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Study on Antidepressant Activity of Various Extracts of *Camellia sinensis*

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Abstract: *This study evaluated the antidepressant activity of aqueous, ethanolic, and methanolic extracts of Camellia sinensis leaves in Swiss albino mice using Forced Swim Test and Tail Suspension Test. Methanolic extract at 400 mg/kg showed the highest activity, significantly reducing immobility time comparable to imipramine, with no CNS stimulant effect. The activity correlated with higher phenolic and flavonoid content. Results suggest methanolic extract of C. sinensis has potent antidepressant-like potential and may serve as a source for plant-based antidepressant development.*

Depression is a prevalent neuropsychiatric disorder with significant morbidity. Conventional antidepressants exhibit delayed therapeutic onset, incomplete efficacy, and adverse effects, prompting investigation into safer plant-derived alternatives.

Camellia sinensis, commonly known as tea plant, is one of the most widely consumed medicinal plants in the world. Green tea leaves contain biologically active compounds such as catechins, polyphenols, flavonoids, alkaloids, caffeine, epigallocatechin gallate (EGCG), and L-theanine. These phytoconstituents possess antioxidant, neuroprotective, anxiolytic, anti-inflammatory, and antidepressant properties.

The results showed significant antidepressant activity in all extracts compared to control groups. Among the tested extracts, methanolic extract exhibited maximum antidepressant activity, followed by ethanolic extract. Reduction in immobility time in both FST and TST indicated significant antidepressant

The study concludes that Camellia sinensis possesses promising antidepressant activity and can serve as a potential herbal alternative for the management of depression.

Keywords: Camellia sinensis, Anti-depressant, FST, TST, methanolic extract

I. INTRODUCTION

Tea polyphenols are one of the main components in the formation of the color and flavor of tea soup and are also important ingredients for tea with health functions The species, processing method, and fermentation degree are the key factors that affect the content of tea polyphenols in tea .Gao et al. analyzed the content of 16 common tea leaves and found that the content of tea polyphenols in green tea was the highest . They suggested that green tea was the preferred tea source for the development of tea polyphenol functional foods In recent years, numerous domestic and foreign studies are focused on the chemical composition and pharmacological effects of green tea. At present, there is a lack of systematic and comprehensive review on the research results of green tea. In this paper.

A large number of researchers have confirmed that green tea possesses chemical ingredients that are closely related to human health. Tea polyphenols, caffeine, theanine, tea polysaccharides, and other components which are extracted and separated from green tea have pharmacological activities such as anti-cancer [3], anti-oxidation [4], protecting the nervous system [5], and lowering blood sugar [6]. Green tea has been considered to be suitable for patients with hypertension, hyperlipidemia, coronary heart disease, arteriosclerosis, and diabetes. However, it is important to keep in mind that “natural” does not mean perfectly safe.

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Although the toxic side effects of green tea are relatively small, it must be used with caution in pregnancy, children, and the elderly population. Tea polyphenols are one of the main components in the formation of the color and flavor of tea soup

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

II. THE NEUROBIOLOGY AND PHARMACOLOGY OF DEPRESSION

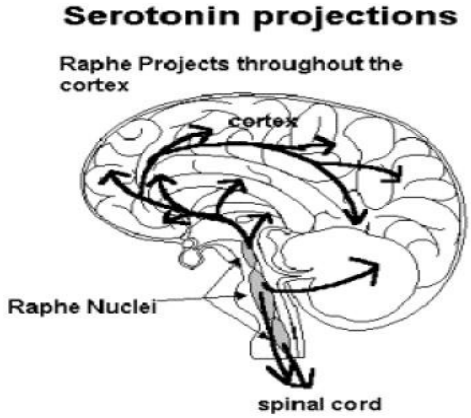
1. Neurotransmitter Systems

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., 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

(Figure No. 1 for an illustration of the serotonin projections

Figure No. 2 for an illustration of the noradrenergic projections). Multiple serotonergic and noradrenergic pathways may be dysfunctional in depression, generating many different symptoms.



No. 1: The projections of the serotonin system

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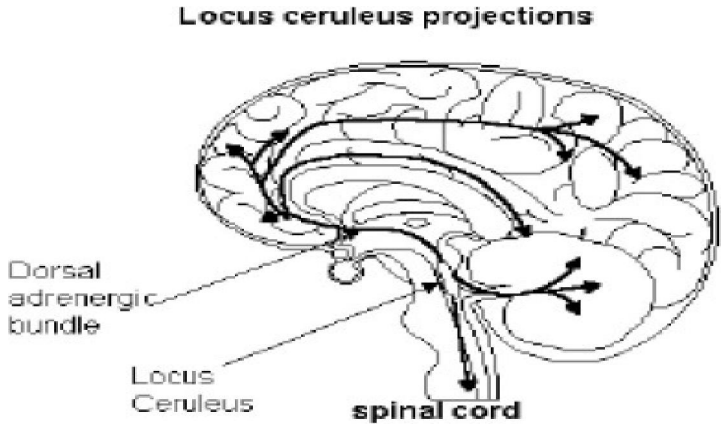

Fig. No. 2: The projection of the noradrenaline system

The nuclei of the dorsal raphe projects the serotonin system and the raphe Magnús.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 auto receptor. The 5 – HT2 receptors occur in high concentrations in the frontal cortex and nucleus accumbens (Van Evelien D., et al.,2003)

II. HPOTHESES 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 5ox let5am 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 (Cordi 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 downregulating 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 Solomo Snyder and linked schizophrenia with dopamine (DA) activity. Later, this hypothesis was extended to include depression following the observation that manyanti depressants influence the metabolism of dopamine. Following chronic antidepressant treatment, the presynaptic DA receptors become sub sensitis released this gets in an enhancement of DA release. A reduction in homoallylic 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 Prag 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).

