation of thinking

1.3.3 Classification of mental disorder

The classification of mental disorders, also known as psychiatric nosology or taxonomy, is a key aspect of psychiatry and other mental health professions and an important issue for consumers and providers of mental health services. The widely used Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) generally employ as in operational definitions. There

is a significant scientific debate about the relative validity of a "categorical" versus a "dimensional" system of classification, as well as significant controversy about the role of science and values in classification schemes and the professional, legal and social uses to which they are put (Sadler, 2008). The classification of mental disorder or mental illness are summarized in table 1.3.

Table 1.3 Classification of mental disorder (Kramer et al., 1979; Sartorius, 1976; Jablensky et al., 1983; Aboraya, 2010).

Description	*Disorder/ Disease*
Developmental disorder	Attention Deficit Hyperactivity Disorder (ADHD), Mental Retardation, Epilepsy
Delirium, dementia, amnesia and other cognitive disorders	Alzheimer's disease
Mental disorders due to a general medical condition	AIDS-related psychosis
Substance-related disorders	Alcohol abuse
Schizophrenia and other psychotic disorders	Delusional disorder
Mood disorders	Major depressive disorder, Bipolar disorder
Anxiety disorders	General anxiety disorder
Somatoform disorders	Somatization disorder
Factitious disorders	Münchausen syndrome
Dissociative disorders	Dissociative identity disorder
Sexual and gender identity disorders	Dyspareunia, Gender identity disorder
Eating disorders	Anorexia nervosa, Bulimia nervosa
Sleep disorders	Insomnia
Impulse control disorders not elsewhere classified	Kleptomania
Adjustment disorders	Adjustment disorder
Personality disorders	Narcissistic personality disorder
Other conditions that may be a focus of clinical attention	Tardive dyskinesia, Child abuse

cell death (neurotoxicity and apoptosis). Each process provides possible targets for cognition enhancement and selective forgetting in healthy people, while processes important in disease-associated cognitive decline are important targets for early therapeutic intervention.

1.3.4.1 Screening for memory enhancement and learning behavior

The following parameters are recorded (Vogel, 2002):

Inhibitory (passive) avoidance tests

- Step down test
- Step through test
- Two compartment test
- Up hill test
- Trial-to-criteria inhibitory test
- Scopolamine induced amnesia in mice
- Memory impairment by basal forebrain lesions in rats
- Ischemia induced amnesia in gerbils
- Cognitive deficits on chronic low dose MPTP-treated monkeys

Active avoidance tests

- Runway avoidance
- Shuttle box avoidance (two-way shuttle box)
- Jumping avoidance (one-way shuttle box)

Discrimination learning tests

- Spatial habituation learning
- Spatial discrimination
- Spatial learning in the radial arm maze
- Visual discrimination
- Spatial learning in the water maze
- Olfactory learning

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. Strategies and treatments for cognition enhancement include:

- General measures such as exercise and environmental enrichment
- Correction of underlying factors such as hypertension
- Pharmaceuticals (Table 1.5)
- Nutrients or herbal supplement or herbal formulation (Table 1.6)
- Herbal medicines (Table 1.7)
- Psychological and learning strategies
- Electromagnetic interventions e.g. transcranial magnetic stimulation, brain-computer interfaces (Robbins et al., 2005).

Table 1.5 Summary of the effects of some drugs frequently used as cognitive enhancers (Husain & Mehta, 2011)

Cognitive enhancer	Neuromodulatory mechanism	Cognitive function improved
• Methylphenidate, • amphetamine	Dopamine and noradrenalin reuptake inhibitors	Response inhibition, working memory, attention, vigilance
• Caffeine	Non-selective adenosine receptor antagonist	Vigilance, working memory, incidental learning
• Nicotine	Nicotinic cholinergic receptor agonist	Working memory, episodic memory, attention
• Modafinil	Unknown, but effects on dopamine, noradrenalin and orexin systems proposed	Working memory, episodic memory, attention
• Atomoxetine, Reboxetine	Noradrenalin reuptake inhibitors.	Response inhibition, working memory, attention
• Donepezil, Galantamine, • Rivastigmine (AChEI)	Blocks enzymatic breakdown of acetylcholine	Episodic memory, attention
• Memantine	Noncompetitive, low-affinity, open channel blocker of the NMDA receptor	Episodic memory, attention

Table 1.7 Plants of Traditional system of medicine used in mental illness

Plant Name, Family, common Name	Traditional /Pharmacological Use	Bioactive Chemicals	References
	Plants and Ageing		
Lycium barbarum (Wolfberry) Solanaceae	The fruit belongs to "Yintonifying herb" and is believed to be effective in replenishing any deficient "Yin" (a kind of vital energy); hence balancing homeostasis in our body.	Polysaccharides, Betaine, and β-carotene.	Ho et al., 2010
Panax ginseng (Ginseng) Araliaceae	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.	Ginsenosides	Ho et al., 2010
Lavendula stoechas L. (Lavender) Lamiaceae	To strengthen a 'stupid' and dizzy brain	β-Pinene, Eucalyptol, β-Terpineol, Menthone, Menthol, Pulegone.	Adams et al., 2007;
Salvia officinalis L. (Garden sage) Lamiaceae	Remedies help those who shiver and suffer the effects stroke and strengthen weak minds and memories, for a sensitive stomach, general debility, irregular menstruation and dementia	The α-thujone, Salvene, Pinene, Cineol, Borneol, Some esters, Salviol, Dextro Camphor in trace, Vitamin A and C.	Adams et al., 2007; Oniga et al., 2010; Boszormenyi et al., 2009
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)	Adams et al., 2007; Norman et al., 1992; Conforti et al., 2007
Barbieria pinnata (Pers.) Baill. (Barberry) Fabaceae	The Kubeos prepared a tea of the seeds for elderly men with various mental problems	Argmme	Adams et al., 2007; Evans et al., 1985
Lundia erionema De Candolle (Schultes et Cabrera) Bignoniaceae	Crushed leaves mixed with Jessenis oil are given to elderly 'who speak crazily without making sense'	Nothing is known of the chemistry of Lundia.	Adams et al., 2007; Lopes et al., 2002; Schulte, 1993
Mandevilla steyermarkii Woodson (Periwinkle) Apocynaceae	Given to the aged and the sick	Little is known of the constituents of the genus ***Mandevilla*** beyond the presence in one species of hydrocarbons, lipids and triterpenes (mainly α-amyrin) and leucoanthocyanine	Adams et al., 2007; Schulte, 1993; Schultes and Raffauf, 1990; Hegnauer, 1964.
Pagaea recurva Benth. (Bentham et Hooker fil) Gentianaceae	Amongst the Muinane Indians a decoction of the whole plant was prepared for debiliating forgetfulness in the elderly	No report	Adams et al., 2007; Schulte, 1993.
Schlegia macrophylla Ducke Bignoniaceae	Leaves given to people who refuse to eat and lose appetite	No report	Adams et al., 2007
*Tabernaemontana heterophylla*Vahl. (Milkwood) Apocynaceae	Tukano Indians prepared a tea of the leaves for the old folks who are slow and forgetful	The tree contains a number of indole & bisindole alkaloids	Adams et al., 2007; Wolter et al.,1983; Chaturvedula et al., 2003.
Unonopsis veneficiorum (Mart.) R.E.Fries *(We-wit-kat-ku)* Annonaceae	Puinave Indians at Rio Vaup´e mixed dried leaves in the food of elderly people who forgot how to talk	Azafluorenones & bisapor-phinoids	Adams et al., 2007; Laprevote et al., 1988.

