CHAPTER – 1
INTRODUCTION & REVIEW OF LITERATURE
PART – 1: DEPRESSION

Depression: It is basically acknowledged as illness with symptoms such as anxiety and sleep disturbances (Stahl S.M. 2000). It can be a persistent, recurring illness that can cause many personal suffering for individuals and their families. At present, disability caused by depression is estimated to be the fourth most important cause of worldwide loss of life years (Mulrow C.D., et al., 1998). This has resulted into a requirement of search for effective treatments, including antidepressant drugs, herbal remedies, psychotherapy and electroconvulsive shock therapy.

THE NEUROBIOLOGY AND PHARMACOLOGY OF DEPRESSION

I. Neurotransmitter Systems

Within the central nervous system (CNS), the catecholamines, adrenaline, noradrenaline and dopamine forms the adrenergic systems. Out of these, few of the adrenergic neurons are radiating from the ancient limbic system and plays to role of discharging the catecholamines within the frontal cortex. Thus, the catecholaminergic pathways are claimed to be responsible for mood, alertness and stress responses. The primary neurotransmitter, which modulates the excitatory catecholamine systems of the CNS is Serotonin. The Serotonin neurons are responsible for the control of memory, mood, sex drive and appetite (Stahl S.M., 2000).

The systems of serotonin and noradrenaline are the important their main cell small bodies in brainstem areas that serve as headquarters for shipping axonal projections by the brains in specific pathways that mediate specific functions (See Figure No. 1 for an illustration of the serotonin projections and Figure No. 2 for an illustration of the noradrenergic projections).

Multiple serotonergic and noradrenergic pathways may be dysfunctional in depression, generating many different symptoms (Stahl S.M., 2000).
The nuclei of the dorsal raphe projects the serotonin system and the raphemagnus. The serotonin receptors (5-HT) have been identified into various sub-types with the 5-HT1 and 5-HT2 sub-types being of greater interest in psychiatry. The most important of the 5-HT1 subclass is 5-HT1A which is concentrated in the hippocampus and raphe. The release of this 5-HT from presynaptic neurons is
modulated by this autoreceptor. The 5-HT2 receptors occur in high concentrations in the frontal cortex and nucleus accumbens (Van Oekeilen D., et al., 2003).

II. Hypotheses of Depression

Several hypotheses of the biological determinants of depression have emerged over the past century. The most important of these and the implications thereof are reviewed below. Today it is generally accepted that depression is not necessarily due to a shortage of one vital brain neurotransmitter, but rather to a disruption in the equilibrium between different regulatory systems.

A. The Biogenic Hypothesis of depression

The most common characteristic of depression as claimed by monoaminergic hypothesis are a result of inadequate concentration of serotonin and noradrenaline in the synaptic clefts of the neurons in the brain (Cord A.A., et al., 2001). This hypothesis has evolved to consider the possibility that depression may be the result of a deficiency in signal transduction from the monoamine neurotransmitter to its postsynaptic neuron, even with normal levels of neurotransmitter and receptor being present (Stahl S.M. 2000). Emerging theories that link genetic and environmental risk factors for depression suggest that stress can cause depression by down-regulating certain genes, resulting in less key gene products, such as the brain-derived neurotrophic factor (BDNF), being produced. BDNF sustains the viability of neurons, so if the encoding gene is repressed the result may be atrophy or even apoptosis of neurons (Stahl S.M., 2000).

B. The dopamine hypothesis of depression

The original hypothesis was formulated in the late nineteen seventies by Solomon Snyder and linked schizophrenia with dopamine (DA) activity. Later, this hypothesis was extended to include depression following the observation that many antidepressants influence the metabolism of dopamine. Following chronic antidepressant treatment, the presynaptic DA receptors become subsensitised and this gets in an enhancement of DA release. A reduction in homovanillic acid (HVA), the main metabolite of dopamine, in the cerebral spinal fluid (CSF) of depressed patients who demonstrate marked motor retardation has also been reported (Van Praag H.M., 1982).
Therefore, a decrease in the ratio of HVA to DA is indicative of decreased turnover of DA. This hypothesis is also supported by reports of significantly reduced dopamine turnover in depressed suicide victims (Bowden C., et al., 1997).

C. The permissive hypothesis of depression

This hypothesis emphasizes 5-HT as a neuro-modulator and its importance as a focus for antidepressant action. According to this theory, a lowered concentration in the central nervous system (CNS) of 5-HT results in an affective state regulated by NA. Decreased 5-HT and NA levels will give rise to depression. This averages that 5-HT may act as a ‘permissive’ modulator of neurotransmitter function through connections between serotonergic pathways and make connections with noradrenergic and dopaminergic pathways via the associated receptors (Harvey B.H., 1997).

D. The glutamatergic N-methyl-D-aspartate hypothesis

As per recent researches, one of the important roles involved in the mechanism of depression is dysfunction of CNS glutamatergic pathways. Many of the researches confirm that the compounds, which induce reduction in the activities at the N – Methyl – D – Aspartate receptors produce effects similar to pharmacologically active antidepressants. Hence, it is assumed that the common pathway affected by antidepressant drugs, whenever there are adaptive changes in NMDA receptor complex (Heresco-Levy and Javitt, 1998).

E. The kynurenine hypothesis

This hypothesis emerges from the premise that depression arises from altered levels of serotonin (5-Hydro. Trypt.) in the mind. Serotonin is a metabolite of the essential A. A. tryptophan (TRP) and all 5- Hydro. Trypt required by the neurons in the brain is synthesized in the brain because 5- Hydro. Trypt is unable to cross the BBB. Therefore, the availability of TRP is essential for the synthesis of 5-HT in CNS. There are several factors which affect the production and transport of TRP from the blood stream into the CNS, in which deficiency of Vit. B6, Stress, escalated cortisol levels and even high doses of TRP (2000m.g. of TRP). These are the factors simulating the conversion of TRP into kynurenine, which further results into reduced TRP level (Green A.R., et al., 1980). Therefore, the inhibition of liver enzyme tryptophan 2,3-
dioxygenase (also known as tryptophan pyrrolase) during the first and rate-limiting step of the pathway of kynurenine would enhance circulating levels of TRP and thereby lead to increased neural production of 5-HT (Badawy A.A.B., et al., 1981).

### III. Treatments for Depression

MAOIs & tricyclic antidepressants (TCAs) were launched as the drug products approximately 60 years ago. These were found to have many side effects and to be highly toxic in the treatment of depression. This resulted into introduction of the selective noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), which are better tolerated and safer. However, these have not been shown to be conclusively superior to the TCAs and MAOIs (Muller W.E. and Kasper S, 1997).

The chemical structures of antidepressant drugs vary significantly and therefore cannot be considered to be the most important factor in the search for new drugs with antidepressant activity. However, the mechanism of action of these drugs has provided insights into the pathology of depression. The basic biochemistry and possible Mode of action of major categories of antidepressant drugs are discussed below.

#### A. Tricyclic Antidepressants (TCA)

These drugs all have a characteristic three ring structure (See Figure No. 3) and are chemically similar to the phenothiazines. The discovery of their antidepressant action was fortuitous when imipramine, originally considered as a neuroleptic was found to have antidepressant activity.

Thereafter, first generation antidepressants emerged which display activity as mixed noradrenaline and serotonin reuptake inhibitors (Hollister L.E. and Potter W.Z., 1998). The reuptake of monoamine neurotransmitters into the presynaptic neuron is inhibited by many of the TCAs by competitive inhibition of the ATPase in the membrane pump. Some TCAs are more selective than others but this has not been shown to influence the efficacy of the drug (Waller D.G., et al., 2001). The different monoamine reuptake properties can also include an increase in dopaminergic activity via a presynaptic mechanism for amitriptyline and a post synaptic mechanism for desipramine and imipramine (Besson A., et al., 1999).
The major drawback of the TCA drugs is the side effects which result from their antimuscarinic, antihistaminic and alpha adrenoceptor-blocking activity.

Figure No. 3: Chemical structures of some tricyclic antidepressants
B. Heterocyclics

Between 1980 and 1996 “heterocyclic” antidepressants were discovered. Examples of these can be seen in Figure No. 4 shown below. Amoxapine and maprotiline resemble the structure of the TCAs while trazadone is distinctly different. Maprotiline is similar to the TCA, desipramine in being a potent noradrenaline reuptake inhibitor and it has less sedative and antimuscarinic side effects. Amoxapine is a metabolite of the antipsychotic drug loxapine and displays some dopamine receptor antagonism. Trazadone has shown unpredictable efficacy in the clinical setting (Potter W.Z. and Hollister L.E., 1998).

Figure No. 4 Chemical Structures of Some Heterocyclic Antidepressants

C. Selective Serotonin Reuptake Inhibitors (SSRI)

Unlike the tricyclic antidepressants, the SSRIs reduce the neuronal uptake of serotonin but have no effect on noradrenaline. Therefore the SSRIs have a better side effect profile in comparison with TCAs because these drugs have a low affinity for muscarinic, histaminergic and adrenergic receptors (Waller D.G., et al., 2001).
Fluoxetine was the first SSRI to be used clinically followed by paroxetine and sertraline. The latter two have shorter half lives and different potencies as inhibitors of specific P450 isoenzymes (Potter W.Z. and Hollister L.E., 1998). The chemical structures of these SSRIs are shown in Figure No. 5 below.

**Figure No. 5: Chemical Structures of Some SSRI Antidepressants**

**D. Monoamine Oxidase Inhibitors (MAOI)**

The mechanism of action of MAOIs is complex, but their primary action is to inhibit the enzyme, monoamine oxidase (MAO), which is responsible for degrading free monoamines. There are two isoforms of MAO, designated MAO-A and MAO-B, with MAO-B being the predominant in many parts of the brain. MAO inhibitors have many side effects, but recently the reversible MAO-A inhibitor, moclobemide, was introduced which has fewer side effects (Waller D.G., *et al.*, 2001). Today, many people are searching for natural remedies to overcome depression. These have fewer side effects and are easily obtainable.
In general, depression is belongs to the group of most common psychological disorders. It is a heterogeneous disorder that has been characterized and classified in a variety of ways. Affective disorders are characterized primarily by change of mood (depression or mania) rather than by thought disturbance (Rang, et al., 1999). Depression may vary from a mild condition to severe depression known as psychotic depression including delusions and hallucination (Katzung, 2000).

In the brain, the functional deficit of monoamine transmitters results into depression (as explained by biochemical theory of depression i.e. "monoamine hypothesis"). All currently available antidepressants act by re-uptake or selective receptor antagonism of serotonin, norepinephrine or both (Rang, et al., 1999). According to WHO (World health Organization), as per estimations, approximately 350 million people are suffering from depression (Web – 1). There are five main categories of antidepressant drugs: ‘Tricyclics’ (TCA), ‘Serotonine and Nor epinephrine Re uptake inhibitors’ (SNRIs), ‘Select. Serotonine Re uptake Inhibitors’ (S. S. R. I.), ‘Noradrenaline & Specific Serotoninergic Antidepressants’ (NASSAs), Monoamine oxidase inhibitors’ (MAOIs) (Web – 2)

The most commonly prescribed drug for depression such as imipramine, desipramine, fluoxetine etc. nowadays have been limited due to their potential side effects like anorexia, ant cholinergic effect (drug mouth, constipation, blurred vision, urinary retention), cardiovascular collapse, diarrhea, difficulty in concentrate, dizziness, drowsiness, dysphoria, dysrhythmas, epigastic distress, excessive central stimulation (excitement, convulsions), hypothermia, hypotension, insomnia, liver damage, loss of libido and failure of orgasm, mania, metallic taste, nausea, palpitation, postural hypotension, restlessness, sedation, seizures, tachycardia, tremor, weakness and fatigue, weight gain, and many other (Rang, et al., 1999; Katzung, 2000; Baldessrini, 1998).