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C. The permissive hypothesis of depression

This hypothesis emphasizes 5-HT as a neuro-modulator and its importance as a focus for 6ox let 6amuse6t 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 (Harsco-Levy and Javitt, 1998).

E. The kynurenine hypothesis

This hypothesis emerges from the premise that depression arises from altered levels of serotonin (5-Hydro. Trypot.) in the mind. Serotonin is a metabolite of the tryptophan (TRP) and all 5- Hydro. Trypot required by the neurons in the brains synthesized in the brain because 5- Hydro. Trypot 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 pyrroles) 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 7ox let7amuse7to (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.

3. 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).

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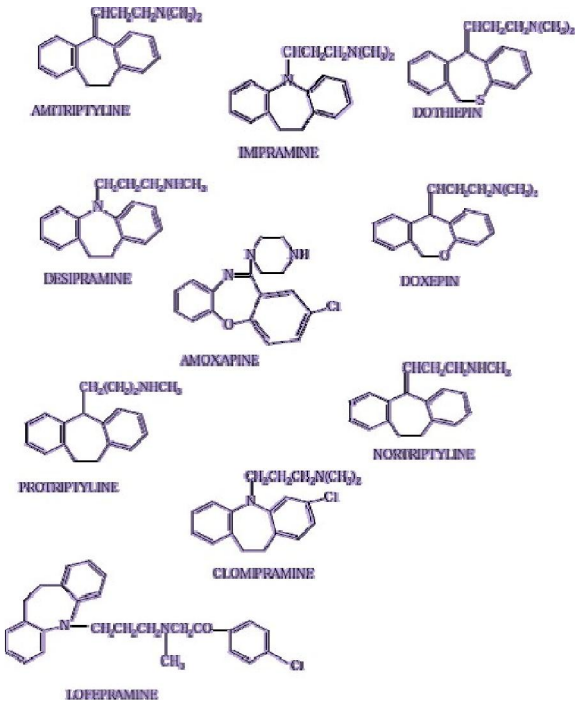

Fig No. 3: Chemical structures of some tricyclic antidepressants

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 the antipsychotic drug oxepine and displays some dopamine receptor antagonism. Trazadone has shown unpredictable efficacy in the clinical setting
(Potter W.Z. and Hollister L.E., 1998).

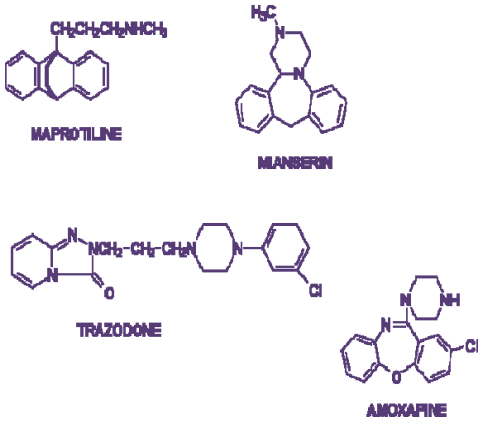

Fig No. 4 Chemical Structures of Some Heterocyclic Antidepressants

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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 d 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.

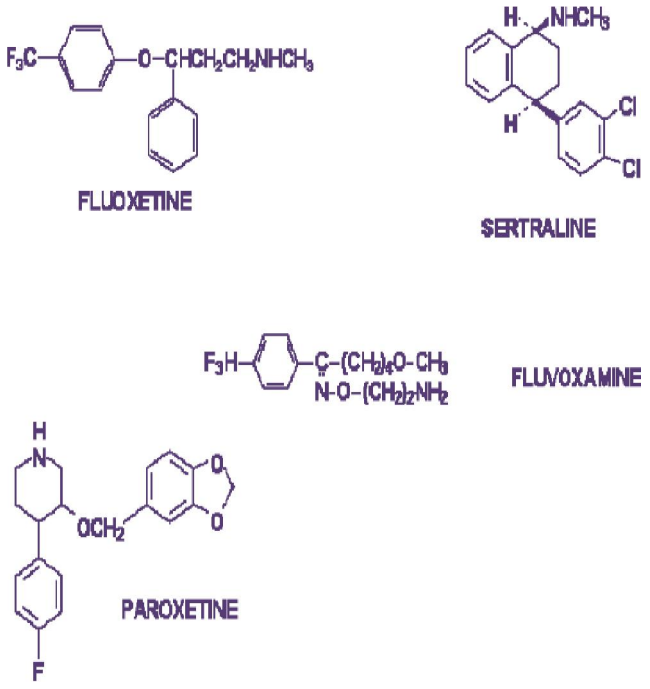

Fig No. 5: Chemical Structures of Some SSRI Antidepressants

2. PATHOPHYSIOLOGY

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 up to 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.61

PERMISSIVE HYPOTHESIS OF DEPRESSION

In the early 1970s, Orange and his colleagues postulated the 11ox let11am 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

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cause depression, and elevated NE levels cause mania. According to this hypothesis, correcting the deficiency in 5-HT activity corrects the affective disease62

3.Classification of Anti-depressant drugs

A. Reversible inhibitors of MAO-A:- Cordyline, moclobemide.
B. Tricyclic antidepressants:
a) 5 HT + NA reuptake inhibitors: - amitriptyline, Trimipramine, clomipramine, dothiepin, Impramine, doxepin.
b) Predominantly NA reuptake inhibitors: - desipramine, amoxapine, nortriptyline.
C. SSRIs:\ - paroxetine, Fluoxetine, citalopram, sertraline, fluvoxamine
D. Miscellaneous antidepressants' - mainspring , venlafaxine, mirtazapine, bupropion, Trazodone etc.

