CHAPTER - 2

REVIEW OF LITERATURE
CHAPTER 2

Review of Literature

2.1 *Oldenlandia corymbosa*

![Image of *O. corymbosa* Plant](image)

Figure 2.1 – *O. corymbosa* Plant

**Botanical name:** *Oldenlandia corymbosa*

**Synonyms:** *Hedyotis corymbosa*

**Family:** Rubiaceae

**Vernacular name:**

- **Sanskrit:** Parpata, parpataka, Kshetraparpata
- **English:** Flat top mille grains, Diamond flower, Five leaved fumitory
- **Hindi:** Daman pappar, pitpapra
- **Bengali:** Khet-papra
- **Gujarati:** Parpat, khet-papra
- **Marathi:** Papti, Phapti, khet-papda, paripat
- **Kannada:** Parpatahullu, Kallasabatrasige
Telugu: Verrinella- vemu

Malayalam: Parpatakapullu

Tamil: Parpatagam, kattucayaver, pappanpuntu

Habitat:

*Oldenlandia coymbosa* is an annual herb distributed in the tropical and subtropical region of the world.

Description:

*Oldenlandia corymbosa* is an annual, terrestrial, dichotomous, slender ascending herb growing up to 50 cm. The leaves are 1.3 – 2 cm by 0.8 - 3 mm, the lower leaves are often broader than upper ones, linear, acute, glabrous, usually with recurved margins. Flowers are white in pairs or in threes, usually on solitary axillary peduncles longer than the calyx. Fruits are loculicidal capsules, globose and the seeds are minute, pale brown, angular, testa tetriculate.

Taxonomy classification:

Kingdom : Plantae
Phylum : Angiosperms
Class : Dicotyledonae
Subclass : Asteridae
Order : Gentianales
Family : Rubiaceae
Subfamily : Rubioideae
Genus : Oldenlandia
Species : corymbosa
Ethnopharmacological information:

- The plant is reported to have immunopotentiation activity and in China, it has been used to treat some tumors\(^2\).
- It is considered as a cooling medicine in the treatment of fever caused by deranged air and bile and also treats remittent fever with gastric irritability and nervous depression.
- In Konkan, the juice is applied to cool the burning sensation felt in the palms of the hand and soles of the feet. Internally, the juice is given with a little milk and sugar to cool the burning pit of the stomach. The decoction is used in remittent fever, heat eruptions and also applied to the surface of the body. The plant extract is used in jaundice and as an anthelmintic. The plant is used as a febrifuge in Indo China\(^3\).

Phytochemical review

The chemical constituents reported in different parts of *Oldenlandia corymbosa* are mentioned beneath.

- Different phytochemical studies shows the presence of proteins, carbohydrates, phenols, tannins, flavanoids, saponins, steroids, terpenoids and glycosides. Some of the isolated compounds from whole plants are Geniposide, iridoid glycosides, 6 alpha – hydroxygeniposide, scadoside methyl ester (6 beta - hydroxygeniposide), 10-o-benzoylsandoside methyl ester, asperulosidic acid, asperuloside, deacteylasperuloside, 10-o-p-hydroxy benzoylsandoside methyl ester, rutin and (+)- 1yoniresinol-3-alpha -o-beta glucopyranoside\(^4\).
- The plant also contains ursolic acid, oleanolic acid and \(\gamma\)-sitosterol. The air dried plant contains 0.12% of alkaloids – bifloron and biflorin, these two alkaloids are interconvertible. It also contains 13.55% of inorganic ash, which is mainly responsible for its cooling effect\(^5\).
- An aqueous extract of the plant yielded a polysaccharide, composed of rhamnose, arabinose, zylose, mannose, galactose and glucose\(^2\).
- The methanol extracts of *Oldenlandia corymbosa* showed the presence of flavonols such as Quercetin, 3”-Methoxy quercetin and 3”, 4”-Dimethoxy quercetin. Phenolic acids like vanillic, syringic acid, melilotic acid, p-hydroxy benzoic, p-coumaric,
ferulic and caffeic acids are also present. Anthocyanidins like cyanidin and pelargonidin are present. Iridoids and alkaloids are also present.  

Pharmacological activity

Pandey et al., 2012 demonstrated the anticancer activity of ethanol extract of the leaves of Oldenlandia corymbosa on k562 human leukemia cell lines. The cell viability was measured by SRB (sulforhodamine B) assay. The cell lines were grown under RPMI1640 medium containing 2 mM L-glutamine, 10% fetal bovine serum. The results were recorded on an ELISA plate reader at 540 nm to 690 nm wavelength. The nontoxic dose of Oldenlandia corymbosa showed anticancer activity as compared to the standard drug Adriamycin.