Curcuma longa L. (Turmeric) Zingiberaceae	Regarded as a 'rasayana' herb in Ayurveda (to counteract ageing processes).	Curcumin, demethoxycur-cumin, bisdemethoxycur-cumin and calebin-A (and some of its synthetic analogues)	Howes & Houghton, 2003
Ginkgo biloba L. (Ginkgo, Maidenhair Tree) Coniferae	The use of *G. biloba* (Coniferae) in circulatory disorders dates back to the 1960s, but it has also been used in TCM for respiratory disorders and memory.	Ginkgolides A B C, Proa -nthocyanidins, ginkgolic acid, ascorbic acid, carotenoids, and Bilobalide	Howes & Houghton, 2003 Chi et al., 1997
Huperzia serrata Thunb. (Firmoss) Lycopodiaceae	The prescription of the plant has been used in TCM to alleviate problems of memory loss.	Huperzine A	Howes & Houghton, 2003; Ashani et al., 1992; Laganiere et al., 1991; McKinney et al., 1991; Wang et al., 1986.
Lycoris radiata Herb (Spider lily) Amaryllidaceae	It is reported to be more selective for AChE than BuChE, and provides complete oral bioavailability. Galantamine is licensed in Europe for AD treatment and was well tolerated and significantly improved cognitive function when administered to AD patients, in multicentre randomized controlled trials	Galantamine and lycoramine.	Howes & Houghton, 2003; Bickel et al., 1991; Fulton & Benfield, 1996; Harvey, 1995; Wilcock et al., 2000; Wilkinson & Murray, 2001; Bores et al., 1996; Irwin & Smith, 1960.
Magnolia officinalis Rehder & Wilson (Talauma) Magnoliaceae	The bark of the root and stem of M. officinalis has been used in TCM to treat anxiety and nervous disturbances.	Biphenolic lignans (honokiol and magnolol).	Howes & Houghton, 2003
Polygala tenuifolia Willd (Chinese Senega) Polygalaceae	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 unders-tanding and strengthening the memory.	Polygalasaponins, onjisapon-in F, the cinnamic acid derivative sinapinic acid.	Howes & Houghton, 2003; Chang & But, 2001; Duke & Ayensu, 1985; Chung et al., 2002; Huang, 1993; Tang & Eisenbrand, 1992; Yabe et al., 1997.
Salvia miltiorrhiza Bung. (Chinese sage) Lamiaceae	It is prescribed in TCM to stabilize the heart and calm nerves Official indications for the root include treatment of blood circulation disorders, insomnia, neurasthenia and alleviation of inflammation	Dihydrotanshinone, tanshino -ne I, methylene, tanshin-quinone, cryptotanshinone, tanshinone IIa, salvianolic acids A and B, rosmariquinone (also known as miltirone) and several other phenolic compounds	Howes & Houghton, 2003; Huang, 1993; Tang & Eisenbrand, 1992; Weng & Gordon, 1992; Zhang et al., 1990; Du et al., 2000; Guanhua & Juntian, 1997; Huang & Zhang, 1992; Kang et al., 1997; Liu et al., 1992; Weng & Gordon, 1992).
Biota orientalis (Oriental Arborvita) Coniferae	It is used in TCM for insomnia and amnesia.	Quercetin and rutin,α- cedrol.	Howes & Houghton, 2003 Zhu et al., 2004
Codonopsis pilosula (Bastard Ginseng) Campanulaceae	In TCM, root is used for various disorders including amnesia, and is believed to promote blood circulation and enhance vitality	Hesperidin, n-hexyl beta-sophoroside, atractylenolide, lobetyolin, lobetyolinin, tara-xerol, taraxeryl acetate, alpha-spinasterol,9,10,13-trihyd-roxy-(E)-11-octadecenoic acid,β-sitosterol,,β-daucosterol and sugar.	Howes & Houghton, 2003; Duke & Ayensu, 1985. Qi et al., 2011

Crocus sativus saffron Iridaceae	It was used in TCM to treat disorders of the nervous system.	Crocin	Howes & Houghton, 2003; Soeda et al., 2001.
Evodia rutaecarpa (Wu-Chu-Yu, Evodia fruit) Rutaceae	Evodia rutaecarpa (Rutaceae) is used in TCM for cardiotonic, restorative and analgesic effects.	Rutaecarpine, rutaecarpine limonin dehydroevodiamine and dehydroevodiamine	Howes & Houghton, 2003; Matsuda et al., 1998; Moon et al., 1999; Park et al., 1996; Haji et al., 1994).
Evolvulus alsinoids (EA) *Convolvulus pluricaulis(CP)* Convolvulaceae *Canscora decussata (CD)* Gentianaceae (Shankhpushpi)	Shankhpushpi 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	Sethiya et al., al., 2009a; 2009b; 2009c; 2010a; 2010b;2010c; Sethiya & Mishra, 2010a; 2010b
		Herbal antidepressants	
Echium amoenum (Borage) Boraginaceae	Depression, anxiety and anxiolysis shown in an animal model(elevated plus maze test), where as antidepressant mechanismcurrently unknown	Rosmarinic acid, thesinine	Sarris et al., 2011.
Lavandula spp. (Lavender) Lamiaceae	Depression, anxiety, soma-tictension, GABA modulation based on volatile constituents) and anxiolysis shown in animal models (elevated plus maze and open field tests)	Linalool, linayl acetate	Sarris et al., 2011.
Albizia julibrissin (Mimosa) Fabaceae	Depression, anxiety, insomnia, 5-HT1A receptor binding affinity, 5-HT2C receptor binding affinity, antidepressant, anxi-olytic effects in animal models (elevated plus maze and tail suspension tests) and significantly decreased sleep latency and increased sleep duration in pentobarbital-induced sleep	Julibroside	Sarris et al., 2011.
Rhodiola rosea (Roseroot) Crassulaceae	Fatigue, cognitive impairment, depression, anxiety, neuro-endocrine modulation (inhibition of cortisol, stress-induced protein kinases, nitric oxide), Monoamine oxidase A inhibition, Monoamine modulation and normalization of 5-HT and anti-stress effects in animal depression models	Salidrosid, tyrosol and rosavin	Sarris et al., 2011
Hypericum perforatum (John's wort) Hypericaceae	Depression, bipolar depression, modulation of monoaminetrans-mission via Na+ channel, nonselective inhibition of re-up take of serotonin, dopamine, norepinephrine, decreased degr-adation of neurochemicals ,increased binding/sensitivity /density to 5-HT1A,B, dopami-nergic activity (prefrontal co-rtex), inhibited neuronal release of glutamate, neuroendocrine modulation and Anti-depressant and anxiolytic activity in animal models	Hyperforin, hypericin	Sarris et al., 2011.

Bacopa monniera (Brahmi) Scrophulariaceae	Cognitive impairment, anxiety, depression, nervous exhaustion, metal chelation/β-amyloid protection, cholinesterase inhibit-ion, 5HT2C modulation, antioxid-ant effects and antidepressant effects in forced swim and learned helplessness animal models	Bacoside A, bacoside P	Sarris et al., 2011.
Eschscholzia californica (California poppy) Papaveraceae	Anxiety, insomnia, pain, binding affinity with GABA receptors (flumazenil antagonist) and anxiolysis in animal models (familiar environment and anti-conflict tests)	Escholidine, cheilanthifoline	Sarris et al., 2011.
Matricaria recutita (Chamomile) Asteraceae	Anxiety, insomnia, stress, binding to GABA receptors, modulates monoamine neuro-transmission and neuro-endocrine modulation	Apigenin, α-bisabolol	Sarris et al., 2011.
Ginkgo biloba (Ginkgo) Ginkgoaceae	Cognitive impairment, anxiety, depression, modulation of cholinergic and monoamine pathways, antioxidant, anti-PAF, anti-inflammatory effects, GABAergic effects and nitric oxide activity	Ginkolide, bilobalide	Sarris et al., 2011.
Centella asiatica (Gotu cola) Umbelliferae	Anxiety, stress, cognitive impairment, GABA transaminase inhibition, animal models have shown anxiolytic effects (elevated plus maze, open field, social interaction tests) and inhibition of acoustic startle response in human RCT	Asiaticoside	Sarris et al., 2011.
Piper methysticum (Kava) Piperaceae	Anxiety, comorbid depression, anxious insomnia, ADHD, pain, GABA channel modulation (lipid membrane structure and sodium channel function), Weak GABA binding (increased synergistic effect of[3H]muscimol binding to GABA-α-receptors) β-adrenergic down regulation, MAO-B inhibition and Re-uptake inhibition of norepinephrine in the prefrontal cortex	Kawain, dihydrokawain	Sarris et al., 2011.
Melissa officinalis (Lemonbalm) Lamiaceae	Acute stress, anxiety, depression, potent in vitro inhibitor of rat brain GABA transaminase (GABA-T), MAO-A inhibition and acute dosing caused a significant increase in self-rated calmness on a human stress tests	Citranellal, geraniol	Sarris et al., 2011;
Passiflora spp. (Passionflower) Passifloraceae	Anxiety, insomnia, GABA-system mediated anxiolysis, benzodiazepine receptor partial agonist, animal behavioural models have shown non-sedative anxiolytic effects(elevated-plus maze, light/dark box choice tests)	Harman, chrysin	Sarris et al., 2011;
Scutellaria lateriflora (Scullcap) Lamiaceae	Anxiety, nervous exhaustion, insomnia, posited GABA-α binding affinity and anxiolysis in animal maze-test model	Scutelaterin A, baicalin	Sarris et al., 2011;