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 α2 and 5 HT1 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 desensitize5 HT1 auto receptors and 12ox let12amu α2 b receptors 71.
- some have weak H1 blocking property as well however most are potent
- anticholinergics, - trimipramine, doxepin, amitriptyline.
- 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.

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 desmethylimipramine, imipramine, nor amitriptyline ,amitriptyline,
- Half life of doxepin, imipramine and amitriptyline is longer – once daily dosing.
- Therapeutic window phenomenon is seen at a dose of 50-200 ng/ml in amitriptyline, nor-treptilamine imipramine72.

Adverse effects

- Discomfort due to anti cholinergic effects is seen.
- Weakness, confusion and sedation are seen in doxepin, trimipramine and amitriptyline.
- 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.

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- Postural hypotension is observed..
- most of TCAs produce cardiac arrhythmias.

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 action74.

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
Mainspring	Mirtazapine

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.

Mainspring

- Increases turnover and release of NA in brain by blocking presynaptic alpha 2 receptors Mainspring 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.

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Tianeptine

Believed to increase rather than block the reuptake of 5-HT 76.

- Does not produce sedation or drowsiness.
- Beneficial in endogenous depression and antidepressive 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 I 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 bulimia, 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 Bupropion

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 nonseasonal episodes of major depression88.

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 examinations89 Increasingly, people are turning to alternative forms of therapy, such as herbal medications. Several evaluations have found that the

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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 manufacturer90.

IV. REVIEW OF LITERATURE

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 Pindrop 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. Pindrop having glucopyranoside, hydroxy-flavone and chalone glycoside, bioflavonoids.

2. Hasrat J.A., et. Al., (1997)

Found that the fruits and leaves extract of Anona
muricate inhibit binding of [3H] rauwoliscine to 5-Serotonergic 5-HT IA receptor in Calef hippocampus & showed antidepressant activity . The three alkaloids (is quinoline derivative) annonacin, nonuniformed and assimilating isolated from the extracts of fruits.

3. Hoong D.T.L., et al., (2002)

Fractionated and isolated of dichloromethane fraction of Aquilaria agalloch by bioassay-directed fractionation. Four compounds having MOA inhibitory effect were isolated by repeated silica gel column chromatography.

There structures were established as psoralen, 17ox let17a, alpha amyrin acetate and 5-hydroxymethylfurfural with the help of their physiochemical and spectral data. Among these compounds psoralen and 17ox let17a 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 Apocynin Veneto 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 F5fraction 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

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 Cordyline. The ethanolic extracts produced a marked reduction in the immobility time without affecting the spontaneous motor activity, suggesting its antidepressant activity.

7. Vadala R.K. and Singh R.H. (1996)

Studied Bacopa Monnier for antidepressant activity. Thirty six patient of cathode via-a-vis anxiety neurosis were selected for the clinical study and were randomly divided into two groups. Extract of the drug Aindri (B. Monnier) was administered both the groups in a dose of 1.5 gems representing 7.5 gems of dry crude extract daily for a period of four

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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 behaviour in albino rats The standardized methanolic extract of Bacopa Monnier (Bacoside-A 38.0 ± 0.9) was showed comparable effective with the standard antidepressant drug, imipramine (15 mg./kg, i.e.).

8. Sairam et al., (2002)

Reported that when Bacopa Monnier 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 Bajakian oligosaccharide (MW-97). The PC12 cells were incubated with MW-97 in presence of corticosterone's (2 × 10-4 moll/L) could protect PC12 cell from the 19oxhle done by corticosterone in a concentration dependent manner. It also has neuro-protective effects. Bajakian is a medicinal plant named Indian mulberry.

10. Vural K., et al., (1996)

Reported antidepressant and anxiolytic activity of two endemic Ballota species;
B. lavandin and B. nigra. It was found that both of these species showed antidepressant activity. B. Laren dana also showed anxiolytic activity. Antidepressant activity was also compared with that of diazepam

11. Lehning A. and Winter off 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 19ox let19amu and 19ox let19amuse 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 serotonins turnover to HIAA was significant reduced, an effectwhich could be caused by an inhibition of the enzyme MAO and aldehyde hydrogenase. In addition the dopamine concentration was increase

12. Almeida R.N., et al., (1999)

Reported that ethanolic extract of the leaves of CISs Ampelos sympodial is showed effect similar to Imipramine (IMI)

13. Komori T., et al., (1996a)

Investigated antidepressant affect of various odorants 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 cartel, 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 tothe mice, produced significantly reduction of motionless time in the T. S. T and F. S. T in rat.

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16. Lahners M.C., et al., (1997)

Evaluated CNS activity of lyophilized aqueous extract of E. Hirte. It's aqueous extract exhibit slight antidepressant effect against reserpine– induced ptosis and extemporize-induced hypothermia.