Endrini et al., 2011 also demonstrated the anticarcinogenic property of methanol extract of the whole plant by Microculture tetrazolium salt (MTT) assay on the MCF-7 human breast carcinoma dependent hormone cell lines. The highest anticancer activity on MCF-7 cell line observed with IC 50 value of 22.67 µg/ml. The anticancer activity of the plant extract is mainly due to its antioxidant activity.

Rathi et al., 2009 evaluated hepatoprotective activity against Perchloroethylene, CCl₄ and D-Galactosamine induced liver damage in experimental animals. Ethanol extract of Oldenlandia corymbosa was studied for hepatoprotective activity on perchloroethylene induced hepatic damage in Wistar albino female rats. The extract was administered orally at the dose of 400 mg/kg of body weight for ten days, showed significant reduction in liver marker enzymes (AST, ALT, LDH), lipid peroxidation and with a significant increase in antioxidant enzyme levels. The results show potent hepatoprotective activity upon perchloroethylene induced hepatic damage in rats and also have anti lipid peroxidative and free radical scavenging activities.

Chimkode et al., 2009 also assessed hepatoprotective activity of ether, ethanol, butanol, butanone, petroleum ether and ethyl acetate extract fraction of Oldenlandia corymbosa against CCl₄ induced hepatic damage in albino rats. An acute toxicity study was carried out in albino rats of either sex for determining LD 50 values for different extracts. The
petroleum ether and ethyl acetate extract does not show any significant hepatoprotective activity. The elevated levels of SGPT and SGOT were significantly decreased in ether and butanol extracts at P < 0.001 and in butanone and ethanol at p < 0.005. The enzymatic levels and histopathological studies showed that ether, butanol, ethanol, butanone extracts of *Oldenlandia corymbosa* have hepatoprotective activity in CCl₄ induced hepatic damage¹⁰.

**Gupta et al., 2012** reported antihepatotoxic activity of methanol extract of *Oldenlandia corymbosa* against D-Galactosamine induced hepatotoxicity in Wistar rats. The extract significantly reduced increased levels of marker enzymes with D-galactosamine (AST, ALT, ALP, γ-glutamyltransferase) and showed the significant reduction in lipid peroxidation at the dose of 200 mg/kg¹¹.

**Agrawal et al., 2013** evaluated alcoholic and aqueous extract of whole plant of *Oldenlandia corymbosa* for antiulcer activity against aspirin in rats. The extracts were administered in two doses 200 mg/kg and 400 mg/kg by oral route 45 minutes prior to the administration of aspirin. The drug lansoprazole 8 mg / kg was used as standard. Both the extracts showed significant decrease in ulcer compared to control group which is characterized by reduction in ulcer index, gastric volume, free acidity, total acidity and pH. The percentage protection in alcoholic and aqueous extract at 200 mg/ kg, 400mg/kg showed 65.7%, 33% respectively in comparison with standard lansoprazole 88.89%¹².

**Sasikumar et al., 2010** studied antioxidant activity of methanol extract of aerial parts of *Oldenlandia corymbosa* by different in vitro methods such as; 1,1 diphenyl-2-picryl hydroxyl (DPPH) assay, 2,2’-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) cation decolorization test, ferric reducing power (FRP), scavenging capacity towards hydroxyl ion (OH.) radicals and nitric oxide (NO) radical inhibition assay. The extract showed high antioxidant activity against DPPH, ABTS, Nitric oxide and hydroxyl radical at 82, 130, 150, 170 µg/ml respectively. The study showed that methanol extract effectively attenuates the oxidative stress via antioxidant property¹³.
Fatema et al., 2014 demonstrated analgesic activity of ethanol extract of *Oldenlandia corymbosa* in mice using three different models; hot plate reaction time, acetic acid writhing test and formalin induced pain method, with ketorolac as standard drug. The extract was administered two doses 200 mg/kg and 400 mg/kg by oral route. Formalin test procedure revealed the involvement of both peripheral and central mechanisms. The acetic acid writhing test involved the peripheral mechanism and the hot plate method involves the central mechanism. The extract showed a significant dose dependent anti nociceptive activity\(^{14}\).

Mishra et al., 2009 evaluated Antimalarial activity of the methanol extract of *Oldenlandia corymbosa* by both in vitro and invivo methods. The extract showed significant antimalarial activity on chloroquine sensitive (MRC-pf20) and chloroquine sensitive (MRC-pf 303) strains of *Plasmodium falciparum*. The in-vivo antimalarial activity of the extract was studied using mice. Drug treatment was initiated 1 day (24 hour) prior to the parasite treatment starting from 4\(^{th}\) day post infection. Every alternate day, the blood was collected from tail to check the level of parasitemia. The combination of plant extract with curcumin showed more effective antimalarial activity\(^{15}\).