Therefore people are reverting back to herbal preparation since the data provided by herbal professionals and the health care policy makers have found the herbal product exhibit high levels of satisfaction.

1.2 MOOD DISORDERS AND MANIFESTATIONS IN CLINICAL PRACTICE.
Mania and major depression are two extremes of affective disorders. Major or melancholic depression displays symptoms like melancholia, change in appetite and sleep, low energy, guilt, sad mood, psychomotor retardation, loss of interest and pleasure and suicidal thoughts. Mania manifests itself as elation, hyperactivity, progressive loss of contact with reality, accelerated speech or irritable mood, racing thoughts and violent behavior. In bipolar disorders opposite cycles of mood swings occur in the patient from depression to mania.

Common psychiatric ailments encountered in routine life include mood disorders (affective disorders) and are further subdivided into bipolar disorders and depressive disorders. Major change or alteration in mood is a common characteristic feature of these disorders. Mood is a state of mind, thinking, and sustained emotion that governs a person's interaction with the society. Sudden disturbance, fluctuation or variation in the mood of a person, such as for most of the time calm and peaceful, and at other times, irritated, disturbed, or ruffled or with episodes of gloom and despair is observed.

Patients with depressive disorders might also have episodes of mania or hypomania. Mania is a state of mind whereby a person is hyperactive. Depression is opposite of mania, i.e., gloom, despair, sadness and a tendency of the patient to seek pleasure and satiety with the negative side of life. A variety of names (or classifications) are used to describe depressive disorders, such as reactive depression, neurotic, psychotic, unipolar, endogenous and exogenous, retarded and agitated, secondary or primary and so on. The use of this standardized classification has vastly improved clinicians’ ability and skill to correctly diagnose and appropriately treat depressive disorders. The depressive state which is most commonly found in today’s scenario is the major depressive disorder also called the dysthymic disorder.

Depressive disorders are a common health problem of today’s life. Depression results in disability of the patient’s interaction with the society. Only a few of the patients stick to a strict regimen of drugs complying with the side effects and duration of antidepressant treatment. Apart from this, difference between research investigations and clinical manifestations is too great in the management of depression.
A neuro-developmental model has been proposed as a possible explanation for investigating the occurrence of depressive disorders. Continuous discoveries of safe and efficacious drugs, has rendered the management of depression easy and less cumbersome. Education of physicians in the advent of recent trends may help to lessen the difference between clinical practice and research findings\(^40\).

**Fig 4 : Drug action on NA/5-HT transmission in the treatment of Depression**  
D-dopamine receptor, DOPAC-dihydroxyphenyl acetic acid

Major depressive disorder is manifested as recurrent episodes of depressed mood, social isolation (feeling of worthlessness including apathy and decreased ability to experience pleasure), and symptoms of somatic origin (decreased energy and sleep, slowing of movement with speech latency, changes in appetite and muscle pain). Major life stresss, may precipitate depressive disorder. It may also occur spontaneously. Minimum 2 weeks or even longer is the duration up to which a single depressive episode must last and must cripple the patient’s daily functions, for example personal relationships and work. An episode is not considered to be Major depressive disorder if it is due to bereavement (i.e., depressive symptoms within the first 2 months of a loved one’s death is considered normal grief) or to a general medical condition such as hypothyroidism or Cushing’s disease\(^41, 42\).

There are three clinical subtypes of Major depressive disorder: typical (or melanchonic) depression, atypical depression (which is actually more common than typical depression), and psychotic depression. In all depressed patients, it is crucial to determine whether there is any suicidality and whether there is coexisting...
psychosis. Although psychosis is more typical of bipolar disorder, severely depressed patients may become psychotic, and either suicidality or psychosis is an indication for prompt referral to a psychiatric hospitalization.  

Typical (or melancholic) depression is characterized by early morning awakening (e.g. waking up spontaneously at 2:00 AM with inability to return to sleep), decreased appetite with weight loss and marked social disengagement. Atypical depression is characterized by neurovegetative signs that are the reverse of those seen in typical depression. Patients have hypersomnia and increased appetite, particularly for high-fat/high carbohydrate foods. They are particularly sensitive to criticism (they view even innocent comments by others as intensely critical of their actions), but unlike typically depressed patients, they are capable of feeling brief periods of pleasure and indulge in pleasure-seeking behaviors such as overeating and shopping.

Psychotic depression is the least common subtype of depression and is often the most severe and disabling. SSRIs and antipsychotics are considered first line agents for this subtype of depression, but patients may require electroconvulsant therapy if the symptoms are refractory to the first line agents.

1.3 BIOLOGICAL REASONS RESPONSIBLE FOR OCCURRENCE OF DEPRESSION

Although a specific abnormality has not been discovered, however there are proofs which suggest that depression is hereditary in nature. The availability of relatively effective and selective drugs for treating schizophrenia has rendered the treatment of these disorders less cumbersome. Apart from this a variety of agents have been shown to mimic or resemble some of the symptoms of severe psychiatric problems. These include LSD, which produces hallucinations, delusions and altered mental states; antihypertensive drugs such as reserpine, and CNS stimulants, which can produce manic or psychotic conditions when taken in large amounts. This includes agents such as dexamphetamine, cannabis, methamphetamine, amphetamine etc. Observations made during therapy of antidepressants give rise to a generalization that deficiency of neuronal transmission along with alteration in the turnover of specific neurotransmitters in the synaptic nerve endings in the CNS might cause depression, whereas an excess may result in mania. Further, antipsychotic, anti
manic agents antagonize the neurotransmitter actions of dopamine in the forebrain, suggesting a possible state of functional overactivity of dopamine in the limbic system or cerebral cortex, in schizophrenia or mania. In other words it can be inferred that, an endogenous psychotomimetic compound might be produced either uniquely or in excessive quantities in psychotic patients. This leads to a “pharmacocentric” concept that has generated interest in genetic and clinical biochemical studies, and has lead to a neurotransmitter concept behind the occurrence of depression. Moreover, results of genetic studies have demonstrated that inheritance accounts for only a portion of the causation of mental illnesses, leaving room for environmental and psychological factors such as stress.

Depression is due to guilty or shameful conditions, which might be due to subconscious impressions of acts committed in childhood or young age or due to antipsychotic drugs. Catecholamines (NA, 5HT, DA) are the substances that produce CNS stimulation and hypertention. When the level of these catecholamines in our brain is reduced below the normal level the stage is known as depression.

When stimulus triggers the post-synaptic vesicles or granules, then there is release of catecholamines (neurotransmitters) that act on post synaptic receptors and after that the remaining catecholamines are reuptaken by protein transporter and α$_2$, D$_2$ autoreceptor. So the drugs that inhibit reuptake by protein transporter and autoreceptor are known antidepressant. They may be noradrenaline selective and serotonin selective reuptake inhibitors. Other category is MAO inhibitors. Monoamine oxidase is the the enzyme that is responsible for metabolism of catecholamines. so the drugs that inhibit MAO act as antidepressants. This enzyme is found in mitochondria that are responsible for metabolism of catecholamines.

![Diagram of neurotransmitter actions]

**Serotonin selective reuptake Inhibitors (SSRI)**
- fluoxetine, fluvoxamine, sertraline, paroxetine

**Tricyclic**
- citalopram, venlafaxine
Noradrenaline selective Inhibitors
(NESRI) → (Nisoxetine, reboxetine)

Antidepressants
Non selective Tricyclic (Imipramine, Desimpramine
Amitriptyline, Nortriptyline)

Irreversible (Tranylcypromine,
Phenelzine, Chlorgyline, selegiline)

MAO Inhibitors

Reversible (Moclobemide, Toloxatone)

The drugs inhibit the enzyme by two manners; one non selective irreversible inhibitors that are traditional. Others are newer selective reversible inhibitors.

Mechanism of action of MAO (Mono Amino Oxidase)

\[
\begin{align*}
\text{R} \quad \text{R} \\
\text{H-C-NH}_2 \quad \text{R-C-NH}_2 \\
\text{H-N-H} \quad \text{H-N-H} \\
\text{-Lysine} \quad \text{-Lysine}
\end{align*}
\]

MAO act by forming schiff base and then Schiff base oxidizes the amine to corresponding aldehyde, then this is converted to acid and methylated by COMT.

Side effects of maximum MAO inhibitors are irreversible, and they increase the level of pressor amines. So during therapy; the patient must not eat food that contains tyramine or other catecholamines, must not be eaten because the level of pressor will increase and causes hypertensive crises. So the drugs that inhibit the MAO enzyme in a reversible way are most widely used like moclobemide.

MAO inhibitors (non selective Irreversible)

Irreversible (Tranylcypromine,
Phenelzine, Chlorgyline, selegiline)

MAO Inhibitors

Reversible (Moclobemide, Toloxatone)
The drugs inhibit the enzyme by two manners; one non-selective irreversible inhibitors that are traditional. Others are newer selective reversible inhibitors.

**Mechanism of action of MAO (Mono Amino Oxidase)**

\[
\begin{align*}
\text{R} & & \text{R} & & \text{R} \\
\text{H-C-NH}_2 & & \text{-C-NH}_2 & & \text{CH} & & \ldots \\
\text{H-N-H} \rightarrow & & \text{H-N-H} \rightarrow & & \text{N} \rightarrow & & \text{H-N-H} + \text{RCHO}
\end{align*}
\]

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**MAO inhibitors (non-selective Irreversible)**

Iproniazid: - To increase the activity of isoniazid in tuberculosis; isopropyl group is introduced in place of H, but CNS stimulation is major side effect. So the drug is used in CNS depression and is found effective. Other drugs are Isocarboxazide, Phenelzine Pargyline and tranylcypromine.
**Selectively Irreversible**

In this category chlorgyline that is MAO-A selective and Selegiline is MAO-B selective that is useful in Parkinson’s disease.

Reversible inhibitors of MAO (RIMA):-these types of drugs inhibit the MAO enzyme reversibly so these are most widely used because there is no risk of hypertensive crisis. The drugs are moclobemide and toloxatone that are MAO-A selective. In this type of therapy there is no need to control the level of tyramine containing diet.

Pharmacological action of these drugs start after 2-3 week and there are many side effects. Therapy of antidepressant drugs are slow and take one or two week for initiation.
**Tricyclic antidepressants (TCAs)**

These drugs contain the tricyclic ring system that is different from antipsychotic drugs. Antipsychotic drugs posses planner symmetric tricyclic ring while antidepressant drugs possess asymmetric antiplanner (anticlinal) tricyclic ring. There are two types of rings; dibenzoazepine and dibenzocycloheptadiene.