17. Baez D.H., et al., (1999)

Reported that the species G. nevadensis is known as dictum real. Xanthones were detected in dichloromethane and ethyl acetate extract and their fractions. Bellidiflorin and dimethyl bellidiflorin 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 antiinfection agent.

18. Singh S.K., et al., (2003)

Reported that two herbal drugs namely Mucci pruriens (Pikachu) and With Ania somniferous (Ashwagandha) 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 behavioural despair test. The ginseng extract (33 mg./kg) showed the same effects as the reference antidepressant drug. Ginsenoside Rag (2.2 mg./kg) to be the major component responsible for theactivity of P. ginseng marketed tea Some of the product available in Indian market with antidepressant activity.

"HEBAL PRODUCT"

(Available in Indian market)

Product	Ingredients	Company
ALERT	Ingredients:- Jyotishmati Taila, Cow ghee, Shuddha amla Sara Gandhara, Processed with Sankalps, Vacha, Jatamansi and Berengaria	VASU
AYUDEP CAPSULE	Ingredients:- each capsule of 400 mg. contains ext. of St. john's wort	AYUSH
BRAINCARE CAPSULE	Ingredients:- Bacopa Manieri Nardo Stachys atamans, Celastrus pandiculates, Nelumbo speciosm,Crocus statives, Terminalia arjuna, Cycas criminalist, Hemedesmusindicus, Kallner parp am, Parampara, Velli parp am, Rasa parp am	SANJEEV
BRENTREX	Ingredients:- Brahmi, Shankhapushpi, Shankha 22oxhle, Ashwagandha, Shatavari, Jatamansi, Vacha, Sarpa Gandha, Shuk tika Bhasma	ANUJA
HIBRIL	Ingredients:- Shankhapushpi, Mandaean, Aindri, Ashwagandha, Shatavari, Vacha, Yashthimedhu, Jyothishmathi	VITALCARE

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KAMENTOSE	Ingredients:- Sarpa Gandha, Tumbi beeja, Shatavari, Jatamansi, Aswagandha, Bala, Bhringaraja, Khas, Ajmmoda, Swarna makshika	AJMERA

V. NATURAL PRODUCT EXTRACTION, ISOLATION AND PURIFICATION

The systemic investigations of plant materials for its photochemical behaviour 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 24ox let 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 25ox let 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 prepare 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 necessitates further purification of plant extracts, which can be performed by various techniques like fractional crystallization, fraction liberation, sublimation, distillation, etc.(Kok ate K.C., et al., 1999).

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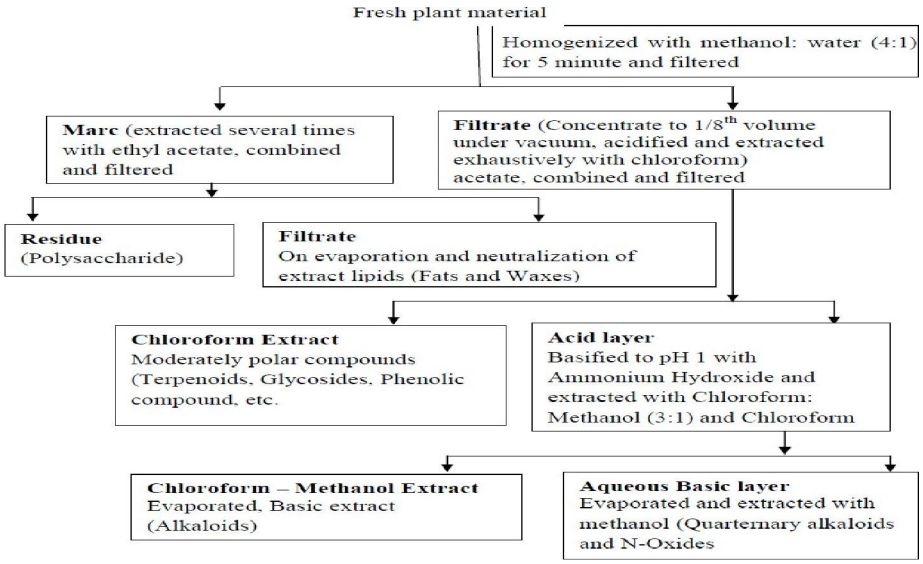

Fig.6 Schematic diagram Soxhlet Apparatus

VI. ANIMAL MODEL FOR THE EVALUATION OF ANTIDEPRESSAN 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.

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b. Depth of approximately 15 to 30 cm.
c. Temperature of water should be kept approximately 25±1^{0}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. Focal material should be removed from the jar after each experiment with a small mesh net.

