2.1 CENTRAL NERVOUS SYSTEM: NEUROTRANSMISSION AND DISORDERS

Central nervous system (CNS) is functionally very complex than any other systems in the body as the relationship between the behavior of individual cell and that of the whole organ is less direct. CNS includes brain and spinal cord. Brain is an array of interrelated neural systems that regulate their own and each other’s activity through intercellular chemical transmission.

2.1.1 Neurochemical Transmission in CNS

Four processes occur in relation to nerve transmission in CNS – neurotransmission, neuromodulation, neuromediation and mediation through neurotropic factors. Analogously such chemical secretions are called neurotransmitters, neuromodulators, neuromediators and neurotropic factors, respectively.

**Neurotransmitters** – are synthesized in presynaptic neurons and are released into synaptic cleft to rapidly stimulate or inhibit postsynaptic neurons.

eg. Acetylcholine, dopamine, norepinephrine (epinephrine in reticular formation), 5-hydroxytryptamine, gamma-amino butyric acid, glycine, glutamate, aspartate, endogenous opioids, cholecystokinin, tachykinins, etc.

**Neuromodulators** – are released by neurons and astrocytes to produce slower pre-or postsynaptic responses. Neuromodulation generally relates to synaptic plasticity that means long-term changes in synaptic transmission, connectivity and efficacy following pathological damage (as
in epilepsy or drug dependence) or following physiological alterations in neuronal activity (as in learning and memory).

eg. Carbon dioxide, locally released adenosine, some purines, peptides, prostaglandins, arachidonic acid metabolites and Nitric oxide.

**Neuromediators** – are second messengers that play crucial role in elicitation of postsynaptic responses produced by neurotransmitters.

eg. cAMP, cGMP and inositol phosphate.

**Neurotropic factors** – are mainly released by CNS neurons, astrocytes and microglia and act longer than neuromodulators to regulate the growth and morphology of neurons and control long-term changes in brain (synaptic plasticity, remodeling, phenotype characteristics) mainly by affecting gene transcription by acting through tyrosine kinase-linked receptors.

eg. Cytokines, chemokines, growth factors.

### 2.1.2 CNS Neurotransmitters and their receptors

**Amino Acids:** The CNS contains high concentrations of certain amino acids mainly, glutamate and gamma-amino butyric acid (GABA). The dicarboxylic acids (glutamate and aspartate) produce excitation and monocarboxylic ω-amino acids (GABA, glycine, β-alanine and taurine) produce inhibition.

**GABA and its receptors:**

GABA is the major inhibitory neurotransmitter in the CNS. It has three receptor subtypes – GABA	extsubscript{A} (postsynaptic ionotropic receptor and is a ligand-gated Cl⁻ ion channel, agonists- muscimol, isoguvacaine and antagonists- bicuculline, picrotoxin), GABA	extsubscript{B} (presynaptic metabotropic
G_{i}-protein coupled receptor and inhibits adenylyl cyclase, activates K⁺ channels and reduce Ca²⁺ conductance, agonist- baclofen), GABA\textsubscript{C} (transmitter gated Cl⁻ channel). Pentameric GABA\textsubscript{A} receptor is most abundant in the brain and has seven subunit families six α, three β, three γ and single δ, ε, π, and θ in uncertain stoichiometry. The inclusion of variant ratios of subunits in GABA\textsubscript{A} alters the pharmacological profile of various benzodiazepines.

GABA\textsubscript{A} receptor has various binding sites that include a GABA binding site, a modulatory site to bind benzodiazepines (at the interface between α and γ subunits, also their antagonist such as flumazenil and inverse agonist such as carbolins), the modulatory as well as blocking site at Cl⁻ ion channel as for barbiturates (α and β subunits) and picrotoxin.

![GABA\textsubscript{A} Receptor](image)

**Figure 2.1.1** GABA\textsubscript{A} Receptor
Benzodiazepines (BZDs) enhances GABA activity by increasing the frequency of channel opening and barbiturates potentiates GABA mediated inhibition by prolonging the duration of channel opening and at higher doses exhibits GABA mimetic action.

The most commonly found isoform of GABA\textsubscript{A} is $2\alpha_1:1\beta_2:1\gamma_2$. Studies on transgenic mice led to the findings that $\alpha_1$ subunits in GABA\textsubscript{A} mediate sedation, amnesia and possibly antiepileptic actions of BZDs. $\alpha_2$ subunits mediate antianxiety and muscle relaxant actions and $\alpha_5$ subunit is involved in at least some of the memory impairment caused by BZDs.

**Glycine and its receptors:**

Glycine is another inhibitory neurotransmitter present mainly in medulla, spinal cord, lower brain stem and the retina. Its agonists are $\beta$-alanine, taurine and antagonist is strychnine. Glycine receptor is also linked to Cl\textsuperscript{-} ion channel. Glycine and its competitive antagonist strychnine bind to $\alpha$ subunit while tetanus toxin acts by preventing the release of Glycine and causing excessive hyper-excitability and violent muscle spasms (lock jaw).

**Glutamate, Aspartate and their receptors:**

Glutamate and aspartate are the two excitatory neurotransmitters concentrated in cortex, basal ganglia and sensory pathways. Besides acting as neurotransmitters they also play a role in intermediary metabolism in neural tissue, viz., in detoxification of ammonia in brain, as building blocks in the synthesis of peptides, proteins and GABA.

There are five receptors for excitatory neurotransmitters, they are –
NMDA (N-methyl-D-aspartate) receptors- Ionotropic receptors linked to Ca$^{2+}$ and involved in neurophysiological and pathological processes like memory acquisition, development of synaptic plasticity, epilepsy and neuronal excitotoxicity due to cerebral ischemia. NMDA receptor is a pentamer composed of subunits NR-1 and NR-2. It has various binding sites for binding glutamate (or NMDA), modulatory site that binds glycine (glutamate is ineffective unless glycine is bound to this site), polyamines (spermine and spermi-dine) binding site which facilitates channel opening, binding site for phencyclidine (PCP binding site) and related antagonists (ketamine), a voltage dependant Mg$^{2+}$ binding site (at resting state Mg$^{2+}$ blocks the receptor) and a voltage-independent Zn$^{2+}$ binding site near the mouth of the channel (Zn$^{2+}$ produces voltage independent inhibitory action on NMDA receptor ion channel).

Figure 2.1.2  NMDA Receptor
**AMPA** (*α*-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors – pentameric ionotrophic receptor linked to Na⁺ and consists of GLUR₁₋₄ subunits. AMPA and quisqualate are the agonists.

**Kainate** – pentameric ionotrophic receptor linked to Na⁺ and consists of GLUR₅₋₇ and KA₁₋₂ subunits. Kainate and domoate are agonists.

**AP-4** (1,2-diamino-4-phosphobutyrate) – inhibitory autoreceptor.

**ACPD** (1-amino-cyclopentane-1,3-dicarboxylic acid) – G-protein coupled receptors and either stimulate phospholipase-C-IP₃ system or inhibit and adenylyl cyclase.

**Acetylcholine (ACh) and its receptors:**

Cholinergic neurons are present in cerebral cortex, ascending reticular activating system, basal ganglia, limbic system, cerebellum and spinal cord. Ach modulates arousal, respiration, motor activity, vertigo and memory. Both muscarinic and Nᵣ receptors are present in brain. Centrally acting antimuscarinic drugs are useful in Parkinsonism and anticholinesterases such as tacrine, donepezil and rivastigmine are used to improve cognitive functions in Alzheimer’s disease.

**Biogenic amines:** Amine neurotransmitters include dopamine, norepinephrine (epinephrine), 5-hydroxytryptamine and histamine.

**Dopamine and its receptors:**

Dopamine is primarily an inhibitory neurotransmitter. Its deficiency causes extrapyramidal disturbances. There are five receptors identified – D₁₋₅. Activation of D₁ and D₅ stimulate adenylyl cyclase and increase the release of cAMP; D₂₋₄ inhibits adenylyl cyclase and decrease the release of cAMP. The locations of these receptors are –
D₁ – Nigrostriatal pathway (putamen, nucleus accumbens and olfactory tubercle). Its inhibition causes extrapyramidal disorders.

D₅ – Hypothalamus and hippocampus. Its exact role is not known.

D₂ – Striatum, substantia nigra and pituitary. It is involved in the control of the behavior, voluntary movements, prolactin release and other endocrine consequences.

D₃ – Midbrain, nucleus accumbens and hypothalamus.

D₄ – Mesocortical pathway (frontal cortex, medulla and midbrain). Some of the atypical neuroleptics possess D₃ and D₄ antagonistic activity, but their exact role in schizophrenia is not yet fully established.

**Norepinephrine and Epinephrine:**

Norepinephrine is a neurotransmitter of brainstem neurons within locus ceruleus (pons and neurons of reticular formation) with projections to cortex, cerebellum and spinal cord. In CNS it is thought to modulate affective disorders (depression), learning, memory, arousal and pain perception. Mammalian CNS contains both α- and β-adrenoceptors. Unlike dopamine and norepinephrine, concentration of epinephrine is very low and is localized primarily in reticular formation and its precise role in CNS is not known.