Hussain et al., 2013 studied antibacterial activity of methanol extract of *Oldenlandia corymbosa* by disc diffusion method against gram positive and gram negative bacteria (Bacillus, Klebsiella, Escherichia coli, Proteus, Staphylococcus aureus and Pseudomonas). The extract significantly inhibited the growth of both gram positive and gram negative bacteria and has a broad spectrum of antibacterial activity. The order of inhibition was found to be Proteus (22mm) < Pseudomonas (26mm) < Bacillus (27mm) < Staphylococcus aureus (28mm) < Escherichia coli (32mm) < Klebsiella (33mm)\(^{16}\).

Hussain et al., 2013 assessed antifungal activity of whole plant extract of *Oldenlandia corymbosa* against Candida albicans and Aspergillus nigar. The maximum antifungal activity was found in Candida albicans. The activity was due to the presence of the constituents like steroids and glycosides\(^{16}\).
Nikolajsen et al., 2011 evaluated the effect of ethanol extract of *Oldenlandia corymbosa* in the isolated uterine horn preparation of virgin female Sprague Dawley rat. The extracts were tested in different concentration 0.014, 0.14, 0.44 and 1.40 mg/ml. The De Jalon solution was used as the physiological solution and the response was compared against the standard (acetylcholine) and blank (ethanol). The extract showed significant uterine contraction.
2.2 *Grangea maderaspatana*

![G. maderaspatana plant](image)

**Botanical name:** *Grangea maderaspatana*

**Synonyms:** *Grangea adansonii, Artemesia maderaspatana*

**Family:** Asteraceae

**Vernacular name:**

- **English:** Madras carpet
- **Gujarati:** Jhinkimundi, Nahanigora, Khamundi
- **Hindi:** Mukhatari, Mustaru
- **Malayalam:** Nelampala
- **Marathi:** Mashipatri
- **Tamil:** Mashipatri
- **Telugu:** Machi-Patri
- **Urdu:** Afsantin
- **Kannada:** Dodda gaadaari
Habitat: Madras Carpet is an annual herb commonly seen in flat bunches in harvested fields, dry river and pond beds.

Description:
Grangea maderaspatana is a common weed usually grown in sandy soil and waste places. This hairy, branched herb spreads from the roots and grows up to 70 cm in height. The stems are prostrate, spreading from the centre, 10-30 cm long, hairy with soft white hairs. Leaves are numerous, alternate, sessile, 2.5-6.3 cm. long, sinuately pinnatifid with 2-4 pairs of opposite or subopposite lobes smaller towards the base, the largest terminal lobe, all coarsely serrate-dentate, pubescent on both surfaces, oblong or oblanceolate.

Flowers: The inflorescence is terminal, truncate spherical head, 6-10 mm in diameter, solitary or 2-3 together, yellow and many flowered. The peduncle is 1-4 cm long. The involucral bracts are 2-3 seriate where the outer ones are oblong and acute while the inner ones are elliptical, yellow, involucral bracts elliptic, obtuse, rigid, densely pubescent, Pappus a short tube with fimbriate mouth. Achenes glandular, 2.5 cm long including the pappus-tube.

Taxonomy classification:
Kingdom: Plantae
Subkingdom: Planta Tracheophyta
Subdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida (Dicotyledons)
Subclass: Asteridae
Order: Asterales
Family: Asteraceae
Ethnopharmacological information:

- The herb is antipyretic and good for pain in the eyes and ears.
- The root is an appetizer, astringent to the bowels, diuretic, anthelmintic, emmenogogue, galactogogue and stimulant. They are useful in griping, in troubles of the chest and lungs, headache, paralysis, rheumatism in the knee joint, piles, pain in the muscles, diseases of the spleen and the liver, troubles of the ear, the mouth and the nose; lessens perspiration (Unani).
- Plant is stomachic and uterine stimulant. Infusion of the leaves with ginger and sugar added is used in dyspepsia, hysteria and obstructed menses.
- Externally it is useful as an anodyne and antiseptic for inflamed and painful parts. The powdered leaves are applied to wounds and ulcers as an antiseptic. Juice of the fresh leaves is instilled into the ear for earache.

Phytochemical review:

The chemical constituents reported in different parts of *G. maderaspatana* L. are mentioned below.