3. Testy procedures
a. Test durations (4-20 minutes) have been reported (Crawley J.N.,2007)

VII. AIM AND OBJECTIVE

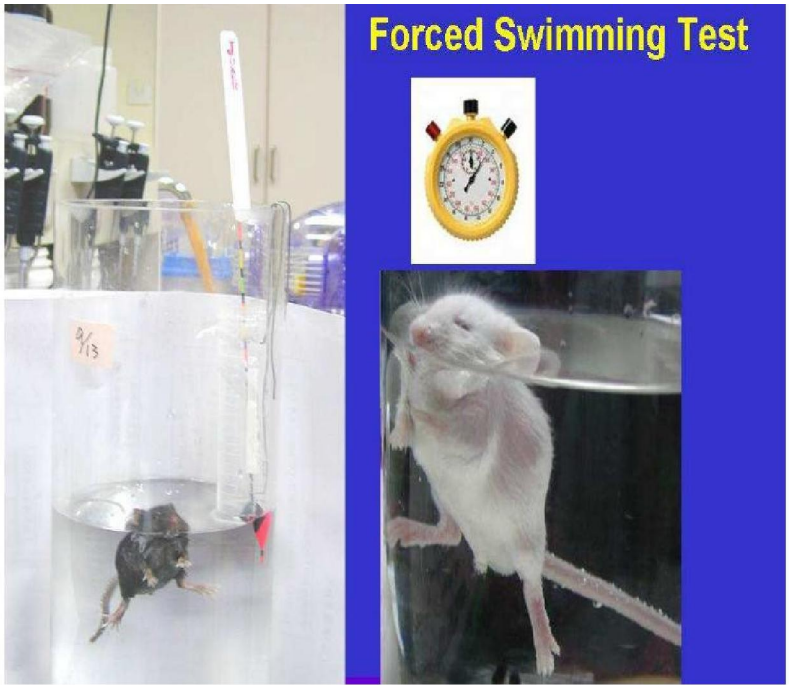

Fig No. 7: Representative diagram for Forced Swim Test

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 willtry to escape this stressful situation. 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).

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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 mise adhesive tape should be applied in a consistent position ¾ of the distance from the base of the mice's tail (Porzelt, et al., 2009).

3. Some strains (for example, C57BL/6J) may not perform very well in TST, to tail climbing behaviour. These types of mice should not be used in the TST. (Bergner, et al., 2010).

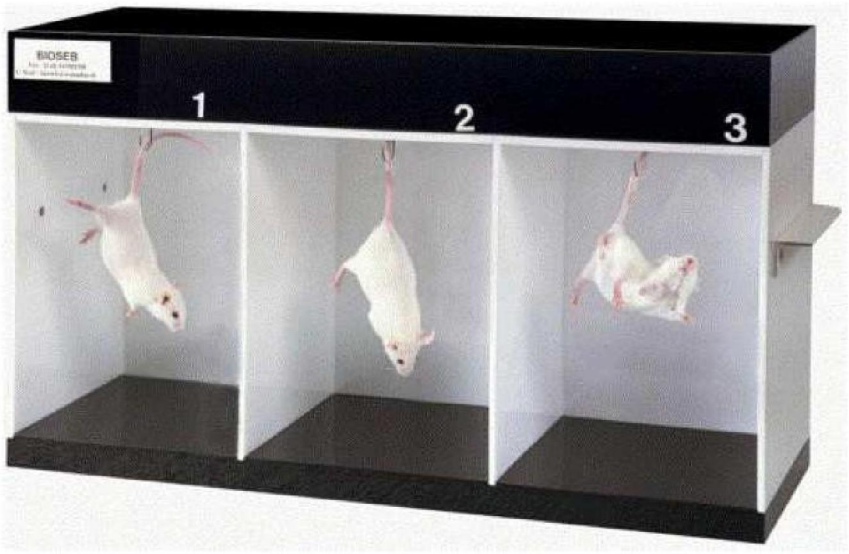

Fig No. 8: Representative diagram for Tail Suspension Test

VIII. 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. Serotonin 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.

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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.

IX. MATERIALS & METHODS

This work embodies the result of plant materials for antidepressant activity study on Camellia sinensis Linn. The plants materials C. sinensis used for the present studies were commercially procured from local market of Indore, Madhya Pradesh, India. C. sinensis (commonly known as Tea, Hindi – Chai). Tea plants are recognized as Camellia sinensis by botanists. They are small bushy plants about 3 o 4 feet high.

Tea leaves are picked three to four times between spring and fall of each year. Green tea is prepared from leaves that are picked and heated quickly and are most often consumed in Western societies (Liao, et al., 2001). It has been generally believed for a long time in oriental cultures that tea has medicinal properties and being used in the treatment and prevention of diseases. According to Chinese history, about 47 centuries ago, Emperor Sheng-Nong found that many of the poisons of the body can be dissolve by drinking of a cup of tea, daily (Committee, 1991). Tea is antibacterial agents and being used as food preservative (Chung, et al., 1998).

There are nearly 4000 bioactive compounds present in the tea in which 1/3 presented as polyphenols (Tariq, et al., 2010). Other compounds are amino acids, carbohydrates, chlorophyll, alkaloidal (caffeine, theophy lline & theobromine), fluoride, polypeptide, volatile organic chemicals, aluminium, minerals and trace elements (Cabrera, e.t al., 2003). Polyphinolic chemicals present in tea are mostly flavonoids (Sumption, et al., 2006). The polyphenols, group contains catechins

The health benefits of the tea may be due to presence of flavonoids and catechins (Cabrera, et al., 2006). Main catechins are epicatechin gallate (ECG), epicateichin (EC), epigallocatechin (EGC) and epigallocatechin gallate (EGCG). The catechin present in green tea is epigallocatechin – 3 – gallate (EGCG), which is most active and abundant.

Black tea contains relatively smaller contents of these catechins as compare to Green tea (Wu, et al., 2006). A combination of simple polyphenols, such as catechins andcomplex Polyphenols are reported in the Oolong tea (Mukhtar H. and Ahmad A., 2000).

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Fig No. 9: Typical diagram of Camellia sinensis plant.