**5-hydroxytryptamine (5-HT) and its receptors:**

Serotonergic neurons are found primarily near the midline raphe nuclei of the brainstem and project to the cortex, cerebellum and the spinal cord. 90% of 5-HT is present in enterochromaffin cells and remaining 10% in brain and platelets, yet it is implicated as a potential neurotransmitter in the mediation of wide variety of brain functions. It
plays important role in schizophrenia, depression, temperature regulation and eating disorders. It is a precursor of melatonin in pineal gland. It may also be involved in the hypothalamic control of the release of pituitary hormones. Its receptors are 5-HT\textsubscript{1A-7} with several subtypes. All the receptors are metabotropic, except 5-HT\textsubscript{3} which is ionotropic. 5-HT\textsubscript{1A} receptor agonists (buspirone) are used to treat anxiety disorders, 5-HT\textsubscript{1D} receptor agonists (sumatriptan) are used to treat migraine and cluster headaches, 5-HT\textsubscript{2A/2C} receptor antagonists (clozapine) are used to treat schizophrenia, 5-HT\textsubscript{3} antagonists (ondansetron) are used to prevent chemotherapy induced emesis, 5-HT\textsubscript{4} agonists (metoclopramide) are used as antiemetic and prokinetic drugs and 5-HT reuptake inhibitors (SSRIs-fluoxetine) are used to treat depression and obsessive-compulsive disorders.

**Histamine and its receptor:**

Histaminergic neurons originate from posterior hypothalamus, and project to cerebral cortex, limbic system, caudate, putamen, globus pallidus, brain stem, substantia nigra, dorsal raphe, cerebellum and spinal cord. Histaminergic neurons and postsynaptic central H\textsubscript{1} receptors play a major role in arousal, in coupling neuronal activity with cerebral metabolism and in neuroendocrine regulation.

**Peptides:** There are number of peptide neurotransmitters in CNS involved in diverse functions of CNS besides their peripheral actions. Some of them are vasopressin (facilitate learning and memory), oxytocin (mating and parenting behavior), tachykinins (pain transmission), neurotensin (lowers body temperature), vasoactive intestinal peptide
(pain transmission), endogenous opioids (analgesia, euphoria and reduces stress), cholecystokinin (appetite regulation), angiotensin II (centrally influences drinking behavior) and neuropeptide Y (increases feeding/orexigenic, hypothermia, cerebral vasoconstriction).

Imbalance among these various neurotransmitters &/or damage to the neurons or parts of CNS leads to various disorders.

2.1.3 CNS Disorders

Motor Disorders

Epilepsy: Damage to the cerebral cortex and imbalance between excitatory and inhibitory neurotransmitters of brain (discussed in detail in Chapter 2.3) results in epilepsy. The behavioral manifestations of a seizure are determined by the functions, normally served by the cortical site at which seizure arises.

Behavioral Disorders

Behavioral disorders result due to damage to one or more parts of CNS, i.e., cortex, limbic system, hypothalamus and brainstem.

Depression: Deficiency of aminergic transmission in CNS results in depression (discussed in detail in Chapter 2.4).

Mania: Excess of aminergic transmission in CNS results in mania. It is particularly associated with changes in mood.

Schizophrenia: Functional over activity of dopamine in limbic system or cerebral cortex leads to schizophrenia. It is particularly associated with changes in thought processes.
**Neurodegenerative Disorders**

*Alzheimer’s disease:* Loss of hippocampal and cortical neurons which leads to abnormalities of memory and cognitive ability.

*Parkinson’s disease and Huntington’s disease:* Loss of neurons of basal ganglia leads to abnormalities in control of movement.

*Amyotrophic lateral sclerosis (ALS):* Degeneration of spinal bulbar and cortical motor neurons lead to muscular weakness.

There are several other CNS diseases that result due to cerebrovascular accidents, physical injury to CNS, infections, etc.
2.2 EPILEPSY AND ANTIEPILEPTIC DRUGS

Epilepsy is a common and frequently devastating disorder affecting millions of people worldwide. The term \textit{seizure} refers to a transient alteration of behavior due to the disordered, synchronous and rhythmic firing of populations of brain neurons. The term \textit{epilepsy} refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. The word \textit{fit} is often used colloquially to describe an epileptic seizure. \textit{Convulsions} are involuntary, violent and spasmodic or prolonged contractions of skeletal muscle. That means, a patient may have epilepsy without convulsions and vice versa.\cite{19,20,21}

\subsection*{2.2.1 Signs and Symptoms of Seizures} \cite{22}

Seizures have a beginning, middle and end. Sensory, emotional and physical symptoms appear before, during and after seizures.

\textit{Sensory / Thought Symptoms:}

\textit{Aura / early seizure symptoms (warnings)} - Déjà vu, jamais vu, smell, sound, taste, visual loss or blurring, racing thoughts, stomach feelings, strange feelings and tingling feeling.

\textit{Seizure symptoms} - Black out, confusion, deafness/sounds, electric shock feeling, loss of consciousness, smell, spacing out, out of body experience and visual loss or blurring.

\textit{Post-ictal/ after-seizure symptoms} - Memory loss and writing difficulty.
**Emotional Symptoms:**

Aura / early seizure symptoms (warnings) - Fear/panic, pleasant feeling.

Seizure symptoms – Fear/panic.

Post-ictal/after-seizure symptoms - Confusion, depression and sadness, fear, frustration, shame/embarrassment.

**Physical Symptoms:**

Aura/early seizure symptoms (warnings) - Dizziness, headache, light headedness, nausea and numbness.

Seizure symptoms - Chewing movements, convulsions, difficulty in talking, drooling, eyelid fluttering, eyes rolling up, falling down, foot stomping, hand waving, inability to move, incontinence, lip smacking, making sounds, shaking, staring, stiffening, swallowing, sweating, teeth clenching/grinding, tongue biting, tremors, twitching movements, breathing difficulty and heart racing.

Post-ictal/after-seizure symptoms - Bruising, difficulty talking, injuries, sleeping, exhaustion, headache, nausea, pain, thirst, weakness, urge to urinate/defecate.

**2.2.2 Age of Onset of Epilepsy**

Epilepsy primarily affects the very young and the very old, although anyone can get epilepsy at anytime. Twenty percent of cases develop before the age of five. Fifty percent develop before the age of 25.
2.2.3 Causes of Epilepsy

In about 70 percent of cases there is no known cause. Of the remaining 30 percent, the following are the most frequent causes:

- Arteriovenous malformation (AVM)
- Head injury
- Intoxication with drugs
- Drug toxicity, eg. aminophylline or local anesthetics
- Brain tumors
- Normal doses of certain drugs that lower the seizure threshold, eg. Tricyclic antidepressants
- Infections, eg. encephalitis or meningitis
- Febrile convulsions
- Metabolic disturbances, eg. hypoglycemia, hyponatremia or hypoxia
- Sudden withdrawal of certain drugs eg. anticonvulsants and sedatives such as barbiturates, and benzodiazepines; alcohol.
- Space-occupying lesions in the brain (abscesses, tumors)
- Eclampsia.
- Binaural beat brainwave entrainment may trigger seizures in both epileptics and non-epileptics
- Stroke may cause seizures, eg. embolic strokes, cerebral venous sinus thrombosis.
2.2.4 Classification of Seizures

**Partial Seizures (Localized/Focal Seizures)**

*Simple Partial Seizures (Jacksonian Epilepsy) (SPS)* – Duration 20-60sec, consciousness is not impaired. SPS results from rapid neuronal discharges in one part of the brain, usually the cortex or limbic system. These seizures take different forms like motor, sensory, autonomic and psychic and are characterized by strange or unusual sensations, for example odors or visual abnormalities, sudden or restless movement, hearing distortion, stomach discomfort, and a sudden sense of fear. The *International League Against Epilepsy (ILAE)* introduced
International Classification for Epilepsies and Epileptic Syndromes (ICES)\textsuperscript{[24]} which categorized simple partial seizures into four subtypes-

**Motor** (cause changes in muscle activity. For example, a person may have abnormal movements such as jerking of a finger or stiffening of part of the body), **Sensory** (cause changes in any one of the senses. People with sensory seizures may smell or taste things that aren't there; hear clicking, ringing, or a person's voice when there is no actual sound; or feel a sensation of "pins and needles" or numbness), **Psychic** (cause changes in how patients think, feel, or experience things. They may have problems with memory, garbled speech, and inability to find the right word, or trouble understanding spoken or written language. They may suddenly feel emotions like fear, depression, or happiness with no outside reason. Some may feel as though they are outside their body or may have feelings of déjâ vu ("I've been through this before") or jamais vu ("This is new to me"—even though the setting is really familiar). They are called simple partial seizures of temporal lobe origin or temporal lobe auras), and **Autonomic** (cause changes in the part of the nervous system that automatically controls bodily functions. These include strange or unpleasant sensations in the stomach, chest, or head; changes in the heart rate or breathing; sweating; or goose bumps).

Simple partial seizures lead to complex partial seizures or to tonic-clonic convulsions.
**Complex Partial (CPS/Psychomotor/Temporal Lobe Epilepsy) Seizures** – Duration 30sec-2min with impaired consciousness. CPS occurs when epileptic activity spreads to involve a major portion of the brain but does not become generalized. They often are preceded by aura and occur after a simple partial seizure particularly when it is of temporal lobe origin. CPS often begin with a blank look or stare and then may progress to chewing or uncoordinated activity, meaningless bits of behavior, which appear random and clumsy (automatisms) and patients may appear afraid, try to run and struggle. These seizures are followed by a state of confusion that lasts even longer. Once the pattern of the seizures is established it will usually be repeated with each subsequent seizure. CPS sometimes resists anticonvulsant medication. In some cases CPS may lead to tonic-clonic seizures.