**Tricyclic non selective (NA, 5HT) reuptake Inhibitors**

There are two major categories:

**Tricyclic antidepressant (TCA)**

- Dibenzoazepine Derivatives
  - R=CH₃, Imipramine
  - R=H, Desipramine

- Dibenzocycloheptadiene Derivatives
  - R=CH₃, Amitriptyline
  - R=H, Nortriptyline

When side chain contains tertiary amine like imipramine and amitriptyline then the drugs show selective serotonin reuptake inhibitor activity. When side chain contains secondary amine like desipramine then TCAs shows selective noradrenaline reuptake inhibitor activity. Other drugs like amoxapine that is dibenzoazepine derivative and doxepin acts as atypical antidepressant.
Amoxapine is N-demethyl derivative of antipsychotic drug loxapine.

**Synthesis - Dibenzoazepine**

- R = -(CH₂)₃-N(CH₃)₂  Impiramine
- R = -(CH₂)₃-NHCH₃  Desmpiramine
- R = -(CH₂)₃-N(CH₃)₂  Clomipiramine

and 3-Chloro

[5-{3-dimethylamino propyl-10,11 dihydro dibenzo(b,f)azepine]

**Synthesis - Dibenzocycloheptadiene**

- R = -(CH₂)₃-N(CH₃)₂  Amitriptyline
- R = -(CH₂)₃-NH-CH₃  Nortriptyline

Selective serotonin (5HT) reuptake inhibitors: these are fluoxetine, paroxetine, sertraline, fluvoxamine and citalopram. Fluoxetine shows geometric isomerism and E-form is active.
Selective noradrenalin reuptake inhibitors:

Nisoxetine
Reboxetine

Newer non selective (5-HT selective) reuptake inhibitor: - vanlafaxine

Selective serotoninergic reuptake inhibitors and 5-HT2A antagonist: - trazadone

1.3.1 Monoamine Theory.
It suggests that depression results from functionally deficient mono-aminergic (NA and or 5 HT) transmission in the CNS. The theory was based on the ability of known antidepressant drugs (TCAs and MAOIs) to enhance monoamine transmission. Drug therapy of depression aims at increasing monoamine activity by either inhibition of amine destruction (MAOIs) or by increasing release or preventing amine-reuptake (tricyclic antidepressants, TCA and selective serotonin re-uptake inhibitors; SSRIs). Biochemical studies on depressed patients do not, in general, support monoamine hypothesis in its simple form, though pharmacological manipulation of monoamine transmission remains the most successful approach.\(^{55}\)

The antipsychotic, anti-anxiety, anti-manic, anti-stress or antidepressant drugs have effects on cortical, limbic, hypothalamic, and brainstem areas, of brain that are important in the regulation of arousal, consciousness, motor, sensory and autonomic functions. Physiological, pharmacological and biochemical modifications of these brain regions may have important behavioral consequences and useful clinical effects regardless of the underlying cause of any mental disorder. The lack of diagnostic or even syndromal specificity of most psychotropic drugs decreases the chances of finding a discrete metabolic abnormality for a particular or a specific psychiatric ailment. Finally, technical problems in studying changes in brain metabolism in vivo or the postmortem chemistry of the human brain are many. Amongst these are artifacts introduced by drug treatment itself. It also includes degenerative changes brought in the brain of a patient by prolonged psychiatric treatment spanning many years.\(^{56}\)

Thus there is a sure and definitive link between discrete biological lesions and the pathogenesis of most mental illnesses (other than delirium and the dementias). Even without such a link, effective medical treatment can be provided for psychiatric patients. It is inappropriate to underestimate the importance of physiological & socioeconomical factors in the manifestation of brain illnesses, or to overlook psychological aspects of the conduct of biological therapies which also includes patient counseling.\(^{57,58}\)

### 1.4 ETIOLOGY OF DEPRESSIVE DISORDERS

Numerous studies have shown neuropsychological abnormalities as early as in four years of age in individuals who later develop depression. The etiology of depressive disorders is very complicated and difficult to explain. A variety of reasons cause depression. In case of major depression there is an alteration in the turnover of
neurotransmitters, in the brain especially dopamine, serotonin, nor-epinephrine (NE), and epinephrine. Life is filled with unexpected events that cause pain. Most individuals adjust to life's challenges and suffer only mild, mood offs, but the psychiatric patients exposed to these events experience major depressive episodes. The cause of depression is usually multifactorial; that is multiple patho-physiologic abnormalities may play a role in producing depressive states. Certain factors (e.g., stressful events, medical illnesses monoamine-depleting drugs) may place predisposed individuals, especially people having a history of depression in their family, at a high risk for developing major depressive episode\textsuperscript{59, 60}.

1.5 PATHOPHYSIOLOGY

1.5.1 Biogenic amine hypothesis

The primary path physiologic abnormality in depression may occur due to an imbalance of multiple neurotransmitters in brain. The biogenic amine hypothesis came about in the early 1950s. It was noted that reserpine depleted synaptic granules of NE, 5-HT, and DA. It was discovered that the hallucinogenic agent, lysergic acid diethylamide (LSD) blocked peripheral serotonin receptors. The mind-changing actions of LSD were considered secondary to similar effects on central nervous system due to serotonin. However, this early hypothesis failed to explain the actual cause of depression. Although reuptake blockade of monoamine oxidase (MAO) inhibition receives quickly on oral route of an antidepressant, the antidepressant effect of drugs are not reveals in patients upto 4 weeks of treatments. Understanding the precise path physiology of depression requires further research, perhaps with a focus on the adaptive changes induced by antidepressants\textsuperscript{61}.

1.5.2 PERMISSIVE HYPOTHESIS OF DEPRESSION

In the early 1970s, Orange and his colleagues postulated the permisive hypothesis of depression, regarding possible role of both NE and 5-HT levels which permit the expression of the depressed phase. Decreased NE and 5-HT levels cause depression, and elevated NE levels cause mania. According to this hypothesis, correcting the deficiency in 5-HT activity corrects the affective disease\textsuperscript{62}.

1.6 THEORIES INVOLVING POSTSYNAPTIC CHANGES IN THE BRAIN

Depression is a complex disorder and occurs due to changes involving the content of a variety of neurotransmitters in synapses in the human brain. A more perplexing
aspect of the observed effects of antidepressants is the discrepancy between monoamine reuptake blockade (immediate) and any measurable improvement in depressive symptomatology (delayed). It has been established in numerous studies that longer, but not short, administration of antidepressants to animals causes desensitization of NE-stimulated cyclic AMP synthesis. In fact, for most antidepressants, down regulation of β-adrenergic receptors accompanies this desensitization.

Studies of many antidepressants have demonstrated that either desensitization or down regulation of NE receptors corresponds to a clinically relevant time course for antidepressant effects. Other studies have revealed a down regulated state of 5-HT$_2$ receptors produced by prolonged administration of antidepressants.

1.6.1 Dysregulation hypothesis of depression
Such findings incorporate the difference in antidepressant property and alterations happening by virtue of sensitization of receptor over several weeks. In this theory, emphasis is placed on a failure of homeostatic mechanism or a change in its activities. According to this hypothesis, effective antidepressant agents restore efficient regulation to the dysregulated neurotransmitter system.

1.6.2 5-HT/NE Link Hypothesis
There is concrete proof that the serotonergic nerve endings are altered in depression. The 5-Hydroxy Tryptamine /Nor Epinephrine hypothesis postulates that serotonergic, adrenergic and noradrenergic nerve endings must have an excess accumulation of their respective neurotransmitter to alleviate depression.

1.7 TREATMENT: DEPRESSIVE DISORDERS
Treatment aims at proper return of the patient to the mainstream of life and he should start taking interest in life. Although the path physiology of major depression remains elusive, the clinicians have the choice to prescribe from a variety and abundance of agents. In case of failure to obtain the desired therapeutic response the physician can change the drug.

Classification of Anti-depressant drugs
A) Reversible inhibitors of MAO-A:
- Clorgyline, moclobemide.

**B) Tricyclic antidepressants:**

a) 5 HT + NA reuptake inhibitors:
- amitryptiline, Trimipramine, clomipramine, dothiepine, Impramine, doxepin.

b) Predominantly NA reuptake inhibitors:
- desipramine, amoxapine, nortriptyline.

**C) SSRIs:**
- paroxetine, Fluoxetine, citalopram, sertraline, fluvoxamine

**D) Miscellaneous anti-depressants:**
- mainserin, venlafaxine, mirtazapine, bupropion, Trazodone etc.

**MAO (Mono Amino Oxidase)**

MAO is involved in deamination reactions of catecholamines and is an enzyme found in mitochondria. Dopamine, adrenaline, nor-adrenaline, 5-hydroxy tryptamine are the catecholamines degraded by MAO.

- MAO-A – deaminates NA and 5-HT and is inhibited by moclobemide and chlorgyline.
- MAO-B -- is inhibited by selegline^{68, 69}.
- Elevates the mood and mental set up in depressed patients, this sometimes causes mania or hypomania.
- Produces cheese reaction.

**Moclobemide:**

- selective and reversible inhibitor of MAO-A.
- Efficacy is similar to TCAs. Lacks cognitive, sedative, psychomotor and anticholinergic side effects of typical TCAs.
- Suitable for those having cardio-vascular disease and the elderly.
- Useful in mild cases of depression and phobias. Dose is 150 mg BD-TDS.

**Tricyclic Antidepressants (TCAs)**

- Imipramine – prototype TCA inhibits serotonin and nor-epinephrine reuptake in neurones.
- Interacts with histaminic H\textsubscript{1}, 5-HT\textsubscript{1}, 5-HT\textsubscript{2}, occasionally D\textsubscript{2}, muscarinic, alpha adrenergic receptors.
Newer SSRIs and antipsychotics interact very less with other receptors, exhibit fewer side effects and have more selective actions.\(^70\).

**Pharmacological actions**

1) **CNS:** sedation is seen in depressed patients. TCAs produce mood elevation after 2-3 weeks of regular administration. For depressed patients showing anxiety and agitation more sedative drugs are useful. TCAs might produce seizures. Should be carefully given to patients having epilepsy.

**Mechanism of action:**

- Active uptake of pressor amines into their respective neurons is inhibited by TCAs which potentiate their action.
- DA uptake is inhibited by bupropion.
- Therapeutic effect takes few weeks to develop but blockade of uptake of pressor amines takes place immediately.
- Initially the presynaptic \(\alpha_2\) and 5 HT\(_1\) auto receptors are activated and result in decreased firing of serotonergic and NA neurons.
- On long term administration TCAs lead to increased monoaminergic transmission and desensitize 5 HT\(_1\) auto receptors and presynaptic \(\alpha_2\) receptors.\(^71\).
- **ANS:** some have weak H\(_1\) blocking property as well however most are potent anticholinergics, - trimipramine, doxepin, amitriptyline.
- **CVS:** Lethal at high doses and prominent effects at therapeutic concentrations.
- Arrhythmia, Tachycardia, postural hypotension seen in overdose.
- SSRIs are safer and better. Elderly people are at risk when treated with TCAs.