Plants and CNS

Psychoanaleptic (stimulant) plants with emphasis on anorectic or weight-reducing properties

Ephedra sinica Stapf Ephedra spp (Ma Huang) Ephedraceae	In a telephone survey conducted in the United States, 1% of 14,649 individuals reported use of ephedra products for weight loss purposes	Ephedrine, pseudoephedrine and phenylethylamine type of substances that possess CNS stimulant effects similar to those of amphetamines	Carlini, 2003; Blanck et al., 2001; Glennon & Young, 2000.

*Paullinia cupana*var *sorbilis* (Mart.)Guarana (Paullinia sp.) Sapindaceae	The famous Brazilian guarana' has the botanical name of Paullinia cupana var sorbilis (Mart.) Many qualities are attributed to guarana', from a stimulant to an aphrodisiac.	Caffeine, theophylline, theo-bromine and tannins.	Carlini, 2003
	Plant Adaptogens		
Withania somnifera (L.) (Dunal) Solanaceae	They have effects that involve, albeit indirectly and improvement of several CNS functions	Steroid lactones.	Carlini, 2003
Catha edulis Forssk. (Bush-like plant) Celastraceae	This bush-like plant, or "khat," has been known for centuries in East Africa, the Middle East, including Ethiopia, Tanzania and North Yemen. Khat induces a clear anorectic effect, together with euphoria, excitation and cheerful sensation	Phenylpropanolamines, cathi-none, cathine, nor pseudoephedrine, nor ephedrine	Carlini, 2003; Zelger & Carlini,1980; Nencini et al., 1986)
	Plants with psychodysleptic properties		
B caapi Malpighiaceae and *P viridis* Rubiaceae Ayahuasca (hoasca in Portuguese)	In the beginning of the 20th century, a new religion appeared in Brazil, utilizing hoasca (also called iage and caapi), the beverage consumed by certain Indians in the Amazon area. Hoasca is particularly interesting, as its pharmacological activity is dependent on a synergism between two plants, *P viridi s*and *B caapi*	The *B caapi* contains β-carboline alkaloids mainly harmine and harmaline, whereas *P viridis* has N,Ndimethyltryptamine (D-MT) in it	Carlini, 2003
T iboga Baill (Bwiti) Apocynaceae	The Iboga nation living in Gabon and other nearby West African countries chew the roots of this plant at the religious cult of Bwiti (Bouiti) in order to communicate with their ancestors). Apart from this religious use eating the roots, according to European explorers in the 19thcentury, had also stimulant and aphrodisiac effects and greatly increased endurance	Ibogaine was isolated and identified in the beginning of the 20th century; at least 12 more indole alkaloids have been isolated from the plant	Carlini, 2003; Emboden, 1972; Popik et al., 1995; Schultes & Hofmann, 1979; Shulgin &Shulgin, 2001.
Psycholeptic plants			
Papaver somniferum (Opium poppy) Papaveraceae	Juice of the opium poppy is used for treating psycholeptic pain.	Phenanthrene group, with or without the gamma-phenyl-N-methyl-piperidine	Carlini, 2003
Salix alba L (White Willow) Salicaceae	Decoction of the plants is used for treating pain.	Salicin and salicylic acid, a large number of alkaloids, terpenoids, capsaicinoids, ste-roids, flavonoids, xanthines, tannins, xanthones, lignans, saponins, lactones, glycosides	Carlini, 2003; Rios et al., 1989; Hua et al., 1997; Calixto et al., 2000.

decrease in transfer latency as compared to the control group in EPM. PHF also produced significant improvement in passive avoidance acquisition and memory retrieval, as compared to the controls and reduced the latency to reach the shock free zone (SFZ) after 24 hours. The PHF produces significant improvement in passive avoidance acquisition and memory retrieval in rats, which needs further investigation (Shah & Goyal, 2011).

1.5.4 EGb 761

Extracts from *Ginkgo biloba* (mainly EGb 761—a standardized extract marketed by Wilmar Schwabe GmbH) have been proven effective in clinical trials as a treatment for Alzheimer type dementia and vascular dementia (Gertz & Kiefer, 2004). Ginkgo extracts also has a favourable safety profile (Andrieu et al., 2003; Stromgaard et al., 2005).

1.5.5 TJ-54

Yokukansan, or TJ-54, is a Kampo herbal remedy. It consists of seven herbs, namely *Angelica acutiloba* (Danggui), *Atractylodes lancea* (Baishu), *Bupleurum falcatum* (Chaihu), *Poria cocos* (Fuling), *Cnidium officinale* (Chuanxiong), *Uncaria rhynchophylla* (Gouteng) and *Glycyrrhiza uralensis* (Gancao) (Mizoguchi et al., 2010). This remedy is used for the treatment of psychiatric disorder, the possible therapeutic effects on dementia symptoms are under investigation. Both clinical and preclinical studies on Yokukansan support its use in dementia treatment. A randomized, observer-blind, controlled trial found that a 4-week TJ-54 treatment improved the behavioral and psychological symptoms of dementia (BPSD) (Iwasaki et al., 2005). Other studies also found that Yokukansan was safe and effective in treating BPSD in AD and even PD patients (Kawanabe et al., 2010; Okahara et al., 2010). Yokukansan might modulate the glutamatergic neurotransmitter system and protecting neurons against excitotoxicity. Yokukansan provided direct protection on neurons or through modulating them to glutamate reuptake by astrocytes (Kawakami et al., 2009). Yokukansan also affected the expression of serotonin receptor in the frontal cortex of mice injected with 2, 5-dimethoxy-4- iodoamphetamine (Egashira et al., 2008).

1.5.11 Chromium

Chromium is a widely used nutritional supplement marketed for a wide range of applications. Recent clinical and experimental studies have also reported antidepressant activity of chromium in affective disorders and particularly in atypical depression, characterized by increased appetite, hyperphagia, and carbohydrate craving. Chromium also exerts a normalizing effect on insulin sensitivity and appetite with antidepressant action, therefore it may be a promising therapeutic option in patients with atypical depression and a subtype of depression typically associated with overeating & weight gain.

1.6 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 (Tomer et al., 2009a; 2010). Some of the active constituents (Figure 1.4) obtained from several sources or native to one sources of plants are promising against mental illness are:

1.6.1 Evolvine hydrochloride (An isolated alkaloids of E. alsinoids)

The hydrochloride salt of alkaloid, evolvine 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 (Krishnamurthy, 1959).

1.6.2. 5. 5-Hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is an aromatic amino acid produced by the body from the essential amino acid L-tryptophan and involved in the synthesis of serotonin. It is produced commercially by extraction from the seeds of the African plant *Griffonia simplicifolia*, and is typically available as the L-enantiomer. 5-HTP has been used clinically for over 30 years for the treatment of depression and a wide variety of conditions, including fibromyalgia, insomnia, and binge eating associated with obesity, cerebellar ataxia & chronic headaches.

1.6.3. 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 in various fruits (Clements and Darnell, 1980). Inositol is an important growth factor for human cells (Ross, 1991), acting in the synthesis of membrane phospholipids and as a precursor in the phosphatidylinositol (PI) cycle (Baraban et al., 1989). 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 or subtypes that interact with this signal transduction pathway (Iovieno et al., 2011).