*[Figure 2.2.2 Simple Partial Seizures][23]*
Figure 2.2.3 Complex Partial Seizures

Partial Seizures evolving to Secondarily Generalized Seizures – Duration 1-2min. Seizures of this kind start as a partial seizure that is, they start in one limited area of the brain and then (sometimes so quickly that the partial seizure is hardly noticed) the seizure spreads throughout the brain, becoming "generalized."

Generalized Seizures

Absence (Petit mal) Seizures - epileptic activity occurs throughout the entire brain. It is a milder type of activity, however, causes unconsciousness without causing convulsions. An absence seizure consists of a period of unconsciousness with a blank stare, and begins and ends abruptly, without warning. There is no confusion after the seizure; seizures may be accompanied by chewing movements, rapid breathing, or rhythmic blinking. Absence seizures are short, usually lasting 2-10 seconds. They are very mild, and may go unnoticed and may recur frequently during the day. Typical Absence Seizures - are non-
convulsive and muscle tone is usually preserved. The seizure event usually lasts for less than 10 seconds in duration. **Atypical Absence Seizures** - are longer in duration than typical absence seizures with or without loss in muscle tone and often tonic/clonic-like movements are observed.

**Myoclonic Seizures** - occur in several different types of epilepsy. The seizures involve abrupt muscle jerks in part or all of the body, eg. a hand suddenly flinging out, shoulder shrug, foot kicking, or the whole body may jerk. The events may occur individually, or in a series. Consciousness is not impaired. Myoclonic Seizures are not tics or “startle” responses.

**Clonic Seizures** – characterized by repetitive muscle jerks.

**Tonic Seizures** – characterized by rigid violent muscular contraction with stiff and fixed extended limbs.
**Tonic-Clonic (Grand mal) Seizures** - Generalized seizures occur when epileptic activity occurs throughout the brain. Patient becomes unconscious from the start, and will have a major convulsion with both tonic (stiffening) and clonic (jerking) phase. After the seizure, the patients are unconscious and then groggy for a while. They may want to sleep. There will be no memory of what went on during the seizure. The seizure begins with a fall, possibly accompanied by a sudden cry, followed by tonus and then, after a while, clonus. There may be shallow breathing or temporarily suspended breathing, with bluish skin or lips and loss of bladder or bowel control. Towards the end of the seizure, patients may salivate profusely. Tonic-clonic seizures usually last 1 to 3 minutes, seldom longer.

![Figure 2.2.5 Generalized Tonic-Clonic Seizures](image)

**Atonic Seizures** - Although relatively uncommon, they are hard to deal with as they occur without warning. The individual abruptly loses consciousness, collapses and falls to the floor. There is no convulsion,
but the patients may injure themselves as they fall. Recovery occurs after a few seconds.

**Unclassified Epileptic Seizures (Status Epilepticus)**

Status epilepticus (SE) refers to continuous seizure activity with no recovery between successive seizures. It is a life-threatening condition. A tonic-clonic seizure lasting longer than 5 minutes (or two minutes longer than a given person's usual seizures) is usually considered grounds for calling the emergency services.

**Figure 2.2.6 Status Epilepticus**

**Seizure Syndromes**

There are many different epilepsy syndromes, each presenting with its own unique combination of seizure type, typical age of onset, EEG findings, treatment, and prognosis. Below are some common seizure syndromes:

- *Infantile Spasms (West syndrome)*
- *Childhood Absence Epilepsy*
• Dravet's Syndrome
• Benign Focal Epilepsies of Childhood
• Juvenile Myoclonic Epilepsy (JME)
• Temporal Lobe Epilepsy
• Fetal Alcohol Syndrome
• Frontal Lobe Epilepsy
• Lennox-Gastaut Syndrome

2.2.5 Endogenous Antiseizure Substances[21]

It is suggested that some sort of regulatory mechanism must be existing in the body as spontaneous arrest of seizure activity occurs after an attack and also brain remains seizure free for sometime between the two intervening attacks (postictal refractory period). Elevated adenosine levels have been reported immediately after the seizure activity both in animal models as well as in patients. Adenosine has been shown to inhibit spontaneous firing of cells in virtually all areas of brain including cerebral cortex. It causes hyperpolarization and exhibits A₁ receptor mediated anticonvulsant effects in animal models when administered exogenously. Since it is released postictal and it is not tonically active, A₁ receptor antagonists per se do not exhibit any convulsant activity.
### Table 2.2.1 ANTIEPILEPTIC DRUGS

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Class/Drugs</th>
<th>Mechanism of Action</th>
<th>Therapeutic Uses</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>1</td>
<td><strong>Hydantoins:</strong>&lt;br&gt;eg. Phenytoin</td>
<td>At therapeutic concentrations - limits the repetitive firing of action potentials and stabilizes neuronal membrane by slowing of the rate of recovery of voltage-sensitive Na+ channels and prolonging inactivated state that governs the refractory period of the neuron. At higher/toxic concentrations - reduction in Ca(^{2+}) influx, inhibition of glutamate and facilitation of GABA responses are seen.</td>
<td>Effective against partial and tonic-clonic but not absence seizures.</td>
<td>At therapeutic concentrations - gum hypertrophy, hirsutism, coarsening of facial features, acne, and hypersensitivity reactions like rashes, disseminated lupus erythematosus (DLE), lymphadenopathy, neutropenia, megaloblastic anemia, osteomalacia, hyperglycemia and produces fetal hydantoin syndrome when used during pregnancy. At high plasma levels - Cerebellar and Vestibular manifestation: Ataxia, vertigo, diplopia, nystagmus; Drowsiness, behavioral alterations, mental confusion and hallucinations; Epigastric pain, nausea, vomiting; I.V. injections cause fall in B.P. and cardiac arrhythmias.</td>
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<tr>
<td>2</td>
<td><strong>Barbiturates:</strong>&lt;br&gt;eg. Phenobarbitone</td>
<td>At therapeutic concentrations - potentiates GABA mediated inhibition by prolonging the duration of Cl(^{-}) ion channel opening of GABA(_A) receptor (by binding to α and β subunits). At higher concentrations - limits sustained repetitive firing by direct action on GABA(_A) receptor (GABA mimetic action). This may underlie some of the antiseizure effects of higher concentrations of Phenobarbitone achieved during therapy of status epilepticus.</td>
<td>Generalized tonic-clonic and partial seizures.</td>
<td>Sedation (but tolerance develops during chronic medication), nystagmus, ataxia at higher doses, irritability and hyperactivity in children, and agitation and confusion in the elderly. Hypoprothrombinemia with hemorrhage has been observed in the newborn of mothers who have received Phenobarbitone during pregnancy. Megaloblastic anemia that responds to folate and osteomalacia occur during chronic therapy of epilepsy.</td>
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<td>3</td>
<td><strong>Iminostilbenes:</strong>&lt;br&gt;eg. Carbamazepine</td>
<td>By slowing the rate of recovery of voltage-sensitive Na+ channels from inactivation.</td>
<td>Generalized tonic-clonic, simple and complex partial seizures, trigeminal and glossopharyngeal neuralgias.</td>
<td>Acute toxicity - stupor or coma, hyperirritability, convulsions and respiratory depression. Long-term therapy - drowsiness, vertigo, ataxia, diplopia, and blurred vision. Late complication - retention of water, with decreased osmolality and concentration of Na(^+) in plasma, especially in elderly patients with cardiac disease.</td>
</tr>
<tr>
<td>4</td>
<td><strong>Succinimides:</strong>&lt;br&gt;eg. Ethosuximide</td>
<td>Reduces low threshold Ca(^{2+}) currents (T-currents) in thalamocortical neurons which are involved in absence seizures. Selectively</td>
<td>Absence seizures but not tonic-clonic seizures.</td>
<td>Gastrointestinal complaints (nausea, vomiting and anorexia) and CNS effects (drowsiness, lethargy, euphoria, dizziness, headache, and</td>
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<tr>
<td>5.</td>
<td><strong>Aliphatic carboxylic acid</strong>: eg. Valproic acid</td>
<td>suppresses T current without affecting other types of Ca(^{2+}) or Na(^{+}) currents.</td>
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<td></td>
<td>hiccough, restlessness, agitation, anxiety, aggressiveness, inability to concentrate, and other behavioral effects have occurred primarily in patients with a prior history of psychiatric disturbance. Urticaria and other skin reactions, including Stevens-Johnson syndrome—as well as, eosinophilia, leucopenia, thrombocytopenia, pancytopenia, and aplastic anemia are seen.</td>
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<td></td>
<td></td>
<td>Absence, myoclonic, partial, and tonic-clonic seizures.</td>
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<td></td>
<td>Gastrointestinal symptoms, including anorexia, nausea, and vomiting. Effects on the CNS include sedation, ataxia, and tremor. Rash, alopecia, and stimulation of appetite have been observed occasionally. Valproic acid has several effects on hepatic function.</td>
</tr>
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<td>6.</td>
<td><strong>Benzodiazepines</strong>: eg. Diazepam</td>
<td>Act preferentially on midbrain ascending reticular formation and on limbic system. A primary medullary site of action produces muscle relaxation and ataxia due to action on cerebellum. Enhances presynaptic/postsynaptic inhibition by binding to specific BZD binding site (interface of a and γ subunits) on GABA(_A) receptor-Cl(^{-}) channel complex and increases the frequency of Cl(^{-}) channel opening. BZDs have only GABA facilitatory but no GABA mimetic action.</td>
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<td></td>
<td>Absence seizures, status epilepticus, local anesthetic induced seizures and in children at high risk of developing febrile convulsions. Also useful as adjuvants in myoclonic and akinetic epilepsy and may afford some benefit in infantile spasms.</td>
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<td>Sedation and dullness (can minimize by starting at low dose), some tolerance develops with chronic therapy. It is liable to cause respiratory depression and to increase the salivary and bronchial secretions. Sedation and development of tolerance even for antiepileptic action is limiting the use of BZDs.</td>
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<td>7.</td>
<td><strong>Newer Drugs</strong>: eg. Tiagabine</td>
<td>Inhibits the GABA transporter, GAT-1, and thereby reduces GABA uptake into neurons and glia. In CA1 neurons of the hippocampus, tiagabine increases the duration of inhibitory synaptic currents.</td>
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<td>Add-on therapy for refractory partial seizures with or without secondary generalization.</td>
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<td>Dizziness, somnolence, and tremor; they appear to be mild to moderate in severity, and appear shortly after drug initiation.</td>
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<td><strong>b.</strong></td>
<td><strong>eg. Lamotrigine</strong></td>
<td>Directly blocks voltage sensitive Na(^+) channels and thus stabilizes the presynaptic membrane and prevents the release of excitatory neurotransmitters, glutamate and aspartate. It does not block NMDA receptors.</td>
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<td><strong>c.</strong></td>
<td><strong>eg. Zonisamide</strong></td>
<td>Inhibits the T-type Ca(^{2+}) currents, inhibits the sustained, repetitive firing of spinal cord neurons, presumably by prolonging the inactivated state of voltage-gated Na(^+) channels</td>
</tr>
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<td><strong>d.</strong></td>
<td><strong>eg. Levetiracetam</strong></td>
<td>Mechanism of antiseizure effect not clearly known. However, it binds stereo selectively to synaptic plasma membrane in the brain and affects allosteric modulations of not only GABA receptors but also of high voltage activated Ca(^{2+}) and K(^+) channels.</td>
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<tr>
<td><strong>e.</strong></td>
<td><strong>eg. Gabapentin</strong></td>
<td>Increases synthesis and release of GABA to increase the GABA concentration in the brain. It also binds to L-type Ca(^{2+}) Channels and inhibits the high frequency voltage-activating Ca(^{2+}) channel currents in therapeutic doses and also functions as GABA(_{\text{B}}) agonist.</td>
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<tr>
<td><strong>f.</strong></td>
<td><strong>eg. Vigabatrin</strong></td>
<td>Inhibitor of GABA-transaminase, which degrades GABA.</td>
</tr>
</tbody>
</table>
The choice of drug depends largely on the seizure type and so correct diagnosis and classification are essential. Table 2.3.1 lists the main indications for the more commonly used antiepileptic drugs currently available.