Fig No. 10: Picture of leaves of Camellia sinensis plant. Identification Features

- **Leaves:** Smooth, shiny, dark green, and oval-shaped
- **Edges:** Small serrations (toothed margins)
- **Texture:** Thick and slightly leathery
- **Growth:** Leaves grow alternately on woody stems

This plant is one of the world's most important beverage crops. Young leaves and buds are harvested for making tea.

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Tea from these leaves contains:

- Antioxidants
- Caffeine
- Polyphenols

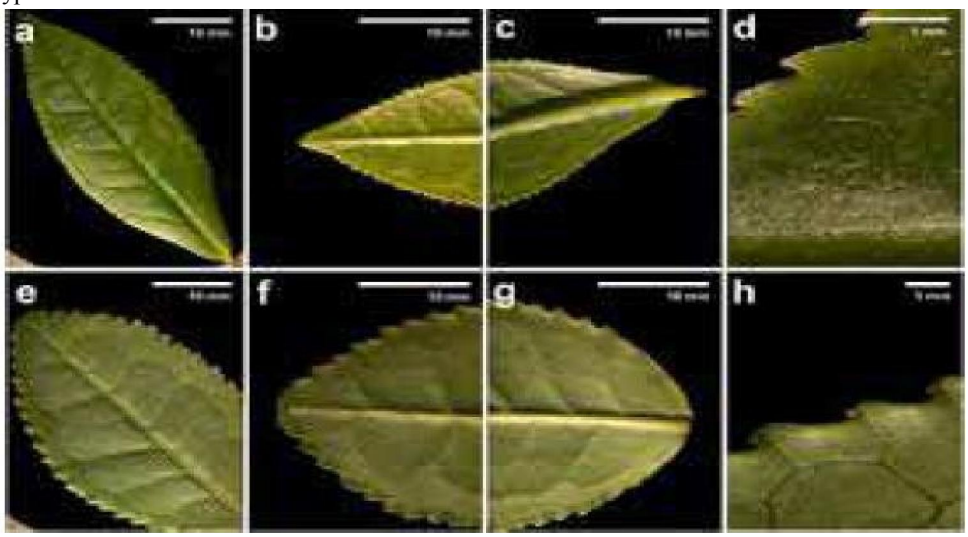

Fig No. 11: Typical picture of margins of leaf of Camellia sinensis plant

The image shows a comparative study of leaves from the Camellia sinensis under different magnifications and views. The panels labeled a–h display the morphology (shape and structure) and surface characteristics of tea leaves, likely observed for botanical or scientific analysis. The upper panels (a–d) show smoother and narrower leaves, while the lower panels (e–h) show broader leaves with more visible serrated edges and surface textures. These differences may represent variations between tea cultivars, leaf maturity stages, or environmental adaptations. Tea leaves are generally lance-shaped or elliptical with pointed tips, a central midrib, and fine serrations along the margins. The glossy green appearance indicates healthy chlorophyll-rich tissue important for photosynthesis and tea quality.

Fig No.12: Typical photograph of flowers and fruits of Camellia sinensis plant

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The image shows a close-up view of a flowering plant branch with a beautiful white flower, green fruits, and glossy dark green leaves. The flower has soft white petals arranged in a circular pattern with a bright yellow cluster of stamens in the center, making it visually attractive and fresh. Alongside the flower, two round green fruits or buds are visible, indicating different stages of the plant's growth and development. The stem appears woody and brown, supporting the flower and fruits. The shiny leaves surrounding the branch suggest that the plant is healthy and evergreen. This type of image is commonly used in botany and biology studies to explain the reproductive parts of flowering plants, including petals, stamens, buds, fruits, and leaves. The contrast between the white flower, yellow center, and green fruits creates a natural and vibrant appearance, highlighting the beauty and life cycle of the plant.

Fig No. 13: Typical photograph of ripe fruit with seeds of Camellia sinensis

The image shows a mature fruit of a flowering plant that has naturally split open to reveal its seeds inside. The outer covering of the fruit is brown, rough, and hard, indicating that it is fully ripened. As the fruit opens, shiny dark brown to black seeds can be seen arranged around a pale white central structure. The split fruit demonstrates the process of seed dispersal, where mature fruits open to release seeds for reproduction. Surrounding the fruit are smooth, elongated green leaves that provide a healthy and natural background. The image is useful for studying plant morphology and reproductive biology because it clearly displays the structure of a mature fruit, including the fruit wall, seeds, and internal arrangement. The contrast between the brown fruit shell, dark seeds, and green leaves creates an attractive natural appearance and highlights the final stage of the plant's reproductive cycle.

Fig No. 14: Picture of fruits of Camellia sinensis plant with measurement.

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The image shows several small, round to oval-shaped brown seeds placed beside a measuring scale for size comparison. The seeds appear hard, smooth, and dark brown in color, with a slightly glossy outer surface. The ruler in the background indicates that the seeds are approximately 1 to 2 centimeters in size. Their tough outer covering protects the inner embryo and stored food material, which are essential for germination and the growth of a new plant. The arrangement of the seeds on a plain surface makes it easier to observe their shape, texture, and dimensions clearly. Such images are commonly used in botany, agriculture, and plant taxonomy studies to identify plant species based on seed characteristics. The photograph highlights the importance of seeds in plant reproduction, as they contain the genetic material necessary for producing the next generation of plants.