**Dependence and tolerance.**

- Anti-dopaminergic action is sustained however tolerance to anticholinergic and hypotensive actions develops slowly.
- Gradual withdrawal is necessary. Do not carry abuse potential but produce mild physical dependence.
Pharmacokinetics

- TCAs are well absorbed after oral administration.
- Strongly bind to plasma proteins and distributed in all tissues.
- Metabolized in liver by CYP1A2, CYP2D6 and CYP3A4 etc. Common drugs are desmethylinipramine, imipramine, noramitriptyline, amitriptyline.
- Half life of doxepin, imipramine and amitryptiline is longer – once daily dosing.
- Therapeutic window phenomenon is seen at a dose of 50-200 ng/ml in amitryptiline, nor-tryptiline and imipramine.\(^2\)

Adverse effects

- Discomfort due to anticholinergic effects is seen.
- Weakness, confusion and sedation are seen in doxepin, trimipramine and amitryptiline.
- Weight gain and increased appetite – except SSRIs and bupropion.
- Bipolar illness is unmasked.
- Fine tremors and sweating.
- Seizures might be produced in epileptics – SSRIs and desipramine are safer.
- Postural hypotension is observed.
- Most of TCAs produce cardiac arrhythmias.

Acute poisoning

- Mostly suicidal and frequently observed.
- Muscle spasms, delirium, excitement, tremors, convulsions, coma. Respiratory depression, hypotension, ventricular arrhythmias and tachycardia, seen in poisoning with TCAs.
- Treatment includes providing respiratory support, performing gastric lavage, administration of intravenous diazepam, fluids and lignocaine or propanolol should be used for prevention and treatment of arrhythmias.

Interactions

- TCAs potentiate the actions of CNS depressants.
Aspirin, chlorpromazine (CPZ), phenytoin and phenylbutazone can displace TCAs from their protein binding sites.

Some enzyme inducers and carbamazepine can enhance the metabolism of TCAs.

Combination of SSRIs with TCAs leads to dangerous toxicity.

**Amoxapine**

- Amoxapine has additional D\textsubscript{2} receptor blocking property. Apart from inhibiting NA uptake.
- Patients of psychotic depression can fully avail the benefits of TCAs.

**Selective serotonin reuptake inhibitors (SSRIs)**

- Better therapeutic action profile than TCAs (tricyclic antidepressants).
- Less cardiovascular neurological and anticholinergic side effects.
- Low safety of margin compared to TCAs.
- Do not exhibit α-receptor blocking property.
- Do not exacerbate arrhythmias or seizures. No weight gain associated with use of SSRIs.\textsuperscript{73}
- Ecchymosis and epistaxis might be produced at high doses.
- Plasma levels of 3A4 and CYP2D6 noted. Might elevate the blood levels of clozapine, warfarin, β blockers, TCAs and haloperidol.
- Prolonged use is associated with development of tolerance to its adrenergic actions.

**Fluoxetine**

- 2 days of half life. Is the longest acting SSRI.
- In children elder than 7 years it is used for OCD and depression.
- In poorly compliant patients it is suitable for maintenance therapy.
- Therapeutic dose is 20-60 mg/day
- Mild side effects include insomnia, diarrhea, nervousness, anorexia and restlessness.
**Fluvoxamine**
- Shorter half life than fluoxetine.
- Nauseating is the most commonly seen discontinuation reaction.
- Very useful in anxiety disorders and obsessive compulsive disorders.

**Paroxetine**
High side effects of the gastrointestinal tract.

**Citalopram**
- Therapeutic profile similar to sertraline, should be avoided in patients with suicidal tendencies. Dose is 20-40 mg/day.

**Mechanism of action of SSRIs.**
- SSRIs block the reuptake of serotonin into the presynaptic cells. And augment the level of serotonin at synapses, and display delayed onset of action.\(^7^4\).

**Other uses of SSRIs**
- First choice of drugs for panic disorders, eating disorders, obsessive compulsive disorder, and social phobias. Also displays anxiolytic effect.

**Atypical antidepressants**
- Atypical antidepressants also named heterocyclics contain the following drugs.
  - Bupropion
  - Venlafaxine
  - Nefazodone
  - Tianeptine
  - Trazodone
  - Maprotiline
  - Mainserin
  - Mirtazapine

**Mechanism of action**
- The reuptake of NA, 5 HT and dopamine is blocked by all the atypical antidepressants except Bupropion which is a phenylethylamine compound inhibiting the reuptake of dopamine.
- For resistance cases of depression, Trazodone is a very useful drug.\(^7^5\)
- Atypical antidepressants differ from TCAs in
  - Less anticholinergic and sedate action.
  - Overdose does not cause acute toxicity.
  - Efficacy in patients showing non-compliance to other drugs.

**Trazodone**

- Shows weak 5-HT₂ antagonistic action, selective 5-HT uptake blocking action and a prominent alpha receptor blocking agent.
- Suitable for elderly, may cause priapism in few cases, no distressing anticholinergic actions, less sedative and less likely to cause arrhythmias.
- Does not exacerbate epileptic seizures.
- 50-200 mg/day.

**Mainserin**

- Increases turnover and release of NA in brain by blocking presynaptic alpha 2 receptors Mainserin does not inhibit NA or 5-HT reuptake.
- Suppresses panic disorders, is sedative in action, may cause blood dyscrasias, relieves associated anxiety and might produce liver dysfunction.
- 30-100 mg/day.

**Tianeptine**

Believed to increase rather than block the reuptake of 5-HT 76.
- Does not produce sedation or drowsiness.
- Beneficial in endogenous depression and anxiodepressive states.
- Produces insomnia, tremors, dry mouth, flatulence epigastric pain and body ache.
- 12.5 mg BD-TDS.

**Venlafaxine**

- A Novel antidepressant drug.
- Does not interact with histaminic, cholinergic or adrenergic receptors.
- Side effects include vomiting, dizziness, nausea, anxiety and impotence. Dose is 75-150 mg/day

**Mirtazapine**

- Serotonin and norepinephrine release is enhanced.
- An antidepressant which is specifically serotonergic.
- It is not antidopaminergic nor anticholinergic and displays sedative property.
- Dose is 15-45 mg/day.

**Bupropion**

- A nor-epinephrine and dopamine reuptake Inhibitor.
- No sedative property, however displays excitant action. May be used in smoking cessation.
- Can cause agitation, precipitation of seizures, dry mouth and insomnia
- 150 mg BD.

**Uses**

Very useful in the treatment of endogenous (major) depression.
Front line agent in the treatment of obsessive compulsive disorders and phobias.
- A useful drug in the management of bullima, kleptomania and compulsive buying.
- Also useful in the treatment of melancholic depression
  for exacerbations of generalized anxiety disorders they may be used along with BZDs
- Neuropathic pain, diabetic and other vague pains and aches are considerably relieved by Buprapion

**Anti-Manic – Mood Stabilizers**

- Carbamazepine, atypical antipsychotics, lithium carbonate and divalproate are the front line drugs
**Lithium carbonate**
- Frontline drug in the management or prophylaxis of mania in bipolar manic depressive illness.

**Action and mechanism**

1) CNS
- When given for 1-2 weeks, acute mania is gradually suppressed. Continuous treatment resolves cyclic mood changes. Lithium interferes with Na\(^+\)-K\(^+\)ATPase pump and replaces Na\(^+\) ions in body.

2) Other actions
- A diuretic like state, with frequent urination is produced.
- Lithium increases the count of leucocytes.
- Glucose metabolism is increased

**Pharmacokinetics**
- Lithium is eliminated by kidneys and well absorbed from GIT.
- Lithium is secreted in mother’s milk. It is not metabolized and produces late onset of therapeutic effect.
- Whenever blood serum levels of Lithium increases above 1.5 meq/l adverse effects are produced.

**Adverse Effects**
- Vomitting, loose motions and diarrhea.
- Polyuria and dryness of mouth.
- At therapeutic blood levels tremors of extremities and sometimes fits are produced.

**CNS toxicity**
- Coarse tremors, giddness, ataxia, motor incoordination, nystagmus, confusion, slurred speech, hyper reflexia. Seen at 1.5 meq/l or more.
- Acute intoxification – symptoms progress to muscle twitching, drowsiness, delirium, coma and convulsions. Also hypertension, cardiac arrhythmias.
- Treatment includes – osmotic diuretics and sodium bicarbonate infusion, diabetes insipidus occurs on long term treatment.
- Lithium is contraindicated in pregnancy.
- Lithium is not given to patients having sick sinus syndrome.

**Uses:**

1) Acute episodes of mania.
   Response is slow to develop, IM neuroleptic help to treat the acute episode, Li is continued for next 6-12 months after the attack of mania.
   - 600 mg/day - 1200 mg/day\(^{81}\)

2) For bipolar disorders prophylaxis.
   Mania as well as depression attacks are blunted.

3) recurrent neuropsychiatric maladies, cluster headaches and nonbipolar major depression resolve well with the use of Lithium

### 1.7.1 Non-pharmacologic therapy

Apart from prescribing drugs, the patient should also be assessed by psychotherapy, and counseling should be provided about the spheres of life in which the patient is facing problem with. This strategy can also be employed in case of severe and/or psychotic, major depressive disorders. Combined treatment may be advantageous for patients with partial responses to single therapy for those with a chronic course of illness. However, for uncomplicated, non-chronic major depressive disorders, combined treatment may provide no unique advantage.\(^{82,83}\) The patient should be under observation with one of the family member so that he could not feel loneliness and do not go for suicide. Good company of patient change negative thinking of person and feel pleasure. Positive thinking changes the behavior of the patient. Playing games with patient make some positive attitude of the patient. Some psychological idea may change mood of the patients\(^{84,85}\).

#### 1.7.1.1 Electro-convulsive therapy

Other means of treating depression include ECT and light therapy. Patients are candidates for ECT when fast recovery is required; risks for other treatment
outweighs potential benefits, and when the patient expresses a preference for ECT. ECT is effective and safe in all types of depressive conditions\textsuperscript{86}.

Several conditions must be considered in the administration of ECT to patients of depression. These include age of the patient, his general health, or if the patient is suffering from any other concomitant illness such as hypertension, diabetes, or unstable vascular condition and so on. The use of an anesthetic as well as non-depolarizing neuromuscular blocking agent decreases the morbidity associated with ECT\textsuperscript{87}.

1.7.1.2 Light therapy

Some individuals experience depressive episodes during a particular season. This is referred to as seasonal affective disorder (SAD) and occurs most commonly in winter, with remission in spring or summer. Reduced environmental light during winters, as in cold countries may precipitate depression. It has been assessed that depression might also occur due to a disturbance of the circadian rhythm which might be caused by de-synchronization of the biological clock of the body. Bright-light therapy is used to resynchronize the disturbed rhythm. The patient looks into a light box in the morning or evening for approximately 2 hours. Some individuals require antidepressant therapy in addition to light therapy or antidepressants for non-seasonal episodes of major depression\textsuperscript{88}. The light therapy generally is easily tolerated by the patient with very few complaints of adverse effects. Consequently, anyone undergoing light therapy should receive baseline and periodic eye examinations\textsuperscript{89}.