1.6.4. Convolvine (An isolated alkaloids of CP)

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 (Asthana et al., 1996; Mirzaev & Aripova, 1998).

1.6.5. 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 condition of Alzheimer disease (Marco-Contelles et al., 2006).

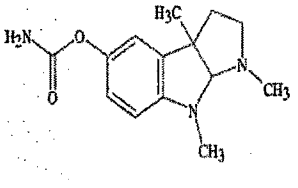
1.6.6. Huperzine A

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

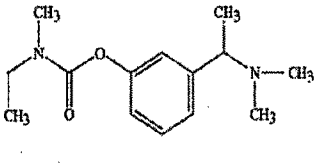
mitochondria-caspase pathway. Huperzine A facilitates cholinergic neurotransmission by increasing the concentration of acetylcholine in the CNS about 100 times more effectively than tacrine, a drug used for AD (Anekonda & Reddy, 2005). In cell culture studies huperzine A decreased neuronal cell death caused by toxic levels of glutamate (Bores et al., 1996). 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 (Frank & Gupta, 2005). Possible side effects are nausea, vomiting, diarrhoea and muscle cramps have been observed.

1.6.7. Selegiline

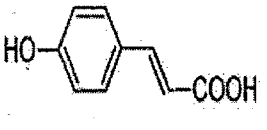
Selegiline is a type B monoamine oxidase inhibitor (MAOI) that is metabolized to amphetamine and methamphetamine stimulant compounds that may be useful in the treatment of Attention deficit hyperactivity disorder (ADHD). (Akhondzadeha et al., 2003)



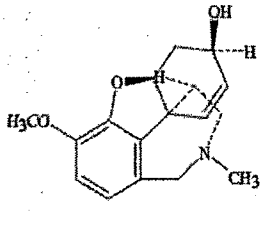
Physostigmine



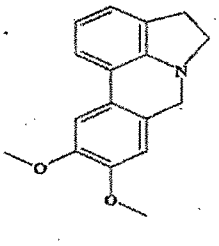
Rivastigmine



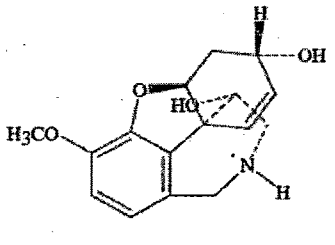
p-Hydroxycinnamic acid



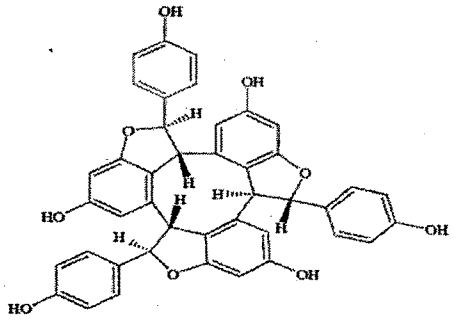
Galantamine



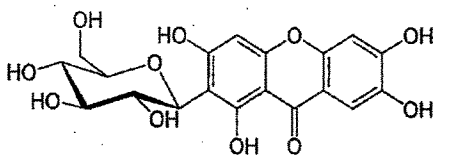
Assoanine



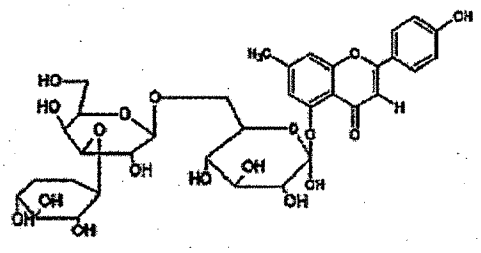
Epinorgalantamine



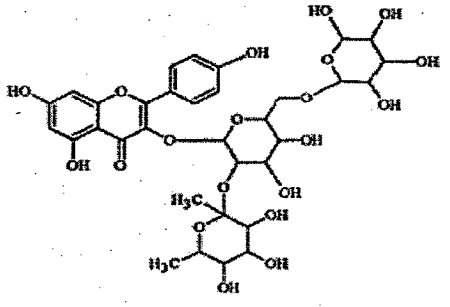
(+)-α-Viniferin



Mangiferin



Flavanol glycoside



Clitorin

Figure 1.4 Chemical structures of plant metabolites used in mental illness (Mukherjee et al., 2007; Sethiya et al., 2009b)

1.6.8. Acetylcholinesterase Inhibitors bioactive from plants

1.6.8.1. 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 *Lycorus 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) (Lopez et al., 2002; Rahman & Choudhary, 2001; Rhee et al., 2001; Rizzi et al., 1999; Ingkaninan et al., 2003; Roddick, 1989).

1.7 HERB-DRUG INTERACTIONS

Undesirable drug interactions of selective herbs have been demonstrated to occur with various classes of compounds of synthetic origin e.g. antibacterial, cancer chemotherapeutic agents, hypnotics and memory enhancers (James et al., 1988).

1.7.1 Shankhpushpi (SRC)

There was unexpected loss of seizure control and reduction in plasma phenytoin levels were noticed in two patients who were also taking 'Shankhapushpi' (SRC), an Ayurvedic preparation. On attempt to know the cause, it was found that single dose SRC and phenytoin (oral/i.p.) co administration did not have any effect on plasma phenytoin levels but decreased the antiepileptic activity of phenytoin significantly, but the multiple-dose co administration, SRC reduced not only the antiepileptic activity of phenytoin but also lowered plasma phenytoin levels. (Dandekar et al., 1992).

1.7.2 Echinacea

There have been no specific case reports of echinacea–drug interactions. However, due to the potential immune stimulatory nature of echinacea, some sources raise the issue that concomitant use with immune-suppressants is contraindicated. To date, this contraindication is speculative since documentation is lacking. Evidence from in vitro and in vivo studies suggests potential interactions with substrates of cytochrome P450 3A4 (CYP3A) or CYP1A2. No clinical studies have assessed the potential nature of interactions involving CYP3A4 or CYP1A2 (Chavez et al., 2006).

1.7.3 *Ginkgo biloba*

G. biloba has been reported to cause spontaneous bleeding in patients who are generally healthy, possibly due to the antiplatelet effects of the ginkgolide B component. Case reports of *G. biloba* possible interactions resulting in bleeding have been reported with aspirin, ibuprofen, and warfarin. Another report of possible herbal–drug interaction involved a 71-year-old male patient taking 40 mg of *G. biloba* extract daily for over 2 years for the treatment of occasional dizziness. Concurrent use of *G. biloba* with anticoagulants, aspirin and ibuprofen should be avoided. *G. biloba* may act as an antagonist of gamma-aminobutyric acid (GABA) activity at

1.7.11 Shoseiryuto

Shoseiryuto (a herbal preparation containing Schizandra fruit, Ephedra herb and Cinnamon bark) exhibit a strong inhibitory effect on cytochrome P450 3A4 (CYP3A4). However, whilst the *in vitro* effects of shoseiryuto and grapefruit juice on rat CYP3A4 activity were comparable, shoseiryuto did not significantly alter the plasma concentration profile of nifedipine in rats to the same degree as grapefruit juice. These results indicate that *in vivo* experiments with extracts of herbal medicines prepared in the same dosage form as would be administered to human patients are absolutely essential in order to provide useful and accurate information about herb–drug interaction (Panossian & Wikman, 2008).

1.8 ADVERSE HERB REACTION

1.8.1 Kava

Kava (*Piper methysticum*) has traditionally been used for a variety of purposes in the tropical islands of Polynesia but is becoming more frequently available in the United States health supplement market due to its calming effects in patients with anxiety. The side effect profile is poorly known but has recently gained the attention of the Food and Drug Administration (FDA). Although hepatitis and liver failure have been described with chronic ingestion and the effects of acute overdose are poorly described (Perez & Holmes, 2005).

1.8.2 *Ginkgo biloba*

A case of persistent postoperative bleeding following total hip arthroplasty in which, initially, no obvious cause was identified. *Ginkgo biloba* is an anticoagulant that inhibits platelet-activating factor and is contraindicated with aspirin (Bebbington et al., 2005).