- Various parts of the plant have been reported to contain steroidal constituents like hardwickiic acid, the corresponding 1, 2-dehydro derivative and acetylenic compounds.
- Eight new clerodane diterpenes including five clerodane, a nor clerodane, a secoclerodane and a norsecoclerodane derivatives along with auranamide were also isolated.
- A clerodane derivative, 15-hydroxy-16-oxo-15,16H-hardwickiiic acid has been isolated from the aerial parts of *G. maderaspatana*.
- Three components viz., eudesmanolide, (-) frullanolide, (-) -7-alpha-hydroxyfrullanolide and a new eudesmanolide (+) -4 alpha, 13-dihydroxyfrullanolide have been isolated from the whole plant of *G. maderaspatana*. A new eudesmanolide was named (+) – Grangolide.
- Penta and hexamethoxy flavones have been isolated as 3 "5- dihydroxy- 3',4',5 ',6,7-pentamethoxy flavone, 4',5-dihydroxy-3,3 ',5 ',6,7-pentamethoxy flavone (murrayanol) and 5-hy droxy-3,3 ',4 ',5 '6,7-hexamethoxy flavone in addition to previously reported clerodane diterpenes from the Diethyl ether – Petrol – Methanol (1:1:1) extract of the aerial parts of *Grangea maderaspatana*.
Two new 5-deoxyflavones, 6-hydroxy-2',4',5'-trimethoxyflavone, 6-hydroxy-3',4',5'-tri-methoxyflavone and a known flavone, 7,2',4'-trimethoxyflavone have been isolated from the whole plant of *Grangea maderaspatana*<sup>29</sup>.

The plant contains diterpenoid compounds of labdane and clerodatetrean type, 15, 16-epoxy-7-hydroxy-3, 13, 14-clerodatrien-18-oic acid; steroids, chondrillasterone and chondril -lasterol; diterpene, strictic acid, a phenylalanine derivative, auranamide and the allergenic compounds, eudesmanolides, (-)-frullanolide, (-)-hy-droxyfrullanolide and (+)-grangolide<sup>30</sup>.

A new diterpenoid has been isolated as 8-hydroxy- 13 E -labdane-15yl-acetate from the acetone extract of *Grangea maderaspatana*<sup>31</sup>.

The aerial parts of *Grangea maderaspatana* (L.) Poir contain 91.5% of oil constituting 21 different constituents. It was characterized by the dominant presence of sesquiterpenoids (sesquiterpenoid hydrocarbons 36.1 % and oxygenated sesquiterpenoids 28.4 %). Most abundant compounds are γ-gurjunene (26.5%), terpinyl acetate (20.8%) and hinesol (11.7%)<sup>32</sup>.

**Pharmacological activities:**

**Jain et al., 1993** assessed a mixture of flavonoids extracted from the *Grangea maderaspatana* plant for oestrogenicity and antiimplantational activities, in the mouse. In the 3 day uterotrophic bioassay, administration of the drug at a dose of 20 mg/kg body weight per day, intramuscularly to ovariectomized females, resulted in a highly significant (p<0.001) increase in the wet uterine and vaginal weights. However, in comparison with conjugated oestrogen, the extract proved to be mildly oestrogenic. Flavonoids, administered orally at the same dose level effectively interfered with all stages of pregnancy. Maximum interceptory efficacy was recorded when the drug was administered from days 4-6 post coitum. However, there was a reduction in antinidational activity only if the drug was administered from days 1-3 and 7-9 post coitum<sup>33</sup>.

**Ahmed et al., 2001** evaluated Analgesic activity of methanol extract of *Grangea maderaspatana* (1 and 3 g/kg, p.o.) in acetic acid induced writhing in mice. The extract significantly and dose-dependently inhibited writhing in mice. The lower dose (1 mg/kg, p. o.) found to as effective as aminopyrine (50 mg/kg, p.o.) which was used as a reference<sup>34</sup>.
Rachchh et al., 2013 also assessed Analgesic activity of methanol extract of the plant (500 mg and 1 g/kg, p.o.) by tail flick model. The plant extract in both dose significantly increased latency for tail flick indicated analgesic activity\textsuperscript{35}.

Ruangrungsi et al., 1989 evaluated cytotoxic activity of crude chloroform extract of Grangea maderaspatana in the KB cell culture assay. The extract exhibited strong cytotoxic activity (ED\textsubscript{50}=2 μg/ml)\textsuperscript{27}.

Patel et al., 2009 evaluated the antioxidant activity of the methanol extract of Grangea maderaspatana using five in vitro assays and was compared to standard antioxidant ascorbic acid. The extract exhibited significant (p<0.05) reducing power ability, 1,1-diphenyl- 2-picrylhydrazyl (DPPH) radical scavenging activity, nitric oxide radical scavenging activity, hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) scavenging activity and inhibition of β-carotene bleaching. The activity depends on concentration and increased with increasing amount of the extract. The free radical scavenging and antioxidant activities may be attributed to the presence of phenolic and flavonoid compounds present in the extract\textsuperscript{36}.

Singh et al., 2013 also assessed in vitro antioxidant potential of the oil obtained by steam distillation of extract of aerial parts of Grangea maderaspatana (L.) Poir., using, DPPH radical scavenging, metal chelating and reducing power assays. The oil showed antioxidant potential with significant reducing power (ASE/mL 2.01 ± 0.00), chelating activity (IC\textsubscript{50} 1.80 ± 0.15) and DPPH radical scavenging activity (IC\textsubscript{50} 2.90 ± 0.96)\textsuperscript{32}.