Increasingly, people are turning to alternative forms of therapy, such as herbal medications. Several evaluations have found that the main ingredient present in St. John's wort is a safe and useful measure to treat depression. Side effects appear to be mild. Although this may allow certain advantages such as reduced cost of therapy and self-treatment, it also has the potential to result in circumvention of the health care system. St. John's wort undergoes large amount of drug interactions with HIV medications (e.g., indinavir) and digoxin. A single-source product should be used continuously from a reputable and trusted manufacturer\textsuperscript{90}.

1.7.2 Pharmacologic therapy
Antidepressants are classified in many ways. One way is by the category to which they belong.

1.7.2.1 Mixed, serotonin and nor-epinephrine reuptake inhibitors
Among the TCAs imipramine and amitriptyline have been extensively studied. Maprotiline and amoxapine are both inhibitors of nor-epinephrine reuptake, having less influence on reuptake of 5-HT. Maprotiline has high incidence of seizures than imipramine or amitriptyline. Amoxapine is less sedating than some antidepressants, blocks cholinergic receptors, causing clinically significant anti-cholinergic effects.

1.7.2.2 Selective serotonin reuptake inhibitors
The impetus for the development of the SSRIs was the perceived need for development of antidepressants with improved efficacy. There is ample evidence which shows that SSRIs are very effective in treating all forms of depression especially the melancholic type. As a class, the SSRIs cause minimal to low anti-cholinergic effects.

SSRIs are useful drugs in treating all categories of depression, and have a low rate of discontinuation because of very nominal adverse effect profile. The main adverse effects, which generally are mild and short lived, are gastrointestinal symptoms and sexual dysfunctioning in both men and women. Although the SSRIs as a group are known to improve the anxiety symptoms associated with depression, a few patients experience an increase in anxiety symptoms or psychomotor agitation early in treatment. The diversity of the SSRIs is evident not only in their chemical structures but also in their pharmacokinetic profiles. SSRIs are extensively bound to blood proteins (94% to 99%). The SSRIs are extensively distributed to the tissues, and with the possible exception of citalopram, may have a nonlinear pattern of drug accumulation with long-term administration.

1.7.2.3 Selective nor-epinephrine reuptake inhibitors
The elimination half-life of reboxetine is 13 hours. Reboxetine displays linear pharmacokinetics, with elimination being primarily renal. In addition, no inhibitory effects on the isoenzymes of the cytochrome 450 system have been observed. In clinical trials to date, reboxetine has been well tolerated. Side effects seen most frequently include, dry mouth, constipation hypotension, urinary hesitancy, and
paresthesias. No significant effects on laboratory parameters, body weight, or vital signs have been noted. 

1.7.2.4 Triazolopyridines

Trazodone and nefazodone have remarkable profile in treating all types of depression especially the resistant type of depression. They also appear to enhance 5-HT$_{1A}$-mediated neurotransmission. These drugs have negligible affinity for cholinergic and histaminergic receptors. Trazodone's use as an antidepressant agent has diminished greatly, side effects (e.g., dizziness and sedation) and has increased availability of it, being used as an alternative. Nefazodone also has low affinity for α$_1$-adrenergic receptors. The adverse effect profile for nefazodone is different from that of the other antidepressants. Trazodone and nefazodone have minimal anticholinergic effects and 5-HT agonist side effects, but cause orthostatic hypotension, sedation, cognitive slowing, and dizziness are the most frequent dose-limiting side effects associated with trazodone.

1.7.2.5 Aminoketones

Bupropion, the only marketed aminoketone antidepressant, appears to have a unique mechanism of drug action. The occurrence of seizures in patients taking bupropion appears to be strongly associated with dose. At daily doses of 450 mg (the ceiling dose) or less, the incidence of seizures is 0.4%.

1.7.2.6 Mixed serotonin-nor-epinephrine inhibitors

In clinical trials of patients taking mirtazapine, the commonest complaints include weight gain, dry mouth, and constipation. In all these cases agranulocytosis and liver functions test (LFT) elevations have been reported. The incidences appear to be rare, and therefore, routine monitoring of blood indices is not recommended. Additionally, LFT elevations were observed 1.4 times more frequently than with placebo. No specific guidelines for LFT monitoring are recommended, but prescribers should consider obtaining baseline LFTs and monitoring these periodically throughout the course of therapy.

1.7.2.7 Monoamine oxidase inhibitors

Studies of several MAO inhibitors have demonstrated that, similar to the TCAs, chronic therapy causes changes in receptor sensitivity (i.e., down regulation of β-adrenergic, and serotoninergic receptors). Moclobemide is an antidepressant
marketed in India and trials of moclobemide have reported efficacy equal to TCAs and superior to placebo. MAO inhibitors display nominal side effects, and include postural hypotension; which is more likely to occur with phenelzine than with tranylcypromine. Hypotensive reactions may be minimized, through divided dosage scheduling. Anticholinergic side effects especially dry mouth and constipation, are common but are mild compared with those associated with the TCAs. Phenelzine, the most frequently prescribed MAO inhibitor, has mild to moderate sedating effects. Tranylcypromine may exert a stimulating effect, and insomnia may occur; so the last dose of the day should be administered in the early afternoon. Dose-related impotence and anorgasmia in males and orgasmic inhibition in females have been reported. In addition, fever, myoclonic jerking, and brisk deep tendon reflexes may occur. Phenelzine, a hydrazine, has been associated with hepato-cellular damage and weight gain\textsuperscript{97, 98}. Tranylcypromine is a non-hydrazine MAO inhibitor and should not be given to patients with a history of liver disease. If a MAO inhibitor is to be used, as in the past, hypertensive crises arising with concurrent use of MAO inhibitors along with foods rich in Tyramine, such as cheese were treated with, sublingual nifedipine, but recent reports of adverse events secondary to an uncontrollable fall in blood pressure and resulting rebound catecholamine release have lead to concerns over this practice. Alternative agents, such as captopril, should be considered\textsuperscript{99, 100}.

1.7.2.8 TCAs and other heterocyclics. Certain adverse effects which are commonly observed on taking TCAs often have an impact on patient tolerance and adherence. In general, anti-cholinergic effects and sedation are more severe during therapy with tertiary TCAs than with secondary. Orthostatic hypotension may be symptomatic, resulting in syncope, which usually carries an increased risk of falls and subsequent fractures. Tilting the head of the bed upward can be helpful for some patients. Adequate fluid intake should be maintained, and blood pressure should be monitored both in supine and standing positions. Antigravity support garments also can be helpful. Adequate ambulation and hydration along with proper selection, gradual dose increase, and patient education can minimize the risk of symptomatic orthostatic hypotension\textsuperscript{101, 102}. 
TCA overdose can produce severe arrhythmias. Abrupt withdrawal of TCAs is associated with symptoms such as syncope especially if the daily dose exceeds 300 mg. Amoxapine, the demethylated metabolite of loxapine, has intermediate sedative and anti-cholinergic potency. Because of its post-synaptic receptor DA-blocking effects, its use offers no advantage over standard TCAs or other antidepressants. Maprotiline, a tetra cyclic drug, blocks reuptake of NE with little effect on 5-HT receptors. It has intermediate sedative action than imipramine; however, rashes occur in approximately 4% of patients. Maprotiline displays seizures and is contraindicated in patients having epilepsy\textsuperscript{103}.

1.7.2.9 Venlafaxine
The most commonly reported adverse effects associated with venlafaxine include sweating, nervousness, dizziness, asthenia, dry mouth, abnormal ejaculation/orgasm, and anorexia. These side effects are believed to be dose related.

1.8 SPECIAL POPULATIONS
1.8.1 Elderly patients
Many elderly depressed patients are undiagnosed or inadequately treated. Diagnosis is often missed or mistaken for another disorder, such as dementia. In an elderly depressed patient, depressed mood; the typical signature symptom of depression-may be less prominent than the other depressive symptoms such as sleeplessness, anergia, loss of appetite, cognitive impairment. Somatic complaints are quite frequent in elderly depressed patients\textsuperscript{104, 105}. Before initiating antidepressant treatment, the patient should be examined for any other physical problems. Elderly depressed patients are often over or under treated. Over treatment often occurs when age-related pharmacokinetic and pharmacodynamic factors are overlooked. Under treatment often results from an overly conservative approach as a result of the patient's advanced age or concurrent medical problems. Plasma concentration monitoring for TCAs can be a useful tool for managing drug therapy in such patients. A TCA would not be an appropriate first choice for a depressed patient with cardiac conduction delay. However, in the healthy elderly, cautious use of a secondary amine TCA (e.g., desipramine or nortriptyline) is indicated because of their defined therapeutic plasma concentration ranges, well-established efficacy, and well-known adverse-effect profiles\textsuperscript{106, 107}. 
SSRIs are frontline antidepressants in the treatment of elderly, and they may enable the clinician to avoid some of the more problematic adverse effects commonly associated with the TCAs; for example sedative, anti-cholinergic and cardiac side effects. Venlafaxine, Nefazodone and bupropion and are also often chosen because of their milder anti-cholinergic and less frequent cardiovascular side effects.

Although phenelzine has been used safely and effectively in well-selected patients, the MAO inhibitors are usually reserved for treatment-resistant elderly patients, because of the availability of newer, better-tolerated agents and the hypotensive side effects of the MAO inhibitors. Dietary and medication restrictions can also be a concern.

### 1.8.2 Pediatric patients

Accumulating evidence indicates that childhood depression occurs quite commonly. Symptoms of depression in the young may vary from accepted diagnostic criteria and include several nonspecific symptoms such as boredom, anxiety, failing adjustment, and sleep disturbances. Demonstration of efficacy in children is confounded by the high placebo response rate. However, the TCAs and the SSRIs remain two viable treatment options. Toxicity in overdose is important in the adolescent population, where suicide is a major concern. Antidepressant compounds are used to treat depressed children and adolescents because no other definitive therapies are available. Plasma concentration monitoring of TCAs is important to ensure safety. As in the adult population, plasma concentrations above 450 mg/kg are associated with increased risk of serious adverse effects including delirium, seizures, delayed cardiac conduction and sudden death. A baseline electrocardiogram (ECG) is recommended before initiating a TCA in children and adolescents and many clinicians recommend an additional ECG when steady-state plasma concentrations are achieved.

Although three antidepressants are approved for use in children, none are approved for childhood depression. Imipramine is an effective drug for treatment of eneurosis and OCD. Fluvoxamine is very useful for panic disorder in young children of about 8 years of age. Anti-depressants should be initiated in this patient population at a dosage somewhat lower than in adults; however, adolescents usually require adult doses of TCAs and 6 to 8 weeks may be required before an antidepressant
response is evident. The daily dose of imipramine, if administered, should not exceed 5 mg/kg of body weight\textsuperscript{114}.

Several reviews have found that the SSRIs can be administered safely to pediatric patients (6 to 18 years of age). The dosing range and dosing titration as well as profile of adverse effects is similar to that in adults\textsuperscript{115}.