1.8.3 Khat-induced neurotoxicity

There have been reports of severe and disabling neurological illness associated with khat chewing. Electroencephalogram (EEG) and Magnetic resonance imaging (MRI) findings indicated progressive leucoencephalopathy but this could not be linked with khat use. In addition, the CNS stimulating effect of khat has shown to reach the level of acute and chronic toxicity as evidenced by growing reports of psychiatric morbidity associated with khat use (Feyissa & Kelly, 2008).

1.9 PLANT PROFILES

Evolvulus alsinoides

Convolvulus pluricaulis

Clitorea ternatea

Canscora decussata

1.9.1 *Shankhpushpi*

Shankhpushpi is considered as '*Medhya Rasayana*' in *Ayurvedic* texts. *Shankhpushpi* of Ayurvedic Pharmacopoeia of India consists of whole plant of *Convolvulus pluricaulis* Choisy (Convulvulaceae) (syn; *Convulvulus microphyllus*

Evaluated Characters	*E. alsinoides*	*C. pluricaulis*	*C. ternatea*	*C. decussata*
Apex	Mucronate	Obtuse-muronate	Mucronate	Acute
Surface	Pubescent	Hairy	Hairy	Glabrous
Midrib				
Outline in T.S.	Plano-convex;dorsal bulge prominent	Concavo-convex	Concavo-convex, Dorsiventral	Concavo-convex; dorsal bulge irregularly lobed
Collenchyma	Present on either side	Present beneath upper epidermis	-	Absent on either side
Calcium oxalate	Present as rosette	Plenty, along veins	Prismatic crystal along with vein	Absent
Lamina	Isobilateral, palisade in 2 layers on either side	Isobilateral, palisade in 3 and 2 layers beneath upper and lower epidermis respectively	Dorsiventral, palisade in either side.	Dorsiventral, palisade in 1 layer
Cuticle	Striated	Striated	Striated, weavy	Ridged
Trichomes	Present; similar as in stem	Present; similar as in stem	Present; similar as in stem	Absent
Stomata	Both anisocytic and paracytic type on either side.	Both anisocytic and paracytic type on either side.	Subcoriaceous, rubiaceous stomata with wavy cell present on both side	Anisocytic; upper epidermis has a few stomata
Quantitative analysis				
Stomatal number				
Upper Surface	280-328-405	202-216-238	291-342-411	Very few
Lower Surface	270-336-424	184-212-248	188-223-251	52-72-108
Stomatal index				
Upper Surface	14.5-15.5-16.5	17.0-18.0-19.9	16.9-18.0-19.1	Very few
Lower Surface	15.7-17.0-18.7	13.8-15.8-16.9	14.8-16.3-17.2	16.9-21.0-24.6
Vein-islet number	18.0-19.0-20.0	21.0-23.0-25.0	7.5-8.0-9.0	1-2.5-3.25
		EXTRACTIVE VALUES (% w/w)		
Water soluble	19.80	17.08	18.21	10.00
Alcohol soluble	18.20	14.04	16.14	13.92

1.9.6 Phytochemical Profile

Table 1.11 Different Phytochemicals features of controversial sources of *Shankhpushpi*

E. alsinoides	*C. pluricaulis*	*C. ternatea*	*C. decussata*
		Carbohydrates	
	D-glucose, maltose, rhamnose, sucrose, starch and other carbohydrate (Shah & Quadry, 1990; Bisht & Singh, 1978 Deshpande & Srivastava, 1969)	Water-soluble mucilage, delphinidin 3, 3, 5-triglucoside (Macedo & Xavier-Filho, 1992). Oligosaccharides or flutulene (Revilleza et al., 1990). Mucilage contains Anhydrog-aacatan, Anhydropentosan and Methyl-pentosan (Sinha, 1960a).	
		Proteins and Amino acids	
Ergot alkaloids (Nambiar & Mehta, 1981; Nair et al., 1987)	Proteins and amino acids (Bisht & Singh, 1978; Deshpande & Srivastava, 1969).	Amino acids and amides (Rajagopalan, 1964), Characterization of amino acid (Tiwari & Gupta, 1957). Protein finotin and three unidentified trypsin inhibitors (Kelemu et al., 2004).	
		Alkaloids	
Betaine, shankhapushpine and evolvine (Guruswamy et al., 1956; Krishnamurthy, 1959; Aulakh et al., 1988; Baveja & Singla, 1969), Tropane alkaloids (Encyclopedia, 2007)	Only convolamine has been identified, but other alkaloids (convoline, convolidine, convolvine, confoline, convosine, etc.) found in other species from this family. The plant contains alkaloid shankhapushpine ($C_{17}H_{25}NO_2$). Melting point-162-164°C (Basu & Dandiya, 1948; Lounasmaa, 1988; Prasad et al., 1974; Singh & Bhandari, 2000; Mirzaev & Aripova, 1998; Razzakov & Aripova, 2004; Gapparov et al., 2007; 2008).	An alkaloid (Sinha, 1960a; Malabadi & Nataraja, 2003).	Alkaloid (Ghosal et al., 1971).

1958; Kapoor & Mahoor, 1981; Van Valkenburg & Bunyapraphatsara, 2001). EA-1, a phytochemical marker has been isolated by preparative TLC and characterized by IR, FAB-MS, NMR and elemental analysis techniques (Patil & Dixit, 2005). Estimation of Scopoletin by Spectrofluriometry (Nahata & Dixit, 2008).		Saito et al., 1985; Kazuma et al., 2003; 2004), Delphinidin (Kazuma et al., 2003b), Acylated anthocyanins (Terahara et al., 1990b), Flavonoids, Malonylated flavonol glycosides (Kazuma et al., 2003a; b). Yadava and Verma (2003) isolated antimicrobial flavonol glycoside, Banerjee and Chakravarti (1963- 64) reported the isolation and identification of pentacyclic triterpenoid, taraxerol and taraxerone from the roots. Content of Taraxerol in root of CT was determined through HPTLC (Kumar et al., 2008).	
	Plant Growth Regulator		
Phytohormones (Austuin, 2008).		Indole acetic acid, kinetin, ABA and gibberelic acid (Ahmad et al., 1984; Roy & Basu, 1992)	