Fig No. 15: Typical photograph of roots of Camellia sinensis plant

X. INSTRUMENTS

1. Glassware

The glassware utilized for the purpose of extraction comprised of round bottom flasks of 2.5 liters capacity, soxhelete apparatus, weighing bottles and beakers. Before use the glasswares were dipped in chromic acid cleansing mixture diluted suitably with water and left for about 24 hours to soften an a dry material sticking to the inner sides of the glassware, followed by very thorough washing with stiff jet of tap water.

Then apparatus thoroughly brushed with detergent “Teepol” (Soap Solution) followed by an effective tap water wash and finally rinsed with distilled water.

The glassware inverted and left to dry.

2. Extraction medium.

Solvents i.e. Pet. ether, CH3Cl, alcohol and aqueous solutions used in the extraction process. Chemicals used of analytical reagent grade.

3. Extraction method and conditions of leaves, fruits, marketed tea, flower and roots of C. sinensis

The leaves, fruits, marketed tea, flowers and roots dried in shade and then at 37◦C. Leaves, fruits and roots cut into suitable size and reduced to coarse powder by grinder and passed through a sieve #10. The coarsely powdered of leaves, fruits, marketed tea, flower and roots (200 gm, each) extracted separately with petroleum ether (60-80◦C), chloroform, ethanol (95 % v/v) successively using soxhlet apparatus till few drops of the last portion of the elute did not leave perceptible residue on drying.

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The ultimate dried mark of these three parts macerated with warm distilled water and filtered.

Then the extractives obtained dried by evaporation of solvent under reduced pressure by 'Rotavapour Apparatus'. Water extractives obtained by evaporation of water extract on hot plate in china dish. The extractives thus obtained from petroleum ether, chloroform, ethanol and water examined for their colour, phytoconstituents and antidepressant activities and results were noted.

Fig No. 16: Typical photograph herb grinding mill.

The image shows a mechanical industrial machine commonly used for crushing, grinding, or pulverizing agricultural and food materials such as grains, spices, seeds, herbs, or other solid substances. The machine consists of a strong metal frame painted in blue, which supports the entire structure and provides stability during operation. At the top, there is a hopper or feeding chamber where raw materials are inserted into the machine. The central metallic chamber contains the grinding or crushing mechanism that processes the material into smaller particles or powder. A powerful electric motor is attached at the lower side of the machine.

Fig No. 17: Typical photograph of Rotavapor apparatus.

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3. Physical study of extracts

Different extractives of leaves, fruits, marketed tea, flowers and roots subjected to physical evaluation to detect their colours and chemical constituents.

Phytochemical investigations were carried out as per the standard procedures mentioned in herbal pharmacopoeia.

4. Biological study 4.1Animals

Albino mice (Laca strain) weighing 20-25 gm, breed Central Animal House of Pinnacle Biomedical Research Laboratories, Bhopal (Madhya Pradesh), India used for the study. The animals housed under standard 12 ± 1 hours light / dark cycle with food (Golden feed, New Delhi) and tap water ad libitum. The animals selected at random (male and female). The experiments conducted between 9.00 am to 5.00 pm.

Fig No. 18: Typical photograph of laboratory cage containing mice.

4.2 Drugs

The following extractives subjected to antidepressant studies:

Leaves, fruits, marketed tea, flowers and roots extractives of C. sinensis

(i.) Petroleum ether extractives

(ii.) Chloroform extractives

(iii.) Ethanol extractives

(iv.) Water extractives

4.3 Preparation of doses

Dried extractives suspended Tween 80 (2-5%) and then suspended in distilled water, to disperse the dose of the extractives and standard drug. Imipramine (Intas Pharmaceutical Limited, Ahmadabad) (10 m.g./kg) taken as the standard drug. All the drugs prepared afresh at the beginning of each experiment

Fig No. 19: Typical photograph of weighting bottles for dose preparation.

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4.4 Statistical analysis

Each experiment consisted of a group of minimum six animals. The data expressed as average immobility time ± Standard Error of Average. All the extractives have been compared with control and imipramine (standard) separately using one way analysis of variance (ANOVA) followed by Dunnett's Method. Results at $P<0.001$ were considered statistically significant.

4.5 Animal model for antidepressant activity Forced swim test (FST)

The mice were divided into 3 groups (n=Six). First group (control) which received Tween 80 suspended in distilled water (10 ml/kg) orally and second group which received reference drug 10 m.g./kg (orally) of Imipramine and third group which received extractives at 100, 200, 300 and 400 m.g./kg (orally).

The FST wasperformed on mice by individually mice forced to swim in an open glass cylindrical jar (Height 25 cm and Diameter 10 cm), containing 15 cm of water at 25 ± 1°C. The total duration of immobility during the six minutes of test was recorded.

Decrease in the duration of immobility during the FST taken as a measure of antidepressant activity (Porsolt, et al., 1977; Peng, et al., 2007).

Fig No. 20: Typical photograph of cylinders for forced swim test.

The image shows two transparent cylindrical glass containers placed side by side on a plain background. One container is taller and narrower, while the other is shorter with a slightly wider appearance. Both are made of clear glass with smooth surfaces and rounded bases, giving them a simple and elegant design. These types of glass vessels are commonly used in laboratories, homes, hotels, restaurants, and decorative settings. In laboratories, such cylindrical containers may be used for storing liquids, conducting experiments, or measuring substances.

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Fig No. 21: Typical photograph of thermometer.