**Table 2.2.2 Antiepileptic Drugs for Different Seizure types.[22]**

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>First-line Treatment</th>
<th>Second-line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partial Seizures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple Partial</td>
<td>Carbamazepine</td>
<td>Vigabatrin, Zonisamide</td>
</tr>
<tr>
<td>Complex Partial</td>
<td>Phenytoin</td>
<td>Clobazam,</td>
</tr>
<tr>
<td>Secondarily Generalized</td>
<td>Valproate, Lamotrigine</td>
<td>Phenobarbitone, Acetazolamide, Gabapentin, Topiramate, Zonisamide</td>
</tr>
<tr>
<td><strong>Generalized Seizures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic</td>
<td>Valproate</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Tonic</td>
<td>Carbamazepine</td>
<td>Clobazam</td>
</tr>
<tr>
<td>Clonic</td>
<td>Phenytoin, Lamotrigine</td>
<td>Phenobarbitone</td>
</tr>
<tr>
<td>Absence</td>
<td>Ethosuximide, Valproate</td>
<td>Clonazepam, Lamotrigine, Acetazolamide</td>
</tr>
<tr>
<td>Atypical absences</td>
<td>Valproate</td>
<td>Phenobarbitone</td>
</tr>
<tr>
<td>Atonic</td>
<td>Clonazepam, Clobazam</td>
<td>Lamotrigine, Carbamazepine, Phenytoin, Acetazolamide</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Valproate, Clonazepam</td>
<td>Phenobarbitone, Acetazolamide, Topiramate</td>
</tr>
</tbody>
</table>

The adverse effects of these drugs especially on chronic use lead to search for alternative medicines and their efficacy in different epileptic models.
2.3 DEPRESSION

The term depression is often misleading. Everyone in normal course of life experience altercations in mood. Hence lowered mood as a response to ups and downs in life are termed sadness or unhappiness or grief and is considered normal. Sadness or grief is usually accompanied by an intact self-esteem, while depression is marked by a sense of worthlessness. Depression is the most common of the affective disorders (disorders of mood not thought or cognition) and is a major cause of disability and premature death worldwide.[26-30]

2.3.1 Symptoms of Clinical / Psychic Depression

The symptoms of depression include emotional and biological components:[26-30]

- Emotional Symptoms
  - Sadness and despair,
  - Misery, apathy and pessimism
  - Low self-esteem, feelings of guilt, inadequacy and ugliness
  - Mental slowing, loss of concentration, indecisiveness and loss of motivation
  - Self depreciation, variable agitation or hostility
  - Melancholia and suicidal thoughts

- Biological Symptoms
  - Retardation of thought and action
  - Loss of libido
- Sleep disturbances (insomnia or hypersomnia and changes in appetite (anorexia and weight loss or overeating and weight gain)
- Disruption of the normal circadian and ultradian rhythms of activity, body temperature and many endocrine functions.

### 2.3.2 Causes of Depression

Depression may be the final outcome of

- Genetic disposition and familial (eg. a variant of gene encoding serotonin transporter protein)
- Neurotransmitter dysfunction (norepinephrine, serotonin and dopamine)
- Psychosocial stress (eg. divorce, unemployment or death of loved one, etc.)
- Chronic illness (eg. Cancer, AIDS, myocardial infarction, hypothyroidism, neurological disorders, diabetes, SLE, etc.)
- Endocrine disorders (eg. Hypothyroidism, cushing’s syndrome). The endocrine system, especially hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-thyroid axis is implicated in the development of affective disorders.
- Drugs (eg. Analgesics, antidepressants, antihypertensives, anticonvulsants, opiate withdrawal, BZD withdrawal, antipsychotics, antiparkinsonism agents, steroids, oral contraceptives.

### 2.3.3 Types of Depression\[26-30\]

There are two types of depression –
- **Unipolar Depression** – Seen in 80% of depression cases. Mood swings are always unidirectional, i.e., either depression with a feeling of worthlessness or depression with ground less irritability. The latter type is rare. Unipolar depression if further of two types.
  - **Reactive Depression** - About 75% of unipolar depression cases show symptoms of reactive depression characterized by disproportionate feeling of sadness, grief and anxiety as a consequence of stressful life-events such as bereavement of loved one, unemployment, physical illness or social problem. It is non-familial, self limiting and often responds to antianxiety drugs.
  - **Endogenous Depression** - About 25% of unipolar depression patients show endogenous depression characterized by a familial pattern unrelated to external stresses can occur at any age and is not self limiting. It should be treated with appropriate antidepressant drugs or by electroconvulsive therapy.

- **Bipolar Affective Disorder (Manic Depressive Disorder)** – Seen in about 20% of depression cases and is characterized by cyclic manifestations of depression followed by mania. It is not self limiting and should be treated with antidepressant drugs &/or Electroconvulsive therapy (ECT).

2.3.4 **Theories of Depression**[26-30]

1. **The Monoamine Theory of Depression**

This theory was proposed by Schildkraut in 1965, which states that
depression is caused by a functional deficit of monoamine transmitters (NE &/or 5-HT) at certain sites in the brain, while mania results from a functional excess. The evidences supporting this theory are as follows:

**Pharmacological Evidence**

- The ability of NE and 5-HT uptake inhibiting or monoamine oxidase-A (MAO-A) inhibiting drugs to facilitate NE/5-HT neurotransmission and show effective antidepressant activity.
- Drugs like reserpine, which deplete NE/5-HT cause depression.
- Drugs like tryptophan, which increases 5-HT synthesis, elevates mood.

**Biochemical Evidence**

- CSF levels of 5-hydroxyindole acetic acid (5-HIAA), a metabolite of 5-HT and urinary levels of 3-methoxy-4-hydroxyphenyl glycol (MHPG), a metabolite of NE are found to be low in depression.
- Lower tryptophan in patients of depression.

**Inconsistencies in the Monoamine Theory**

- Although antidepressant drugs produce blockade of NE/5-HT reuptake within hours, their clinical benefits appear after several weeks of treatment, implicating neuroadaptive changes in receptor regulation and second messenger system.
- Amphetamine and cocaine, which facilitate NE transmission, are not useful as antidepressants.
— Some antidepressant drugs have atypical actions and lack any NE/5-HT uptake inhibition activity.

2. **Receptor Down-Regulation Theory**

The evidence for this theory proposed by several authors comes from the observation that, the most consistent adaptive changes seen with different types of antidepressant drugs are the down-regulation of $\beta_1$, $\beta_2$, $\alpha_2$ adrenoceptors and 5-HT$_2$ receptors. ECT also causes down regulation of $\beta_1$ and $\beta_2$ receptors.

*Inconsistencies in the Receptor Down-Regulation Theory*

$\beta$ – blockers do not possess antidepressant action, rather they produce depression in patients after prolonged use.