1.9.7 Structures of Chief Secondary Metabolites

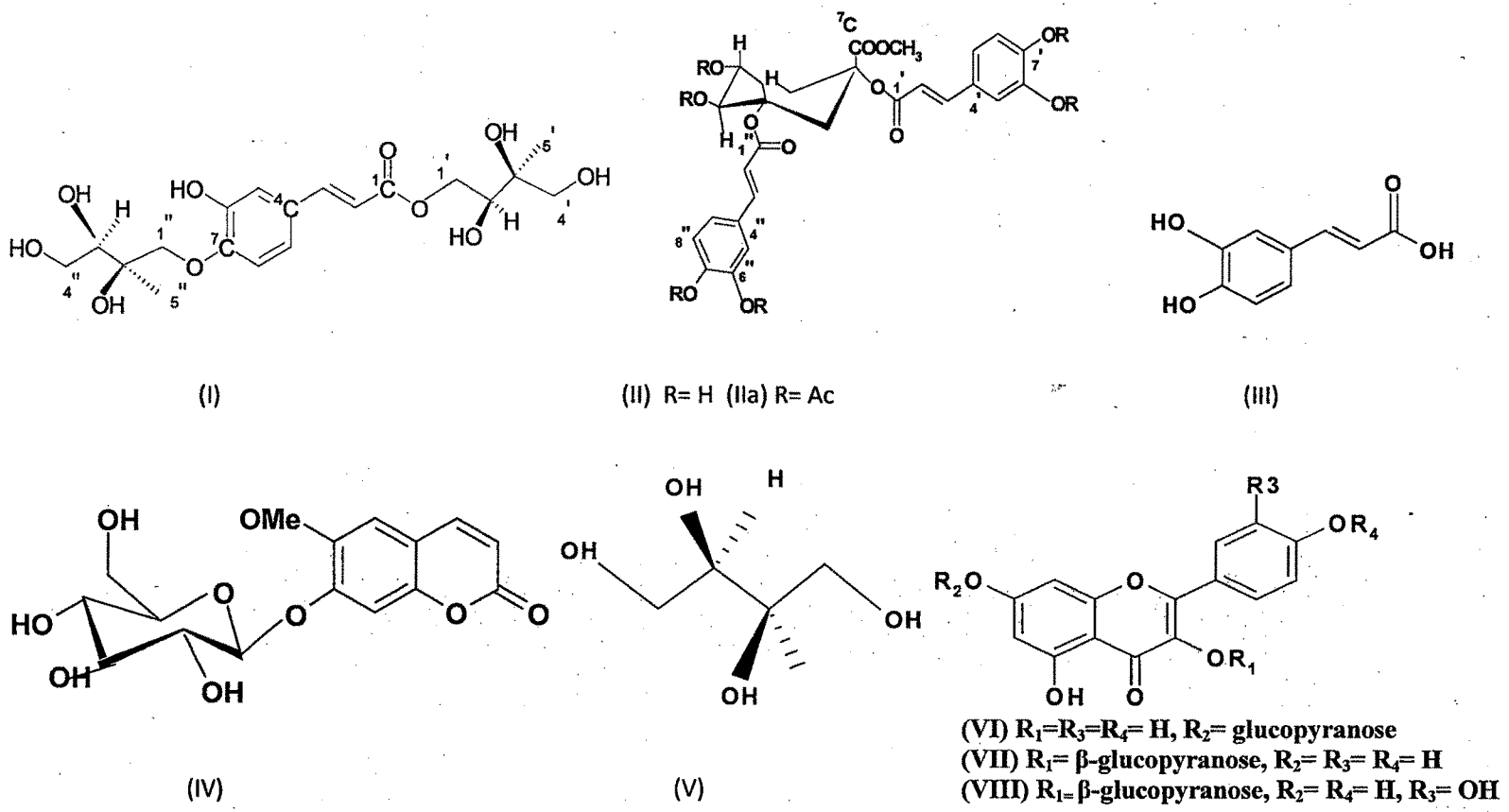
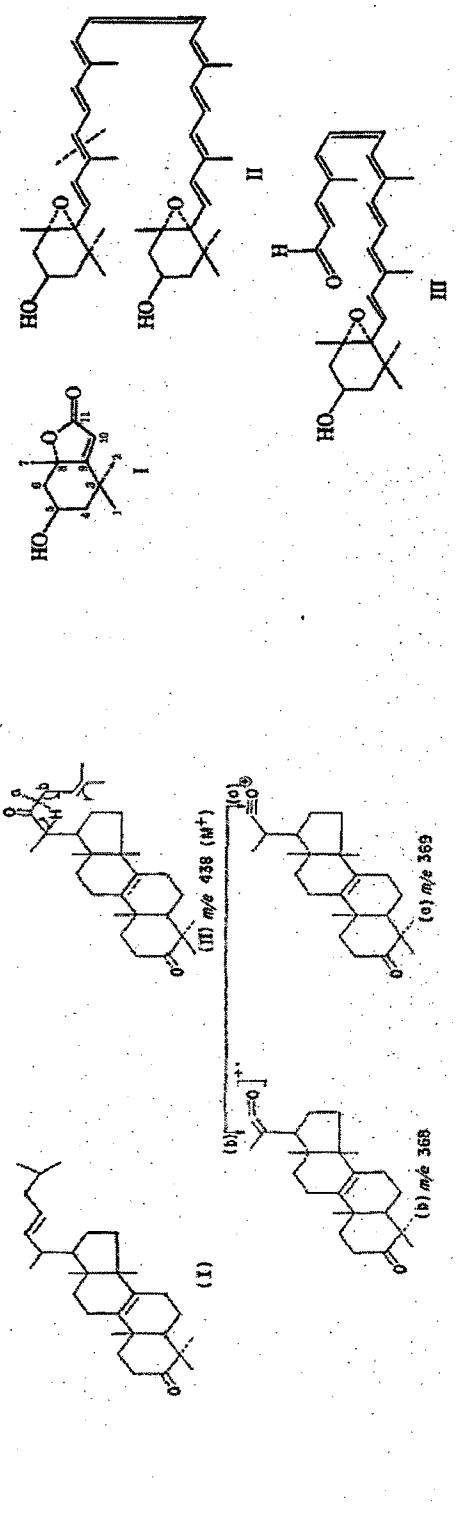


Fig: 1.5. Chemical Structures of Antistress Components isolated from *E. alsinoides* (Gupta et al., 2007).



(B) Structures of different Lanostrene triterpenoids of *C. decussata*

(C) Structures of different Loliolides of *C. decussata*

Figure 1.8 Chemical Structures of Isolate from *C. decussata* (Sethiya et al., 2009; 2010).

1.9.8 Pre-clinical and clinical applications of *Shankhpushpi*

1.9.8.1 *Evolvulus alsinoides* (EA)

Toxicology

Ayurvedic medicine regards EA highly for its effect on the central nervous system (CNS). Moderate doses (200 mg/kg) of the alcoholic extract of EA caused drowsiness, stupor and less mobility in albino mice; higher doses showed it to be neither toxic nor lethal. Laboratory studies revealed the herb as anticatatonic and a central nervous system depressant with an LD_{50} of 450 mg/kg. (Aulakh et al., 1988; Agarwal & Dey, 1997)

Learning Behavior and Memory Enhancement Activity in Rodents

The effects of EA, considered as *Shankhpushpi* on learning and memory in rodents, using Cook and Weidley's pole climbing apparatus, passive avoidance paradigms and active avoidance tests were used to test learning and memory (nootropic activity). The ethanolic extract has been shown to improve learning and memory and it significantly reversed the amnesia induced by scopolamine. EA also exhibited potent memory enhancing effects in the step-down and shuttle-box avoidance paradigms (Nahata et al., 2009).

Adaptogenic, anxiolytic and anti-amnesic activity

Ethanol extract of the aerial parts of the drug was evaluated for CNS activity using elevated plus maze test, open field exploratory behavior and rota rod performance experiments. The ethanol extract as well as its ethyl acetate and aqueous fractions were tested in experimental models employing rats and mice. The extracts were also studied for their *in vitro* antioxidant potential to correlate their anxiolytic activity (Nahata et al., 2009). The improvement in the peripheral stress markers and scopolamine induced dementia by EA in the chronic unpredictable stress and acute stress models indicated the adpatogenic and anti-amnesic properties of EA, against a well known adaptogen i.e. *Panax quinquefolium* (Siripurapu et al., 2005). Phenolics and flavonoids, isolated form bioactivity-guided purification of *n*-BuOH soluble fraction from the ethanol extract of EA, were screened for anti-stress activity in acute stress models. Stress exposure resulted in significant increase of plasma glucose, adrenal gland weight, plasma creatine kinase, and corticosterone levels. One

constituent displayed most promising antistress effect by normalizing hyperglycemia, plasma corticosterone, creatine kinase and adrenal hypertrophy, while others were also effective in normalizing most of these stress parameters (Gupta et al., 2007). Effects of methanolic extracts of roots of EA (MEEA) on acute reserpine induced orofacial dyskinesia showed increased frequencies of VCMs and TPs in acute reserpine treated animals compared with vehicle treated animals. Chronic treatment significantly reversed the reserpine induced VCMs and TPs in a dose dependent manner, decreased the locomotor activity as well as the transfer latency in acute reserpine treated rats. (Murlidharan & Manoj, 2008)

Antiulcer and anticatatonic activity

The in vivo evaluation of the ethanolic extract of EA revealed its marked antiulcer and anticatatonic activity. (Purohit et al., 1996)

Antioxidant activity

Antioxidant substances were isolated and identified from EA by preparing fractions of phenolic and non-phenolic compounds. Results of antioxidant activities of EA from DPPH assays were not as high as expected. The need of more antioxidant tests with different action mechanisms and also in-vivo studies with EA were suggested (Cervenka et al., 2008). Ethanolic extracts and water infusions of EA, *Cynodon dactylon* and *Sida cordifolia* were tested for their antioxidant activity in the 2, 2′-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid radical cation (ABTS) decolonization assay. The results showed that the ethanolic extract of *Sida cordifolia* was found to be most potent, followed by EA and *Cynodon dactylon.* The relative antioxidant capacity for the water infusions was observed in the following order: EA > *C. dactylon* > *S. cordifolia.* The results of water infusions on lipid peroxidation were as follows: EA > *S. cordifolia* > *C. dactylon (*Auddy et al., 2003*).*