The mice were divided into 3 groups (n=Six). First group (control) which receivedTween 80 suspended in distilled water (10 ml/kg) orally and second group Which received reference drug 10 m.g./kg (orally) of Imipramine and third group which received extractive at 100, 200, 300 and 400 m.g./kg (orally). Mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time recorded during a 6 minutes test (Steru, et al., 1985; Peng, et al., 2007). The antidepressant activity of extractives and drug was evaluated by administering drug and extractives before 30 minutes of the evaluation of activity.

XI. CONCLUSION

In this paper, the phytochemical constituents and pharmacological activities of green tea were systematically and comprehensively reviewed. Catechin, caffeine, theanine, tea polysaccharide, and other chemical components in green tea have pharmacological activities and health care functions, such as antioxidant, anti-tumor, hypoglycemic, and so on. As a natural antioxidant, tea polyphenols have been widely used in the food industry and cosmetics. In addition, the catechins in green tea also play an important role in the prevention and treatment of diabetes, hepatitis, microbial/viral infections, cancer, and skin inflammation.

In 2006, the FDA approved “Veregen ointment”, a green tea extract external preparation, for clinical use and it has already appeared on the market in the United States. However, the research on the pharmacological activity of green tea is still in the laboratory research stage. Therefore, how to carry out in-depth research on the mechanism of green tea active ingredients and realize the conversion from research to clinical application is still a major challen facing researchers. Finally, there are few reports on toxicological studies of green tea, mainly related to hepatotoxicity and cytotoxicity. Therefore, toxicity studies are still a potential research area in the future Furukawa et al. investigated whether EGCG Observed that EGCG promoted the formation Of 8-oxide, a characteristic oxidative damage Could cause oxidative damage to in vitro bovine thymus DNA under the action of metal ions and H2O2 oxidative stress. They to DNA that is strongly associated with mutations and cancer [128]. Therefore, they came to the conclusion that that this oxidative damage to EGCG could be considered as a potential predisposing factor for EGCG carcinogenicity [129]. One study showed that EGCG (20, 40 and 80 μM, 10, 60, and 240 min) caused DNA damage in both human lymphocytes and Nalm6 cells in a dose-dependent manner. When the maximum dose of EGCG was 100 μM, the survival rate of Nalm6 and human Lymphocyte decreased by 50% and 25%, Respectively .

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XII. RESULTS

1. Chemical study

1.1 Extraction of leaves, fruits, marketed tea, flowers and roots of C. sinensis The leaves, fruits, marketed tea, flowers and roots were dried, powdered and extracted with petroleum ether, chloroform, ethanol and water as described under "Materials and Methods". The colours of extractives were noted in Table No. 2 to 6.

The phytochemical investigations of various extractives obtained from leaves, fruits, marketed tea, flowers and roots were performed and observations noted in Table No. 7 to 11.

2. Antidepressant activity study

The extractives of leaves, fruits, marketed tea, flowers and roots of C. sinensis subjected to antidepressant activity study as described under "Materials and Methods".

2.1 Antidepressant effect of deferent extractives in forced swim test (FST) and tail suspension test (TST) of leaves, fruits, marketed tea, flowers and roots of C.

Green tea is a popular beverage, especially in China and Japan. There are no reports of clinical toxicity on whether there is a health hazard in drinking a large amount of green tea every day. In 2008, Chenglei's et al. first conducted safety studies on standardized green tea catechin (GTC) preparations, as well as heat-sterilized (GTC-H) and non-heat-sterilized (GTC-UH) preparations, and found that the level of no observed adverse effects of the three preparations (NOAEL) was 2000 mg/kg/day [119]. Another study demonstrated that GTC-H did not affect embryonic development in female rats. Its NOAEL was also2000 mg/kg/d [120]. Furthermore, Hsu et al. used a subacute exposure paradigm to evaluate that green tea extract.

That the level of no observed adverse effects of the three preparations (NOAEL) was 2000 mg/kg/day [119]. Another study demonstrated that GTC-H did not affect embryonic development in female rats. Its NOAEL was also 2000 mg/kg/d [120]. Furthermore, Hsu et al. used a subacute exposure paradigm to evaluate that green tea extract (2500 mg/kg, i.g., for 28 days) would not cause death or toxicity in ICR mice .These valuable data provide the basis for the safe application of green tea extract in food production.

Green tea is often developed as a weight-loss beverage, and they are usually considered as safe. However, the United States Pharmacopoeia (USP) has conducted a safety review and counted adverse events (AES) after the use of high-dose GTE preparations, most of which were liver injury reports [122,123,124,125]. In 2010, in an in vivo experiment, Lambert et al. reported for the first time that plasma alanine

Review and counted adverse events (AES) after the use of high-dose GTE preparations, most of which were liver injury reports [122,123,124,125]. In 2010, in an in vivo experiment, Lambert et al. reported for the first time that plasma alanine aminotransferase (ALT) in male CF-1 mice increased 138 times after treatment with high-dose EGCG (1500 mg/kg, e.g., for 7 days). Therefore, they came to the conclusion that high doses of EGCG had a hepatotoxic effect.

This mechanism of toxicity might be relate To the induction of oxidative stress in the Liver. However, the observed toxic doses Were much higher than normal tea Consumption [126]. In 2018, Hu et al.Evaluated the safe dosage of green tea for Adults based on toxicological data and AES.The safe intake for adults should be controlled below 338 mg EGCG/day [127]

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