### 1.8.3 Pregnant and lactating patients

Approximately 10\% of pregnant women develop serious depression. Studies have been conducted evaluating birth anomalies, growth impairment and behavioral teratogenicity. An additional evaluation compared birth defects in neonates exposed to fluoxetine and TCAs and women exposed to agents felt not to increase the baseline teratogenic risks (such as penicillin or dental x-rays). Comparable rates of malformations have been found to occur across all three groups. However, a higher rate of miscarriages have been seen in the fluoxetine and TCA group (13.5\% a 12.2\%, respectively), when compared with the control group (6.8\%). This raises questions about the effect of depression, in addition to that of the antidepressant, on the rate of miscarriage. Studies evaluating the development of children exposed prenatally to TCAs, fluoxetine, or non-teratogens found no differences in rates of prenatal complications, incidence of major malformations, and mean global IQ scores\textsuperscript{116}.

Some concern regarding the use of fluoxetine arises as a result of an evaluation of neonates where exposure to fluoxetine occurred early, versus exposure during the third trimester (late exposure) additionally, birth weight, birth length and maternal weight gain were less in group which was exposed in the third trimester, compared with the early-exposure and control groups. Evaluations to date do not support any teratogenic effects of fluoxetine but do raise questions regarding premature birth and fetal growth rate. If a TCA is withdrawn during pregnancy, it should be tapered gradually to avoid maternal or fetal withdrawal symptoms. If possible, drug tapering is usually begun 5 to 10 days before the estimated day of confinement. Further evaluations of the new anti-depressant agents are required Additional, risks of not treating depression in a pregnant woman should not be minimized\textsuperscript{117}.

### 1.9 IN VITRO METHODS
1.9.1 Noradrenaline transport is inhibited in mice synaptic vesicles

Aims and objectives

Process of regain of nor-adrenaline from synapses is a very useful physiological system for inactivating and removing nor-adrenaline in the junctional clefts. This regain is inhibited by centrally acting amphetamines, certain MAO inhibitors like phenelizine, moclobemide, tranylcypromine, tropane alkaloids erythroxylon, coca etc. This particular mode of action is amongst the most useful and important modes of action of antidepressants.. In the cerebrum, the hypothalamus exhibits the greatest uptake and the highest level of nor-epinephrine. Thus this particular area is utilized for examining useful antidepressant agents\textsuperscript{118, 119}.

Method

Preparation of tissue for experiment

Male albino wistar rats are sacrificed and the forehead quickly removed. The hypothalamic area is formulated, weighed, and grinded in 9 parts of ice-cool 32 M glucose solution using a very recent technique in a Potter-Elvejhem homogenizer. The residue is centrifuged at 4000 revolutions per minute at 0–4 degree centigrade temperature for 10 minutes. The upper part is poured and collected in other port and utilized for further practicals.

Testing

200 µl of tissue solutions are kept in incubator with 800 µl of 62.5 nM nor-adrenaline in Krebs-Henslett buffer at 37 degree centigrade under a 95% O\textsubscript{2} and 5% Carbon dioxide atmosphere for 5 minutes. For every test, 3 tubes are kept under constant temperature with 20 µl of vehicle at 0\textdegree C in an ice bath. After incubation, all tubes are quickly centrifuged at 4000 revolutions per minute for 10 minutes. The superficial fluid is aspirated and the pellets dissolved by adding 1 ml of solubilizer (Triton X-100 + 50% ethanol, in a ratio of 1: 4). The tubes containing the solution are shaken, poured into scintillation vials and decanted in 10 ml of liquid scintillation cocktail.

Analytical report.
The percentage inhibition at every concentration is the mean of 3 observations. $IC_{50}$ values are obtained from log plus benefit evaluation. $IC_{50}$ values for the standard drugs desipramine and nortriptyline are near 20 nM\textsuperscript{120}.

1.9.2 Inhibition of mice striatal synaptic vesicles by dopamine uptake.

Need and utility
Dopamine has been found to be present in different tissue preparations of the brain, by high binding, saturable temperature and sodium dependent transport. Striatum corpus and Substantia nigra have a much high level of dopamine and is a very good substitute for advanced experimentation. Cocaine, few phenylethylamines and antidepressants like nomifensine and bupropion inhibit DA back entry. Tricyclic antidepressants are ineffective. These special methods can be utilized to explore the mechanism of action of antidepressant agents.

Method

Preparation of tissue for experiment
Albino rats of either sex are sacrificed and their brains are collected. Corpus striatum of each albino rat is made ready for weighing and homogenized in ice cold 0.32 Molar solution of sucrose utilizing a Potter-Elvejhem apparatus. The homogenate is collected and centrifuged at 22000 revolutions per minute at 0–4 degree centigrade for 10 minutes. The supernatant liquid is poured in bottle and further made available for next practical\textsuperscript{121}.

Testing
100 µl of tissue suspension are grinded with 900 µl 55.5 nM 3H-dopamine soln in Krebs-Henslett bicarbonate buffer and 20 µl of drug solution in appropriate concentration. The test tubes are kept in an incubator at a temperature of 37°C in presence of 5% CO\textsubscript{2} and 95% O\textsubscript{2} for 5 minutes. For performing each assay, these tubes are incubated with 20 µl of vehicle at 0°C. After incubation the liquids are immediately centrifuged at 4000 revolutions per minute for 10 minutes. The fluid which issupernatant is a spirated and the pellets dissolved utilizing 1 ml of solubilizer (50% ethanol + Triton X-100, 4:1).
Analysis

The inhibition of percentage at each drug concentration is the average of 3 observations. IC50 values are obtained from log-probit analyses. for tricyclic antidepressants IC50 values are >20 000 nM but for nomifensine they are 460 nM.

Latest method

Elsworth et al. (1993) founded difference among cocaine insensitive and sensitive and dopamine uptake in different brain regions. Pharmacological characterization and. Cloning and of bovine, rat and human dopamine transport channel have been explained. Dopamine transporter and its binding characteristics were studied. [3H]-3β-(p-fluorophenyl)tropan-2β-carboxylic acid methyl ester ([H]WIN 35,428) have been used as ligands for the dopamine transporter [H]GBR12-935 (1[2-(diphenylmethoxy)ethyl]-4- (3-phenylpropyl)piperazine). Receptors of cocaine are particularly labeled with [H]WIN 35,428 demonstrating function of the dopamine reuptake pattern in mediating the behavior and the drug abuse of cocaine. Some researchers have described emission computed tomography (SPECT) of single photon imaging of serotonin and dopamine transport channel in non-human primates.

1.9.3 Dopamine uptake inhibits rat striatal synaptic vesicles.

Need and Utility

Researchers have found that patients with hypofunction of serotonin constitute a depression sub group ,and have claimed that the mood changes associated with affective disorders were due to changed serotonergic function .A great number of antidepressants which are clinically useful inhibit the transport of serotonin.. Apparently, catecholamine uptake is different from the 5-HT3 transport. So such experimentation could be utilized to find out drugs that block 5-hydroxy tryptamine transport into rat brain synaptic vesicles and such drugs might be potential antidepressants.

Tissue preparation.

Method.
Wistar albino rats of either sex were sacrificed and brains immediately removed. Cerebellum or the hypothalamus is weighed and homogenized in 9 volumes of ice-cold 0.32 M sugarcane solution using a Potter-Elvejhem homogenizer. The homogenate is centrifuged at 12000 revolutions per minute at 0–4°C for 10 minutes. Upper part of the liquid is collected and used for further experimental work.

**Analysis report**

The percent inhibition of each drug concentration is the mean of 3 observations. $IC_{50}$ values are obtained from log-probit analyses. Standard drugs, such as clomipramine show $IC_{50}$ values in the order of 10 nM for 5-hydroxy tryptamine uptake in rat synptical vesicles from hypothalamus.

**Evaluation of method**

While several antidepressants stop the transfer of 5-hydroxytryptamine *in vitro*, few drugs like tianeptine were found to increase 5-OH tryptamine transmit *in vivo* test. Hence, it appears suspicious to attach the benificial effect seen in man to a single mechanism observed in *in vitro* test.

**Some Alteration in Procedure**

**Methodology**

**Human transport channel**

The Ca$^{2+}$ symporter directly controls the Human 5 hydroxy tryptamine transport channel cDNA. The hypothalamic cells, and also the Ca$^{2+}$ symporter, transflect and directly bind the human dopamine transporter cDNA into the gene expression vector pcDNA3.

**Cell line culture**

Petridishes (150 mm) with 17.5 ml of Dulbeco’s modified Eagle’s medium containing 1 Unit/µl penicillin and streptomycin solution, 0.1 mM non compulsory amino acid solution and 5% fetal clonebovine serum product are used to cultivate and grow the
cell lines. They are kept under constant temperature in 10% CO₂ and 90% O₂ at 37 degree centigrade. For culture of cells expressing the norepinephrine transport channel the antibiotic, geneticin sulfate (250 µg/ml) is used.

**Method for membrane preparation**

The medium is removed by aspiration, for preparation of the homogenates. 10 ml of 100 mM EDTA solution is used to wash the cells along with Purck’s D1 solution (4l modified, solution 1) and then incubated for 5 min at 37 degree centigrade. With the help of a rubber spatula the cells are separated from the surface by scraping, and collected by centrifugation at 14,000 revolutions per minute, at of a temperature 4 degree centigrade for 5 minutes. Most top part of the liquid preparation is removed. By the application of a Polytroin (Brinkeman Instruments, Westbery, NY) solid residues are resuspended, for 10 s at setting 6 in the respective binding assay buffer. For a time period of 10 minutes at a temperature of 4 degree centigrade, the mixture is centrifuged at 35,600 revolutions per minute. The centrifugation is repeated and the pellets are suspended in the same volume as that of the respective buffer. Top most liquid is poured and the final pellets are suspended in the respective buffer and stored at −80 degree centigrade until assayed. The final protein concentration is determined by the Lowrey assay using bovine serum albumin as standard.

Halsterom et al. (1976) discovered the uptake of dopamine and 5-hydroxytryptamine by the platelets in patients suffering from depression. Blakely et al. (1991) and Hofman et al. (1991) studied the identification of functional serotonin transport channel and realized the role played by serotonin in the mechanism of action of antidepressant compounds.

1.10.4 Study of mono amine transport channel for binding affinities to receptors

**Objective**

There are evidences that damage done to the noradrenergic and serotonergic systems are responsible for occurrence of depression and that antidepressant therapy can, to some extent compensate the damages done to these systems. Therapeutic compounds such as psychostimulants, antidepressants and the habit forming agent cocaine target mainly the biogenic catecholamine transport channels. Quick passage of the neurotransmitter released by high affinity transport channel is
responsible for the termination of neurotransmitter release. A family of genes (such as Na+/Cl− transport channel) link maximum transport channels. Amino acid transport channels, GABA-transport channels, biogenic monoamine transport channels, “orphan” bacterial transport channels. During the last decade researchers described the pharmacological profiles of various antidepressants drugs utilizing human monoamine transport channels.

**PART – 2: PLANTS AND THEIR CONSTITUENTS REPORTED TO POSSESS ANTIDEPRESSANT ACTIVITY.**

1. **Singh R.K., et al., (1998)** reported that Benzene (BE), Petroleum ether (PE), Acetone (AE), ethanolic (EE), Chloroform (CE) extractive obtained from dried leaves of *Abies pindrow* showed significant antidepressant activity in rats when given 30-45 min before. Chemically extract showed the presence of glycoside, steroid, terpenoids and flavonoids. It has been reported that ethanolic extract of *A. pindrow* having glycopyranoside, hydroxy-flavaone and chalone glycoside, bioflavonoids.