Immunomodulatory activity

The crude extracts of *Emblica officinalis* and EA were evaluated for immmunomodulator activity in adjuvant induced arthritic rat model. Both the drugs showed a marked reduction in inflammation and edema. At cellular level immunosuppression occurred during the early phase of the disease. The induction of

nitric oxide synthase was significantly decreased in treated animals as compared to controls. (Ganju et al., 2003)

Evolvine hydrochloride

The hydrochloride of alkaloid evolvine 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. (Krishnamurthy, 1959)

Activity related to formulations of EA

Mentat

BR-16A (Mentat) is a herbal formulation consisting of: Brahmi (*Bacopa monnieri*), Mandookparni (*Centella asiatica*), Ashwagandha (*Withania somnifera*), Jatamansi (*Nardostachys jatamansi*), Shankhapuspi (*Evolvulus alsinoides*), Tagar (*Valeriana wallichi*), Vach (*Acorus calamus*), Guduchi (*Tinospora cordifolia*), Malkangni (*Celastrus paniculatus*), Kuth (*Saussurea lappa*), Amla (*Embelica officinalis*) and the other ingredients of Triphala (*Terminalia chebula* and *Terminalia belerica*). Mentat (100 mg/kg) and piracetam (100 mg/kg) induced statistically significant nootropic effect in all the test parameters of learning and memory, and can be categorized as a nootropic agent (Bhattacharya, 1994). In one of the experiments on thirty one adult trails for epileptics, aged between 23-42 years, 6 were newly diagnosed cases, while the remaining 25 were old ones already taking some antiepileptic drugs. Mentat, 2 tablets (b.i.d.), along with the other drugs for a period of six weeks brought about significant reduction in seizure frequency. Thus Mentat served as a valuable adjuvant to commonly used antiepileptic drugs. No side effects were observed with Mentat administration (Moharana & Moharana, 1994). Pre-clinical research has found that BR-16A (Mentat) enhances cognition and protects against both anterograde and retrograde amnesia induced by electroconvulsive shocks (ECS) in rats (Andrade,1994; Andrade et al., 1995; Joseph et al.,1994; Faruqi et al., 1995). Studies on the mechanism of action of BR-16A (Mentat) have indicated that it may have opioid peptidergic activity (Kulkarni & Verma, 1992). BR-16A (Mentat) does not appear to influence α-2 adrenergic receptor functioning but enhances the

activity of dopamine postsynaptic receptors in vivo in laboratory rats (Andrade et al., 1994). In the laboratory rat, it also enhances dopamine postsynaptic receptor functioning. This suggests a potential application in Parkinson's disease. Conventionally, drugs considered useful to treat tremor in Parkinson's disease have anticholinergic properties. Curiously, BR-16A (Mentat) showed no anticholinergic activity at least as could be evidenced by the absence of peripheral anticholinergic adverse effects (Andrade, 1996). I n another experiments of Mentat, on -patients with post-stroke disability. Out of 24 patients in the study, 13 received Mentat and 11 received a placebo for 12 weeks. EMG recording following neuromuscular stimulation was done at the beginning of the study and after 12 weeks. The final EMG responses in the trial group were found to be better than in the control group during study (Agarwal et al., 1994). The antistress effects of BR-16A, a polyherbal preparation and its interaction with GABAergic modulators against social isolation-induced shown significant result on prolongation of onset and decrease in pentobarbitone-induced sleep, increased total motor activity and stress-induced antinociception. When diazepam (0.5 mg/kg), a benzodiazepine agonist, was co-administered with BR-16A (100 mg/kg), it significantly potentiated the reversal of pentobarbitone-induced shortening of sleep time effects; increased locomotor activity and stress induced antinociceptive effects. However, the sleep latency was not decreased significantly (Sethiya et al., 2009b).

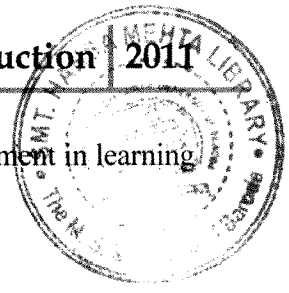
1.9.8.2 *Convulvulus pluricaulis* (CP)

Toxicological assessment

The LD50 of the whole extract of *C. microphyllus* was found to be 1250 (1000–1400) mg/kg p.o. Mice treated with the extract showed a sedative effect at doses greater than 200 mg/kg and reflected a moderate to marked decrease in locomotor activity which lasted nearly for 1–2 h. (Pawar et al., 2001)

Learning, memory and behavior

Nootropic activity using Cook and Weidley's Pole Climbing Apparatus, passive avoidance paradigms and active avoidance tests were used to test learning and memory. The ethanolic extract of CP and its ethyl acetate and aqueous fractions were



evaluated for their memory enhancing properties. Significant improvement in learning and memory in rats was noted. (Nahata et al, 2008)

Anxiolytic and Antiamensic activity

Alcoholic extract of CP was found to cause an antagonist effect against amphetamines and tremorine, a potentiator of acetylcholine effect, of pentobarbitone-induced hypnosis and morphine analgesia, without having own sedative properties. A protective action on muscle against electroshocks has been shown (Mudgal, 1975; Barar et al., 1965; Sharma et al., 1965).The chloroform fraction of the total ethanolic extract of CP elicited a significant antidepressant-like effect in mice by interaction with the adrenergic, dopaminergic, and serotonergic systems (Dhingra & Valecha, 2007a; 2007b). Methanolic extract of the whole plant produce alterations in the general behaviour pattern, reduction in spontaneous motor activity, hypothermia, potentiation of pentobarbitone-sleeping time, reduction in exploratory behavioural pattern, and suppression of aggressive behaviour.(Pawar et al., 2001) Ethyl acetate and aqueous fractions of ethanolic extract showed an anxiolytic effect in the elevated plus maze. The ethyl acetate fraction at dose of 200 mg/kg p.o. significantly reduced the neuromuscular coordination indicative of the muscle relaxant activity (Nahata et al., 2009). Nitrogen containing active principle of drug produced marked reduction in I-131 uptake, PBI, acetylcholine; suggested its effect on various glands through neurohumors particularly acetylcholine (Prasad et al., 1976). Upadhyay (1986) studied the therapeutic role of Ayurvedic herbs in mental disorders and classified CP as a brain tonic. CP in a dose of 100 mg/100 g body weight exhibited a barbiturate potentiation effect in albino rats; this effect was weaker than that of diazepam, but stronger than that of *Centella asiatica* Linn. (Syn: *Hydrocotyle asiatca* Linn.) (Dandiya, 1990; Handa, 1994; Sharma et al., 1965).

Anticonvulsant activity

The water soluble portion of ethanolic extract abolished spontaneous motor activity and the fighting response, but did not affect the escape response; electrically induced convulsive seizures and tremorine-induced tremors were antagonized by the extract (Sharma et al., 1965). It was observed that the animals treated with the methanolic extracts of stem callus, leaf callus and whole plant of CP, showed significant protection against tonic convulsion induced by transcorneal electroshock,

Drug Interactions

There was unexpected loss of seizure control and reduction in plasma phenytoin levels in two patients who were also taking '*Shankhapushpi*' (SRC), an Ayurvedic preparation containing CP as an ingredient. In an attempt to know the cause, it was found that single dose SRC and phenytoin (oral/i.p.) co-administration did not have any effect on plasma phenytoin levels but decreased the antiepileptic activity of phenytoin significantly, but in multiple-dose co-administration, SRC reduced not only the antiepileptic activity of phenytoin but also lowered plasma phenytoin levels (Dandekar et al., 1992).

Activity of Convolvine – an alkaloid isolated from CP

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. (Asthana, et al., 1996; Mirzaev & Aripova., 1998).