3. **Neuroendocrine Theory**

Neuroendocrine abnormalities that reflect the symptoms of endogenous depression include

— Increase in cortisol and corticotrophin-release hormone levels.
— Increase in adrenal size.
— Failure of dexamethasone to bring a fall in cortisol levels (dexamethasone test).
— A blunted response of thyroid stimulating hormone (TSH) level to induce thyroid releasing hormone (TRH).
— Reduction in growth hormone levels.
— Increase in prolactin levels.
Antidepressant treatment leads to the normalization of these pituitary-adrenal abnormalities.

All these theories are complex and imprecise and the relationship between such findings and antidepressant activity are not consistent (except for consistently observed down-regulation of receptors). Hence, monoamine theory despite its inconsistencies serves the basis for understanding the actions of majority of antidepressant drugs.

The mechanism of action and adverse effects of the current therapy available for treatment of depression are shown in Table 2.3.1
### Table 2.3.1 Antidepressant Drugs

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Class/Drug</th>
<th>Mechanism of Action</th>
<th>Therapeutic Uses</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. i)</td>
<td>Tricyclic Antidepressants: NE + 5-HT Reuptake Inhibitors: eg. Imipramine, Amitriptyline, Doxepin</td>
<td>TCAs inhibit active reuptake of biogenic amines NE and 5-HT into their respective neurons and thus potentiate them. They indirectly facilitate dopaminergic transmission in forebrain and add to the mood elevation action. Uptake blockade occurs within few hours but antidepressant takes few weeks to develop. Initially the presynaptic α2 and 5-HT, autoreceptors are activated by the increased amount of NE/5-HT in a synaptic cleft resulting in decreased firing of locus ceruleus (noradrenergic) and raphe (serotonergic) neurons. However, on long-term administration, antidepressants desensitizes presynaptic α2 / 5-HT1A, 5-HT1D autoreceptors and induce other adaptive changes in the number and sensitivity of pre- and post synaptic NE &amp;/or 5-HT receptors as well as amine turnover of brain, the net effect of which is enhanced noradrenergic and Serotonergic transmission. Thus, the uptake blockade appears to initiate a series of time dependent changes that culminate in antidepressant effect.</td>
<td>Endogenous and bipolar depression, neuropathic pain, attention deficit-hyperactivity disorder in children, enuresis, migraine and pruritus.</td>
<td>Anticholinergic – Dry mouth, bad taste, constipation, epigastric distress, urinary retention, blurred vision, palpitation. CNS – Sedation, mental confusion, weakness, sudden switch over to dysphoric-agitated state or mania (mostly these are cases of bipolar depression, the other pole being unmasked by the antidepressant), sweating, lowering of seizure threshold, postural hypotension. Cardiac – Arrhythmias precipitate especially in ischemic heart disease and may be responsible for sudden death in these patients.</td>
</tr>
<tr>
<td>1. ii)</td>
<td>Predominantly NE Reuptake Inhibitors: eg. Desipramine, Nortryptiline, Amoxapine</td>
<td>Imipramine Desipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Selective Serotonin Reuptake Inhibitors (SSRIs): eg. Sertraline, Fluoxetine, Fluvoxamine, Citalopram, Paroxetine.</td>
<td>SSRIs selectively inhibit membrane associated SERT (Serotonin transporter)</td>
<td>Unipolar and bipolar depression, obsessive compulsive disorder (OCD), panic disorder, social phobia, eating disorders, premenstrual dysphoric disorder and post traumatic</td>
<td>Prominent effects are gastrointestinal – nausea (5-HT3 receptor stimulation, but tolerance develops), interferes with ejaculation and orgasm. Mild side effects – nervousness, restlessness, insomnia, anorexia, dyskinesia, headache and diarrhea. Epistaxis and ecchymosis may</td>
</tr>
<tr>
<td><strong>Fluoxetine</strong></td>
<td>Stress disorder. They are also being used for many anxiety disorders, body dysmorphic disorder, compulsive buying and kleptomania.</td>
<td>occur probably due to impairment of platelet function.</td>
<td></td>
<td></td>
</tr>
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<td>---</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3. **Atypical Antidepressants:**

- **Trazodone, Nefazodone, Bupropion, Mirtazapine, Mianserin, Venlafaxine.**

**Trazodone** – inhibits uptake of 5-HT, causes desensitization of α₂ and 5-HT presynaptic autoreceptors, H₁ histaminic and α₁ adrenoceptor.

**Mianserin** – blocks presynaptic α₂ receptors and thus increase the NE levels in brain. **Venlafaxine** – increases NE, 5-HT and DA levels in the synaptic cleft by blocking the reuptake of these neurotransmitters.

#### Unipolar and bipolar depression.

### 4. **Antidepressants of Natural origin:**

- **St. John’s Wort (Active principle: Hyperforin)**

St. John’s Wort (Hypericum perforatum) is freely available and being used in many European countries. Its active principle is Hyperforin which is a monoamine reuptake inhibitor, mild MAO inhibitor and a stimulant at GABA receptor.

#### Nutritional supplement

A potent enzyme inducer and lowers the therapeutic efficacy of warfarin, oral contraceptives, antipsychotics and HIV reverse transcriptase inhibitors like zidovudine.
2.3.5 Electroconvulsive Therapy (ECT)

ECT in humans involves stimulation through electrodes placed on either side of the head, with the patient lightly anaesthetized, paralyzed with a neuromuscular-blocking drug so as to avoid physical injury, and artificially ventilated. More recently, a technique involving transcranial magnetic stimulation, which does not require these precautions, has been introduced. It appears to be the most effective treatment for severe suicidal depression.

The main disadvantage of ECT is that it often causes confusion and memory loss lasting for days or weeks.

The numerous adverse reactions of these drugs encouraged to take up a study of the benefits of alternative medicines.
2.4 DRUGS

The following drugs were selected after consultation with the specialists in the respective fields.

**Dr. Bhadra Dev**, Professor and Head, Department of Rasa Shastra, Government Ayurvedic Medical College, Erragadda, Hyderabad, Andhra Pradesh, India, suggested the two Ayurvedic drugs – Panchagavya Ghrutham (for antiepileptic activity) and Kushmanda Lehyam (for antidepressant activity).

**Dr. Mohd. Ahsan Farooqui**, Associate Professor, Government Unani Medical College, Erragadda, Hyderabad, Andhra Pradesh, India, suggested the two unani drugs – Hab-e-Jund (for antiepileptic activity) and Itrifal Kishneezi (for antidepressant activity).

**Dr. K. Madhava Chetty**, Assistant Professor, Department of Botany, S.V. University, Tirupati, Andhra Pradesh, India, had suggested and authenticated the two herbal drugs – *Cynodon dactylon* (for antiepileptic activity) and *Barleria cristata* (for antidepressant activity).

2.4.1 Panchagavya Ghrutham (PG)

PG was obtained from M/s Nagarjuna Herbal Concentrates Ltd., Idukki, Kerala and was used as received. The formulation was prepared according to Ashtangahrudayam (an ancient reference text for preparation of various ayurvedic formulations).[31]
**Method of Preparation:**

Every 200g formulation must be prepared out of 1.14g each of *Cyperus rotundus* (nut grass), *Elettaria cardamomum* (cardamom), *Plumbago rosea* (red leadwort), *Embelia ribes* (embelia), *Glycyrrhiza glabra* (liquorice), *Curcuma longa* (turmeric), *Rubia cordifolia* (Indian madder), *Cyclea peltata* (pata), *Acorus calamus* (sweet flag), *Scindapsus officinalis*, *Picrorhiza kurroa* (picrorhiza), *Terminalia chebula* (chebulic myrobalan), *Terminalia belerica* (beleric myrobalan), *Emblica officinalis* (Indian gooseberry), *Adhatoda vasica* (malabar nut), *Vitis vinifera* (grapes), *Coscinium fenestratum* (tree turmeric) and Panchagavya (50g of cow dung, 100ml of cow urine, 200g of clarified butter (from cow milk), 800ml milk and 250ml curd). All the ingredients should be marinated together for 24 hours and heated on slow fire till the water content evaporates and filtered.

**Dose:** 5-10g (1-2tsp) before food in the morning and after food at night.

**Therapeutic Uses:**

In ayurveda PG is prescribed for epilepsy, mental disorders, memory enhancement, longer life, handsomeness and sexual potency.