Omhare et al., 2012 identified that the aqueous and ethanol extract (250 mg/kg, 500 mg/kg, p.o.) of Grangea maderaspatana Poir. effectively inhibited CCl\textsubscript{4} and paracetamol induced changes in the serum marker enzymes (SGOT, SGPT and ALP) in a dose-dependent manner as compared to the normal and the standard drug silymarin treated groups. Hepatic steatosis, hydropic degeneration and necrosis observed in CCl\textsubscript{4} and paracetamol treated groups were completely absent in histology of the liver sections of the animals treated with the extracts. The results suggest that the ethanol extract of G. maderaspatana possess significant hepatoprotective activity\textsuperscript{37}.
Singh et al., 2013 demonstrated an Antimicrobial activity of the oil obtained by steam distillation of aerial parts of *Grangea maderaspatana* (L.) Poir. against gram positive bacteria, gram negative bacteria and fungi using agar well diffusion method. The zone of inhibition (ZOI) values of the oil was in the range of 2.67 ± 0.58 to 11.00 ± 0.00 mm and minimum inhibitory concentration (MIC) of the oil was ranged from 5 to 30 μL/mL for tested microorganisms. The activity was more pronounced against Candida albicans (ZOI = 11.00 ± 0.00 mm, MIC = 5 μL/mL) followed by Streptomyces candidus (ZOI = 9.33 ± 0.58 mm, MIC = 5 μL/mL), while the oil was least effective against Aeromonas hydrophila and Klebsiella pneumoniae.

Rachchh et al., 2013 evaluated Anti-inflammatory activity of methanol extract of *G. maderaspatana* (1000 mg/kg, p.o.) using acute model of carrageenan induced rat paw edema. Indomethacin was used as standard in this model. The extract showed significant protection against carrageenan induced rat paw edema indicating its anti-inflammatory activity.

Rachchh et al., 2013 also evaluated Antiarthritic activity of methanol extract of *G. maderaspatana* (1000 mg/kg, p.o.) using Complete Freund’s Adjuvant (CFA) induced arthritis in rats. Dexamethasone was used as a standard in this model. The degree of arthritis was evaluated by hind paw swelling, body weight changes, erythrocyte sedimentation rate, rheumatoid factor, Creactive protein and arthritic index supported by histopathology of ankle joints. The extract treatment declined CFA induced rise of erythrocyte sedimentation rate, rheumatoid factor, Creactive protein significantly in rats. Histopathological study of ankle joint revealed that extract inhibited edema formation and cellular infiltration induced by CFA.

Ahmed et al., 2001 assessed diuretic activity of *Grangea maderaspatana* (L.) Poir.

Omhare et al., 2012 evaluated Acute oral toxicity by following Organization of Economic Co-operation and Development (OECD) guidelines 420- Fixed Dose Procedure (FDP). Results indicated that the aqueous and alcohol extract of *G. maderaspatana* up to a dose of 2000 mg/kg; p.o. did not produced any mortality.
2.3 Basics of Psychopharmacology

Psychopharmacology is the systematic study of the drugs effect and their effects on mood, sensation, thinking and behavior\(^{40}\). At the heart of Psychopharmacology lie two important things; psychoactive drugs and mental sickness as a clinically diagnosed disorder. Psychopharmacology refers to the study of drugs, pharmakon, that influence the human mental state, psyche, and behavior. It is a medical condition that disrupts a person's thinking, feeling, mood, ability to connect to others and daily operation\(^{41}\).

Mood disarrangement are described by a distress in the regulation of mood, conduct and affect. They are segmented into Depressive disorders, Bipolar disorders and Depression in association with medical illness\(^{42}\). Major despair is a collective condition that lasts to result in extensive morbidity and mortality despite major advances in treatment\(^{43}\).

The occurrence of sadness in common people is assessed to be around 5%. Currently 121 million individuals are expected to suffer from depression. As per assessed value, 5.8% of men and 9.5% of women are suffering by a depressive event in their lifespan. Suicide is one of the most common outcomes of depression\(^{44}\). According to the World Health report (WHO, 2001), roughly 450 million community suffer from a emotional or behavioral distemper, yet only a small minority of them get even the most fundamental treatment. This amounts to 12.3% of the broad overload of illness, and will increase to 15% by 2020\(^{45}\).

Mental disorders have become highly prevalent due to ambitious lifestyle, urbanization, and stressful environment. Psychosis is a one of the most debilitating, complex, and costly illness. The meaning of “psyche” is mind or soul, and word “-osis” corresponds to an abnormal condition in Greek. Hence, psychosis is often described as involving a “loss of contact with reality.” These illnesses alter a person’s ability to think clearly, make good judgments, respond emotionally, communicate effectively, understand reality and behave appropriately. It is characterized by three general types of symptoms: Positive symptoms, negative symptoms and cognitive symptoms. Positive symptoms refer to a loss of contact with reality and comprise of hallucinations, delusions, bizarre behavior and positive formal thought disorders. Negative symptoms refer to a diminution in or absence of normal behaviors and include flat
affect, alogia, avolition, and anhedonia. Cognitive symptoms manifest as deficits in attention, learning, memory, concentration, and executive functions\textsuperscript{46}.