2. **Hasrat J.A., et. al., (1997)** found that the fruits and leaves extract of *Anona murieicata* inhibit binding of [3H] rauwoliscine to 5-Serotonergic 5-HT IA receptor in Calef hippocampus & showed antidepressant activity. The three alkaloids (isoquinoline derivative) annonaine, nornuciferime and asimilobine isolated from the extracts of fruits.

3. **Hoong D.T.L., et al., (2002)** fractionated and isolated of dichloromethane fraction of *Aquilaria agollocha* by bioassay-directed fractionation. Four compounds having MOA inhibitory effect were isolated by repeated silica gel column chromatography. There structures were established as psoralen, bergaptan, alpha amyrin acetate and 5-hydroxymethylfurufural with the help of their physiochemical and spectral data. Among these compounds psoralen and bargapten showed high inhibitory activities in vitro against mouse brain monoamine oxidase hence proved as antidepressant.

4. **Nishibe S., et al., (2002)** reported that leaves extracts of *Apocynum venetum* considerably lower the total immobility time of mice / rats in FST. This indicated significant anti-depressant activity of the leaves extracts.
5. Dar A. and Khatoon S., (1997b) studied the antidepressant property of hexane (F2) and aqueous (F5) fraction of *Areca catechu* fruit in mice by TST, FST and locomotion test. The effects of the water alcoholic extract fractions F1, F2 & F5 on the M.A. Oxidase activity were found in rat mind homogenates. The F2 and F5 fraction of A. catechu cause as clear and amount of drug dependent decrease in the period of the immobility time using either TST or FST. The F1, F2 and F5 fraction inhibits (MAO) in rat brain homogenates and showing antidepressant like effects.

6. Dar A., *et al.*, (1997a) reported that aqueous fractions of *Areca catechu* seem to be the most potent inhibitor of Mono Amino Oxidase and its effects are similar to that Clorgyline. The ethanolic extracts produced a marked reduction in the immobility time without affecting the spontaneous motor activity, suggesting its antidepressant activity.

7. Vadawa R.K. and Singh R.H. (1996) studied *Bacopa monniera* for antidepressant activity. Thirty six patient of cittodvega via-a-vis anxiety neurosis were selected for the clinical study and were randomly divided into two groups. Extract of the drug Aindri (*B. monniera*) was administered both the groups in a dose of 1.5 gms representing 7.5 gms of dry crude extract daily for a period of four weeks. The trial treatment produced significant improvement in the level of depression and anxiety, mental fatigue rate and memory span. Aindri also showed improved learning behavior in albino rats. The standardized methanolic extract of *Bacopa monniera* (Bacoside-A 38.0 ± 0.9) was showed comparable effective with the standard antidepressant drug, imipramine (15 m.g./kg, i.p.).

8. Sairam *et al.*, (2002) reported that when Bacopa monniera extract is administered orally, once daily for 5 days in the doses of 20 and 40 m.g./kg, it was noticed that significant antidepressant activity in learned helplessness model and in FST. This response was as good as to Imipramine.

9. Yunfeng L., *et al.*, (2000) studied that the possible mechanism of antidepressant effect of Bajitian oligosaccharide (MW-97). The PC12 cells were incubated with MW-97 in presence of corticosterones (2 × 10⁻⁴ moll/L) could protect PC12 cell from the lession done by corticosterone in a concentration dependent manner. It also has neuro-protective effects. Bajitian is a medicinal plant named Indian mulberry.

10. Vural K., *et al.*, (1996) reported antidepressant and anxiolytic activity of two endemic Ballota species; *B. larandana* and *B. nigra*. It was found that both of these
species showed antidepressant activity. B. larendana also showed anxiolytic activity. Antidepressant activity was also compared with that of diazepam.

11. **Lohning A. and Winterhoff H. (2000)** reported that *Cimicifuga racemosa* extract reduced immobility time of female mice significantly giving hints of an antidepressant activity in the TST. The mode of action of neurotransmitter levels were determined in striatum hippocampus and hypothalamus after a 21 days pretreatment period while no differences to controls were observed in hippocampus or hypothalamus. Significant changes in neurotransmitter concentration were measured in the striatum. The serotonin turnover to HIAA was significant reduced, an effect which could be caused by an inhibition of the enzyme MAO and aldehydehydrogenase. In addition the dopamine concentration was increased.

12. **Almeide R.N., et al., (1999)** reported that ethanolic extract of the leaves of *Cissampelos sympodialis* showed effect similar to Imipramine (IMI) as indicated by reduction in immobility time during FST performed on mice.

13. **Komori T., et al., (1996a)** investigated antidepressant affect of various odourants by forced swimming test. It was observed that *Citrus fragrance/ lemon odour* showed reduction in total immobility time and thus added to the imipramine induced anti-depressant effect.

14. **Komori T., et al., (1996b)** also reported that the effect of citral, which is one of the main constituent of lemon odour, was as strong as those of lemon odour. The immune function and neuro-endocrine hormone level are normalized by treatment with citrus fragrance and was rather more effective than antidepressant.

15. **Zu Z.F., et al., (2002)** reported that upon oral administration of C. longa extract to the mice, produced significantly reduction of motionless time in the T. S. T and F. S. T in rat.

17. Baez D.H., et al., (1999) reported that the species *G. nevadensis* is known as dictamnus. Xanthones were detected in dichloromethane and ethyl acetate extract and their fractions. Bellidifolin and desmethybellidifolin were isolated, both have been reported as inhibitors of monoamine oxidase (MAO). The result of this study suggest that *G. nevadensis* could be possible antidepressant and anti-infection agent.

18. Singh S.K., et al., (2003) reported that two herbal drugs namely *Mucuna pruriens* (Kapikacchu) and *Withania somnifera* (Aswagandha) were clinically tried in 15 cases of depressive illness for two to three months period with encouraging results showing notable symptomatic improvements, decrease with degree of depression and anxiety.

19. Maity T.K., et al., (2000) evaluated the effects of a methanolic extract of *Ocimum sanctum* on FST. *O. sanctum* extract treated mice showed increased average swimming time, which indicated anti-stress activity (antidepressant) and / or central nervous system stimulation.

20. Della L.R., et al., (1996) evaluated antidepressant activity of a ginseng extract or its fraction and/or two ginsenoside in behavioral despair test. The ginseng extract (33 m.g./kg) showed the same effects as the reference antidepressant drug. Ginsanoside Rg (2.2 m.g./kg) to be the major component responsible for the activity of *P. ginseng* marketed tea.

21. Takeda H., et al., (2002) reported that effects of a water extract of Perilla Herba (*P. frutescens*) and six fractions there from were evaluated in mice by FST. An oral administration of a water extract of Perillae Herba considerably reduced the duration of immobility as antidepressant substance.

22. Perez O.I., et al., (1991) reported that as a traditional medicine in Navarra (Spain), plant Prunus spinosa L. blackthorn, is being used commonly. The Plant parts i.e. flowers, leaves and fruits of *P. spinosa* are many responsible for it’s therapeutic effects. The effect of aqueous (PSA) and ethanolic (PSE) extract of *P. spinosa* fruits in different psycho-pharmacological test, in order to determine their possible activity
on central nervous system. In behavioral despair in mice, PSA reduced significantly the Average time of duration immobility, where as PSE was no effective in this test. Amitryptiline significantly increased the struggle time in mice.

23. Castiella E., et al., (1991) reported that in antagonism to reserpine, the treatment with (Prunus spinosa stem extract) PSA produced statistically significant antagonism of ptosis induced by resperpine. PSA and PSE also antagonized, but not significantly, akinesia and hypothermia. Result from these test shows that PSA appears to a pattern of antidepressant–like activity, being effective in those entire tests involving a possible serotoninergic stimulation

<table>
<thead>
<tr>
<th>Table No. 1: Some of the product available in Indian market with antidepressant activity.</th>
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<tbody>
<tr>
<td><strong>Product</strong></td>
</tr>
<tr>
<td>ALERT</td>
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<tr>
<td>AYUDEP CAPSULE</td>
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<tr>
<td>BRAINCARE CAPSULE</td>
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<tr>
<td>BRENTREX</td>
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<td>ELEVAL CAPSULE</td>
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</tbody>
</table>
### Table of Ingredients and Companies

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOOD ON</td>
<td>Ingredients:- each capsule contains in m.g. of St.john's wart ext 300 m.g. (standardised to hypericine 0.3%) and <em>Emblica officinalis</em> 150 m.g.</td>
<td>BERGEN</td>
</tr>
<tr>
<td>NORMETA</td>
<td>Ingredients:- Ashwagandha, Amalaki, Gokshura, Shatavari, Yashtimadhu, Guduchi, Shweta musali, Kapikacchu, Shunthi, Maricha, Pippali, Ajamoda, Shuddha shilajituj, Nagakeshara</td>
<td>AYURCHEM</td>
</tr>
<tr>
<td>NUBEX CAPSULE</td>
<td>Ingredients:- Ashwagandha, Brahmi, Shankhpushpi, Pushkaramula, Arjuna</td>
<td>TRIO</td>
</tr>
<tr>
<td>SHANTI SAGAR CAPSULE</td>
<td>Ingredients:- Brahmi, Jatamansi, Amruta satva, Shankhpushpi, Sarpagandha, Amla, Swaramakshika, Mukthashuki, Shuddha gairika, Shwethaparpati</td>
<td>RATAN</td>
</tr>
<tr>
<td>SIO TONE</td>
<td>Ingredients:- Ashwagandha, Shatavari, Kapikacchu, Tulsi, Shuddha shilajitu</td>
<td>ALBERT DAVID</td>
</tr>
<tr>
<td>Brand</td>
<td>Ingredients</td>
<td>Company</td>
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<td>---------------</td>
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</tr>
<tr>
<td>SUMIND</td>
<td>Jatamansi, Bhringaraja, Tagara, Vacha, Shankhpushpi, Brahmi, Jyothishmati, Ashwagandha</td>
<td>AFDIL</td>
</tr>
<tr>
<td>SUNOVA EASYLIFE</td>
<td>Ashwagandha, Shuddha shilajitu, Shatavari, Trikatu powder</td>
<td>SANAT</td>
</tr>
<tr>
<td>BANXIA HOUPA DECCTION</td>
<td>Pinellia ternate, Mangolia officinalis, Poria cocos, Perilla frutescens, Zingiber officinale</td>
<td>---</td>
</tr>
<tr>
<td>EUPHYTOSE ¤</td>
<td>Passiflora incarnate, Valeriana officinalis, Cola nitida, Cratagus oxyacantha, Ballota foetida</td>
<td>---</td>
</tr>
<tr>
<td>MENTAT (BR-16)</td>
<td>Brahmi (Hydrocotyl asiatica), Aswagandha (Withania somnifera), Shatavari (Asparagus racemosus), Buch (Acorus calamus), Amla (Emblica officinalis), Shankhpushpi (Evolulus officinalis), Triphala.</td>
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</table>
PART – 3: ACTIVITIES SHOWN BY THE PLANTS (*Camellia sinensis*) AND THEIR CONSTITUENTS.