The chemical constituents and uses of individual ingredients are given in the following Table 2.4.1 followed by their photographs. [31-130]
Table 2.4.1 PANCHAGAVYA GHRUTHAM (Antiepileptic) Ingredients:

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients / Scientific name</th>
<th>Vernacular names</th>
<th>Chemical Constituents</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Cyperus rotundus</em> (Cyperaceae)</td>
<td>E- Nut grass</td>
<td>Volatile oil, sesquiterpene, hydrocarbons, epoxides ketones, Cu, Fe, Mg, Ni, β-sitosterol</td>
<td>Spasms, stomach disorders, irritation of bowel, arthritis, intellect promoting, diarrhea, dysentery, leprosy, bronchitis, amenorrhea, blood disorders, analgesic anti-inflammatory, antipyretic and antioxidant hypotensive, emmenagogue, antihyperlipidemic, antidiabetic.</td>
</tr>
<tr>
<td>2</td>
<td><em>Elettaria cardamomum</em> (Zingiberaceae)</td>
<td>E- Cardamom</td>
<td>Volatile oils, 1,8-cineole, α-terpinyl acetate, limonene, α-terpineol, sabinene, linalool. Palmitic, oleic, linoleic and linolenic acids, α-tocopherol, desmosterol, campesterol.</td>
<td>Carminative, antiemetic, stomachic, orexigenic, anti-gripe, antiasthmatic, antispasmodic, antiseptic, antiflatulence, appetizer, colic, bronchitis, asthma, headache, rheumatism, antioxidant, hypotensive.</td>
</tr>
<tr>
<td>4</td>
<td><em>Embelia ribes</em> (Myrsinaceae)</td>
<td>E- Embelia</td>
<td>Embelin, embolic acid</td>
<td>Ascaricidal, anthelmintic, carminative, diuretic, astringent, anti-inflammatory, antibacterial, Febrifuge, diseases of chest and skin, oestrogenic, weakly progestogenic, bechic, Antidiarrhoeal, spermicidal, oxytocic, diuretic, blood purifier. anaemia, genitourinary tract infections, diarrhea, diseases of the liver.</td>
</tr>
<tr>
<td>5</td>
<td><em>Glycyrrhiza glabra</em> (Leguminosae)</td>
<td>E- Liquorice</td>
<td>Terpenoids- glycyrrhizin, glycyrrhizic acid, Flavonoids- Liquiritin, isoliquertin</td>
<td>Tonic, demulcent, diuretic, laxative, piles, wounds, dysentery, epilepsy, adenocorticoid insufficiency, hepatoprotective, antidepressant, ulcers.</td>
</tr>
<tr>
<td>6</td>
<td><em>Curcuma longa</em> (Zingiberaceae)</td>
<td>E- Turmeric</td>
<td>Phenolic compounds – curcumin, curcuminoinds, Volatile oil- sesquiterpene ketone (curcuminone)</td>
<td>Anti-inflammatory, cholagogue, hepatoprotective, blood-purifier, antioxidant, detoxifier and regenerator of liver tissue,</td>
</tr>
<tr>
<td>No.</td>
<td>Species</td>
<td>Parts</td>
<td>Main Constituents</td>
<td>Uses</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>[62.68] T- Pasupu</td>
<td></td>
<td>antiasthmatic, anti-tumour, anticutaneous, antiprotozoal, stomachic, carminative. Reduces high plasma cholesterol. Antiplatelet activity offers protection to heart and vessels. Also protects against DNA damage in lymphocytes.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cyclea peltata (Menispermaceae)</td>
<td>E- Pata root S- Patha H- Path T- Ballepu aku teega</td>
<td>Alkaloid- tetrandrine</td>
<td>Smallpox, bone fractures, malarial fever, jaundice, stomachache. Anti-inflammatory, antihypertensive, vasodilator, cardiac depressant, antiallergic</td>
</tr>
<tr>
<td>4</td>
<td>Acorus calamus (Araceae)</td>
<td>E- Sweet flag S- Vacha H- Vasaka T- Vasa</td>
<td>Sesquiterpenes, volatile oil - asarone</td>
<td>Nervine tonic, psychoneurosis, epilepsy, hypotensive, tranquilizer, sedative (with neuroleptic and antianxiety properties), analgesic, spasmolytic, bronchial catarrh, chronic diarrhea, dysentery.</td>
</tr>
<tr>
<td>5</td>
<td>Scindapsus officinalis (Araceae)</td>
<td>S- Gajakrishna H- Gajapeepar T- Enugupippallu</td>
<td>Glycosides- Scindapsin A, B, sugars</td>
<td>Stimulant, carminative, diaphoretic, antihelmintic, anti diarrhoeal, asthma, hypoglycaemic, rheumatism.</td>
</tr>
<tr>
<td>6</td>
<td>Picrorhiza kurroa (Scrophulariaceae)</td>
<td>E- Picorhiza S- Tikta H- Kutki T- Katukarohini</td>
<td>Bitter glycosides- kutkin, picroside, kutkoside, phenolic glycoside-androsin</td>
<td>Stomachic, anti diarrhoeal, cholagogue, hepatoprotective, hepatitis, chronic dysentery, amoebiasis, jaundice, dyspnoea, skin diseases, antioxidant.</td>
</tr>
<tr>
<td>7</td>
<td>Terminalia chebula (Combretaceae)</td>
<td>E- Black myrobalan S- Haritaki H- Harad T- Karakkai</td>
<td>Shikimic, gallic, triacontanoic and palmitic acids, beta-sitosterol, daucosterol, chebulic acid, ellagitannin, terchebulin, punicalagin, teaflavin A, phloroglucinol, pyrogallol, ferulic, vanillic, p-coumaric and caffeic</td>
<td>Flatulence, constipation, diarrhoea, dysentery, cyst, digestive disorders, vomiting, enlarged liver and spleen, cough and bronchial asthma, metabolic harmony, diuretic, antioxidant, hypolipidemic, anticancer, hepatoprotective</td>
</tr>
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</tr>
<tr>
<td></td>
<td>16. <em>Vitis vinifera</em> (Vitaceae) [118-121] 1.14g</td>
<td>E- Wine grape S- Mridvika H- Angoor T- Draksha</td>
<td>Flavonoids, tannins, tartrates, inositol, carotenes, choline, sugars tartaric and malic acids, pectin, flavone glycosides, vitamins A, B₁, B₂, C, minerals, anthocyanin, phenols</td>
<td>Anaemia, jaundice, dyspepsia, constipation, haemorrhagic diseases, gout, cough, dyspnoea, alcoholism, antioxidant.</td>
</tr>
<tr>
<td></td>
<td>17. <em>Coscinium fenestratum</em> (Menispermaceae) [122-125] 1.14g</td>
<td>E- Tree turmeric S- Daruherida H- Jhar-i-haldi T- Manupasupu</td>
<td>Alkaloids- berberine, jatrorrhazine. ceryl palmitic acid, oleic acid</td>
<td>Stomachic, diuretic, hypotensive, antidysenteric, antibacterial, antifungal, bitter tonic, dyspepsia, debility, fractures, for dressing wounds and ulcers, cutaneous leishmaniasis, hepatoprotective, antidiabetic..</td>
</tr>
<tr>
<td></td>
<td>18. Panchagavya [36,37,126-130] <em>Bos Taurus</em> (Bovidae)</td>
<td>Five products from cow-milk, curd, urine, clarified butter, dung.</td>
<td>Ingredients from cow: Panchagavya: Cow dung-water (1:1)- 50g, urine – 100ml, ghee (clarified butter) – 200g, milk – 800ml, Curd – 250ml</td>
<td>Memory enhancer, rejuvenator, antioxidant, hepatoprotective.</td>
</tr>
</tbody>
</table>

Images of Sources of Ingredients of Panchagavya Ghrutham
Images of Sources of Ingredients of Panchagavya Ghrutham (Contd..)
Images of Sources of Ingredients of Panchagavya Ghrutham (Contd..)
Plate 2.4.13 Terminalia belerica
Plate 2.4.14 Emblica officinalis
Plate 2.4.15 Adhatoda vasica
Plate 2.4.16 Vitis vinifera
Plate 2.4.17 Coscinium fenestratum
Plate 2.4.18 Panchagavya Ghrutham
2.4.2 HAB-E-JUND (HJ)

The formulation Hab-e-jund (HJ) was obtained from M/s Asian Pharmacy, Shakargunj, Hyderabad, India. It consists of 12% each of *Paeonia officinalis* (peony), *Delphinium denudatum* (larkspur, jadwar), Castoreum (castor sac scent glands of beaver), *Pimpinella anisum* (anise, sounf), *Aloe barbadensis* (aloe), *Wrightia tinctoria* (indigo), *Trachyspermum ammi* (*Ptychotis ajowan*, carum, ajwain) and 15% cow gall bladder stones and 1% musk (odoriferous gland secretions from musk deer) \(^{[131-133]}\)

**Method of Preparation:**

All the above ingredients are powdered and made into pills of 250mg each.

**Dose:**

Morning 1 pill and night 1 pill to be taken along with cow milk.

The chemical constituents and uses of individual ingredients are mentioned in the following Table 2.4.2 followed by their photographs.\(^{[32-36,131-152]}\)
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Ingredients / Scientific name</th>
<th>Vernacular names</th>
<th>Chemical Constituents</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Paeonia officinalis</em> (Paeoniaceae) [134]</td>
<td>E- Paeony U- Ood Saleeb</td>
<td>Monoterpenes and glucosides of the pinen-type (including paeoniflorin); anthocyanin; tannins (pentagalloyl glucose); flavonoids.</td>
<td>Antispasmodic, sedative, smooth muscle relaxant, vasodilatory, hypotensive, anti-inflammatory, analgesic, emmenagogue, hepatoprotective, fissures, haemorrhoids, diseases of respiratory tract, nervous conditions and skin, arthritis, neuralgia, neurasthenia, migraine, epilepsy, allergic disorders, whooping cough, painful spams.</td>
</tr>
<tr>
<td>3.</td>
<td><em>Castoreum canadensis</em> (Castoridae) [131-133,139]</td>
<td>E- Beaver</td>
<td>Dried and macerated castor scent glands from male or female beaver (rodent) 4-propylphenol, ethyl guaiacol, cinnamic acid, salicylic acid derivatives, tetramethyl isoquinolinone.</td>
<td>Antiseptic, antispasmodic, epilepsy, hysteria, asthma, muscular tremors and as emmenagogue, perfume industry.</td>
</tr>
<tr>
<td>6.</td>
<td><em>Wrightia tinctoria</em></td>
<td>E- Pala indigo U- Indarjao shireen</td>
<td>Cycloartanes, cycloartenone, cycloecalenol, α- , β- amyrin, β-sitosterol,</td>
<td>Antidysenteric, piles, skin diseases, astringent, febrifuge, anthelmintic, flatulence, bilious</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td><em>Trachyspermum ammi</em>/<em>Ptychotes ajowa</em> (Umbelliferae/Apiaceae) [149-151] 12%</td>
<td>E- Ammi, Carum U- Nankhwaah, ajawaayin H- Ajwain T- Vamu, voma Protein, fat, carbohydrates, mineral matter, sugars, tannins, flavones, sterol, phenolic glucoside, Ajowan oil- phenols, mainly thymol and some carvacrol. Carminative, antispasmodic, anticholiner, antidiarrhoeal, bechic, stimulant, tympanitis, constipation, colic, helminthiasis, expectorant in emphysema, bronchial and other respiratory ailments, rheumatism, diuretic, febrifuge Thymol is a powerful antiseptic and antifungal used in deodorants, mouth-washes, tooth pastes, gargles.</td>
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<tr>
<td>8</td>
<td>Cow gall stones (<em>Calculus bovis</em>) [131,152] 15%</td>
<td>E- Cow gallstones U- Bezoar Bile acids, fatty acids, cholesterol Used in alternative medicines in febrile convulsions, fever, convulsions, stroke and other illnesses</td>
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<td></td>
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<tr>
<td>9.</td>
<td><em>Musk</em> (<em>Moschus moschiferus</em>)[131] 1%</td>
<td>E- Musk Odoriferous secretion derived from the musk gland present under the abdomen near the pubis, (between stomach and genitals) of the male musk deer. Odoriferous alkaloid- muscone, steroids, proteins, esters, waxes, urogenic salts, ammonia, fats, resins, male hormone- androsterone In traditional Chinese medicines- cardiac and general stimulant, aphrodisiac, anti-spasmodic; perfume industry; antiseptic, antihistaminic, antianginal, spasmylytic, central nervous system depressant, stimulant, antibacterial.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Images of Sources of Ingredients of Hab-e-Jund