**Overview of mechanisms of action**

Psychopharmacology is very complex and extensive division of medicine with roots in the mechanisms of action of psychotropic drugs. Generally, the mechanism of action of drugs is largely due to pharmacodynamic factors. On the other hand, the onset, duration and magnitude of drug action are determined by pharmacokinetic factors.

Psychotropic drugs are amphiphilic in nature i.e. they possess both hydrophilic and hydrophobic properties. Because of this physical property, psychotropic drugs rapidly reach their sites of action. Psychotropic drugs either permeate through plasma membrane (hydrophilic) or build up in the hydrophobic interior of lipid bilayer of cell membranes\textsuperscript{47}.

**Neurotransmitters**

Neurotransmitters are endogenous chemicals in the human body that are responsible for the transmission of nerve impulses between neurons and target cells across a synapse. For a signal to get transmitted across, an optimum amount of neurotransmitters in the synaptic space must be present\textsuperscript{48}. In mentally healthy individuals, there is a balance between the amount of neurotransmitters in the synaptic space and in the presynaptic neuron. It is the disruption of this balance that leads to mental and metabolic disorders affecting sleep, mood, weight, etc\textsuperscript{49}. Some of the important neurotransmitters implicated in psychopharmacology are acetylcholine, serotonin, dopamine, norepinephrine, epinephrine, glutamate and GABA.

**Acetylcholine**

Acetylcholine is used to regulate muscle movement. Its cholinergic neurons are found all over the CNS, especially the brain, where it is involved in numerous functions such as pain perception, neuroendocrine regulation, REM regulation and memory and learning formation. Damage to the cholinergic system is an important pathology implicated in Alzheimer’s disease.
Norepinephrine
Norepinephrine is the neurotransmitter that plays an important role in conditions related to stress. Along with epinephrine, it enables the body to “fight or flight” in emergencies by stimulating the heart rate, blood circulation and respiration to compensate for the increased oxygen requirement of the muscles.

Dopamine
Dopamine is synthesized from the amino acid, tyrosine. Tyrosine is converted to dopamine by the action of enzymes, tyrosine hydroxylase and L-amino acid decarboxylase, respectively. Deficiency of dopamine in the brain is implicated in the pathology of Parkinson’s disease. Overactivity of same dopamine will cause Psychosis (schizophrenia)\(^5\). 

Serotonin
The main function of serotonin is regulation of mood, appetite, sleep, cognition, and blood coagulation. The most widely prescribed and efficacious antidepressants, selective serotonin reuptake inhibitors (SSRIs), and older antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), act on the serotonergic system by inhibiting serotonin reuptake into the presynaptic vesicle.

Glutamate
Glutamate is the primary excitatory neurotransmitter in the brain. An injury to a nerve (e.g. brain injury) results in its release and excessive concentration in the extracellular space, leading to excitotoxicity\(^5\). Excess extracellular glutamate may lead to excitotoxicity in vitro and in vivo in acute insults like ischemic stroke via the overactivation of ionotropic glutamate receptors. In addition, chronic excitotoxicity has been hypothesized to play a role in numerous neurodegenerative diseases including amyotrophic lateral sclerosis, Alzheimer's disease and Huntington's disease\(^5\). Excessive glutamate levels in the brain is a precursor to psychosis in individuals at high risk for developing schizophrenia\(^5\).

GABA
The inhibitory neurotransmitter GABA is synthesized from the amino acid, glutamate, by the enzyme glutamate decarboxylase in the GABAergic neurons\(^5\).
Psychotropic drugs exert their pharmacologic action primarily by agonism or antagonism of neurotransmitter receptors, inhibition of regulatory enzymes or blockade of stimulators of neurotransmitter membrane transporters.

Table 2.1: General mechanisms of action of psychoactive drugs

<table>
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<tr>
<th>General mechanism of actions of psychotropic drugs</th>
<th>Examples</th>
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<td>Synthesis and storage of neurotransmitters</td>
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<td>Release of neurotransmitters from presynapse</td>
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<td>Blockade of receptors</td>
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</table>

Pharmacological treatment of Psychosis

The anti-psychotic drugs are also termed as neuroleptic drugs, or neuroleptics, which is derived from Greek in which neuro refers to the nerves and lept means “to take hold of”. Thus, the word neuroleptic means “taking hold of one’s nerves.” Antipsychotic agents are the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations, delusions, and thought disorders. Antipsychotic medications are commonly classified into two categories: First generation (typical) and second generation (atypical).