Activity of Polyherbal formulation / Clinical studies

- **Maharishi Amrit Kalash (MAK)** is a herbal formulation composed of two herbal mixtures, MAK-4 and MAK-5. These preparations are part of a natural health care system from India, known as Maharishi Ayurveda. A combination of MAK-4 and MAK-5 was found to have cancer inhibiting effects in *vitro* and *in vivo* when both used in combination (Penza, et al., 2007).
- **Thyrocap** is a herbal preparation containing solid extracts *of Bauhinia variegate, Commiphora mukul, Glycyrrhiza glabra* and CP (100 mg of each extract/ capsule) This preparation was tried in 50 patients of simple diffuse goiter at a dose of one capsule three times a day for 3 months. A significant increase in serum T4 and T3 concentration and a decrease in serum cholesterol concentration confirmed its thyroid stimulating property (Pandit & Prasad, 1992).

1.9.8.3 Clitorea ternatea (CT)

Toxicological assessment

Gross behavioral and acute toxicity studies after administration of graded doses of alcoholic extract of aerial parts of CT were carried out. LD50 of the extract in mice

was 2290 mg/kg, ip. An ethanolic extract of aerial parts and root of CT when administered orally to mice, in doses of 1500 mg/kg and above was found to be lethargic instead of CT root extracts which up to 3000 mg/kg administered orally failed to produce any lethality in mice (Kulkarni et al., 1988; Parimaladevi et al., 2004).

Learning, memory and behavior

Effect of CT aqueous root extract on learning and memory in rat pups using open field behaviour test, spontaneous alternation test, rewarded alternation test and passive avoidance test showed that the oral treatment of CT roots extract at different doses significantly enhanced memory in rats (Rai et al., 2000). The alcoholic extracts of aerial parts and roots of CT attenuated electroshock-induced amnesia using conditional avoidance response paradigm. (Taranalli & Cheeramkuczhi, 2000). The authors also studied the possible mechanism through which CT elicits the anti-amnesic effects on central cholinergic activity by evaluating the acetylcholine content of the whole brain and acetylcholinesterase activity at different regions of the rat brain, viz., cerebral cortex, midbrain, medulla oblongata and cerebellum. It was suggested that an increase in ACh content in rat hippocampus may be the neurochemical basis for improved learning and memory (Mukherjee et al., 2008; Rai et al., 2002). In another study, the effect of CT aqueous root extract on the dendritic cyto-architecture of neurons of the amygdale was studied. The study showed a significant increase in dendritic intersections, branching points and dendritic processes arising from the soma of amygdaloid neurons in aqueous root extract treated rats compared with age-matched saline controls (Rai et al., 2005).

Anxiolytic and antistress activities

The ethanolic extract of CT caused reduction in spontaneous activity, decrease in exploratory behavioural pattern by the head dip and Y-maze test, reduction in the muscle relaxant activity by rota rod, 30° inclined screen and traction tests and potentiated the pentobarbitone-induced sleeping time (Boominathan et al., 2003). In another study, the effect of alcoholic extract of aerial part of CT on spatial discrimination in rats followed by oral treatment with alcoholic extract at a dose of 460 mg/kg significantly prolonged the time taken to traverse the maze, which was equivalent to that produced, by chlorpromazine. The lower dose 230 mg/kg was ineffective (Kulkarni et al., 1988).

Anticonvulsant Activity

Methanolic extract from the aerial parts of CT was screened using PTZ and maximum electroshock (MES)-induced seizures in mice at the dose of 100mg/kg p.o. significantly delayed the onset of convulsions in PTZ-induced convulsions and also delayed the duration of tonic hind limb extension in MES-induced convulsions (Jain et al., 2003). At the dose of 230 and 460 mg/kg no significant effects were observed in both tests. (Kulkarni et al., 1988)

Antidiabetic activity

Ethanolic extracts of flowers significantly lowered serum sugar level in experimentally induced diabetes (Sharma & Majumdar, 1990).

Antimicrobial activity

A flavonol glycoside isolated from the ethyl acetate soluble fraction of the roots of CT showed antimicrobial activity against various bacteria and fungi (Yadava & Verma, 2003).

Anti-inflammatory, analgesic and antipyretic activities

Methanolic extract of CT roots was reported to have significant anti-inflammatory activity using carrageenin-induced rat paw edema and acetic acid-induced vascular permeability models in rats (Parimaladevi et al., 2003).

Activity of formulation

Clitorea, Gliricidia and Mucuna was found to be act as nitrogen supplements to Napier grass basal diet in relation to the performance of lactating Jersey cows (Juma et al, 2006; Marin et al., 2003).

1.9.8.4 Canscora decussata (CD)

Anticonvulsant activity

The results of administration of crude fine powder and alcoholic extract of CD against MES, MST and hypnosis potentiation tests, was found to be encouraging. The drugs were also tested for toxicity studies prior to clinical trial (Dixit, 1971). In another set of experiments crude dried powder and its alcoholic extract with reference to Phenytoin sodium (serve as positive control) were found to provide cent percent protection against

1.10 RESEARCH ENVISAGED

Shankhpushpi is considered as "*medhya rasayana*" in Ayurvedic texts. The most widespread application of *Shankhpushpi* is for mental problems, but they have been considered medicine for an array of other human maladies. *Shankhpushpi* is word of Sanskrit which means 'the plant with flowers shaped like a conch'. The conch or *Shankha* is one of Lord Shiva's sacred instruments often used in ritual worship. People in the Indian region often apply *Shankhpushpi* and other Sanskrit based common name, to *Evolvulus alsinoides (EA). Convolvulus pluricaulis (CP), Clitorea ternatea (CT)* and *Canscora decussata (CD)* on the basis of their flower shape. These are pre-European names that are applied to a medicinal plant. Before the establishment of British rule, like the other books, ayurvedic treatises were also hand written. This might be one of the reasons due to which ayurveda could not stand parallel to the western medicine and an, ambiguity is reflected in the interpretation of names and description of drugs found in the books like *Charaka Samhita* and *Sushruta Samhita.*

These synonyms have caused controversy in the identification of plants and hence the correct source sometime is misleading with a fictious plant. It has become terror an important task to generate parameters of identification as well as differentiation among different plant sources having similar name. Since herbal product are prepared using the extracts of plant known for particular activity, the controversial source sometimes lead to inefficacious preparation. Hence generation of parameters based on characterization and identification of chemical and biomarker, using modern method may provide a solution for solving out the controversy.

1.11 AIMS AND OBJECTIVES

The aims and objective set for present study is:

- To assess comparatively the quality of selected plants as per WHO guidelines.
- To develop comparative analytical methods for the qualitative and quantitative assessment of plant sources.
- To isolate the common and ubiquitous chemicals from botanicals of *Shankhpushpi.*
- Comparatives biological activity of extracts and isolated compounds of various *Shankhpushpi* botanicals.

1.11.1 Proposed methodologies

- Comparative morphological and microscopical differentiation.
- Identification of various differentiation parameters according to WHO guidelines
- Comparative TLC fingerprinting of different species.
- Isolation of differentiation chemical components among various species.
- Development of analytical methods for the qualitative and quantitative assessment using:-
  - ✓ HPLC
  - ✓ HPTLC
  - ✓ Spectrofluriometry., etc
- Comparatives toxicity profiling by:-
  - ✓ Brine Shrimp toxicity assay
  - ✓ MTT cytotoxicity assay on cell line

- Comparative in vitro antioxidant studies by:-
  - ✓ DPPH
  - ✓ Ferric chloride
  - ✓ Phsphomolybedate
  - ✓ DPPH TLC bioautography.
- Comparative nootropic activity by:-

  In vitro model
  - ✓ AChE inhibition assay
  - ✓ AChE TLC bioautography
  - ✓ β-amyloid induced neuroprotection on brain cell line.
  - ✓ Serotonin receptor assay

  In vivo model
  - ✓ Pole climbing apparatus for condition avoidance test
  - ✓ Step through model for passive avoidance
  - ✓ Water maize test
- Comparative *in vitro* lipoxygenase (LOX) inhibition assay
- Comparative *in vitro* antimalarial (PfLDH) assay.
- Comparative *in vitro* antimicrobial studies.