Plate 2.4.19 *Paeonia officinalis*  
Plate 2.4.20 *Delphinium denudatum*  
Plate 2.4.21 *Castor canadensis*

Plate 2.4.22 *Pimpinella anisum*  
Plate 2.4.23 *Aloe barbadensis*  
Plate 2.4.24 *Wrightia tinctoria*
Images of Sources of Ingredients of Hab-e-Jund (Contd.)

Plate 2.4.25 *Trachyspermum ammi*  
Plate 2.4.26 Cow gallstones  
Plate 2.4.27 *Moschus moschiferus* (Musk)  
Plate 2.4.28 Hab-e-Jund
2.4.3 *CYNODON DACTYLON* (CD)

*Cynodon dactylon* (CD) belongs to family Poaceae, and commonly called as dhub grass, bermuda grass, devil’s grass. Its sanskrit name is dhurva. CD is a perennial grass with creeping stems, which creep along the grounds and root wherever the nodes touch the ground, forming a dense turf or mat on the soil. The grass grows through out India in pastures, fields, waste grounds, road sides, etc.

*Morphology*[^153]

*Stems* - Creeping, 40cm long, glabrous, terete, mat-forming, from rhizomes and stolons. *Leaves* - Leaf blades 1 to 8cm long, 4mm broad, flat to slightly keeled, pubescent toward the base. *Flowers* - Spikelets with one perfect floret. Glumes 1 to 2mm long, lanceolate, acute at the apex. Lower glume slightly smaller than the upper glume. Anthers 1 to 1.3mm long, tan to yellow. Styles- purple. *Flowering* - June – October.

*Cynodon* is easy to identify in the field because of its creeping habit and its palmately compound inflorescence. It prefers a warm sunny position in a well-drained soil. The plant can grow in very diverse conditions of soil and moisture, withstanding drought well. It spreads quite rapidly, rooting at the nodes, becoming difficult to eradicate and can be a serious weed in cultivated land.

**Chemical Constituents:** Green dhub grass contains - protein 10.47 %, enzymes 28.17 % and ash 11.79 %. Ash contains - calcium 0.77 %,
phosphorus 0.58 %, manganese 0.34 %, sodium 0.23% and potassium 2.08 %.

Dry dhub grass contains - proteins 6.04%, carbohydrate 36.16%. It also contains certain alkaloids and glycosides.

**Therapeutic Uses:**

Traditionally CD is used extensively for diabetes,\(^{153}\) urinary problems,\(^{154}\) jaundice, diarrhea, dysentery, vomiting,\(^{155,156}\) cuts, wounds,\(^{157}\) hysteria, epilepsy, insanity, skin diseases, thirst, hypertension, poisoning, eye diseases and renal colic; as astringent and as diuretic. \(^{32-36,153}\)

Studies suggest that CD has antimicrobial,\(^{158}\) antioxidant\(^{159}\) and antidiabetic activity. \(^{160}\)

*Cynodon dactylon* was procured from the forests of Tirupati and authenticated by Dr. K. Madhava Chetty, Assistant Professor, Department of Botany, S.V. University, Tirupati, Andhra Pradesh, India. A specimen voucher **SUCP/SP/2009/3** is deposited in the herbarium of Sultan-ul- uloom College of Pharmacy, Hyderabad, Andhra Pradesh, India.

The plant material was shade dried, pulverized and extracted in methanol using soxhlet extractor and concentrated. The semisolid mass was then placed in a desiccator and stored in refrigerator. The percentage yield was 28.6%. The extract was studied for acute toxicity in rats, neuropharmacological profile using Irwin test in mice and antidepressant activity in rats and mice.
Photographs of CD, fresh plant growing wild and as lawn grass; its stems, inflorescence, and crude drug are shown in plate 2.4.29.

**Images of *Cynodon dactylon* (Antiepileptic):**

Plate 2.4.29 *Cynodon dactylon* (fresh wild plant, as lawn, stems, inflorescence and crude drug)
2.4.4 KUSHMANDA LEHYAM (KL)

KL was procured from M/s Jivaka Ayurvedic and Allied Products Industrial Cooperative Society Ltd., Tenali, Guntur, Andhra Pradesh, India, sponsored by Khadi and Village Industries Board, Government of Andhra Pradesh. The formulation was prepared as per Ayurvedic Formulary of India. The drug was used as procured.

KL consists of *Benincasa hispida* (ash gourd-4.8Kg), *Piper longum* (Indian long pepper-96g), *Zingiber officinale* (dry ginger-96g), *Cuminum cyminum* (cumin-96g), *Cinnamomum zeylanicum* (cinnamon-24g), *Elettaria cardamomum* (cardamom-24g), *Cinnamomum tamala* (Indian bay leaf-24g), *Piper nigrum* (pepper-24g), *Coriandrum sativum* (coriander-24g), clarified butter (768g), candy sugar (kanda – 4.8g), honey (384g).[161]

**Method of Preparation:**

*Benincasa hispida* fruit is cut into pieces and the skin and the seeds are removed. Thereafter, it is cut into smaller pieces and boiled in a small quantity of water. The fluid is strained and kept separately. The pulp is made into paste and bundled in a piece of cloth, which is then squeezed by hand to remove the remaining fluid. The paste then fried in half the quantity of clarified butter over a low fire till the color becomes honey brown, at which stage, there will be no moisture. To the strained fluid of *Benincasa hispida*, sugar is added and boiled to lehya paka (thick consistency). To this the fried paste is added and stirred well.
The vessel is then removed from the fire, powders of remaining ingredients (except honey and clarified butter), are added and mixed and the remaining clarified butter is added. Honey is added when cool.

**Therapeutic Uses:**

KL is used in ayurveda as a digestive, appetizer, carminative, restorative, hematinic, haemostatic, expectorant, rejuvenator, aphrodisiac and in tuberculosis, cough, fever and impotence.