The typical antipsychotics are classified according to their chemical structure while the atypical antipsychotics are classified according to their pharmacological properties. The major difference between the two types of antipsychotics is that the first generation drugs block dopamine and the second generation drugs block dopamine and also affect serotonin levels. Although atypical antipsychotics are generally considered to be more effective and to have reduced side-effects compared to typical antipsychotics. Evidence suggests that some of the second generation drugs have milder movement related side effects than the first generation drugs.
Herbal medicines are in great demand in the developed as well as developing countries for primary healthcare because of their wide medicinal activities, higher safety margins, and lesser costs. Dietary supplements along with herbal medicines may improve symptoms of psychosis.

However, the management and treatment plans may include one or more of these interventions:

1. Psychopharmacologic treatment
2. Psychotherapy approaches
   - Brain stimulation
   - Institutionalization / rehabilitation programs
   - Psychodynamic therapy
   - Cognitive-behavioral therapy
   - Group therapy
   - Family intervention
   - Social rhythm therapy
3. Self-care

Other interventions and services may include:

1. Employment assistance
2. Housing assistance
3. Reintegration measures into society
4. Psychosocial rehabilitation
5. Assertive community treatment

Additionally, several healthcare personnel may be involved in the execution of the management and treatment plans such as:

1. Family clinician
2. Psychotherapist
3. Psychiatrist
4. Pharmacist
5. Social worker
6. Family members
Classification of Psychotropic drugs

In a medical context, psychotropic drugs refer to a class of prescription medications that primarily exert their therapeutic effects on the central nervous system. Whether taken orally or administered intravenously, psychotropic drugs are absorbed by the blood and transported into the brain. They pass through the protective membrane, the blood brain barrier (BBB) and into the brain circulation.

Psychotropic drugs, on the other hand, are formulated especially to cross the BBB and act directly on the brain to alter perception and mood, induce behavioral changes and affect consciousness along with cognition. The basic purpose of these drugs is to bring about the desired changes in mood and behavior to treat and manage psychiatric disorders.

Psychotropic medications are generally categorized into the following:

- Antipsychotics
- Antidepressants
- Anxiolytics
- Mood stabilizers
- Prescription stimulants
- Sedative-hypnotics
- Miscellaneous drugs (e.g. herbal supplements)

Antipsychotics

This subgroup contains a large number of medications that are used to treat psychosis. Psychosis is a generic term that encompasses disorders resulting from abnormal perception of reality accompanied by a defective insight. Psychotic patients primarily experience these two characteristics:

- Hallucinations: Sensory perceptions without an actual stimulus being present
- Delusions: False beliefs about reality

Antipsychotics are used in the treatment of mental illnesses such as schizophrenia, bipolar disorder, delusional disorders, and also wide range of non-psychotic disorders such as Tourette syndrome, autism, and dementia.
Antidepressants
Antidepressants comprise a wide variety of drugs that are basically indicated to treat the various symptoms of depressive disorders. However, many off label indications for using antidepressants also exist and conditions such as anxiety, sleep disorders, obsessive compulsive disorders, eating disorders, neuropathic pain, ADHD, migraines and substance abuse benefit from its use.

Anxiolytics and sedatives
Anxiolytics, as the name suggests, are medications that are used to curb anxiety. Tricyclic antidepressants and monoamine oxidase inhibitors also relieve anxiety but are rarely prescribed because of their extensive side effect profile. Barbiturates and benzodiazepines exhibit dose-dependent effects on the CNS, i.e. the higher the dose, the deeper the sedation-anxiolysis-anesthesia on the CNS. Benzodiazepines are primarily used for panic disorders and generalized anxiety disorder.

Mood stabilizers
Mood stabilizers are a group of antipsychotic medications that are primarily used to treat the symptoms associated with mood shifts in bipolar disorder, schizoaffective disorders, and sometimes even borderline personality disorders. The main purpose of the drug is to stabilize the intense mood shifts between depressive and manic episodes. The classic drug in this category is lithium carbonate.

Stimulants
Stimulants are psychoactive drugs that elevate mood and improve physical and mental functioning for a temporary period of time. They are used worldwide as prescription drugs and also have been widely abused as recreational substances. Essentially, stimulants increase brain activity within the central nervous system and peripheral nervous system. They are used to treat lethargy, obesity, excessive appetite, narcolepsy, and improve concentration in ADHD patients.

There are many type of stimulants i.e. ampakines, amphetamine related substances, eugeroics, norepinephrine reuptake inhibitors (NERIs), norepinephrine dopamine reuptake inhibitors (NDRIs), xanthine and caffeine-related drugs. Each type has a unique mechanism of action.
**Sedatives / hypnotics**

Sedatives or tranquilizers are a group of drugs that induces sleep by decreasing the excitatory mechanisms of the brain. Many of the drugs mentioned above have sedative effects, namely benzodiazepines. Barbiturates and antihistamines can all act as sedatives. Sedatives, when used prior to medical surgeries, are called sedative-hypnotics because their effects on the CNS are dose-dependent i.e. at lower doses; they may act as anxiolytics but at higher doses, can induce unconsciousness. They are used to induce sleep and are adjuncts to general anesthesia.