1. **Cristina P., et al.,** (2004) reported that anti-trypanosoma cruzi activity of catechins obtained from green tea on 2 various stages of development of *Trypanosoma cruzi*. The Ethyl acetate extract obtained from *C. sinensis* leaves, which mainly contains the polyphenolic compounds and it exhibited maximum anti-trypanosoma activity. Galallocateichin galate and epigalocatechin galate were the main active compounds.

2. **Aucamp J., et al.,** (1997) reported that five tea catechins and two flavones exhibited inhibition of xanthine oxidase (XO). This suggested a new mechanism i.e. prevention of oxidative stress related diseases by tea drinking. Polyphenols are antioxidants and they can reduce oxidative stress.

3. **Yam T.S., et al.,** (1997) reported that a wide range of pathogenic bacteria is inhibited by aqueous extracts of teas (*Camellia sinensis*), which includes methicillin resistant *S. aureus*. The extracts contained in a cup of tea showed bactericidal activity when studied on staphylococci and *Yersinia enterocolitica*. This activity was due to content of epicatechin gallate, epigallocatechin gallate and epigallocatechin.

4. **Sano M., et al.,** (1995) used tissue slice antioxidant evaluation method and reported the antioxidant effects in the liver and kidney exhibited by 2 lipid peroxidation inducers. After 50 days on the diets (containing 3 % green / black tea leaves powder), the results indicated that the above mentioned diet had antioxidant effects.

5. **Vijaya K., et al.,** (1995) reported that compounds extracted from *Camellia sinensis* showed bactericidal effects against *Shigella* spp., which causes dysentery. The antibacterial activity was tested using non cytotoxic concentration of the extract against the bacterial cyto-pathic dose. The results showed the extracts to be effective antibacterial agents and non – cytotoxic.

6. **Kapadia G.J., et al.,** (1976) studied the carcinogenicity of *Camellia sinensis* (tea) extract in N.I.H. Black mice by injecting subcutaneously. The tanin fractions from *Camellia sinensis* were observed to be highly active and lead to tumor formation at the site of injection in the treated animals. These tumors were observed
to be malignant-fibrous-histiocytomas. This indicated that the plant materials used for the studies can result into tumor in human body.

7. **Chan E.W.C., et al., (2007)** determined the total phenolic amount (TPA) and antioxidant activity (AOA) of CH$_3$OH extracts of fresh tea leaves from a lowland plants in Malaysia. TPC and AOA were observed in following manner shoots > young leaves > mature leaves. There were higher AOA and TPC shown by young dried leaves of green tea dried in microwave oven.

8. **Claudia A., et al., (2008)** determined that as per ISO, when the antioxidant capacity was tested by 1,1 – diphenyl – 2 - picrylohydrazyl free-radical scavenging assay and ferric thiocyanate method (FTC), lesser polyphenol content were shown by black tea than green tea. The TPC were correlated with the antioxidant activities.

9. **Lee I. P., et al., (1997)** concluded that upon performing comparative study of Sister chromatid exchange (SCE) rates among smokers and non – smokers, the studies showed that green tea and coffee on smoking healthy male subjects, green tea showed significant chemopreventive effects, while coffee did not show any remarkable effects on SCE rates in the smoking subjects.

10. **Sur P., et al., (2001)** reported anti-inflammatory and in vitro antioxidant activity of 2 saponins i.e. TS - 1 and TS - 2, which were isolated from extracts of tea. The paw oedema induced by carra-geenan in rats was inhibited by the 2 groups of saponins. The xanthine oxidase system was used to study the antioxidant activity.

11. **Miller J.M.T., (2001)** reported that tea leaves extract have direct antibacterial effect against S. sobrinus and Streptococcus mutants, which causes dental caries. This is a result of prevention of adherence of bacteria to teeth; inhibition of glucosyl transferase, which results into limiting the bio - synthesis of sticky glucan, human and bacterial amylases.

12. **Gomes A, et al., (1995)** evaluated the anti-diabetic activity of “Black-Tea-Extracts” (C. sinensis) in diabetes induced through streptozotocin (STZ) in rats. The experiments confirmed reduced blood glucose levels were induced by the extracts. This concludes that the extracts have curative and preventive effects on diabetes.
13. **Yoshikawa M., et al., (2005)** reported that \( n \) – butanol - soluble fraction obtained from methanolic extract of flowers of *Camellia sinensis* suppress the elevation of serum tri - glyceride in mice treated with olive oil and it showed anti – hyperlipidemic activities.

![Chemical Structure](image)

14. **Chattopadhyay P., et al., (2004)** reported that an extract of 1 : 1 methanol - water obtained from *C. sinensis* induces antipyretic, analgesic and anti - inflammatory activities. It was claimed that these activities are due to the saponins present in the extract.

15. **Maity S., et al., (1995)** reported that hot-water-extracts of *C. sinensis* lead to reduction in ulceration caused by cold-restraint-stress (CRS) and ulcerogens in rats. It was claimed that this anti ulceration effect may be caused by the prostaglandins.

16. **Yoshikawa M., et al., (2008)** reported that 1 – butanol - soluble fraction containing flora-theasaponins ‘A’,'B' and ‘C’ obtained from the CH\(_3\)OH extract of flower buds of *C. sinensis* showed hypo-glycemic and gastro-protective activities. This was claimed on the basis of fact that the extract showed inhibitory effects on gastric mucosal lesions caused by ethanol and indo-methacin in rats.
PART – 4: NATURAL PRODUCT EXTRACTION, ISOLATION AND PURIFICATION

The systemic investigations of plant materials for its photochemical behavior involve four different stages.

1. The procurement of raw materials and its quality control

2. Extraction, purification and characterization of the constitutes of pharmaceutical interest and in process quality control

3. Investigations of biosynthetic pathway to particular compound

4. Qualitative and quantitative evaluations

Extraction is defined as a technique for separation of active substances from the crude drugs. It involves use of solvents. This requires proper identification and authentication of the crude drug to be extracted. During the extraction, generally powdered plant material being used. Extraction of aromatic acids and phenols requires acidification of the plant materials. Generally, glycosides are soluble in water and alcohol. Water, alcohol and ethyl acetate are good solvents for the Tannins, which are phenolic compounds. Extraction by percolation or by continuous extraction using soxhlet extractor or may be performed by repeated maceration with agitation.

Preliminary photochemical screening:

The plants are source of the food materials such as carbohydrates, proteins and lipids that are utilized as food by man, but also other compounds like alkaloids, glycosides, tannins, volatile oil, etc., that bring to bear a physiological and therapeutic effects.

The powdered plant is extracted by soxhlet apparatus using different grade of solvents from n-hexane, n-heptane, DMF, CCl₄, ethyl acetate, alcohols, water & Acetic acid in increasing polarity.
The concentrated extract is generally obtained by distillation of the solvent under low pressure followed by evaporation until dryness. The extracts with different solvents can also be prepared by successively maceration (cold extraction) of the powdered drug in order of increase polarity.

The general approach for extraction of different constituents from the freshly plant material may be briefly described in the described in the following chart.
It is quite obvious that the extract of phytoconstituents prepared by maceration or percolation method must be as pure as possible and unless it is reasonably so, the test reaction may not be accurate. Therefore, some purification procedures are usually adopted prior to characterization of individual components. There is always a necessity for further purification of plant extracts, which can be performed by various techniques like fractional crystallization, fractionation, sublimation, distillation, etc. (Kokate K.C., et al., 1999).

Figure No. 6: Schematic diagram Soxhlet Apparatus
PART – 5: ANIMAL MODEL FOR THE EVALUATION OF ANTIDEPRESSANT ACTIVITY

Following consideration should be considered during experiments:

1. Water depth and temperature
   a. Mice may not touched the bottom with its tail or feet.
   b. Depth of approximately 15 to 30 cm.
   c. Temperature of water should be kept approximately 25±1°C (Web - 4).
   d. The rats should be dry in a warm environment after removal from the H₂O after test.
   e. A heating source directed over or underneath the cage has been provide warmth.

2. Water changes
   a. The container should be emptied, cleaned and disinfected
   b. Fecal material should be removed from the jar after each experiment with a small mesh net.

3. Test procedures
   a. Test durations (4-20 minutes) have been reported (Crawley J.N., 2007).
Tail-suspension test (TST) in mouse (rat) was developed for human as a potential screening test for antidepressant drugs. It is a stressful animal situation based on the assumption that the animal will try to escape this stressful situation. If it is impossible to escape, finally, animal stopped trying to escape (give-up). In the tail-suspension test, Mouse or Rat hanging in the air and their body faces downward.
The test period is six or more minutes. The test can be repeated several times. At the beginning, rat will try to climb on a solid surface. The animal struggles to escape from this situation after that stops and finally give up. Long periods of immobility is indicates a depressive state. The verification of the validity of treatment with an antidepressant medication decreases the immobility time of the animal (Thierry B., et al., 1986).

Following considerations should be considered during the TST are:

1. Mice should be suspended above the “cushioned” surface, to help prevent injury to the mice if it falls. Mice that may experienced a fall should be removed from the experiment (Bergner, et al., 2010).

2. Vinyl or medical adhesive tapes is recommended for the hanging of mice. **The adhesive tape should be applied in a consistent position ¾ of the distance from the base of the mice’s tail** (Porsolt, et al., 2009).

3. Some strains (for example, C57BL/6J) may not perform very well in the TST, due to tail climbing behavior. These types of mice should not be used in the TST. (Bergner, et al., 2010).
Figure No. 8: Representative diagram for Tail Suspension Test
PART – 6: STATEMENT OF THE PROBLEM

As per world Health Organization (WHO), worldwide, depression is a common illness, it was estimated that 350 million people are affected from this illness. Everyday life’s mood fluctuations i.e. usual and short-lived emotional responses to challenges, can not be called as depression. Depression is generally long lasting and with moderate or severe intensity. Depression is one of the serious health conditions. Suicides can be result of the depression. It has been estimated that every year, approximately 1 million deaths occurs due to depression.

Depression is commonly treated with antidepressant medications. Select. serotonine reuptake inhibitors (SSRIs) are generally preferred types of antidepressants. The examples of SSRIs are Citalopram, Escitalopram, Fluoxetine, Paroxetine and Sertraline.

The most common side effects of antidepressants associated with SSRIs and SNRIs include, Agitation, Nausea, Headache, Sleeplessness or drowsiness, reduced sex drive, problems having and enjoying sex that can be persist men and women, both. Side effects like Blurred vision, Bladder problem, Constipation, Drowsiness, Dry mouth, Sexual problems are associated with tricyclic antidepressants.

From centuries, St. John's wort has been used as folk and herbal remedies. It is being used commonly to treat mild to moderate depression in Europe. In traditional Chinese and Indian medicine, practitioners used green tea to improving mental processes and health (Web – 5).

Dating back more than 4,000 years, as per Chinese tradition, Chinese green tea could cure anything from depression, body aches, headaches, pains to constipation (Web–6).

In the present study, plant *Camellia sinensis* shall be evaluated for antidepressant activity. Literature shows that traditionally this plant is being use in the treatment of depression but no scientific and research data is available / reported to treat depression using this plant.

Our attempt is to establish the scientific data of this plant as common, cheap and affordable, safe, effective, readily available alternative antidepressant agent.