**Dose:** 6-12g (1-2tsp) with water or milk.

The chemical constituents and uses of individual ingredients are given in the following Table 2.4.3 followed by their photographs.[31-36,43-45,161-214]
Table 2.4.3 Kushmanda Lehyam (Antidepressant) Ingredients:[31-36,43-45,161-214]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Ingredients / Scientific name</th>
<th>Vernacular names</th>
<th>Chemical Constituents</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Benincasa hispida (Cucurbitaceae) [162-166] 4.8Kg</td>
<td>E- Ash gourd S- Kushmanda H- Pethakaddu T- Budida gummadi</td>
<td>Triterpenes: alnusenol, multiflorenol, iso-multiflorenol; flavone: iso-vitexin; and sterols: lupeol, lupeol acetate, and beta-sitosterol; amino acids</td>
<td>Tranquilizing activity, mild CNS depressant, antiallergic laxative, diuretic, tonic, aphrodisiac, cardiotonic, urinary calculi, insanity, epilepsy, jaundice, dys-pepsia, fever, and menstrual disorders, antiulcer, antiinflammatory, antihistaminic, antidepressant, gastroprotective, morphine withdrawal.</td>
</tr>
<tr>
<td>2.</td>
<td>Piper longum (Piperaceae) [167-172] 96g</td>
<td>E- Indian long pepper S- Pippali H- Pipal T- Pippallu</td>
<td>Alkaloids and amides- piperine, methyl piperine, pipernonaline, piperettine, asarinine, pellitorine, piperunodecalidine, piperlongumine, piperlonguminine, retrofractamide A, pergumidiene, brachystamide-B, dimer of desmethoxypiplartine, N- isobutyldecadienamide, brachysamide- A, brachystine, piperclide, etc; Lignans- Sesamin, pulviatilol, fargesin; Esters; Volatile oil – caryophyllene, bisabolene, thujine, terpinolene, zingiberene, p-cymene, dihydrocarveol.</td>
<td>Cough, bronchitis, asthma, sedative (in insomnia and epilepsy); cholangue, emmenagogue, digestive, appetizer and carminative, general tonic, haematinic, muscular pains, inflammation, antipyretic, hypotensive, analeptic, CNS stimulant, antifertility, immunomodulatory, respiratory depression, antiasthmatic, hypocholesteromic, hepatoprotective, antiamoebic, antibacterial, bioavailability enhancer, antiallergic.</td>
</tr>
<tr>
<td>3.</td>
<td>Zingiber officinale (Zingiberaceae) [173-180] 96g</td>
<td>E- Dry ginger S- Sunthi H- Sonth T- Sonthi</td>
<td>Essential oil- monoterpenes- geranial and neral; sesquiterpenes- β-sesquiphellandrene, β-bisabolene, ar-curcumene and alphazingiberene; pungent principles- gingerols, shogaols and related phenolic ketone derivatives; Others- diarylheptenones, diterpenes, gingesulphonic acid, monoacyl digalactosyl glycerols</td>
<td>Antiemetic (post operative emesis, motion sickness, vomiting in pregnancy), Antiflatulent, hypocholesterolaemic, analgesic, antipyretic, antiinflammatory, antispasmodic, expectorant, circulatory stimulant, cardiotonic, diaphoretic, irritable bowel, diarrhea, colds, influenza, migraine, dyspepsia, loss of appetite, tymanitis, anaemia, rheumatism, cough, dyspnoea, anorexia, bronchitis, sedative, Hypotensive, hepatoprotective, antiplatelet, bioavailability enhancer.</td>
</tr>
<tr>
<td></td>
<td><strong>Species</strong></td>
<td><strong>Family</strong></td>
<td><strong>Parts Used</strong></td>
<td>** Constituents**</td>
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<tr>
<td>5.</td>
<td><em>Cinnamomum zeylanicum</em> (Lauraceae)</td>
<td>24g</td>
<td>E- Cinnamon S- Tvak H- Dalchini T- Dalchina chekka</td>
<td>Volatile oil – Cinnamaldehyde, Eugenol, camphor; phlobatannins, mucilage, calcium oxalate, starch</td>
</tr>
<tr>
<td>8.</td>
<td><em>Piper nigrum</em> (Piperaceae)</td>
<td>24g</td>
<td>E- Black pepper S- Maricha, H- Kali mirch T- Miryalu</td>
<td>Volatile oils: pinenes, camphenes, B-bisabolene, camphene, B-caryophyllene; Pungent principles: piperin, piperettin; Alkaloids: piperine, piperdine, pipernan, piperettine, piperolein A and B; Mono- and Polysaccharides: galac-</td>
</tr>
<tr>
<td>No.</td>
<td>Description</td>
<td>Content</td>
<td>Properties</td>
<td></td>
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<tr>
<td>9.</td>
<td><em>Coriandrum sativum</em> (Umbelliferae) [204-211]</td>
<td>E- Coriander S- Dhanya H- Dhaniya T- Dhaniyalu</td>
<td>Volatile oil - δ-linalool, α-pinene, terpinine, flavonoids, coumarins, Phthalides, phenolic acids, coriandrin, acetyl choline, choline.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increases intelligence, memory enhancer, appetizer, psychological disorders, epilepsy, antioxidant, bioavailability enhancer, distribution of drugs to central nervous system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.8kg</td>
<td></td>
<td>Cough, sour throat, acidity, sweetener</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Honey [212-214]</td>
<td>S- Madhu H- Shahed T- Tene</td>
<td>Fructose, glucose, some sucrose, maltose; antioxidants- chrysin, pinobanksin, vitamin C, catalase, and pinocembrin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>384g</td>
<td></td>
<td>Cough, sour throat, acidity, sweetener, diabetic ulcers, colitis, wound healing,</td>
<td></td>
</tr>
</tbody>
</table>
Images of Sources of Ingredients of Kushmanda Lehyam (Antidepressant)

Plate 2.4.30 Benincasa hispida
Plate 2.4.31 Piper longum
Plate 2.4.32 Zingiber officinale
Plate 2.4.33 Cuminum cyminum
Plate 2.4.34 Cinnamomum zeylanicum
Plate 2.4.35 Elettaria cardamomum
Images of Sources of Ingredients of Kushmanda Lehyam (Contd.)

Plate 2.4.36 Cinnamomum tamala  
Plate 2.4.37 Piper nigrum  
Plate 2.4.38 Coriandrum sativum  
Plate 2.4.39 Kushmanda Lehyam
2.6.5 ITRIFAL KISHNEEZI (IK)

IK was obtained from M/s Hamdard (Wakf) Laboratories, Ghaziabad, Uttar Pradesh, India. IK contains three kinds of *Terminalia chebula* (Myrobalan) – black Myrobalan (unripe fruit-0.435g), yellow myrobalan (fresh ripe fruit-0.435g), brown myrobalan (dried ripe fruits-0.435g); *Terminalia belerica* (0.435g); *Coriandrum sativum* (0.435g); clarified butter (0.866g) and honey (6.953g).[131-133]

**Method of Preparation:**

All the dry ingredients must be fine powdered and roasted in clarified butter, and cooled. To this cooled mixture honey should be added and mixed well, bottled and stored.

**Therapeutic Uses:**

IK is used in unani for chronic catarrh, gastric problems - flatulence, indigestion, hyperacidity; head ache, eye pain and as a stimulant.

**Dose:** 10g (1tsp) at bed time.

The chemical constituents and uses of individual ingredients are mentioned in the following Table 2.4.4 followed by their photographs.[31-36,87-97,108-113,204-214]
### Table 2.4.4 ITRIFAL KISHNEEZI (Antidepressant) Ingredients: [31-36,87-97,108-113,204-214]

Each 10g contains

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Ingredients / Scientific name</th>
<th>Vernacular names</th>
<th>Chemical Constituents</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Terminalia chebula</em> (Combretaceae) [87-93,108-113]</td>
<td>E- Myrobalan (Black, yellow, brown) U- Haleela (siyah, zard, kabuli) H- Harad T- Karakkai</td>
<td>Shikimic, gallic, triacontanoic and palmitic acids, beta-sitosterol, daucosterol, chebulic acid, ellagitannin, terchebulin, punicalagin teaflavin A, phloroglucinol, pyrogallol, ferulic, vanillic, p-coumaric and caffeic acids, chebupentol, arjungenin,</td>
<td>Flatulence, constipation, diarrhoea, dysentery, cyst, digestive disorders, vomiting, enlarged liver and spleen, cough and bronchial asthma, metabolic harmony, diuretic, antioxidant</td>
</tr>
<tr>
<td>4.</td>
<td>Clarified butter from cow [31]</td>
<td>U- Ghee H- Gai ka ghee T- Avu neyyi</td>
<td>Saturated fats, triglycerides, diglycerides, monoglycerides, phospholipids, β-carotene, Vitamin E</td>
<td>Increases intelligence, memory enhancer, appetizer, psychological disorders, epilepsy, antioxidant, bioavailability enhancer, distribution of drugs to central nervous system</td>
</tr>
</tbody>
</table>
Images of Sources of Ingredients of Itrifal Kishneezi (Antidepressant)

Plate 2.4.40 Embelica officinalis
Plate 2.4.41 Terminalia chebula
Plate 2.4.42 Terminalia bellerica
Plate 2.4.43 Coriandrum sativum
Plate 2.4.44 Itrifal Kishneezi
2.6.6 Barleria Cristata Linn. (BC)

*Barleria Cristata* Linn. (Acanthaceae) is a hairy shrub (60-100cm) found widely in subtropical Himalaya, Sikkim, Khasi Hills, Central, and Southern India at a height of 1,350m. It is also grown as ornamental plant. The common names are Philippine violet, crested purple nail dye (English), sahachara (Sanskrit) and decemberalu (Telugu).

**Morphology:**

*Leaves:* are elliptic-oblong to lanceolate, ciliate, acute, attenuate base, 6-7 pairs of lateral nerves, dark green upper surface and light green lower surface.

*Flowers:* purplish-pink, violet or white.

The plant is used traditionally for cough, diabetes, inflammation, as stimulant and demulcent. The leaves are chewed in toothache.[215] Barleria cristata plant has flavonoids type phenolic compounds, especially apigenin, quercetin, quercetin-3-O-β-D-glucoside, naringenin, luteolin, and apigenin glucuronide. Roots have anthraquinones.[32-34]

Though several activities of other species of Barleria viz., *Barleria prionitis* are extensively studied, BC is relatively very less studied. The plant is shown to have anti-inflammatory activity[216] and useful in snake bites.[217] The traditional use of BC as a stimulant encouraged to study the antidepressant activity of this plant. The plant was procured from the forests of Tirupati and authenticated by Dr. K. Madhava Chetty, Assistant Professor, Department of Botany, S.V. University, Tirupati, Andhra Pradesh, India. A specimen voucher **SUCP/SP/2009/3** is
deposited in the herbarium of Sultan-ul-uloom College of Pharmacy, Hyderabad, Andhra Pradesh, India.

The plant material was shade dried, pulverized and extracted in methanol using soxhlet extractor and concentrated. The semisolid mass was then placed in a desiccator and stored in refrigerator. The percentage yield was 57.3%. The extract was studied for acute toxicity in rats, neuropharmacological profile using Irwin test in mice and antidepressant activity in rats and mice.

Photographs of BC, fresh plant, its flowers and crude drug are shown in Plate 2.4.45.

*Images of Barleria cristata Linn.*