**Miscellaneous drugs: complementary, herbal and over the counter**

In the last 10 years, herbal formulations have been gaining popularity in the U.S. for the treatment of psychiatric disorders. These supplements are widely purported by their manufacturers to exhibit fewer and lighter side effects compared to their counterparts that require prescription. The herbal supplement, St. John’s Wort, is one such example. It is obtained from the flowers and leaves of the herb, Hypericum perforatum. It is known by a number of other names including Tipton's weed, rosin rose, Amber, Amber Touch-and-Heal, goatweed, and Klamath weed.

Several studies propose the significant role of St. John’s Wort in the treatment of mild to moderate depression. Some users have also reported experiencing therapeutic benefits in the treatment of anxiety and related disorders.

**Overview of newer vs. older psychotropic medications**

The 19th and 20th centuries saw the emergence of psychotropic drugs that were initially used to treat other medical conditions. Bromides were introduced in 1857 as an anticonvulsant, and the oldest group of depressants, barbiturates, in 1912 for insomnia. These two groups of drugs were found to have sedative effects. Other drugs soon emerged such as amphetamines for depression and lithium for agitation in manic states. The first antipsychotic, chlorpromazine, was first studied for its sedative properties in anesthesiology. Tricyclic antidepressants and monoamine oxidase inhibitors became the standard of treatment for depression in the 1950s. The most widely prescribed anxiolytics today, benzodiazepines, were introduced in the 1960s.
Animal model review

Forced swim test:

Purpose and rationale

Forced swim test was proposed as a model to test for antidepressant activity. It was suggested that mice or rats forced to swim in a restricted space from which they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression\(^67\).

![Figure 2.3 Forced Swim Test Instrument](image)

Procedure

Rats of any sex were independently forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), comprising 19 cm of water at 25 ± 1\(^\circ\) C. All the rats were divided in different groups. The total duration of immobility was recorded during the last 6 min of the 10-min period. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. A decrease in the duration of immobility is indicative of an antidepressant-like effect\(^68\).
Evaluation

Duration of calmness is assessed in different groups of animals. Antidepressant drugs, but also stimulants like amphetamine and caffeine, reduce duration of immobility. 69

Hole-board test

Purpose and rationale

The evaluation of certain components of behavior of mice such as curiosity or exploration has been attempted by Boissier et al. (1964) 69 and Boissier and Simon (1964) 70. They used an open field with holes on the bottom into which the animals could poke their noses. The “hole-board” test has become very well accepted and has been altered and automatized by many authors.

Procedure

Mice of any sex having weight between 18 and 22 g are used. The dimension of hole-board is 40× 40 cm. There are 16 holes with a diameter of 3 cm each are scattered uniformly on the floor. The board is raised so that the mouse poking its nose into the hole does not see the bottom. Nose-poking is assumed to specify curiosity and is measured by visual observation. Generally, six animals are used for each group. After 30 min, the extract is administered and the first animal is placed on the hole-board and evaluated for 5 min.

Critical assessment of the method

The nose poking into a hole is a characteristic behavior of mice which specify certain degree of curiosity. Assessment of this type of activities has been demonstrated to be relatively beneficial. Benzodiazepines have a tendency to decrease nose-pocking at somewhat small doses.

Elevated plus maze test

Purpose and rationale

Out of various possibilities to alter maze tests (e.g. water maze (Danks et al. 1991) 71, the Y-maze, the radial maze (Di Cicco 1991) 72, and the elevated plus maze (Montgomery 1958) 73; Pellow et al. 1985) 74; Corbett et al. 1991) 75 have found recognition in various laboratories. The test has been recommended for selective identification of anxiolytic and anxiogenic drugs. Anxiolytic compounds, decrease anxiety, increase the open arm exploration time while anxiogenic compounds have the reverse effect.
Procedure
The EPM consists of two open arms, 50× 10 × 40 cm, and two enclosed arms, 50 × 10 × 40 cm, with an open roof, organized so that the two open arms are opposite to each other. The maze is elevated to a height of 50 cm. The mice are divided into different groups having 6 mice for each dose. After 30 min. of administration of test or standard, the mouse is kept in the center of the maze, facing any of the enclosed arms. For the duration of a 5 min. the following measures are taken: the no. of entries into and time spent in the open and enclosed arms. If possible, the activity is assessed in a sound attenuated room.

Critical assessment of the method
The method is relatively time consuming, but can be considered as a reliable degree of anxiolytic activity. Currently computerized automatic systems are available to overcome these problems.
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